CHAPTER 1A

Embryologic development of the liver, biliary tract, and pancreas

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OVERVIEW OF LIVER AND BILIARY TRACT DEVELOPMENT

Developmental biologists have often marveled at the enormous regenerative capacity of the liver after injury, and such growth represents one of the fastest by mammalian tissues. Presumably this process is based on the recapitulation of embryonic signals in the liver, but our understanding of the mechanisms of liver development is relatively poor. The liver is the largest internal organ and consists of diverse cell types that arise from various embryologic origins. The two principle cell types of the liver are the *hepatocytes*, which comprise nearly 70% of the mass of the adult organ, and the *cholangiocytes*. Both cells are derived from the embryonic endoderm. Other cell types of the liver include hematopoietic, Kuppfer, stromal, and stellate cells, all of which are of mesodermal origin (Fig. 1A.1). Despite their homogeneous appearance, hepatocytes do not all function identically; they perform various roles, depending on their physical location within a hepatic lobule, the primary functional unit of the liver. Thus, liver development entails not only hepatocyte and cholangiocyte differentiation but also further cellular differentiation within the hepatocyte population (Fig. 1A.1).

During the third week of gestation, the liver primordium first appears as an outgrowth of the ventral foregut endoderm at the caudal end of the foregut. The proliferation of the epithelial cells in this liver bud leads to its growth and branching with resulting expansion of the growing bud into the surrounding mesenchyme, giving rise to the liver and intrahepatic biliary tree. As it grows caudally, traversing the septum transversum, the persistent connection between the branching epithelium and the foregut develops into the extrahepatic bile ducts and gallbladder (Sadler & Langman, 2006). The hepatoblasts eventually differentiate into hepatocytes and cholangiocytes. The final liver structure continues to develop through the postnatal period. In addition to giving rise to the liver and biliary tract, the proximal endoderm (foregut) also gives rise to respiratory epithelium and the glandular cells of the thyroid, thymus, and pancreas.

ENDODERMAL PATTERNING

Embryologically, the liver, biliary tract, and pancreas develop through a series of reciprocal interactions between the endoderm and the surrounding mesenchyme. The primitive gut tube, which is derived from the endodermal germ layer during gastrulation, is divided into the foregut, midgut, and hindgut domains, each of which gives rise to specialized regions (Grapin-Botton, 2005). This specialization is initiated by transcription factors expressed in different regions, such as pancreatic and duodenal homeobox gene 1 (*PDX1*) and pancreas-specific transcription factor 1a (*PTF1A*), whose coexpression in the endoderm gives rise to the pancreas (Fig. 1A.2) (Grapin-Botton, 2005; Moore-Scott et al, 2007). The definitive endoderm is formed at the ventral side of the vertebrate embryo during gastrulation. Evagination of the endoderm at the anterior end of the embryo generates the ventral foregut, which will eventually give rise to the liver, lung, thyroid, and the ventral pancreas. The dorsal region of the definitive endoderm develops into the intestines and the dorsal pancreas (see Fig. 1A.2).

This complex dialogue between the endoderm and mesoderm appears to be critical for the final patterning of the gut tube, where several signaling pathways have been implicated in the regulation of foregut endoderm development, promoting specification along its anterior–posterior axis for organs such as the thyroid, lung, liver, and pancreas. The plasticity of the endoderm was demonstrated by experimentally recombining the posterior mesoderm with early foregut endoderm, leading to repression of liver and pancreatic development in favor of intestinal development (Wells & Melton, 2000; Kumar et al, 2003).

Specific signals from the surrounding mesoderm in the foregut region lead to hepatic specification and subsequent morphogenesis (Guadi et al, 1996). The molecular pathway linking endodermal patterning to the initiation of liver and pancreatic development has been partially elucidated by recent studies in the *Xenopus* model, supporting a role for *FGF4* and *WNT* signaling from the posterior mesoderm in inhibiting foregut fate and promoting hindgut formation; these signals are inhibited in the anterior endoderm to allow foregut development (McLin et al, 2007). β-Catenin repression in the anterior endoderm is specifically necessary to initiate liver and pancreas development; β-catenin repression in the endoderm then initiates reciprocal signaling with the mesoderm, leading to hepatic induction. To illustrate β-catenin's role in this process, forced β-catenin expression in the anterior endoderm led to downregulation of the hematopoietically expressed homeobox gene (*HHEX*) and inhibition of liver formation, whereas repressing β-catenin in the posterior endoderm—future hindgut that normally expresses β-catenin—induced ectopic *HHEX* expression and ectopic liver bud initiation (McLin et al, 2007). *HHEX* is a direct target of β-catenin and is one of the earliest foregut markers (Thomas et al, 1998) that is essential for ectopic and normal liver and ventral pancreas development in mice (Keng et al, 2000; Bort et al, 2004). In addition to repressing *HHEX,* β-catenin also downregulates

other foregut markers for liver (for1) (Seo et al, 2002), pancreas (*PDX1*), lung/thyroid (*NKX2-1*) (Goss et al, 2009), and intestine (Endocut) (Costa et al, 2003). Similarly, inhibiting β-catenin in the posterior mesoderm led to ectopic expression of other liver and pancreas markers (for1, *PDX1,* elastase, and amylase) along with inhibition of the intestinal marker Endocut (McLin et al, 2007).

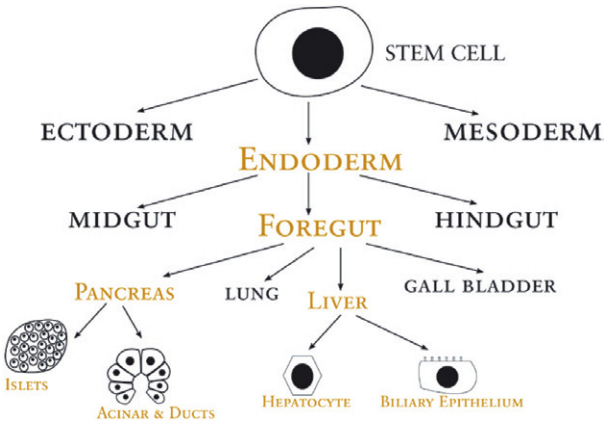


FIGURE 1A.1. Cell lineage schematic for hepatic and pancreatic development from a multipotent progenitor stem cell.

Studies in mouse and chick models demonstrated the need for an *FGF2* signal from the cardiogenic mesoderm and bone morphogenetic proteins (BMPs) from the septum transversum mesenchyme (Rossi et al, 2001; Zhang et al, 2004) for liver development. In addition, *WNT2B* has also been shown to be an important signal for liver specification in Zebrafish (Ober et al, 2006).

Other examples of transcription factors implicated in foregut patterning include the *HOX* genes. *HOXD13* is expressed in the hindgut of mouse and chick embryos (Yokouchi et al, 1995; Roberts et al, 1995; Dolle et al, 1991). Knockout mice homozygous and null mutant for *HOXD13* develop with hindgut defects (Kondo et al, 1996). Similarly, when *HOXD13* is misexpressed in chick embryo midgut mesoderm, hindgut features are seen in the midgut epithelium (Roberts et al, 1998). The exact mechanism of how the *HOX* genes induce endodermal patterning remains unknown, as the exact downstream targets are not clear. In addition to *HOX* genes, retinoic acid signaling has been implicated in this foregut patterning, probably through regulating *HOX* gene expression. Specifically, retinoic acid signaling appears to specify the position of the pancreatic domain in the foregut of *Xenopus*, Zebrafish, and mice (Huang et al, 1998; Chen et al, 2004; Martin et al, 2005; Stafford et al, 2004). Goss and colleagues (Goss et al, 2009) demonstrated that *WNT2* and *WNT2B* play an essential role in specifying lung endoderm without affecting the specification of other foregut-derived tissues. *WNT2/2B* double-knockout (DKO) mutants display complete lung agenesis. *NKX2-1,* the earliest known transcription factor marker for the developing lung,

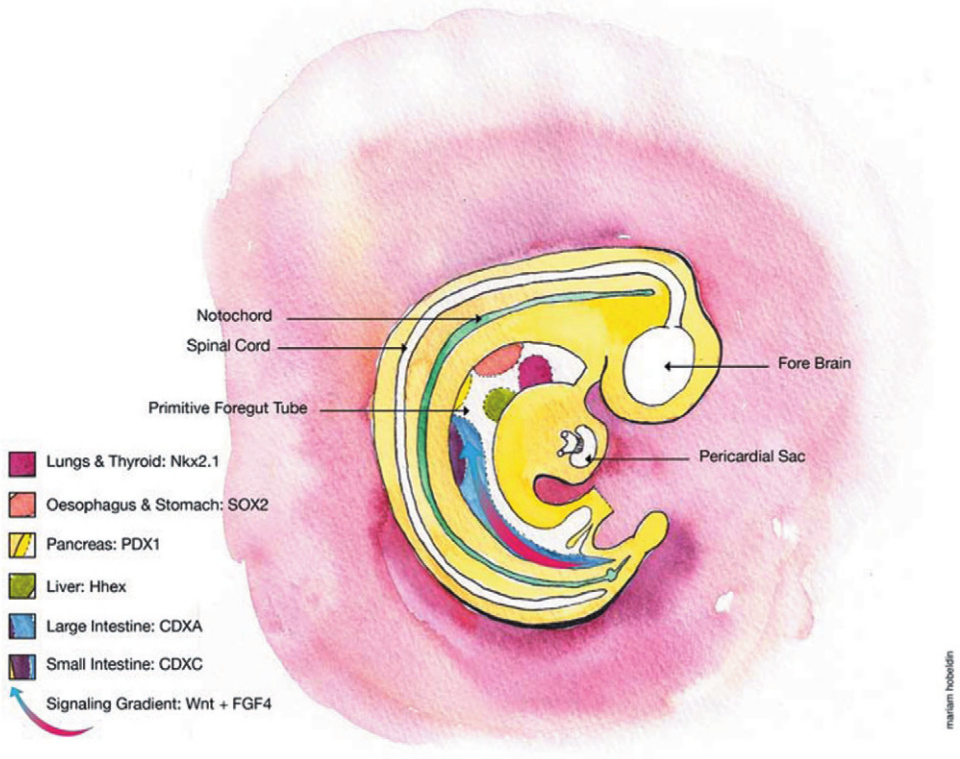


FIGURE 1A.2. Schematic representation of the regional specification of the primitive foregut tube (~E8.5) with the various transcription factors. Wnt and FGF4 (a fibroblast growth factor) are secreted from the posterior mesoderm in a gradient and repress foregut fate and promote hindgut development. Wnt and FGF4 inhibition in the anterior endoderm promote foregut fate. *(Image courtesy Mariam Hobeldin.)*

was also lost from the anterior foregut, confirming the loss of trachea and lung development.

Despite our growing knowledge of molecular signals that regulate endodermal patterning of the primitive foregut tube, most of the pathways remain poorly understood; exactly how these pathways confer regional identity remains unresolved. For example, the way in which the Wnt, Fgf, Bmp, and retinoic acid pathways functionally interact in the endoderm is not known.

Hepatic Competence

Hepatic competence, or the ability to form liver from the foregut endoderm, is considered the first step in a two-step process for the specification of the liver in vertebrates. Competence is a prerequisite for the endoderm to respond to specific signals, such as Fgfs from the surrounding mesoderm, which then leads to the second step, the induction of liver specific genes such as *ALB* (albumin). This "competence" is facilitated through the *FOXA* gene transcription factor family that includes *FOXA1* and *FOXA2* (forkhead box proteins A1 and A2). *FOXA* gene expression precedes the induction of the hepatic program by *FGF* signals in the endoderm, and *FOXA2* binding revises α-fetoprotein (*AFP*) gene transcription in vitro (Crowe et al, 1999). Deletion of *FOXA1* and *FOXA2* led to no liver bud formation with the loss of *AFP* expression in the ventral foregut, which would indicate that hepatic specification had failed to initiate (Lee et al, 2005). The forkhead box (*FOX*) proteins are an extensive family of transcription factors that share homology with the winged helix/forkhead DNA binding domains (Kaestner et al, 2000) that play important roles in regulating expression of genes involved in cellular differentiation, proliferation, transformation, and metabolic homeostasis (Wang et al, 2001; Zaret et al, 1999; Duncan, 2000). In vitro explant cultures demonstrated that Fgf was sufficient to induce ventral foregut endodermal cells to differentiate into hepatoblasts (Guadi et al, 1996). However, when *FOXA1*/*FOXA2*-deficient endoderm was cultured with exogenous Fgf2, no liver expression was seen (Lee et al, 2005). This result would indicate the need for *FOXA1* and *FOXA2* for the onset of hepatogenesis. In vivo DNA-binding studies revealed that the liver-specific albumin gene *ALB* has an important upstream regulatory binding site for *FOXA* factors (Guadi et al, 1996; Bossard & Zaret, 1998). Prior to *FOXA* or *GATA4* binding, the *ALB* gene is transcriptionally silent with a closed chromatin. After binding with *FOXA* and *GATA4,* the chromatin domain is thought to become exposed (Cirillo et al, 2002), thus increasing the ability of the gene to be activated. By the E9.5 gestation stage, other transcription factors—CCAAT/enhancer binding protein-β (*CEBPB)* and *NF1,* nuclear factor 1—bind to sites adjacent to the *FOXA* site, and as a result, the albumin gene becomes active (Zaret, 2002). The critical binding of *FOXA* to chromatin increases the ability of the gene expression to be activated by allowing other transcription factors to bind, hence the hepatic competence.

Hepatic Induction

Fgf from the cardiogenic mesoderm and Bmps from the septum transversum mesenchyme have been implicated in the induction of liver fate in mouse and chick embryonic endoderm. In vitro studies were performed in which the ventral foregut and cardiogenic mesoderm were cocultured in the presence of fibroblast growth factor inhibitors, resulting in the inhibition of liver induction (Jung et al, 1999). Culturing foregut endoderm without the cardiogenic mesoderm in the presence of a low concentration of exogenous FGF2 (2 to 5 ng/mL) rescued hepatic gene expression (Jung et al, 1999) and simultaneously suppressed the expression of the pancreas program (*PDX1* expression) (Deutsch et al, 2001), whereas a high concentration of FGF2 (10 to 500 ng/mL) induced *NKX2-1,* an early marker for respiratory epithelium but not albumin gene expression (Serls et al, 2005). Ventral foregut endoderm cocultured with noggin (Nog), a Bmp inhibitor, inhibited hepatic gene induction, an effect that was rescued when Bmp2 or Bmp4 were added. Despite these results, however, embryos that were homozygous mutant for *BMP4* still exhibited normal hepatic gene induction (Rossi et al, 2001; Smith & Harland, 1992). These data indicate that the cardiac mesoderm, a source for *FGF* signaling, is crucial for the hepatic induction from the ventral foregut endoderm and subsequent morphogenesis, whereas Bmp aids in the process as well (Fig. 1A.3).

Morphogenesis of the Hepatic Bud

Following hepatic specification (E8.5 to E9.0), the liver starts to express liver-specific genes (*ALB, AFP, HNF4A*) that eventually form the liver bud. Hepatic bud morphogenesis is facilitated by two transcription factors, *HHEX* (hematopoietically expressed homeobox, discussed above) (Crompton et al, 1992) and *PROX1* (prospero-related homeobox 1) (Oliver et al, 1993). *HHEX* is expressed in the anterior endoderm at E7.0, eventually giving rise to the ventral pancreas and liver. *HHEX*-null embryos grow without a liver, thyroid and develop forebrain defects at E11.5; however, evidence of endodermal epithelial thickening suggest a possible defect in differentiation as evidence of possible hepatic induction (Martinez-Barbera et al, 2000).

In a separate study on *HHEX*-null embryos, liver genes *ALB* and *PROX1* were expressed in the ventral foregut endoderm at around E8.5, with the thickening of the hepatic endoderm region at E9.0 being smaller compared with heterozygote embryos. In addition, a significantly lower proliferation rate was seen in the prospective hepatic domain compared with controls, as demonstrated by bromodeoxyuridine (BrdU) staining, with no evidence of apoptosis (Bort et al, 2004). The basal membrane layer, which is rich in laminin, surrounds the hepatic endoderm and degrades around E9.0 to E9.5, so that the hepatocytes start migrating into the septum transversum mesenchyme (STM) to form the liver bud. This degradation is facilitated by the hepatoblasts, which under normal conditions downregulate E-cadherin. However, in *PROX1*-null mutant embryos, the progenitor liver cells fail to migrate into the STM as a result of excess E-cadherin and basement membrane proteins laminin and collagen 4. The basal lamina fails to degrade, and the cells remain trapped in the hepatic diverticulum with an overall reduction in liver size (Sosa-Pineda et al, 2000). The bulk of the liver lobe lacks hepatocytes, suggesting that the mesenchymal component contributes most of the liver mass in *PROX1*-null mutant embryos. A similar phenotype is seen with *ONECUT1* and *ONECUT2* double mutants, which are required for basal lamina degradation (Margagliotti et al, 2007). Furthermore, pharmacologic inhibition of matrix metalloproteinases (MMPs), extracellular matrix remodeling enzymes usually expressed by hepatoblasts and STM cells,

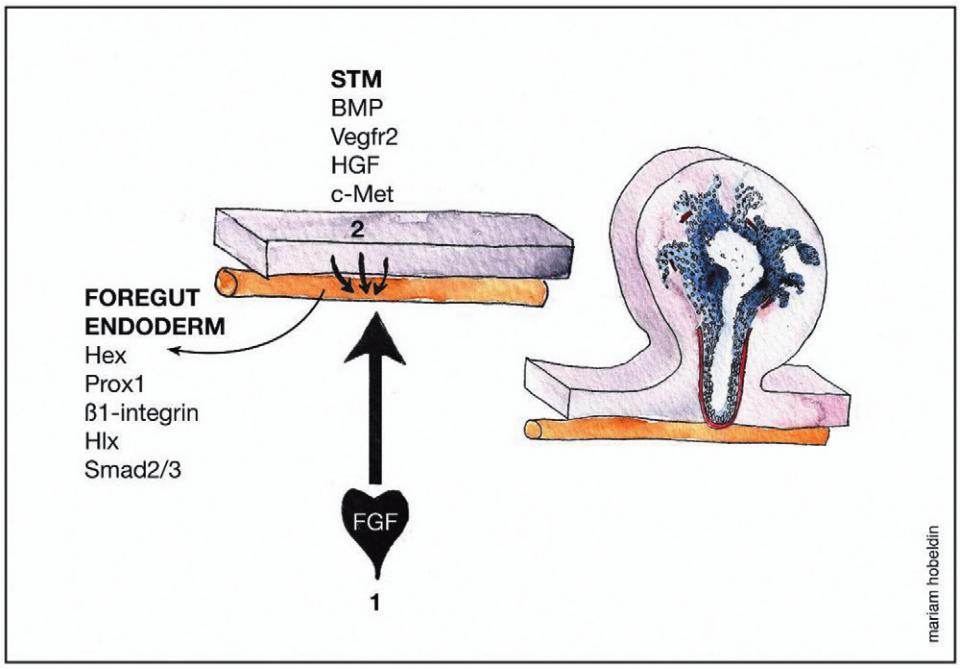


FIGURE 1A.3. Schematic for liver ontogeny controlled by factors released from the cardiogenic mesenchyme (*1*) and septum transversum mesenchyme (*STM, 2*), which induce hepatic specification. Signaling molecules (e.g., Vegfr2, HGF) and transcription factors (e.g., Prox1, Hlx) from STM and endothelial cells leads to delamination and migration of endodermal cells into the STM to subsequently form the liver bud. BMP, bone morphogenetic protein; HGF, hepatocyte growth factor; c-Met, HGF receptor; Vegfr2, vascular endothelial growth factor receptor 2. *(Image courtesy Mariam Hobeldin.)*

inhibits hepatoblast migration in culture (Margagliotti, 2008). To further illustrate the importance of the extracellular matrix in hepatic bud morphogenesis, hepatoblasts deficient in laminin receptor β1-integrin fail to colonize the liver bud (Fassler & Meyer, 1995). These β1-integrins are among those that act as receptors for extracellular matrix proteins, such as laminins and collagens (Hynes, 1992).

In summary, *PROX1* and *ONECUT* factors are important in regulating delamination and in controlling hepatoblast migration through regulating MMPs and hepatoblast interactions with the extracellular matrix. Without an appropriate extracellular matrix, cell migration into the STM will be disrupted.

The role of endothelial cells in liver organogenesis has also been studied, with the liver vasculature providing a vital source for hematopoiesis in early life. Endothelial cells are positioned as a loose chain of cells interceding between the thickening hepatic epithelium and the STM (Matsumoto et al, 2001). Embryos that were null mutant for *VEGFR2* (also known as *KDR*) had failure of delamination and subsequent migration by the hepatoblasts (Matsumoto et al, 2001). These results imply that the endothelial cells interact with nascent hepatic cells and aid in liver bud outgrowth.

Liver Bud Growth

The STM cells are closely related to the ventral endoderm and contribute to hepatic induction and growth. This epithelial–mesenchymal interaction is essential for the formation of the liver bud as well as for further expansion and differentiation. During this phase (E9.5 to E15), the liver bud undergoes a tremendous amount of growth and also becomes an important site for hematopoiesis. Factors and signals regulating this critical stage arise from both the hepatic mesenchyme and the STM. These signals include Fgf and Bmp, which promote liver growth in addition to their role in hepatic specification. Bmp4 is strongly expressed in the STM and continues to be expressed at E9.0, during which the liver bud migrates into the STM (Rossi et al, 2001). *BMP4*-null mutant embryos were developed to assess for a role in liver organogenesis. These null-mutant mice had a delay in the growth of the liver bud, which would indicate that Bmp constitutes an important growth signal for the liver (Rossi et al, 2001).

Another factor that has been implicated in liver growth is *HLX,* which is expressed prominently in the visceral mesenchyme (STM), into which the liver will expand (Hentsch et al, 1996). *HLX*-null embryos exhibited severe liver hypoplasia without affecting liver specification (Hentsch et al, 1996). A similar finding was observed in embryos that were null mutant for hepatocyte growth factor (Hgf) (Schmidt et al, 1995). In contrast to *HLX*–/– embryos, apoptosis was the underlying cause for the severe reduction in liver size. Hgf is produced by the cells lining the sinusoids, which are of mesenchymal origin, mediating its effects through the c-Met tyrosine kinase receptor produced by hepatocytes (Schmidt, 1995). TGF-β signaling is also involved in liver outgrowth. It mediates its signals through SMAD2 and SMAD3, which after phosphorylation translocate to the nucleus to either upregulate or downregulate gene expression. Embryos that were heterozygous mutants for both *SMAD2* and *SMAD3* exhibited severe liver hypoplasia as a result of a decrease in β1-integrin expression (Weinstein et al, 2001).

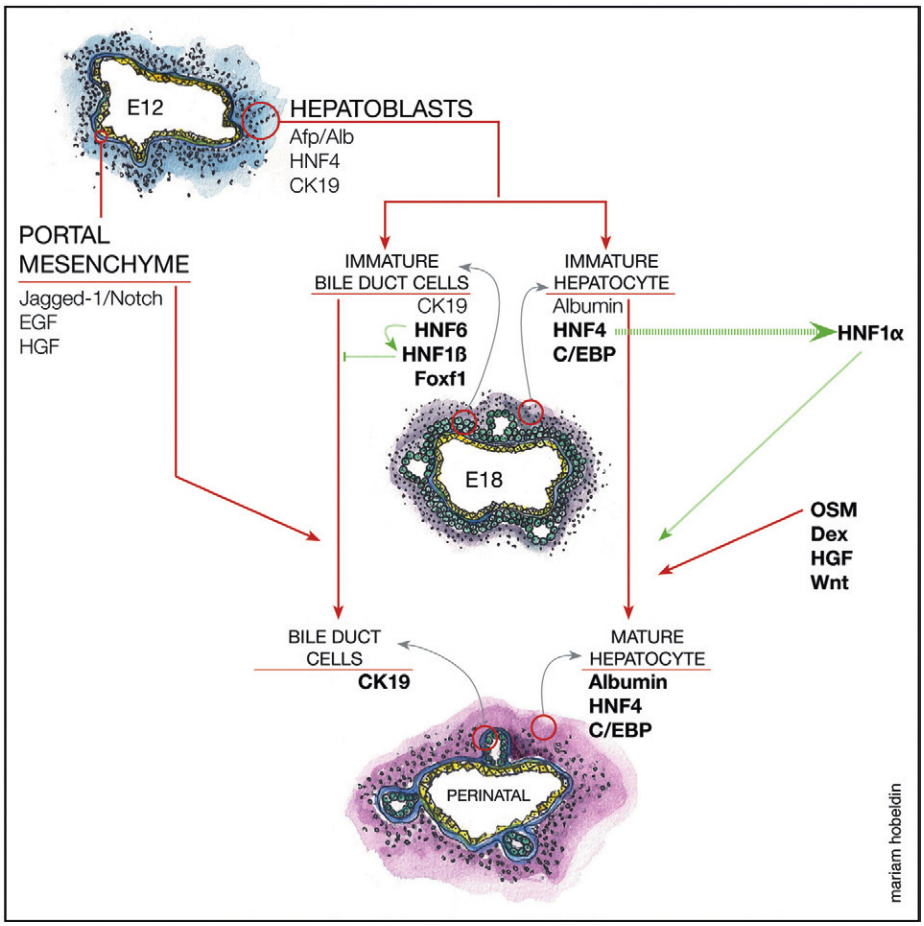


FIGURE 1A.4. Overview of differentiation of hepatoblasts into mature hepatocytes and bile duct cells. Bipotential hepatoblasts initially express markers for both hepatocytes (Alb, Afp) and biliary epithelial cells (KRT19). Hepatoblasts in the periportal mesechymal area upregulate KRT19 and downregulate hepatogenic transcription factors (HNF4, CEBP) to form mature biliary epithelial cells. Further signaling from the portal mesenchyme (Notch, HGF) aid duct remodeling. The rest of the hepatoblasts upregulate hepatogenic factors. Other factors (OSM, dexamethasone) help in maturation of mature hepatocytes. HGF, hepatocyte growth factor; EGF, epidermal growth factor; OSM, oncostatin M; Dex, dexamethasone; Alb, albumin; Afp, α-fetoprotein; HNF, hepatocyte nuclear factor. *(Image courtesy Mariam Hobeldin.)*

Intriguingly, this phenotype was rescued when HGF, a potent hepatotrophic growth factor, was added to the culture medium. Presumably, this was a result of the restoration of β1-integrin expression (Kagami et al, 1996), which plays an important role in hepatocytic adhesion to the extracellular matrix; TGF-β and HGF are known to induce the gene (Kagami et al, 1996; Kawakami-Kimura et al, 1997).

OVERVIEW OF HEPATOBLAST DIFFERENTIATION

Hepatoblasts begin to differentiate into mature hepatocytes and biliary epithelial cells at around E13.5. Prior to differentiation, the hepatoblasts express genes for adult hepatocytes (*ALB, HNF4A*), biliary epithelial cells (*KRT19*), and fetal liver (*AFP*) (Lemaigre, 2003; Shiojiri et al, 1991). Hepatoblasts in proximity to the portal vein form a bilayer and eventually differentiate into biliary epithelial cells, upregulating biliary-specific cytokeratin-19 (*KRT19*) and downregulating the other hepatic genes in the process. This bilayer around the portal vein begins to form focal dilations incorporated into the portal mesenchyme to form intrahepatic biliary ducts at E17.0 until birth. Those parts of the ductal bilayer plate not involved in the formation of the ducts progressively regress, and the rest of the hepatoblasts differentiate into mature hepatocytes, arranged in hepatic cords with the bile canaliculi on the apical surfaces (Lemaigre et al, 2003). The bile is produced by the hepatocytes and is secreted into the canaliculi, which are connected to the network of intrahepatic biliary ducts. The bile then flows to the hepatic ducts, transits through the cystic duct, and is stored in the gallbladder; eventually, the bile is excreted into the bowel via the common bile duct. The biliary epithelial cells delineate the lumen of the intrahepatic and extrahepatic biliary tree (hepatic, cystic, and common bile ducts) and the gallbladder (Fig. 1A.4).

Biliary Epithelial Cell Differentiation and Formation of the Ductal Plate

The exact origin of the biliary epithelial cells has been greatly debated; however, the popular school of thought is that they are derived from bipotential hepatoblasts that can differentiate into

either hepatocytes or biliary epithelial cells. This theory is based on the observation that immature hepatoblasts coexpress markers of both hepatocytes (*ALB*) and biliary epithelial cells (*KRT19*). The biliary-specific marker *KRT19* becomes strongly expressed at a later gestational age, as the cells become ductal cells, whereas other cells transiently express the hepatocyte markers *ALB* and *AFP* as they develop into mature hepatocytes (Shiojiri et al, 1991). This theory was further supported when embryonic liver was transplanted into the testes of syngeneic animals, before the emergence of intrahepatic biliary ducts, as it subsequently gave rise to both hepatocytes and typical bile ducts (Shiojiri et al, 1991). However, this finding does not exclude the possibility that ductal cells may be derived from other embryonic cell types. Suzuki and colleagues (Suzuki et al, 2002) used in vitro studies on hepatic "stem" cells from E13 embryonic livers identified as having self-renewing capability and multilineage differentiation potential, to show that these cells could form differentiated hepatocytes, biliary epithelial cells, pancreatic, and intestinal cells.

The first step in triggering the initiation of the transition from a hepatoblast to a biliary epithelial cell is thought to be facilitated through the *ONECUT* transcription factor hepatocyte nuclear factor 6 (*HNF6*), which is expressed in the biliary epithelial cells of the developing intrahepatic biliary ducts and in hepatoblasts, gallbladder primordium, and the extrahepatic bile ducts (Landry et al, 1997; Rausa et al, 1997). HNF6–/– embryos displayed severe biliary anomalies that resulted in an absent gallbladder and the extrahepatic bile duct network being replaced with an enlarged structure connecting the liver to the duodenum. In the intrahepatic biliary ducts, however, it caused abnormal differentiation of biliary epithelial cells, resulting in cholestasis. Closer histologic examination revealed an increased number of *KRT19*-positive cells compared with controls at E13.5, with the development of abnormal large cysts at E15.5 to E16.5 that contained an epithelium of *KRT19*-expressing cells. These abnormal cysts are similar to those seen in Caroli disease, a disorder with ductal plate malformation and ectasias. Although *HNF6* might play a role in the disease, not all of the malformations seen in *HNF6*–/– mice are manifested in Caroli disease, such as the absence of the gallbladder. The abnormal increase in *KRT19*-positive cells at E13.5 lacked any proliferative marker, suggesting that they are postmitotic, resulting from an increased number of hepatoblasts that have differentiated toward a biliary lineage prematurely (Clotman et al, 2002). In addition, the excess *KRT19*-positive biliary epithelial cells formed cordlike extensions within the liver parenchyma, rather than being restricted to the vicinity of the portal vein, as seen in the controls. This observation supports the role of *HNF6* in controlling the differentiation of hepatoblasts into biliary epithelial cells and the morphogenesis of the intrahepatic biliary ducts, confining biliary epithelial cells to the periportal area. A similar morphologic defect of intrahepatic biliary ducts was observed in *HNF1B*–/– embryos. These findings suggest that *HNF6* controls intrahepatic biliary duct development via *HNF1B* (Clotman et al, 2002).

With regard to mesenchymal–epithelial induction of liver primordium and gallbladder, studies have suggested that the mesenchyme contributes to biliary epithelial cell differentiation, where differentiation of hepatoblasts into biliary epithelial cells was stimulated when cocultured with hepatic or lung mesenchyme (Shiojiri & Koike, 1997). It was also noted in the *HNF6*–/– study that biliary epithelial cell differentiation occurred at the interface between the portal mesenchyme and the liver parenchyma (Clotman et al, 2002). A recent study revealed that the forkhead box f1 (*FOXF1*) transcription factor may play an important role in mesenchymal–epithelial signaling, an interface required for the development of organs derived from foregut endoderm, such as the pancreas, liver, gallbladder, and lung (Kalinichenko et al, 2002). *FOXF1* expression is restricted to the gallbladder mesenchyme and STM. In *FOXF1*+/–, the gallbladder develops severe structural abnormalities with significant reduction in size and reduced mesenchymal cell numbers, an absent biliary epithelial cell layer, and a deficient external smooth muscle layer. The reduction in mesenchymal cell numbers was attributed to the reduction in the vascular cell-adhesion molecule (*VCAM1*) and cell-adhesion α5 integrin (*ITGA5*) genes, both of which are essential for mesodermal formation (Mahlapuu et al, 2001; Yang et al, 1993). Defective smooth muscle layer formation was attributed to diminished levels of platelet-derived growth factor receptor α (*PDGFRA*), which is essential for smooth muscle cell differentiation (Jacob et al, 1994). *FOXF1* is not expressed in intrahepatic biliary duct mesenchyme in wild-type mice, and no defects were seen in the intrahepatic biliary ducts of *FOXF1*+/– mice; however, *FOXF1* mRNA levels in the liver were increased, suggesting that it may be a compensatory mechanism to prevent defects in the liver (Kalinichenko et al, 2002). All these data suggest that *FOXF1* is crucial for the development of the extrahepatic bile ducts and gallbladder, with the mesenchyme playing an essential role in biliary epithelial cell differentiation. The interaction between the biliary epithelial cells and the extracellular matrix is also thought to contribute to biliary epithelial cell differentiation.

Integrins are membrane receptors for extracellular matrix proteins that play an important role in mediating the interaction between differentiating cells and the extracellular matrix (Hynes, 1992; Couvelard et al, 1998). Hepatoblasts express integrin heterodimers containing the β1 subunit (α1β1, α5β1, α6β1, and α9β1), and when hepatoblasts differentiate into immature intrahepatic biliary epithelial cells when in contact with the mesenchyme, the morphology of the integrins changes. The primitive intrahepatic biliary epithelial cells upregulate α6β1 expression and lose α1β1, while acquiring several other integrin dimers not previously expressed on hepatoblasts, including α2β1, α3β1, α5β1 and α6β4 (Couvelard et al, 1998). This change is likely due to the different pericellular environment. Intrahepatic biliary epithelial cells are contacted by a basement membrane containing collagen, entactin, and laminin (Desmet, 1985); however, hepatocytes are surrounded by the perisinusoidal matrix, which is devoid of laminin and entactin (Schuppan, 1990). The increase in α6β1 expression—along with the acquisition of biliary-specific expression of α2β1, α3β1, and α6β4, which are integrin receptors for laminin—correlated with the deposition of laminin at the contact points of the portal mesenchyme with the ductal plate (Couvelard et al, 1998).

Remodeling of the Ductal Plate

As mentioned earlier, the double-layered ductal plate around the portal vein begins to form focal dilations incorporated into the portal mesenchyme to form intrahepatic biliary ducts, while the parts of the ductal bilayer plate not involved in the formation of the ducts progressively regresses. This mechanism

of regression is thought to be carried out by apoptosis (Terada & Nakanuma, 1995; Sergi et al, 2000). Cell-matrix interactions are also thought to contribute to the remodeling process. Tenascin was found to be expressed in the mesenchyme around the biliary epithelial cells of primitive ducts migrating into the mesenchyme. In contrast, tenascin was absent in the mesenchyme of peripheral ducts (Terada & Nakanuma, 1994).

Tubulogenesis of ductal cells is thought to be controlled by soluble factors secreted from hepatocytes or biliary epithelial cells. When coculturing human biliary epithelial cells with hepatocytes, a marked ductular morphogenic response was induced, and the biliary epithelial cells formed well-organized luminal ducts. This result was reproduced when biliary epithelial cells were grown in a conditioned medium from previous hepatocyte and biliary epithelial cell coculturing (Auth et al, 2001); however, it remains to be seen whether soluble factors do contribute to tubulogenesis in in vivo studies (Fig. 1A.5).

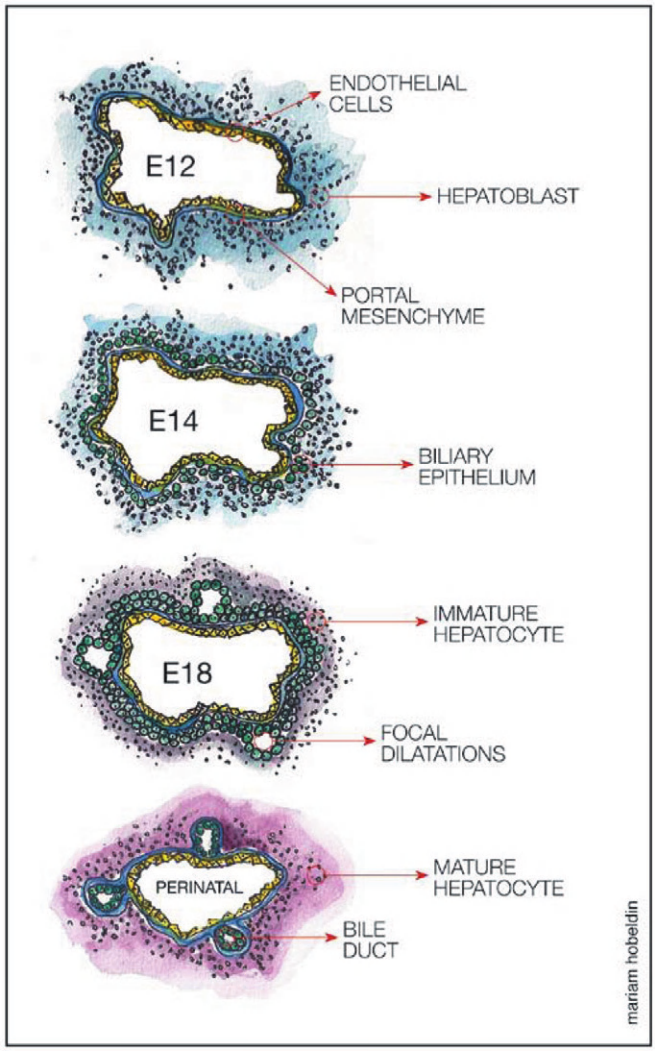


FIGURE 1A.5. Overview of intrahepatic bile duct formation around the portal vein. Hepatoblasts in the portal mesenchyme vicinity begin to acquire the biliary epithelial cell marker (KRT19) and downregulate hepatic genes, first forming a single layer at E14 then a bilayer at E18 with focal dilations that eventually form the intrahepatic bile ducts. The rest of the bilayer regresses. *(Image courtesy Mariam Hobeldin.)*

Developmental Relationship Between the Ducts, Vessels, and Mesenchyme of the Portal Tract

A functional relationship appears to exist between the contents of the portal tract (bile duct, hepatic artery, portal vein) based on observations of a number of human diseases termed *ductal plate malformations*. These diseases include biliary atresia, Caroli disease, and Meckel and Alagille syndromes, in which abnormal biliary ducts are associated with anomalies of the portal mesenchyme and of the portal blood vessels (Lemaigre, 2003). This association was also demonstrated in studies on Notch pathway defects. In Alagille syndrome, an autosomal dominant disease, bile ducts are absent in the portal tract associated with an increased number of arteries and fibrosis. Haploinsufficiency of JAG1, a Notch receptor ligand, is associated with Alagille syndrome, where JAG1 is persistently expressed in the ductal epithelium in humans (Li et al, 1997; Louis et al, 1999). It is also expressed in the endothelial cells of the developing portal vasculature (Crosnier et al, 2000). The animal model for Alagille syndrome was replicated in double-heterozygous mice for mutations in the *JAG1* and *NOTCH2* genes (J1N2+/–). JAG1 protein was expressed in the hepatic vasculature, and NOTCH2 was expressed in a subset of hepatoblasts surrounding the portal vein, hepatic artery, and bile ducts. Interestingly, although neither JAG1 nor NOTCH2 protein was expressed in the bile duct epithelium of these mice, JAG1 is expressed in bile duct epithelium in humans (Louis et al, 1999; McCright et al, 2002). The differences in JAG1 expression between human and mouse most likely reflects species specificity rather than technical artifacts, as mice that are heterozygous or homozygous for the *JAG1* gene did not show the liver symptoms of Alagille syndrome (Xue et al, 1999). Similar biliary abnormalities were observed in *NOTCH2*-null mutant mice (McCright et al, 2002).

Hepatocyte Differentiation

During later stages of development, hepatocytes undergo a transition period from a hematopoietic support role to a mature adult hepatocyte. This change occurs under the control of the transcription factor CEBPα and *HNF4*, the latter being a crucial factor in hepatocyte differentiation. Loss of *HNF4* function led to disruption of the expression of several genes associated with the mature hepatocyte phenotype. In *HNF4*–/– mice, hepatocytes failed to express many mature hepatic enzymes and lacked normal morphology, leading to low glycogen stores, disrupted sinusoids, and gap junction disruption. These results demonstrate that *HNF4* is essential for liver differentiation.

Other factors that have been shown to promote hepatocyte differentiation include oncostatin M (OSM), an interleukin-6 family cytokine, Hgf, and Wnt (Michalopoulos et al, 2003; Tan et al, 2008). Although as discussed earlier in the chapter, the repression of Wnt signaling in the foregut endoderm is necessary for hepatic specification, its role is reversed at later gestational stages to promoting hepatocyte differentiation. β-Catenin, a central component of the canonical Wnt pathway, is essential for normal development; its aberrant activation in liver was associated with tumors, including hepatic adenomas and hepatocellular cancers (Peifer & Polakis, 2000; de La Coste et al, 1998; Zucman-Rossi et al, 2006). Livers that were deficient in

β-catenin displayed decreased numbers of hepatocytes with hepatoblasts that lacked maturation, proliferation, and function (Tan et al, 2008). In addition, CEBPα, a fundamental regulator of hepatocyte differation and maturation (Tan et al, 2008), was decreased. Also noted in these livers was a complete absence of CK-19-positive intrahepatic biliary ducts, suggesting that β-catenin may play a role in biliary differentiation (Tan et al, 2008). In vitro studies showed that OSM, produced by hematopoietic cells in midfetal liver, and Hgf induce hepatic differentiation in the presence of dexamethasone, both working through different pathways (Kamiya et al, 2001). It was demonstrated that embryonic livers at E14.5 expressed G6Pase, tyrosine amino transferase (TAT), and accumulated glycogen, all signs of a mature and differentiated liver when cultured with Hgf or Osm. This finding was further supported when TAT levels, as well as glycogen storage, was significantly reduced in livers derived from mice null mutant for gp130, the common receptor subunit of the IL-6 family cytokines (Kamiya et al, 2001). CEBPα is also critical for the acquisition and maintenance of hepatocyte differention, with knockout mice exhibiting defects in liver growth and architecture as well as an increase in cell proliferation (Flodby et al, 1996). CEBPα is also thought to be a key factor in controlling the switch in the differentiation of bipotential hepatoblasts to become either biliary epithelial cells or hepatocytes. CEBPα starts to be expressed in the endodermal liver primordium at E9.5, and its expression in the nuclei of hepatoblasts and hepatocytes becomes stronger with development. During biliary cell differentiation, CEBPα expression was suppressed in periportal biliary cell progenitors, suggesting that its suppression may be a prerequisite to biliary cell differentiation from hepatoblasts (Shiojiri et al, 2004). Lineage tracing experiments have recently shown that Sox9+ biliary epithelial cells themselves differentiate into mature hepatocytes under normal physiologic conditions (Furuyama et al, 2011). Hepatocyte differentiation from the lineage tagged Sox9+ bile duct cells increased during the hepatic regenerative process, suggesting that the biliary and pancreatic ductal tree (Sox9-expressing domains) contains a previously unappreciated pool of progenitor cells.

OVERVIEW OF PANCREATIC DEVELOPMENT

The pancreas consists of two morphologically distinct tissues, *exocrine* and *endocrine,* which must derive from one simple epithelium. This feature has intrigued developmental biologists for years. The morphologic development of the pancreas is dictated by its two major functions: production of digestive enzymes by the exocrine acinar tissue and regulation of blood chemistry by the endocrine tissue. Some have even described the pancreas as two organs in one because of the disparate function and organization of these two tissues in the pancreas.

The endocrine pancreas is organized into islets of Langerhans, which consist of five cell subtypes—α, β, δ, ε, and PP cells—that secrete glucagon, insulin, somatostatin, ghrelin, and pancreatic polypeptide, respectively. All totaled these cells occupy only 2% of the adult pancreatic mass (Gittes, 2009). The exocrine pancreas, on the other hand, produces digestive enzymes, is composed of acinar and ductal epithelial cells, and accounts for nearly 98% of the adult pancreatic mass.

Basic Pancreatic Embryology

During early development, the pancreas is formed by the dorsal and ventral bud, each originating from the endodermal lining of the caudal part of the primitive foregut tube after regional specification with transcription factor Pdx1 followed by Ptf1a (Sadler & Langman, 2006; Grapin-Botton, 2005; Moore-Scott et al, 2007). The first morphologic evidence of pancreas development is in the form of mesenchymal condensation overlying the dorsal aspect of the primitive foregut tube at the level of the duodenal anlagen, distal to the stomach. Shortly after, at around E9.5 gestation in mice and day 26 of gestation in humans, the dorsal bud begins to evaginate into the overlying mesenchyme (Kallman & Grobstein, 1964; Picte et al, 1972). Approximately 12 hours later in mice, and 6 days after dorsal bud evagination in humans, the ventral bud begins to arise.

The morphologic development of the ventral pancreatic bud is similar to the dorsal bud; however, it is markedly different at the molecular level. After this initial bud evagination, the pancreatic bud then undergoes elongation of the stalk region, a precursor to the main pancreatic duct and branching morphogenesis of the apical region of the bud. Unlike growth patterns seen in the developing lung, kidney, and salivary glands, in which the branching morphogenesis undergoes a typical 90-degree pattern, the pancreas grows in an acute-angled branching pattern, which can lead to the exclusion, or "squeezing out," of mesenchyme from between the closely apposed branches of epithelium. This exclusion of mesenchyme may influence epithelial–mesenchymal interactions and lineage selection (Fig. 1A.6). The ventral pancreatic bud, which arises from the base of the hepatic diverticulum, rotates dorsally and eventually fuses with the dorsal pancreatic bud (6 to 7 weeks gestation in humans, E12 to E13 in mice), contributing to the formation of the uncinate process and inferior part of the head of the pancreas, with the rest of the pancreas arising from the dorsal pancreatic bud. The entire ventral pancreatic duct and the distal part of the dorsal pancreatic duct fuse together to form the main pancreatic duct of Wirsung. The remaining proximal part of the dorsal pancreatic duct is either obliterated or persists as a small accessory pancreatic duct, the duct of Santorini (Sadler & Langman, 2006).

During development the pancreas undergoes a major amplification of the endocrine cell population through two waves of differentiation: an early *primary transition* (pre-E13.5 in mice) followed by the *secondary transition* (E13.5 to E16.5 in mice) (Picte et al, 1972; Jensen, 2004). In a similar gestational window, the exocrine pancreatic precursors undergo rapid branching morphogenesis and acinar cell differentiation (see Fig. 1A.6).

Endodermal Patterning of the Pancreas

As mentioned earlier, the pancreas develops through epithelial–mesenchymal interactions. Prior to this, the dorsal foregut became competent to receive propancreatic signals from the notochord (FGFs) (Wells & Melton, 2000) and from the anterior foregut (retinoic acids and BMPs) (Stafford & Prince, 2002; Tiso et al, 2002). The prepancreatic region of the definitive foregut comes into contact with the notochord, whereas the ventral pancreas contacts the lateral plate mesoderm (Kumar et al, 2003).

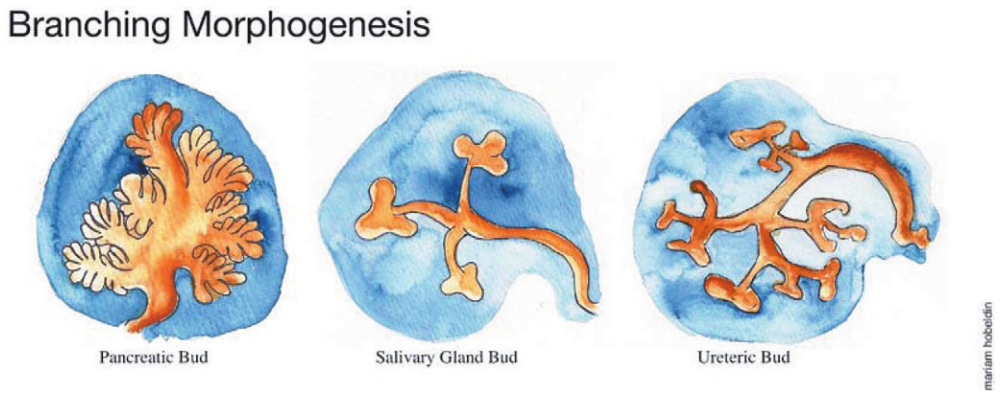


FIGURE 1A.6. Pancreatic branching morphogenesis is different than in other organ systems—such as lungs, kidneys, and salivary glands—which branch in a 90-degree pattern to be fully exposed to the mesenchyme. However, the pancreas has an acute branching pattern; thus some areas are excluded from mesenchymal contact. Mesenchyme contains factors that regulate pancreatic growth and differentiation. *(Image courtesy Mariam Hobeldin.)*

Dorsal and Ventral Pancreatic Bud Development

The notochord is key to the development of the dorsal pancreas, where it remains in contact with the dorsal prepancreatic endoderm until the paired dorsal aortae fuse in the midline (~E8.0). The dorsal pancreas failed to form when the notochord was removed from early chick embryos in vitro (Kim et al, 1997), but no effect was seen on ventral pancreas development, further emphasizing the different molecular controls for dorsal versus ventral pancreas development. The ventral pancreas develops under the control of signals from the overlying cardiogenic mesenchyme, which also produces prohepatic signals (FGFs) to induce liver formation. Lack of prohepatic FGF signaling in regions of the cardiogenic mesenchyme will lead to the endoderm by "default" differentiating into ventral pancreas (Deutsch et al, 2001). Sonic Hedgehog (*SHH*) in the prospective pancreatic endoderm is suppressed by the notochord, which is necessary for dorsal pancreatic development, and *SHH* is otherwise expressed along the entire primitive gut tube epithelium. When the notochord was deleted in chick embryo cultures, ectopic *SHH* was seen in the pancreatic region of the foregut endoderm, and the pancreas failed to develop (Hebrok et al, 1998).

Pancreatic Mesenchyme

The pancreatic epithelium becomes enveloped by mesenchyme, which contains important factors that are pivotal for pancreatic morphogenesis. The mesenchyme has a general proexocrine effect on the pancreas through cell contact and through proendocrine effect, mediated by diffusible factors secreted from the mesenchyme (Li et al, 2004). Mesenchymal contact with the epithelium both enhances notch signaling (*HES1*), which favors the acinar lineage and also inhibits neurogenin 3 expression (*NEUROG3*), leading to the suppression of endocrine differentiation (Duvillie et al, 2006). The "default" differentiation of the pancreatic epithelium in the absence of mesenchyme is endocrine (Gittes et al, 1996). Thus the mesenchyme has both an inductive effect on the exocrine tissue development and a repressive effect on the development of endocrine cells.

The interaction between the mesenchyme and the pancreatic epithelium is regulated by several factors, the most important of which appears to be the FGFs, which are expressed in several epithelial–mesenchymal interface regions of the pancreas and are particularly important in regulating branching morphogenesis (Hogan, 1999). FGFs 1, 7, and 10 mediate their effect through FGF receptor 2B (FGFR2B) to induce epithelial proliferation, favoring exocrine differentiation (Elghazi et al, 2002; Celli et al, 1998; Dichmann et al, 2003). Null mutation for *FGF10* or *FGFR2B* leads to blunting of branching pancreatic morphogenesis with a lack of proliferation of endocrine progenitor cells, indicating that FGF10 induces proliferation of epithelial cells and prevents endocrine differentation (Bhushan et al, 2001; Pulkkinen et al, 2003). These roles for FGFs are primarily for ongoing development of the buds, in contrast to the role of FGF from the cardiogenic mesenchyme, which inhibits ventral pancreatic bud formation in favor of liver development (Deutsch et al, 2001).

TGF-β Signaling

The TGF-β superfamily has been implicated in early pancreatic development. TGF-β isoforms (TGF-β1, -β2, and -β3) are localized to the pancreatic embryonic epithelium as early as E12.5 and progressively become focused to the acinar cells (Crisera et al, 1999). The ligands mediate their actions through TGF-β receptor type II (TBR-II), a heterodimer receptor; however, in late gestation it localizes to the pancreatic ducts (Tulachan et al, 2007). TBR-II inhibition has been shown to recruit an inappropriately high number of ductal cells to become endocrine progenitor cells, suggesting that TBR-II signaling is important for regulating the flow of endocrine progenitors out of ducts (Sanvito et al, 1995; Lee et al, 1995).

Activins, part of the TGF-β superfamily, also play a role in pancreatic development. When exogenous activin was added to embryonic pancreas explant cultures, it inhibited branching morphogenesis, a process associated with ductal and acinar differentiation (Ritvos et al, 1995). This observation was further supported when follistatin, an activin inhibitor expressed in the pancreatic mesenchyme by E12.5, was added to the pancreatic epithelium; it mirrored the mesenchymal effect, promoting exocrine and repressing endocrine development

(Miralles et al, 1998). These observations would support a role for activin in promoting and regulating endocrine differentiation and suppressing exocrine differentiation in the early pancreas. Along similar lines, transgenic mice that express a dominant-negative activin receptor display reduced levels of differentiated islet cells (Kim et al, 2000; Shiozaki et al, 1999; Yamaoka et al, 1998). In vitro in cell lines, activin A favors β-cell differentiation.

SMADs are intracellular signals for the *TGF* superfamily and have gained interest among developmental biologists, since *SMAD4* was specifically identified to be mutated in 50% of pancreatic cancers (Hahn et al, 1996). However, a key role for *SMAD4* has not yet been identified in pancreatic development (Simeone et al, 2006; Bardeesy et al, 2006). *SMAD7* on the other hand, which acts as a general *TGF* signaling inhibitor when expressed under the *PDX1* promoter, results in a dramatic decrease in β cells at birth—by around 90%—and replacement with glucagon cells (Smart et al, 2006).

Notch Signaling

A key step in pancreatic development is the lineage decision by pancreatic progenitor cells between the endocrine and exocrine lineage. Notch signaling has been identified as a master regulator of this fate decision switch (Apelqvist et al, 1999). However, the exact mechanism for Notch signaling in pancreatic lineage selection remains elusive, and ambiguity still surrounds the exact role of Notch signaling through pancreatic development. It appears that the downstream factors of Notch targets are variably expressed at certain times in development of the pancreas. The early pattern of downstream molecules is a key mediator of Notch signaling in determining endocrine versus exocrine differentiation of progenitor cells and in maintaining a stem cell state in some progenitor cells. Later in gestation, the downstream molecules for Notch signaling change to foster cell maturation and differentiation beyond this initial lineage decision between endocrine and exocrine differentiation.

Hedgehog Signaling

As mentioned earlier, Shh suppression in the prospective pancreatic endoderm is a prerequisite for pancreas formation, however, Hedgehog signaling in pancreatic development appears to be complex. *SHH*-null mutant mice do not exhibit an expanded pancreatic field; in contrast, Indian Hedgehog (*IHH*) null mutant mice that develop with a small pancreas indicate a propancreatic role for *IHH* (Hebrok et al, 2000). However, when combining *SHH*-null mutation with heterozygous mutation for *IHH,* an annular pancreas develops. Mice that are null mutant for the Hedgehog Patched receptor Ptc lack Pdx1 and glucagon expression at E9.5, supporting the need to suppress Shh for early pancreatic development (Hebrok et al, 2000). Similarly, transgenic overexpression of Shh or Ihh under the Pax4 promoter led to a significant decrease in endocrine and exocrine tissue mass (Smith et al, 2000).

WNT

As mentioned earlier in the chapter, β-catenin repression in the anterior endoderm is necessary to initiate liver and pancreas development. Consistent with this, *PDX1–WNT1* and *PDX1–WNT5A* transgenic mice developed pancreatic agenesis and severe hypoplasia, respectively, confirming that early Wnt signaling is detrimental for pancreatic development (Heller et al, 2002). Similar to Notch signaling, the role of Wnt signaling beyond endodermal patterning is complex and depends on the time and place of Wnt signaling. β-catenin, which is mostly expressed in the mesenchyme (Heller et al, 2002), when ablated from Pdx1-positive cells resulted in the loss of acinar tissue at birth, confirming earlier studies that exocrine tissue development is mesenchyme dependent (Murtaugh et al, 2005; Wells et al, 2007). Others found a role for Wnt signaling in promoting postnatal pancreatic growth (Heiser et al, 2006), illustrating the complex and multiple roles that Wnts play in pancreatic development.

Endothelial Cells

Recently, an important role for endothelial cells in pancreatic endocrine development has been demonstrated. As mentioned earlier, the notochord separates from the gut endoderm by the fusion of the dorsal aortas around E8.0. Lammert and colleagues (2001) demonstrated that the removal of the dorsal aorta from *Xenopus* embryos led to the absence of pancreatic endocrine development. In addition, aortic endothelial cells were able to induce pancreatic bud formation and subsequent insulin cell differentiation in the adjacent endoderm. Importantly, ectopic *VEGFA* in the intestine and stomach led to ectopic formation of islets in the stomach (Lammert et al, 2001). Interestingly, it appears that ventral pancreas development seems to be not dependent on the endothelium despite its close proximity to the vitelline veins (Yoshitomi & Zaret, 2004).

Glucagon

The first detectable endocrine cells during pancreatic development are the glucagon-containing cells at around E9 in the mouse, and recent studies have shown that glucagon signaling is necessary for early differentiation of insulin-expressing cells, which appear around E13.0 (Picte et al, 1972; Prasadan et al, 2002). Glucagon hormone is generated from proglucagon by the action of prohormone convertase 2 (PC2). When either PC2 or the glucagon receptor is knocked out, mutant mice are generated without glucagon, displaying a delay in islet cell differentiation and maturation but still retaining the large amplification of insulin-positive cells ("secondary wave") later in gestation (Vincent et al, 2003). Exogenous addition of exendin-4, a glucagon-like peptide-1 (GLP-1) analog, was able to rescue the delay in early insulin differentiation (Prasadan et al, 2002). Exendin-4 was also shown also to convert AR42J cells (Zhou et al, 1999; Yew et al, 2004) and ARIP cells (Hui et al, 2001) into insulin-expressing cells. Together these studies strongly support the role of glucagon signaling, through its receptor, in initiating early insulin differentiation.

Extracellular Matrix

The pancreatic epithelium is contained within a continuous sheath of basement membrane, which constitutes the epithelial-mesenchymal interface and plays an important role in guiding pancreatic development (Hisaoka et al, 1993). Basement membrane has also been shown to play an important role in regulating branching morphogenesis in many other organs. Laminin-1

was found to induce duct formation in isolated E11 mouse pancreatic epithelium (Gittes et al, 1996) and to mediate the proexocrine inductive effect of the mesenchyme and the pro–β-cell role later in gestation (Li et al, 2004; Jiang et al, 2001). Cadherins—**ca**lcium-dependent **adhe**sion molecules, critical for cell–cell adhesions—play an essential role in migration and differentiation of pancreatic endocrine progenitor cells. E-cadherin and R-cadherin are initially localized to the ducts, but they become downregulated as cells move out of the ducts to form islets (Dahl et al, 1996; Sjodin et al, 1995). N-CAM, another cell-adhesion molecule expressed in mature α and PP cells (Cirulli et al, 1994), when knocked out led to improper aggregation of endocrine cells within the islet (Esni et al, 1999). Thus, cell-adhesion molecules regulate the adhesive properties of endocrine cells, and these adhesive properties are essential for endocrine cell aggregation into islets.

Transcription Factors

The role of transcription factors has been extensively studied in pancreatic development. The most heavily studied is Pdx1, an early marker for pancreatic progenitors that later restricts to the β cells. It is expressed in the prepancreatic region of the primitive foregut tube at E8.5 then expands to be expressed in distal stomach, common bile duct, and duodenum by E10.5 to 11.5 (Offield et al 1996; Guz et al, 1995). Pdx1 is initially expressed throughout the epithelium; however, its expression becomes suppressed in cells as they commit to the endocrine (Jensen et al, 2000) lineage or ducts (Gu et al, 2002). Its expression reappears as cells differentiate to the insulin-positive β-cell lineage. *PDX1*-null mutant mice and humans developed pancreatic agenesis (Jonsson et al, 1994; Yee et al, 2001; Stoffers et al, 1997a; Stoffers et al, 1997b). Delayed Pdx1 inhibition using a tetracycline-regulatable transgenic knock-in system demonstrated severe blunting of pancreatic development with complete absence of acini and β cells (Holland et al, 2002), indicating that Pdx1 continues to play a role in pancreas development beyond regional specification during endodermal patterning.

PTF1α

Pancreas-specific transcription factor 1α (PTF1α) is an early marker of pancreatic progenitor cells, expressed slightly later than Pdx1 at around E9.5; by E18.5, it becomes progressively restricted to acinar cells (Cras-Meneur et al, 2009). *PTF1A*-null mutant mice develop a phenotype similar to that seen with *PDX1*-null mutants, with severe pancreatic hypoplasia and absent acini and ducts; however, endocrine cells still develop; interestingly, the endocrine cells migrate out through the pancreatic mesenchyme to populate the spleen (Kawaguchi et al, 2002; Krapp et al, 1998). A *PTF1A* nonfunctioning mutation has been seen in humans born without a pancreas (Sellick et al, 2004). Furthermore, *PTF1A* has complex interactions with downstream targets of Notch to control exocrine lineage selection.

NEUROG3

NEUROG3 is one of the earliest markers specific to the pancreatic endocrine lineage, and it is a key driver of endocrine differentiation. It is first expressed at E9.0, and it peaks at around E15.5; it is thought to be antagonized by Notch signaling in cells with an acinar fate (Jensen et al, 2000; Gradwohl et al, 2000). *NEUROG3* cells then proliferate, giving rise to postmitotic cells expressing transcription factors NeuroD, Nkx6.1, and Pax6. *NEUROG3* shuts off at around E17.5 (Jensen et al, 2000; Gu et al, 2002), and forced overexpression of *NEUROG3* leads to cells prematurely committing to an endocrine lineage, with the development of only glucagon-positive clusters (Johansson et al, 2007). Overexpressing *NEUROG3* at different times later in gestation (E11 to E12) resulted in the formation of insulin-positive and pancreatic polypeptide–positive cells (Johansson et al, 2007). However, when *NEUROG3* is deleted from cells, no pancreatic endocrine cells form (Gradwohl et al, 2000); thus it appears to be a critical and essential factor for pancreatic endocrine differentiation.

PAX6

PAX6 is also another marker of endocrine lineage, but unlike *NGN3,* it is not absolutely necessary for endocrine formation because mice null mutant for Pax6 still formed endocrine cells, albeit at a reduced rate (St-Onge et al, 1997). Pax6 expression is retained in cells committed to the endocrine lineage as early as E9.5 in glucagon-positive cells or in insulin-positive cells at E12.5, thereafter beginning hormone expression (St-Onge et al, 1997). Transgenic expression of *PAX6* under the *PDX1* promoter led to islet and ductal hyperplasia, indicating that *PAX6* may have roles in the formation of ducts and in islet growth (Yamaoka et al, 2000). However, when *PAX6* was ectopically expressed in β cells under the insulin promoter, it led to β-cell apoptosis, indicating that *PAX6* promotes proliferation only in pancreatic progenitors, not in mature cells.

PAX4/ARX

PAX4 is another endocrine cell marker and is expressed as early as E9.5; it then peaks at around E13-15, coinciding with the secondary transition of insulin-positive cells (Wang et al, 2004). Its importance was further delineated when β cells and δ cells failed to develop in *PAX4*-null mutant mice. Early embryonic insulin-positive cells were present in these mice, indicating that *PAX4* is only needed for the formation of mature β cells (Wang et al, 2004; Sosa-Pineda et al, 1997). In these mice, the β and δ cells seem to have been replaced by cells coexpressing glucagons and ghrelin, indicating that *PAX4* may act as a transcriptional inhibitor for this expression (Wang et al, 2008). *PAX4* seems also to inhibit the expression of *ARX,* a homeobox-containing gene that enhances glucagon-positive cell differentiation (Collombat et al, 2005). *ARX,* which is downstream of *NEUROG3* and is absent in *NEUROG3*-null mutant mice, when overexpressed in *PDX1*-positive progenitor cells diverted most β- and δ-cell precursors instead toward α- and PP-cell lineages, without a change in the overall number of endocrine cells. When *ARX* was knocked out, no α cells were seen (Collombat et al, 2003). These findings further emphasize the opposing roles for *PAX4* and *ARX* in α and PP cells versus β and δ cells (Collombat et al, 2007).

NKX2-2

NKX2-2 is expressed as early as E9.5, is coexpressed with *PDX1* as a marker of multipotent pancreatic progenitor cells, and eventually becomes restricted to *NGN3*-positive cells, persisting in all endocrine lineages except for δ cells (Sussel et al 1998; Chiang & Melton, 2003). *NKX2-2*–null mutant mice develop with no β cells, reduced PP cells, an 80% reduction in α cells, and no effect on δ cells. However, a large number of

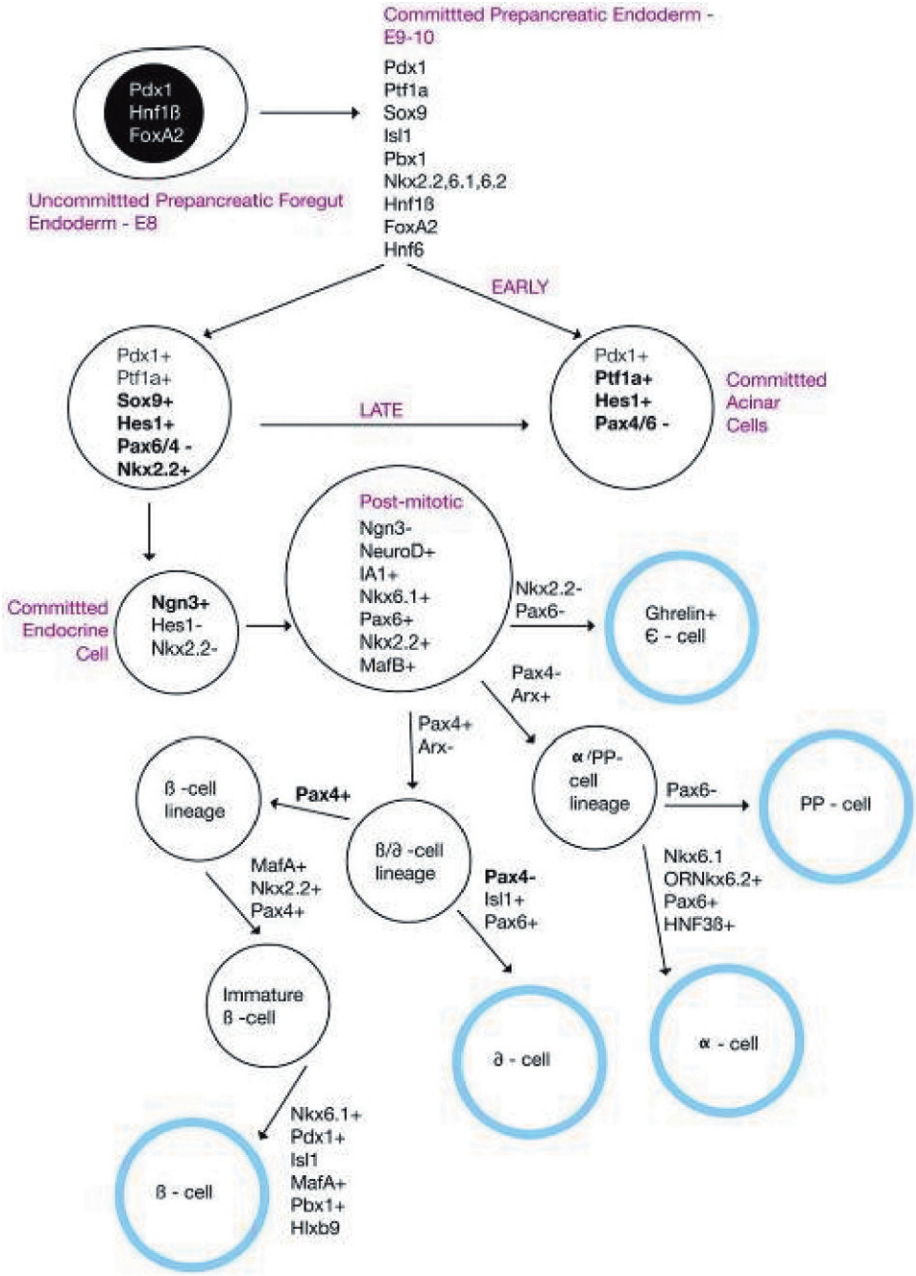


FIGURE 1A.7. Overview of the pancreatic endocrine and exocrine cell lineage.

ghrelin-positive ε cells were found with no glucagon coexpression, indicating that *NKX2-2* normally induces insulin-positive differentiation and represses ε cell formation (Sussel et al, 1998).

NKX6-1 and NKX6-2

Single- and double-null mutant studies for *NKX6-1* and *NKX6-2* have been done and suggest that both molecules, which are expressed early in pancreatic endodermal cells, play central roles in pancreatic development, especially in β-cell development (Henseleit et al, 2005). *NKX6-1,* which is downstream of *PDX1,* becomes restricted to insulin-positive cells; whereas *NKX6-2* is restricted to glucagon-positive and amylase-positive cells, after E15.5, it disappears (Sander et al, 2000). In *NKX6-1*–null mutant mice, an 85% reduction in β cells is seen, whereas *NKX6-1* and *NKX6-2* double-null mutants developed a 92% and 65% reduction in β cells and α cells, respectively, suggesting that *NKX6-1* has an important role in generating β cells. *NKX6-2* plays an important role in β-cell formation and can compensate for *NKX6-1* absence in β-cell formation (Henseleit et al, 2005; Sander et al, 2000). β-cell loss was rescued with transgenic expression of *NKX6-1* or *NKX6-2* under the *PDX1* promoter (Nelson et al, 2007).

MAFA and MAFB

The transcription factor MAFA is a critical regulator of the insulin gene, and it also regulates glucose-responsive expression of insulin (Matsuoka et al, 2003). *MAFA* is first expressed in insulin-positive cells during the "secondary transition" wave of

insulin-cell differentiation; however, it is not absolutely necessary for β-cell formation, because *MAFA*-null mutant mice have a normal proportion of insulin-positive cells at birth (Nishimura et al, 2009). *MAFB* is expressed early in pancreatic endocrine development and, as the pancreas develops, it switches off in insulin-positive forming cells as they form mature β cells that then express *MAFA* (Nishimura et al, 2006). It was demonstrated that early expression of *MAFA* under the *PDX1* promoter was detrimental to pancreatic development, with a severe reduction in pancreatic mass and in the proliferation of progenitors, suggesting that MAFA is a key regulator for the maturation of pancreatic β cells rather than β-cell specification (Nishimura et al, 2009). The same conclusion was drawn in *MAFB*-null mutants mice, in which a delay was seen in the development of early insulin- and glucagon-positive cells, with a reduction by almost half of their total mass (Artner et al, 2007).

HNF *Cascade*

Three *HNF* factors—*HNF6/ONECUT1, HNF1B,* and *HNF3B* (renamed *FOXA2*)—appear to have an interwoven, complex set of interactions that all impact on pancreatic development, starting from the earliest pancreatic specification all the way through to mature pancreatic cell differentiation and function. They are all expressed in the pancreatic epithelium at around E9.0 to E10.0 with *HNF6* appearing to be a key determinant of pancreatic specification (Maestro et al, 2003). This conclusion comes from observations that *HNF6*–/– embryos developed ventral pancreatic agenesis, with an atrophic dorsal pancreas, along with severe biliary anomalies as described earlier (Jacquemin et al, 2003; Haumaitre et al, 2005). *HNF6* is expressed in the foregut–midgut endoderm junction at E8.0 under the control of *HNF1B* (Poll et al, 2006). *HNF6* in turn regulates the expression of *FOXA2,* which is essential for gut formation (Weinstein et al, 1994). *FOXA2,* however, is not necessary for pancreas formation, because its deletion did not affect pancreatic development (Lee et al, 2005). As discussed earlier in the bile duct formation section, *HNF6* also acts upstream of *HNF1B,* where *HNF6* activates *HNF1B* to initiate the formation of endocrine progenitors (Clotman et al, 2002).

SOX9

SOX9 acts as a marker for pancreatic progenitor cells that can give rise to all pancreatic cell types, and it is necessary for maintaining cells in a progenitor state (Akiyama et al, 2005). *SOX9* mutants display pancreatic hypoplasia as a result of depletion of the pancreatic progenitor pool (Seymour et al, 2007). It has also been suggested that *SOX9* mediates *HNF6* and the control of *NEUROG3*-cell formation, because conditional deletion of *SOX9* led to the formation of cystic structures similar to those seen in *HNF6*–/– embryos, associated with absent pancreatic endocrine cells (Seymour et al, 2007). Furthermore, it was found that *SOX9* is transiently coexpressed with *NEUROG3* and frequently colocalizes with *HES1,* which acts as a precursor to *NEUROG3*-positive cells. It was suggested that *SOX9* helps mediate the transition of endocrine progenitors from the nonendocrine *HES1*-positive, *NEUROG3*-negative state to an *HES1*-negative, *NEUROG3*-positive endocrine-committed state (Seymour et al, 2007). Thus, *SOX9* acts as a key mediator of the commitment of *NEUROG3*-positive endocrine progenitors (Fig. 1A.7).

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CHAPTER 2

Assessment of hepatic function: implications for the surgical patient

Charles Cha

PREOPERATIVE CONSIDERATIONS

The proper preoperative evaluation of liver function is arguably one of the most important and challenging assessments to make prior to hepatic resection. It requires analysis and interpretation of a wide variety of factors, including the determination of baseline parenchymal disease (fibrosis, steatosis, cirrhosis), the appropriate extent of resection required, and the predicted volume of the remnant liver, culminating in the prediction of risk of postoperative hepatic failure. The multiple and diverse functions of the liver preclude easy evaluation; therefore it is not difficult to understand that no individual test, or even a panel of tests, completely and accurately assesses preoperative liver function prior to resection.

In recent years, surgeons have increasingly pushed the limits of hepatic resection for a number of diseases, given the improvements in long-term outcome that can be achieved; a particularly striking example is resection for metastatic colorectal cancer (see Chapters 81A and 90A). Additionally, laparoscopic and nonanatomic resections are being performed with increasing frequency, as excellent oncologic outcome is being reported for both primary and secondary hepatic neoplasms. These liver parenchymal–sparing procedures are often performed in the setting of cirrhosis or treatment with potentially hepatotoxic chemotherapy and therefore require a very precise assessment of both preoperative and predicted postoperative liver function.

An ideal assessment of liver reserve would allow surgeons to make real-time decisions, when unexpected lesions or other findings are encountered intraoperatively that require a greater extent of parenchymal sacrifice than anticipated. Preoperative assessment of the functional liver remnant following resection is clearly critical, as it may help select high-risk patients for alternative procedures, such as staged resection, nonanatomic resection, or the incorporation of ablative procedures. Furthermore, such assessment will help select patients for preoperative portal vein embolization (PVE) to induce hypertrophy of the remnant liver prior to resection.

Despite a long list of available functional studies, imaging techniques, and markers to assess preoperative liver function (Table 2.1), no single measure or combination of measures has been demonstrated to be more predictive of outcome following resection than clinical assessment by an experienced hepatic surgeon. With improvements in surgical technique, anesthesia support, and ICU care, surgical mortality following hepatic resection has fallen to less than 3% at many institutions. However, death or complications related to liver failure following resection remains a significant cause of overall morbidity and mortality, with 16% to 50% of all mortality the result of liver failure, even in the setting of metastatic colorectal cancer (Nagao et al, 1987; Nagasue et al, 1993; Doci et al, 1995; Nordlinger et al, 1996). The continued search for an ideal measure of liver function before and after resection promises to allow for better selection of patients as well as better selection of operative procedures. This chapter reviews the measures of liver reserve that are currently available, which can broadly be divided into four categories: 1) clinical scoring systems using standard assessment and laboratory values, 2) measurements of hepatic uptake and excretion, 3) measurements of hepatic metabolism and excretion, and 4) measurements of predicted postoperative liver volume.

CLINICAL SCORING SYSTEMS

The clinical assessment of hepatic function has evolved from the Child's system (Child et al, 1964) and its subsequent modification, the Child-Pugh score (Pugh et al, 1973) as shown in Table 2.2. This scoring system was originally developed to predict mortality in patients with portal hypertension after portocaval shunt operations, and it has evolved to become a useful predictor of liver-related mortality in patients with cirrhosis.

Using a combination of clinical assessments and standard laboratory values, the Child-Pugh score is a quick assessment that can be easily performed on a preoperative patient (see Chapter 70B). The laboratory values included in the scoring system include total bilirubin, serum albumin, and prothrombin time (PT)/international normalized ratio (INR) levels. Bilirubin alone is neither sensitive nor specific for intrinsic liver disease but serves as an indirect measure of the ability of the liver to take up and conjugate bilirubin and to eventually secrete it. Other causes of bilirubin elevations include biliary obstruction, primary biliary cirrhosis, sclerosing cholangitis, and hemolytic conditions. Serum albumin level is a measure of the liver's synthetic ability, as albumin is produced exclusively in the liver. Its half-life is approximately 20 days; therefore it is not sensitive in detecting acute hepatic decompensation. Additionally, protein-losing enteropathies, malnutrition, renal disease, and burns can lead to hypoalbuminemia. PT/INR is also an important measure of liver synthetic function, because the liver is the major site for synthesis of blood clotting factors. Clotting factors V, VII, and prothrombin are critical components of the intrinsic clotting cascade, which the PT directly measures. The half-life of factor VII is around 2 hours; therefore INR is a much more dynamic measure of liver synthetic function than serum albumin levels. Problems with vitamin K absorption and intravascular consumption of clotting factors can lead to elevations in PT/INR as well.

Table 2.1

Overview of Assessment of Hepatic Function

Assessment
Clearance/retention/metabolism tests
Indocyanine green (ICG)
Lidocaine/monoethylglycinexylidide (MEGX)
Galactose elimination capacity (GEC)
Aminopyrine breath test
Caffeine clearance
Antipyrine
Urea synthesis
Sulfobromophthalein clearance
Scintigraphy
Technetium-99m–galactosyl human serum albumin (^{99m}Tc-GSA)
Volumetry
Computed tomography (CT)
Magnetic resonance imaging (MRI)

Table 2.2

Child-Pugh Scoring System

Points	1	2	3
Ascites	None	Small or diuretic controlled	Tense
Encephalopathy	Absent	Mild	Significant
Albumin (g/L)	>3.5	2.8-3.5	<2.8
Bilirubin (mg/dL)	<2	2-3	>3
PT (sec > control) *or*	<4	4-6	>6
INR	<1.7	1.7-2.3	>2.3

INR, International normalized ratio; *PT,* prothrombin time
Class A: 5 to 6 points; class B: 7 to 9 points; class C: 10 to 15 points

Table 2.3

Summary Data from Studies Reporting ICG Clearance and Outcome Following Liver Resection

			TUMOR CHARACTERISTICS		
Study	**Year**	**ICG Measurement**	**HCC**	**CRC**	**Findings**
Sawada et al	2007	Serum 15 min	—	61	ICG >10% was not associated with increased morbidity after hepatic resection.
Lee et al	2007	Serum 15 min	117	—	Liver remnant volume combined with ICG retention correlated with liver dysfunction postoperatively ($P < .001$).
Shimada et al	2007	Serum 15 min	319	—	ICG retention compared with long-term survival after resection (no correlation). ICG retention >15% was associated with decreased survival after initial recurrence.
Sugimoto et al	2006	Pulse densitometry	51	—	Postoperative ICG clearance predicted liver failure after surgery.
Ohwada et al	2006	Pulse densitometry	75	—	Perioperative ICG clearance rate predicted postoperative liver failure (sensitivity, 88%; specificity, 82%).
Erdogan et al	2004	Serum 15 min	54	25	Good correlation between ^{99m}Tc-mebrofenin and ICG clearance; no correlation was made with postoperative liver dysfunction.
Okochi et al	2002	Pulse densitometry	22		ICG clearance constant demonstrated a significant decrease after hepatectomy and was able to predict postoperative morbidity.
Lau et al	1997	Serum 15 min	127		ICG clearance was the best discriminating test for evaluating postoperative mortality after liver resection (>14%).

ICG, Indocyanine green; *HCC,* Hepatocellular carcinoma; *CRC,* colorectal carcinoma liver metastases; *spectro,* spectrophotometry; *GEC,* galactose elimination capacity; *MEGX,* monoethylgycinexylidide formation.

Adapted from Garcia G, 2009: Predicting liver failure following major hepatectomy. Dig Liver Dis 41:798-806.

Two additional components of the Child-Pugh classification include a subjective assessment of ascites and encephalopathy. Patients are divided into three classes based on points given for each category. In patients with cirrhosis, the 1-year mortality related to liver failure is minimal (<5%) for Child-Pugh class A patients, compared with 20% and 55% for class B and C patients, respectively (Conn, 1981; Table 2.3).

When used for risk stratification prior to hepatic resection, class B and C patients clearly have a higher mortality rate and lower survival rate compared with class A patients (Franco et al, 1990; Nonami et al, 1997). Indeed, very few patients with Child-Pugh class B cirrhosis would be considered candidates for even limited hepatic resection, and none would tolerate a major hepatectomy; class C cirrhosis is an absolute contraindication for even the most minor intervention. The major limitation of the Child-Pugh system is that it is not considered applicable to noncirrhotic patients or to those with other conditions, such as steatosis (see Chapters 65 and 87). Furthermore, there is variability among class A patients in terms of their ability to tolerate a major hepatectomy, but a few good-risk class B patients may also be candidates. Therefore surgeons are faced with using their best judgment to determine "poor-risk" class A patients and exclude or alter plans for resection and to identify "good-risk" class B patients.

Within the class A category, an additional means of determining risk of postoperative hepatic decompensation is to

assess for subtle signs of portal hypertension prior to resection. In the absence of splenomegaly or varices on imaging, which are rarely present in such patients, the platelet count may be used as a surrogate marker of subclinical portal hypertension. In a cirrhotic patient with otherwise good hepatic function, thrombocytopenia is highly suggestive of significant hypersplenism and portal hypertension severe enough to contraindicate resection in most cases. A direct way to assess for this is measurement of portal venous wedge pressure (Bruix et al, 1996), which can effectively stratify class A patients into high- and low-risk groups; however, this test requires expertise that is not widely available and is not routinely used.

The model for end-stage liver disease (MELD) is a clinical scoring system currently used to predict survival of patients with end-stage liver disease awaiting liver transplantation (Kamath et al, 2001; Wiesner et al, 2001). The MELD score considers bilirubin, INR, and creatinine to assess kidney function. The MELD score is derived from a complex calculation as follows:

$$0.957 \times \mathrm{Log_e}(\text{creatinine mg/dL}) + 0.378 \times \mathrm{Log_e}(\text{bilirubin mg/dL}) + 1.120 \times \mathrm{Log_e}(\text{INR}) + 0.6431$$

In cirrhotic patients, the MELD score predicts the development of postoperative liver failure following hepatectomy for hepatocellular carcinoma (HCC), with a cutoff score greater than 11 predictive of worse outcome (Freeman et al, 2002; Teh et al, 2005; Cucchetti et al, 2006; see Chapters 70B, 90A and 90F, 97A).

Both the MELD and Child-Pugh scores are meant to assess cirrhotic patients in particular and are considered unreliable in noncirrhotic patients (see Chapters 65 and 87). Furthermore, the subjective assessment of ascites and encephalopathy requires considerable input from the hepatic surgeon with regard to the suitability for resection. It is likely that it is this input that allows the experienced surgeon to impart clinical judgment to selected patients for resection, and it is why the Child-Pugh score alone has been demonstrated to be equivalent to most of the functional dynamic liver reserve studies published (Albers et al, 1989).

DYNAMIC LIVER TESTS

Measurement of Hepatic Uptake and Elimination

Indocyanine green (ICG) is an anionic organic dye that is protein bound and selectively taken up by hepatocytes and excreted unchanged via the bile. Plasma extraction of ICG by the liver is an active process that can be saturated with high doses of ICG (Faybik et al, 2006). Therefore maximal removal of ICG can be measured, and it reflects the uptake and excretional capabilities of the liver, which can be extrapolated to reflect hepatocyte blood flow and functional hepatocyte mass (Caesar et al, 1961).

Assessment of ICG clearance typically involves measuring serum levels at several points following intravenous administration (see Table 2.3). Clearance at 15 minutes is the most commonly used measurement; ICG retention values above 10% to 15% at 15 minutes are considered abnormal and are used as a cutoff to identify patients at high risk for liver failure following liver resection (Lam et al, 1999; Fig. 2.1). Poon and colleagues

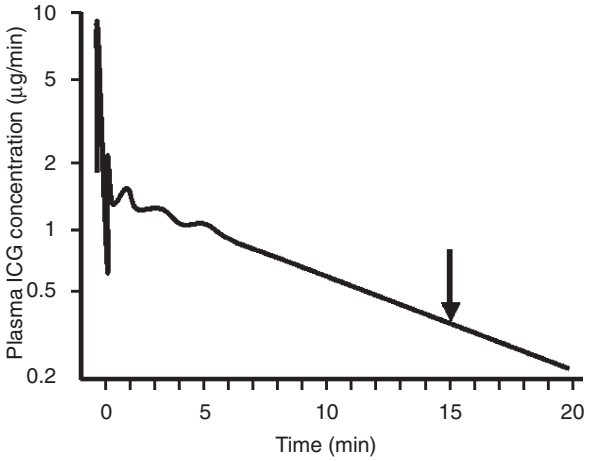


FIGURE 2.1. A typical Indocyanine green (ICG) clearance curve, which can be obtained by serial plasma sampling or optical pulse spectrophotometry. The arrow marks the ICG 15-minute retention value used most frequently to judge the adequacy of liver function.

have recently recommended a safe limit as high as 20% in Child-Pugh class A patients (Poon et al, 2004). Pulse infrared spectroscopy can also be used detect real-time, continuous blood levels, similar to pulse oximetry, without the need to obtain serum measurements (Okochi et al, 2002).

ICG elimination is by far the most widely used and published functional assessment of liver reserve worldwide (Yumoto et al, 1994; Kwon et al, 1997; Fujioka et al, 1999; Tanaka et al, 1999; Wakabayashi et al, 2002; Kokudo et al, 2003; Satoh et al, 2003; Bennink et al, 2004). Imamura and colleagues (2003) reported a 0% mortality rate in a series of 1056 hepatic resections for HCC and cirrhosis using an ICG-15 cutoff of less than 10% for a safe extended resection, 10% to 20% for hemihepatectomy, 20% to 30% for segmentectomy, and only enucleation for an ICG-15 greater than 40%. Noguchi and colleagues (1990) used the ICG maximal removal rate of 0.8 μg/kg cm^3 as a cutoff for safe resection, and Ohwada and collagues (2006) found real-time monitoring of ICG beneficial in evaluating hepatic reserve before, during, and after hepatic resection. ICG clearance has also been useful in predicting short-term prognosis in liver transplant patients (Clements et al, 1988; Lamesch et al, 1990; Oellerich et al, 1991; Yamanaka et al, 1992; Jalan et al, 1994; Tsubono et al, 1996; Igea et al, 1999; Plevris et al, 1999; Jochum et al, 2006). Tsubono and colleagues (1996) noted that a day 1 ICG elimination constant was a better predictor of graft outcome than any other conventional liver function test, and Clements and colleagues (1988) found ICG clearance to be impaired with graft rejection, but it improved as rejection resolved.

Unfortunately, the findings for ICG have not been consistent, with many authors finding a lack of correlation between ICG levels and successful liver resection (Wakabayashi et al, 1997; Lam et al, 1999). This has been particularly true in the setting of PVE, and this variability is thought to be the result of the dependence of ICG clearance on total hepatic blood flow, with regional variations markedly altering retention values (Cherrick et al, 1960). This has led a number of surgeons to suggest that no quantitative liver function tests provide a clear advantage beyond Child-Pugh score for predicting outcome following resection (Albers et al, 1989; Bennett et al, 2005).

In a recent study of 111 patients, Child-Pugh score better predicted postoperative morbidity secondary to transient liver failure compared with ICG clearance tests, and this lack of superiority of ICG clearance compared with Child-Pugh score has been confirmed by others (Albers et al, 1989; Merkel et al, 1989; Kokudo et al, 2002). Bennett and Blumgart noted significant overlap in ICG parameters between patients with cirrhosis and healthy controls, and in their institutional experience of 1800 liver resections, there were only six deaths without the reliance on any dynamic functional tests (Jarnagin et al, 2002; Bennett et al, 2005).

Hepatobiliary Scintigraphy and Single-Photon Emission Computed Tomography

Radionuclide scintigraphy of the liver can provide information far beyond basic liver anatomy, allowing for assessment of functioning hepatocyte mass as well as hepatic hemodynamics. Uptake of liver-specific radionuclides can be used to quantify overall hepatic function, and calculations of the relative contributions to perfusion by the portal vein and hepatic artery can be used to estimate the presence of liver metastases and cirrhosis. Beyond the classic sulfur and gold colloid scans and liver uptake and excretion imaging of aminodiacetic acid derivatives (HIDA, DISIDA), more recent synthetic, radiolabeled asialoglycoproteins have been developed that are taken up by hepatocyte-specific receptors through an active transport process (Kudo et al, 1990). Reduction in receptor numbers is seen in patients with chronic liver disease; because receptors are absent from the surface of hepatocellular carcinoma cells, scintigraphy can be used to provide a functional assessment of the liver through its ability to take up and clear these compounds. One such asialoglycoprotein is technetium-99m-galactosyl human serum albumin (^{99m}Tc-GSA). Patients undergoing a Tc-GSA scan receive a bolus injection of 185 MBq of ^{99m}Tc-GSA, and a dynamic scintigraph is obtained with gamma cameras located over the heart and liver. Typical curves are shown in Figure 2.2 (Ha-Kawa et al, 1997).

Kwon and colleagues (1995) were among the first to use ^{99m}Tc-GSA to evaluate preoperative and postoperative hepatic reserve, finding that GSA uptake was similar to ICG-15 clearance in terms of its ability to predict liver function. Fujioka and colleagues (1999) assessed ^{99m}Tc-GSA uptake at 15 minutes and found it to correlate with postoperative complications, hepatic regeneration, and ICG-15 clearance.

Single-photon emission computed tomography (SPECT) has also been used to assess liver function prior to surgery. Hwang and colleagues (1999) used ^{99m}Tc-GSA with SPECT in 114 patients, 55 of which underwent hepatectomy. A good correlation was found between SPECT results and ICG clearance and between predicted versus actual ^{99m}Tc-GSA clearance postoperatively. Five patients with postoperative complications as a result of hepatic insufficiency had significantly lower ^{99m}Tc-GSA clearance than those without complications. Satoh and colleagues (2003) developed a predictive residual index and found that a cutoff of greater than 0.38 predicted postoperative hepatic failure (see Chapter 15).

Scintigraphic imaging of the liver has the added advantage of providing an assessment of liver volume, and some authors suggest the volumetric analysis is better than that obtained with CT volumetry, because it measures only the functional volume; stromal and fibrous tissues are excluded because of the lack of the asialoglycoprotein receptors (Kwon et al, 2006). Scintigraphy may be a more accurate assessment of the regenerating liver than CT volumetry, given the lag time in cross-sectional imaging changes that are not seen with ^{99m}Tc-GSA clearance (Kwon et al, 2001; Kokudo et al, 2002). Age-related differences seen in ^{99m}Tc-GSA scintigraphic clearance in patients with similar CT liver volumes also seem to suggest a more accurate functional assessment of the liver (Wakabayashi et al, 2002), and ^{99m}Tc-GSA scintigraphy has also been used to assess liver volume following PVE (Hirai et al, 2003; Nanashima et al, 2006). Hirai and colleagues looked at liver volume and function using CT and ^{99m}Tc-GSA and found a rapid increase in uptake during the first week following PVE, but little thereafter. These changes were more pronounced on scintigraphy when compared with changes seen on CT alone, and patients with hepatic insufficiency postoperatively had poorer ^{99m}Tc-GSA uptake. Nanashima and colleagues (2006) had similar findings, demonstrating that ^{99m}Tc-GSA scintigraphy was better than CT alone for demonstrating functional liver volume following PVE.

In addition, ^{99m}Tc-GSA scintigraphy has also been investigated for use in the assessment of graft parenchymal function following liver transplantation (Kita et al, 1998; Sakahara et al, 1999; Hori et al, 2006). Most recently, Hori and colleagues (2006) found good correlation between ^{99m}Tc-GSA and ICG clearance following liver transplantation; however, the advantages of ICG over scintigraphy was that ICG clearance is

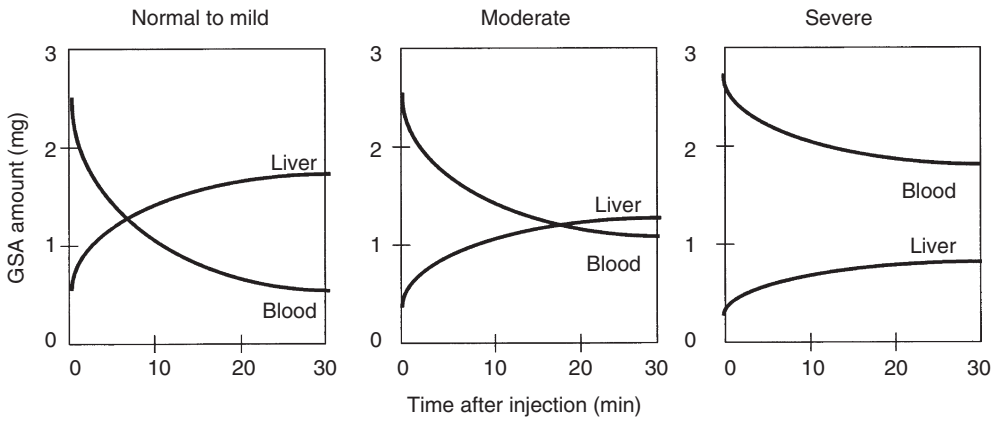


FIGURE 2.2. Tc-GSA curves for normal to mildly impaired, moderately impaired, and severely impaired liver function.

portable, quick, and can be easily repeated without the need for a radioactive tracer. Other disadvantages of ^{99m}Tc-GSA scintigraphy is its complex tracer kinetics in terms of uptake and distribution. Finally, ^{99m}Tc-GSA is currently only available for clinical use in Japan; it is not available in the United States or in Europe.

Measurements of Hepatic Metabolism and Elimination

Lidocaine Metabolism

Unlike ICG, lidocaine is metabolized by hepatocytes and converted to monoethylglycinexylide (MEGX) by oxidative N-dealkylation using the cytochrome P-450 system and is the basis of the MEGX test of liver function (Bargetzi et al, 1989). Thus, both MEGX and galactose elimination capacity (GEC) require uptake and metabolism by the liver to quantify hepatic function, unlike IGC clearance, which relies on uptake alone. Serum MEGX levels are measured at regular intervals after infusion of 2% lidocaine hydrochloride at 1mg/kg over 1 to 2 minutes. Typical values at 15 minutes after infusion are between 60 and 96 ng/mL. Oellerich and colleagues (2001) noted that in patients with chronic liver disease awaiting transplantation, only those with a MEGX value less than 10 ng/mL died; Lee and colleagues (2005) used a cutoff level of 30 ng/mL as a predictor of prolonged hospital stay following hepatic resection.

Recently, preoperative MEGX levels at 30 minutes after administration of lidocaine also predicted postoperative liver failure and mortality in noncirrhotic patients following liver resection (Lorf et al, 2008). Ravaioli and colleagues (2003) found that MEGX levels below 25 ng/mL were associated with a higher level of liver dysfunction and postoperative complications in cirrhotic patients following hepatectomy.

The main drawback of the MEGX test is the wide variability in test results among individuals, as evidenced by the lack of a standard cutoff level for what is considered safe for resection. Furthermore, because it requires liver metabolism via the cytochrome P-450 pathway, medications may interfere with the results.

Galactose Elimination Capacity

The galactose elimination capacity (GEC) is another dynamic liver function test that assesses hepatic metabolism in addition to uptake and elimination. Galactose is not protein bound and has up to 95% hepatic extraction. In this test, 50% galactose (0.5 g/kg) is administered intravenously, and its elimination is measured via serum at 20 to 50 minutes after injection. Urine and breath samples have also been utilized to assess GEC. A normal level is greater than 6 mg/kg/min. A comparison of GEC, MEGX, and ICG tests by Zoedler and colleagues (1995) revealed that GEC and ICG were best at predicting postoperative liver failure following hepatic resection. Redaelli and colleagues (2002) demonstrated that GEC was predictive of postoperative complications and liver failure in 258 patients undergoing hepatectomy, using a cutoff of less than 6 mg/kg/min to predict poorer outcome. GEC has also been demonstrated to correlate to severity of cirrhosis and predict complications in these patients (Merkel et al, 1992), but a paucity of data exists regarding GEC in liver transplantation. Nadalin and colleagues (2004) combined GEC with MRI volumetry in live-donor transplantation and found that GEC decreased 25% by day 30 and then increased to 125% by day 180.

The main disadvantage of the GEC test is the variable renal excretion that can occur, requiring close monitoring. Furthermore, genetic variation in galactokinase activity may occur among individuals, leading to inaccurate assessments. Finally, a large number of serial samples must be acquired to obtain an accurate measurement, making the test cumbersome to perform.

Measurement of Predicted Postoperative Liver Volume

Volumetric Assessment of the Liver

Cross-sectional imaging can be used to provide quantitative information regarding tumor size, overall liver volume, and an estimate of liver volume following a planned resection. Hepatic functional reserve is based both on the presence of underlying liver dysfunction and on the quantity of liver cells; radiologic quantification of liver volume represents an assessment of liver cell mass only, and as an isolated measurement, it provides no information regarding function.

COMPUTED TOMOGRAPHY

CT volumetry is the most common means of predicting the volume of functional liver remnant following a proposed resection. It typically involves the ratio of resected volume to total liver volume (see Chapter 16). More sophisticated analyses include a three-dimensional reconstruction of images, often combined with CT angiography, to allow for better visualization of a tumor in relation to vascular and biliary structures, which can alter surgical plans related to resection margin and devascularized areas of the liver that would need to be incorporated into the resection (Yamanaka et al, 2007). Such images can help to better predict surgical resection planes and can allow for "virtual" simulations of the resections.

Shoup and colleagues (2003) found that in noncirrhotic patients who had less than 25% liver volume following resection, 90% of patients developed hepatic insufficiency, compared with 0% of patients who had more than 25% residual volume, using a volumetric analysis of CT scans. Schindl and colleagues (2005) confirmed these findings, reporting a cutoff of 26.6% residual volume, below which a high risk of hepatic dysfunction was found. Shirabe and colleagues (1999) reported that hepatic failure after resection in patients with cirrhosis was associated with a postoperative liver volume of less than 250 mL/m^2. Other authors have combined volumetric analysis with ICG-15 scores and Child-Pugh scores to guide indications for resection (Kubota et al, 1997; Yigitler et al, 2003; Hsieh et al, 2006). The benefits of volumetric analysis is seen in the setting of preoperative PVE, which is typically used before extended resections that push patients to the limit in terms of size of residual liver remnant; PVE will be discussed in detail in Chapters 65 and 93A and 93B. However, a number of investigators have noted that a remnant liver volume of 25% or less is associated with increased risk of postoperative hepatic failure and that PVE can provide an additional 10% to 15% parenchymal mass that can make resection safer (Vauthey et al, 2000; Hemming et al, 2003).

Magnetic resonance imaging (MRI) has also been used to evaluate patients before and after resection to predict outcome. Nadalin and colleagues (2004) combined MRI with GEC clearance and found that patients had a 61% volume loss following right hepatectomy in the setting of a live donor transplant, and that these patients recovered function within 10 days, yet this

only represented 74% of initial liver size. GEC tests performed suggested that actual recovery of hepatic function was much slower than volume recovery.

The main drawback of volumetric imaging is that there is no information with regard to hepatocyte parenchymal function, other than response to PVE, because the calculated volume of liver mass does not necessarily correlate to liver function. This is exacerbated in situations of liver parenchymal dysfunction, such as toxic injury following chemotherapy, fibrosis, or cirrhosis, or simply older patient age (Wakabayashi et al, 2002). In patients with cirrhosis, the predicted remnant-liver cutoff for safe resection has been established by a number of investigators to be 40% in patients without cirrhosis, rather than 25%; the use of PVE in patients with cirrhosis also appears to be helpful (Azoulay et al, 2000; Hemming et al, 2003).

Ultimately, a combination of imaging volume assessment and grading of parenchymal function would represent the ideal test; however, results have been mixed (Table 2.4). Unfortunately, many of these multiassessment trials merely compared one test with another, rather than analyzing efficacy of the combination. The few trials that did specifically look at a combined approach found only moderate improvement over individual assessments in predicting outcomes after hepatectomy (Tu et al, 2007). It is apparent from these studies that, in patients analyzed by both volumetric and functional analyses, volume recovery precedes functional recovery after hepatectomy.

Other Measures of Liver Function

A number of other measures of liver function with varying degrees of success have been reported in the literature. Serum levels of hyaluronate, hepatocyte growth factor, prealbumin, retinol-binding protein, and lectin-cholesterol acyltransferase have all been described as simple markers of liver function (Mizuguchi et al, 2004; Katsuramaki et al, 2006). Many of these markers are used as nutritional indicators and as such are affected by overall nutritional status. However, following trends or following postoperative levels may be useful in determining how the liver reacts to resection. Sinusoidal endothelial cells take up hyaluronan and degrade it by a receptor-mediated mechanism with a short half-life of 2 to 5 minutes (Yachida et al, 2000). Thus serum levels of hyaluronate are a function of hepatic clearance, rather than mesenchymal cell production, and they have been shown to predict liver function in patients with cirrhosis. Serum hyaluronate levels can also predict hepatic regeneration following resection (Ogata et al, 1999; Mehta et al, 2008).

Elastography, the assessment of liver fibrosis using an intraoperative tactile sensor, has been proposed as a measure of liver function; however, this requires direct contact with the liver surface (Kusaka et al, 2000). Ultrasound-guided transabdominal elastography has been investigated as well to determine fibrosis or cirrhosis noninvasively, although minimal data are available in the prehepatectomy setting (Berzigotti et al, 2010; Laurent et al, 2008). Other methods of assessing functional liver reserve with varying degrees of success include preoperative measurement of portal vein pressures (Bruix et al, 1996), Doppler ultrasound measurement of hepatic flow (Annet et al, 2003; Lim et al, 2005), and bromosulfophthalein clearance (Yamanaka et al, 2001). The aminopyrine breath test (Merkel et al, 1992), antipyrine clearance (Sotaniemi et al, 1986), and caffeine clearance (Shrestha et al, 1997) are utilized infrequently, as they have largely been replaced by the less cumbersome and more predictive ICG clearance (Fan et al, 1995; Lau et al, 1997a; 1997b).

CONCLUSION

As surgeons have pushed the limits of extensive resections for metastatic and primary tumors of the liver and biliary tree, adequate assessment of liver reserve prior to resection, as well as the prediction of adequate functioning liver parenchyma following a major liver resection, has assumed great importance. Furthermore, with the increased utilization of laparoscopic approaches and a trend toward more limited anatomic resections, assessment of hepatic function must also be a dynamic and flexible one. Several major surgical organizations have established guidelines and consensus statements regarding indications and contraindications for surgical resection of liver tumors (Vauthey et al, 2006), and the main limitation of resection is no longer the size or number of tumors but rather the ability to leave adequate functioning liver behind, while preserving vascular and biliary support. This typically means leaving behind at least 20% of a normal liver or 40% of a diseased liver.

Recent liver-related mortality following hepatectomy in noncirrhotic patients has been reported to be as low as 2.8% in

Table 2.4

Summary Data from Studies Investigating Volumetric Analysis in Combination with Other Hepatic Functional or Scintographic Tests in Patients Undergoing Hepatic Resection

Study	Year	Assessment Method	n	Findings
Dinant et al	2007	^{99m}Tc-GSA, CT volumetry	46	^{99m}Tc-GSA was an independent predictor of postoperative liver failure.
Kwon et al	2006	^{99m}Tc-GSA using SPECT, CT volumetry	178	Postoperative liver failure was predicted by ^{99m}Tc-GSA.
Bennink et al	2004	^{99m}Tc mebrofenin, ICG, and CT volumetry	15	Remnant volume on scintigraphy correlated well to CT volume postoperatively, but not as well to regeneration.
Kwon et al	2006	^{99m}Tc-GSA, ICG, and CT volumetry	47	Correlation was seen among scintigraphy, ICG retention, and CT volumetry preoperatively; ^{99m}Tc-GSA recovery lagged behind CT-assessed regeneration postoperatively.
Kokudo et al	2002	^{99m}Tc-GSA, ICG, and CT volumetry	111	Scintigraphy in remnant liver predicted morbidity following resection.

^{99m}Tc-GSA, Technetium-99m-diethylenetriamine-pentaacetic acid-galactosyl-human serum albumin; *CT,* computed tomography; *SPECT,* single-photon emission computed tomography; *ICG,* Indocyanine green.

1059 resections (Mullen et al, 2007), calling into question whether any routine preoperative functional liver assessment is necessary in patients without cirrhosis beyond standard clinical assessment, including preoperative labs and contrast-enhanced cross-sectional imaging. For patients with cirrhosis, some additional assessment of preoperative liver function would likely be useful in subcategorizing good-risk from poor-risk Child-Pugh class A patients and to identify a population of Child's class B patients who would potentially do well following resection. The Child-Pugh score can be supplemented by the addition of volumetric measurements, ICG retention, MEGX clearance, and perhaps Tc-GSA scintigraphy. However, no test has been demonstrated to reliably augment or improve upon the Child-Pugh score alone, in the hands of an experienced surgeon, in the selection of patients for hepatic surgery. The ideal preoperative liver assessment would include a combination of functional and volumetric analyses with clear anatomic imaging; until such a test is available, clinical assessment by an experienced hepatic surgeon using the Child-Pugh score remains the gold standard.

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CHAPTER 3

Pancreatic physiology and functional assessment

Michael Steer

THE PANCREAS

The pancreas is a complex organ. In addition to nerves, blood vessels, and connective tissue, it is composed of endocrine and exocrine elements. The *endocrine pancreas* consists of 10^5 to 10^6 islets of Langerhans, each of which contains approximately a thousand endocrine cells. Together the islets constitute approximately 2% of the normal human pancreas. The *exocrine pancreas* includes the *acinar cells,* which account for 75% to 90% of the pancreatic mass, and the *duct cells,* which account for approximately 5%. Most of the currently available evidence indicates that all endocrine and exocrine pancreatic cells are derived from a common stem or progenitor cell (Fishman & Melton, 2002; Zaret & Grompe, 2008). Commitment to become either a duct cell or an acinar cell is believed to occur relatively early during embryogenesis. Subsequently, the endocrine cells undergo terminal differentiation into islet and acinar cells, but some also still may be capable of differentiating into duct cells (Gu et al, 2003). Conversely, some duct cells may be capable of differentiating into endocrine cells.

The endocrine and exocrine elements of the pancreas are under tight and complex neurohormonal control, and derangements of endocrine and exocrine pancreatic function are commonly noted in association with various pancreatic diseases. This chapter reviews some of the basic features that characterize normal pancreatic endocrine and exocrine physiology, and it describes the various approaches that can be used clinically to evaluate pancreatic function in patients suspected of having common pancreatic diseases, such as chronic pancreatitis. The literature regarding each of these issues is extensive, and a comprehensive review of these subjects is beyond the scope of this chapter; however, this chapter will provide a selective review that focuses on general concepts and clinically relevant issues.

ENDOCRINE PANCREAS

Structure and Innervation

The islets of Langerhans are composed of four different cell types evenly distributed throughout the pancreas. Approximately 15% of islet cells are *α cells,* which secrete glucagon; 70% to 80% are *β cells,* which secrete insulin; 5% to 10% are *δ cells,* which secrete somatostatin; and 15% to 25% are pancreatic polypeptide (*PP*) *cells,* which secrete pancreatic polypeptide (Kulkarni, 2004). The PP cell type is only sparsely present in the dorsal pancreas, neck, body, and tail; most PP cells are found in the portion of the pancreas derived from the ventral pancreatic bud (the head and uncinate process). Rodent islets consist of a core composed of β cells surrounded by the other cell types, but in humans, the various cell types are intermixed within each islet. These islets contain a rich capillary network, and they receive substantial blood flow.

The islets of Langerhans are innervated by parasympathetic and sympathetic nerves. Vagal stimulation increases insulin release, and vagal stimulation may play a key role in mediating the cephalic phase of insulin secretion; that is, insulin release in response to the sweet taste of glucose. Although a cephalic phase of insulin secretion has been shown to occur in rats and dogs, it is not certain that a cephalic phase occurs in humans. Stimulation and inhibition of insulin release have been associated with sympathetic nervous stimulation in experimental animals, but the role of sympathetic nerves in regulating insulin release in humans has not been established (Nauck, 1998).

Synthesis and Storage of Insulin

Insulin is assembled within the endoplasmic reticulum as preproinsulin (Madsbad et al, 1992; Malaisse, 1992; Steiner & James, 1992). With cleavage of a signal sequence, the intermediate product proinsulin is formed, packaged within Golgi-derived vesicles that evolve into immature storage granules and eventually become mature secretory granules. During this process of granule maturation, proteolytic processing of insulin continues, liberating mature insulin from its C-peptide. Mature insulin, its C-peptide fragment, and other processing intermediates are stored together within the secretory granules, until they are all discharged at the cell surface. Normally, that secretion occurs primarily in response to external stimuli (regulated secretion). In insulinomas, insulin and its processing intermediates often are released continuously, however, without the need for external stimuli (constitutive secretion; see Chapter 61).

Stimulus–Secretion Coupling for Insulin Secretion

Glucose, certain amino acids (e.g., arginine), acetylcholine, and incretins such as gastric inhibitory peptide (GIP) and glucagon-like peptide (GLP-1) are the most important regulators of insulin release by β cells (Nauck, 1998). To varying degrees, the intracellular mechanisms responsible for insulin release in response to each of these types of regulators are different (Fig. 3.1). The "first phase" of insulin release seems to involve mechanisms that differ from the mechanisms in the later phase of sustained insulin secretion. This review focuses on

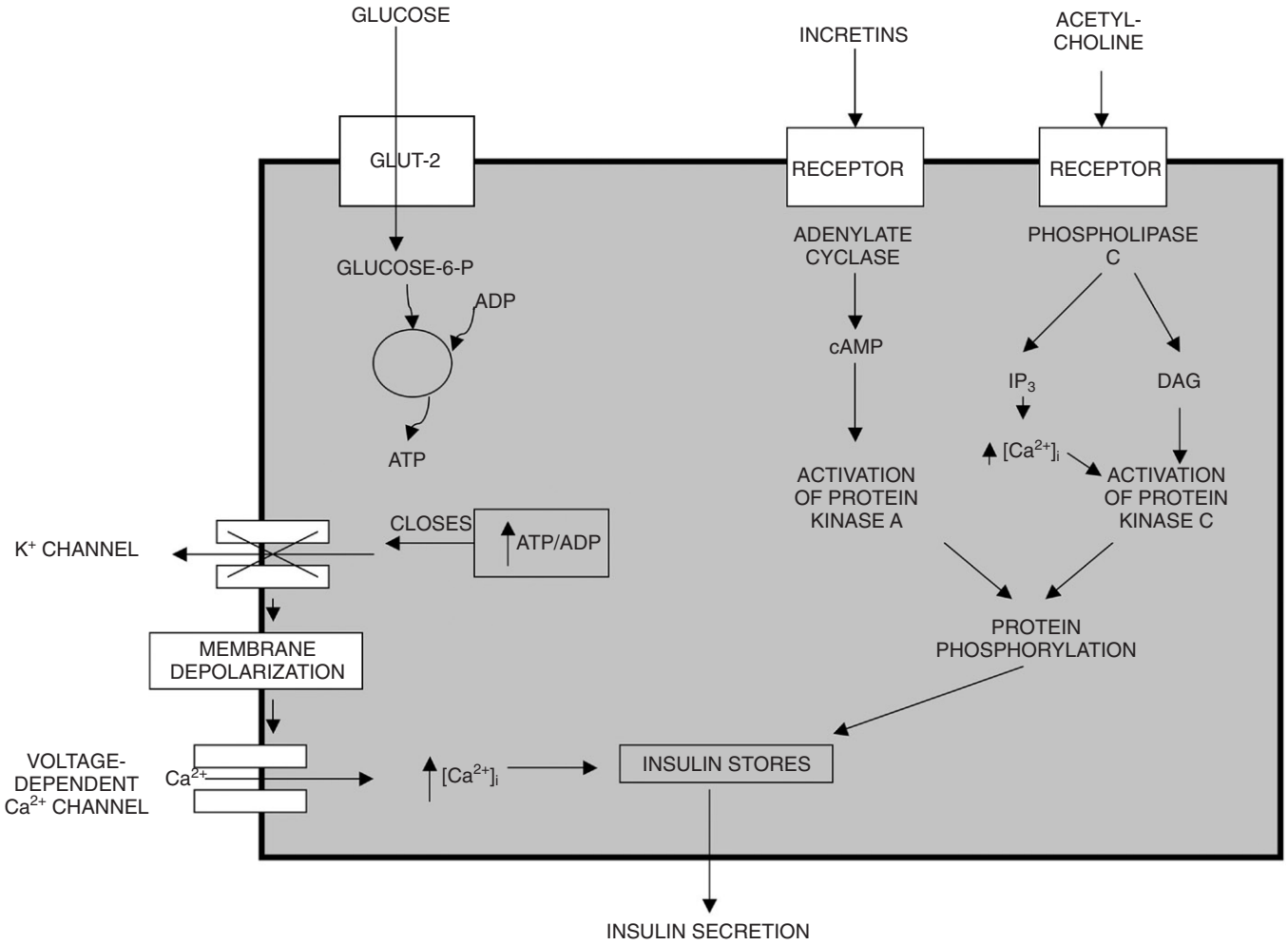


FIGURE 3.1. Stimulus–secretion coupling for insulin secretion. The major stimulants of insulin secretion are glucose, acetylcholine, and the incretins. Glucose enters the cell via the GLUT-2 transporter, and it is phosphorylated to glucose-6-phosphate by hexokinase. Metabolism of glucose-6-phosphate yields ATP (adenosinetriphosphate), and the increased ATP–ADP (adenosinediphosphate) ratio closes a membrane K^+ channel. This depolarizes the membrane, opening voltage-dependent calcium channels and causing calcium levels in the cell to increase. The increase in cytoplasmic calcium triggers exocytosis of secretory vesicles containing insulin. Acetylcholine, released from vagal efferents, binds to surface membrane receptors coupled to phospholipase C. Activation of phospholipase C yields IP_3, which triggers release of intracellular calcium and DAG, which activates protein kinase C. The incretins (GIP and GLP-1) bind to receptors coupled to activation of adenylate cyclase. Elevated cAMP levels lead to activation of protein kinase A. Activation of protein kinase C and protein kinase A leads to protein phosphorylation and secretion of insulin. *cAMP,* cyclic adenosine monophospate; *DAG,* diacylglycerol; *GIP,* gastric inhibitory peptide; *GLP,* glucagon-like peptide; *IP_3,* inositol triphosphate.

events believed to underlie that first phase of insulin secretion (Rutter, 2001).

Glucose, the most important regulator of insulin release, enters β cells via a highly efficient glucose transporter, GLUT-2, which for the most part equalizes intracellular and extracellular glucose concentrations (Unger, 1991). Subsequent to its uptake by the cell, glucose is phosphorylated by glucokinase (Meglasson & Matschinsky, 1986), which, because of its high michaelis-menten constant (K_m), acts as a glucose sensor. Glucokinase catalyzes the formation of glucose-6-phosphate, and as a result, glucose-6-phosphate accumulates within the cell at concentrations closely related to the intracellular concentration of glucose. Glucose-6-phosphate is metabolized, leading to formation of adenosine triphosphate (ATP); this results in an increased ATP–ADP (adenosine diphosphate) ratio, which causes closure of an ATP-dependent potassium channel in the plasma membrane of β cells (Henquin, 1988). Closure of this channel results in membrane depolarization, which leads to activation of voltage-dependent L-type calcium channels and calcium influx into the cell (Misler et al, 1992). The resulting increase in cytoplasmic calcium levels triggers exocytosis of the secretory granules that contain insulin (Eliasson et al, 2008). In contrast to the initial phase of insulin secretion, it is believed that the later phase of sustained secretion does not involve closure of ATP-dependent potassium channels (Rutter, 2001).

Amino acids such as arginine also upregulate insulin secretion by being metabolized and causing ATP levels to increase, increasing the ATP–ADP ratio and triggering calcium influx. The incretins, including GIP and GLP-1, are believed to upregulate insulin secretion by activating adenylate cyclase, increasing cyclic adenosine monophosphate (cAMP) levels, activating protein kinase A, and causing phosphorylation and activation of exocytosis-related proteins; cAMP also may promote insulin secretion by mechanisms that involve activation of L-type

calcium channels and accelerated calcium influx. Insulin secretion also can be stimulated by acetylcholine released from cholinergic nerves. Acetylcholine binds to receptors on the cell surface, causing activation of phospholipase C and generation of the secondary messengers, inositol triphosphate (IP_3), and diacylglycerol (DAG). IP_3 triggers release of calcium (Ca^{2+}) from intracellular storage pools, which causes release of insulin. DAG binds to and activates protein kinase C, which, like protein kinase A, promotes insulin secretion by phosphorylating and activating exocytosis-related proteins (Persaud et al, 1989; Prentki & Matschinsky, 1987).

Incretins and the Regulation of Insulin Secretion

Insulin secretion in response to orally administered glucose and other nutrients is 25% to 50% greater than that after intravenous administration (Creutzfeldt, 1979; Tillil et al, 1988). This so-called incretin effect is mediated by hormones released from the gut, primarily GIP and GLP-1 (Fiesler et al, 1995; Nauck et al, 1993). GIP is produced by K cells in the duodenum and upper jejunum, and it is released into the circulation after ingestion of nutrients. GLP-1 is synthesized in enteroglucagon or L cells, which also contain peptide YY (PYY) and enteroglucagon. These L cells are primarily located in the distal small bowel, colon, and rectum. Of the two hormones GIP and GLP-1, GIP is probably the major physiologic incretin. Glucose and amino acids are considered to be "primary" or "direct" stimulants of insulin secretion, but insulin secretion is also modulated by the incretins. These incretins cause little or no insulin release in the absence of glucose or amino acids, but they can alter insulin release dramatically in response to either glucose or amino acids.

Glucagon and Other Islet Hormones

In addition to insulin, the islets of Langerhans secrete somatostatin, pancreatic polypeptide, glucagon, and possibly ghrelin. Clinically, pancreatic diseases generally are not associated with disorders of somatostatin, because somatostatin is synthesized and released by many other organs besides the pancreas. Pancreatic polypeptide, released from the ventral region of the pancreas in response to food, does not seem to have any specific physiologic function, and as a result, abnormal pancreatic polypeptide secretion is not associated with clinically recognizable abnormalities. Glucagon, released from islet α cells, is a functionally important hormone, and disorders of glucagon secretion can result in clinically recognizable functional changes (Lefebvre, 1992).

Glucagon is a 29–amino acid hormone that functions to regulate hepatic glucose output. Acting via adenylate cyclase and cAMP, glucagon stimulation of hepatocytes accelerates glycogenolysis and gluconeogenesis, causing blood glucose levels to increase. Hypoglycemia promotes glucagon release, and hyperglycemia inhibits glucogon release (Lefebvre, 1992; Unger, 1985). In some species, glucagon has other effects, including accelerating lipolysis, promoting gastric emptying, and stimulating insulin secretion. In type 1 diabetes, there is a low insulin–glucagon ratio, and this worsens hyperglycemia by promoting hepatic glucose output. In type 2 diabetes, glucagon secretion seems to be increased, and it is not suppressed by hyperglycemia. As a result, plasma glucagon levels are normal or elevated. With total pancreatectomy, patients become profoundly glucagon deficient and consequently prone to hypoglycemia. This leads to so-called brittle diabetes, which is characterized by swings in blood glucose levels, from marked hyperglycemia to marked hypoglycemia.

Endocrine Pancreas in Diabetes

Type 1 diabetes is a chronic autoimmune disease that leads to the destruction of β cells (Powers & Eisenbarth, 1995). Consequently, disordered insulin secretion in type 1 diabetes is primarily related to progressive loss of β cells, and clinical diabetes occurs when 80% to 90% of β cells are destroyed. In type 1 diabetes, serum insulin and C-peptide levels are usually extremely low (Polonsky et al, 1986). In contrast, the islets of Langerhans usually appear histologically normal in patients with type 2 diabetes, or the cells may be normal, but the islet may contain deposits of islet amyloid polypeptide. Despite this appearance, however, β-cell mass may be reduced by 50% in patients with type 2 diabetes, especially in patients who require insulin therapy. For the most part, patients with type 2 diabetes secrete increased amounts of insulin, proinsulin, and insulin conversion intermediates such as C-peptide, and elevated circulating levels of these factors can be detected (Porte, 1991).

Endocrine Pancreas in Chronic Pancreatitis

In chronic pancreatitis, there is progressive scarring of the pancreas with replacement of the gland by fibrous tissue. The islets become embedded in these areas of fibrosis, and eventually islets and islet cell mass are lost. This loss leads eventually to the loss of β cells and α cells (Diem, 2002). Functional testing may reveal a reduced response to oral and intravenous glucose and to glucagon and arginine. Approximately 10% of patients with exocrine pancreatic insufficiency secondary to chronic pancreatitis have clinically significant diabetes, whereas 30% have impaired glucose tolerance (Larsen et al, 1987; Sjoberg & Kidd, 1989).

EXOCRINE PANCREAS

On a tissue-weight basis, the exocrine pancreas synthesizes and secretes more protein per day than any tissue in the body other than the lactating breast, and approximately 90% of that newly synthesized protein consists of digestive enzymes. On a daily basis, the normal human pancreas secretes 6 to 20 g of digestive enzyme protein in 2.5 L of bicarbonate-rich fluid (Case, 1998). Derangements of exocrine pancreatic function commonly are observed in patients with pancreatic disease, and pancreatic functional assessment mostly involves tests of exocrine pancreatic function. The structure of the exocrine pancreas, its neurohormonal control, and the cell physiology of exocrine pancreatic secretion are reviewed in this section, and when possible, this review emphasizes information known to be valid for humans. Most of the literature concerning these issues is based, however, on work performed using various nonprimate species—rats, mice, guinea pigs, cats, rabbits, dogs, and pigeons—or work performed in vitro using isolated cells. To a great extent, this literature has indicated that there may be important differences in pancreatic exocrine function and physiology among the various species as well as important differences between the in vivo and in vitro setting. Although many

of the overall concepts covered in this section are no doubt relevant to the human in vivo setting, there may be important exceptions to this generalization (Case, 1998).

Structure

The exocrine pancreas is composed of two functional elements: a *ductal tree* and a mass of *pancreatic acini* (Case, 1998; Konturek et al, 2003). Each acinus consists of a grapelike cluster of acinar cells that surround a central or acinar lumen, which is continuous with the ductal space. Acinar cells constitute 75% to 90% of the gland. They are highly polarized cells that possess abundant, rough endoplasmic reticulum, located almost entirely within the basolateral region of the cell. The nucleus also is located in the basolateral region, and a prominent Golgi complex is located near the center of the cell. Secretory vesicles consisting of zymogen granules and their immature condensing vacuole precursors fill the apical portion of acinar cells.

The ductal component of the exocrine pancreas includes centroacinar cells present at the junction between the acinar and ductal lumina and cells lining the progressively larger ducts that connect the acinus to the duodenum (intercalated ducts, intralobular ducts, interlobular ducts, and main pancreatic ducts). These cells contain large numbers of prominent mitochondria but few secretory vesicles. Centroacinar cells are cuboidal cells, but the ductal cells become more columnar with progression distally in the ductal tree.

The pancreas is innervated by extrinsic and intrinsic parasympathetic and sympathetic nerves. These autonomic nerves have been shown to use a vast array of neurotransmitters in addition to acetylcholine and catecholamines, including nitric oxide, vasoactive intestinal peptide (VIP), gastrin-releasing peptide, neuropeptide Y, galanin, substance P, calcitonin gene-related peptide, gastrin/cholecystokinin (CCK), and enkephalins (Case, 1998; Case & Argent 1993). From a purely functional standpoint, the most important of the neurotransmitters seems to be acetylcholine, which in addition to functioning as a neurotransmitter also acts as a paracrine hormone released near acinar cells to regulate their function. Evidence indicates that many of the intrapancreatic cholinergic vagal nerves possess CCK receptors, and that at least in humans, the hormonal effects of CCK on pancreatic acinar cells may be mediated by vagal afferents in response to CCK stimulation (Owyang & Logsdon, 2004). Whether or not CCK can directly stimulate acinar cell secretion of enzymes in humans is a controversial issue (Murphy et al, 2008; Owyang & Logsdon, 2004).

Neurohormonal Regulation of Exocrine Pancreatic Function

The exocrine pancreatic response to a meal traditionally is considered to involve three phases (Konturek et al, 2003): 1) the *cephalic phase,* triggered by the sight or smell of food, accounts for 10% to 20% of the pancreatic secretion during a meal; 2) the *gastric phase,* triggered by food entering the stomach and by gastric distention, accounts for 15% to 20% of meal-stimulated pancreatic secretion; and 3) the *intestinal phase,* triggered by food and acid entering the duodenum and proximal jejunum, accounts for 60% to 70% of meal-stimulated pancreatic secretion (Table 3.1). In humans, the cephalic and gastric phases are thought to be vagally mediated and to primarily involve stimulation of digestive enzyme secretion rather than bicarbonate secretion (Anagnostides et al, 1984; Case, 1998; Konturek et al, 2003). The intestinal phase is neurally and hormonally regulated, however, and it involves secretion of a pancreatic juice that is rich in bicarbonate and digestive enzymes.

Table 3.1

Three Phases of Pancreatic Secretion

Phase	Contribution Output	Stimulus	Mediators
Cephalic	10%-20% enzymes	Sight and smell	Vagus
Gastric	15%-20% enzymes	Gastric distension Food in stomach	Vagus
Intestinal	60%-70% enzymes and bicarbonate	Food and acid in duodenum	Vagus, CCK, secretin

CCK, Cholecystokinin.

The intestinal phase of meal-stimulated pancreatic secretion has been the most fully characterized phase (Fig. 3.2). The entry of gastric chyme into the duodenum and proximal jejunum triggers vagovagal (centrally acting) reflexes and enteropancreatic neural reflexes that together primarily stimulate digestive enzyme secretion from pancreatic acinar cells. Acidification of the duodenum (pH <4.5) causes specialized cells within the mucosa to release secretin into the circulation, and secretin potently stimulates duct cell secretion of fluid and bicarbonate (Case & Argent, 1993). Release of secretin and stimulation of fluid/bicarbonate secretion also are elicited by various products of digestion, especially fatty acids and bile salts (Rhodes et al, 1988; Riepl et al, 1990). Fatty acids and polypeptides released by the partial digestion of food also stimulate release of CCK from other specialized cells within the duodenal and jejunal mucosa, and elevated CCK levels cause acinar cells to secrete digestive enzymes and other proteins into the pancreatic juice (Dale et al, 1989).

Pancreatic duct cells express secretin receptors, and it is generally believed that secretin stimulation of fluid/bicarbonate

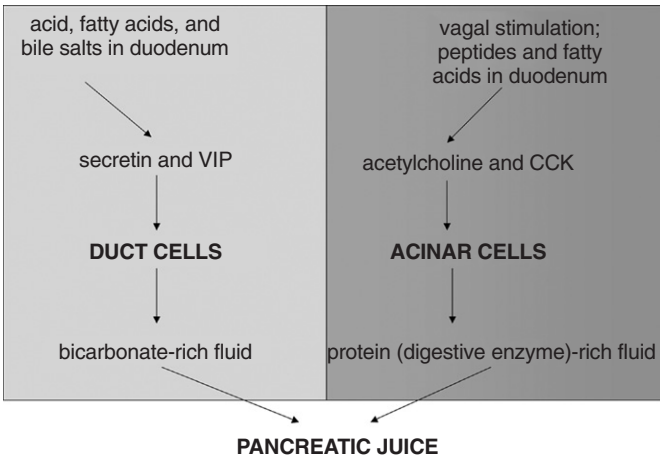


FIGURE 3.2. The two components of the exocrine pancreas. Acidification of the duodenum and the entry of fatty acids or bile salts into it trigger release of secretin and vasoactive intestinal peptide (*VIP*). Secretin and VIP stimulate pancreatic duct cells to secrete a bicarbonate-rich fluid. Vagal stimulation and the entry of either peptides or fatty acids into the duodenum cause release of acetylcholine and cholecystokinin (*CCK*), which stimulate acinar cells to secrete a fluid rich in digestive enzyme proteins.

secretion by duct cells reflects the direct effect of secretin—and possibly other hormones, such as VIP—on those duct cells. Acinar cells express receptors for acetylcholine and several other candidate secretagogues, and it is generally believed that neurally stimulated acinar cell secretion of digestive enzymes reflects the direct effects of those neurally released factors on acinar cells, acting via their specific receptors. However, the mechanisms responsible for CCK-stimulated acinar cell secretion seem to be more complex and may be species specific. The acinar cells of many species (e.g., mice, rats) express CCK receptors, and in those species, CCK may stimulate secretion by directly interacting with those acinar cell receptors (Owyang & Logsdon, 2004; Soudah et al, 1992). For many years, it was widely believed that human acinar cells do not express CCK receptors (Ji et al, 2001). This has been recently challenged by Murphy and colleagues (2008), who suggested that human acinar cells may express functional CCK receptors coupled to digestive enzyme secretion. On the other hand, it has long been known that human CCK-stimulated digestive enzyme secretion can be almost entirely prevented by cholinergic blockade (Li & Owyang, 1993; Li et al, 1997), which would suggest that CCK-stimulated secretion is mediated via cholinergic mechanisms and that CCK receptors on acinar cells, even if they do exist, are unlikely to play a major role in mediating meal-stimulated secretion in humans.

Diversion of pancreatic juice from the duodenum causes circulating levels of secretin and CCK to increase. This increase stimulates pancreatic secretion of fluid, bicarbonate, and digestive enzymes. The mechanisms behind this phenomenon have been the subject of considerable interest, and at present, diversion-induced upregulated secretion is believed to reflect the presence of trypsin-sensitive "releasing factors" for secretin and CCK within the duodenal lumen. These factors are believed to be released into the duodenum from specific cells of the mucosa (Lu et al, 1989; Miyasaka et al, 1989) or secreted into pancreatic juice (Iwai et al, 1987) and degraded by luminally active trypsin when food-stimulated secretion is adequate; as a result, the stimulus for further secretion is dampened. When food-stimulated secretion is inadequate, however, all of the secreted trypsin is bound to proteins within the duodenal lumen; as a result, trypsin-induced degradation of the releasing factors does not occur, and CCK or secretin release into the circulation is increased.

The physiologic importance of this "feedback" mechanism for regulating pancreatic secretion in humans is unclear, but it has been invoked to explain the observation that, at least in some series, patients with painful, chronic pancreatitis seem to obtain pain relief by ingesting exogenous pancreatic enzyme preparations that contain trypsin. It is argued that patients with chronic pancreatitis secrete inadequate amounts of digestive enzymes (trypsin) into the duodenum, and as a result, levels of intraluminal CCK-releasing factor may be chronically elevated, leading to continuous CCK-induced stimulation of the pancreas and possibly to chronic pain. In this setting, provision of exogenous enzyme preparations that include trypsin could terminate that signal for pancreatic secretion by promoting intraluminal degradation of the CCK-releasing factors, and this could ameliorate the pain of chronic pancreatitis (Toskes, 2002). Most patients with painful chronic pancreatitis and steatorrhea continue to have pain, however, despite ingesting exogenous pancreatic enzymes (Mossner et al, 1992); this has led many investigators to question the role of the feedback mechanism in the regulation of human pancreatic function and the role of CCK in the genesis of chronic pancreatitis pain.

Electrolyte Secretion

Small interlobular ducts are the major site of fluid and bicarbonate secretion in the pancreas. That secretion is primarily regulated by secretin, but VIP and acetylcholine also may play a role in this process. CCK and acetylcholine also may augment fluid and electrolyte secretion by stimulating the secretion of a chloride-rich fluid from acinar cells, but little is known regarding the events involved in acinar cell fluid and electrolyte secretion. Most knowledge regarding cellular mechanisms responsible for fluid and electrolyte secretion in the pancreas has been derived from studies involving duct cells in nonprimate species, and its applicability to humans remains to be established.

Currently, the most widely accepted model for duct cell secretion in humans is the one shown in Figure 3.3 (Case & Argent 1993; Ishiguro et al, 2009). Initially, carbon dioxide diffuses into the cell from the circulation, and it is hydrated by carbonic anhydrase to form H_2CO_3 (carbonic acid), which dissociates into H^+ and HCO_3^-. The H^+ back-diffuses across the basolateral cell membrane and is cleared into the circulation. The HCO_3^- is carried across the luminal cell surface by a Cl^-/HCO_3^- exchanger, SLC26A6, the activity of which depends on

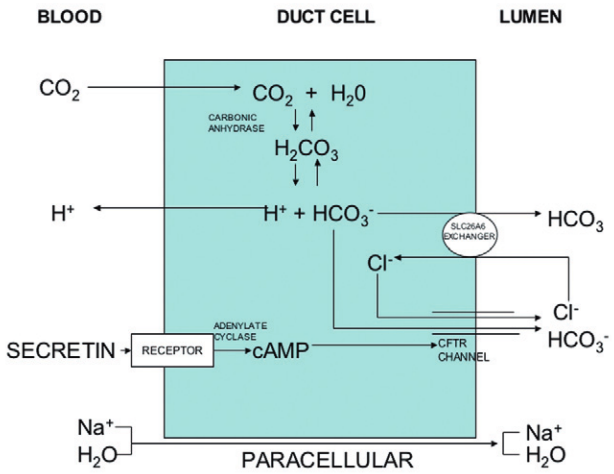


FIGURE 3.3. Stimulus-secretion coupling in pancreatic duct cells. Carbon dioxide (CO_2) diffuses from the blood across the basolateral surface of duct cells and is hydrated by carbonic anhydrase within the duct cell to yield carbonic acid. Carbonic acid dissociates into protons and bicarbonate. The bicarbonate is transported across the luminal plasma membrane into the ductal space by a chloride–bicarbonate exchanger (SLC26A6). In some species (e.g., human, guinea pig), bicarbonate secretion through the apical membrane may also reflect passage of bicarbonate through the cystic fibrosis transmembrane regulator (CFTR). The function of CFTR is regulated by the hormone secretin, which binds to receptors on the basolateral surface of duct cells, activating adenylate cyclase and accelerating the formation of cAMP, which in turn activates CFTR on the luminal cell surface, thus opening a channel that allows chloride and, in at least some species, bicarbonate to pass from the cell into the ductal space. The net passage of bicarbonate across the duct cell generates an ionic and osmotic gradient, which favors paracellular passage of sodium and water into the ductal space.

the availability of Cl^- in the duct lumen; this luminal Cl^- is maintained by the cAMP-stimulated opening of the cystic fibrosis transmembrane regulator (CFTR), which is a Cl^- channel. In this system, cAMP is generated by secretin-induced activation of adenylate cyclase at the basal surface of the cell. In many species, including mice, the maximal concentration of HCO_3^- in pancreatic juice is only 80 mmol/L, which can be achieved by secretion of HCO_3^- via the HCO_3^-/Cl^- exchanger SLC26A6. In humans and guinea pigs, however, maximal HCO_3^- concentrations in pancreatic juice can reach 140 mmol/L; to achieve these high concentrations, another mechanism is required—secretion via CFTR in response to activation by cAMP (Ishiguro et al, 2009). In an overall sense, the secretion of HCO_3^- at the luminal surface generates a net negative transepithelial current and an ionic gradient, and these changes draw Na^+ and water into the lumen via paracellular pathways.

The electrolyte composition of pancreatic juice varies widely among different species and with different rates of juice flow. For the most part, Na^+ and K^+ concentrations resemble those in serum. At high flow rates, HCO_3^- and Cl^- concentrations are approximately 140 and 20 mmol/L, respectively; but in some species, and at lower flow rates, HCO_3^- and Cl^- concentrations may be equal.

Stimulus-Secretion Coupling in Duct Cells

Duct cells express seven-transmembrane G protein–coupled receptors for secretin, acetylcholine, and other possible regulators of fluid and electrolyte secretion. Occupancy of secretin receptors leads to G protein changes that trigger activation of adenylate cyclase, generation of cAMP, and activation of protein kinase A. As noted earlier, this leads to the activation of CFTR and to the opening of the Cl^- channel, which may mediate both Cl^- secretion and HCO_3^- secretion at the luminal cell surface. Occupancy of acetylcholine receptors leads to changes in other G proteins that trigger activation of phospholipase C, generation of IP_3 and DAG, elevation of intracellular free calcium levels, and activation of protein kinase C, but it is not clear how this ultimately promotes fluid and electrolyte secretion into the ductal space (Case, 1998).

Acinar Cell Biology

Amino acids enter the acinar cell, against a concentration gradient, through at least four membrane transporters, and they bind to vacant transfer RNA in the cytoplasm. They are used to assemble newly synthesized proteins within the rough endoplasmic reticulum by a complex, extensively studied process that involves docking to the endoplasmic reticulum surface and elongation of the nascent polypeptide chain within the cisternae of the rough endoplasmic reticulum. On reaching a termination sequence, translation ceases and cleavage occurs, leaving the newly synthesized protein free to assume its tertiary and quaternary structure within the cisternae of the endoplasmic reticulum. After their synthesis, many of the newly synthesized proteins within acinar cells, particularly the proteins destined for secretion, are transported to the Golgi stacks in small vesicles; within those stacks, they are posttranslationally modified, usually by glycosylation or phosphorylation or both, and sorted into three groups: *secretory, lysosomal,* or *structural.* Secretory proteins, including digestive enzymes and their inactive zymogens, are packaged in immature secretory vesicles (condensing vacuoles), which migrate toward the cell surface as they mature into more dense zymogen granules. At the cell surface, and in response to secretory stimulation, the limiting membranes of the zymogen granules fuse with the luminal plasmalemma, secretory or fusion pores develop, and the granule contents are discharged into the acinar lumen (Palade, 1975; Rothman, 1994).

Digestive Enzyme Activation

The acinar cells of the pancreas synthesize and secrete numerous digestive enzymes. Some (amylase, lipase, RNase, and DNase) are synthesized as active enzymes, whereas others (trypsinogen, chymotrypsinogen, procarboxypeptidase, and proelastase) are synthesized as inactive proenzymes or zymogens. Zymogen activation usually involves proteolytic cleavage of the zymogen, exposing the activated enzyme after an activating peptide has been released. For the most part, the digestive enzyme zymogens are not activated until they reach the duodenum, where the brush-border enzyme enteropeptidase activates trypsinogen, and trypsin activates the other zymogens. Considerable evidence suggests that the synthesis of specific digestive enzymes may be controlled to some extent by diet—in other words, that ingestion of a high-fat diet promotes synthesis of lipolytic enzymes, ingestion of a high-protein diet favors synthesis of proteolytic enzymes, and ingestion of a starch-rich diet increases the synthesis of amylolytic enzymes—but the mechanisms underlying this control are unclear (Case, 1998).

Stimulus–Secretion Coupling in Acinar Cells

Many neurohormones can stimulate acinar cell digestive enzyme secretion; but to a great extent, the mechanisms involved differ, depending on the hormone involved (Fig. 3.4; Williams, 2001, 2002). Secretin and VIP bind to their specific G protein–coupled receptors and cause activation of adenylate cyclase, generation of cAMP, and activation of protein kinase A. Acetylcholine, bombesin/gastrin-releasing peptide, CCK, PAR-2–activating proteases, and substance P bind to their specific G protein–coupled receptors. CCK appears to bind to high-affinity CCK-A receptors, which in humans may be located on intrapancreatic cholinergic nerves; in other species these are on the surface of acinar cells. The receptors for acetylcholine and substance P are on acinar cells, and they are type 4 muscarinic receptors and NK-1 receptors, respectively. Activation of those receptors causes activation of phospholipase C, leading to the generation of DAG and IP_3; release of calcium from intracellular stores, leading to a rise in cytoplasmic calcium levels; and activation of protein kinase C. The ultimate process of secretion is believed to be regulated by specific proteins that are phosphorylated (activated) by the activated protein kinases A and C (Williams, 2001, 2002; Yule & Williams, 1994).

ASSESSMENT OF PANCREATIC FUNCTION

Endocrine Function

In the past, numerous attempts were made to use changes in circulating glucagon or pancreatic polypeptide levels or both in response to stimulation as a diagnostic test for patients with suspected mild to moderate chronic pancreatitis; because of very poor sensitivity, those tests were abandoned and are of

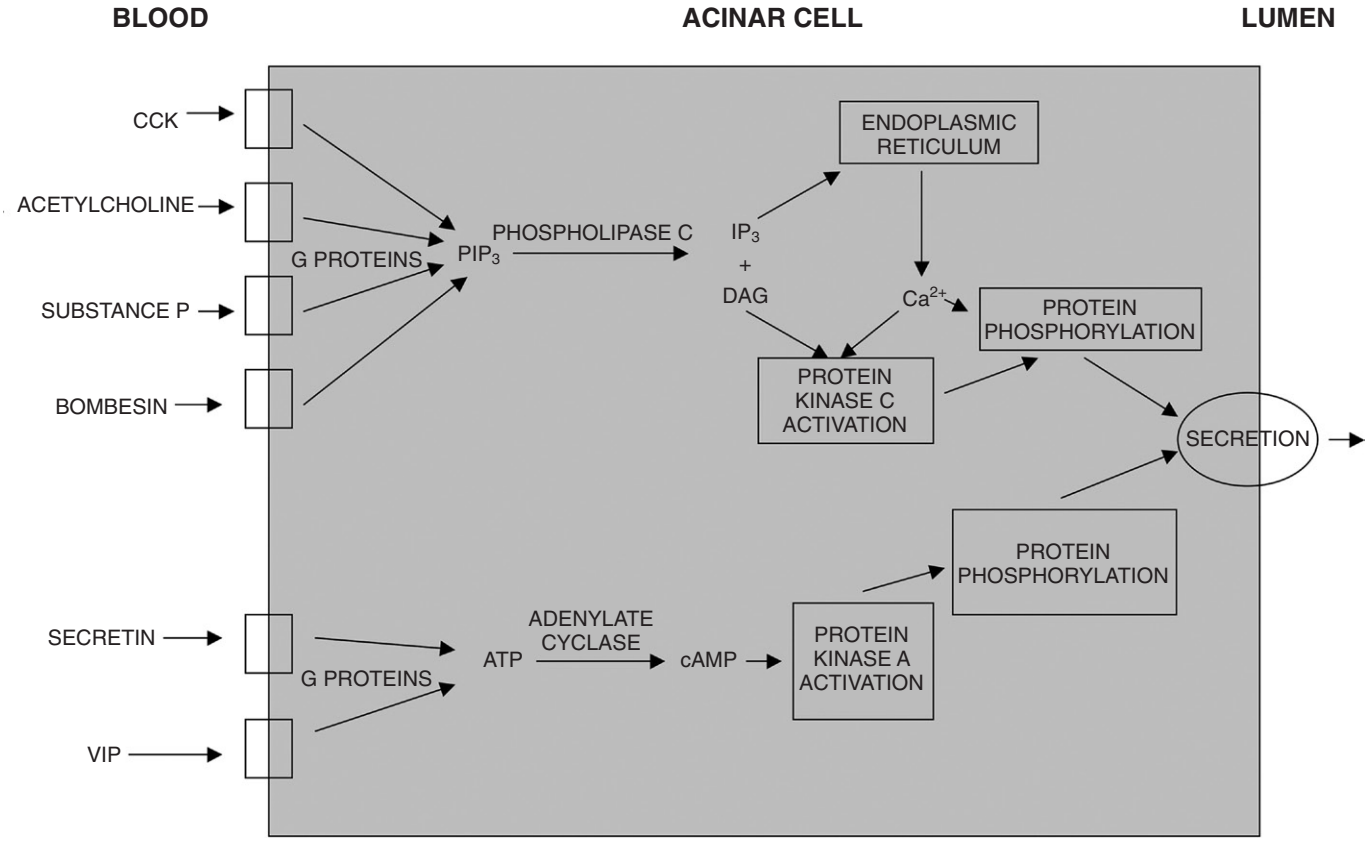


FIGURE 3.4. Stimulus–secretion coupling in pancreatic acinar cells. Stimulating factors and hormones bind to two types of cell surface receptors: G protein–coupled receptors associated with phospholipase C and G protein–coupled receptors associated with adenylate cyclase. Activation of phospholipase C leads to the formation of inositol triphosphate IP_3 and diacylglycerol (DAG), whereas activation of adenylate cyclase leads to generation of cyclic adenosine monophosphate (cAMP). IP_3 stimulates release of calcium into the cytoplasmic space from stores in the endoplasmic reticulum, which promotes calcium influx into the cell. Elevated cytoplasmic calcium and DAG levels cause activation of protein kinase C, leading to protein phosphorylation and digestive enzyme secretion. Elevated cAMP levels cause activation of protein kinase A, which also leads to protein phosphorylation and digestive enzyme secretion. Cholecystokinin (CCK) regulates secretion by binding directly to acinar cells in many species, but more recent evidence indicates that human acinar cells lack CCK receptors; in humans, CCK may regulate acinar cell secretion via a vagal, cholinergic pathway. *ATP,* adenosine triphosphate; *cAMP,* cyclic adenosine monophospate; *CCK,* cholecystokinin; *DAG,* diacylglycerol; *IP_3,* inositol triphosphate; *PIP_3,* phosphatidyl inositol, *VIP,* vasoactive intestinal peptide.

historical interest only (Toskes, 1986). At present, functional assessment of the endocrine pancreas in patients suspected of having chronic pancreatitis involves evaluation of insulin secretion and glucose metabolism. Endocrine pancreatic insufficiency in chronic pancreatitis may eventually result in clinical diabetes mellitus, because with time, functional islet cell mass and insulin secretion are lost; approximately 90% of β-cell mass must be lost before clinical diabetes develops. Twenty-five years after the onset of chronic pancreatitis, the incidence of clinical diabetes mellitus has been reported to exceed 80%, and more than 50% of the patients have insulin-dependent diabetes mellitus (Malka et al, 2000). With careful testing, many patients with lesser degrees of endocrine loss can be identified at an earlier time after the onset of chronic pancreatitis (Diem, 2002). In addition to an abnormal glucose tolerance test, these patients have depressed C-peptide secretion; consequently, circulating and urinary C-peptide levels may be low. In most cases, insulin-dependent diabetes develops, but in some patients, non–insulin-dependent diabetes may be seen; in these patients, C-peptide secretion may be normal. Diabetic ketoacidosis is unusual in patients with diabetes caused by chronic pancreatitis, but glucagon secretion is also often depressed, and a "brittle" form of diabetes may evolve (Angelopoulos et al, 2005). Pancreatic endocrine and exocrine insufficiencies in chronic pancreatitis evolve with different time dependencies, and in most cases, clinically apparent exocrine insufficiency precedes endocrine insufficiency by many years (Layer et al, 1994). Exocrine insufficiency is more closely correlated with morphologic changes (fibrosis, calcifications) than is endocrine insufficiency.

Assessment of Exocrine Function

Pancreatic exocrine functional testing is needed most often in the assessment of patients suspected of having chronic pancreatitis. For patients with severe and advanced chronic pancreatitis, the diagnosis usually is easily made on the basis of imaging studies, and the purpose of functional testing is to confirm the severity of the exocrine insufficiency and to gauge the adequacy of therapy with exogenous enzymes. Functional assessment also might be used to identify patients with milder or earlier forms of chronic pancreatitis, in whom imaging studies may be of less value; over the past century, numerous attempts have been made to develop tests for that purpose. That goal has remained elusive, primarily because the normal exocrine pancreas

Table 3.2

Tests of Pancreatic Function

Indirect Tests	Direct Tests
Fecal fat staining	**Noninvasive tests**
72-hour fecal fat excretion	Serum trypsinogen
Bentiromide test	Fecal chymotrypsin
Pancreolauryl test	Fecal elastase
	MRCP function tests
	Invasive tests
	Secretin test
	Secretin-CCK test
	Intraductal secretin test
	Lundh test

MRCP, magnetic resonance cholangiopancreatography; *CCK,* cholecystokinin.

possesses considerable functional reserve, and the tests that have been developed do not identify changes until much of that reserve has been lost. For the most part, pancreatic function tests have the common characteristic of being relatively specific but very poorly sensitive as diagnostic tests of chronic pancreatitis.

Tests of exocrine pancreatic function can be divided into two major groups (Table 3.2): *indirect tests* monitor the intestinal effects of secreted pancreatic digestive enzymes; *direct tests* monitor the actual secretion of pancreatic exocrine products (enzymes, fluid, and bicarbonate). The indirect tests are the least invasive and most widely available of the tests, but they also are the least sensitive, and such tests are most likely to be normal in patients with mild degrees of pancreatic functional loss.

Indirect Pancreatic Function Tests

Conceptually, fecal fat analysis is the simplest of the indirect pancreatic function tests. It is based on the fact that pancreatic lipase is the enzyme responsible for most fat digestion, and diminished lipase secretion results in fat malabsorption. Fecal fat analysis can be accomplished by staining stool samples for fat with Sudan stain or by quantifying fecal fat when the patient is on a controlled-fat diet (Chowdhury & Forsmark, 2003; Lieb & Draganov, 2008). In the latter case, the patient is placed on a diet consisting of 100 g of fat per day for 5 days. Stool is collected on days 3 to 5, and fat content is measured. Fecal fat output of greater than 7 g/day is considered to be abnormal and diagnostic of steatorrhea; but fecal fat measurement is notoriously insensitive for the diagnosis of chronic pancreatitis, and it is most commonly abnormal only in patients with overtly symptomatic steatorrhea.

The bentiromide and the pancreolauryl tests are noninvasive, indirect pancreatic function tests. The former involves ingestion of the chymotrypsin substrate bentiromide, which is hydrolyzed by chymotrypsin to yield paraaminobenzoic acid, which is absorbed in the small intestine, conjugated in the liver, and excreted in the urine. The test is completed by collecting urine for 6 hours and quantifying urinary paraaminobenzoic acid recovery, which is considered to be abnormal if less than 50% (Niederau & Grendell, 1985). The pancreolauryl test involves ingestion of fluorescein dilaurate, which is hydrolyzed by pancreatic esterases to yield lauric acid and free fluorescein. The fluorescein is absorbed, conjugated in the liver, and excreted in the urine. Similar to the bentiromide test, the pancreolauryl test is completed by collecting urine, in this case for 10 hours, and measuring fluorescein excretion; in this test, excretion is compared with the patient's excretion of orally ingested free fluorescein several days later. The bentiromide and pancreolauryl tests may be falsely abnormal in the face of liver or kidney disease and when certain drugs are present. The pancreolauryl test is not available in the United States, but the bentiromide test is commercially available and widely used, primarily because it is easy to perform; however, low sensitivities of 37% to 46% have been reported in patients with mild degrees of chronic pancreatitis (Naruse et al, 1980; Toskes, 1983; Ventrucci et al, 1983), so this test is of only limited value.

Other indirect tests of pancreatic function include the triglyceride breath tests (Loser et al, 1998) and the dual-label Schilling test (Brugge et al, 1980; Chen et al, 1989). Both tests have been the subject of numerous clinical studies, but for the most part, their sensitivity and reproducibility have been poor. At present, they are not used clinically for the diagnosis of chronic pancreatitis.

Direct Pancreatic Function Tests

Direct pancreatic function tests can be subdivided further into *noninvasive* and *invasive* tests. The noninvasive tests involve measuring fecal or serum levels of pancreas-derived digestive enzymes (serum trypsinogen, fecal chymotrypsin, and fecal elastase). Recently, direct function tests combining MRCP with secretagogue stimulation have been proposed (Schneider et al, 2006; Czako, 2007). These MRCP functional tests aim to either quantify juice flow into the duodenum or to provide contrast enhancement of the pancreatic parenchyma after hormonal stimulation; to date, however, the overall sensitivity and specificity of these MRCP-based tests remain to be determined, and their overall value as diagnostic tests for early chronic pancreatitis is unproven. The invasive tests involve placing a collecting device into the duodenum or pancreatic duct, stimulating pancreatic exocrine secretion, and measuring the output or concentration of exocrine pancreatic products.

Circulating levels of trypsinogen are easily measured and frequently low in patients with severe pancreatic insufficiency (Jacobson et al, 1984). Although measurement of serum trypsinogen may be helpful in evaluating the severity of chronic pancreatitis, the test has low sensitivity for the diagnosis of mild pancreatitis. Fecal levels of chymotrypsin and elastase also can be measured and used to assess exocrine pancreatic function (Dominguez-Munoz et al, 1995; Dominici & Franzini, 2002; Goldberg, 2000; Katschinski et al, 1997; Loser et al, 1996; Luth et al, 2001). Because trypsin is degraded as it passes through the intestinal tract, measurement of fecal trypsin levels is not a useful pancreatic function test. Fecal levels of chymotrypsin and elastase can be measured easily using commercially available assays; the levels of these enzymes are reduced in patients with advanced chronic pancreatitis; however, the sensitivity of fecal chymotrypsin and elastase measurement in diagnosing mild or moderate pancreatic insufficiency is only 40% to 60%.

The invasive, direct pancreatic function tests are the most sensitive of the tests used to identify patients with mild to moderate chronic pancreatitis. In these tests, pancreatic secretions are continuously aspirated from either the duodenum or the pancreatic duct after administration of a pancreatic

stimulant; this stimulant varies among the different tests. In some, secretin is administered to stimulate pancreatic secretion, and bicarbonate in duodenal juice is measured. In others, a combination of secretin and CCK or one of its analogs is used, and bicarbonate and protein (or pancreatic enzymes) in duodenal juice are measured (Chowdhury & Forsmark, 2003). The Lundh test involves stimulating pancreatic secretion by administration of a standardized meal and measuring pancreatic enzymes in the aspirated duodenal juice (Lundh, 1962). Secretin usually is used as the stimulant when pancreatic secretions are collected directly from the cannulated pancreatic duct; these so-called intraductal pancreatic function tests usually involve measurement of bicarbonate (Denyer & Cotton, 1979; Ochi et al, 1997).

Hundreds of reports have described these various invasive, direct pancreatic function tests and their seemingly endless minor variations (Chowdhury & Forsmark, 2003). Most tests that involve aspiration of duodenal juice require the use of multilumen tubes that permit the investigator to aspirate separately and discard gastric secretions to prevent the secretions from diluting or neutralizing the secreted pancreatic juice. Some tests involve measurement of either bicarbonate or enzyme output (amount/time), and in those tests, markers such as polyethylene glycol or distally occluding balloons or both may be needed to ensure high recovery rates. The markers add an additional level of complexity, and for this reason, those tests of output are less commonly employed than tests that simply measure the peak concentration of the secreted element (bicarbonate).

Perhaps the most frequently employed and most reproducible of the invasive, direct pancreatic function tests is the secretin test performed using a double-lumen (Dreiling) tube. Under fluoroscopic control, the tube is passed into the third or fourth portion of the duodenum, while the "discard port" is positioned in the stomach. Passage can be time consuming and difficult for the investigator and the patient, and for this reason, I prefer to pass the tube over a wire that is itself passed through an endoscope. In my experience using this approach, the total time needed to pass and position the tube properly rarely exceeds 10 minutes (Waxman et al, 1996). When the tube is properly positioned, secretin is intravenously administered, and duodenal juice is collected over four consecutive 15-minute periods. Peak bicarbonate concentration is measured in each of the four samples, and a positive test diagnostic of pancreatic insufficiency is defined as one in which the peak bicarbonate concentration does not exceed 60 mEq/L. Borderline values are defined as ranging from 60 to 80 mEq/L; a normal response is defined as one in which at least one of the values exceeds 80 mEq/L. The sensitivity of this secretin test in diagnosing chronic pancreatitis has been reported to be 60% to 100%, but to a great extent, the sensitivity depends on the gold standard being used to confirm the diagnosis of chronic pancreatitis—endoscopic retrograde cholangiopancreatography (ERCP)—and on the case mix of pancreatitis severity.

General Approach to Exocrine Pancreatic Function Testing

Tests of pancreatic function have little or no role in the diagnosis and management of patients with advanced chronic pancreatitis and well-established morphologic changes that can be shown by imaging studies, although in this setting, exocrine function testing may play a role in gauging the adequacy of enzyme therapy. Function tests may be useful in a patient with symptoms suggestive of chronic pancreatitis (i.e., "pancreatic" pain), whose imaging studies show no changes and who have no obvious symptoms of pancreatic maldigestion (clinical steatorrhea). In that setting, an initial noninvasive test might be preferred, and because of its simplicity, measurement of fecal elastase-1 or the bentiromide test may be the most appropriate of those tests. Measurement of fecal fat is aesthetically unpleasant to patients and technicians, and it requires administration of a diet with measured fat content. Because of the poor sensitivity, however, chronic pancreatitis cannot be excluded in patients with normal fecal elastase-1 or bentiromide tests, and in this setting, performance of an invasive pancreatic function test would be appropriate. For this purpose, the secretin test is generally considered to be the gold standard pancreatic function test in the United States. In Europe, many clinicians prefer the secretin-cerulein test or the intraductal secretin test (Boeck et al, 2001). Performance of magnetic resonance cholangiopancreatography (MRCP) or ERCP should be considered in patients with convincing symptoms and a normal or borderline invasive pancreatic function test.

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CHAPTER 4

Liver blood flow: physiology, measurement, and clinical relevance

Flavio G. Rocha

LIVER BLOOD FLOW OVERVIEW

The hepatic circulation is the most complicated of any organ system. This chapter outlines the physiologic control of the liver's blood supply, describes the techniques used for its measurement in both human and animal models, and explores its function in various clinical situations.

PHYSIOLOGY

Liver Blood Supply

The liver normally receives about one quarter of the total cardiac output despite constituting only 2.5% of total body weight; it obtains its blood supply from two main sources, the hepatic artery and the portal vein. Approximately 75% to 80% of the blood entering the liver is partially deoxygenated portal venous blood drained from the stomach, intestine, spleen, and pancreas. The remainder is well-oxygenated blood from the aorta, carried by the hepatic artery. Mixing of arterial and portal blood occurs in the sinusoids, which are drained by the hepatic venous system into the inferior vena cava. Hepatic blood volume accounts for 10% to 15% of total blood volume with 40% of hepatic blood held in large vessels such as the hepatic arteries, portal vein, and hepatic veins; the remaining 60% is held in the sinusoids (Lautt, 1977; Greenway & Stark, 1971).

Hepatic Artery

The hepatic artery normally supplies about 25% of the total blood flow to the liver, or 30 mL/min per 100 g of liver tissue; however, it provides 30% to 50% of the liver's oxygen requirement because of the greater oxygen content found in arterial blood. In addition, the hepatic artery provides the exclusive blood supply to the intrahepatic bile ducts through the peribiliary plexus.

The hepatic arterioles empty directly or via a peribiliary plexus into the sinusoids and terminal portal venules. Direct artery-to-hepatic vein connections do not usually exist but may arise in liver disease. Reduction of pressure in the arterial system toward that existing in the portal circulation is achieved mainly by 1) the presinusoidal arteriolar resistance in the peribiliary plexus and 2) the intermittent closure of the arterioles, which protect the portal bloodstream from arterial pressure (Rappaport, 1973).

In the event of hepatic arterial occlusion, numerous small arteries provide a source for the formation of a collateral circulation. Upon interruption of hepatic arterial flow, collaterals can arise from 1) the inferior phrenic arteries, which can develop connections with hepatic arteries within the liver, and 2) from the gastroduodenal arteries, which derive blood flow from the superior mesenteric artery and supply the liver via the peribiliary arterial plexus around the intrahepatic bile ducts (Rappaport & Schneiderman, 1976). The precise nature of the functional collateral supply after hepatic arterial ligation depends on the site of occlusion. If the common hepatic artery is interrupted, revascularization occurs through both major routes; if only the right or left hepatic artery is interrupted, intrahepatic translobar anastomoses reestablish arterial flow in the ligated system (Mays & Wheeler, 1974). Ligation of the proper hepatic arteries leads to revascularization mainly via a hypertrophied inferior phrenic circulation (Jefferson et al, 1956). Complete long-term dearterialization of the liver by any form of arterial vascular occlusion is difficult to achieve.

Portal Vein

The inferior and superior mesenteric veins join with the splenic vein to form the portal vein, and jointly they collect the venous outflow from the entire prehepatic splanchnic vascular bed (the intestinal tract from the lower esophagus to the rectum plus the pancreas and spleen). This valveless system is a low-pressure/low-resistance system regulated by the degree of constriction of mesenteric and splanchnic arterioles coupled with the intrahepatic vascular resistance. The portal vein normally carries about 75% of the total blood flow to the liver, or 90 mL/min per 100 g of liver weight; normal portal pressure is 5 to 8 mm Hg. Portal blood is postcapillary and partly deoxygenated, but because of its large volume flow rate, it may supply 50% to 70% of the liver's normal oxygen requirement. During fasting states, the oxygen saturation in the portal blood approaches 85%, which is greater than other systemic veins. Hepatic oxygen supply is diminished if portal blood flow is significantly reduced, but the effect is minimized by an increase in oxygen extraction from the hepatic arterial blood and not by increasing flow. In fact, isovolemic hemodilution or upregulation of hepatic enzymes leading to oxygen deprivation does not result in hepatic artery dilatation, refuting the concept that arterial flow is regulated by liver cell metabolism (Lautt et al, 1987).

Hepatic Veins

The hepatic venous system is the systemic drainage tract of the entire splanchnic circulation. A total liver blood flow (LBF) of 1.5 L/min is considered the normal value in the average male, but the range can be quite wide (1 to 2 L/min). Although the free pressure in a hepatic vein is 1 to 2 mm Hg, the wedged

hepatic venous pressure, which is useful for estimating sinusoidal pressure, may be an indicator of portal venous pressure (Boyer et al, 1977). The sinusoidal pressure is estimated to be slightly higher than that of the vena cava, or 2 to 4 mm Hg (Eipel et al, 2010). Hepatic venous blood is normally about two-thirds saturated with oxygen, but this may be markedly reduced during periods of low delivery of oxygen to the liver, when oxygen is extracted by hepatocytes. In resting states, the liver accounts for approximately 20% of the total oxygen consumption of the body.

Control of Liver Blood Flow

Hepatic blood flow is controlled by physiologic mechanisms that are independent of extrinsic innervation or vasoactive agents. Instead, the interrelationship of arterial and portal inflow circuits is the major contributor to hepatic perfusion. The portal venous blood supply normally encounters minimal resistance in the portal venules and in the hepatic sinusoids and is effectively controlled outside the liver by the action of the arterial resistance vessels within the splanchnic organs.

Some controversy surrounds the autoregulation of hepatic arterial vasculature. Although some studies have suggested nonlinear pressure-regulated changes in arterial resistance in denervated dogs (Hanson et al, 1966), others have demonstrated a more direct relationship (Torrance, 1961). The pressure-flow dynamic in the portal system has been found to have little to no autoregulation, as evidenced by partial collapse of the portal vascular bed in response to reduced portal pressure (Condon et al, 1962).

Intrahepatic Vascular Resistance in Health

Intrahepatic vascular resistance (IHVR) seems to be located at the level of the portal venules (presinusoidal) or sinusoids (Sherman et al, 1996; Shibayama & Nakata, 1985; Zhang et al, 1994, 1995). Knisley suggested the presence of sphincter-like structures at the entrance and exit of sinusoids that maintain tremendous portal venous pressure gradients, but these may be species dependent (Knisley et al, 1957). In dogs and cats, IHVR is located at the level of hepatic venules (postsinusoidal) under resting conditions (Lautt et al, 1986, 1987), whereas it may be shifted to presinusoidal sites during neural stimulation (Greenway & Lautt, 1970; Legare & Lautt, 1987). Sinusoidal contraction in response to the vasoconstrictor endothelin (ET) 1 has been observed despite the lack of smooth muscle (Bauer et al, 1994, 1995; Okumura et al, 1994; Zhang et al, 1994, 1995). This contractility is mainly attributed to hepatic stellate cells—also called *Ito cells, lipocytes,* and *fat-storing cells*—which are distinguished by autofluorescence derived from their intracellular vitamin A (Suematsu et al, 1995; Zhang et al, 1994). ET-1 causes reversible and graded contraction of isolated stellate cells in tissue culture and results in narrowing of sinusoidal lumens in perfused livers (Pinzani et al, 1992; Rockey & Weisiger, 1996; Rockey et al, 1992; Zhang et al, 1994). Hepatic stellate cells have been compared to pericytes, because they contain smooth muscle–specific intermediate desmin-like and actin-like filaments that encircle neighboring sinusoids (Greenwel et al, 1991; Martinez-Hernandez, 1985; Martinez-Hernandez & Amenta, 1993; see Chapter 6).

Studies using intravital fluorescent microscopy showed that the sites of sinusoidal dilation and constriction is colocalized with that of an autofluorescent vitamin A substance (Suematsu et al, 1995, 1996; Zhang et al, 1994, 1995). Hepatic stellate cells acting as liver-specific pericytes (Friedman, 1997; Martinez-Hernandez, 1985; Martinez-Hernandez & Amenta, 1993) may play a crucial role in modulating IHVR and blood flow, especially at the sinusoidal level (Bauer et al, 1994; Okumura et al, 1994; Pannen et al, 1996; Zhang et al, 1994, 1995). Endothelium-derived nitric oxide (NO) in the hepatic sinusoids may modulate portal resistance under physiologic circumstances (Bauer et al, 1997; Shah et al, 1997). Electron microscopy studies have also demonstrated the presence of smooth muscle cells in the sublobar veins (Aharinejad et al, 1997), as well as terminal hepatic venules (Sasse et al, 1976), which may contribute to IHVR.

Relationship between Hepatic Artery and Portal Vein Blood Flow

Individual control of the hepatic arterial and portal venous circulations is complicated by the existence of a complex interaction between the two systems within the liver. Studies have shown an increase in hepatic arterial blood flow following reduction of portal blood flow (Kock et al, 1972; Mathie et al, 1980a; Schenk et al, 1962); however, a compensatory increase in portal flow following decreased arterial perfusion has rarely been observed (Mathie, 1997). Intraoperative measurements of hepatic artery and portal vein flow in anesthetized patients demonstrated a significant increase in hepatic arterial flow, up to 30% of baseline, with temporary occlusion of the portal vein and no effect on portal flow on occlusion of the hepatic artery (Jakab et al, 1995).

The ability of the hepatic artery to respond acutely to changes in portal flow is referred to as the *hepatic arterial buffer response* (Lautt, 1981). Highlighting its early embryonic origin, in experiments measuring fetal hepatic arterial blood flow, it has been shown that this regulatory process is even present prenatally (Ebbing et al, 2008). Experimental studies support the view that adenosine, accumulating in the liver as a result of reduced hepatic outflow or released from the walls of blood vessels in response to partial tissue hypoxia, has a significant role in the regulation of the buffer response (Lautt & Legare, 1985; Mathie & Alexander, 1990). This adenosine washout hypothesis is supported by the fact that portal infusion of adenosine increases hepatic arterial blood flow by one half to one third the amount of direct arterial instillation (Lautt et al, 1987). The demonstration of receptors mediating dilation to adenosine in the hepatic arterial vascular bed reinforces this view (Mathie et al, 1991; Fig. 4.1).

Metabolism

Hepatic arterial blood flow has not been traditionally linked to liver metabolism (Lautt, 1983; Mathie & Blumgart, 1983a). It has been shown that neither altered oxygen supply nor bile secretion causes a dependent change in arterial flow (Lautt, 1983); instead, the physiologic role of the buffer system is to maintain hepatic clearance in the face of reduced portal flow and to maintain adequate tissue oxygenation. This is despite the fact that the liver receives more oxygen than it requires and can therefore extract more by hepatocyte metabolism if needed. Therefore arterial flow is independent of oxygenation and is secondary to the nutrient and hormonal needs of the liver.

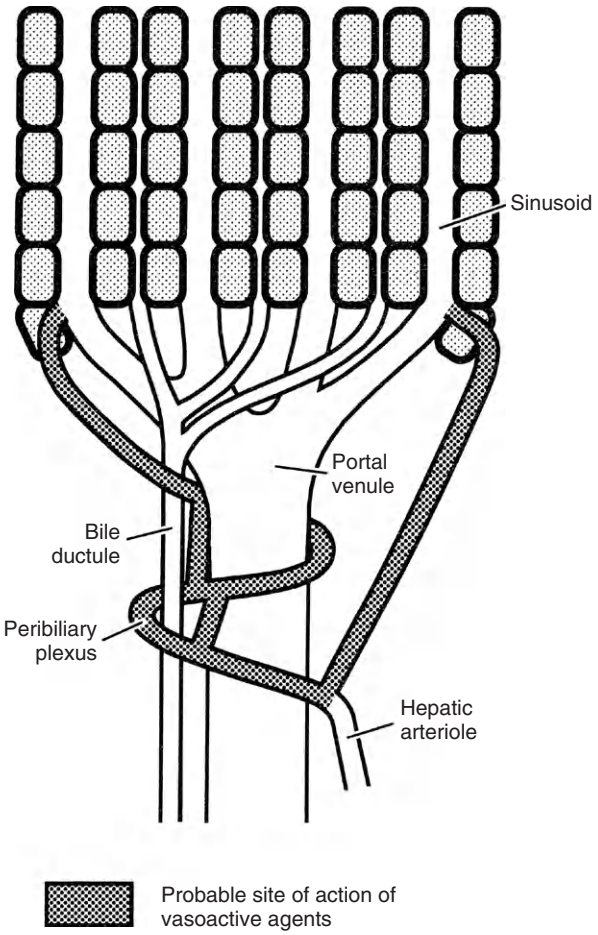


FIGURE 4.1. Diagrammatic representation of the microvascular bed of the liver, showing the anatomic association between hepatic arterioles, portal venules, and bile ductules. The probable site of action of vasoactive agents on the hepatic arterial circulation is indicated.

Blood Gas Tensions

Experimental studies have attempted to clarify the role of arterial blood gas tensions and pH on the hepatic circulation. Hypercarbia ($Paco_2$ > 70 mm Hg) increases portal venous flow and decreases hepatic arterial flow in dogs (Hughes et al, 1979a), whereas hypocarbia ($Paco_2$ < 30 mm Hg) decreases both (Hughes et al, 1979b). Systemic hypoxia (Pao_2 < 70 mm Hg) causes a decrease in arterial flow but has no effect on the contribution from the portal vein (Hughes et al, 1979c). The response to metabolic acidosis is similar to that induced by hypercarbia, whereas metabolic alkalosis has essentially no significant effect (Hughes et al, 1980b). The sympathetic nervous system is thought to be responsible for the hepatic arterial vasoconstriction observed in hypercarbia and hypoxia (Mathie & Blumgart, 1983b).

Sympathetic Nervous System

Denervation experiments have shown that the sympathetic nervous system is not involved in basal arterial tone in the liver (Mathie & Blumgart, 1983b). Hepatic sympathetic nervous stimulation causes hepatic arterial vasoconstriction and reduced blood flow, but this is secondary to the autoregulatory response (Greenway & Stark, 1971). Sensory denervated rats and pigs have a diminished arterial buffer response on partial occlusion of the portal vein (Ishikawa, 1995). Portal pressure increases as a result of an increase in portal venous resistance, but portal flow does not decrease, unless there is a decrease in intestinal or splenic blood flow caused by simultaneous sympathetic stimulation of these vascular beds. The liver is a significant blood reservoir, and 50% of its blood volume may be mobilized by nerve stimulation (Greenway & Lautt, 1989).

Although the hepatic artery contains both α-adrenergic and β-adrenergic receptors, the portal venous system is believed to contain only α-receptors (Richardson & Withrington, 1981). At low doses, epinephrine causes hepatic and mesenteric arterial vasodilation, whereas at high doses, vasoconstriction occurs in the hepatic arterial and portal venous vascular beds and in the mesenteric circulation (Greenway & Stark, 1971; Richardson & Withrington, 1981).

Other Endogenous Vasoactive Agents

Hepatic blood flow is profoundly increased by glucagon as a consequence of its strong vasodilatory action on the mesenteric vasculature, but insulin has little hemodynamic effect on the hepatic circulation. Histamine causes hepatic arterial dilation and, in the dog only, hepatic venous constriction. Bradykinin is a potent hepatic arterial vasodilator that has little effect on the portal venous system. The hepatic arterial vascular bed is dilated by most prostaglandins; however, prostacyclin does not affect hepatic arterial flow but increases portal blood flow through a vasodilator effect on the prehepatic vascular bed. NO causes vasodilation in the hepatic arterial and mesenteric vascular beds as discussed earlier. Each of the gut hormones—gastrin, secretin, cholecystokinin, and vasoactive intestinal peptide—causes vasodilation of the hepatic artery. In addition, antagonists of calcitonin gene–related peptide and neurokinin significantly reduce hepatic arterial blood flow, suggesting the presence of their receptors on the arterial vasculature (Biernat et al, 2005).

Angiotensin decreases hepatic arterial and portal blood flow and is one of the few substances to produce a significant vasoconstrictor effect on the hepatic artery. However, the ETs that can exert a powerful and prolonged generalized systemic constriction (Miller et al, 1989; Zhang et al, 1994) also have a direct effect on the hepatic blood flow. ETs reduce hepatic perfusion (Kurihara et al, 1992), increase portal pressure (Bauer et al, 1994; Isales et al, 1993; Tanaka et al, 1994; Tran-Thi et al, 1993), and reduce sinusoidal diameter (Bauer et al, 1994; Okumura et al, 1994; Zhang et al, 1994). Vasopressin decreases portal flow and pressure by mesenteric arterial vasoconstriction but has variable effects on the hepatic artery. Serotonin is believed to mediate vasoconstriction of portal radicles and has been targeted as a substance involved in the maintenance of portal hypertension, which will be discussed later. In contrast, hydrogen sulfide either endogenously or exogenously can reverse the norepinephrine-induced vasoconstriction in an NO-independent fashion (Fiorucci et al, 2005). Intraportal administration of exogenous vasoactive agents affects hepatic arterial resistance (Lautt et al, 1984); the mechanisms underlying this intrahepatic transvascular effect are not understood, but

it is likely that the close anatomic association between arterioles and venules (see Fig. 4.1) could permit this and may be a means by which hepatic arterial blood flow is finely controlled by endogenous agents such as gut hormones.

Anesthetic Agents

Hepatic arterial and portal venous blood flow decreases passively in parallel with cardiac output during halothane inhalation, with little change in vascular resistance (Hughes et al, 1980a; Thulin et al, 1975). Hepatic oxygen consumption is not diminished by halothane because of a marked increase in the oxygen extraction rate from the reduced blood supply (Andreen et al, 1975). Enflurane has been found to have similar effects to those of halothane, although there is a decrease in hepatic arterial vascular resistance as part of a generalized decrease in peripheral vascular resistance (Hughes et al, 1980a). Cyclopropane and methoxyflurane reduce LBF, mainly by increasing the mesenteric vascular resistance (Batchelder & Cooperman, 1975). NO in concentrations of 30% to 70% reduces hepatic artery and portal vein flow, possibly as a result of a generalized stimulatory action on α-adrenergic receptors (Thomson et al, 1982). Isoflurane seems to have minimal effects on hepatic arterial and portal venous flows, and the intravenous agent fentanyl may have little effect on prehepatic splanchnic blood flow (Nagano et al, 1988); thiopentone in low doses vasoconstricts the hepatic arterial and mesenteric vascular beds (Thomson et al, 1986).

MEASUREMENT OF LIVER BLOOD FLOW

The earliest methods of measuring LBF involved direct invasive techniques, such as intravascular devices or venous outflow collection (Burton-Opitz, 1910, 1911; MacLeod & Pearce, 1914). Indirect determination of blood flow by the use of a variety of indicator-clearance techniques were subsequently developed but were confounded by the presence of liver disease. The available methods are discussed under three broad headings: 1) flow in single blood vessels, 2) total LBF, and 3) hepatic tissue perfusion. The techniques currently employed for experimental and clinical investigations are listed in Table 4.1.

Table 4.1

Summary of Methods Currently Used for Measuring Liver Blood Flow

Flow in Single Vessels	Total Liver Blood Flow
Electromagnetic flowmeter	Clearance techniques
Doppler ultrasound	Hepatocyte excretion
	Indocyanine green
Hepatic Tissue Perfusion	Galactose
Inert gas clearance	Reticuloendothelial uptake
Krypton 85	Sulfur colloid (technetium 99m)
Xenon 133	Indicator dilution
Hydrogen	Red blood cells (chromate 51)
Laser Doppler flowmetry	Serum albumin (iodine 131, technetium 99m)
	Indicator fractionation
	Microspheres (various labels)

Flow in Single Vessels

Electromagnetic Flowmeter

The direct and continuous measurement of hepatic arterial and portal venous blood flow with electromagnetic flow probes remains the best available means of assessing individual vessel flow. Although the technique has found widespread application in experiments using large animals, its use in clinical situations has been limited by the relatively extensive vascular dissection required for placement of the probes and by the overestimation of true hepatic tissue blood flow, which occurs in the presence of portosystemic shunts. In addition, relative movements of the probes can give rise to errors and the need for repetitive calibrations. Total LBF in anesthetized subjects was determined to be approximately 1 L/min, of which about 25% was supplied by the hepatic artery (Schenk et al, 1962). Electromagnetic probes have been used intraoperatively to assess the hemodynamic status of the liver in cirrhosis (Ohnishi et al, 1987) after liver surgery or transplantation (Takaoka et al, 1990). A typical experimental preparation using electromagnetic flow probes is illustrated in Fig. 4.2.

Doppler Ultrasound

Named after Christian Doppler for the phenomenon he described, the principle of flow estimation by Doppler flowmetry is simple: flow is a product of the average velocity of the blood measured in the vessel of interest and the cross-sectional area of the vessel. Two forms of Doppler ultrasound devices exist: The first consists of a flowmeter with an ultrasound probe that is placed directly on the vessel; measurement with such a device is invasive. The second consists of a combined image scanner and flowmeter (duplex) with which flow in a vessel can be measured transcutaneously and noninvasively.

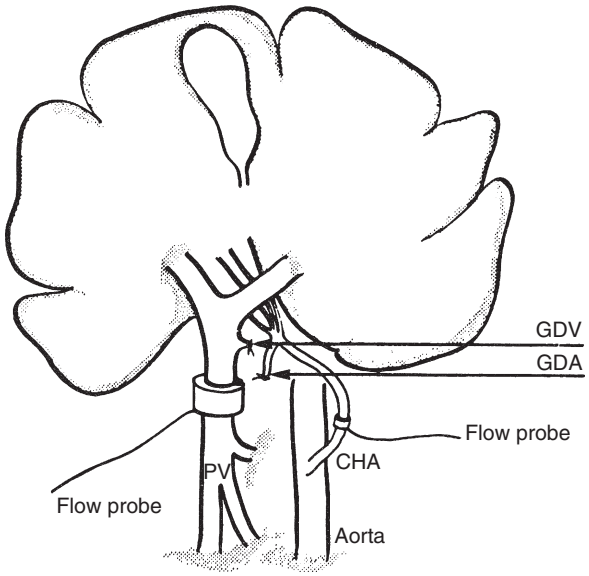


FIGURE 4.2. Experimental arrangement for measuring liver blood flow in the dog with electromagnetic flow probes. Probes are placed around the portal vein (*PV*) and common hepatic artery (*CHA*). The gastroduodenal vein (*GDV*) and gastroduodenal artery (*GDA*) are ligated as illustrated to ensure that the flows measured by the probes are those that actually perfuse the liver.

INVASIVE. Because the ultrasound probes are fitted directly to the vessel, such systems have been used successfully in the intraoperative (Henderson et al, 1991) and postoperative measurement of portal venous and hepatic arterial blood flow in liver transplant patients (Payen et al, 1990).

NONINVASIVE. In experiments performed on anesthetized dogs, good correlation was found between portal venous flow measured by a transcutaneous Doppler duplex system and electromagnetic flow probes fitted to the portal vein (Dauzat & Layrargues, 1989). However, the clinical application of transcutaneous Doppler ultrasound to obtain quantitative hepatic blood flow measurements in the portal vein have been more difficult (Burns et al, 1987). This technique has been utilized to assess postoperative hemodynamic consequences of portosystemic shunt procedures, such as transjugular intrahepatic portosystemic stent shunt (TIPS) (see Chapter 96; Fung et al, 1998), and for diagnosis of cirrhosis and portal hypertension (Iwao et al, 1997). In normal subjects, portal blood flow of 600 to 900 mL/min was reported (Brown et al, 1989; Moriyasu et al, 1986), whereas blood flow in the common hepatic artery was reported to be approximately 250 mL/min (Nakamura et al, 1989). The use of color Doppler has improved the suitability of the Doppler method for routine clinical use (Rosemurgy et al, 1997). The availability of ultrasound echo-enhancing materials, such as the galactose-based microbubble agent Levovist (Ernst et al, 1996), may further improve the precision of hepatic blood flow measurement and imaging using the Doppler technique.

Total Liver Blood Flow

Clearance Techniques

The rate of disappearance from the bloodstream of an indicator substance exclusively cleared by the liver is proportional to LBF. First applied to humans by Bradley and colleagues in 1945, indirect clearance methods of LBF measurement rely on the Fick equation. The flow measurement obtained by Bradley's group depended on the fact that intravenously injected bromosulfophthalein is removed from the bloodstream and into the bile entirely by hepatocytes. They derived a value for the rate of hepatic bromosulfophthalein removal indirectly by determining the rate of intravenous infusion of dye that maintained the arterial concentration at a constant level, and by measuring the arteriovenous concentration difference of bromosulfophthalein, they were able to calculate total hepatic blood flow. The mean value obtained in a group of normal subjects was 1.5 L/min.

Other substances dependent on hepatocyte extraction into bile have also been applied, such as indocyanine green (Caesar et al, 1961). None of these substances achieve complete hepatic removal, and hepatic vein cannulation is necessary to allow calculation of the true extraction efficiency. Many investigators now use a simplified version of the original method, in which indocyanine green is administered as a bolus, instead of as an infusion, and hepatic extraction efficiency is determined from an analysis of the clearance curve derived from blood samples taken from a peripheral vein, instead of from the hepatic vein (Grainger et al, 1983). Limitations of this technique include extrahepatic shunting, which is common in liver disease and results in an underestimation of blood flow. Other hepatic clearance techniques have been used, such as colloidal clearance by the hepatic Kupffer cells (Dobson & Jones, 1952) and hepatocyte removal of galactose (Keiding, 1988), sorbitol (Zeeh et al, 1988), rose bengal (Combes, 1960), or propranolol (George, 1979). The more complete hepatic extraction of these substances overcomes the need to cannulate a hepatic vein in patients with normal liver function.

A modification of the colloid extraction method developed in the 1980s allows the derivation of the ratio of hepatic arterial to total LBF, termed the *hepatic perfusion index*. The basis of the technique is the ability to determine by dynamic scintigraphy the temporal separation of accumulating hepatic activity from the arterial and portal supplies after the intravenous administration of a bolus of technetium-99m–sulfur colloid (Fleming et al, 1981; Parkin et al, 1983).

Indicator Dilution

The indicator dilution method relies on the application of the Stewart-Hamilton principle, also derived from the Fick equation (Stewart, 1897). In principle, the hepatic blood flow is proportional to the amount of hepatic blood that has diluted an introduced indicator. This method involves the injection into the hepatic artery and portal vein of a labeled substance that is not removed by the liver; changes in hepatic vein concentration are measured by blood sampling or by monitoring the hepatic isotope activity with an external detector. Such a method is therefore independent of hepatocellular function and reliable, provided the indicator remains in the vascular space and is not excreted prior to sampling. In addition, sampling must not be done in such a manner that affects hepatic circulation, or not more than 30 mL/min in dogs (Cohn et al, 1969).

Portal vein flow may be determined separately using a modification of this technique by sampling portal blood after splenic vein or superior mesenteric artery injection (Chiandussi et al, 1968; Huet et al, 1973). Hepatic artery flow may be calculated as the difference between total hepatic flow and portal flow. In addition, a modified thermal dilution technique has been used to measure portal blood flow in humans (Biber et al, 1983). Indicator dilution methods overestimate true blood flow to hepatic tissue when intrahepatic or extrahepatic shunts are present, although it is possible to measure azygos blood flow by thermal dilution in patients with cirrhosis (Bosch & Groszmann, 1984).

Indicator Fractionation

The measurement of regional blood flow by fractional distribution of cardiac output was first described by Sapirstein in 1956. Briefly, a known amount of radioactive microspheres is injected into the left ventricle, and a reference sample is withdrawn from a peripheral artery at a known rate. The microspheres are then extracted from the various vascular beds, where they have lodged in proportion to the cardiac output. The hepatic arterial blood flow is determined directly by this method, but the portal flow contribution is found indirectly by addition of the flow values in the prehepatic splanchnic organs. Examination of the intrahepatic distribution of microspheres provides a means of assessing the pattern of arterial flow in different regions of the liver (Greenway & Oshiro, 1972). Because the microsphere method requires the postmortem removal of the organs of interest for radioactivity or colorimetric measurement, the additional determination of tissue weight enables flow per gram (i.e., tissue perfusion) to be calculated. Microspheres

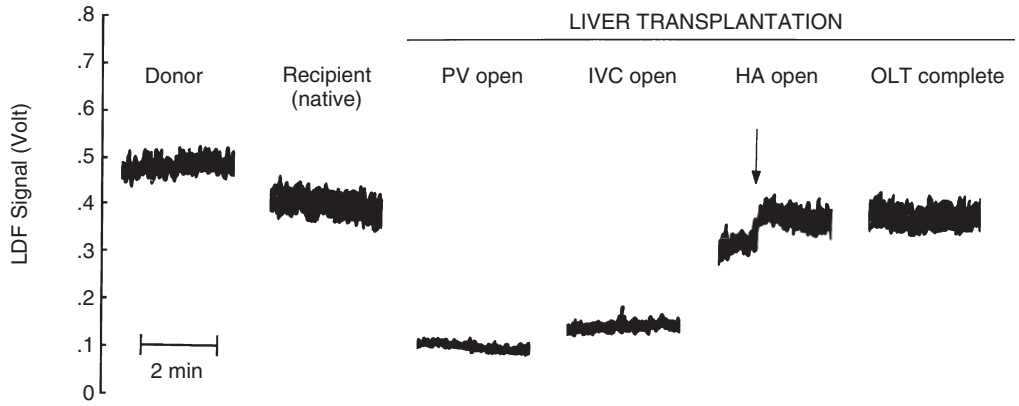


FIGURE 4.3. LDF measurements during a single liver transplantation in the rat. The *arrow* shows the point at which the hepatic artery was opened. HA, hepatic artery; IVC, inferior vena cava; LDF, laser Doppler flowmetry; OLT, orthotopic liver transplantation; PV, portal vein. *(From Wheatley AM, Zhao D, 1993: Intraoperative assessment by laser Doppler flowmetry of hepatic perfusion during orthotopic liver transplantation in the rat. Transplantation 56:1315-1318.)*

may be employed to determine the extent of portosystemic shunts: the fractional distribution in the liver may be measured with respect to systemic (lung) activity after portal vein injection, or it may be estimated by injecting a second radioactive microsphere directly into the splenic or mesenteric venous system (Groszmann et al, 1982).

Hepatic Tissue Perfusion

Inert Gas Clearance

By exploiting the fact that radioactive gases such as krypton (^{85}Kr) and xenon (^{133}Xe) distribute equally between tissue and blood according to a specific partition coefficient, the rate of clearance of such gases can be measured after their injection into the hepatic blood supply. After injection and rapid diffusion throughout the liver, the gas clears from the tissue into the blood and is almost completely eliminated from the body after a single passage through the lungs. The clearance rate is proportional to hepatic tissue perfusion, which may be calculated using a standard formula (Leiberman et al, 1978). Beta-emissions of ^{85}Kr are recorded by a Geiger-Müller tube or semiconductor (silicon) detector placed on or immediately above the exposed liver surface, while the γ-emissions of ^{133}Xe are monitored transcutaneously by a single scintillation crystal or a γ-camera; the latter device allows simultaneous measurement of hepatic tissue perfusion in many regions of interest.

Inert gas techniques involve minimal trauma to the patient, and their accuracy is not markedly affected by the presence of hepatic cellular disease or nonperfusion shunts; however, some variability does occur, even within the same subject, when multiple studies are performed. The first to use the inert gas method in the hepatic circulation were Aronsen and colleagues (1966), who recorded the γ-emissions of ^{133}Xe after the injection of a saline solution of the isotope into the portal vein.

Laser Doppler Flowmetry

Laser Doppler flowmetry (LDF) is a more recent but established technique for the real-time measurement of microvascular red blood cell perfusion in the liver. By illuminating the tissue with low-power laser light and capturing the backscattered light with independent photodetectors, the Doppler shift of moving cells can be transmitted as an electrical signal. Linearity of the LDF signal from the liver with total organ perfusion has been shown (Almond & Wheatley, 1992; Shepherd et al, 1983, 1987), and the technique has been shown to be sensitive to rapid changes in organ flow (Almond & Wheatley, 1992). In a rat model, the technique provided a good measure of hepatic perfusion in vivo (Wheatley et al, 1993a; Fig. 4.3). LDF has also been used successfully to assess LBF during shock and resuscitation (Wang et al, 1995) and during drug-induced changes in LBF in the rat (Kurihara et al, 1992), and the technique has been applied successfully to measure LBF during liver transplantation in humans (Seifalian et al, 1997). A major drawback of the technique is that, owing to the small volume of tissue interrogated by the laser, the LDF signal can only be used to measure arbitrary, instead of absolute, blood perfusion in a single area. The development of laser Doppler perfusion imaging devices that estimate tissue perfusion by scanning an area of tissue using a laser may overcome the problem of signal calibration (Wardell et al, 1993).

In Vivo Fluorescent Microscopy

Intravital microscopy was first described in the microvessels of the frog tongue by Waller in 1846. Using this technique, individual sinusoids and terminal venules can be visualized, and changes in their diameters and the velocities with which erythrocytes pass through them can be seen (Menger & Messmer, 1991; Fig. 4.4). The introduction of fluorescent dyes has broadened the spectrum of in vivo microscopy in the liver from morphologic analysis to the study of pathologic events. However, from a hemodynamic point of view, intravital fluorescent microscopy has problems of interpretation (Sherman et al, 1990). In perfused liver, a 2.5-fold increase in portal venous blood flow has been found to be associated with only a 22% increase in sinusoidal red blood cell velocity, suggesting that changes in portal venous blood flow have only a minor effect on the capillary transit time (Sherman et al, 1996). In the regenerating liver; however, a 50% increase in portal venous blood flow resulted in a similar (66%) increase in sinusoidal red blood cell velocity (Wheatley et al, 1996; Zhang et al, 1997).

Near-Infrared Spectroscopy

Near-infrared spectroscopy is a new noninvasive technique that utilizes light transmission and absorption to measure

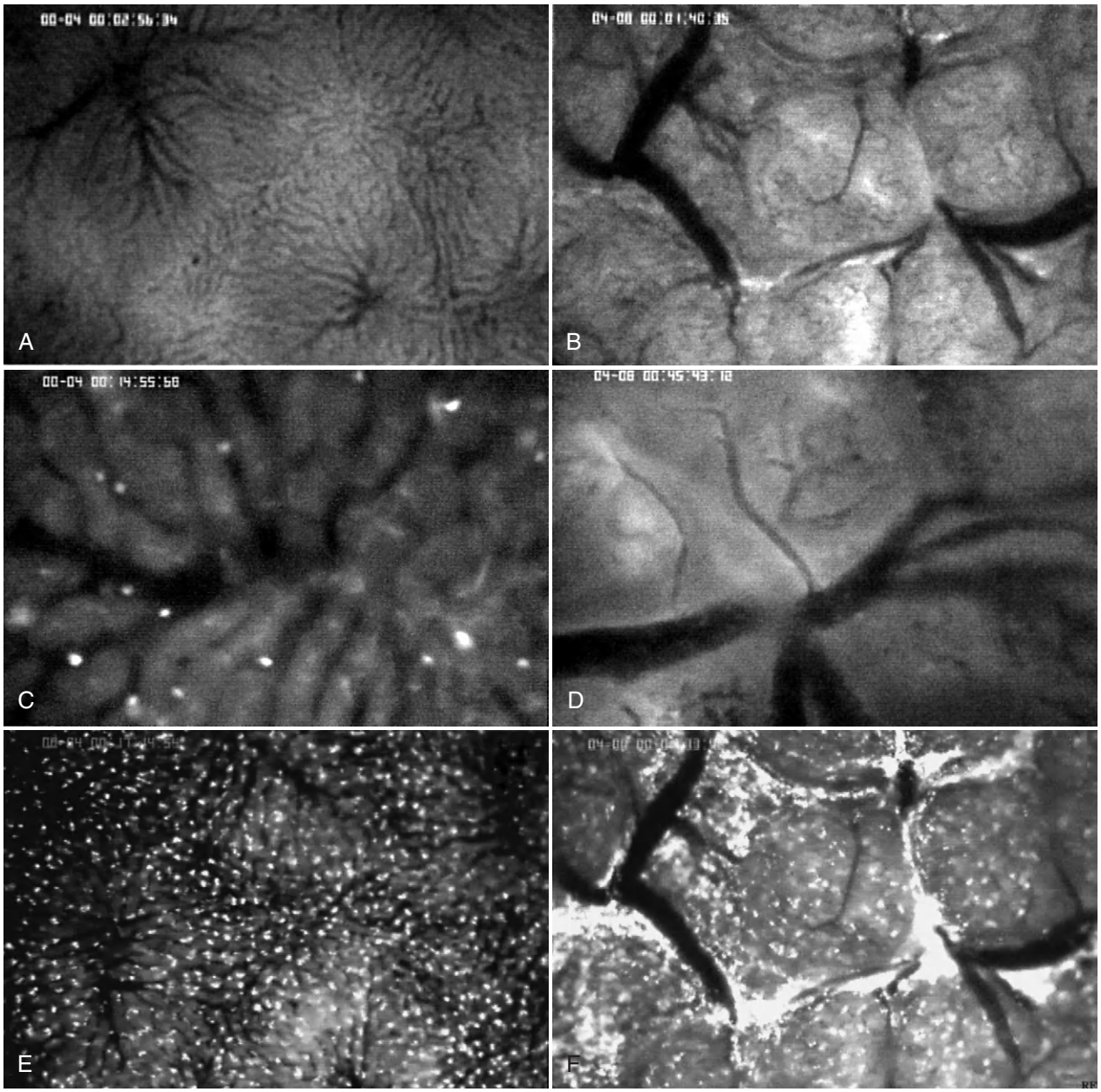


FIGURE 4.4. Hepatic hemodynamic and cellular alterations observed in cirrhotic livers with intravital fluorescent microscopy. Note the characteristic alterations in cirrhotic livers with regard to distension of the central veins (**A,** control vs. **B,** cirrhotic), reduction in number of sinusoids feeding directly into the central veins (**C,** control vs. **D,** cirrhotic), and movement of hepatic stellate cells (as measured by their vitamin A autofluorescence) from a homogeneous distribution in control livers (**E**) to a heterogeneous distribution focused around and along fibrous bands connecting the central veins (**F**).

hemoglobin and mitochondrial oxygenation. In contrast to visible light, which can only penetrate a few millimeters, near-infrared light (700 to 1000 nm) can be detected through up to 80 mm of tissue. The application of this technology to monitor liver oxygenation has been validated in models of endotoxic shock in pigs (Nadhum, 2006) and by intraoperative quantification of congestion and mitochondrial redox during hepatic vein occlusion in living-donor transplantation (Ohdan, 2003).

New and Future Developments

Orthogonal polarized spectral imaging has been used to obtain images of the liver microcirculation comparable to those of fluorescence microscopy but without the need for fluorescent dyes (Langer, 2001). This system relies on the absorbance of hemoglobin and can discriminate a single red blood cell in an individual capillary with a diameter of 5 microns. Studies with hand-held devices using this technology have been applied to healthy living donors to obtain sinusoidal red blood cell velocity and columetric blood flow (Puhl et al, 2003). A recent successor to spectral imaging is sidestream dark field imaging, whereby a light guide surrounded by diodes can detect both red and white blood cells in the microcirculation without the surface reflections (Czerny et al, 2009). Portal venous blood flow measured by noninvasive magnetic resonance imaging (MRI) has been

found to correlate well with flow measured by Doppler ultrasound flow probes (Pelc et al, 1992); subsequently, the technique has been used to measure portal venous blood flow in human liver transplantation candidates (Kuo et al, 1995). Further methodology improvements in MRI (e.g., dynamic contrast enhancement) and in other techniques, such as positron emission tomography, may lead to their increasing use in the study of hepatic hemodynamics in humans (Chow et al, 2003).

CLINICAL RELEVANCE

Hemorrhagic Shock, Hypoperfusion, and Ischemia-Reperfusion Injury

Total LBF decreases approximately in relation to the degree of the hemorrhage, and portal venous blood flow decreases in parallel to cardiac output; but similar to the coronary, pulmonary, and cerebral circulations, hepatic arterial flow does not decrease until extremely low blood pressures are reached. As a result, the hepatic oxygen supply tends to be maintained, although oxygen extraction greatly increases to preserve normal total oxygen consumption (Smith et al, 1979). Hepatic blood volume can increase significantly in cardiac failure and can compensate up to 25% of hemorrhage from its large capacitance vessels (Lautt, 2007).

The clinical entity known as *shock liver* has long been recognized, typically related to cardiogenic or hemorrhagic shock (Birgens et al, 1978; Bynum et al, 1979). Hepatic dysfunction caused by hypoperfusion is manifested pathologically by centrilobular necrosis and clinically by abdominal pain, cholestatic jaundice, and marked elevation of serum transaminases. Three phases of liver injury attributed to ischemia were proposed by Champion, whereby the initial hepatic dysfunction would resolve as long as no additional insults (e.g., sepsis) were incurred (Champion et al, 1976). Gottlieb and colleagues (1983) showed that hepatic dysfunction in humans after trauma was related to a reduced hepatic blood flow rate up to 70% of resting levels. Hepatic blood flow was markedly reduced after injury, and although total splanchnic oxygen delivery was decreased, oxygen consumption remained normal as a result of increased hepatic extraction.

In the ischemic state, upregulation of acute-phase proteins (C-reactive protein, fibrinogen, ceruloplasmin, haptoglobin) is prioritized over production of other hepatic proteins such as albumin and transferrin (Sganga et al, 1985).

More recently, hemorrhagic shock has been recognized to result in generalized vascular endothelial dysfunction and impaired endothelial biosynthesis of NO. Endothelial NO that continues to be expressed by the liver during ischemia is believed to protect against the initial hepatic injury arising from severe hemorrhage. By contrast, more prolonged hemorrhagic shock (>6 hours' duration) induces greatly increased production of NO owing to activation of an inducible NO synthase enzyme in hepatocytes and Kupffer cells (Peitzman et al, 1995).

Survival has been demonstrated after portal vein ligation to control hemorrhage after traumatic injury (Pachter et al, 1979) or after temporary portal occlusion during difficult biliary tract surgery. Similarly, survival after hepatic artery ligation for trauma, aneurysm, hemobilia, or neoplasms has been described (Rappaport & Schneiderman, 1976). In the transplantation era, the consequences of ischemia and reperfusion for the liver have been increasingly investigated and understood. The damage to the hepatic endothelium and parenchyma that results from postischemic reperfusion is caused by numerous interrelated phenomena, including the action of locally liberated oxygen-derived free radicals and excess formation of vasoconstrictor agents (Wendon, 1999). Endogenous NO tends to protect the liver in the early reperfusion period after hepatic ischemia (Shimamura et al, 1996; Wang et al, 1995). Ischemia is also the primary signal for heat-shock protein production in liver tissue. Experimental studies of heat-shock protein preconditioning through intermittent portal clamping demonstrated attenuated transaminase elevations and improved bile production after ischemia (Terajima et al, 1999).

Liver Atrophy

Liver atrophy results from a significant reduction of LBF containing hepatotrophic substances (see Chapter 5). The degree of atrophy depends on the degree of blood flow deprivation and may be distributed according to the source of deprivation, including portal venous or hepatic artery blood flow or their combination.

Atrophy and fatty degeneration of the canine liver after total portal diversion through an Eck fistula initially was reported more than a century ago (Hahn et al, 1893). Partial or complete diversion of portal vein blood flow from the liver results in atrophy. Complete portal venous flow diversion with interruption of all portal venous collaterals results in more profound liver atrophy than the partial deviation of portal venous flow resulting from side-to-side portacaval anastomoses (Bollman, 1961). A precise relationship between the degree of liver atrophy and the reduction of portal venous blood flow is still to be determined, primarily because of the relative composition and contribution of portal flow and resultant compensatory hepatic arterial flow.

Liver atrophy after portal diversion is not believed to be the result of a decrease in absolute volume flow but instead is due to the effective loss of hepatotrophic substances in the portal blood. Rats subjected to portal flow diversion with portacaval transposition had a decrease in relative liver weight (Guest et al, 1977) despite the effective preservation of portal perfusion from the inferior vena cava (Ryan et al, 1978). Dogs with "partial portacaval transposition" (Marchioro et al, 1967) or "splanchnic flow division" (Starzl et al, 1973, 1975) with diversion of pancreaticogastroduodenosplenic blood had atrophy in liver lobes, although normal tissue perfusion was shown in all regions of the liver (Mathie et al, 1979). Starzl hypothesized that insulin was the factor responsible for preventing atrophy.

The fate of the liver after ligation of the hepatic artery depends largely on the extent of a functional collateral arterial circulation (Rappaport & Schneiderman, 1976). If limited collaterals are present, liver infarction and necrosis may occur after hepatic artery ligation, resulting in death. However, hepatic artery ligation results only in transient ischemic changes in the periphery of the hepatic acinus (zone 3) in the presence of adequate collaterals. Atrophy after hepatic artery ligation can occur in liver segments that have compensatory collateral supply to prevent necrosis. The effects of hepatic artery flow absence are magnified by the presence of low portal venous blood flow, limited oxygen saturation, and superimposed infection (Rappaport & Schneiderman, 1976). Histologically, arterial obstruction results in ischemic changes such as mitochondrial swelling, cell membrane disruption, platelet

aggregation, and widening of the spaces of Disse (Mallet-Guy et al, 1972).

Liver Resection and Regeneration

As exemplified in Greek mythology by the myth of Prometheus, the adult liver exhibits a remarkable potential to restore its cellular mass in response to injury through hepatocyte hyperplasia. After the removal of two thirds of liver mass in the rat by partial hepatectomy, liver mass and function are fully recovered by 2 to 3 weeks. In the early stages of regeneration, as a consequence of hepatocyte division, clusters of hepatocytes develop with a reduced distribution of sinusoids (Martinez-Hernandez & Amenta, 1995). Hepatic regeneration of the normal liver remnant proceeds rapidly after partial hepatic resection (see Chapters 4 and 80; Aronsen et al, 1970; Blumgart et al, 1971).

Major resection is associated with a significant and persistent increase in portal pressure (Lee et al, 1987; Morsiani et al, 1995; Wu et al, 1993). Partial liver resection without devascularization normally would be expected to produce little change in total blood flow to the liver. This occurs because the major contributor to total flow, the portal vein, is affected less by events occurring within the liver than by control mechanisms in the arterial resistance vessels of the prehepatic splanchnic bed. On the other hand, the failure of the liver to directly control its portal venous flow may have the result of portal hyperperfusion of a reduced parenchymal mass. Because essentially the same total blood flow is redistributed to a smaller mass of liver tissue, a corresponding increase in tissue perfusion (mL/min per unit tissue weight) would be anticipated in the in situ remnant. Experimental studies support these expectations; an increase in hepatic tissue perfusion was observed in rats immediately after two-thirds hepatectomy (Rice et al, 1977; Wheatley et al, 1993b; Wu et al, 1993). This increase in hepatic perfusion is due primarily to portal venous inflow (Wu et al, 1993), because hepatic arterial blood flow is low, and hepatic arterial resistance is high even 24 hours after partial hepatectomy in rats (Wheatley et al, 1996). Similar studies in patients showed an immediate increase in tissue perfusion of approximately 120% in the remnant (Mathie & Blumgart, 1982). Recent experimental evidence has suggested that intrahepatic shear stress from increased portal flow is a regulator of liver regeneration (Schoen et al, 2001). The significance of blood flow in relation to liver regeneration has been debated frequently in the years since Mann (1944) suggested that regenerative hyperplasia of the liver after partial resection was a function of portal blood flow, and that the process could be prevented by portal flow diversion. However, regenerative hyperplasia normally occurs after partial liver resection in portacavally transposed animals, in which there is no direct supply of portal blood nor the usual posthepatectomy increase in hepatic tissue perfusion. A similar response is seen during portal vein embolization for preoperative expansion of the liver remnant (see Chapter 93).

Blood Flow in Hepatic Tumors

It has been demonstrated that tumors of the liver, whether primary or secondary, are perfused almost exclusively with arterial blood (Breedis & Young, 1954). Several investigators have attempted to achieve differential diagnosis of patients by measuring the proportion of the hepatic arterial contribution to total flow, adopting the hepatic perfusion index obtained by scintigraphy (Leveson et al, 1985) or the Doppler perfusion index obtained by ultrasound (Leen et al, 1991a). Such measurements have shown an increased hepatic arterial contribution in patients with confirmed liver metastases compared with normal subjects. Patients who have colorectal cancer with no observed liver metastases were found to have altered hemodynamics that overlapped those of the other groups, suggesting the presence of occult hepatic disease (Leen et al, 1991b). The Doppler perfusion index has been shown to be more sensitive than computed tomography, conventional ultrasound, or laparotomy alone in the detection of colorectal liver metastases (Leen et al, 1995).

Taking advantage of this phenomenon, the application of the vasoconstrictors epinephrine, phenylephrine, or angiotensin has improved cytotoxic drug delivery to tumor-bearing areas in human and animal models (Bloom et al, 1987; Goldberg et al, 1991; Hemingway et al, 1991). This approach is feasible because the neovasculature of tumor tissue lacks smooth muscle and therefore does not respond to vasoconstrictor agents, enabling increased delivery of chemotherapeutic drugs. Biodegradable microspheres also have been used for enhancing targeted therapy; they cause temporary blood flow interruption, resulting in improved uptake of chemotherapeutic agents in tumor tissue and consequent reduced systemic toxicity (Ball, 1991). Multiple drugs have been utilized in the palliative setting for percutaneous intrarterial instillation, and these can be loaded into the two current commercially available microsphere systems, DC Bead and QuadraSphere (Liapi et al, 2010).

Bile Duct Obstruction

Bile duct obstruction can affect hepatic hemodynamics significantly (see Chapter 7). In general, LBF is reduced in the presence of chronic biliary obstruction, leading to hepatic dysfunction. Conversely, acute increases in bile duct pressure from early obstruction result in a reflexive increase in LBF, which attempts to maintain adequate flow in the face of an increased pressure gradient opposing secretion and excretion of bile. Most evidence suggests that the hemodynamic response of the liver to biliary obstruction is related, directly or indirectly, to changes in bile duct pressure. Given the limited space of Mall in the portal triad, it is conceivable that increased biliary pressures may compress the portal capacitance vessels, leading to increased arterial flow (Kanda et al, 1996). Nagorney and colleagues (1982) showed that acute serial increases in bile duct pressure in dogs with complete bile duct obstruction increased hepatic arterial blood flow by 250% but did not affect portal venous blood flow.

Chronic bile duct obstruction is associated with a decrease in total LBF. In addition, dilation of the sinusoids and elevation of portal pressure in dogs was noted after 4 weeks of complete bile duct obstruction (Ohlsson et al, 1970). Relief of long-term obstruction does not result in the return of normal hemodynamics, suggesting irreversible intrahepatic vascular damage (Aronsen et al, 1969). Furthermore a 23% reduction in effective LBF persisted for 1 to 5 years after operative decompression in patients with choledocholithiasis and jaundice for more than 2 weeks preoperatively (Aronsen, 1968). Hunt (1979) serially measured LBF daily for 1 week after bile duct ligation in rats, using the ^{133}Xe clearance technique to document the early hemodynamic response. Total LBF decreased steadily after the first postoperative day to a plateau level of approximately 50%

of the preoperative value 5 days after operation. Mathie and colleagues (1988) confirmed the decrease in total LBF after bile duct ligation by measuring the individual portal venous and hepatic arterial components of LBF. Using electromagnetic flowmeters in dogs with complete bile duct ligation, hepatic arterial and portal venous blood flow were observed to decrease by 36% and 44%, respectively; they also showed a 200% increase in intrahepatic portal resistance but a lesser increase in hepatic arterial resistance. Similarly, Bosch and others (1983) showed that dogs with chronic bile duct ligation had decreased portal venous flow and had developed sinusoidal portal hypertension and extensive portosystemic shunting.

The precise mechanism for reduction in LBF after chronic bile duct obstruction is unknown. Although increased portal vascular resistance is the accepted underlying cause, the primary site of this resistance change has been considered to be presinusoidal (Reuter & Chuang, 1976), sinusoidal (Bosch et al, 1983), or postsinusoidal (Tamakuma et al, 1975). Bosch and colleagues (1983) also showed the development of significant portosystemic shunting with an inverse correlation between shunting and portal venous blood flow, suggesting that the site of shunting is predominantly extrahepatic (Ohlsson, 1972).

Chronic biliary obstruction results in two hemodynamic consequences: portal hypertension associated with secondary biliary fibrosis and shock after biliary tract decompression. Approximately 20% of patients with prolonged biliary obstruction develop clinically significant portal hypertension (Adson & Wychulis, 1968; Blumgart et al, 1984; Sedgwick et al, 1966). The operative risk of biliary decompression in these patients is significant. Technical difficulties of stricture repair—dense fibrous adhesions, hilar ductal involvement, and infection—are complicated by the risk of hemorrhage from subhepatic and periductal varices and potential postoperative liver failure. Portosystemic shunts may be performed before biliary decompression in patients with bleeding esophageal varices or previous intraoperative hemorrhage that precluded successful stricture repair (Adson & Wychulis, 1968; Sedgwick et al, 1966).

In addition to the hemodynamic consequences of chronic bile duct obstruction, sudden decompression of the obstructed biliary tree also may have profound hemodynamic effects. Tamakuma and colleagues (1975) studied the significance of clinical shock after biliary decompression and noted that hypotension and shock could develop in the immediate postoperative period. They showed that biliary decompression resulted in an abrupt decrease in wedged hepatic vein pressure, portal vein pressure, and arterial pressure within 30 minutes of decompression. Similarly, Steer and colleagues (1968) reported that rapid needle decompression of an obstructed biliary tree in jaundiced dogs induced a decreased arterial pressure, central venous pressure, and portal venous pressure within 1 hour; they concluded that sudden decompression of chronic biliary obstruction leads to sequestration of fluid within the liver, resulting in a decrease in the effective circulating plasma volume and subsequent hypotension.

Portal Hypertension (See Chapters 70 and 74)

Hemodynamics

Portal hypertension is a state of sustained increase in the intraluminal pressure of the portal vein and its collaterals. A mean pressure greater than 12 mm Hg is the accepted target, as variceal bleeding does not occur at lower pressures than this (Garcia-Tsao et al, 1985). Hemodynamic factors that influence portal hypertension are best understood by application of the flow-resistance principle that applies to the portal venous system. Portal pressure depends on two basic components: portal blood *flow* and hepatic portal vascular *resistance*. Portal hypertension may result from a significant increase in hepatic portal inflow from the prehepatic splanchnic vasculature, an increase in intrahepatic portal resistance, or both. Although simple in concept, multiple factors may influence both the components of the system and the pathophysiology of portal hypertension.

Increased portal pressure, diminished hepatic portal blood flow, and an extensive extrahepatic collateral venous network supplied by a hyperdynamic splanchnic and systemic circulation characterize the hemodynamics of portal hypertension (e.g., in cirrhosis). The traditional view of the source of increased portal pressure is fibrotic encroachment around portal radicles, leading to increased intrahepatic portal resistance. In cirrhotic patients, extrahepatic shunts may account for at least 50% of the portal flow, whereas 80% of portal flow actually reaching the liver has been observed to bypass the sinusoidal vascular bed via intrahepatic shunts (Okuda et al, 1977). The magnitude of extrahepatic shunt flow in patients with cirrhosis was measured directly by thermal dilution assessment of azygos blood flow; a value 300 mL/min greater than in patients without portal hypertension was noted (Bosch & Groszmann, 1984). The hepatic artery probably provides a greater relative contribution to the total LBF in patients with cirrhosis than in normal subjects, although it also was shown that 33% of the arterial blood may flow through intrahepatic shunts to the systemic venous circulation (Groszmann et al, 1977).

The direction of portal blood flow has been proposed as a contributor to the pathophysiology of portal hypertension. The progression of intrahepatic disease and increasing sinusoidal pressure has been postulated as contributing to reversal of flow in the portal vein, which further aggravates the injury by depriving the liver of nutrients (Warren & Muller, 1959). However, reversed, or *hepatofugal,* portal vein flow has rarely been documented. Hemodynamic information from 273 cirrhotic patients collected from the literature in the 1970s revealed no case of spontaneous flow reversal (Moreno et al, 1975), and Gaiani and colleagues (1991) reported an incidence of only 3.1% in a sample of 228 patients.

The hypothesis that the low peripheral vascular resistance in portal hypertension may be caused by the stimulated production of NO induced by endotoxemia was proposed by Vallance and Moncada in 1991. The initial experimental evidence was provided by Pizcueta and others (1992), who showed an increase in systemic and splanchnic vascular resistance in cirrhotic rats after the administration of an NO inhibitor. Although endotoxemia is likely responsible for the decompensation in end-stage cirrhosis, the hemodynamic alterations are due to NO (Lee et al, 1995; Niederberger et al, 1995). Constitutive NO synthase seems to be upregulated in discrete anatomic locations, such as in the endothelium of the mesenteric artery and in the esophageal, gastric, and jejunal mucosa (Mathie, 1999).

Intrahepatic Vascular Resistance in Liver Cirrhosis

Liver cirrhosis occurs in response to chronic liver injury and is characterized primarily by a disruption of hepatic architecture, with the development of fibrous septa and abnormal nodules

and circulation, leading to a sustained increase in portal vascular resistance and portal pressure. In addition, afferent (portal venules and hepatic arterioles) and efferent vessels (hepatic venules) can be found within the fibrous septa (Kelty et al, 1950). The pathogenesis of cirrhosis involves initial hepatocyte necrosis and inflammation with subsequent transformation of hepatic stellate cells into myofibroblasts (see Chapter 6). Microscopically, excessive accumulation of collagen leads to the collagenization of the space of Disse and to Ito cell activation (Greenwel et al, 1991; Martinez-Hernandez, 1985; Martinez-Hernandez & Amenta, 1993). Capillarization of sinusoidal endothelial cells occurs by defenestration or loss of endothelial cell pores and the appearance of a basement membrane (Varin & Huet, 1985). In the cirrhotic liver, the sites of vascular resistance are still unclear; however, because portal and hepatic venules can be found within the fibrous septa, constriction or distortion of portal venules, hepatic venules, or both may be involved (Kelty et al, 1950). As portal venous blood flow progressively decreases in cirrhosis, arterial resistance may decrease through an increase in arterial flow, suggesting an intact buffer response. Studies in cirrhotic rats have demonstrated higher hepatic arterial flows compared with normal controls under baseline conditions (Richter et al, 2000). This finding was confirmed using intraoperative measurements in patients with end-stage cirrhosis undergoing living-donor liver transplantation (Aoki et al, 2005).

Until recently, it was thought that the elevated IHVR in cirrhosis was irreversible. Evidence now suggests that it can be reduced pharmacologically with vasodilators (Bhathal & Grossman, 1985; Reichen & Le, 1986). IHVR can be marginally reduced by prostaglandin E_2 (Ballet, 1991) and isoprenaline and more substantially by nitroprusside, papaverine, and verapamil (Ballet, 1991; Bhathal & Grossman, 1985; Reichen & Le, 1986). Groszmann (1990) reported that intravenous nitroglycerin caused a 24% decrease in IHVR in cirrhotic patients.

In alcoholic patients, a significant correlation is seen between the extent of hepatic stellate cell activation and the level of portal vascular resistance (Rockey & Chung, 1995). Several factors have been implicated in stellate cell activation such as inflammatory mediators, cytokines, and growth factors (Friedman, 1993, 1997; Gandhi et al, 1994; Greenwel et al, 1991) and ET (Pinzani et al, 1996; Rockey & Weisiger, 1996; Rockey et al, 1998). ET-induced contractility of isolated hepatic stellate cells increases in proportion to the degree of hepatic stellate cell activation (Rockey & Weisiger, 1996). Overexpression of ET-1 has been found in patients with cirrhosis (Housset et al, 1993; Rockey & Weisiger, 1996), which probably contributes to the elevated IHVR, probably by increased hepatic stellate cell contraction (Housset et al, 1993; Rockey & Weisiger, 1996). Microscopically, ET-1 receptors (ET_a and ET_b) are detected on all cell types in rat liver, especially Ito cells, as well as in cirrhotic human subjects (Leivas et al, 1995; Pinzani et al, 1996; Rockey et al, 1998). ET-1-induced hepatic sinusoidal contractility is enhanced in ethanol-induced fatty liver but not in cirrhotic liver, indicating that ET-1 may be involved in the regulation of sinusoidal flow in the early stage of liver cirrhosis in rats (Bauer et al, 1995).

Decreased endothelial NO synthesis and release by the liver (Gupta et al, 1998; Rockey & Chung, 1998) coupled with an associated increase in portal vascular resistance may potentiate by the effect of increased ET-1 expression by hepatic endothelial and hepatic stellate cells (Pinzani et al, 1996). The interplay between NO, ET, and other local regulatory mechanisms controlling sinusoidal hemodynamics is depicted in Figure 4.5. Groszmann (1990) suggested that the increased mesenteric blood flow in the hyperdynamic stage of portal hypertension may be relatively less important than the elevated intrahepatic portal resistance in maintaining increased portal pressure. Clinically, the vasodilaton of the splanchnic circulation likely serves to increase flow in the extrahepatic collateral circulation, leading to variceal hemorrhage.

Treatment (See Chapters 70 and 74)

Medical and surgical management strategies for portal hypertension strive to improve patient survival by the reduction of pressure and flow in extrahepatic variceal vessels, mainly esophageal and gastric vessels, while preserving adequate portal flow to the liver. Portosystemic shunting and pharmacologic reduction of portal flow can provide effective decompression, but both deprive the liver of portal flow. Surgical treatment of portal hypertension may be performed by one of the many portosystemic shunt procedures (see Chapter 76B); the initial clinical application of the portacaval shunt was reported 50 years after its description by Eck (Whipple, 1945). The hemodynamic consequences of shunt surgery depend on the particular shunt performed, the nature and severity of the disease, and the hemodynamic condition of the patient. End-to-side portacaval shunts divert all portal blood flow away from the liver, whereas less complete diversions reduce portal flow in proportion to the degree to which the shunt reduces portal pressure. The hepatic artery flow may increase by 100%, but even a maximal flow increase can usually only partly compensate for loss of portal flow (Mathie & Blumgart, 1983a). Hepatic oxygen consumption tends to be maintained by increased oxygen extraction from the available arterial supply.

Total portacaval shunts are very effective in reducing portal pressure and preventing bleeding from esophageal varices. However, because of bypass of the hepatic circulation, liver failure and encephalopathy are common complications of the operation (see Chapter 76A). Therefore, partial shunts—such as the side-to-side (see Chapter 76B), mesocaval (see Chapter 76D), and proximal or distal splenorenal shunts (see Chapter 76C)—have gained popularity. Transjugular intrahepatic portosystemic shunting (TIPS), first reported by Rössle and colleagues (1989), is currently the treatment of choice for recurrent variceal bleeding in patients who are refractory to conservative medical management (see Chapters 75A and 76E; Iannitti & Henderson, 1997).

Pharmacologic reduction of portal hypertension (see Chapter 75B) initially was based largely on an attempt to diminish hepatic portal inflow from the mesenteric vascular bed by the use of vasoconstrictor agents. At a dose that decreases the heart rate by 25%, the β-adrenoceptor antagonist propranolol significantly reduced the risk of rebleeding in cirrhotic patients who were otherwise in good condition (Lebrec et al, 1981). Propranolol exerts its action by two mechanisms: decreased cardiac output as a result of β_1-adrenergic cardiac receptor blockade and antagonism of β_2-adrenoceptors in the splanchnic vasculature that leaves the vasoconstrictive influence of α-adrenergic receptors unopposed, resulting in a decrease portal flow and pressure. Vasopressin causes generalized peripheral vasoconstriction (Bosch et al, 1988), whereas the effect of somatostatin is specific to the splanchnic vascular bed (Kravetz et al, 1984) and is the result of an inhibition of glucagon release

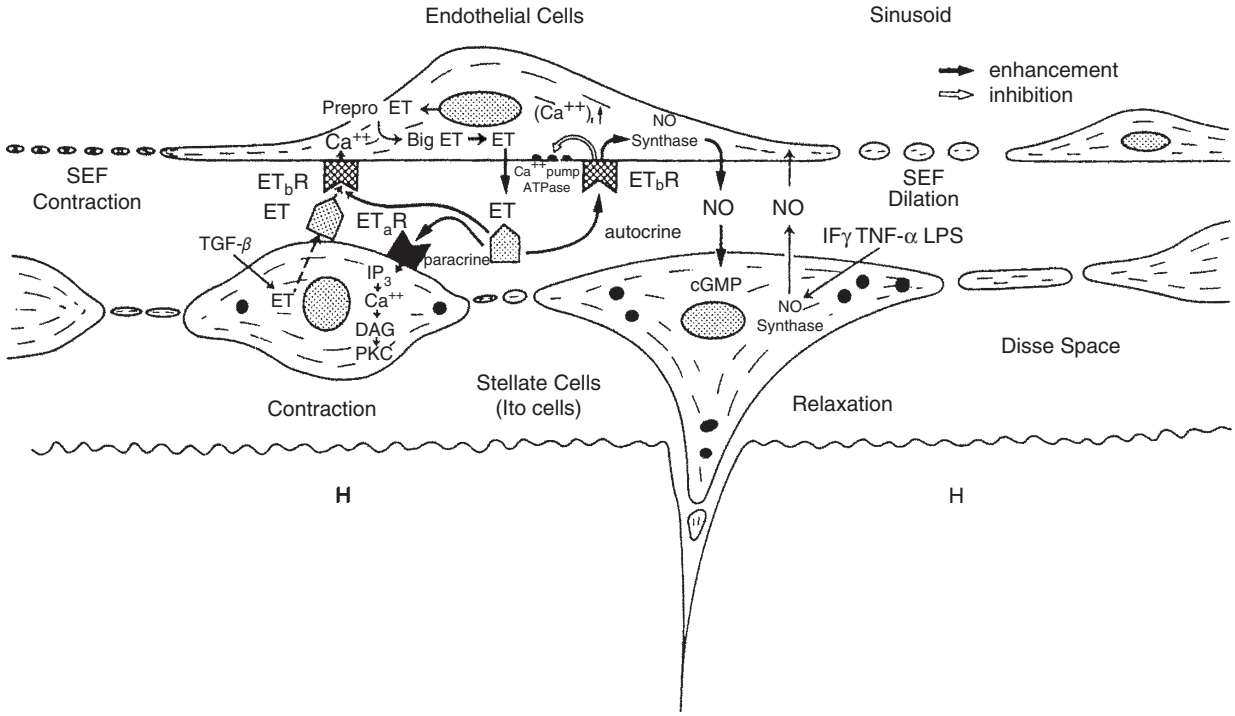


FIGURE 4.5. Local regulatory mechanisms of hepatic sinusoidal microcirculation. [Ca^{++}], concentration of intracytoplasmic free calcium ion; cGMP, cyclic guanosine monophosphate; DAG, diacylglycerol; ET, endothelin; ET_aR, endothelin-α receptor; ET_bR, endothelin-β receptor; H, hepatocyte; IFγ, interferon-γ; IP_3, inositol triphosphate; LPS, lipopolysaccharide; PKC, protein kinase C; SEF, sinusoidal endothelial fenestrae; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α.

and direct vasoconstriction. Somatostatin is at least as effective as vasopressin in controlling bleeding, and with fewer side effects; it may be the agent of choice in acute management of variceal hemorrhage. Serotonin may play a significant role in maintaining increased portal pressure, and smooth muscle serotonin-receptor antagonists have been shown to lower the pressure in cirrhosis (Hadengue et al, 1987; Mastaï et al, 1989).

The nitrovasodilators isosorbide dinitrate and isosorbide mononitrate were observed to lower the portal pressure in portal hypertensive animals (Blei & Gottstein, 1986) and to increase hepatic (but not azygos) blood flow in cirrhotic patients (Navasa et al, 1989), suggesting that they may act by reducing intrahepatic portal vascular resistance. Application of nitroglycerin by transdermal tape to cirrhotic patients resulted in a reduction in portal pressure without affecting hepatic blood flow (Iwao et al, 1991).

These experiments support the previous discussion of NO and ET-1 control of hepatic sinusoidal tone. An ET receptor antagonist was reported to reduce portal pressure in cirrhotic rats by nearly 30% (Reichen et al, 1998). The combined effects of the long-acting nitrovasodilator molsidomine plus propranolol have been found by some (Hori et al, 1996) but not others (Garcia-Pagán et al, 1996) to be a more effective portal hypotensive regimen than propanolol alone.

Hemodynamic Studies and Human Liver Transplantation

Orthotopic liver transplantation (OLT) (see Chapters 97 and 98) of a normal donor organ does not normalize the splanchnic and systemic hemodynamic alterations of end-stage liver disease (Henderson, 1993). In fact, total hepatic blood flow remains elevated 6 months after OLT (Hadengue et al, 1993; Henderson et al, 1989; Navasa et al, 1993) mainly because of portal venous blood flow (Henderson et al, 1992a, 1992b; Henderson, 1993; Paulsen & Klintmalm, 1992). Azygos flow also remains elevated, and other portosystemic shunts have been documented up to 4 years after OLT (Navasa et al, 1993). Ligation of these portosystemic collateral pathways has been shown to increase portal venous blood flow (Fujimoto et al, 1995). Cardiac output data have been conflicting, with one group reporting persistently elevated values (Hadengue et al, 1993) and others showing decreases 2 weeks and 2 months after OLT (Navasa et al, 1993). Gadano and colleagues (1995) emphasized that factors such as anemia and sepsis may account for the deranged hemodynamics after OLT.

Effect of Liver Transplantation on Liver Blood Flow

Henderson and others (1989) demonstrated that LBF remains elevated for a prolonged period after liver transplantation, suggesting that baseline LBF may be under direct sympathetic control, which is lost after OLT, leading to an unopposed rise. The hemodynamic consequences of OLT in human patients are difficult to interpret for several reasons: 1) the causes of liver failure in end-stage transplant candidates are diverse; 2) immunosuppressive drugs are used, such as cyclosporine, which causes arterial hypertension; and 3) to control systemic hypertension after OLT, patients may also be given vasodilators such as hydralazine, which can cause persistently increased cardiac output.

The hepatic artery buffer reponse is conserved following OLT despite denervation. This was demonstrated in a series of experiments by Payen and colleagues (1990), who serially clamped the portal vein every 12 hours for 7 days following OLT and reported reciprocal increases in hepatic arterial flow.

The advent of living-donor partial liver transplantation has introduced the phenomenon of small-for-size syndrome, whereby the pressure of the full portal flow traveling through a small liver remnant leads to decreased arterial flow, presumably through an intact hepatic arterial buffer response (Michalopoulos, 2010). The reduced hepatic arterial flow is hypothesized to be diverted to the splenic and gastroduodenal circulation. Prospective studies have demonstrated that ligation or embolization of the splenic artery leads to improved hepatic arterial inflow and improved graft function (Lo et al, 2003; Umeda et al, 2007).

Effect of Laparoscopy on Liver Blood Flow

The use of a carbon dioxide pneumoperitoneum in laparoscopic donor surgery has been demonstrated to substantially reduce portal venous flow in parallel with the intraperitoneal pressure (Schilling et al, 1997; Jakimowicz et al, 1998). The hepatic artery buffer response is usually preserved during laparoscopy, however, conflicting data exist in support of the maintenance of this effect in high-pressure pneumoperitoneum. Rat models using fluorescent microspheres supported preserved hepatic arterial flow during decreased portal venous flow (Yokoyama et al, 2002), but this was not supported by others (Richter et al, 2001), who saw a parallel decrease in arterial and portal venous flows during laparoscopy. Some groups have suggested the avoidance of head-up positioning and pressures greater than 15 mm Hg during laparoscopy to preserve LBF (Junghans et al, 1997; Klopfenstein et al, 1998).

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CHAPTER 5

Liver regeneration: mechanisms and clinical relevance

Jeroen De Jonge and Kim Marie Olthoff

LIVER REGENERATION

The ability of the liver to regenerate was recognized by the Greeks in the ancient myth of Prometheus, the Titan god of forethought, who gave fire to the mortals and angered Zeus. Prometheus was chained to the Caucasus mountains, and each day he would be tormented by Zeus' eagle, Ethon, as it devoured Prometheus' liver. Each night, the damaged liver would mend, so the eagle could begin anew, illustrating the incredible capacity of the liver to regenerate.

In contrast to other solid organs, the human liver has the unique ability to regenerate after toxic injury, chronic inflammation, and surgical resection. The terms *regeneration, hyperplasia,* and *hypertrophy* are used synonymously in literature, but *hyperplasia* is the most precise term from a cellular standpoint. The damaged hepatic lobes do not grow back in the same way a lizard's tail regrows, but rather a hyperplastic response is seen, defined as increasing cell numbers in the remnant liver, leading to its hypertrophic appearance and enlargement of the liver (Lory et al, 1994). This process is highly regulated and involves multiple cell types, extrahepatic signals, complex molecular pathways, and cellular interactions. A delicate balance is achieved in the initiation of regeneration and exertion of an intracellular growth response to restore lost liver mass, while maintaining the normal metabolic function necessary for survival. The inability to maintain this process may lead to poor liver function and ultimately liver failure after surgery.

CLINICAL RELEVANCE OF LIVER REGENERATION

Today, liver surgery is routinely and safely accomplished for malignant and benign disease. This substantial progress in both resection and transplantation relies on the ability of the liver to regain most of its functional mass within 2 weeks (Marcos et al, 2000a; Humar et al, 2004; Kamel et al, 2003; Pomfret et al, 2003). Factors that limit the achievement of curative tumor resection and small-for-size (SFS) transplantation are the high morbidity and mortality rates associated with insufficient volume of the liver remnant or graft (Fig. 5.1).

As hepatobiliary and transplant surgeons continue to expand the magnitude and complexity of liver resection and explore beyond the boundaries of transplantation, understanding liver regeneration becomes increasingly relevant. Many tumors once considered unresectable are now amenable to complete resection through induction chemotherapy and innovative treatment strategies to increase liver remnant volume (see Chapters 86 and 88) (Clavien et al, 2007). Portal vein embolization (PVE) or ligation causes atrophy of the ipsilateral hemiliver and hypertrophy of the contralateral side and appears to be particularly valuable in patients who have underlying liver disease (see Chapter 93A). Because of the increased success of liver surgery and improved anesthetic techniques, more patients with underlying liver disease are now considered suitable candidates for liver resection.

There remains, however, a subset of patients who cannot tolerate significant liver resection, often because of the inability of the liver to regenerate appropriately. Patients with underlying cirrhosis have increased morbidity and mortality (Das et al, 2001; Nagasue et al, 1987), and patients with metabolic syndrome, morbid obesity with concomitant steatosis, or nonalcoholic steatohepatitis (NASH) have increased risk of liver failure after liver surgery (Belghiti et al, 2000; McCormack et al, 2007) as do elderly patients with restricted hepatic reserve and decreased regenerative capacity (McCormack et al, 2007). In colorectal malignant disease, about 50% of patients will develop liver metastases in the course of their disease. With substantially improved chemotherapy for colorectal cancer over the last decade, the resectability rate has gradually increased to 20% to 30% (Khatri et al, 2005). As a consequence, more patients are having liver surgery after neoadjuvant or induction chemotherapy, which also has considerable side effects on liver regeneration.

Regeneration is also crucial in liver transplantation (see Chapter 97A). In deceased-donor transplantation, hepatocyte loss occurs in the form of ischemia/reperfusion (I/R) injury owing to the necessary preservation period from procurement to implantation and damage that may have occurred in the donor. Due to the scarcity of organs, more marginal organs are accepted for transplantation; this has increased the need for regeneration in the environment of I/R injury and use of immunosuppressive drugs. One of the landmark advances in liver transplantation is the ability to use partial liver grafts obtained from either a deceased donor or a living donor. In the latter setting, success of the procedure relies on hepatic regeneration in both donor and recipient. The minimal amount of functional liver necessary for successful transplantation is a major concern. Because of the need for regeneration, as well as recovery from concomitant I/R injury, a larger liver mass is needed for transplantation than might be required after liver resection (Tanaka & Yamada, 2005).

BASIC CHARACTERISTICS OF LIVER REGENERATION

Models of Liver Regeneration

In the past 50 years, much has been learned about what initiates liver regeneration, how it is sustained, and what inhibits it. Liver

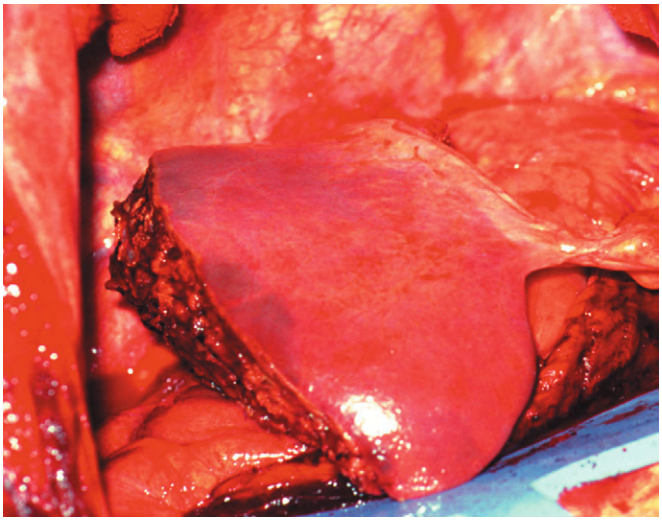


FIGURE 5.1. Remnant liver or liver graft volume limits tumor resection and small-for-size transplantation. Here an example of an "extreme" liver resection, leaving only segment IV of the liver, in case of colorectal liver metastases. In this situation, the patient's recovery depends solely on robust liver regeneration. *(Courtesy C. Verhoef, MD, PhD, Rotterdam, The Netherlands, Erasmus MC).*

regeneration is most clearly shown in the experimental model that was pioneered in 1931 by Higgins and Anderson. In this model, a simple two-thirds partial hepatectomy (PHx) was performed, without damage to the lobes left behind. This led to enlargement of the residual lobes, which made up for the mass of the removed lobes in 5 to 7 days. Other well-known models of liver regeneration are associated with extensive tissue injury and inflammation and include the use of hepatic toxins—such as ethanol (EtOH) (Kaplowitz, 2002), carbon tetrachloride (CCl_4) (Reynolds, 1963), and galactosamine (GalN) (Dabeva & Shafritz, 1993)—bile duct ligation (Kountouras et al, 1984) or portal vein ligation (Bilodeau et al, 1999), and I/R injury (Jaeschke, 1998). Newer models include transgenic albumin promoter urokinase-type plasminogen activator (u-PA) fusion constructs (Heckel et al, 1990) and PHx in Zebrafish (Kan et al, 2009). In each model, different toxic agents injure specific liver cell subpopulations; PHx is therefore the preferred in vivo model to study the regenerative response. It has also been demonstrated that regenerative signaling observed in a rat liver transplant model of I/R injury is similar to that observed after PHx (Debonera et al, 2001).

General Features of Liver Regeneration

Liver regeneration after surgical resection is carried out by proliferation of existing mature cellular populations. These include hepatocytes, biliary and fenestrated endothelial cells, Kupffer cells, and cells of Ito (stellate cells; Fig. 5.2) (Gressner, 1995).

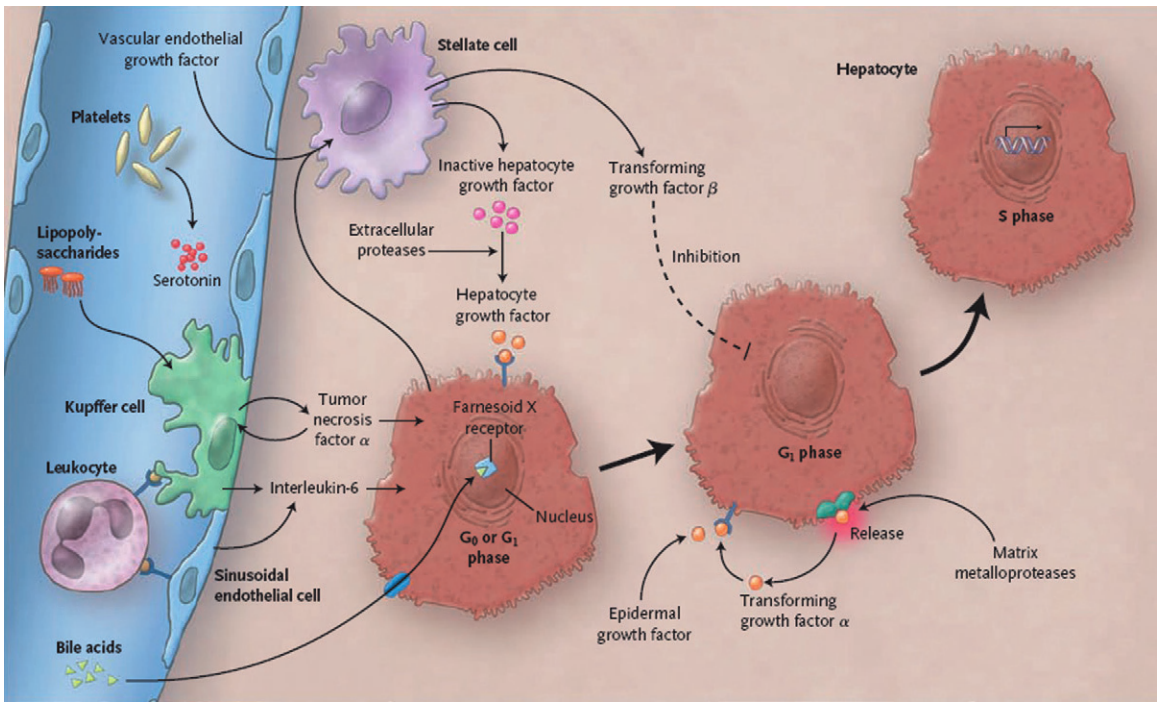


FIGURE 5.2. Pathways of liver regeneration initiated by major hepatectomy. After hepatectomy, nonparenchymal cells—stellate cells, Kupffer cells, leukocytes, and platelets—are activated by soluble factors. As a result, Kupffer cells release tumor necrosis factor-α and interleukin-6. The cytokines cause a priming of the remnant hepatocytes, and concurrently, extracellular proteases, such as urokinase-type plasminogen activator, convert inactive hepatocyte growth factor to its active form. The cytokines and the growth factors act in concert to initiate the reentry of quiescent hepatocytes (in the G_0 phase) into the cell cycle from the G_1 phase to the S phase, resulting in DNA synthesis and hepatocyte proliferation. The metabolic burden is indicated by the accumulation of bile acids in the blood, which enter the hepatocytes and drive increased protein and DNA synthesis. To signal the end of proliferation, transforming growth factor-β blocks further replication. *(From Clavien P-A, et al, 2007: Strategies for safer liver surgery and partial liver transplantation. N Engl J Med 356:1545-1559. Reprinted with permission.)*

The kinetics of cell proliferation and the growth factors produced by proliferating hepatocytes suggest that hepatocytes provide the mitogenic stimuli that lead to proliferation of the other cells; the degree of hepatocyte proliferation is directly proportional to the degree of injury (Bucher & Swaffield, 1964).

Immediately after liver resection, the rate of DNA synthesis in hepatocytes begins to increase, as they exit the resting state of the cell cycle (G_0) and enter G_1, traverse to DNA synthesis (S phase), and ultimately undergo mitosis (M phase). The induction of DNA synthesis occurs later in the nonparenchymal cells, at about 48 hours for Kupffer and biliary epithelial cells and at about 96 hours for endothelial cells (Grisham, 1969; Widmann & Fahimi, 1975). The first peak of DNA synthesis occurs at 40 hours after resection in rodents and at 7 to 10 days in primates. In small animals, the regenerative response returns the liver to the preresection mass in 1 week to 10 days. Clinical studies suggest that significant regeneration in humans is evident within 2 weeks after resection and is nearly complete at 3 months (Nagasue et al, 1987; Yamanaka, 1993). Studies in living donors, however, suggest that many donors do not reach 100% of starting liver volume by 3 months after donating their right lobe, and some are even lacking at one year (Pomfret et al, 2003; Nadalin et al, 2004; Ibrahim et al, 2005).

On a cellular level, hepatocyte proliferation starts in the periportal areas of the lobules (Rabes et al, 1976) and proceeds to the pericentral areas by 36 to 48 hours. Liver histology at day 3 to 4 after PHx is characterized by clumps of small hepatocytes surrounding capillaries, which change into true hepatic sinusoids. The hepatic matrix composition also changes from high laminin content to primarily containing fibronectin and collagen types I and IV. After a 70% hepatectomy, restoration of the original number of hepatocytes theoretically requires 1.66 proliferative cycles per residual hepatocyte. In fact, most of the hepatocytes in the residual lobes (95% in young and 75% in very old rats) participate in one or two proliferative events (Stocker & Heine, 1971). However, hepatocytes have an almost unlimited capacity to regenerate, and transplantation of several hundred healthy hepatocytes can repopulate a whole, damaged liver in a calculated minimum of 69 doublings (Rhim et al, 1994).

Liver Stem Cells

In contrast to other regenerating tissues, such as bone marrow and skin, primary liver regeneration after surgical trauma is not dependent on a small group of progenitor cells (stem cells). However, in some circumstances, such as in response to liver damage inflicted by agents such as galactosamine, hepatocytes are unable to replicate.

Endogenous Hepatic Progenitor Cells

In this situation a population of cells known as *oval cells* proliferates to replace the hepatic parenchyma (Fausto & Campbell, 2003). In humans, hepatic progenitor cells (HPCs) participate in repopulation of the liver after acute massive necrosis and have also been identified in chronic liver disease (Roskams et al, 1998). The oval cells are thought to derive from biliary epithelial cells, and human HPCs seem to originate from the canals of Hering (Theise et al, 1999) and play an important role in acetaminophen-induced injury (Kofman et al, 2005). Recent data suggest that in addition to mature hepatocytes and HPCs, a third compartment of cells can participate in liver regeneration (Alison et al, 2009; Duncan et al, 2009). Several studies in rodents and humans have demonstrated that transplanted bone marrow stem cells can enter the liver from the circulation and give rise to hepatocytes and cholangiocytes (Petersen et al, 1999; Theise et al, 2000a; Alison et al, 2000). These stem cells usually make little contribution to regeneration, but after fusing with metabolically defective hepatocytes, they can be reprogrammed to contribute in a major way to restoring liver function or to stimulating liver regeneration via paracrine effects (Lagasse et al, 2000; Wang et al, 2003a; Kallis et al, 2007).

Exogenous Mobilized Progenitor Cells

Mesenchymal stem cells (MSCs) isolated from human umbilical cords (Yan et al, 2009), adipose tissue (Banas et al, 2008), and bone marrow (Kuo et al, 2008; Abdel Aziz et al, 2007) have been shown to promote liver repair in cases of acute liver damage (e.g., carbon tetrachloride injections). The major fraction of mobilized progenitor stem cells expresses the chemokine receptor CXCR4. At the same time, the mRNA level of its ligand, SDF-1, was increased in the damaged liver tissue. These results provide a clue that CXCR4–SDF-1 interaction may be important for the mobilization of progenitor stem cells from bone marrow to the damaged liver (Khurana & Mukhopadhyay, 2007). In the damaged liver, these MSCs could generate cells that function as normal hepatocytes, but a second mechanism by which MSCs could promote liver repair is secretion of soluble factors. For instance, infusion of human MSC-conditioned medium into rats with acute liver damage improved liver function after 24 hours (Parekkadan et al, 2007; van Poll et al, 2008) with a 90% decrease in apoptotic hepatocytes and a threefold increase in the number of proliferating hepatocytes. Very recently, human liver-derived stem cells were shown to accelerate hepatic regeneration after hepatectomy by shuttling mRNA from microvesicles into the regenerating hepatocytes (Herrera et al, 2009).

Induction of Proliferation: Priming and Cell-Cycle Progression

Within minutes after PHx, specific immediate early genes are activated in remnant hepatocytes (Haber et al, 1993). These genes include protooncogenes, which play an important role in normal cell-cycle progression—such as in *JUN, FOS, MYC,* and *KRAS* (Thompson et al, 1986; Morello et al, 1990; Taub, 2004)—and the transcriptional factors nuclear factor (NF) κB, signal transducer and activator of transcription 3 (STAT3), activator protein-1 (AP-1), and CCAAT enhancer–binding protein β (CEBPβ) (Cressman et al, 1995; FitzGerald et al, 1995). Historically, the onset of liver regeneration has been attributed to a flow-dependent response, by which increased relative flow after PHx resulted in hepatocyte proliferation and hyperplasia (Starzl et al, 1977). Experiments in parasymbiotic rats demonstrated the existence of humoral factors in the induction of liver growth after PHx (Moolten & Bucher, 1967). Interleukin (IL)-6 and tumor necrosis factor (TNF)-α have since been identified as the earliest factors triggering activation of several transcription factors during regeneration (Fig. 5.3) (Cressman et al, 1996; Yamada et al, 1997). In IL-6–deficient or TNF-α receptor–deficient mice, liver regeneration after hepatectomy is delayed (Streetz et al, 2000) but not completely abolished (Michalopoulos et al, 1984; Fujita et al, 2001). Therefore, other blood-derived mitogens, such as hepatocyte growth factor (HGF), were identified as a putative hepatic

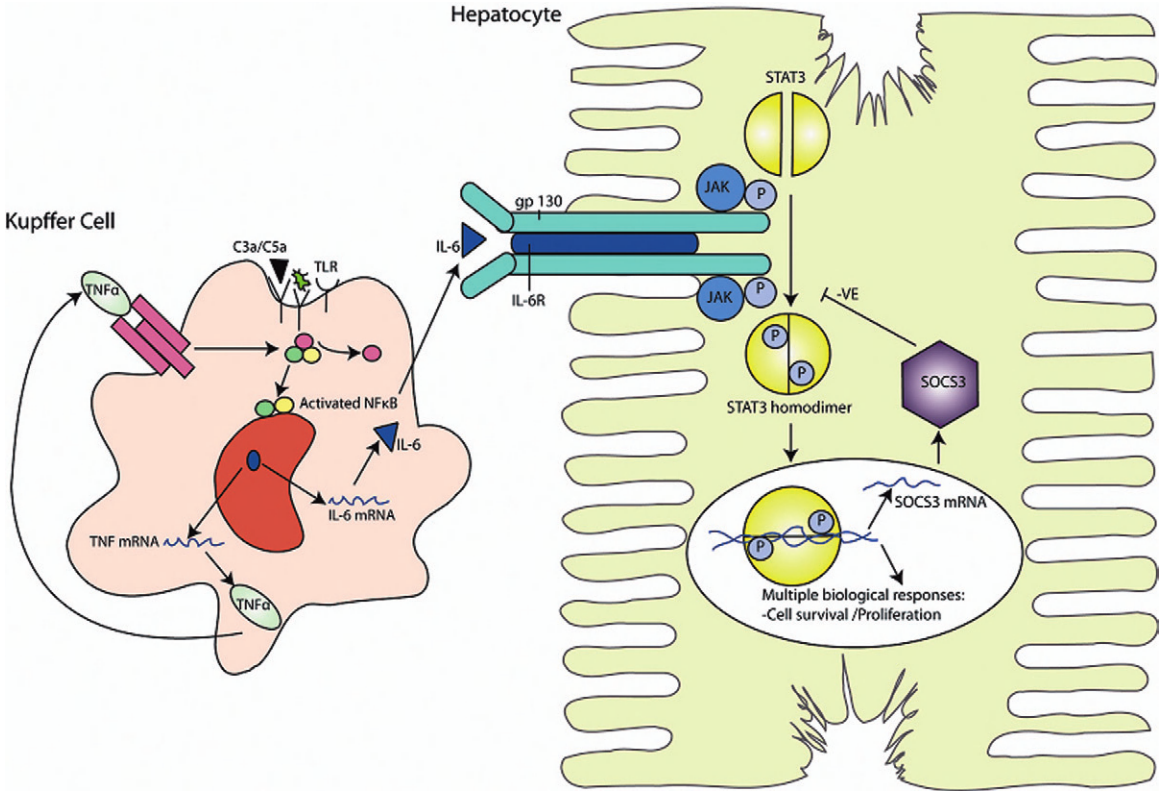


FIGURE 5.3. Stimulated by components of the innate immune system, Kupffer cells produce and secrete interleukin (IL)-6 and tumor necrosis factor-α (TNFα) to kick-start the regenerative response. IL-6 helps stimulate hepatocyte proliferation via transcription 3 (*STAT3*) activation; in turn, this response is negatively regulated by cytokine signaling-3 (SOCS3). *(From Alison et al, 2009: Stem cells in liver regeneration, fibrosis and cancer: the good, the bad and the ugly. J Pathol 217:282-298. Reprinted with permission of John Wiley & Sons.)*

growth factor during liver regeneration (Fausto, 2000). Hepatocytes in normal liver will not respond to mitogenic signals without a set of "priming" events that switch them into a responsive state. This has been described by Webber and colleagues (1994), who identified *priming factors*, involved in initiating and triggering hepatic response to injury, and concomitant *growth factors* and their receptors, which allow competent hepatocytes to progress through the cell cycle. Priming is accomplished by the release of preformed cytokines that subsequently activate transcription factor complexes and allow the cell to exit G_0 into G_1 in the cell cycle. This group includes TNF-α and IL-6 (Aldeguer et al, 2002). Growth factors include the potent hepatocyte mitogens HGF, transforming growth factor (TGF)-α, and heparin-binding epidermal growth factor (HB-EGF). This process is further controlled by *comitogens*—such as insulin, glucagon, steroid and thyroid hormones, and epinephrine—that facilitate activity of the mitogens and by downregulation of growth factor inhibitors, such as activin A and TGF-β.

So far, few factors have been identified as possibly responsible for the release of these priming cytokines and growth factors in the onset of liver regeneration. The first is endotoxin lipopolysaccharide (LPS), produced in the gut by gram-negative bacteria. Circulating LPS appears to be a strong signal for Kupffer cells to start the cascade that results in hepatocyte replication. Rats treated with antibiotics and germ-free rodents have a delayed peak of DNA replication after PHx, confirming the importance of LPS (Cornell et al, 1990). Another major finding is the demonstration that cytokine activation and DNA replication are severely impaired in mice lacking the complement components C3a and C5a (Strey et al, 2003). In particular, mice lacking both C3a and C5a have impaired production of TNF-α and IL-6 after PHx and poor activation of NFκB and STAT3. In the initiation of growth factors, urokinase-type plasminogen activator (uPA) appears to play an important role; uPA and its downstream effector, plasminogen, increase within 1 to 5 minutes after PHx and rapidly cleave the HGF precursor, pro-HGF. Blocking uPA delays the appearance of HGF and thereby delays liver regeneration, whereas blocking plasminogen-activator inhibitor (PAI) accelerates the release of HGF and accelerates liver regeneration (Currier et al, 2003).

More recently, new important factors in the initiation of liver regeneration have been identified. Extracellular adenosine triphosphate (ATP) has emerged as a rapid-acting signaling molecule that leads to quick and transient activation of JNK signaling after PHx, induction of immediate early genes c-*FOS* and c-*JUN*, and activator protein 1 (AP-1) DNA-binding activity (Thevananther et al, 2004; Gonzales et al, 2009). Also recently, an important role for blood platelets in I/R injury and after partial liver resections has been demonstrated. Thrombopenic animals exhibited reduced hepatocyte proliferation 48 hours after the initial ischemic insult, with diminished expression of TNF-α and IL-6 as early as 4 hours after reperfusion (Nocito et al, 2007). In a model of partial hepatectomy, the effect was shown to be mediated by serotonin, because mice lacking platelet serotonin displayed a lack of liver regeneration (Lesurtel et al, 2006). About 95% of all serotonin found in blood is stored in platelets and in vitro, and serotonin is a potent mitogen that stimulates hepatocyte mitosis (Balasubramanian

& Paulose, 1998). The platelet effect on liver regeneration after PHx was mediated through the 5-HT2A and 2B receptor subtypes on hepatocytes and could be restored by injection with the serotonin precursor 5-HTP. These results suggest that a molecular action of serotonin is involved in the induction of hepatoctye proliferation after a major loss of hepatic tissue and that it may involve the release of growth factors, such as IL-6 (Clavien, 2008).

Intracellular Pathways and New Profiling Techniques

The importance of liver regeneration in sustaining life is characterized by the plethora of pathways involved and the fact that liver regeneration is usually only blunted or delayed in experimental models that lack a "critical" pathway. There are nonetheless several well-described patterns in liver regeneration. The immediate early genes that are activated in regenerating liver were first identified by Mohn and colleagues (1990) and Haber and colleagues (1993), who described induction patterns of more than 70 genes activated in the first week after two-thirds PHx in a rat model, genes normally not expressed in the quiescent liver. The development of cDNA microarray technologies set the stage for studying genome-wide expression and expanded this list to about 180 genes (Su et al, 2002; Arai et al, 2003).

A mouse cDNA array has also been used to study the crucial role of IL-6 in liver regeneration in IL-6–deficient mice after hepatectomy, showing a 36% reduction in the early gene expression compared with wild-type mice. In the absence of IL-6, activation of genes such as u-PA receptor (*PLAUR*) and *SERPINE1,* crucial for HGF activation and the MAPK pathway, were remarkably delayed (Li et al, 2002). IL-6 activates the JAK/STAT3 and MAPK signaling pathways via the gp130/IL-6R complex. This leads to activation of an array of immediate and delayed early genes required for normal liver-specific metabolic functions, repair, and protection from injury (Taub, 2003; Zimmers et al, 2003; Wuestefeld et al, 2003). STAT3 is crucial for cells to progress from the G_1 to S phase and for activating the *MYC* gene required for cell-cycle progression. Other intracellular signaling pathways that involve the receptor tyrosine kinases p38 MAPK, pERKs, and *c-jun* N-terminal kinase (JNK) are also rapidly activated.

Progression through the cell cycle is regulated by cyclins and cyclin-dependent kinases (CDKs). Various combinations bind to form kinase complexes that are active at distinct points within the cell cycle and tightly controlled by several mechanisms, including binding by CDK-inhibitory proteins, such as p21. Feedback signals to this process are provided by the suppressor of cytokine signaling-3 (SOCS3) and TGF-β, also regulated by IL-6. Other studies confirmed the importance of NFκB (Arai et al, 2003; Fukuhara et al, 2003; Togo et al, 2004) and showed immediate upregulation of apoptotic genes (*FAS* and caspases) in livers that failed owing to excessive resection (Fig. 5.4) (Morita et al, 2002). The cytokine-induced form of nitric oxide

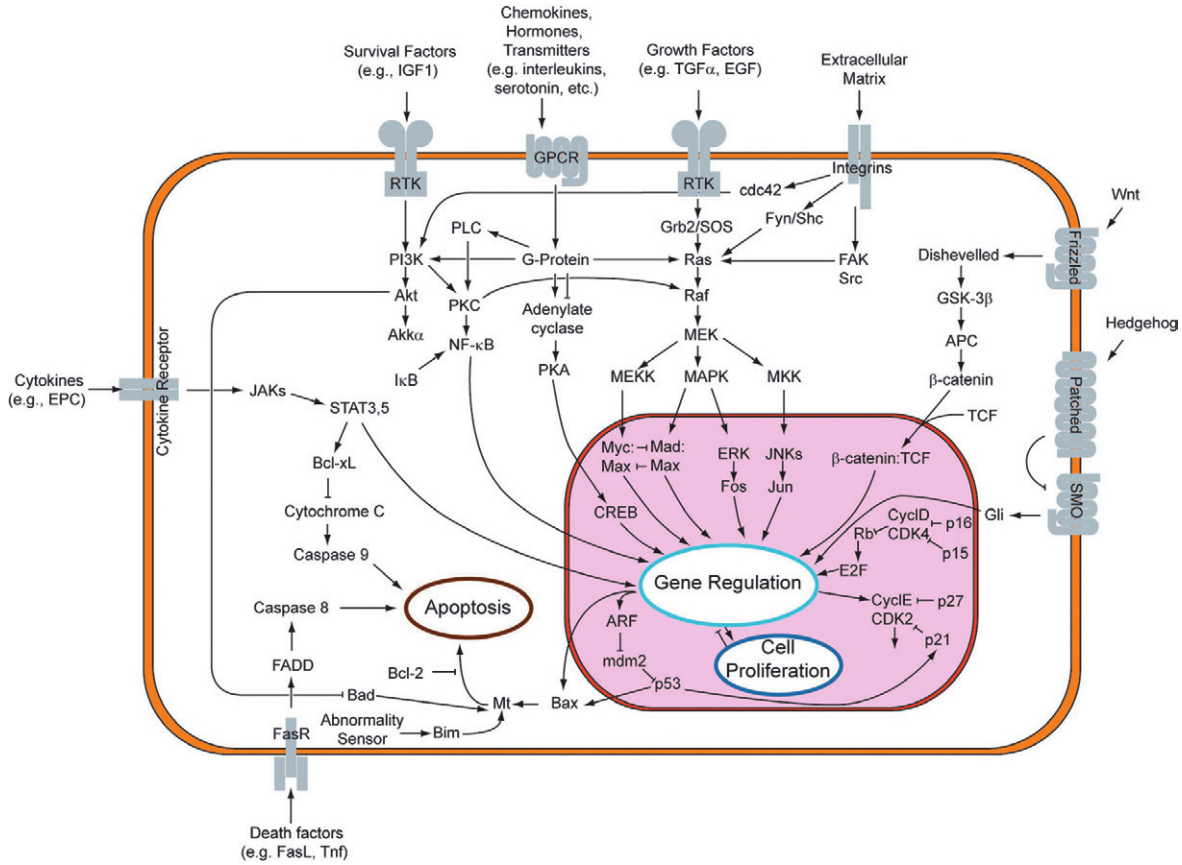


FIGURE 5.4. Intracellular pathways of liver regeneration. Multiple intracellular signaling pathways are rapidly activated. Progression through the cell cycle is regulated by cyclins and cyclin-dependent kinases (CDKs) tightly controlled by several mechanisms, including binding by CDK-inhibitory proteins, such as p21. *(From http://en.wikipedia.org/wiki/File:Signal_transduction_pathways.png.)*

synthase (iNOS) seems to plays an important role in scavenging oxygen radicals and offering protection from apoptosis caused by a proinflammatory response mediated through IL-6 and TNF-α (Rai et al, 1998).

The HGF/*c-Met* pathway is important for sustaining DNA synthesis after injury and activates various downstream pathways that involve PI3K, ERK/MAPK, and AKT1 (Huh et al, 2004). This pathway cross talks with the wnt/β-catenin signaling pathway, which has come to the forefront in liver biology over the last several years (Monga, 2009). Increased levels of HGF results in β-catenin dissociation along with nuclear translocation (Monga, 2002) and upregulation of downstream targets of this pathway, such as cyclin D1, *MYC, PLAUR,* matrix metalloproteinases (MMPs), and epidermal growth factor receptor (Michalopoulos & DeFrances, 1997). Vascular endothelial growth factor (VEGF) interacts with endothelial cells in the liver to increase HGF production from nonparenchymal cells (LeCouter et al, 2003).

In the transplant setting, microarray analysis of SFS rat liver grafts showed upregulation of vasoconstrictive and adhesion molecule genes at early time points postreperfusion, with later increases in genes associated with inflammation and cell death and downregulation of genes related to energy metabolism (Man et al, 2003), which was recently confirmed in the situation of clinical deceased-donor and living-donor liver transplantation (de Jonge et al, 2009).

Remodeling of the Liver

Remodeling of the newly regenerated liver tissue begins with the repopulation and maturation of nonparenchymal cells, such as endothelial cells, stellate cells, and biliary epithelial cells. Newly formed hepatocytes form clusters into which replicating endothelial cells invade to form new sinusoids. To restore normal architecture, stellate cells, located between endothelial cells and hepatocytes, synthesize extracellular matrix proteins and TGF-β1, which can regulate the production of hepatic extracellular matrix (see Chapter 6). VEGF, angiopoietins 1 and 2, TGF-α, fibroblast growth factors (FGFs) 1 and 2, and HGF all are likely involved in the angiogenic process. Angiostatin, an inhibitor of angiogenesis, causes delayed and suppressed liver regeneration in mice (Drixler et al, 2002; Vogten et al, 2004). Remodeling of the extracellular matrix is associated with the activation of the urokinase-plasminogen pathway and the membrane-bound matrix metalloproteinase (MMP) pathway. MMP-9 is one of the most active proteins during liver remodeling and regeneration (Kim et al, 2000). The MMPs—in combination with HGF, EGF, and TGF-β1—act to remodel the extracellular matrix, changing the levels of several extracellular matrix proteins such as collagen, fibronectin, laminin, and entactin. The maturation and thickening of the extracellular matrix seems to have an inhibitory effect on proliferating hepatocytes, potentially signaling the end of rapid regeneration (Kim et al, 1998).

Maintaining Liver Function During Regeneration

After volume loss, hepatocytes must adapt rapidly and seek a compromise between maintenance of continued differentiated function and cellular replication to permit survival. After toxic injury, resection, or transplantation, the balance is dramatically shifted to the crucial tasks of recovery and regeneration at the expense of normal hepatic metabolism. The success of restoring lost liver mass, repairing tissue injury, and resolving inflammation determines the ability of the liver to support normal metabolic function and determines its ability to recover (Fig. 5.5) (Strey et al, 2004). Several of the expressed immediate early genes encode enzymes and proteins involved in regulating gluconeogenesis, a critical process after PHx to compensate for the lost glycogen content and to produce sufficient glucose for the whole organism (Haber et al, 1995; Rosa et al, 1992). Rapid and increased expression of genes involved in glucose homeostasis is seen after PHx in animal models. Most notably, these include *PCK,* glucose-6 phosphatase (G6Pase), and *IGFBP1,* controlled at the level of transcription by insulin (downregulation), glucagon and cAMP (upregulation), and glucocorticoids (upregulation) (Mohn et al, 1990; Diamond et al, 1993). Livers lacking *IGFBP1* display abnormal liver regeneration (Leu et al, 2003).

Decreased expression of genes that oppose gluconeogenesis also occurs rapidly posthepatectomy. Insulin itself can be a potent growth factor mediated through the insulin receptor, and insulin and glucagon have long been established as important "gut-derived" growth factors (Starzl et al, 1975). Liver-specific transcription factors—hepatocyte nuclear factors (HNFs)—play an important role in determining the level of glucose production, fatty acid metabolism, and liver-specific secreted proteins. CAAT/enhancer binding protein (C/EBP) α regulates expression of genes involved in hepatic glucose and lipid homeostasis, has antiproliferative proprieties, and is downregulated during liver regeneration after hepatectomy (Mischoulon et al, 1992; Costa et al, 2003).

During early regeneration, the liver accumulates fat. Neither the mechanisms responsible for nor the functional significance of this transient steatosis has been determined. Suppression of hepatocellular fat accumulation is associated with impaired hepatocellular proliferation after PHx, indicating that hepatocellular fat accumulation is specifically regulated during, and may be essential for, normal liver regeneration (Shteyer et al, 2004). Some data show that decreasing lipid peroxidation levels by vitamin treatment after PHx produces an attenuation of cellular apoptosis and a marked increase in the proliferation process, suggesting that the modulation of lipid peroxidation has a role in the liver regeneration process (Ronco et al, 2002). Hepatocytes in the periportal regions that divide and replicate after PHx require mitochondrial fatty acid β-oxidation. Peroxisome proliferator-activated receptor α, *PPARα,* may be a crucial modulator, controlling energy flux important for repair of liver damage and regeneration (Anderson et al, 2002). Expression of many other liver-specific genes, such as *IGFBP1* and G6Pase, is regulated in the basal state by hepatic nuclear factor-1 (*HNF1A*). The transcriptional activity of *HNF1A* is upregulated during liver regeneration by the binding of *HNF1A* to the growth-induced transcription factors STAT3 and AP-1 (Leu et al, 2001). Together, growth-induced and tissue-specific transcription factors enable the liver to maintain metabolic function, despite the loss of two thirds of its functional mass.

In a microarray analysis of gene expression profiles after living-donor liver transplantation, it was recently demonstrated that C/EBPα was immediately downregulated, as was as HNF4α and PPARα (de Jonge et al, 2009). The immediate, marked downregulation of genes associated with pathways of lipid, fatty acid, and carbohydrate metabolism demonstrate how a liver segment needs to balance regenerating efforts with

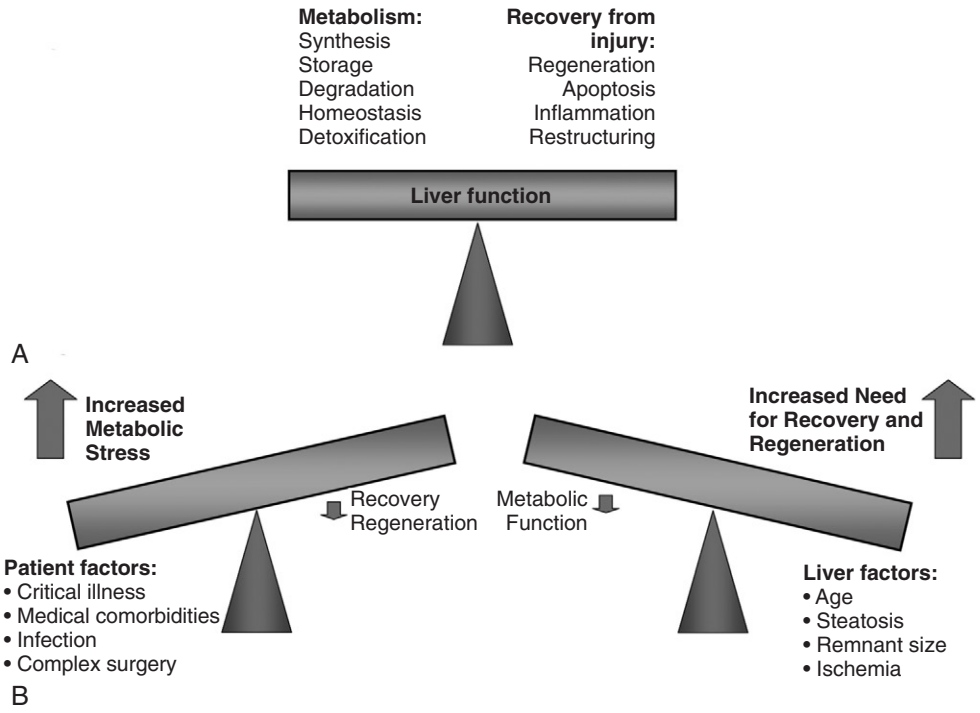


FIGURE 5.5. Metabolic balance between regeneration and maintaining liver function. **A,** In times of relative quiescence, there is a balance within the liver of metabolic function and continuous liver cell replacement or restructuring as needed. **B,** In times of stress or after injury or resection, the need for metabolic function or regeneration and recovery is increased. If metabolic need is great as a result of conditions within the patient, energy balance within the liver may not be sufficient to regenerate sufficiently, and the liver may not recover. If the requirements for regeneration and repair are overwhelming, metabolic function may be decreased, affecting patient outcome.

metabolic needs. It is this balance that limits the size of liver segment that can be transplanted or the size of remnant liver after donation or resection.

Termination of Proliferation

The size of the liver is highly regulated and is controlled by the functional needs of the organism. The most well-known antiproliferative factors within the liver are TGF-β and related family members such as activin (Derynck & Zhang, 2003). TGF-β is produced mainly by hepatic stellate cells, but in the early phase, it forms inhibitory complexes with SNoN and SKI proteins (Macías-Silva et al, 2002), rendering hepatocytes initially resistant to TGF-β (Koniaris et al, 2003). Later on, TGF-β acts through a heteromeric receptor complex, which subsequently phosphorylates proteins of the SMAD family, particularly SMAD2 and SMAD3 (Lonn et al, 2009). The SMAD2/SMAD3-SMAD4 complex translocates into the nucleus and activates target genes that negatively regulate the cell cycle (Nakao et al, 1997). Reactive oxygen species (ROS) enhance synthesis and activation of TGF-β (Koli et al, 2008), which may account for the reduced regeneration after ischemia and reperfusion. Interacting with the TGF-β/SMAD signaling could restore regeneration in a model of SFS liver grafts (Zhong et al, 2010).

Similarly, activin A blocks hepatocyte mitogenesis and shows diminished signaling during liver regeneration when its cellular-receptor level is reduced; its receptor level is restored once liver regeneration is terminated (Date et al, 2000). The level of activin-receptor mRNA expression was shown to be an important determinant in the magnitude of regeneration in portal vein ligation and PHx (Takamura et al, 2005a, 2005b). Suppressors of cytokine signaling (SOCS) are important negative regulators of cytokine signaling that prevent the tyrosine phosphorylation of STAT proteins. It has been shown that IL-6 signaling in the liver causes rapid upregulation of *SOCS3,* which correlates with the subsequent downregulation of phosphorylated *STAT3,* thereby terminating the IL-6 signal (Campbell et al, 2001).

Recent work strongly implicates the detection of blood bile acid levels by nuclear receptors as a regulator of liver growth (Huang et al, 2006). In addition, mammalian genes comparable to those in the *Drosophila* Hippo kinase-signaling cascade, which regulates wing mass during development, can also control hepatocyte proliferation (Dong et al, 2007). Overexpression of *YES1*-associated protein (YAP), the mammalian counterpart to *yorkie* (yki)—the last gene in the *Drosophila* Hippo kinase cascade—in a transgenic mouse model leads to massive liver hyperplasia, reaching 25% of body weight. YYA1P1 transcriptionally activates cell-cycle proteins, such as Ki-67 and c-Myc, and also activates inhibitors of apoptosis, and its phosphorylation by way of activation of the Hippo pathway blocks its ability to shuttle to the nucleus (Reddy & Irvine, 2008). It is therefore possible that the Hippo kinase pathway has a decisive role in determining overall liver size (Duncan et al, 2009).

LIVER ATROPHY

Classically, atrophy is triggered by an obstruction of portal venous blood flow or is the result of chronic obstruction of the bile duct. When atrophy occurs unilaterally, the opposite lobe of

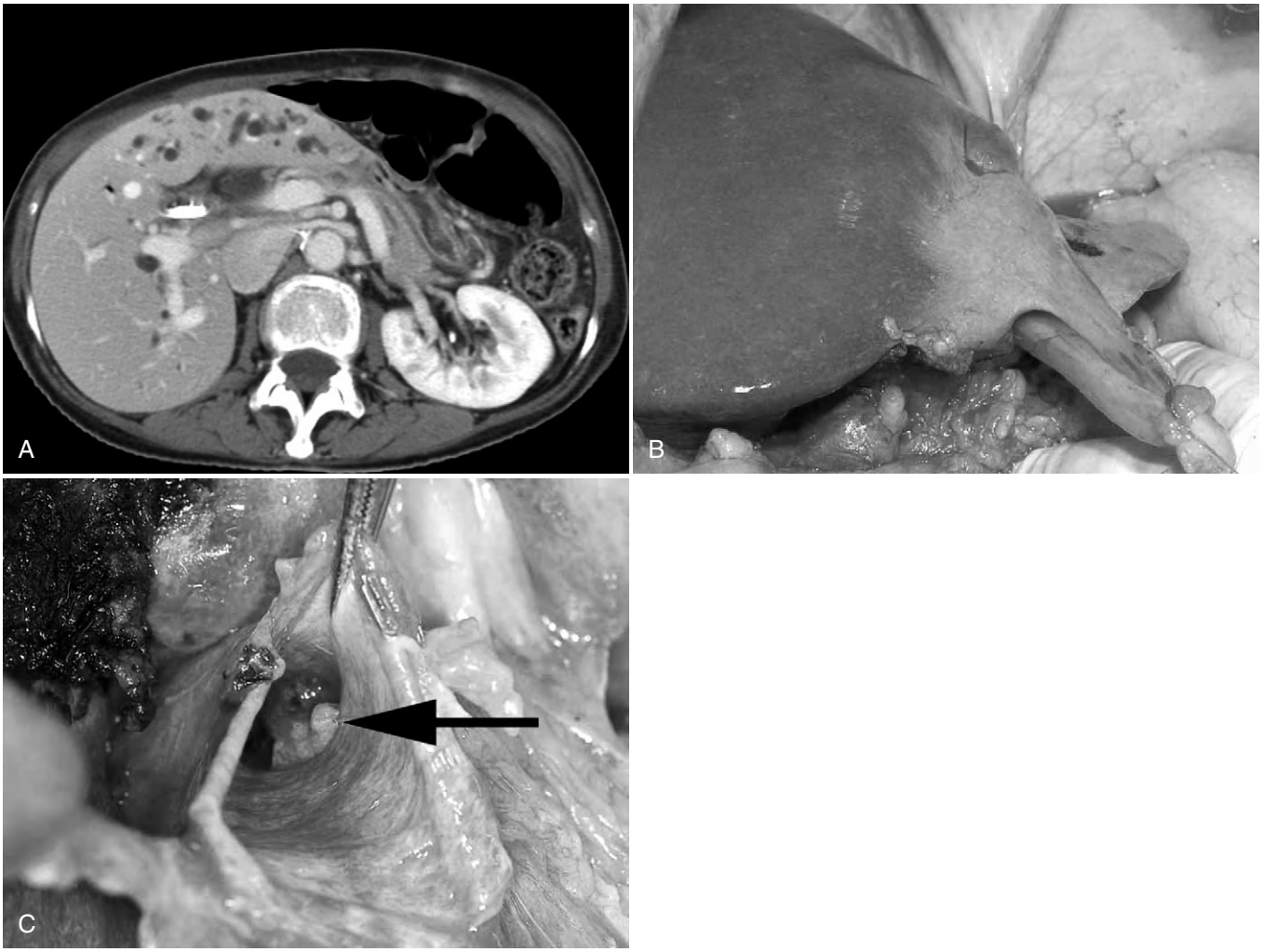


FIGURE 5.6. Hepatic atrophy. **A,** Appearance of the liver on computed tomography in a patient with papillary hilar cholangiocarcinoma involving the left hepatic duct. Note the atrophic left lobe and intrahepatic ductal dilation, predominantly on the left. **B,** Gross appearance of the liver in the same patient. **C,** Intraluminal view of the common bile duct, with tumor extruding from the left hepatic duct (*arrow*).

the liver responds with a hypertrophic response, which may result in a rotation of the liver around the hilar axis. The liver can become grossly distorted with marked changes in anatomic landmarks, most commonly seen accompanied by a rotation of the portal triad structures (Fig. 5.6). In recent years, the anatomic changes accompanying atrophy led surgeons to utilize preoperative embolization of the portal vein in areas involved with malignancy, hoping to induce hypertrophy in areas of the contralateral liver to increase the potential for resection and to reduce postoperative morbidity (see Chapter 93A).

Mechanisms of Liver Atrophy

The cause of liver cell death in atrophy is generally divided between necrosis and apoptosis. The distinction is important, because necrosis is a nonregulated traumatic disruption of a cell that occurs when it encounters overwhelming injury, whereas apoptosis is an inducible, highly orchestrated cascade of physiologic events. Necrotic cells lose membrane integrity, leak lysosomal enzymes, and induce a substantial inflammatory response. Apoptosis is energy dependent and allows cells to shrink and die without inducing inflammation. Apoptotic cells are characterized by plasma membrane blebbing, chromosomal condensation, and nuclear DNA fragmentation (Steller, 1995).

Portal Vein–Induced Hepatic Atrophy

The most common clinical scenario of hepatic atrophy is portal vein–induced atrophy, wherein occlusion of the portal vein leads to ischemia in areas of the liver; atrophy in this setting is a result of liver cell death secondary to necrosis and apoptosis (Ikeda et al, 1995; Shibayama et al, 1991). Ischemic necrosis of centrilobular areas of the liver predominates in the first 3 days of cell death. Areas peripheral to the necrotic liver cells predominantly undergo apoptotic cell death, and apoptosis persists long after necrosis subsides. Oxygen levels and mitochondrial function help determine which cells will undergo necrosis or apoptosis (Nishimura et al, 1998). Models of portal vein ischemia in rats have confirmed a caspase-dependent apoptosis and have indicated that Kupffer cells are involved in generating reactive oxygen substrates and other acute-phase reactants, culminating in mitochondrial dysfunction and apoptosis (Kohli et al, 1999).

Biliary-Induced Hepatic Atrophy

The molecular mechanisms involved in biliary obstruction leading to hepatic atrophy are much more centered on apoptosis, with little or no involvement of acute necrosis. Cholestasis results in the accumulation of toxic bile salts, which induce apoptosis through the Fas-mediated pathway. In this case, TNF-α and Fas ligand bind to the Fas death receptors, leading to a cascade of intracellular events, including cytochrome-c release from mitochondria and activation of apoptosis-mediating caspases. In Fas-deficient mice, bile duct ligation resulted in impaired apoptosis and less injury and fibrosis compared with wild-type mice (Canbay et al, 2002; Gujral et al, 2004; Miyoshi et al, 1999). More recent data, however, suggest a nonischemic model of necrosis/oncosis as the predominant process leading to cell death after common bile duct ligation, with cell swelling and without apoptotic caspase 3 activation (Fickert et al, 2005).

Clinical Causes of Atrophy

Hilar cholangiocarcinoma is a frequent cause of biliary atrophy, induced by occlusion of a major bile duct. Biliary occlusion, often accompanied by portal vein compromise, leads to atrophy of the liver approximately 20% of the time with this disease and has significant surgical implications. Also, postcholecystectomy bile duct strictures lead to hepatic atrophy 10% to 15% of the time (Hadjis & Blumgart, 1987; Pottakkat et al, 2009). Choledocholithiasis and hepatolithiasis are infrequent causes of atrophy, as are benign tumors such as papillomas, cystadenomas, and granular cell tumors (Blumgart et al, 1984; Blumgart & Kelley, 1984). Strictures caused by parasitic biliary infections, such as by *Clonorchis sinensis* and *Ascaris lumbricoides,* also have been known to cause biliary obstruction and associated atrophy of the liver. Occlusion of the hepatic artery alone would not induce atrophy.

Compensatory Regeneration Triggered by Atrophy

In the embolized portion of the liver, Kupffer cells release TNF-α and induce hepatocyte swelling and hyperplasia in the contralateral liver. Additionally, increased portal flow in the nonembolized lobe induces proliferation and activates several cytoplasmic growth-promoting signal-transduction pathways involved in hepatic regeneration, including JUN and the mitogen-activated protein kinase pathways. Kupffer cells in the contralateral liver begin to produce TNF-α as well, stimulated either by increased portal flow or through the direct effect of circulating growth factors (Kim et al, 2001). Nonparenchymal cells in the injured portion of the liver produce HGF. Messenger RNA levels of HGF in the ischemic portion of liver were noted to be 10 to 20 times that of normal, with most upregulation occurring in Kupffer cells (Hamanoue et al, 1992).

FACTORS INFLUENCING LIVER REGENERATION

Patient-Related Factors

Age

Liver age is a significant factor in hepatocellular regeneration. Older livers do not regenerate as quickly as younger livers and show delayed regeneration after acute injury and impaired function after liver transplantation (Burroughs et al, 2006; Feng et al, 2006). Rodent models have shown reduced and delayed thymidine kinase uptake in older animals after PHx, and a striking difference is seen in the magnitude of DNA synthesis and timing of hepatocyte replication between young and old livers (Taguchi et al, 2001). Treatment of old mice with growth hormone could restore hepatocyte proliferation (Krupczak-Hollis et al, 2003; Jin et al, 2009). Aging also represses activation of the c-Myc promoter in old livers after hepatectomy and in tissue culture models(Timchenko, 2009; Iakova et al, 2003).

On a clinical level, little is known regarding differential gene expression in old versus young livers, but results from the United Network for Organ Sharing (UNOS) database show reduced resistance in old donor livers to prolonged cold ischemia times (Cassuto et al, 2008), possibly as a result of high mitochondrial susceptibility to oxidative stress (Lenaz et al, 2000). In living-donor transplantation, some studies have shown that increasing donor age significantly affects posttransplant function (Abt et al, 2004; Iida et al, 2009) and rate of regeneration in the donor (Yokoi et al, 2005).

Biliary Obstruction

Cholestasis results in the accumulation of toxic bile salts, which induce apoptosis through the Fas-mediated pathway. In this pathway, TNF-α and the Fas ligand bind to the Fas death receptors, leading to cytochrome-c release from mitochondria and activation of apoptosis-mediating caspases. In Fas-deficient mice, bile duct ligation resulted in impaired apoptosis and less injury and fibrosis compared with wild-type mice (Canbay et al, 2002; Gujral et al, 2004; Miyoshi et al, 1999). Other molecular mechanisms involved in reducing regenerative capacity with biliary obstruction are suppressed expression of *MYC* (Tracy et al, 1991), *C/EBP*, and cyclin E (Nakano et al, 2001). Production of HGF (Hu et al 2003), EGF (Bissig et al, 2000), and IL-6 (Fujiwara et al, 2001) is also altered. Finally, biliary obstruction also impairs enterohepatic circulation and thus negatively affects the regenerative capacity. It is clinically relevant that external biliary drainage for obstructive jaundice markedly suppresses liver regeneration after hepatectomy (Suzuki et al, 1994), whereas internal biliary drainage preserves this capacity (Saiki et al, 1999).

Diabetes Mellitus

Insulin is one of the most important hepatotrophic factors in portal venous blood (Starzl et al, 1975). The binding protein of insulin-like growth factor (IGF), a molecule similar to insulin, also rises substantially after hepatectomy (Demori et al, 2000; Ghahary et al, 1992). Thus, impaired secretion of insulin and IGF in diabetic patients prevents liver regeneration following hepatectomy, as reflected by decreased synthesis of RNA, DNA, and protein on the first postoperative day (Yamada et al, 1977). Enhancement of mitochondrial phosphorylative activity in the remnant liver following hepatectomy is inhibited in proportion to the severity of impaired insulin secretion. Insulin gene transfer via the spleen enhances liver regeneration without causing liver damage and improves nutritional status after hepatectomy in diabetic rats (Matsumoto et al, 2003). Multiple regression analysis in clinical portal vein embolization (PVE) has shown that diabetes mellitus is a risk factor for reduced hypertrophy in the nonembolized lobe (Imamura et al, 1999). These results demonstrate the importance of insulin in hepatic regeneration,

and strict glucose control should be aimed for in liver surgery and PVE (Yokoyama et al, 2007a).

Nutritional Status

Hepatic regeneration is metabolically intensive and requires a great deal of energy. Liver regeneration after hepatectomy is associated with a derangement in energy metabolism, measured by a decrease in the ratio of ATP to its hydrolysis product, inorganic phosphate. This depleted energy status is mirrored in biochemical indices of liver function, and restitution parallels the course of restoration of hepatic cell mass (Mann et al, 2002). Nutritional support is undoubtedly the most physiologically sound means to enhance liver regeneration, but there is still little if any clear information regarding the effects of specific nutrients on liver regeneration in humans (see Chapter 24) (Holecek, 1999). From animal models we know that malnutrition is associated with higher postoperative mortality and reduced regeneration following PHx (Skullman et al, 1990). When improving nutritional status, enteral feeding should be preferred, as rats given enteral nutrition showed much better weight gain after 70% hepatectomy than those given isocaloric nutrition parenterally (Delany et al, 1994). Supplementation of glutamine, one of the sources of DNA and protein synthesis, has been shown to promote liver regeneration in dogs (Ito & Higashiguchi, 1999). Essential fatty acids, components of the cell membrane and precursors of several functional mediators, also play an important role in hepatic regeneration. Interestingly, dextrose supplementation had an inhibitory effect on liver regeneration, associated with increased expression of *C/EBPα, CDKN1A*, and *CDKN1B* in mice (Weymann et al, 2009), but in a randomized clinical trial, dextrose infusion was associated with improved nutritional status and earlier normalization of nitrogen balance (Nishizaki et al, 1996).

Gender

Sex steroids are known to induce transient hepatocellular proliferation and to improve fatty acid metabolism (Repa et al, 2000). Estrogen receptors are found on hepatocytes, and serum estradiol is increased substantially after hepatectomy in rodents and humans (Francavilla et al, 1989a). Pretreatment of rats with 17β-estradiol induces hepatocyte DNA synthesis in vitro and accelerates liver regeneration in vivo; administration of tamoxifen, a mixed estrogen agonist/antagonist, slows regeneration when given soon after PHx (Francavilla et al, 1989b). In contrast, testosterone levels decline in men and in male rats after PHx; however, there is no clinical evidence in humans that shows significant differences between the sexes after liver resection.

Intrinsic Liver Disease

The regenerative response of the liver can be seriously affected by preexisting intrinsic liver conditions such as steatohepatitis, fibrosis, and cirrhosis. Hepatic steatosis affects regeneration on several molecular levels. Lipid accumulation has been associated with hepatocyte mitochondrial damage caused by free-radical injury. Steatotic livers in rats show delayed mitosis and increased mortality after PHx, which may be due to abnormal TNF-α and IL-6 signaling (Selzner et al, 2000). The coordinated induction of Jnks and Erks is disrupted after partial hepatectomy in fatty livers of ob/ob mice (a model for steatohepatitis), with enhanced AKT and inhibition of PEPCK (Yang et al, 2001). Cyclin D1 induction is abolished along with Stat3 and reduced ATP levels, which may arrest cell-cycle progression. Hepatocyte mitochondrial damage associated with lipid accumulation is caused by free-radical injury from fatty acid oxidation. Abnormalities in induction of cytochrome P-450 may be one mechanism in the pathophysiology of these findings in fatty livers and may contribute to poor regeneration (Farrell, 1999; Kurumiya et al, 2000; Neuschwander-Tetri & Caldwell, 2003).

In clinical practice, the presence of underlying steatosis has considerable impact on operative morbidity and mortality after major hepatic resection (Behrns et al, 1998), with a significantly higher rate of complications if marked steatosis (≥30%) is present (see Chapters 65 and 87; Kooby et al, 2003). Steatohepatitis, or acute inflammation in the setting of fatty infiltration, carries an even higher risk and eventually results in fibrosis and cirrhosis. In transplantation, liver grafts with severe steatosis (≥60%) have higher rates of primary nonfunction, higher transaminases, and poorer graft survival in the transplant setting (Verran et al, 2003), possibly as a result of the inability to initiate repair and regeneration mechanisms. Progressive scarring and hepatic fibrosis lead to accumulation of abnormal collagen secreted into the extracellular matrix by stellate cells (Kim et al, 1998). Impaired regeneration is thought to be the result of the decreased diffusion of nutrients and hepatotrophic factors to the hepatocytes, and ultimately the architectural liver abnormalities created by scar contracture form a physical barrier that prevents hepatocytes from proliferating (Poynard et al, 1997).

Pharmacologic Therapy

Many exogenous agents can affect liver regeneration, including frequently prescribed drugs and neoadjuvant chemotherapy. Numerous medications are associated with impaired liver regeneration secondary to the induction of steatosis, including certain antiarrhythmic agents, antibiotics, antiviral agents, anticonvulsants, steroids, calcium channel blockers, statins, and antiglycemic medications. β-Blockers and nonsteroidal antiinflammatory drugs (NSAIDs) exert a more direct negative influence on liver regeneration. Liver regeneration after PHx is delayed in rodents treated with β-blockers and NSAIDs (Hong et al, 1997; Rudnick et al, 2001). β-Blockers may impair liver regeneration by decreasing portal blood flow to the liver and blocking the trophic effects of epinephrine. NSAIDs directly inhibit cyclooxygenase, part of the *C/EBPA*-mediated liver regenerative pathway. Although these effects have not been reflected in increased morbidity or mortality after liver resection in patients taking β-blockers or NSAIDs, the potential harmful effect of any medication on hepatic regeneration must be considered before resection.

In the past decade, more patients had liver surgery after neoadjuvant or induction chemotherapy. Major drawbacks of this hepatotoxic chemotherapy are the sinusoidal obstruction syndrome (SOS) associated with oxaliplatin (Rubbia-Brandt et al, 2004) and chemotherapy-associated steatohepatitis (CASH) (Vauthey et al, 2006), which is associated with irinotecan (see Chapters 65 and 87). Sinusoidal obstruction impairs liver regeneration after extensive liver resection and increases postoperative morbidity, but this may be prevented by administration of aspirin; CASH increases postoperative mortality—specifically, it increases deaths from postoperative liver failure (Fernandez et al, 2005).

Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF) in combination with cytotoxic chemotherapy, appears to improve survival in patients with metastatic colorectal cancer (Hurwitz et al, 2004). Well-designed preclinical studies have demonstrated that inhibition of angiogenesis can inhibit wound healing (Scappaticci et al, 2005). Interestingly, no published studies have examined the effect of anti-VEGF therapy on human liver regeneration. Animal studies have demonstrated that liver regeneration depends on VEGF and angiogenesis (Drixler et al, 2002). In a murine model, anti-VEGF receptor therapy slightly impaired liver regeneration and cell proliferation after PHx compared with controls (Van Buren et al, 2008); however, no preclinical animal data on the effect of bevacizumab on liver regeneration has been shown, because it specifically recognizes human VEGF, not murine VEGF. Clinically no differences in postoperative liver insufficiency were seen if therapy was stopped at least 6 to 8 weeks before hepatic resection (Reddy et al, 2008; Zorzi et al, 2008).

Liver Transplantation

Regeneration is also crucial in liver transplantation. In deceased-donor transplantation, hepatocyte loss occurs in the form of I/R injury owing to the necessary preservation period from procurement to implantation and damage that may have occurred in the donor. Regenerative mechanisms are actively engaged after transplantation, depending on the length and degree of preservation injury (Debonera et al, 2001; Olthoff, 2002). Similarly, hepatocytes lost to the alloimmune response require replacement. Regeneration is also necessary when transplanting an SFS graft into a larger recipient. This is the sometimes the case in the setting of adult-to-adult living-donor transplantation (AALDLT) (Olthoff, 2003) and split-liver transplantation. Ischemic injury is minimized in AALDLT, because the preservation period is short; however, this technique supplies a graft that is by definition too small, requiring vigorous and immediate hepatocyte proliferation. By transplanting only 50% to 60% of what is the expected liver volume in adults, recipients (and donors) must rely on the rapid regeneration of a partial liver in addition to maintaining the basic metabolic functions required of the liver.

Warm and cold ischemic injury is an unavoidable component of transplantation. After prolonged cold ischemia of whole liver grafts, initiation of the cell-cycle pathways with upregulation of markers of liver regeneration occurs as described earlier. When ischemic injury is significant, a greater expression and activation of cytokines, transcription factors, and immediate early genes and a greater magnitude of hepatocellular replication is seen (Debonera et al, 2001). However, the liver can tolerate ischemic injury only to a certain "point of no return," after which the damage is too extensive, and the liver or allograft cannot maintain functional homeostasis and regenerative capabilities, which results in liver dysfunction and graft failure (Debonera et al, 2002).

The amount of liver mass transplanted has been shown to be an important variable after transplantation. Early experimental studies addressing regeneration after transplantation showed that an SFS graft adapts to its environment and achieves a size equal to the original native liver (Kam et al, 1987). It became apparent that graft size–recipient ratio was crucial, as grafts that were too small had decreased survival (Francavilla et al, 1994). These findings correlated with clinical experience, in that SFS grafts regenerate to an appropriate size for the recipient; however, significant functional impairment of these grafts can occur, shown by prolonged cholestasis and histologic changes consistent with ischemic injury (Emond et al, 1996; Kiuchi et al, 1999; Lo et al, 1999; Zhong et al, 2006).

Using animal models of partial liver graft transplantation, the interplay between the regenerative response and ischemic injury in the setting of 50% and 30% size grafts was studied. The partial grafts showed a robust regenerative response if the ischemic injury was minimal. It became apparent, however, that when these partial grafts were subjected to ischemic injury for moderate to prolonged periods, a significant effect on survival was seen, with extensive hepatic necrosis, the inability to initiate or maintain the regenerative response, and decreased survival. These findings show the diminished tolerance of SFS grafts for additional injury beyond transplantation itself (Selzner et al, 2002; Debonera et al, 2004).

The amount of critical liver mass required for transplantation in living donation remains in question. Most centers have defined liver mass as graft-to-recipient body weight ratio (GRBWR) or as a percentage of the standard liver volume. No uniform method of measuring or reporting graft volume in relation to the recipient has been established. Clinical experience with living-donor and split grafts has led to an accepted lower limit of 0.8% GRBWR, or 40% of the standard liver volume (SLV), although significantly smaller grafts have been transplanted successfully. As mentioned before, donor liver and recipient characteristics may significantly influence these minimal accepted standard volumes. Patients with fulminant hepatic failure and those with significant metabolic stress may require more liver volume than stable patients transplanted under elective conditions (Marcos et al, 2000b).

Although it has been performed successfully, many centers are not performing AALDLT in acutely ill patients with fulminant failure because of the uncertainty of knowing whether a partial graft offers enough volume to support the recovery of such a recipient. As seen in experimental models, the accumulation of additional stressful stimuli, such as sepsis or renal failure, may push a relatively small graft into failure. Despite the actual measurement, if a small graft has any dysfunction, it can progress to what is termed *small-for-size syndrome* (SFSS). Within only 3 to 5 days after surgery, signs of liver failure—presence of two of the following on three consecutive days: bilirubin greater than 100 μmol/L, INR greater than 2, encephalopathy grade 3 or 4—with ascites, as well as renal and pulmonary failure, may become apparent (Dahm et al, 2005).

Effect of Immunosuppression

Within the graft environment, the host immune response needs to be inhibited to avoid acute allograft rejection, and inhibition of this response may interfere with the recovery of liver grafts, requiring active regeneration of hepatocytes. Glucocorticoids routinely used in immunosuppression protocols have been shown to inhibit cell-cycle progression markedly in PHx models and in transplant models with ischemic injury (Debonera et al, 2003; Nagy et al, 1998; Tamasi et al, 2001). Cyclosporine and tacrolimus may have differential effects on regeneration in a dose-dependent fashion (Francavilla et al, 1991). Sirolimus, with its antiproliferative action, interferes with hepatocyte replication (Francavilla et al, 1992; Palmes et al, 2008). The rapid hepatocyte replication and smaller liver

mass may also interfere with the metabolism and pharmacokinetics of certain drugs. Preliminary studies have shown that AALDLT recipients require lower doses of tacrolimus in the early postoperative period than patients receiving whole grafts (Trotter et al, 2002). The ability to measure functional recovery of these recipients would help in the assessment of hepatocellular function and metabolic demands in those regenerating partial liver grafts.

Donor Age

As with liver regeneration in the nontransplant setting, old grafts do not regenerate as quickly as young livers. A clinical study of living donors showed a greater graft/standard liver volume in the young donor livers posttransplant compared with middle-aged and old donor grafts. The old livers also had a higher prothrombin time in the early period postoperatively (Ikegami et al, 2000). Statistics from the UNOS database show that the graft survival of older living-donor grafts is inferior to those of grafts from younger living donors (Abt et al, 2004). In the deceased-donor transplant setting, grafts older than 55 to 60 years of age have poorer long-term survival combined with those exposed to longer cold ischemic times (Cassuto et al, 2008). Age may affect the regeneration and recovery of the living donor and the recipient, and many groups limit the age of the donor, although no definite age limit has been specified.

Viral Hepatitis and Bacterial Infections

Very little is known about how rapid hepatocellular proliferation affects other processes. Some viral infections, such as hepatitis B and C and murine cytomegalovirus (Tralhao et al, 2002; Marshall et al, 2005; Sun & Gao, 2004), have been reported to inhibit hepatic regeneration. The precise mechanism responsible for viral infection–related suppression is unclear, but it may be partly mediated by the inhibition of cell-cycle–dependent molecules. Because most transplant recipients in the United States have the hepatitis C virus (HCV), it is important to know whether this vigorous regenerative response in the transplanted graft has a significant effect on the kinetics of viral replication in HCV-positive individuals. Investigators have noted that HCV RNA replication is enhanced in proliferating cells, suggesting that viral replication is regulated by cell-cycle–dependent factors (Erhardt et al, 2002). Clinically, progressive liver disease has been reported to be associated with increased hepatocyte proliferation (Poynard et al, 1997). Alternatively, HCV core proteins have been shown to have significant interaction with cellular promoters and regulators of cell growth, which may affect liver regeneration (Ray et al, 1998; Shrivastava et al, 1998; Hayashi et al, 2000; Lee et al, 2002; Blindenbacher et al, 2003). Early single-center studies suggest that recipients of living-donor liver transplants may have an earlier and more severe recurrence of HCV compared with recipients of whole deceased-donor liver grafts; however, this has not been shown in a prospective controlled study (Ghobrial et al, 2002; Shiffman et al, 2004; Berenguer, 2006).

Concomitant bacterial infections also alter liver regeneration. Earlier reports showed enhanced liver regeneration in rats after inflammation prior to hepatic resection as the result of stimulation of lipopolysaccharide upregulation of proinflammatory cytokines, such as IL-6 and TNF-α, and HGF (Weiss et al, 2001; Sekine et al, 2004), all of which are chief mediators of hepatic regeneration. A recent study more in line with clinical observations showed a significantly delayed regeneration kinetic in a rat model of combined liver resection and intraperitoneal sepsis with hyperinflammation and increased liberation of proinflammatory cytokines (Seehofer et al, 2007).

Other Factors

Several other factors may influence the regenerative response after transplantation. Increased portal venous flow has been implicated in more rapid regeneration (Jiang et al, 2009). In addition to the reduced cell mass of the graft itself, portal blood flow dynamics are altered, and the graft is subjected to increased portal blood flow and pressure. The significance of this situation is unclear: increased portal flow is associated with increased recovery (Eguchi et al, 2003); however, portal hyperperfusion is on the other hand regarded as central to the problem in SFS grafts, leading to decreased regeneration and increased mortality (Tracy et al, 1991). Some centers advocate surgical manipulations—such as splenic artery ligation, splenectomy, or portocaval shunting—to minimize portal hypertension in the setting of a SFS graft (Tucker & Heaton. 2005). Poor hepatic venous drainage has been shown to inhibit regeneration (Scatton et al, 2008), and segments with poor venous drainage become atrophied with time.

As in liver resection, female gender may have a positive effect on regeneration of partial grafts in murine models (Yokoyama et al, 2007b). Estrogen may be responsible for the better tolerance to various stresses as a result of reduced inflammatory response and reduced oxygen radical production, leading to improved hepatic regeneration. However, also in transplantation, no clinical evidence supports the results of these experimental studies.

EXPERIMENTAL STRATEGIES TO PROMOTE LIVER REGENERATION

After major hepatectomy or in the setting of an SFS liver graft in liver transplantation, usually a robust priming reaction by highly elevated levels of IL-6 and TNF-α is present, but induction of cell-cycle progression fails (Debonera et al, 2004). In an animal model, this problem was overcome by a single injection of heparin-binding epidermal growth factor (HB-EGF) (Mitchell et al, 2005). Another strategy that may be useful in an SFS situation is blockage of the receptor for advanced glycation endproducts (RAGE). Blockage of RAGE greatly improved survival after an 85% hepatectomy in a mouse model by increasing TNF-α and IL-6 production and enhancing expression of the antiinflammatory cytokine IL-10 (Cataldegirmen et al, 2005).

Recently, the role of TGF-β as the most potent growth-inhibitory polypeptide currently known was assessed in a model of SFS liver transplantation, after which a sharp rise in TGF-β1 was found, forming a heteromeric receptor complex. Phosphorylation of this complex activates proteins of the Smad family, particularly Smad2 and Smad3 (Lonn et al, 2009). Activated Smad2 and Smad3 form a complex with Smad4, move into the nucleus, and activate target genes, expressing regulatory proteins and exerting an inhibitory effect on hepatocyte proliferation. Smad7, an inhibitory Smad, associates stably with the TGF-β receptor complex and was shown to inhibit the TGF-β–dependent cell-cycle arrest (Zhong et al, 2010). Therefore anti–TGF-β therapy holds promise as a new strategy to improve regeneration of SFS grafts in clinical practice.

CLINICAL IMPLICATIONS

Stimulating Liver Regeneration Preoperatively

The assessment of hepatic function before resection is difficult, but we do know that the risk for perioperative complications increases when the remnant liver volume is too small, particularly in diseased livers (see Chapter 2; Yigitler et al, 2003). Hepatic function seems to recover quickly after resection but is difficult to measure. Conventional clinical blood tests and liver biopsy are inadequate measures of hepatic function. Child-Turcot-Pugh classification and the Model for End-Stage Liver Disease (MELD) score apply primarily to patients with cirrhosis and are only rough estimates of functional reserve. Bilirubin, albumin, international normalized ratio, and platelet count become abnormal only in advanced cirrhosis. Magnetic resonance imaging or computed tomography can measure residual liver volume accurately, but quantitative functional testing is not as precise. Traditional techniques to measure the volume of resection prior to hepatectomy can lead to inaccurate estimates of functional residual liver (FRL) volumes because of the presence of dilated bile ducts, multiple tumors, undetected lesions, compromised liver volume as a result of cholestasis or previous chemotherapy, cholangitis, vascular obstruction, steatosis or cirrhosis, or segmental atrophy and/or hypertrophy from tumor growth (Azoulay et al, 2000; Kubota et al, 1997).

In living-donor liver transplantation, volumetric imaging is used to determine total liver volume (TLV) and what the FRL volume will be following resection, and it can roughly be used to predict postresection function, as the donor liver is normal. In the recipient, the TLV of the diseased liver is not a useful index of function. Values calculated from GRBWR or standardized liver volume (SLV) based on recipient body surface area are used to predict minimum adequate graft volume (Vauthey et al, 2000; Higashiyama et al, 1993). A GRBWR greater than 0.8% or SLV greater than 35% are recommended to achieve successful graft and patient survival (Lo et al, 1999). For donor safety, the transplant community has recommended that at least 35% of TLV remain in the donor following resection for living donation. In comparison, extended resection of 80% of functional parenchyma can be performed in the absence of chronic liver disease for hepatobiliary malignancies (Abdalla et al, 2002). Recommended minimal FRL volume following extended hepatectomy is greater than 25% in a normal liver and greater than 40% in an injured liver, with moderate to severe steatosis, cholestasis, fibrosis, or cirrhosis, or following chemotherapy (Shoup et al, 2003).

Quantitative liver function tests measure the liver's ability to metabolize or extract test compounds and can identify patients with impaired function at earlier stages of disease, but these tests have limited application in predicting a liver's ability to regenerate after major resection (see Chapter 2). Clearance of indocyanine green is regarded as an accurate assessment of functional reserve that can help predict mortality (Lau et al, 1997), but more is being learned about measuring hepatic function in diseased livers using quantitative functional testing, such as methionine breath tests, cholate clearance, liver single-photon emission computed tomography scans, liver scintigraphy, and phosphorus 31 magnetic resonance spectroscopy (Corbin et al, 2002). When compared with indocyanine green (ICG) clearance and computed tomographic volumetric data, hepatobiliary scintigraphy is a reproducible and accurate tool to assess functional liver uptake and excretion, preoperative liver function reserve, and remnant liver function, and it allows monitoring of postoperative liver function regeneration (Dinant et al, 2007). Assessment of future remnant volume distinguishes those who will most likely benefit from preoperative liver enhancement techniques with PVE or hepatic artery embolization.

Portal Vein Embolization to Promote Liver Regeneration

Selective embolization techniques increase tolerance to major hepatic resection by reducing the liver volume that requires resection and inducing hypertrophy of the FLR to approximate target limits in patients with large tumors or abnormal liver function. Criteria for selection of patients for PVE prior to major hepatectomy are FLR size, factors compromising liver function—including previous chemotherapy, hepatitis, and cirrhosis—and the planned complexity of the procedure (Yigitler et al, 2003; Abdalla et al, 2001). PVE is recommended when predicted FLR is less than 20% to 25% in a normal liver and less than 40% in a liver with compromised function (Hemming et al, 2003). Stimulation by PVE increases circulating IL-6 and TNF-α (Koga & Ogasawara, 1991; Feingold et al, 1988), with activation of the mitogenic cascade similar to partial hepatectomy. In fact, marginal (<5%) contralateral regeneration after PVE is a strong predictor of liver failure after subsequent liver resection (Ribero et al, 2007). A significant increase in DNA synthesis and mRNA expression of HGF has been observed in the nonligated lobe (Uemura et al, 2000), whereas HGF expression is only slightly elevated; negative regulators of hepatocyte proliferation, such as TGF-β and IL-1β, are strongly expressed in the shrinking ligated lobe. It is important to keep in mind that these factors may also promote tumor outgrowth in the FLR, and continuation of chemotherapy during PVE for malignant conditions should be considered (Covey et al, 2008; Pamecha et al, 2009).

Ischemic Preconditioning to Stimulate Regeneration

Liver resection, transplantation, and trauma can result in prolonged deprivation of tissue oxygen, converting cellular metabolism to anaerobic pathways. Reperfusion and, consequently, the restoration of oxygen delivery lead to liver injury, and this ischemia/reperfusion injury impairs liver regeneration (Selzner et al, 1999).

The first clinical attempt to minimize ischemic injury during liver resection was performed by interrupting long ischemic intervals with multiple short periods of reperfusion (Makuuchi et al, 1987). The protective effect of ischemic preconditioning (IPC) involves many different mechanisms, including inhibition of apoptosis and preservation of cellular ATP content in patients undergoing major liver resection (Clavien et al, 2003; Rudiger et al, 2002). A recent cDNA microarray study in humans demonstrated that IPC triggers the overexpression of IL-1Ra, iNOS, and Bcl-2, which counteracts the ischemia-induced proinflammatory and proapoptotic activation (Barrier et al, 2005). IPC has also been described as promoting liver regeneration via the upregulation of cytokines such as TNF-α and IL-6, various heat-shock proteins, and the downregulation of TGF-β (Gomez et al, 2007). IPC by 10 minutes of portal triad inflow occlusion and 10 minutes of reperfusion proved effective both in liver resection, particularly noted in patients with mild to moderate steatosis (Clavien et al, 2003), and in liver transplantation (Jassem et al 2009; Franchello et al, 2009). No

difference was seen in protection between intermittent clamping (15 minutes ischemia and 5 minutes reperfusion) or IPC with subsequent inflow occlusion for a maximum of 75 minutes, except for patients older than 65 years, who benefited more from intermittent clamping to attenuate liver injury. Pharmacologic induction of heat-shock proteins could play a beneficial role in the recovery of liver function after hepatectomy, but clinical trials have yet to be performed to confirm this.

Regenerative Potential of the Liver After Chemotherapy

As discussed earlier, an increasing number of patients with tumors undergo extensive chemotherapy with multiple drugs before surgery (see Chapter 87). The complication rate and mortality after major liver resection is increased in those patients, compared with patients not receiving these drugs (Vauthey et al 2006; Fernandez et al, 2005). The deleterious effect of chemotherapy on regeneration seems to increase with the total number of cycles given and shows a sharp rise after five courses (Karoui et al, 2006). Therefore no more than six cycles of chemotherapy containing 5-fluorouracil, leukovorin, and oxaliplatin/irinotecan are generally recommended before liver resection, with a 3-week interval in between. The anti-VEGF monoclonal bevacizumab has a long half-life and theoretically should be stopped 6 to 8 weeks prior to surgery, necessitating close collaboration with the medical oncologist in the timing of surgery. Results from PVE before major liver resection under continuous bevacizumab, however, showed no deterioration in increase in FLR volume 4 weeks after PVE (Zorzi et al, 2008). Recently, significantly impaired hypertrophy was reported in the same situation (Aussilhou et al, 2009), but this might also be attributed to extensive concomitant chemotherapy (Vauthey et al, 2009). Therefore the optimal window between the completion of bevacizumab and surgery remains uncertain (Clavien et al, 2007).

Supporting Liver Regeneration Under Difficult Clinical Conditions

After major liver resection or transplantation of an SFS liver graft, the energy balance is dramatically shifted to the critical task of regeneration of functional mass and injury recovery at the expense of normal hepatic metabolism (de Jonge et al, 2009; Mann et al, 2002; Corbin et al, 2002; Mann et al, 2001). In the situation of a severely ill recipient, which requires the expenditure of an unusual amount of metabolic energy by the liver, this balance may be disrupted and may lead to blunted regeneration. Similarly, when factors in the remnant liver or donor graft demand increased efforts for repair or regeneration of the graft, the balance tips in the opposite direction, not leaving enough energy to maintain metabolic function (Mann et al, 2001). The clinical consequences of this postoperative liver failure are jaundice, coagulopathy, ascites, edema, and/or hepatic encephalopathy (Sass & Shakil, 2005). Data concerning liver function on different days after uncomplicated hepatic resection show an initial increase of serum bilirubin and a decrease of prothrombin time before normalization of these values on the seventh postoperative day (Suc et al, 1992). However, when the prothrombin index dropped below 50% and serum bilirubin exceeded 50 µmol/L on postoperative day 5, the risk of early mortality increased significantly (Balzan et al, 2005). In this situation, avoidance of any new energy-costing challenge, such as systemic infection, is pivotal to graft regeneration. The number of major complications is progressively increasing, from about 30% after resection of two segments to 75% in patients who underwent resection of six segments, with a similar trend in operative mortality, from less than 1% in those who had five or six segments resected to 5% and 7.8%, respectively (Jarnagin et al, 2002).

Management principles resemble those applied to patients with acute liver failure, acute-on-chronic liver failure, or sepsis; the focus is put on support of liver and end-organ function (Rivers et al, 2001). Goal-directed therapy should be provided for circulatory disturbances, renal and ventilatory dysfunction, coagulopathy, malnutrition, and hepatic encephalopathy (Jalan, 2005). A strong link between infection and postoperative liver failure is evident, so frequent cultures for bacteria and fungi are essential. The use of prophylactic antibiotics after hepatectomy for the prevention of infectious complications is not supported by evidence from the literature (Wu et al, 1998); however, the administration of antibiotics in patients suffering from acute liver failure is associated with a significant decrease in infectious complications, and this practice can be advocated in the presence of liver failure following resection (Rolando et al, 1993). An aggressive approach to intraabdominal infection is also advocated—such as percutaneous treatment of biloma, infected hematoma, and abscesses—as is vigorous control of ascites in the setting of imminent postoperative liver failure.

NEW HORIZONS AND FUTURE PERSPECTIVES

Therapeutic Use of Stem Cells

In addition to the classical first pathway (hepatocyte proliferation) and second pathway (hepatic progenitor cells) in liver regeneration, new evidence using bone marrow transplantation has begun to crystallize the existence of a third, extrahepatic pathway: the ability of bone marrow and cord-blood derived cells to engraft as hepatocytes (Friedman & Krause, 2009; Theise & Kraus, 2002).

Adult bone marrow includes two well-defined populations of stem cells: *hematopoietic stem cells* (HSCs), which give rise to all mature lineages of blood, and *mesenchymal stem cells* (MSCs), which can differentiate into bone, cartilage, muscle, and fat. Evidence for transition from bone marrow (BM) to hepatocyte has been demonstrated by analyzing liver samples after male-to-female BM transplantation in rodents and humans (Alison et al, 2000; Lagasse et al, 2000; Theise et al, 2000b). However, the extent to which this occurs and the mechanisms involved are still under debate (Fausto, 2004; Oertel & Shafritz, 2008). Estimates of repopulation by hematopoietic stem cells vary from 0.01% up to 40%, depending on the experimental conditions.

In the discussion about the mechanisms whereby the HSCs acquire a hepatocytic phenotype, both fusion of stem cells and hepatocytes (Wang et al, 2003b; Vassilopoulos et al, 2003) and transdifferentiation of stem cells into hepatocytes have been proven (Harris et al, 2004; Jang et al, 2004). The highest levels of BM-derived hepatocytes were found in humans with severe liver disease, suggesting that tissue damage may promote BM-derived cells engraftment as hepatocytes. Also, the release of adult stem cells from BM was shown after partial liver resection for benign and malignant conditions (Gehling et al, 2005; De Silvestro et al, 2004), and BM-derived stem cells increased the regeneration of contralateral liver after clinical PVE by 250% (Esch et al, 2005).

Recent studies report that MSCs promote liver repair in cases of liver damage (Alison et al, 2009). MSCs isolated from human umbilical cords (Yan et al, 2009), adipose tissue (Banas et al, 2008), bone marrow (Kuo et al, 2008), or rat bone marrow (Abdel Aziz et al, 2007) improved liver function in rodents suffering from acute liver damage (e.g., carbon tetrachloride injections). Infusion of hepatocyte-like cells, which were differentiated in vitro from MSCs, improved liver function following acute injury and appears to be therapeutically useful to animals with ongoing chronic hepatic damage (Fang et al, 2004; Zhao et al, 2005; Sakaida et al, 2004; Oyagi et al, 2006; Higashiyama et al, 2007). MSC therapy is sometimes considered to be a double-edged sword, and concerns were raised about MSCs promoting liver cirrhosis by differentiatng into myofibroblasts, which are involved in the fibrotic response (Russo et al, 2006; di Bonzo et al, 2008). The latest publications in this field indicate that the use of MSCs is safe and has a beneficial effect on liver fibrosis (Zhao et al, 2009; Chang et al, 2009; Roderfeld et al, 2009). Some phase I trials involving the injection of autologous BM cells into patients with cirrhosis have reported modest improvements in clinical scores (Lin et al, 2008; Houlihan & Newsome, 2008). Thus MSC-mediated liver therapy is a highly promising field; such therapy significantly improves liver function and increases animal survival in experimental liver-injury models; however, its role in liver regeneration after surgery remains to be determined.

Use of Antisense MicroRNAs

Recent studies have uncovered profound and unexpected roles for a family of tiny regulatory RNAs known as *microRNAs* (miRNAs) in the control of diverse aspects of hepatic function and dysfunction, including hepatocyte growth, stress response, metabolism, viral infection and proliferation, gene expression, and maintenance of hepatic phenotype (Elmen et al, 2008; Ambros, 2004). Some of these miRNAs are specific to the liver, and silencing of these resulted in increased expression of several hundred genes, including those normally repressed in hepatocytes. The significance of miRNAs in regenerating liver has not been established, but in a murine model, there was upregulation of some miRNAs with increasing age (Maes et al, 2008). In particular, three upregulated miRNAs may contribute to the aging-related decline in oxidative defense by targeting various classes of glutathione S–transferases. Other proteins in decline in old liver and targeted by the upregulated miRNAs are involved in mitochondrial functions or maintenance. Antagonizing these miRNAs may reverse the decline of regeneration and oxidative defense mechanisms in aging liver.

SUMMARY

In the last century, knowledge about liver regeneration has rapidly evolved from a truly mythical black-box event into a growing understanding of the pathways involved in this amazing, multistep process. However, even with our better understanding, large knowledge gaps still exist. Interestingly, much was learned about the dynamics and redundant intracellular signaling pathways of liver regeneration. Still, much less is known about the exact signals that initiate and stop liver regeneration. The advances in our knowledge of liver regeneration have led to safer extreme liver resections for benign and malignant diseases and the use of live donors in liver transplantation. New challenges lie ahead in the use of therapeutic strategies to enhance liver regeneration in patients in whom normal regeneration fails and will thus push the possibilities of liver resection to the next level. Furthermore, even as we promote liver cell proliferation, we must be very cautious not to stimulate tumor growth in patients with primary or metastatic liver tumors with our therapy.

References are available at expertconsult.com.

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CHAPTER 6

Liver fibrogenesis: mechanisms and clinical relevance

Diana Vetter and Scott L. Friedman

LIVER FIBROGENESIS

Liver fibrosis represents a scarring response to either acute or chronic cellular injury. Following acute liver injury, parenchymal cells regenerate to successfully preserve hepatocellular mass and function. This acute process is associated with an inflammatory and fibrogenic response but limited deposition of extracellular matrix (ECM). In contrast, prolonged liver injury leads to sustained production of growth factors, proteolytic enzymes, angiogenic factors, and fibrogenic cytokines. These events culminate in the accumulation of ECM, forming septa that coalesce into broad bands of scar tissue that encircle nodules of hepatocytes and lead to altered microvascular structure (Friedman, 2004). This late stage of fibrosis, termed *cirrhosis*, ultimately impairs liver function and leads to portal hypertension and its complications (see Chapter 70A).

Progression of fibrosis to cirrhosis typically evolves over decades before clinical events ensue, but disease may progress more rapidly following repeated episodes of severe acute alcoholic hepatitis; subfulminant hepatitis, especially as a result of drug toxicity; and fibrosing cholestasis in patients with hepatitis C virus (HCV) reinfection after liver transplantation (Berenguer et al, 2003). In addition, rapidly progressive acute HCV with fibrosis in men coinfected with human immunodeficiency virus (HIV) has been reported recently (Fierer et al, 2008).

Genetic and environmental factors also influence the course of the disease. For example, polymorphisms in a number of candidate genes involving the inflammatory (TLR4; Guo et al, 2009) or immune response (specific human leukocyte antigen-II [HLA-II] alleles; Powell et al, 2000) may influence the progression of liver fibrosis in humans. Validated groups of single nucleotide polymorphisms (SNPs) can be used to calculate a disease-specific risk assessment for fibrosis progression (HCV: DDXminor allele, DDX-5POLG2 haplotype [Huang et al, 2006]; alcohol-related or chronic cholestatic disorders: TNF-α, interleukin [IL]-1B [Jarvelainen et al, 2001; Donaldson et al, 2001]). These findings have led to the development of a seven-gene signature with good prognostic value in assessing the risk for cirrhosis development in HCV patients (Huang et al, 2007).

The main etiologies of liver fibrosis in Western countries are chronic HCV and HBV infection, alcohol abuse, and nonalcoholic steatohepatitis (NASH; see Chapters 64 and 65). As a generalized tissue response to chronic injury, fibrosis also occurs in many other organs—including the heart, lung, and kidneys—and typically represents the result of ongoing inflammation. Remarkably, up to 45% of all deaths are related to some kind of fibrosis, which emphasizes the importance of this response and explains the growing interest in this field of research (Fig. 6.1).

For decades fibrosis was seen as an irreversible disease that progresses to cirrhosis, with a greater risk for developing hepatocellular carcinoma (see Chapters 8C and 80) and liver failure. This meant the only potential treatment for liver fibrosis once it had progressed to cirrhosis was transplantation. Research over the past 30 years has yielded increasing insight into the cellular and molecular mechanisms of this disease, uncovering an orchestrated pathophysiology and identifying the hepatic stellate cell (HSC) as the central cell type in fibrogenesis (Friedman, 1985). Most importantly, this revealed the potential reversibility of this disease and the discovery of potential therapeutic targets.

MOLECULAR AND CELLULAR MECHANISMS OF FIBROSIS

The anatomical arrangement of parenchymal and nonparenchymal cells of the liver contributes to its unique role as an immunity-modulating organ (see Chapter 9) and helps explain how the liver responds to an insult. The liver is composed primarily of epithelial cells, hepatocytes and cholangiocytes, and resident nonparenchymal cells that include hepatic macrophages (Kupffer cells), sinusoidal endothelium, and HSCs. In addition to Kupffer cells, a growing list of specialized immune cells have been characterized, including dendritic cells (DCs), natural killer (NK) cells, and natural killer T (NKT) cells, which indicate that the liver represents a key organ in the regulation of innate immunity.

The liver capsule extends as septa into the liver, delineating hepatic lobules that form the structural units of the liver. The lobule forms a hexagonal structure with portal triads—including branches of the hepatic portal vein, the hepatic artery, and the bile duct—localized in the periphery of the lobule and with a portal vein branch in the center. Hepatocyte plates radiate outward from the central vein and are separated from each other by sinusoids. The latter form the connecting element between the branches of the hepatic portal veins and hepatic arteries with the central vein. Kupffer cells, NK cells, NKT cells, and DCs, all of which are important components of the innate immune system, reside in the hepatic sinusoids. The subendothelial space between the sinusoidal endothelium and hepatocytes is termed the *space of Disse*. Thus the HSCs, which lie in the space of Disse, have direct contact with

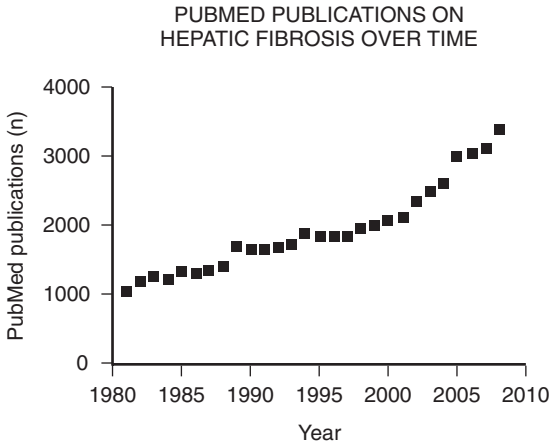


FIGURE 6.1. Growing interest in hepatic fibrosis based on numbers of publications. Hepatic fibrosis is gaining accelerating interest based on citations in PubMed. Graph shows number of citations based on a search of "hepatic fibrosis" annually over a 30-year period.

endothelial cells and hepatocytes. Sinusoidal endothelial cells are highly fenestrated, which allows unimpeded flow of plasma from sinusoidal blood into the space of Disse. Through this arrangement, hepatocytes and HSCs are exposed directly to plasma derived largely from venous blood draining the small intestine.

Common Triggers of Hepatic Fibrogenesis

Ongoing insult to the liver will lead to an increased inflammatory state with activation of hepatic stellate cells, which ultimately tilts the profibrotic–antifibrotic balance toward fibrosis. Ethanol, viral infection, reactive oxygen species (ROS), and bile acids are among the most common stress signals for the liver (Fig. 6.2). An in vitro study further suggests that free fatty acids promote fibrogenesis by indirect activation of HSCs (Wobser, 2009). Less common causes of hepatocellular injury are autoimmune hepatitis, Wilson disease, or hemochromatosis.

Alcohol decreases gut motility, increases epithelial permeability, and promotes overgrowth of gram-negative bacteria. Consequently, lipopolysaccharide concentration is elevated in portal blood, which activates Kupffer cells through the Toll-like receptor (TLR) 4 complex to generate ROS via reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Wheeler, 2001). Oxidants then upregulate NF-κB in Kupffer cells, which leads to increased tumor necrosis factor (TNF)-α production. TNF-α in turn induces neutrophil infiltration and stimulates mitochondrial oxidant production in hepatocytes, which are then sensitized to undergo apoptosis. Furthermore, acetaldehyde, the main degradation product of alcohol, and ROS both activate HSCs and stimulate inflammatory signals (Maher et al, 1994).

In HCV infection, the virus escapes the HLA-II immune response and infects hepatocytes. This causes oxidative stress,

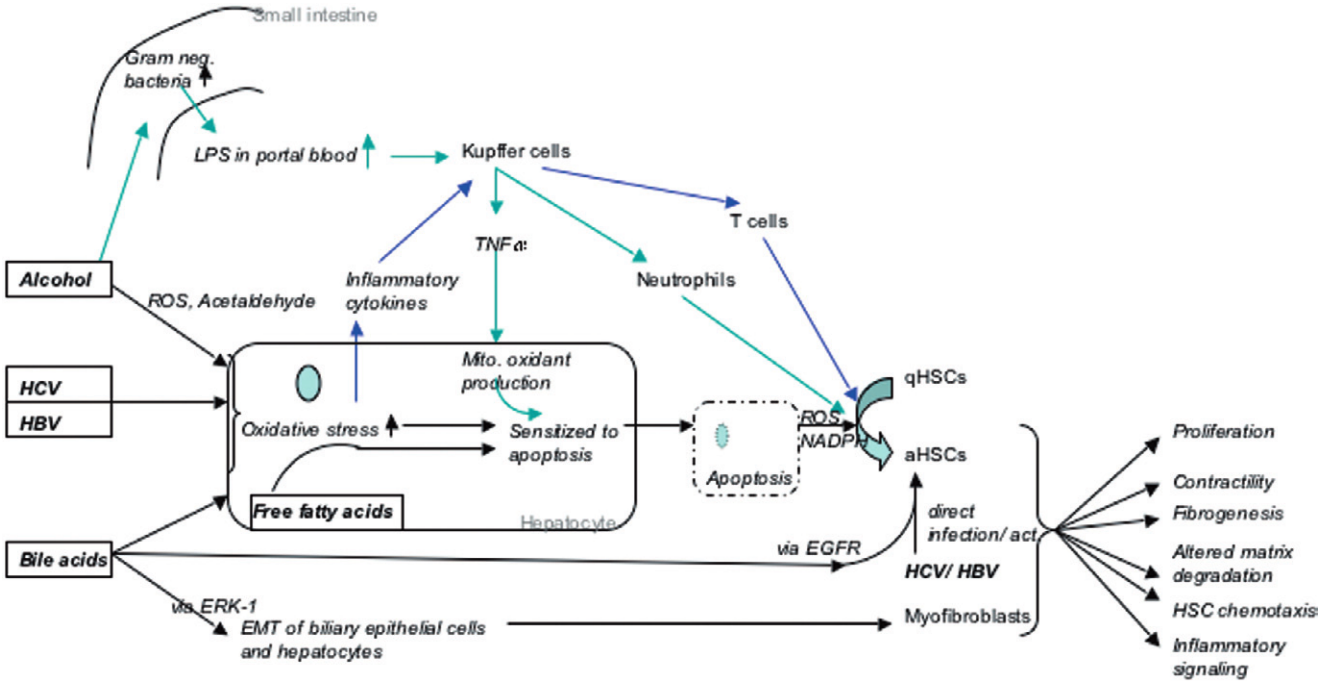


FIGURE 6.2. Pathways of liver injury and fibrosis. This diagram depicts the key pathways of cellular injury and fibrosis. The main causes of chronic liver injury are alcohol, viral infection, and injury by bile acids. All factors activate hepatic stellate cells (HSCs), which is a key event in liver fibrogenesis. Alcohol leads to gram-negative bacteria overgrowth of the small intestine with consequent increase of lipopolysaccharide (LPS) in the portal blood. LPS activates Kupffer cells, which increase the mitochondrial oxidant production in hepatocytes by way of tumor necrosis factor (TNF)-α, thereby sensitizing them to apoptosis. Kupffer cells also support local accumulation of T cells and neutrophils, which, along with apoptotic hepatocytes, stimulate the activation of HSCs. Infection of hepatocytes by hepatitis B and hepatitis C virus (*HCV, HBV*) promotes oxidative stress, further sensitizing hepatocytes to apoptosis. Free fatty acids also increase the intracellular oxidative stress of hepatocytes. Bile acids are directly toxic to hepatocytes and lead to increased secretion of inflammatory cytokines by hepatocytes, which activate Kupffer cells. Bile acids also directly activate HSCs and can promote epithelial–mesenchymal transition (EMT) of biliary epithelial cells and hepatocytes into myofibroblasts. ROS, reactive oxygen species; ERK-1, extracellular signal-regulated kinase-1; mito., mitochondrial; NADPH, nicotinamide adenine dinucleotide phosphate; EGFR, endothelial growth factor receptor; qHSC, quiescent HSC; aHSC, activated HSC.

again leading to recruitment of inflammatory cells and HSC activation. HSCs can also be directly activated by either HCV, through membrane receptors (Mazzocca et al, 2005, Schulze-Krebs et al, 2005), or by HBV (Martin-Vilchez et al, 2008).

Bile acids are hepatotoxic agents that typically target hepatocytes, but they may also injure biliary epithelium (Higuchi & Gores, 2003). Damaged hepatocytes turn apoptotic or necrotic, thereby releasing ROS (Nieto et al, 2002) and NADPH oxidase, which both activate HSCs (Canbay et al, 2004a). Injured hepatocytes also release inflammatory cytokines and soluble factors that activate Kupffer cells and stimulate the recruitment of activated T cells. This inflammatory milieu further stimulates the activation of resident HSCs. Bile acids also directly stimulate proliferation of HSCs by activating the epidermal growth-factor receptor (Svegliati-Baroni et al, 2005). In contrast to hepatocytes, HSCs are protected from bile acid–induced apoptosis by excluding bile acids (Svegliati-Baroni et al, 2005).

Nonalcoholic fatty liver disease (NAFLD) is increasingly prevalent as a result of increased obesity in the United States and Western Europe. NAFLD can progress to NASH with consequent fibrosis and cirrhosis (Carter-Kent et al, 2009). The pathogenesis is not fully understood; however, a two-hit model has been proposed with hyperglycemia and insulin resistance representing the first hit, leading to elevated serum levels of free fatty acids. Histologically this correlates to hepatic steatosis. Additional oxidative stress or proinflammatory cytokines are thought to promote hepatocyte apoptosis and recruitment of inflammatory cells, thereby enhancing fibrogenesis.

Hepatic Stellate Cell Activation and Hepatic Myofibroblasts (MFBs)

The HSC has emerged as a central regulator of the liver's fibrotic and repair responses (Friedman, 2000). In normal liver the HSC is a quiescent cell type that contains cytoplasmic retinoid droplets, representing the major storage site for vitamin A in the body, and expresses the markers desmin and glial fibrillary acidic protein (GFAP; Friedman, 2008).

During liver injury, HSCs undergo activation in response to a range of inflammatory and injury signals (Casini, 1997) produced by damaged hepatocytes and biliary cells; changes in the composition of the ECM; proangiogenic growth factors, like VEGF and angiopoietin; and fibrogenic cytokines that include TGF-β1, angiotensin II, and leptin.

Activation of HSCs is accompanied by loss of retinoid droplets and accumulation of α-smooth muscle actin, a myogenic filament that confers increased cellular contractility. Activated HSCs are characteristically desmin- and α-SMA–positive cells. Highly activated subsets of HSCs are known as *hepatic myofibroblasts* (MFBs; Friedman, 2008), a cell type that is also characteristic of wound healing in a range of tissues: skin, kidney, lung, bone marrow, and pancreas, among others.

HSC activation can be divided conceptually into two phases: *initiation* begins with early changes in gene expression and phenotype that result from paracrine stimulation, primarily due to changes in surrounding ECM and exposure to lipid peroxides and products of damaged hepatocytes (Fig. 6.3); *perpetuation* results from the effects of these stimuli on maintaining the activated phenotype and generating fibrosis. Within the nucleus, a growing number of transcription factors regulate HSC behavior, including peroxisomal proliferator–activated receptors (PPARs), retinoid receptors, NF-κB, JUND, Kruppel-like factor 6 (KLF6), and FOXF1 (Mann & Mann, 2009). A range of general and cell type–specific membrane receptors and signaling pathways also control HSC biology, including receptor tyrosine kinases, chemokine receptors, and integrins (Dodig et al, 2007).

Portal fibroblasts (Beaussier et al, 2007; Ramadori & Saile, 2004) and bone marrow–derived MFBs (Russo et al, 2006) have also been identified as collagen-producing cells in the injured liver. Another emerging source of fibrogenic cells is epithelial-mesenchymal transition (EMT), in which adult hepatocytes of biliary epithelium transdifferentiate into fibrogenic cells (Rygiel et al, 2008). EMT has been extensively characterized in kidney and lung fibrosis, in subsequent animal models and human samples of liver fibrosis, and in the context of hepatocarcinogenesis. Interestingly, key signals regulating EMT also drive activation of HSCs, including TGF-β, RAS, extracellular signal-regulated kinase 1 (ERK1; Zhong et al, 2009), SMAD7, and SHH (Dooley et al, 2008; Lahsnig et al, 2009; Syn et al, 2009).

The relative importance of each cell type in liver fibrogenesis may depend on the origin of the liver injury. In cholestatic liver diseases and ischemia, portal fibroblasts may be especially important (Clouzeau-Girard et al, 2006), whereas hepatic MFBs may be of predominant importance in alcoholic liver disease. In chronic liver injury, progressive recruitment of bone marrow–derived cells may occur over time. However, bone marrow–derived cells may have both fibrogenic and antifibrotic effects (Karlmark et al, 2009). To date, the quantitative contribution to fibrogenesis of nonstellate cell–derived fibroblasts remains unclear.

Functions of Hepatic MFBs

Hepatic MFBs have functions that are distinct from their quiescent cells of origin. They are profibrogenic and promitotic, play a chemotactic and vasoregulatory role, and control the degradation of the ECM (see Fig. 6.3). They also have important immune and phagocytic functions (Friedman, 2008). The regulation of ECM accumulation and degradation by HSCs is reviewed in the next section.

Fibrogenesis

The major profibrogenic signal in the liver is the cytokine TGF-β1 (Bachem et al, 1989a). TGF-β1 is secreted mainly by MFBs (Bissell et al, 1995) but also by platelets (Bachem et al, 1989b) and Kupffer cells (Bilzer et al, 2006). It acts by activating the TGF-βII receptor, which recruits the TGF-βI receptor. SMAD2 and SMAD3 then associate with the TGF-βI receptor (Dooley et al, 2001), are phosphorylated, and recruit SMAD4. This triheteromeric complex then translocates to the nucleus, where it activates profibrogenic transcription factors. TGF-β also activates the MAPK p38 pathway (Cao et al, 2002), which leads to additional, SMAD-independent collagen type 1 synthesis and, in contrast to the SMAD-dependent collagen type 1 synthesis, also leads to a posttranscriptionally regulated stabilization of the collagen type 1 mRNA (Tsukada et al, 2005; Fig. 6.4).

Proliferation

The predominant stimulus to MFB proliferation is the mitogen platelet-derived growth factor (PDGF; Borkham-Kamphorst et al, 2004), in addition to other mitogens that include EGF, VEGF, and FGF. All pathways downstream of PDGF receptor

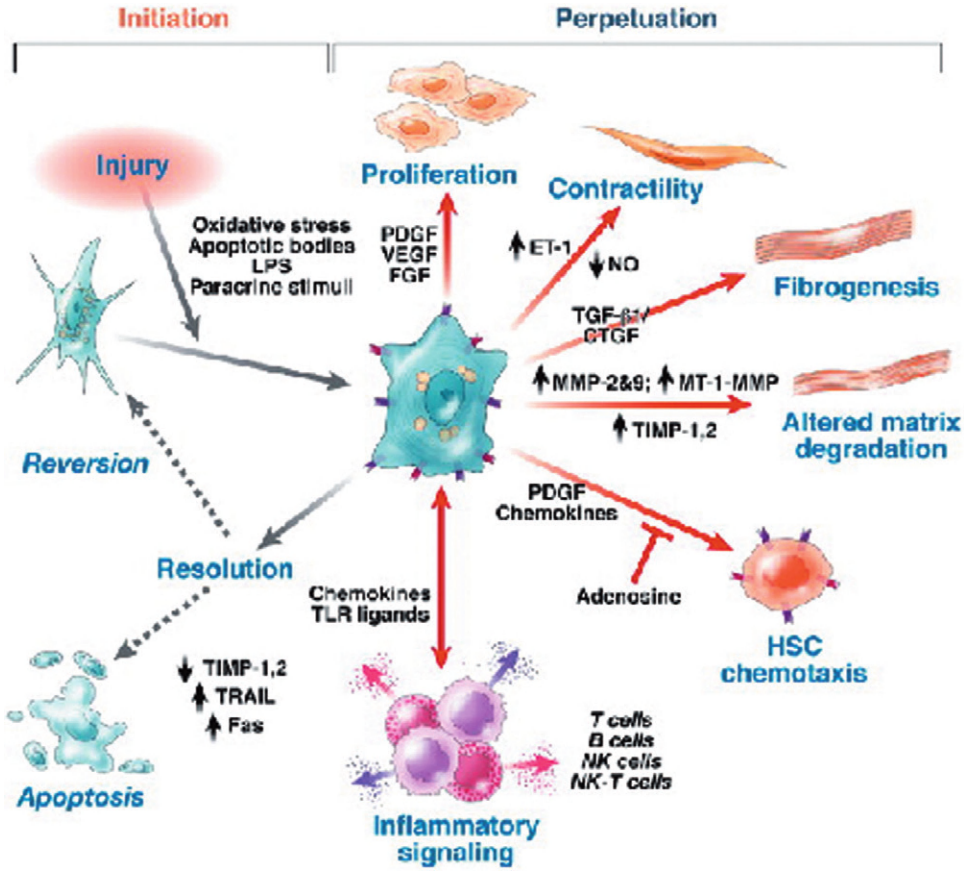


FIGURE 6.3. Key effectors, cellular features, and mediators in HSC activation during liver injury. Features of stellate cell activation can be differentiated into two stages: *intiation* begins with early changes in gene expression and phenotype that results from paracrine stimulation, primarily as a result of changes in surrounding extracellular matrix (ECM) as well as exposure to reactive oxygen species (ROS), apoptotic bodies, lipopolysaccharide (LPS), and paracrine activation by Kupffer cells; *perpetuation* results from the effects of these stimuli on maintaining the activated phenotype and generating fibrosis. PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor; ET-1, endothelin-1; NO, nitric oxide; TGF-β, transforming growth factor β; CTGF, connective tissue growth factor; MMP, matrix metalloproteinase; TIMP, tissue inhibitor metalloproteinase; TRAIL, TNF-related apoptosis-inducing ligand. *(Modified from Ghaissi-Nejad Z, Friedman SL (2008). Advances in antifibrotic therapy. Expert Rev Gastroenterol Hepatol 2:803-816.)*

activation promote proliferation. First, JNK is stimulated through MAPK (Schnabl et al, 2001); second, PDGF receptor stimulates the Ras/Raf complex, followed by MEK and ERK engagement (Schnabl et al, 2001); and third, activation of the PI3K pathway leads to Akt activation and phosphorylation of the 70s6 kinase (see Fig. 6.4; Reif, 2003).

Immunoregulation

The liver is a microenvironment of diminished immunogenicity, which is necessary to cope with the high exposure of antigens from the portal vein (Crispe, 2003). This feature also accounts for the tolerance of liver transplantation across ABO barriers and may contribute to the chronic nature of hepatitis B and C, where the virus persists despite the development of an immune response. Upon entry of antigen into the sinusoid, classical antigen-presenting cells (Kupffer cells, dendritic cells) are first encountered. Subsequently, HSCs in the space of Disse may contact antigens. Indeed, HSCs display a wide range of immunoregulatory functions and are an essential part of the local immunogenicity (Gao et al, 2008; Mehal, 2007; see Chapter 9).

Hepatic MFBs produce a range of proinflammatory (e.g., TNF-α; Tiggelman et al, 1995) and antiinflammatory IL-10 cytokines (Tiegs & Lohse, 2009; Safadi et al, 2004) and they recruit lymphocytes through secretion of chemokines (MCP-1, IL-8, CCL21, RANTES; Marra et al, 1998, 1993; Maher et al, 1998), thus amplifying the inflammatory response. However, upon activation, they exert a profound immunosuppressive activity by inducing T-cell apoptosis (Yu et al, 2004). In the setting of liver transplantation, MFB-induced T-cell apoptosis via programmed death ligand-1 (Yu et al, 2004) may enable local immunotolerance of the liver. In liver fibrosis, MFBs may further regulate the contribution of lymphocytes to the course of hepatic fibrosis by ingesting disease-associated lymphocytes (Muhanna et al, 2008).

The interaction between HSCs and immune cells is bidirectional. T cells activate HSCs by IFN-γ, which upregulates both stimulatory (CD80, CD86, CD54) and inhibitory (B7-H1) surface molecules and enhances both inflammatory and suppressive cytokines. However, the inhibitory molecules are thought to override the stimulatory counterparts, resulting in immunosuppression. Lymphocytes can also mediate hepatic fibrosis by activating HSCs. CD8-positive T lymphocytes are more fibrogenic toward stellate cells than CD4-positive T lymphocytes (Safadi et al, 2004). This may explain in part why

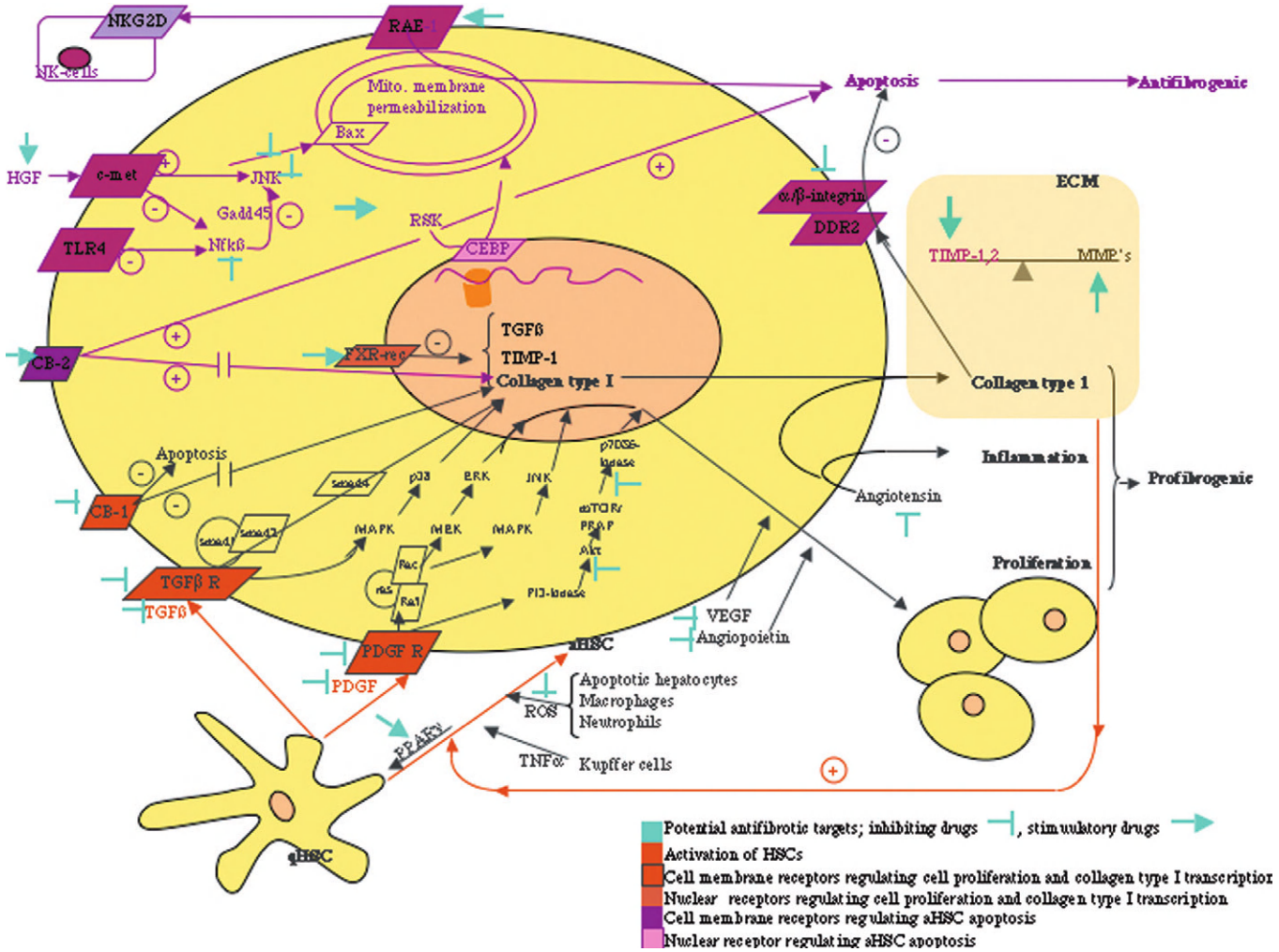


FIGURE 6.4. Cellular and molecular mechanisms of hepatic stellate cell (HSC) activation and potential antifibrotic targets.The HSC can be activated by paracrine stimuli, such as platelet-derived growth factor (PDGF) and transforming growth factor (TGF); by reactive oxygen species (ROS) produced by macrophages, neutrophils, or apoptotic hepatocytes; and by tumor necrosis factor (TNF) secreted by Kupffer cells. The activated HSC or hepatic myofibroblast (MFB) has multiple cell membrane receptors that can either upregulate proliferation (e.g., PDGFR), stimulate collagen type I synthesis (e.g., TGFR, cannabinoid [CB] 1 receptor), inhibit collagen type I transcription (e.g., cannabinoid [CB] 2 receptor), or regulate apoptosis of MFBs (e.g., c-Met receptor, Toll-like receptor 4 [TLR4]), retinoic acid early-inducible protein 1 receptor (RAE-1R), discoidin domain receptor (DDR), or integrin receptor. There are also nuclear receptors that regulate transcription of collagen type I, tissue-inhibitor metalloproteinase-1, and TGF farnesoid X receptor (FXR-R) and that regulate apoptosis of MFBs (CCAAT/enhancer-binding protein [C/EBP]). All of these pathways are potential targets of antifibrotic therapy, as depicted in the figure. NK, natural killer (cells); NKG2D, natural killer group 2D; Bax, Bcl-2–associated X protein; RSK, ribosomal S-6 kinase; TIMP, tissue-inhibitor metalloproteinase; MMP, matrix metalloproteinase; ECM, extracellular matrix; PPARγ, peroxisome proliferator-activated receptor γ; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-related protein kinase; MEK, mitogen-activated protein kinase ; JNK, Jun N-terminal kinase; P3K, phosphoinositide 3-kinase; mTOR/FRAP, mammalian target of rapamycin/FKBP12-rapamycin–associated protein; VEGF, vegetative epidermal growth factor.

patients coinfected with HIV and HCV have accelerated fibrosis, as their CD4–CD8 cell ratios are reduced. Of the CD4-positive T lymphocytes, previously called *T helper cells*, the humoral-mediated immunity by T helper-2 (Th2) cells is profibrogenic in liver injury, whereas the cell-mediated immunity by T helper-1 (Th1) cells via IFN-γ, TNF-α, and IL-2 is antifibrogenic (Shi, 1997).

HSCs can also function as antigen-presenting cells (Winau et al, 2007). They can interact with bacterial lipopolysaccharides directly via TLR4, which amplifies their activation. TLR4 signaling leads to downregulation of a TGF-β pseudoreceptor, BAMBI, which thereby amplifies fibrogenic activity of MFBs (Seki & Brenner, 2008). This might contribute to an accelerated progression of liver cirrhosis, as microbial translocation from the gut to the liver is increased, which is the case in alcoholic liver disease.

Vasoregulation

MFBs play an important role in the regulation of sinusoidal blood flow and may contribute to portal hypertension that is characteristic of advanced liver disease. The release of endothelin-1 (ET-1) can stimulate their contraction through

the ETA receptor (Shi-Wen et al, 2004), thereby promoting tissue contraction, increasing portal resistance, and generating portal hypertension. On the other hand, MFBs and endothelial cells also secrete nitric oxide (NO), which is the physiologic antagonist of ET-1.

Structural Features of Hepatic Fibrogenesis

In hepatic fibrosis the total amount of collagen is increased up to sixfold, whereas the parenchymal mass (e.g., hepatocytes) is progressively diminished. The composition of the ECM changes with progression of disease. Collagen type IV in the space of Disse is replaced by interstitial collagen types I and III. Additionally, the discontinuous basal membrane beneath the sinusoidal endothelial cells is replaced by a continuous basement membrane, and sinusoidal fenestrations are reduced. This decreased porosity, also known as *capillarization*, combined with perisinusoidal fibrosis, scar contraction, and formation of intrahepatic shunts contributes to increased hepatic venous pressure and portal hypertension. Fibrillar collagens produced by MFBs interact with MFBs via discoidin domain receptors and integrins (Olaso et al, 2001), thereby inhibiting apoptosis and increasing MFB proliferation.

With the maturation of the fibrotic scar, not only is the amount of collagen increased, but the scar also becomes increasingly insoluble through chemical cross-linking by transglutaminase, and assembly of collagen fibrils through increased generation of collagen monomers by metalloproteinases from the "ADAM metallopeptidase with thrombospondin type 1 motif"; in addition, metalloproteinase with thrombospondin-type repeats metalloproteinase with thrombospondin type I motif (ADAMTS2; Kesteloot et al, 2007) family. This makes the fibrous septa progressively resistant to proteolysis by matrix metalloproteinases (MMPs). The long-standing clinical dogma—the slower the pace of injury, the less reversible the scar—is supported by animal studies in which even advanced fibrosis of short duration is reversible. Thus, the reversibility of a scar may be limited primarily by the extent of collagen cross linking. Clinically, increased septal thickness and smaller nodule size, both of which reflect more advanced stages of fibrosis, are significant predictors of worse clinical outcomes (Nagula et al, 2006).

Regulation of Collagen Deposition and Degradation

The deposition and degradation of collagen is tightly regulated. MMPs are the key enzymes that degrade fibrillar collagens (types I and III) and noncollagenous ECM substrates. The tissue inhibitor metalloproteinases (TIMPs) are their major antagonists by inactivating proteases and by inhibiting MFB apoptosis (Murphy et al, 2002).

Both decreased levels of interstitial collagenases and increased levels of MMP inhibitors in liver injury create an imbalance that favors reduced degradation of fibrillar collagens in hepatic fibrosis. The interstitial collagenases MMP-1, MMP-8, and MMP-13 in humans and MMP-13 in rodents (Emonard & Grimaud, 1990) unwind the triple-helical collagen type I, which is the principal collagen in the fibrotic liver (Williams & Olsen, 2009), so that each α-chain is presented to the active site of the enzyme (Chung et al, 2004), which cleaves the collagen. Other MMPs (e.g., MMP-2) cannot unwind the triple-helical collagen and thus cannot degrade intact collagen type I alone. In early liver injury, MMP-2 degrades the low-density basement membrane present in the subendothelial space (Zhou et al, 2004a). Its replacement with fibril-forming matrix impairs hepatocyte differentiation and function. During progressive fibrosis, expression of MMP-1 (humans) or MMP-13 (rodents) is decreased, and MMP-2 expression increases (Preaux et al, 1999; Milani et al, 1994). In parallel, the expression of TIMP-1 and TIMP-2, which inhibit the collagen-degrading matrix metalloproteinases, are increased (Kossakowska et al, 1998; Murawaki et al, 1993).

Hepatic macrophages also regulate matrix remodeling (Mitchell et al, 2009), and they are an important source of proteases, including MMP-13 (Hironaka et al, 2000; Fallowfield et al, 2007) in rodents. Macrophages might even be more critical to ECM degradation than HSCs, whose degradation potential is impaired during activation by elevation of the inhibitor TIMP-1. Kupffer cells can further stimulate TIMP-1 expression by hepatic MFBs (Wang et al, 2009), leading to inhibition of MMP activity and also protection of MFBs from apoptosis. In mouse models, macrophages augment fibrogenesis during progression of liver fibrosis, whereas during resolution they hasten matrix degradation through increased production of MMP-13 (Fallowfield et al, 2007).

Although both macrophages and MFBs secrete MMP-1 in humans and MMP-13 in rodents, it is not clear which is the major interstitial collagenase in fibrosis regression, because MMP-1 is only expressed at low levels in liver. Moreover, the cellular origin of those MMPs deemed essential to fibrosis regression remains controversial. Dendritic cells and T lymphocytes are also potential sources, as both can secrete MMP-9 (Chabot et al, 2006; Owen et al, 2003).

DIAGNOSIS AND CLINICAL MONITORING OF HEPATIC FIBROSIS

Many patients with chronic liver disease may initially present with late-stage fibrosis, as earlier stages are often asymptomatic. Thus clinicians must have a high index of suspicion for occult fibrosis, especially in patients with unexplained elevations of liver enzymes, splenic enlargement, stigmata of liver disease, or laboratory or imaging findings suggestive of portal hypertension. When chronic liver disease is suspected, liver biopsy remains the gold standard for diagnosing and staging liver fibrosis, but it is an invasive procedure with risk of adverse events (Bravo et al, 2001; Poynard et al, 2000) and, equally important, a high likelihood of sampling variability (Bedossa et al, 2003) and interpathologist and intrapathologist variability (Bedossa & Poynard, 1996). At least one third of biopsies may deviate by one fibrosis stage between the right and left hepatic lobes in HCV (Regev et al, 2002). Shorter biopsies are associated with an increase in reported diagnoses of mild and moderate fibrosis at the cost of more severe fibrosis, representing an understaging of fibrosis (Colloredo et al, 2003); the smaller the tissue sample, the milder the apparent disease.

Several commonly used histologic staging systems for fibrosis exist. The Histology Activity Index (HAI) score reported by Knodell includes three stages (Knodell et al, 1981), and the Ishak score differentiates six stages, including two stages of cirrhosis, *incomplete* and *complete* (Ishak et al, 1995). The METAVIR score, developed by the French METAVIR Cooperative Study Group, is a simple, widely applied five-stage

scoring system (Bedossa & Poynard, 1996) that is most commonly used worldwide. It incorporates the fibrosis scores F0 through F4 (F0, no fibrosis; F1, fibrosis without septa; F2, few septa; F3, numerous septa without cirrhosis; F4, cirrhosis) and activity scores A0 through A3 that assess the amount of necroinflammation (A0, no necroinflammatory activity; A1, mild; A2, moderate; A3, severe). All these systems were developed primarily for scoring fibrosis associated with viral hepatitis, with the main emphasis on the degree of necroinflammation. The fewer fibrosis stages within a scoring system, the higher the reproducibility among observers.

Scoring systems have also been specifically developed for different etiologies of liver fibrosis: Ludwig and colleagues proposed a four-stage system to describe fibrosis stages for both primary biliary cirrhosis (Ludwig et al, 1978) and sclerosing cholangitis (Ludwig et al, 1981), and Kleiner and colleagues (Kleiner, 2005) quantified fibrosis in NAFLD with a seven-stage system. The Kleiner stages are stage 0, no fibrosis; stage 1, perisinusoidal or periportal fibrosis (1a: mild, zone 3; 1b: moderate, zone 3; 1c: portal/periportal); stage 2, periportal and perisinusoidal fibrosis; stage 3, bridging fibrosis; and stage 4, cirrhosis.

There is a great need for reliable, quantitative, noninvasive diagnostics of fibrosis, and recent studies indicate steady progress. Cross-sectional imaging studies, such as those provided by computed tomographic (CT) and magnetic resonance imaging (MRI) scans, can reliably demonstrate features of advanced liver disease, including nodularity and signs of portal hypertension (splenomegaly, enlarged caudate lobe, esophageal varices). Diffusion-weighted MRI measures the apparent diffusion coefficient of water, a parameter that depends upon tissue structure, and it has compared favorably to other noninvasive measures for determining advanced fibrosis (Lewin et al, 2007).

Biochemical parameters associated with hepatocyte injury (AST, ALT), cholestatic liver injury (bilirubin, alcaline phosphatase), impaired liver synthetic function (apolipoproteins, cholesterol, coagulation factors, α_2-macroglobulin, hyaluronic acid, albumin, globulins), or impaired hepatic clearance of endogenous or exogenous substances from the circulation (bilirubin, bile acid, caffeine, lidocaine metabolites, bromosulfophthalein, indocyanine green, ammonia) can provide information on the presence and cause of the disease. These tests all assess impaired liver function in fibrosis. However, because abnormalities are likely only in more advanced stages of fibrosis, normal values will only exclude severe fibrosis but not mild to moderate fibrosis (METAVIR stages F1, F2). A more direct approach incorporates serum molecules associated with fibrosis, including those involved in deposition or degradation of ECM as well as specific fibrogenic cytokines associated with fibrosis.

Biochemical Tests

A number of combination serum tests have been evaluated for predicting fibrosis stage and outcomes with improving sensitivity and specificity. To date, no single molecule, but rather combinations of different components, demonstrates the best sensitivity and negative predictive values to exclude significant fibrosis.

The most studied combination serum tests are the AST platelet ratio index (APRI; Wai et al, 2003), the FIB-4 index (Sterling et al, 2006), the Forns test (Forns et al, 2002), and the proprietary FibroTest (Imbert-Bismut et al, 2001). Newer, proprietary biomarker scores include the HepaScore (Adams et al, 2005) and the FibroMeter (Cales et al, 2005). The factors included in the various tests were chosen upon multivariate analysis and are included in Table 6.1. All these biochemical tests are sufficient to excellent in ruling out significant fibrosis (F3 to F4) when the proper cutoff value is chosen, but they are less useful in distinguishing mild from moderate fibrosis. The sensitivities of these tests vary based on the etiology of the liver disease. A further difficulty with these tests involves the absence of an ideal "gold standard" in view of the liver biopsy's significant sampling variability and interlaboratory differences (Gressner et al, 2009). A key advantage of the biochemical tests, on the other hand, is that the patients most at risk for false-positive results are well defined, so that the results from these individuals can be evaluated more critically or complemented with further diagnostics.

Table 6.1

Common Noninvasive Tests for Detecting and Staging Liver Fibrosis

Test	Content
FIB-4 (Sterling, 2006)	Age, AST, platelets
APRI (Wai, 2003)	AST, platelets
Forns (Forns, 2002)	Age, GGT, cholesterol, platelets
FibroTest (Imbert-Bismut, 2001)	GGT, haptoglobin, α_2-macroglobulin, bilirubin, apolipoprotein A1, adjusted by age and gender
FibroTest-ActiTest (Imbert-Bismut, 2001)	ALT, GGT, haptoglobin, α_2-macroglobulin, bilirubin, apolipoprotein A1, adjusted by age and gender
Hepascore (Adams, 2005)	Total bilirubin, GGT, α_2-macroglobulin, hyaluronic acid, adjusted by age and gender
Fibrometer (Cales, 2005)	P1, α_2-macroglobulin, hyaluronic acid, age
SHASTA (Kelleher, 2005)	Hyaluronic acid, AST, albumin
ELF (Guha, 2008)	TIMP-1, hyaluronic acid, amino-terminal peptide of pro-collagen III (P3NP)
Fibroscan (Sandrin, 2003)	Liver elasticity measurement (in kilo-Pascals) by pulse-echo ultrasound (50 MHz)

AST, Aspartate aminotransferase; *GGT*, gamma-glutamyl transferase; *ALT*, alanine aminotransferase; *TIMP*, tissue inhibitor of metaloproteinases.

Of the biochemical tests, the FibroTest has been shown to be equal to or better than the others (Thabut et al, 2003; Le Calvez et al, 2004). In particular, it is more sensitive for discriminating between F1 and F2 stages and is more linearly correlated to fibrosis stages when compared with the other markers. Further improvement in prognostic value can be achieved by combining the FibroTest with the ActiTest and/or the FibroScan. The FibroTest combines the parameters gamma-glutamyl transferase (GGT), haptoglobin, α_2-macroglobulin, bilirubin, and apolipoprotein A1, corrected for age and gender; it has a high predictive value for significant fibrosis in patients with chronic hepatitis C and B and nonfatty liver disease (Imbert-Bismut et al, 2001; Poynard et al, 2007) and in patients with chronic alcoholic liver disease (Naveau et al, 2005; Thabut et al, 2006). In contrast to the other tests, the FibroTest has also been evaluated in a longitudinal study in which patients with HCV were followed up by a liver biopsy after α-interferon treatment. Promisingly, FibroTest results correlated well with the

progression or regression of fibrosis after antiviral therapy, and it compared favorably with liver biopsy (Poynard et al, 2002a).

The diagnostic value of the FibroTest has been compared to those of the HepaScore and FibroMeter in patients with chronic HCV (Halfon et al, 2007; Leroy et al, 2007), and the diagnostic and prognostic value was evaluated in patients with alcoholic liver disease (Naveau et al, 2009). All three tests have similar diagnostic accuracy in discriminating between advanced and nonadvanced fibrosis and between cirrhotic and noncirrhotic stages, however, the FibroTest was significantly better than the HepaScore or FibroMeter at predicting 10-year mortality in patients with alcoholic liver disease, and it was similar or even slightly better than the liver biopsy.

Serum Assays of Extracellular Matrix Molecules

Serum assays have been developed that measure circulating molecules involved either in the deposition of ECM or its degradation as well as cytokines involved in fibrogenesis. The best validated of these tests is the Enhanced Liver Fibrosis (ELF) panel (Guha et al, 2008). This test incorporates markers of ECM turnover: TIMP-1, hyaluronic acid, and aminoterminal peptide of procollagen III (P3NP). The ELF test was better at identifying minimal, moderate, or severe fibrosis than a clinical-biochemical panel that considered age, body mass index, presence of diabetes or impaired fasting glucose, aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio, platelets, and albumin. The combination of both clinical and biochemical scores showed further improved area under the receiver operating characteristic curve (AUROC) values in the subset of patients with an altered clinical-biochemical panel in reference to liver biopsies that were staged according to the Kleiner score (Angulo et al, 2007). If the ELF test was used to delineate any fibrosis, using thresholds with a sensitivity and specificity of 90%, the authors concluded that liver biopsy could have been avoided in 48% of patients.

Cytokines and Chemokines Associated with Hepatic Fibrosis

Of the cytokines and chemokines associated with hepatic fibrosis, TGF-β1 is the dominant stimulus for the production of ECM by HSCs. Hepatic mRNA levels of TGF-β1 are increased in chronic liver disease in association with increases in mRNA levels of type I collagen (Annoni et al, 1992). In HCV-related chronic liver disease, serum TGF-β levels correlate with the Knodell fibrosis score but not with clinical, biochemical, or virological parameters (Nelson et al, 1997). Interestingly, TGF-β levels also decreased in a group of HCV patients with histologic decreases in necroinflammation in the absence of changes in fibrosis following interferon treatment (Roulot et al, 1995). Thus TGF-β serum levels not only correlate with fibrosis scores but may also indicate necroinflammation (see Chapter 10). PDGF is upregulated following liver injury (Ikura et al, 1997), and at least one study suggested that the amount of PDGF correlates with the severity of fibrosis (Shiraishi et al, 1994).

Proteomics and Glycomics

Proteomics and glycomics are promising new technologies suitable as noninvasive diagnostic methods. Patterns of proteins or glycoprotein can be assessed by mass spectroscopy of serum samples (Petricoin et al, 2004). Profiles of serum protein N-glycans were found to have AUROC values similar to the FibroTest for the diagnosis of compensated cirrhosis. The combination of serum protein N-glycans with the FibroTest (FT) was able to increase the sensitivity and specificity of glycoprotein assessment alone (Callewaert et al, 2004).

FibroScan

An alternative approach to fibrosis assessment is the measurement of liver stiffness using a device that performs transient elastography. Currently, FibroScan (FS) is the only device to utilize this approach. It measures liver elasticity by using a pulse-echo ultrasound. A vibration of low frequency induces an elastic shear wave that propagates through the liver. The stiffer the liver tissue, the faster the shear wave propagates. Results are expressed in kilopascals (kPas; (Sandrin et al, 2003; Kettaneh et al, 2007). With FS, the virtual cylinder of tissue that is assessed is at least 200 times larger than a biopsy sample and therefore is far more representative of the hepatic parenchyma; thus the FS may provide a more accurate and reproducible picture of cirrhosis than liver biopsy. There is also potential value of FS in early stages of disease, when fibrosis may be unevenly distributed and thus underestimated by liver biopsy. Furthermore, FS has very low interobserver variability, although its accuracy is limited in patients with obesity, ascites, or acute hepatitis. FS has been evaluated extensively (Ziol et al, 2005; Cross et al, 2009; Sanchez-Conde et al, 2009; Boursier et al, 2009), is licensed in several European countries, and is currently being evaluated by the Food and Drug Administration (FDA) in the United States. When FS was combined with the FT in HCV patients, both tests agreed in 70% to 80% of subjects, with increasing concordance in higher stages of liver fibrosis. Compared with the liver biopsy, results were confirmed in 84% to 94% of cases with a tendency of FS/FT to underestimate fibrosis (Castera et al, 2005).

In aggregate, all the noninvasive approaches can accurately distinguish between patients with little or no fibrosis and those with advanced disease, but they are less reliable at discriminating intermediate stages of fibrosis. They show a high level of variability due to interlaboratory differences, but on the other hand, the patients at risk for false-positive results are well defined.

Although the combination of FT, FS, the ActiTest, and the ELF panel in NAFLD patients seems to be a good noninvasive alternative to liver biopsy, the value of these tests in individual patient management over time needs to be established. These tests may even be superior to liver biopsy at correctly staging and grading fibrosis (Poynard et al, 2004), but proving this remains a challenge with liver biopsy being the gold standard. A way to surmount this problem may be to assess the prognostic value of a test with the hard clinical end point of liver-related mortality compared with liver biopsy.

Despite these limitations, to date no single test can match the overall information obtained from liver biopsy histology regarding inflammation, fibrosis, steatosis, and architecture. The role of noninvasive alternatives so far lies in improving the fibrosis staging and grading made from liver biopsies and reducing the number of liver biopsies by screening patients with abnormal liver tests to identify patients with a higher probability of liver fibrosis who need further evaluation or therapy.

There is legitimate hope for the prognostic value of noninvasive tests, and that disease progression or response to therapy can be assessed by serial measurements of serum markers, thereby reducing the need for liver biopsies and improving the treatment of patients with liver disease. This, however, remains to be clarified by longitudinal studies measuring serum markers against clinical outcomes.

THERAPEUTIC STRATEGIES

The elucidation of pathways of hepatic fibrogenesis has provided a rational framework for developing antifibrotic therapies in chronic liver disease. Several points of attack are under development, and it may ultimately be advantageous to combine more than one therapy for maximal efficacy. To date, no antifibrotic therapy has been approved for clinical use, however, the basis for developing such agents is now well established, and meaningful success seems imminent.

Reversibility of Fibrosis: The Point of No Return

The concept of fibrosis as an irreversible and constantly progressing state is no longer accurate. Liver fibrosis of various etiologies is usually reversible by removing the causative agent (Friedman & Bansal, 2006). For example, a decrease in the viral load of HBV patients; clearance of HCV with pegylated interferon and ribavirin (Poynard et al, 2002b), but not maintenance interferon monotherapy (Di Bisceglie et al, 2008); cessation of ethanol intake; weight loss or bariatric surgery in patients with NASH; and decrease in iron or copper or immunosuppressive therapy in autoimmune diseases have been shown experimentally and clinically to limit fibrosis progression and to even regress cirrhosis in some cases. In fact, removing the causative agent is still the most effective therapy.

Although fibrosis, inflammation, and bile duct proliferation decrease when the damaging stimulus is withdrawn, regenerative nodules may become autonomous and grow progressively (Quinn & Higginson, 1965). This raises a key question, whether a "point of no return" exists, wherein even complete clearance of the underlying disease will no longer yield an improvement in cirrhosis. Increased cross linking of the collagen fibrils over time makes the fibrous septa progressively resistant to proteolysis by metalloproteinases, and hypoxia stimulates secretion of proangiogenic factors such as VEGF and angiopoietin-1 by HSCs, which induce proliferation and motility (Nakamura et al, 2007). These findings suggest there may be a positive feedback loop between angiogenesis and fibrogenesis, which persists even when the primary etiology is cleared, leading to sustained abnormalities of the intrahepatic vasculature.

Prevention of Hepatocyte Apoptosis in Liver Injury

Apoptosis of hepatocytes during liver injury is a proinflammatory event associated with Kupffer cell and HSC activation (Canbay et al, 2004); thus agents have been developed to minimize apoptotic death of hepatocytes in chronic liver injury by inhibiting those caspases that contribute to the apoptotic cascade. In the surgical setting, reduced hepatocyte damage is pursued by decreasing the time of vascular occlusion (Pringle maneuver) during resection or by shortening the ischemia/reperfusion (I/R) time in transplant surgery. Experimental approaches to reduce I/R injury (e.g., intermittent clamping, drugs) merit continued development to preserve hepatocyte integrity.

Caspase Inhibitors

Apoptosis is a functional antagonist to mitosis, and together these two processes regulate homeostatic cell turnover. The two main pathways of apoptosis are the *extrinsic pathway*, which is death ligand–death receptor mediated and dependent on caspase 8, and the *intrinsic pathway*, which is regulated by Bcl2-induced mitochondrial dysfunction and downstream activation of caspase 9 and its effector caspases 3, 6, and 7. Blocking caspases downstream of the mitochondria, however, only delays apoptosis; it does not inhibit it (Chen et al, 1998; Strobel et al, 1996). Thus pancaspase inhibitors are being used to assess the therapeutic effect of apoptosis inhibition. In preclinical studies, the pancaspase inhibitor ZVAD-fmk was able to reduce mortality in rats with acute hepatic failure after major hepatic resection (Yoshida et al, 2007). Other caspase inhibitors have reduced I/R injury in rodents (Natori et al, 1999, 2003; Hoglen et al, 2007), decreased fibrogenesis in mice after bile duct ligation (Canbay et al, 2004), and decreased fibrogenesis in a diet deficient in methionine and choline, induced in a NASH mouse model in which hepatic steatosis and fibrogenesis improved without improvement of liver injury (Witek et al, 2009).

Only one clinical trial has been done in which a pancaspase inhibitor was administered in a dose-ranged manner to patients with liver disease of different etiologies. However, this agent, IDN-6556, also inhibits caspase 1, which has an inflammatory effect; thus the drug should be antiinflammatory. In the two weeks of treatment, in the subset of patients with HCV as their underlying disease, AST and ALT levels were significantly reduced without affecting the HCV mRNA levels. No adverse events occured (Pockros et al, 2007). Caspase inhibitors thus far are considered safe, as animals with genetic deletions of death receptors do not show increased spontaneous tumors (Adachi et al, 1995; Pfeffer et al, 1993; Yue et al, 2005). Nonetheless, the potential emergence of tumors following long-term administration remains a lingering concern.

Inhibition of HSC Activation or Inactivation of MFBs

Oxidative stress in the form of ROS released by injured hepatocytes through the action of NADPH represent a major fibrogenic stimulus. Thus antioxidants including vitamin E, silymarin, CYP2E1 inhibitors (Nieto et al, 2002), phosphocholine, or S-adenosyl-L-methionine may benefit fibrosis, particularly in patients with alcohol-induced liver disease and NASH, where oxidative stress plays an especially important role. Efforts to establish the activity of antioxidants are confounded by the uneven quality of commercially available products, because these compounds are typically sold over the counter, and their potency is not monitored.

Immune manipulation also holds promise but is not yet ready for clinical testing. Th1 cells that mediate cellular immunity through IFN-γ, TNF-α, and IL-2 are antifibrogenic, whereas Th2 cells that promote humoral immunity are more profibrogenic via IL-4, IL-5, IL-6, and IL-13 (Shi et al, 1997;

Lee et al, 2001). Thus a shift toward the Th1 cells, away from the Th2 cells, might be beneficial for fibrosis development.

Given their widespread use in diabetes, PPARγ agonists are now being tested in clinical trials both in NASH and HCV (Belfort et al, 2006). PPARγ nuclear receptors are expressed in HSCs, and PPARγ overexpression can regress MFBs to their quiescent state experimentally (Hazra et al, 2004). However, the total amount of HSCs detected by αSMA- or desmin-positive staining is decreased in animals with fibrosis regression (Kim et al, 2005), which suggests that MFB apoptosis, and not reversion into the quiescent form, is the predominant mechanism in vivo that leads to fibrosis regression. Synthetic PPARγ ligands downregulate HSC activation (Zhao et al, 2006).

Wnt signaling has been implicated in pulmonary and renal fibrosis and has also been reported to promote hepatic fibrosis by enhancing HSC activation and survival. This suggests that Wnt antagonism may be a useful target in liver fibrosis (Cheng et al, 2008).

Induction of MFB Apoptosis

Because the natural resolution of fibrosis leads to apoptosis and clearance of MFBs, approaches that exploit these native pathways of resolution merit attention. More specifically, because TIMP is antiapoptotic and blocks matrix proteases, reduced expression or neutralization favors clearance of MFBs through increased apoptosis and enhanced breakdown of scar (Iredale et al, 1998). The translation of this approach to humans will be challenging, however, as human cells appear to have more enhanced antiapoptotic activity through increased expression of the antiapoptotic protein Bcl-2 (Novo et al, 2006).

NF-κB is a nuclear transcription factor that inhibits apoptosis of MFBs, thus any compound that inhibits NF-κB merits evaluation (see Fig. 6.4). For example, bortezomib, a proteosomal inhibitor, prolongs the half-life of IκB-α, which is the naturally occurring cytosolic inhibitor of NF-κB (Oakley et al, 2003), preventing it from translocating to the nucleus and acting as a transcription factor. Related compounds, including gliotoxin or sulfalazine, exert similar effects by regulating transcription of NF-κB. For example, treatment of rodents with the NF-κB–inhibitor gliotoxin that specifically targets MFBs, with the help of targeting technologies (C1-3) selectively induced MFB apoptosis and accelerated regression of fibrosis in experimental liver injury (Douglass et al, 2008). Further, an NF-κB decoy increased TNF-α–induced MFB apoptosis and decreased CCl4-induced fibrosis in comparison to controls (Son et al, 2007).

Affecting the phosphorylation of CCAAT/enhancer-binding protein β (C/EBP-β) may lead to caspase activation and enhanced HSC apoptosis (see Fig. 6.4). C/EBP-β is a transcription factor predominantly expressed in adipose, hepatic, and immune tissue. When C/EBP-β is phosphorylated by ribosomal S-6 kinase (RSK), this leads to activation of caspase 8, which leads to MFB apoptosis (Buck & Chojkier, 2007). Thus, activating RSK or caspase 8 directly will lead to MFB apoptosis.

There are also receptor-ligand–mediated pathways of MFB apoptosis that are potential drug targets. For example, the cannabinoid-1 (CB1) receptor leads to increased collagen deposition and protects MFBs from apoptosis, whereas the cannabinoid-2 (CB2) receptor is proapoptotic via induction of intracellular oxidative stress (see Fig. 6.4). Correspondingly, CB1-knockout mice, CB1 antagonist–treated mice (Teixeira-Clerc et al, 2006), and CB2 receptor–stimulated mice (Munoz-Luque et al, 2008) display less fibrosis and more MFB apoptosis than controls after CCl4 or TAA treatment or bile duct ligation, and CB2-knockout mice showed increased CCl4-induced fibrosis (Julien et al, 2005). Whereas trials of a systemic CB1-receptor antagonist for obesity and NASH were discontinued because of central nervous system (CNS) effects, a new generation of peripheral CB1 antagonists that do not enter the CNS are under development and could play a major role in an antifibrotic strategy.

Natural killer (NK) cells directly interact with the RAE-1 ligand expressed by early-activated MFBs and can lead to apoptosis (Radaeva et al, 2006). This effect is lost, however, in mature MFBs, as these cells lose RAE-1 expression (Radaeva et al, 2007), thereby limiting the potential of therapeutic NK cell–mediated MFB death in advanced fibrosis.

The adipokines adiponectin and leptin are natural counterregulators. Leptin is produced by MFBs, which contributes to their activation (Marra, 2002; Ikejima et al, 2002), and it has a profibrogenic effect on MFBs in hepatic injury (Saxena et al, 2002). In contrast, adiponectin promotes MFB apoptosis (Ding et al, 2005) and inhibits liver fibrogenesis in vitro and in vivo (Kamada et al, 2003). Adiponectin may become a useful antifibrotic agent, particularly in NASH.

Blocking MFB–ECM Interactions

MFBs and ECM interact in a positive feedback mechanism that could be amenable to therapeutic antagonism. MFBs interact with ECM via α- and β-integrins (Zhou et al, 2004b), thereby decreasing apoptosis and increasing proliferation of MFBs. This leads to increased collagen type I deposition, which further promotes survival of fibrogenic MFBs (Issa et al, 2003); thus blocking the MFB–ECM interaction could lead to increased MFB apoptosis (see Fig. 6.4). This has been confirmed by α3β2-integrin disruption with echistatin, neutralizing antibodies, or small interfering RNA (Zhou et al, 2004b). Similar studies exploring antagonism of integrin α5β6 are ongoing.

Antagonizing Compounds That Mediate Inflammation

As inflammation precedes and stimulates liver fibrosis, the use of antiinflammatory drugs has been proposed. A number of agents have antiinflammatory activity. For example, corticosteroids have been used for decades to treat autoimmune hepatitis, and pentoxifylline may exert its antifibrotic activity by downregulating TGF-β1 and connective tissue growth factor signaling (Raetsch et al, 2002). However, pentoxifylline can upregulate TIMP-1, thereby reducing its antifibrotic effect. It also inhibits NF-κB in Kupffer cells, thereby reducing TNF-α production, the impact of which is uncertain.

The renin–angiotensin system may also amplify inflammation, and its role in hepatic fibrosis research has grown. Angiotensin II is a vasoconstrictive peptide expressed by activated HSC in chronically injured livers (Paizis et al, 2002; Bataller et al, 2003a). It induces hepatic inflammation and stimulates fibrogenic actions of HSCs including cell proliferation and migration, secretion of proinflammatory cytokines, and collagen synthesis (Bataller et al, 2000, 2003b, 2003c; see Fig. 6.4). Inhibitors of this system have been in clinical use for antihypertensive therapy for a substantial time, which makes their use in

humans attractive. Preliminary studies in patients with chronic hepatitis C and nonalcoholic steatohepatitis suggest a positive effect on fibrosis progression by administering blocking agents (Yokohama et al, 2004), and several human trials are currently underway (Oakley et al, 2009, Colmenero et al, 2009).

Ursodeoxycholic acid (UDCA) has a beneficial effect on fibrosis in primary biliary cirrhosis. Similarly, a nitric oxide–releasing derivative of UDCA reduces inflammation, fibrosis, and portal pressure in an animal model (Fiorucci et al, 2003). Interestingly, UDCA also activates the pregnane X receptor (PXR), which has antifibrotic properties (Beuers et al, 2009). More recently, ligands of the farnesoid X receptor (FXR), another nuclear receptor, have been developed that are also antifibrotic in animal models (Zhang et al, 2009).

Selectively Antagonizing Pathways of HSC Activation

Fibrogenic, proliferative, proangiogenic, vasoconstrictive, and proinflammatory mediators work synergistically toward hepatic fibrogenesis in the setting of chronic liver injury. Thus, efforts are underway to antagonize the specific mediators driving these pathways. Multiple approaches have been directed toward blocking the profibrogenic TGF-β signaling pathway. The effects of soluble TGF-β receptor type II (George et al, 1999), TGF-β–blocking antibodies, TGF-β–antisense oligonucleotides, or agents that interfere with TGF-β downstream signal transduction have been assessed experimentally (see Fig. 6.4). Systemically blocking the TGF pathway has theoretical limitations; however, because apart from stimulating wound healing and fibrosis, TGF-β is also a central inhibitor of uncontrolled inflammation, and it is essential in inducing epithelial differentiation and in triggering apoptosis. This raises safety concerns for the general and long-term use of TGF-β inhibition, especially in patients with chronic hepatic inflammation. The concern regarding use of TGF-β–blocking agents has further increased as a result of the first clinical study using CAT-192, a recombinant human antibody that neutralizes TGF-β in patients with cutaneous systemic sclerosis, in which a significant increase in morbidity and mortality was shown, with no evidence of a therapeutic effect (Denton et al, 2007). Nonetheless, there are currently two monoclonal antibodies against TGF-β, lerdelimumab and meselimumab, in clinical Phase I through phase III trials for pulmonary fibrosis, systemic sclerosis, and postoperative scarring in glaucoma patients (Yingling et al, 2004).

To antagonize PDGF, administration of a PDGF kinase inhibitor with an HSC-selective carrier (mannose-6-phosphate–modified human serum albumin) significantly reduced bile duct ligation–induced fibrosis (Gonzalo et al, 2007). Imatinib mesylate, a clinically used PDGF receptor tyrosine kinase inhibitor, also attenuates proliferation, migration, and expression of αSMA and α2-(I)-procollagen mRNA in MFBs in a dose-dependent manner (Yoshiji et al, 2005). Furthermore, rapamycin, an immunosuppressive drug used after liver transplantation, has the added benefit of inhibiting HSC proliferation. It acts by inhibiting the p70s kinase, which is a downstream target of PDGF and leads to HSC proliferation (Gabele, 2005; see Fig. 6.4).

Proangiogenic growth factors, such as VEGF-A and angiopoietin 1, induce HSC proliferation and motility. The efficacy of the small-molecule VEGF receptor antagonist sunitinib in hepatocellular carcinoma (HCC) has been complemented by evidence of antifibrotic activity in an animal model (Tugues et al, 2007; see Fig. 6.4).

Apart from blocking HSC-stimulating factors, activating HSC-inhibitory factors is yet another possibility. Hepatocyte growth factor (HGF) inhibits HSC activation, decreases TGF-β, and increases HSC apoptosis (Kim et al, 2005; see Fig. 6.4). However, potential procarcinogenic effects are likely to limit its therapeutic use. Clinical trials with HGF deletion variants and mimetics are underway.

Bone marrow–derived mesenchymal stem cells have an antifibrotic effect, on the one hand increasing HSC apoptosis through secretion of HGF and on the other decreasing proliferation of HSCs through release of IL-10 and TNF-α upon stimulation by IL-6 from hepatic MFBs (Parekkadan et al, 2007). This makes stem cell therapy an interesting direction for fibrosis therapies. However, the bone marrow–derived mesenchymal stem cells also contribute to scar-forming MFBs in various organs, including the liver (Russo et al, 2006).

In rodents the blockade of the ETA receptor, which leads to vasoconstriction or scar contraction upon binding of ET-1, and the administration of vasodilators (prostaglandin E2 and nitric oxide donors) have antifibrotic qualities (Cho et al, 2000). This effect has yet to be confirmed in human studies.

Enhancing ECM Degradation

A number of rational approaches are under development to increase ECM degradation rather than solely block its production. As mentioned earlier, the two main families regulating ECM turnover are the *matrix metalloproteinases* (MMPs) that degrade the collagenous and noncollagenous ECM substrates and the *TIMPs* that inhibit MMP activities and also have an antiapoptotic effect on MFBs (Murphy et al, 2002; see Fig. 6.4). Blocking TIMP-1 with a monoclonal antibody reverses CCl4-induced fibrosis (Parsons et al, 2004).

Other experimental ways to shift the balance toward collagen degradation are the administration of uroplasminogen activator (uPA); it promotes formation of plasminogen out of plasmin, which upregulates MMP-9 synthesis (Hsiao et al, 2008; Hu et al, 2009; see Fig. 6.4). The administration via viral vector of recombinant proteolytically active MMP has shown antifibrotic potential in rodents (Iimuro et al, 2003; Siller-Lopez et al, 2004). However, there is a theoretical concern that MMP administration will lead to increased tumor formation. An advance using proteolytically inactive MMP-9 to solely neutralize TIMP-1 showed promising results without having this potential side effect (Roderfeld et al, 2006, 2007).

Although no antifibrotic drug is approved for clinical use in patients with liver fibrosis, the broad and rational development of a range of promising compounds means that success is likely in the near future. The challenge ahead is to find further targeting points and to show efficiency of these new drugs in vivo and ultimately in clinical trials, thus long follow-up studies are required. Equally challenging is the need to define clear and robust end points for clinical trials to ensure that a therapeutic benefit is apparent. Finding good, noninvasive alternatives for diagnosis and follow-up and assessing prognosis of liver fibrosis are important first steps for developing and evaluating better treatment options.

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CHAPTER 7

Bile secretion and pathophysiology of biliary tract obstruction

Henry A. Pitt, Attila Nakeeb, and N. Joseph Espat

OVERVIEW

Bile secretion is one of the major functions of the liver, and it serves two major purposes: 1) the excretion of hepatic metabolites—including bilirubin, cholesterol, drugs, and toxins—and 2) the facilitation of intestinal absorption of lipids and fat-soluble vitamins. Alterations in bile secretion may contribute to cholelithiasis (see Chapter 30) and its potential complications, such as cholecystitis (see Chapter 31) and choledocholithiasis (see Chapters 35, 36, and 37). On the other hand, obstruction of bile flow results in alterations of coagulation, the immune system, and all organ function. This chapter will discuss the physiology of bile secretion, the pathophysiology of bile obstruction, and the management of obstructive jaundice.

BILE SECRETION

Bile Formation

The two primary roles of bile in normal physiology are the excretion of organic compounds, such as bilirubin and cholesterol, and the intestinal absorption of lipids. Bile secretion results from the active transport of solutes into the canaliculus, followed by the passive flow of water. Water constitutes about 85% of the volume of bile. The major organic solutes in bile are bilirubin, bile salts, phospholipids, and cholesterol. Bilirubin, the breakdown product of spent red blood cells, is conjugated with glucuronic acid by the hepatic enzyme glucuronyl transferase and is excreted actively into the adjacent canaliculus. Normally, a large enzyme reserve exists to handle excess bilirubin production, which might exist in hemolytic states.

Bile salts are steroid molecules synthesized by the hepatocyte. The primary bile salts in humans, cholic and chenodeoxycholic acid, account for more than 80% of those produced. The primary bile salts, which are then conjugated with either taurine or glycine, can undergo bacterial alteration in the intestine to form the secondary bile salts, deoxycholate and lithocholate. The purpose of bile salts is to solubilize lipids and facilitate their absorption. Phospholipids are synthesized in the liver in conjunction with bile salt synthesis, and lecithin is the primary phospholipid in human bile, constituting more than 95% of its total. The final major solute of bile is cholesterol, which is also produced primarily by the liver with a small contribution from dietary sources.

The normal volume of bile secreted daily by the liver is 750 to 1000 mL. Bile flow depends on neurogenic, humoral, and chemical control. Vagal stimulation increases bile secretion, whereas splanchnic stimulation causes vasoconstriction with decreased hepatic blood flow and thus results in diminished bile secretion. Gastrointestinal hormones—secretin, cholecystokinin, gastrin, and glucagons—all increase bile flow, primarily by increasing water and electrolyte secretion. This action probably occurs at a site distal to the hepatocyte. Finally, the most important factor in regulating the volume of bile flow is the rate of bile salt synthesis by hepatocytes. This rate is regulated by the return of bile salts to the liver by the enterohepatic circulation.

Bile Composition

The components of hepatic and gallbladder bile are essentially the same, but the concentration varies considerably because of the ability of the gallbladder to absorb water (Table 7.1). The gallbladder absorbs water both actively via sodium–hydrogen (Na^+/H^+) pumps and passively through aquaporin channels. Both chloride (Cl^-) and bicarbonate (HCO_3^-) are absorbed by the gallbladder epithelium via the cystic fibrosis transmembrane regulator (CFTR; Swartz-Basile et al, 2007). The secretion of hydrogen ions and the absorption of bicarbonate by the gallbladder alter the acid-base balance from basic in hepatic bile to acidic in gallbladder bile.

The gallbladder mucosa also absorbs the calcium (Ca^{++}) and magnesium (Mg^{++}) cations. However, calcium absorption is not as efficient as the absorption of sodium and water, which leads to a significantly greater relative increase in the concentration of calcium in the gallbladder. Similarly, the concentration of bilirubin, which is not actively absorbed by the gallbladder, may be as high as 10-fold. Thus precipitation of calcium bilirubinate crystals, the major component of pigment gallstones, is much more likely to occur within the gallbladder. In addition, the biliary lipids, bile salts, phospholipids, and cholesterol all become more concentrated in the gallbladder. As the gallbladder bile becomes concentrated, several changes occur in the capacity of bile to solubilize cholesterol. The solubility in the micellar fraction is increased, but the stability of the phospholipid–cholesterol vesicles is greatly decreased. Because cholesterol crystal precipitation occurs preferentially by vesicular, rather than micellar, mechanisms, the net effect of concentrating bile is an increased tendency to form cholesterol crystals (Klein et al, 1996).

Bile Salt Secretion

Bile is secreted from the hepatocyte into canaliculi, which drain their contents into small bile ducts. Secretion of bile salts is the major osmotic force for the generation of bile flow. Bile acids are formed at a rate of 500 to 600 mg per day. The bulk of the bile salt pool is maintained in the gallbladder, followed by the liver,

Table 7.1

Composition of Hepatic and Gallbladder Bile

Characteristics*	Hepatic Bile	Gallbladder Bile
Sodium	160	270
Potassium	5	10
Chloride	90	15
Bicarbonate	45	10
Calcium	4	25
Magnesium	2	4
Bilirubin	1.5	15
Protein	150	200
Bile acids	50	150
Phospholipids	8	40
Cholesterol	4	18
Total solids	—	125
pH	7.8	7.2

Significant ranges may be seen.
*All determinations are milliequivalents per liter, except for pH.

the small intestine, and the extrahepatic bile ducts. Bile acids are synthesized from cholesterol via two main pathways: a *classic pathway* leads to the formation of cholic acid, and an *alternate pathway* results in the synthesis of chenodeoxycholic acid. The classic pathway is the predominant mode of bile acid synthesis in humans. As a result, approximately 70% of the bile acid pool consists of cholic acid and its metabolite deoxycholic acid, with chenodeoxycholic acid occurring less commonly in human bile (Kullack-Ublick, 2004).

In plasma, bile acids circulate bound to either albumin or lipoproteins. In the space of Disse within the liver, bile salt uptake into the hepatocytes is very efficient. This process is mediated by sodium-dependent and sodium-independent mechanisms. The sodium-dependent pathway accounts for more than 80% of taurocholate uptake but less than 50% of cholate uptake (Meier & Stieger, 2002). In recent years a number of transport proteins have been identified that play a key role in this process (Fig. 7.1). The bile salt transporter is termed the *sodium-taurocholate cotransporting polypeptide* (NTCP), and it is exclusively expressed in the liver and located in the basolateral membrane of the hepatocyte. Sodium-independent hepatic uptake of bile acids is mediated primarily by a family of transporters termed the *organic anion transporting polypeptides* (OATPs). In contrast to NTCP, these transporters have a broader substrate affinity and transport a variety of organic anions, including the bile salts. OATP-C is the major sodium-independent bile salt uptake system, but OATP-A also takes up bile acids, and OATP-8 mediates taurocholate uptake.

Intracellular bile acid transport occurs within a matter of seconds. Two mechanisms may be responsible for bile acid transcellular movement: one involves transfer of bile acids from the basolateral membrane to the canalicular membrane via bile acid–binding proteins (Crawford, 1996), the other moves cellular bile salt through vesicular transport. In contrast, the transport of bile salts across the canalicular membrane of hepatocytes represents the rate-limiting step in the overall secretion of bile salts from the blood into bile.

Bile salt concentrations are 1000-greater within the canaliculi than in the hepatocytes. This gradient necessitates an active transport mechanism, which is an ATP-dependent process. This bile salt export pump (BSEP) is closely related to the proteins encoded by the multidrug resistance (MDR) gene family of ATP binding cassette (ABC) transporters (Kullack-Ublick, 2004). The ABC transporters mediate the

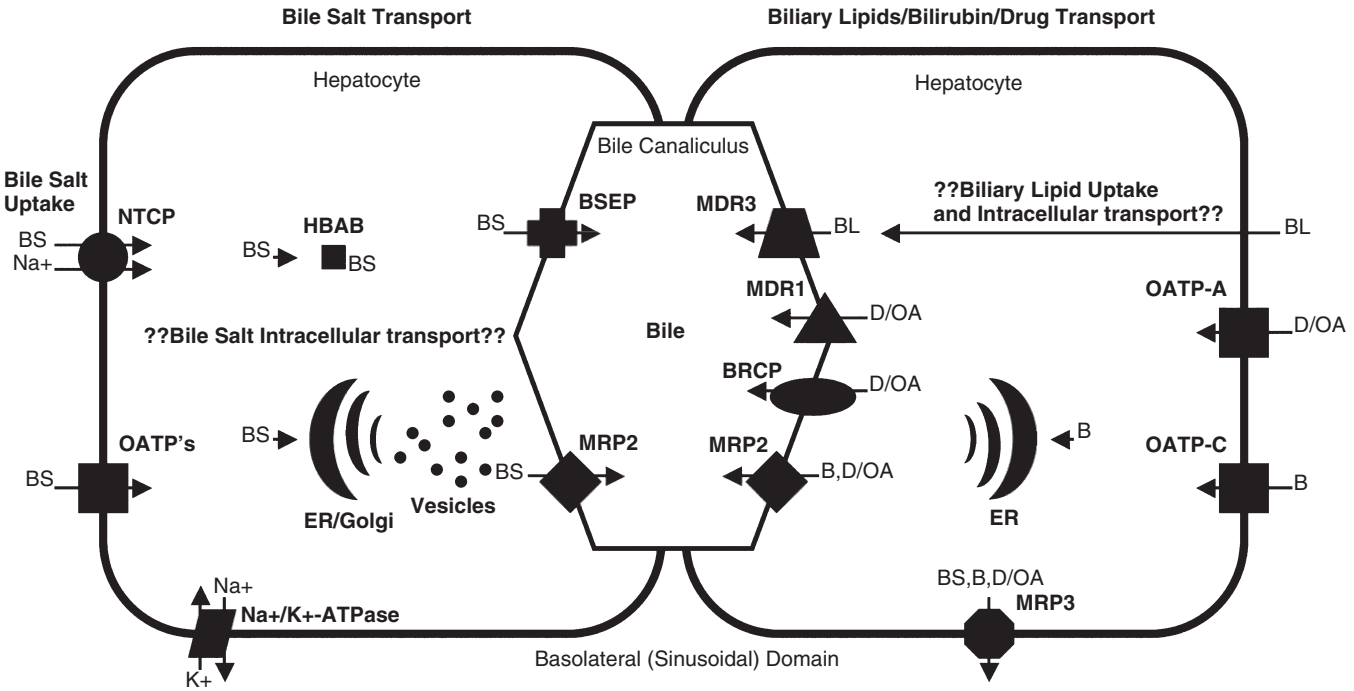


FIGURE 7.1. Bile formation in human liver. B, bilirubin; BL, biliary lipids; BRCP, breast cancer–related protein; BS, bile salts; BSEP, bile salt export pump; D/OA, drugs/organic anions; ER, endoplasmic reticulum; HBAB, hepatic bile acid–binding protein; MDR1 and MDR3, multidrug resistance proteins 1 and 3; MRP3, MDR-related protein-3; NTCP, Na^+–taurocholate cotransporting polypeptide; OATPs (A, C, 8), organic anion transporting polypeptides.

transport of metabolites, peptides, fatty acids, cholesterol, and lipids in the liver, intestines, pancreas, lungs, kidneys, brain, and in macrophages. Although BSEP is the major transporter for monovalent bile salts into the canaliculus, MDR-related protein-2 (MRP2), a member of the multidrug resistance protein family, also transports sulfated and glucuronidated bile salts into the canaliculus. MRP2 also mediates the export of multiple other organic anions, including conjugated bilirubin, leukotrienes, glutathione disulfide, chemotherapeutic agents, uricosurics, antibiotics, toxins, and heavy metals (Gerk & Vore, 2002).

Biliary Lipid Secretion

Compared with bile salts, the biliary lipids, phospholipids, and cholesterol play a secondary role in the formation of bile. Phospholipids and cholesterol are formed primarily from low-density lipoproteins circulating in plasma and from de novo synthesis by hepatocytes. Less is known about the secretion of biliary lipids compared with bile salt secretion; however, biliary lipid secretion is key for cholesterol disposal, intestinal absorption of dietary lipids, and cytoprotection against bile acid–induced hepatocyte and cholangiocyte injury (Arrese & Accatino, 2002).

Phospholipid secretion involves the delivery of phospholipids to the inner leaflet of the canalicular plasma membrane (Elferink & Groen, 2000). In humans the MDR3 transporter translocates phospholipids from the inner to the outer leaflet of the canalicular membrane. Humans with an MDR3 deficiency develop progressive familial intrahepatic cholestasis type 3 (Kullak-Ublick, 2004). These patients have no phosphatidylcholine in bile and therefore do not form mixed micelles with bile salts. As a result, toxic bile salts injure the biliary epithelium, resulting in neonatal cholestasis, cholestasis of pregnancy, and cirrhosis in adults.

Less is known about the role of transporter proteins in cholesterol secretion, but the ABC transporters, ABCG5 and ABCG8, have been demonstrated to be involved in the elimination of plant steroids (Lee, 2004). Cholesterol is highly nonpolar and insoluble in water; thus it is insoluble in bile. The key to maintaining cholesterol in solution is the formation of micelles, a bile salt–phospholipid–cholesterol complex. Bile salts are amphipathic compounds that contain both a hydrophilic and hydrophobic portion. In aqueous solutions, bile salts are oriented with the hydrophilic portion outward. Phospholipids are incorporated into the micellar structure, allowing cholesterol to be added to the hydrophobic central portion of the micelle. In this way, cholesterol can be maintained in solution in an aqueous medium. The concept of mixed micelles as the only cholesterol carrier has been challenged by the demonstration that much of the biliary cholesterol exists in a vesicular form. Structurally, these vesicles are made up of lipid bilayers of cholesterol and phospholipids. In their simplest and smallest form, the vesicles are unilamellar, but an aggregation may take place, leading to multilamellar vesicles. Present theory suggests that in states of excess cholesterol production, these large vesicles may also exceed their capability to transport cholesterol, and cystal precipitation may occur (Fig. 7.2).

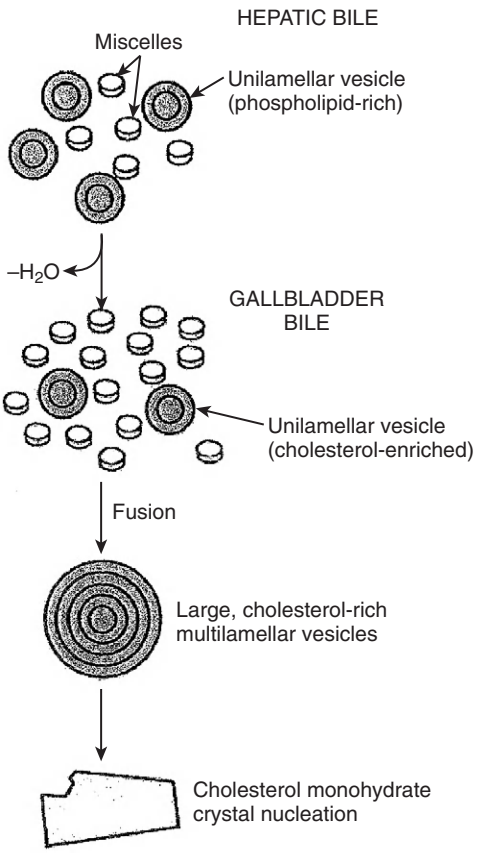


FIGURE 7.2. Concentration of bile leads to net transfer of phospholipids and cholesterol from vesicles to micelles. Phospholipids are transferred more efficiently than cholesterol, leading to cholesterol enrichment of the remaining (remodeled) vesicles. Aggregation of these cholesterol-rich vesicles forms multilamellar liquid crystals of cholesterol monohydrate. *(Modified from Vessey DA, 1990: Metabolism of drugs and toxins by the human liver. In Zakin D, Boyer TD [eds]: Hepatology: A Textbook of Liver Disease, 2nd ed. Philadelphia, WB Saunders, p 1492.)*

Bilirubin Secretion

Released at the time of degradation of senescent erythrocytes by the reticuloendothelial system, heme is the source of approximately 80% to 85% of the bilirubin produced daily. The remaining 15% to 20% is derived largely from the breakdown of hepatic hemoproteins. Both enzymatic and nonenzymatic pathways for the formation of bilirubin have been proposed. Although both may be important physiologically, the microsomal enzyme hemeoxygenase—found in high concentration throughout the liver, spleen, and bone marrow—plays a major role in the initial conversion of heme to biliverdin, which is then reduced to bilirubin by the cytosolic enzyme biliverdin reductase in a nicotinamide adenine dinucleotide (NADH)-dependent reaction before being released into the circulation. In this "unconjugated" form, bilirubin has a very low solubility, and it is bound avidly to plasma proteins, primarily albumin, before uptake and further processing by the liver. The liver is the sole organ capable of removing the albumin–bilirubin complex from the circulation and esterifying the potentially toxic bilirubin to water-soluble, nontoxic, monoconjugated and deconjugated derivatives.

In the sinusoidal membrane of the hepatocyte, bilirubin is taken up by OATP-C, a membrane transporter belonging to the OATP family (Cui et al, 2001). OATP-C is involved with the uptake of both conjugated and unconjugated bilirubin, but unconjugated bilirubin also can cross hepatic sinusoidal

membranes by a diffusion process. In the hepatocyte, bilirubin binds to a driver of gluthathione-S-transferase and is catalyzed by bilirubin uridine-5-diphosphate (UDP)-glycosyltransferase to form bilirubin glucuronides. Mutations in the gene encoding bilirubin UDP-glycosyltransferase are associated with the unconjugated hyperbilirubin syndromes, Crigler-Najjar and Gilbert syndromes (Iganagi, 1998).

Bilirubin glucuronides are excreted into the bile canaliculus primarily via MRP2, which also plays a role in the transport of glucuroniductal bile salts and a wide spectrum of organic anions, including the antibiotic ceftriaxone. MRP3, which is expressed in the basolateral membrane of hepatocytes and cholangiocytes, also participates in the transport of bilirubin monoglucuronide. MRP3 also may prevent intracellular accumulation of conjugated bilirubin, bile salts, and other organic anions in cholestatic situations.

Bile Flow

The bile ducts, gallbladder, and sphincter of Oddi act in concert to modify, store, and regulate the flow of bile. Bile flow is primarily driven by bile salt secretion. During its passage through the bile ductules, canalicular bile is modified by the absorption and secretion of electrolytes and water. Bicarbonate secretion by the bile ducts plays an important role in bile salt–independent bile flow. The gastrointestinal hormone secretin increases bile flow primarily by increasing the active secretion of chloride-rich fluid by the bile ducts. Bile duct secretion is also stimulated by other hormones, such as cholecystokinin and gastrin. The bile duct epithelium is capable of water and electrolyte absorption also, which may be of primary importance in the storage of bile during fasting in patients who have previously undergone cholecystectomy.

The main functions of the gallbladder are to concentrate and store hepatic bile during the fasting state and deliver bile into the duodenum in response to a meal. The usual capacity of the human gallbladder is about 40 to 50 mL. Only a small fraction of the bile produced each day would be stored, were it not for the gallbladder's remarkable absorptive capacity.

The enterohepatic circulation provides an important negative feedback system on bile salt synthesis. Should the recirculation be interrupted by resection of the terminal ileum or by primary ileal disease, abnormally large losses of bile salts could occur. This situation increases bile salt production to maintain a normal bile salt pool. Similarly, if bile salts are lost through an external biliary fistula, increased bile salt synthesis is necessary. However, except for those unusual circumstances in which excessive losses occur, bile salt synthesis matches losses, maintaining a constant bile salt pool size. During fasting, approximately 90% of the bile acid pool is sequestered in the gallbladder.

Enterohepatic Circulation

Bile salts are synthesized and conjugated in the liver; secreted into bile; stored temporarily in the gallbladder; passed from the gallbladder into the duodenum; absorbed throughout the small intestine, especially in the ileum; and returned to the liver via the portal vein. This cycling of bile acids between the liver and the intestine is referred to as the *enterohepatic circulation* (Fig. 7.3). The total amount of bile acids in the enterohepatic circulation is defined as the *circulating bile pool.* In this highly efficient system, nearly 95% of bile salts are reabsorbed. Thus, of the total bile salt pool of 2 to 4 g, which recycles through the enterohepatic cycle 6 to 10 times daily, only about 600 mg is actually excreted into the colon. Bacterial action in the colon on the two primary bile salts, cholate and chenodeoxycholate, results in the formation of the secondary bile salts, deoxycholate and lithocholate. Although some deoxycholate is reabsorbed passively by the colon, the remainder is lost in fecal waste; however, the physiology of bile salt, biliary lipid, bilirubin, bile flow, and the enterohepatic circulation are dramatically altered when the bile ducts become obstructed.

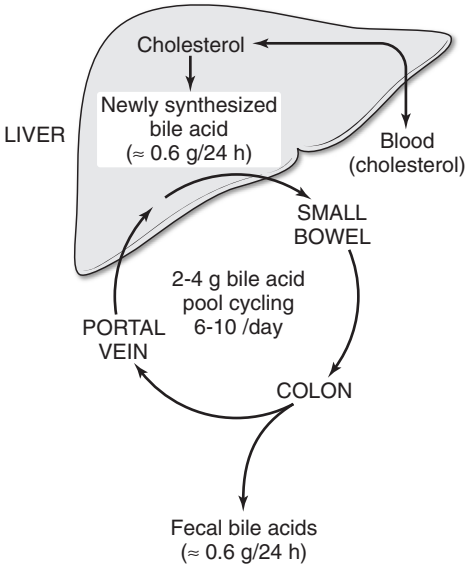


FIGURE 7.3. Enterohepatic circulation of bile salts. Cholesterol is taken up from plasma by the liver. Bile acids are synthesized at a rate of 0.6 g/24 h and are excreted through the biliary system into the small bowel. Most of the bile salts are reabsorbed in the terminal ileum and are returned to the liver to be extracted and reextracted. *(Modified from Dietschy JM, 1972: The biology of bile acids. Arch Intern Med 130:472-474.)*

BILIARY OBSTRUCTION

The evaluation and management of the patient with biliary obstruction is a common problem facing the general surgeon. Over the past 30 years, significant advances have been made in our understanding of the pathophysiology, diagnosis, and management of the jaundiced patient. Similarly, advances have been made in perioperative and operative management that have resulted in improved survival of the jaundiced patient. Obstructive jaundice affects multiple organ systems including hepatic, renal, cardiovascular, hematologic, and immune systems. This section will review the causes, pathophysiology, and management of biliary obstruction.

Causes of Jaundice

Jaundice may result from 1) increased production of bilirubin, 2) impaired hepatocyte uptake of bilirubin, 3) impaired conjugation of bilirubin, 4) impaired transport or excretion of bilirubin into the bile canaliculus, or 5) obstruction of the

Table 7.2

Classification of Jaundice

Defect in Bilirubin Metabolism	Predominant Hyperbilirubinemia	Examples
Increased production	Unconjugated	Congenital hemoglobinopathies, hemolysis, multiple transfusions, sepsis, burns
Impaired hepatocyte uptake	Unconjugated	Gilbert disease, drug induced
Reduced conjugation	Unconjugated	Neonatal jaundice, Crigler-Najjar syndrome
Impaired transport and excretion	Conjugated	Hepatitis, cirrhosis, Dubin-Johnson syndrome, Rotor syndrome
Biliary obstruction	Conjugated	Choledocholithiasis, benign strictures, chronic pancreatitis, sclerosing cholangitis, periampullary cancer, cholangiocarcinoma

intrahepatic or extrahepatic biliary tree (Table 7.2). Overproduction, impaired uptake, and impaired conjugation of bilirubin all lead to a predominently unconjugated hyperbilirubinemia. Impaired transport and excretion and biliary ductal obstruction result in hyperbilirubinemia that is primarily conjugated. Some patients have multiple defects in normal metabolism. For example, a patient with biliary obstruction from a tumor may develop secondary hepatocellular dysfunction. Therefore these classification systems may be simplifications of more complex disease processes.

Diseases causing bile duct obstruction may be further divided into conditions causing 1) complete obstruction, 2) intermittent obstruction, 3) chronic incomplete obstruction, or 4) segmental duct obstruction (Table 7.3). Patients with complete biliary obstruction will have clinical jaundice, and those with intermittent obstruction may develop symptoms (pain, pruritus, fevers) and biochemical changes without necessarily developing clinical jaundice. Patients with chronic incomplete obstruction can eventually develop hepatic fibrosis (see Chapter 6) and biliary cirrhosis (see Chapter 70A).

Table 7.3

Lesions Commonly Associated with Biliary Tract Obstruction

Type I Complete Obstruction

Tumors of the head of the pancreas
Common bile duct ligation
Cholangiocarcinoma
Parenchymal liver tumors (primary or secondary)

Type II Intermittent Obstruction

Choledocholithiasis
Periampullary tumors
Duodenal diverticula
Choledochal cyst
Polycystic liver disease
Biliary parasites
Hemobilia

Type III Chronic Incomplete Obstruction

Strictures of the common bile duct
Congenital
Traumatic (iatrogenic)
Sclerosing cholangitis
Post radiotherapy
Stenosis of biliary-enteric anastamosis
Chronic pancreatitis
Cystic fibrosis
Sphincter of Oddi stenosis

Type IV Segmental Obstruction

Traumatic
Intrahepatic stones
Sclerosing cholangitis
Cholangiocarcinoma

Pathophysiology

Biliary obstruction produces local effects on the bile ducts, which leads to derangements of hepatic function and ultimately to widespread systemic effects. Jaundiced patients are at increased risk for developing hepatic dysfunction, renal failure, cardiovascular impairments, nutritional deficiencies, bleeding problems, infections, and wound complications, and their perioperative mortality is higher.

Hepatobiliary

Hepatocytes are arranged in plates along which blood flows from portal to central veins. Within these plates, the small apical domains of adjacent hepatocytes form a tubular lumen, the canaliculus, which is the site of primary bile formation. From the canalicular network, bile flows to the small ductules and subsequently to the larger ducts. With biliary obstruction, the bile canaliculi become dilated, and the microvilli are distorted and swollen. In patients with long-standing obstruction, intrahepatic bile ductule proliferation occurs with an increase in the length and tortuosity of the canaliculi.

The biliary system normally has a low pressure (5 to 10 cm H_2O); however, in the setting of complete or partial biliary obstruction, biliary pressure can approach 30 cm H_2O. As biliary pressure increases, the tight junctions between hepatocytes and bile duct cells are disrupted, resulting in an increase in bile duct and canalicular permeability. Bile contents can freely reflux into liver sinusoids, causing a marked polymorphonuclear leukocyte infiltration into the portal triads. This inflammatory response is followed by increased fibrinogenesis with deposition of reticulin fibers, which undergo conversion to type I collagen (see Chapter 6). The extrahepatic bile ducts exhibit mucosal atrophy and squamous metaplasia followed by inflammatory infiltration and fibrosis in the subepithelial layers of the bile duct (Karsten et al, 1991).

In addition to the structural effects of biliary obstruction on the bile ducts, elevated biliary pressure can alter bile production by hepatocytes. In the setting of biliary obstruction and elevated biliary pressure, bile becomes less lithogenic because of a relative decrease in cholesterol and phospholipid secretion compared with bile acid secretion. With the relief of biliary obstruction and the normalization of biliary pressures, the

recovery of cholesterol and phospholipid secretion is more rapid than bile acid secretion, therefore bile is more lithogenic in this setting. This phenomenon may lead to premature occlusion of decompressive bilary stents placed for the management of obstructive jaundice.

Several authors have reported impairment of both macrovascular and microvascular perfusion of the liver in obstructive jaundice. Intravital fluorescence microscopy has shown a significant increase in the number of nonperfused sinusoids after 3 days of extrahepatic obstruction. Moreover, in perfused sinusoids, a 35% decrease in the mean diameter and a 25% decrease in flow velocity were noted (Koeppel et al, 1997). This alteration in hepatic perfusion may help explain the increased risk of hepatocellular dysfunction when performing liver resections in patients with obstructive jaundice (see Chapters 50C and 93A). Extrahepatic biliary obstruction and jaundice can also alter important secretory, metabolic, and synthetic functions of the liver. When biliary pressure rises above 20 cm H_2O, hepatic bile secretion is diminished, and hepatocytes cannot excrete efficiently against the high pressure. As a result, excretory products of the hepatocytes reflux directly into the vascular system, leading to systemic toxicity.

Jaundiced patients have a decreased capacity to excrete drugs, such as antibiotics, that are normally secreted into bile (Blenkharn et al, 1985). The increased concentration of bile acids associated with obstructive jaundice results in inhibition of the hepatic cytochrome P450 enzymes and therefore a decrease in the rate of oxidative metabolism in the liver. In addition, bile acids in abnormally high concentrations can induce apoptosis (programmed cell death) in hepatocytes (Patel et al, 1994). The synthetic function of the hepatocyte is also decreased with obstructive jaundice, as evidenced by decreased plasma levels of albumin, clotting factors, and secretory immunoglobulins (IgA).

Kupffer cells are tissue macrophages that are the predominant cell type of the hepatic reticuloendothelial system (see Chapter 9). Normally, infectious agents, damaged blood cells, cellular debris, fibrin degradation products, and endotoxin absorbed or formed in the portal circulation are effectively filtered by Kupffer cells and removed from the systemic circulation. Kupffer cells also play an interactive role with hepatocytes, modulating synthesis of hepatic proteins. Obstructive jaundice has been shown to have profound effects on Kupffer cells, including decreased endocytosis, phagocytosis, clearance of bacteria and endotoxin, and expression of the major histocompatibility complex class II antigen with a consequent diminished ability to process antigen (Nehez & Anderson, 2002; Puntis & Jiang, 1996). Biliary obstruction also has been shown to increase levels of proinflammatory cytokines, including TNF-α and IL-6 (see Chapters 9 and 10).

Cardiovascular

In addition to hepatic dysfunction, obstructive jaundice may cause severe hemodynamic and cardiac disturbances. Experimental animals with obstructive jaundice tend to be hypotensive and exhibit an exaggerated hypotensive response to hemorrhage. Studies in experimental animals have demonstrated that bile duct ligation 1) decreases cardiac contractility; 2) reduces left ventricular pressures; 3) impairs response to β-agonist drugs, such as isoproterenol and norepinephrine; and 4) decreases peripheral vascular resistance (Ma et al, 1999). In a study of 9 patients with obstructive or cholestatic jaundice, Lumlertgul and colleagues (1991) showed a significantly blunted response in left ventricular ejection fraction compared with normal volunteers following the infusion of the positive inotrope dobutamine. Padillo and others (2001) also have shown a negative correlation between serum bilirubin and left ventricular systolic work in 13 patients with biliary obstruction and no previous history of heart, lung, or kidney disease. Successful internal biliary drainage in patients was associated with a significant increase in cardiac output, compliance, and contractility. The combination of depressed cardiac function and decreased total peripheral resistance most likely makes the jaundiced patient more susceptible to the development of postoperative shock than nonjaundiced patients.

Renal

The association between jaundice and postoperative renal failure has been known for many years. The reported incidence of postoperative acute renal failure has been reported to be as high as 10% but varies depending on the nature of the procedure. Moreover, the mortality rate in jaundiced patients who develop renal failure has been reported to be as high as 70% (Fogarty et al, 1995). Important factors that may play a role in the development of renal failure in obstructive jaundice include 1) depressed cardiac function, 2) hypovolemia, and 3) endotoxemia.

The decreased cardiac function associated with obstructive jaundice leads to a decrease in renal perfusion. Decreased cardiac output may also result in stretching of the atrium and increased production of atrial natriuretic peptide (ANP), a hormone known to cause natriuresis, to counter the action of water- and sodium-retaining hormones, to inhibit the thirst mechanism, and to produce peripheral vasodilation. Plasma levels of ANP have been shown to be increased in both experimental animals and in patients with extrahepatic biliary obstruction (Padillo et al, 2001).

In addition to the direct effects of jaundice on the heart and peripheral vasculature discussed above, the increased serum levels of bile acids associated with obstructive jaundice have a direct diuretic and natriuretic effect on the kidney that results in significant extracellular volume depletion and hypovolemia. In dogs, the infusion of bile into the renal artery results in increased urine flow, natriuresis, and kaliuresis. This diuretic effect may be mediated by increased prostaglandin E_2 (PGE_2) production by the kidney (Green & Better, 1994).

The third factor in the development of renal failure is endotoxemia (Fig. 7.4). Approximately 50% of patients with obstructive jaundice have endotoxin in their peripheral blood (Hunt et al, 1982). This phenomenon may be the result of decreased hepatic clearance of endotoxin by Kupffer cells and a lack of bile salts in the gut lumen that normally prevent absorption of endotoxins and inhibit anaerobic bacterial growth. Endotoxin also causes renal vasoconstriction and redistribution of renal blood flow away from the cortex, and disturbances in coagulation that include the activation of complement, macrophages, leukocytes, and platelets (Hunt et al, 1982). As a result, glomerular and peritubular fibrin is deposited. This factor, in combination with reduced renal cortical blood flow, results in the tubular and cortical necrosis observed in jaundiced patients with renal failure. Mechanisms of the pathophysiology of renal failure in obstructive jaundice are summarized in Figure 7.3.

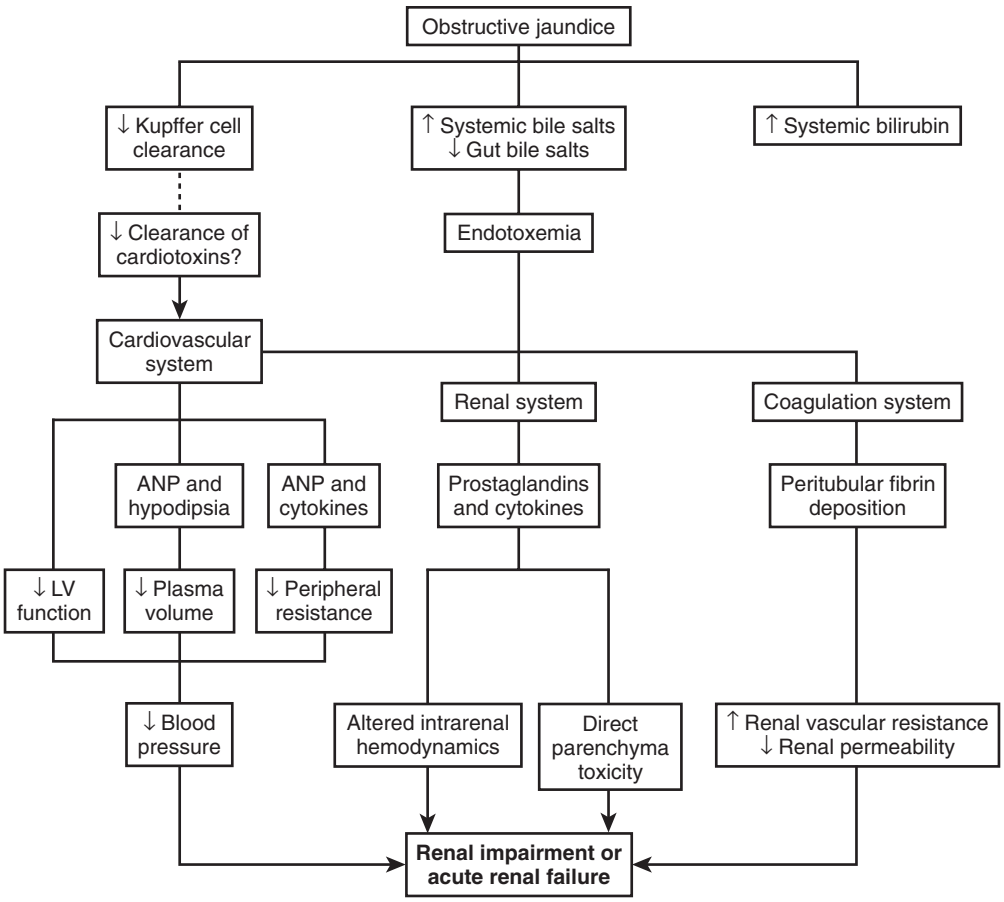


FIGURE 7.4. Obstructive jaundice leads to renal impairment or acute renal failure. ANP, atrial natriuretic peptide; LV, left ventricular.

Coagulation

Disturbances of blood coagulation are commonly present in jaundiced patients. The most frequently observed abnormality is prolongation of the prothrombin time. This problem results from impaired vitamin K absorption from the gut, secondary to a lack of intestinal bile. This coagulopathy is usually reversible with parenteral administration of vitamin K. Decreased bile levels in the small intestine may result in diminished absorption of other fat-soluble vitamins and fats, which results in weight loss and loss of calcium. This latter factor, as well as the above-mentioned increase in circulating endotoxin, may further contribute to clotting abnormalities.

In experimental animals, endotoxin affects metabolism of factors XI and XII and causes platelet and direct endothelial damage (Hunt et al, 1982). Moreover, endotoxin release in jaundiced patients results in a low-grade, disseminated intravascular coagulation with increased fibrin degradation products. Hunt and colleagues have shown that jaundiced patients with circulating endotoxin or increased fibrin degradation product levels before surgery are at increased risk for hemorrhagic complications. In addition to problems with endotoxemia, patients with coexisting cirrhosis often have additional problems related to thrombocytopenia from hypersplenism and fibrinolysis.

Immune System

Surgery in jaundiced patients is associated with a higher rate of postoperative septic complications compared with those without jaundice, due in large measure to defects in cellular immunity that make them more prone to infection (see Chapters 9 and 11). Cainzos and colleagues (1992) have demonstrated an association between jaundice and altered delayed-type hypersensitivity. Only 16% of 118 jaundiced patients were immunocompetent, compared with 76% of 59 healthy controls, when tested with a panel of seven skin antigens. Several authors have shown impaired T-cell proliferation (Thompson et al, 1990), decreased neutrophil chemotaxis (Andy et al, 1992), and defective bacterial phagocytosis (Scott-Conner et al, 1993) following bile duct ligation in rats. As mentioned earlier, the ability of the reticuloendothelial system, specifically Kupffer cells, to clear bacteria and endotoxin from the circulation also is reduced in obstructive jaundice.

The absence of bile from the intestinal tract also plays a role in the infectious complications seen in patients with obstructive jaundice. It has been shown that bacterial translocation from the gut is increased in the setting of bile duct obstruction (Deitch et al, 1990). Obstruction causes a disruption of the enterohepatic circulation and results in loss of the emulsifying antiendotoxin effect of bile acids; therefore a larger pool of endotoxin is available within the intestine for absorption into the portal circulation. The combination of reduced or absent bile in the intestine and impaired cellular immunity and reticuloendothelial cell function appears to be a major factor contributing to more frequent infective complications in the jaundiced patient.

Acute cholangitis is a bacterial infection of the biliary ductal system, and it varies in severity from mild and self-limited to

severe and life threatening (see Chapter 43). The clinical triad associated with cholangitis—fever, jaundice, and pain—was first described in 1877 by Charcot. Cholangitis results from a combination of two factors: significant bacterial concentrations in the bile and biliary obstruction. Although bile from the gallbladder and bile ducts is usually sterile, in the presence of common bile duct stones or other obstructing pathology, the incidence of positive cultures increases; likewise, instrumentation of the biliary tree also greatly increases rates of bile colonization. The most common organisms recovered from the bile in patients with cholangitis include *Escherichia coli*, *Klebsiella pneumonia*, the enterococci, and *Bacteroides fragilis* (Thompson et al, 1990). However, even in the presence of high biliary bacterial concentrations, clinical cholangitis and bacteremia will not develop, unless obstruction causes elevated intraductal pressures (Lipsett & Pitt, 1993).

Normal biliary pressures range from 7 to 14 cm H_2O. In the presence of bacteribilia and normal biliary pressures, hepatic venous blood and perihepatic lymph are sterile. However, with partial or complete biliary obstruction, intrabiliary pressures rise to 18 to 29 cm H_2O, and organisms rapidly appear in both the blood and lymph. The fever and chills associated with cholangitis are the result of systemic bacteremia caused by cholangiovenous and cholangiolymphatic reflux.

The most common causes of biliary obstruction are choledocholithiasis (see Chapter 35), benign strictures (see Chapter 42), biliary-enteric anastomotic strictures (see Chapters 29 and 42), and periampullary or proximal biliary cancers (see Chapters 49, 50, 58, and 59). Prior to 1980, choledocholithiasis was the cause of approximately 80% of the reported cases of cholangitis. In recent years, however, malignant strictures have become a frequent cause, particularly at tertiary referral centers. Endoscopic cholangiography, percutaneous transhepatic cholangiography, and stent placement via either the endoscopic or percutaneous route are all known to cause bacteremia, and these procedures are frequently performed in patients with a presumptive diagnosis of malignant obstruction.

Wound Healing

Delayed wound healing and a high incidence of wound dehiscence and incisional hernia have been observed in jaundiced patients undergoing surgery. Patients with obstructive jaundice have decreased activity of the enzyme propylhydroxylase in their skin. Propylhydroxylase is necessary for the incorporation of proline amino acid residues into collagen, and its activity has been used as a measure of collagen synthesis. Grande and colleagues (1990) measured skin propylhydroxylase activity in 95 patients with extrahepatic bile duct obstruction and 123 nonjaundiced control patients undergoing cholecystectomy. The jaundiced patients had only 11% of the skin propylhydroxylase activity of the controls. In the subgroup of patients with jaundice secondary to malignancy, propylhydroxylase activity was less than 7% of controls. With relief of obstruction, the activity increased to 22% of controls. Interestingly, in patients with jaundice secondary to benign obstruction, the activity increased to 100% of controls.

Other Factors

Other problems that face jaundiced patients are anorexia, weight loss, and malnutrition. Appetite is adversely influenced by the lack of bile salts in the intestinal tract. In addition, patients with pancreatic or periampullary malignant lesions may have partial duodenal obstruction or abnormal gastric emptying, perhaps secondary to tumor infiltration of the celiac nerve plexus. Patients with pancreatic or ampullary tumors also may have pancreatic endocrine and exocrine insufficiency. This latter problem may further compound other nutritional defects that in turn may exacerbate the immune deficits of the jaundiced patient.

Several recent observations suggest that the many physiologic derangements induced by obstructive jaundice take a long time to reverse. For example, Koyama and colleagues (1981) have shown that hepatic mitochondrial function does not return to normal even 7 weeks after relief of obstruction. This same prolonged effect of obstructive jaundice has been noted with lymphocyte, polymorphonuclear, and Kupffer cell function. Therefore even patients who have had temporary relief of biliary obstruction via percutaneous or endoscopic stents are likely to remain at risk for significant complications following surgery, because derangements in hepatic function are likely still present at the time of operation.

Management

In the past, the only option for the relief of obstructive jaundice was operative intervention; however, with the development of therapeutic techniques such as percutaneous (see Chapters 18, 28, and 50D) and endoscopic stenting (see Chapters 18 and 27), balloon dilation, and endoscopic sphincterotomy, many nonoperative options for the relief of obstructive jaundice are now available. The surgeon must determine the safest and most effective therapy for each individual patient and must adequately prepare each patient for surgery or nonoperative therapeutic intervention.

Patients with obstructive jaundice and those with hepatocellular disease severe enough to cause jaundice are prone to develop many secondary problems. Jaundiced patients are at increased risk for the development of renal failure, gastrointestinal bleeding, infections, and wound complications (see the earlier section on the pathophysiology of jaundice). Cardiac, pulmonary, and renal function must be considered in every patient undergoing major abdominal surgery. In addition, special attention must be focused on the jaundiced patient's nutritional status, coagulability, immune function, and presence or absence of biliary sepsis. Patients with chronic liver disease and cirrhosis also may develop complications related to portal hypertension, such as ascites, varices, and encephalopathy, and these may require specific treatment (see Chapters 70B, 74, and 75).

Cardiopulmonary

In assessing cardiopulmonary status, the patient's age, history of recent myocardial infarction, and the presence of congestive heart failure, significant valvular aortic stenosis, or a disturbance of normal cardiac rhythm have all been correlated with increased operative risk (Goldman et al, 1977). In addition, patients with severe pulmonary disease may not be candidates for extensive abdominal surgery.

Renal

Jaundiced patients, especially those with cirrhosis and cholangitis, are at increased risk of developing renal insufficiency. The maintenance of adequate blood volume and the correction of dehydration are extremely important if renal complications are

to be avoided. Fluid management can be quite complex in jaundiced patients, and selected patients may benefit from invasive hemodynamic monitoring with central venous catheters—and less commonly, pulmonary artery catheters—to assist in assessing intravascular volume.

Certain oral bile salts have been shown to be efficacious in preventing the development of postoperative renal dysfunction. In a study by Cahill (1983) 54% of 24 jaundiced patients not given oral bile salts before surgery were found to have systemic endotoxemia, which was associated with renal impairment in two thirds of the cases. In comparison, none of the 8 jaundiced patients given 500 mg of sodium deoxycholate every 8 hours for 48 hours before surgery had portal or systemic endotoxemia. Moreover, none of these 8 patients had evidence of renal impairment.

Nutrition

Malnutrition is a significant risk factor for surgery in the setting of obstructive jaundice (see Chapter 24). Halliday and colleagues (1988) noted that patients who died in the postoperative period following surgery for obstructive jaundice had had a significant reduction in body weight, midarm circumference, total body potassium, and reactivity to skin test antigens prior to operation. In a study from Italy (Foschi et al, 1986), enteral hyperalimentation was found to significantly decrease operative morbidity and mortality in a group of patients treated with 20 days of preoperative percutaneous biliary drainage. Although most patients with benign biliary problems are adequately nourished, various degrees of malnutrition are frequently present in patients with malignant obstruction; therefore patients with malignant obstructive jaundice should be evaluated for evidence of malnutrition and have nutritional support instituted if necessary.

Coagulation

Patients with obstructive jaundice, cholangitis, or cirrhosis are all prone to excessive intraoperative bleeding. The most common clotting defect in patients with obstructive jaundice is prolongation of the prothrombin time (PT), which is usually reversible by the administration of parenteral vitamin K. Patients with severe jaundice and/or cholangitis also may develop disseminated intravascular coagulation (DIC), which may require infusion of platelets and fresh frozen plasma. Reversal of DIC also requires control of the underlying sepsis, which should include biliary drainage in patients with cholangitis in addition to systemic antibiotics.

In cirrhotic patients, clotting abnormalities are often multifactorial and include thrombocytopenia secondary to hypersplenism, prolongation of PT and partial thromboplastin time (PTT), and fibrinolysis. Vitamin K should be administered if the PT is prolonged. If no effect is seen and/or if the PTT is also prolonged, fresh frozen plasma should be given. Thrombocytopenia can usually be managed by intraoperative platelet infusions. If the patient has a shortened clot lysis time and hypofibrinogenemia, ε-aminocaproic acid may be indicated.

Pruritus

Pruritus is often a distressing problem in the jaundiced patient. The exact cause of pruritus remains obscure, but increased circulating levels of bile salts, histamines, and central nervous system opiate receptors have been implicated. In some patients, relief from itching can be obtained by bile salt–binding agents, such as cholestyramine. Various sedatives and antihistamines also can provide relief of itching in jaundiced patients, however, relief of biliary obstruction remains the most effective method for managing pruritis.

Cholangitis

Biliary sepsis also has been identified as a major risk in jaundiced patients (see Chapter 43). Cholangitis occurs when partial or complete obstruction of the bile duct exists, resulting in increased intraluminal pressure and infected bile behind the obstruction. Patients with cholangitis present with right upper quadrant abdominal pain, fever, and jaundice (Charcot triad). Patients with "toxic" cholangitis, Charcot triad plus shock and mental confusion (Reynold pentad), have significant mortality with appropriate antibiotic therapy alone and therefore require emergent biliary decompression.

Gigot and colleagues (1989) identified seven prognostic factors that are indications for urgent biliary decompression: 1) acute renal failure, 2) liver abscess, 3) cirrhosis, 4) high malignant stricture, 5) percutaneous transhepatic cholangiography, 6) female gender, and 7) advanced age. However, emergent surgical treatment is associated with significant morbidity and mortality; therefore both percutaneous and endoscopic biliary drainage have been proposed as effective therapy for the 5% to 10% of patients with cholangitis who are unresponsive to conservative therapy. Lai and colleagues (1992) have shown in a series of 82 patients with severe acute cholangitis that endoscopic drainage is associated with a lower morbidity (34% vs. 66%) and mortality (10% vs. 32%) than operative drainage. A more complete discussion of the bacteriology and antibiotic management of patients with cholangitis can be found in Chapters 11 and 43.

Preoperative Drainage

The preoperative relief of jaundice and the reversal of its systemic effects by either endoscopic or transhepatic biliary decompression has been proposed as a method to decrease the risk of surgery in jaundiced patients. However, several prospective randomized studies have shown that the routine use of preoperative biliary drainage does not reduce operative morbidity or mortality in patients with obstructive jaundice (Hatfield et al, 1982; Lai et al, 1994; McPherson et al, 1984; Pitt et al, 1985; van der Gaag et al, 2010; Table 7.4). In addition, a meta-analysis also concluded that preoperative biliary drainage increased, rather than decreased, overall complications from surgery and the drainage procedure and provided no benefit in terms of reduced mortality or decreased hospital stay (Sewnath et al, 2002). In fact, several retrospective studies have documented a higher incidence of infectious complications (wound infection, pancreatic fistula) and even mortality in patients undergoing pancreatic or biliary tract resection after preoperative biliary decompression (Sewnath et al, 2002; Sohn et al, 2000).

A criticism of some of the prospective studies is that the duration of preoperative drainage (10 to 18 days) may have been inadequate to reverse the multiple metabolic and immunologic abnormalities associated with severe obstructive jaundice. Both animal and human studies demonstrate that the recovery of various metabolic and immune functions requires at least 6 weeks to pass after the relief of biliary obstruction (Clements et al, 1993; Kennedy et al, 1994; Thompson et al, 1990). Similarly, animal studies strongly suggest that return of

Table 7.4

Prospective Randomized Trials of Preoperative Biliary Drainage (PBD)

First Author, Year	Type of Drainage	Overall PBD	Deaths, No PBD	Overall PBD	Morbidity, No PBD
Hatfield, 1982	Percutaneous	4/28	4/27	7/28	4/27
McPherson, 1984	Percutaneous	11/34	6/31	17/34	13/31
Pitt, 1985	Percutaneous	3/37	2/38	30/37	20/38
Lai, 1994	Endoscopic	6/43	6/44	28/43	18/44
van der Gaag, 2010	Endoscopic	9/102	4/94	75/102	37/94
	Total (%)	33/244 (13.5)	22/234 (9.4)	157/244 (64.3)	92/234 (39.3)

bile to the intestinal tract has significant advantages over external biliary drainage (Roughneen et al, 1986).

Although the data suggest that routine preoperative biliary drainage may be of limited benefit, it may have some value in selected patients with advanced malnutrition, biliary sepsis, and hilar malignancies that require liver resection. Regarding the latter, it should be emphasized that most of the published data regarding preoperative biliary drainage focuses on patients with periampullary malignancy. Patients with proximal biliary obstruction undergoing major hepatic resection represent an entirely different subgroup, and although no adequately powered study has addressed this issue specifically in this population, some evidence does suggest a benefit of preoperative biliary drainage of the future liver remnant (see Chapters 50B, 50C, and 93A). Preoperatively placed catheters also may be of value in the operating room during difficult biliary dissections in patients with proximal biliary tumors or strictures, and they may aid in the placement of long-term transhepatic stents.

SUMMARY

Over the past few decades, tremendous strides have been made in our understanding of bile secretion and our ability to care for the jaundiced patient. Clinicians now have a better understanding of normal bile salt, biliary lipid, and bilirubin physiology and can classify the diseases that cause jaundice as defects in normal metabolism. Similarly, investigators are beginning to elucidate more clearly the multiple pathophysiologic effects of jaundice to explain why jaundiced patients are at risk for increased perioperative morbidity and mortality.

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CHAPTER 8A

Pancreatic cancer and premalignant tumors: molecular aspects

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PANCREATIC CANCER OVERVIEW

Pancreatic ductal adenocarcinoma (PDA), commonly known as *pancreatic cancer,* is the fourth leading cause of cancer death in the United States, preceded only by lung, colon, breast (in women), and prostate (in men) cancers (American Cancer Society, 2009). The diagnosis of PDA is devastating because it has one of the highest mortality rates of any cancer (American Cancer Society, 2009). To underscore this point, in 2009 approximately 42,470 Americans were diagnosed with PDA, and about 35,240 will die from it (American Cancer Society, 2009). A diagnosis of PDA is met with the daunting statistic that the patient has an overall 5-year survival rate of less than 5%.

The past 2 decades have seen an exponential increase in our understanding of the molecular basis and etiology behind PDA (Hruban et al, 2001; Jones et al, 2008, 2009). Still, the clinical management of this disease—including primary prevention, early detection, and better targeted treatment options—has not changed significantly over the past decade. Currently, the only cure for this disease is surgical resection. Unfortunately, only 20% of the patient population presents with resectable disease (Winter et al, 2002).

Research studying PDA can be simplistically divided into two eras (Fig. 8A.1). The first is highlighted by the discovery and development of technologies such as gene cloning and isolation of pure tumor tissue (i.e., xenografting primary tumors postresection; Fig. 8A.2, *left*). This era included landmark studies defining the genomic region of *BRCA2* (Goggins et al, 1996), discovering *SMAD4* (Hahn et al, 1996) as a tumor suppressor in PDA, activation of KRAS (Almoguera et al, 1988) as an early and frequent event in pancreatic tumorigenesis, and silencing of the *CDKN2A* (Caldas et al, 1994a) gene. As the result of advances in a number of molecular techniques, we are now upon the early stages of a new second era in genetic pancreatic cancer research, which combines high-throughput sequencing, gene expression and comparative genomic hybridization (CGH) arrays with statistical computational analysis, and large clinical databases (Fig. 8A.2, *right*) (Jones et al, 2008, 2009). This second era has already produced landmark publications that include a precise survey of multiple pancreatic cancer genomes both in sporadic and familial forms of the disease. This chapter aims to 1) provide a summary of the past two decades of pancreatic cancer research; 2) show that even though every tumor has a number of common molecular events, it is the differences between tumors that have clinical implications (Fig. 8A.3); and, finally, 3) set the stage for the future, which will include a discussion of successful early detection and treatment strategies for this deadly disease (Fig. 8A.3).

Progression Model of Pancreatic Ductal Adenocarcinoma

In the first era of pancreatic cancer research (see Figs. 8A.1 and 8A.2), the fields of molecular biology and pathology combined to establish a paradigm that PDA culminates from a multistep progression model (Hruban et al, 2001). This slow, sequential process may be the reason PDA is primarily a disease of people in their sixth and seventh decades of life. Definable pathologic markers on this stepwise progression—which follows a similar model first developed in colon carcinogenesis—are lesions referred to as *pancreatic intraepithelial neoplasia* (PanIN) (Hruban et al, 2001; Figs. 8A.4A and B). These lesions are believed to be precursor lesions to pancreatic cancer. PanIN lesions are thought to develop years before the emergence of PDA and are pathologically graded from low-grade PanIN lesions, PanIN-1 (Fig. 8A.4A), to high-grade lesions, PanIN-3 (see Fig. 8A.4B). Although low-grade PanIN lesions are common incidental findings, high-grade PanIN lesions are more common in pancreata with PDA.

Key evidence that PanIN lesions are precursors to PDA is that similar hallmark molecular defects are found in PanIN lesions adjacent to invasive cancers (Biankin et al, 2003; Luttges et al, 2001a; Maitra et al, 2002; van Heek et al, 2002; Wilentz et al, 2000a). However, although *KRAS* mutations are frequently found in early PanIN lesions (Shi et al, 2009), genes involved in DNA repair mechanisms, such as *TP53* and *BRCA2,* are altered late in this progression model. Because these data are based on limited sample numbers and data points, it remains somewhat counterintuitive that an oncogenic stimulus or stimuli (e.g., *KRAS* activation) precedes DNA damage (mutations). Recently, it was shown that higher density PanIN lesions were found in familial PDA patients compared with patients with sporadic forms of PDA, again arguing in favor of the hypothesis that PanIN lesions are true precursors to PDA (Shi et al, 2009).[15]

Intraductal Papillary Mucinous Neoplasm

Intraductal papillary mucinous neoplasms (IPMNs) are a well-accepted clinical and pathologic entity (Fig. 8A.4C and D; see

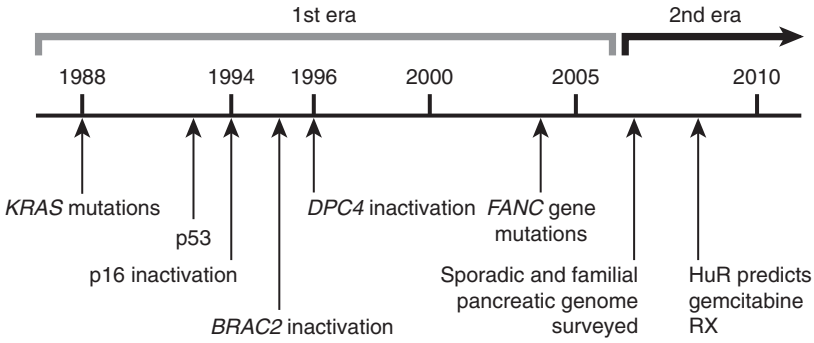


FIGURE 8A.1. Genetic landmark discoveries in pancreatic cancer research. The first era is highlighted by the discovery of tumor suppressor genes such as *DPC4* and loss of p16. The second era is highlighted by genomic profiling of discovery and validating sets of isolated and purified tumors from pancreatic cancer patients.

Chapter 57) (Hruban et al, 2004). IPMNs typically produce radiographically identifiable pancreatic ductal dilation, which may predominantly involve the main pancreatic ducts (main-duct type IPMN), the secondary ducts (branch-duct type IPMN), or both types of ducts (mixed type). The distinction between the branch-duct type and main-duct type is important, because the former arise in younger patients, are more likely to involve the head and uncinate process of the pancreas, and are associated with lower-grade dysplasia and fewer invasive carcinomas. Approximately 30% to 40% of resected IPMNs harbor an invasive adenocarcinoma, and adenocarcinoma is most strongly associated with main-duct IPMNs. Approximately half of invasive carcinomas arising within IPMNs are so-called colloid (mucinous) carcinomas, and most of the remainder are tubular adenocarcinomas, the latter being histologically indistinguishable from invasive ductal adenocarcinomas that arise in the setting of PanINs (Adsay et al, 2002). Colloid carcinomas associated with IPMNs have a relatively good prognosis compared with other pancreatic carcinomas of the ductal type, which have a 5-year survival of 60% (Maire et al, 2002).

PanINs and IPMNs show some overlapping features, such that both are inherently intraductal lesions composed predominantly of columnar, mucin-producing cells that may grow in a flat configuration or may produce papillae; these lesions show a range of cytologic and architectural atypia and can give rise to invasive adenocarcinomas of the pancreas (Fig. 8A.4E

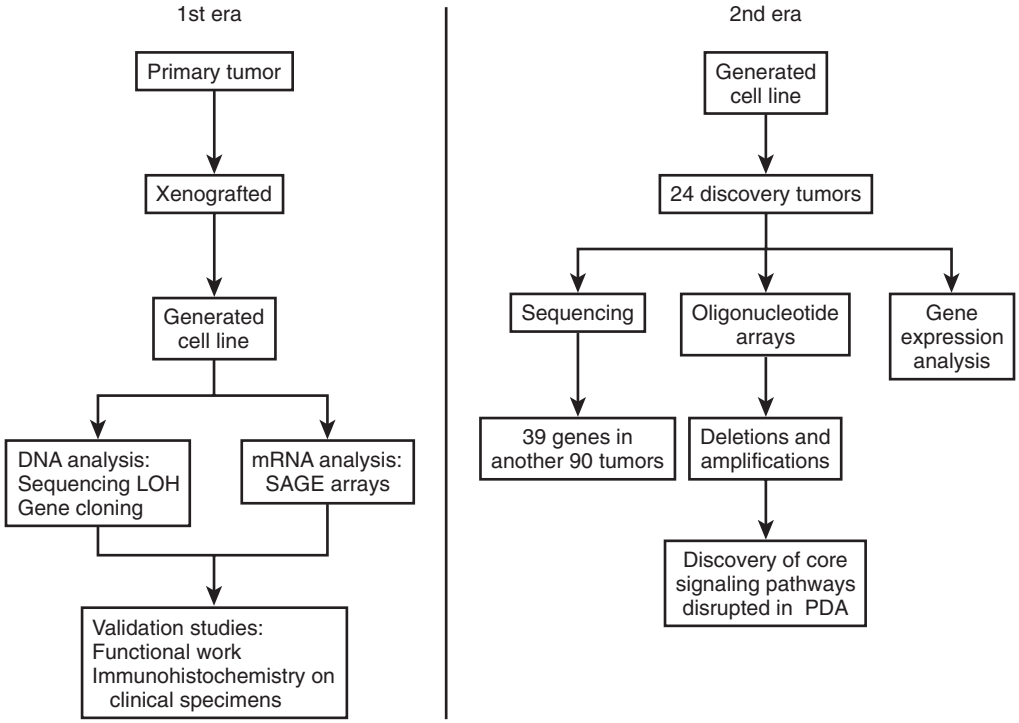


FIGURE 8A.2. Simplified flowchart of genetic discoveries performed in the two eras of genetic research. In the first era (*left*), resected pancreatic cancers were xenografted, and genomic DNA was isolated for genetic analysis of a region or putative tumor suppressor or oncogene. In the second era (*right*), combining advances in equipment and techniques and high-throughput sequencing allowed for a genomic survey of the pancreatic cancer genome. LOH, loss of heterozygosity; PDA, pancreatic ductal carcinoma; SAGE, serial analysis of gene expression.

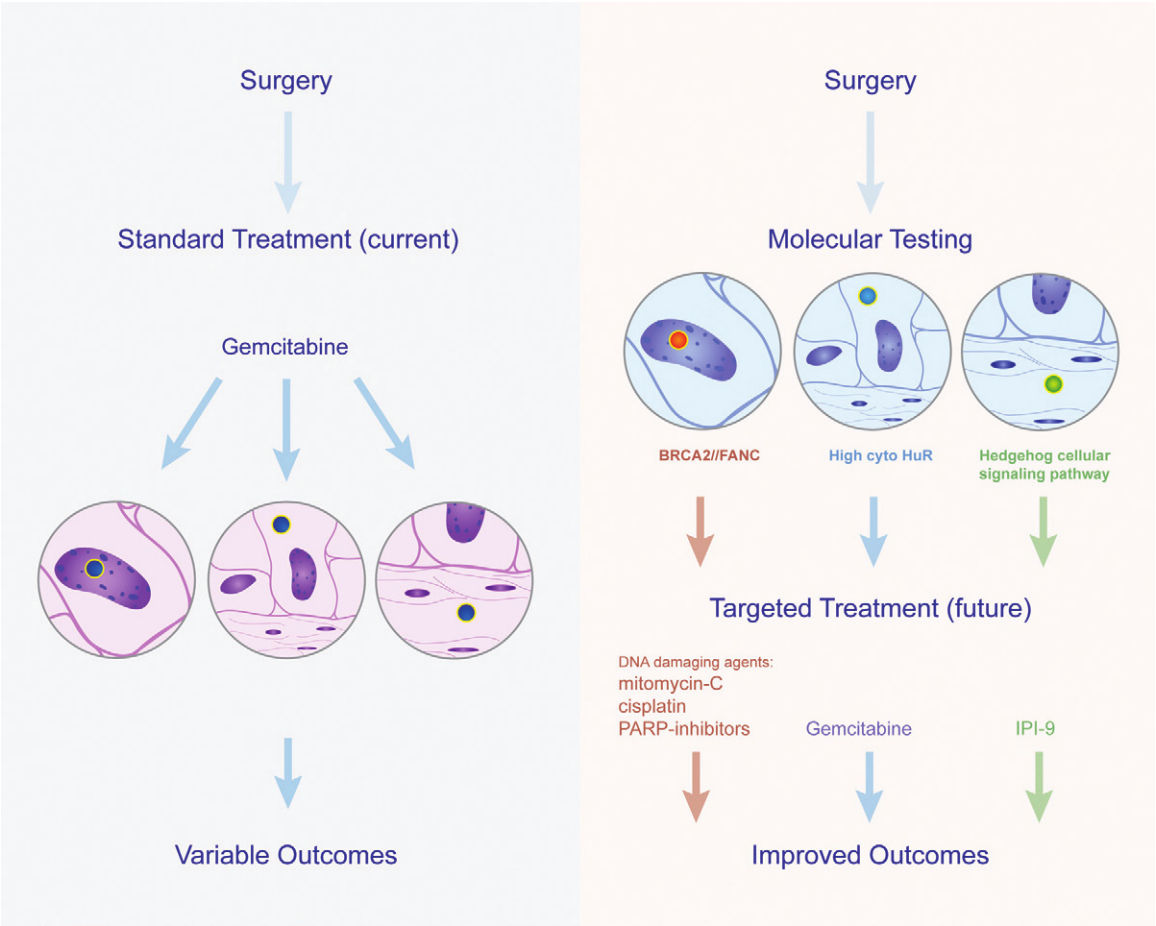


FIGURE 8A.3. Targeted treatment strategy of PDA. *Left*, The current strategy. *Right*, The future. IPI-9 is the abbreviation for IPI-926, an agent that inhibits the Hedgehog cellular signaling pathway (the stromal component of PDA). HuR, human antigen R; PDA, pancreatic ductal adenocarcinoma; PARP, poly(ADP-ribose)polymerase. *(Courtesy Jennifer Brumbaugh, TJU.)*

and F). An important feature that distinguishes the two lesions is that PanINs are microscopic lesions, and IPMNs are macroscopic. Nevertheless, recognition of an IPMN and its distinction from a PanIN lesion is important for two reasons: 1) IPMN-associated colloid carcinomas have a significantly better prognosis than either PanIN- or IPMN-associated tubular adenocarcinomas (Adsay et al, 2001), and 2) IPMNs have a propensity to be multifocal lesions, therefore patients who undergo partial pancreatectomy and are left with a remnant pancreas need to be followed for life, even when the lesion originally resected was a noninvasive IPMN (Sohn et al, 2004).[20]

Genetic analyses of IPMNs have disclosed abnormalities in many of the same genes altered in conventional ductal adenocarcinoma, including mutations in the *KRAS2*, *TP53*, and *CDKN2A* genes, although the frequency and stage of neoplastic progression at which these alterations occur in IPMNs differ from PanINs (Hruban et al, 2004; Sessa et al, 1994). For example, the Peutz–Jeghers gene *STK11* is inactivated in one third of IPMNs, and some patients with Peutz–Jeghers syndrome develop IPMNs (Sahin et al, 2003); this is in contrast to conventional ductal adenocarcinomas, in which loss of *STK11* is a rare event. In contrast to ductal adenocarcinomas and PanIN-3 lesions, abnormalities in the *SMAD4* gene seem to be rare in IPMNs (Iacobuzio-Donahue et al, 2000).

Another distinction between PanINs and IPMNs relates to the expression of the caudal differentiation factor CDX2, a marker of intestinal differentiation. Most IPMNs express *CDX2*, in particular IPMNs associated with an invasive colloid carcinoma, whereas this is uncommon both in PanINs and in the subset of IPMNs that give rise to invasive cancers resembling ductal adenocarcinomas (Adsay et al, 2004). *CDX2* expression in IPMNs usually is associated with expression of *MUC2*, an intestinal epithelial apomucin, whereas absence of *CDX2* usually is associated with expression of *MUC1*, a biliary apomucin, and concomitant lack of expression of *MUC2*. These findings have suggested that there may be two divergent pathways of carcinogenesis within the pancreatic ducts (Adsay et al, 2002). The first is a so-called *intestinal pathway* that gives rise to *CDX2*- and *MUC2*-expressing IPMNs that progress to the better-prognosis colloid carcinomas. The second is a *pancreatobiliary pathway* that gives rise to *CDX2*-negative, *MUC2*-negative, *MUC1*-expressing PanINs and a subset of IPMNs, both of which can progress to the poorer-prognosis conventional ductal adenocarcinomas. More

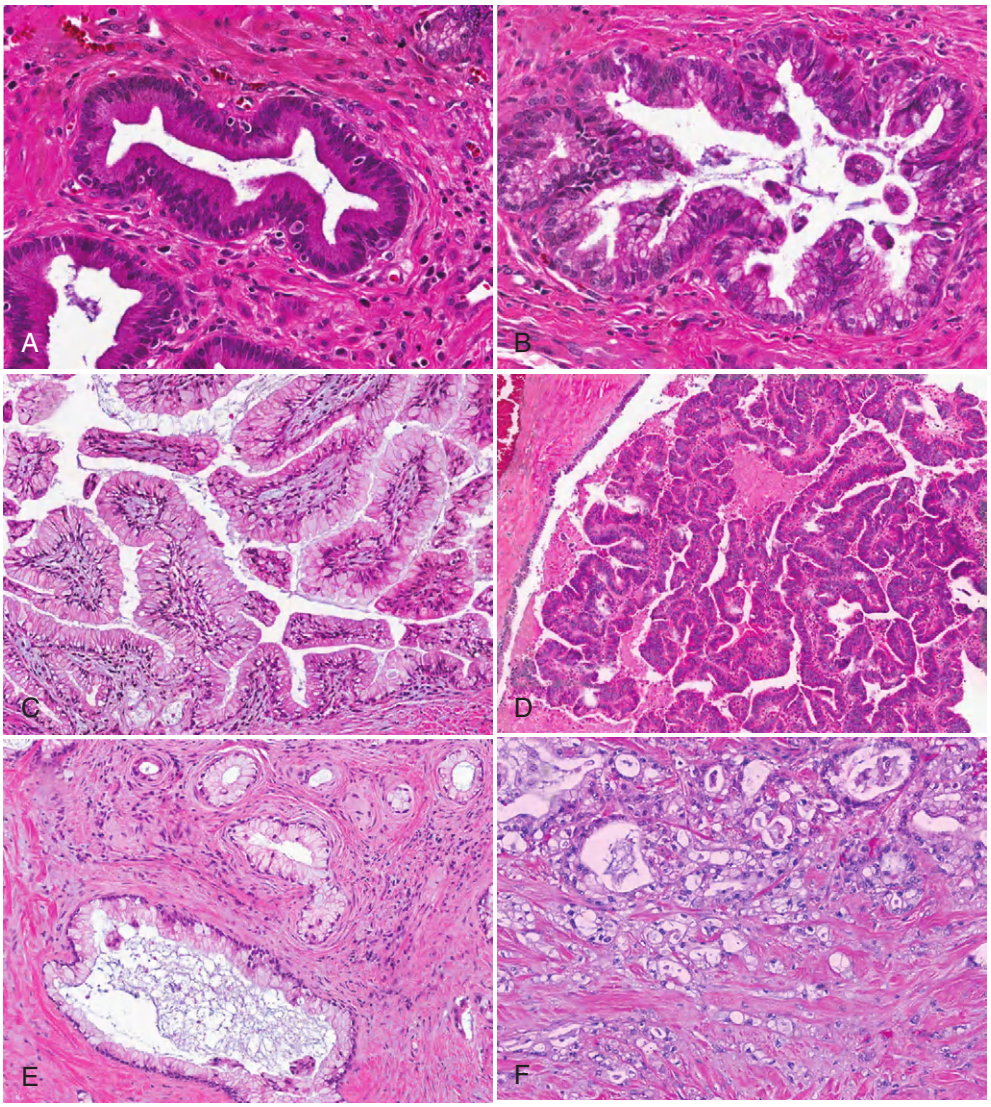


FIGURE 8A.4. Pathologic features of precursor lesions of pancreatic ductal adenocarcioma (PDA). **A,** Pancreatic intraepithelial neoplasia (PanIN). PanIN-1, flat lesion composed of columnar cells with basally located benign appearing nuclei and supranuclear mucin. **B,** PanIN-3 showing complex papillary architecture with budding of epithelial cells into lumen and cytologic atypia of lining cells. **C,** Intraductal papillary mucinous neoplasm (IPMN) with low-grade dysplasia showing well-formed papillae lined by mucin-containing cells. **D,** IPMN with high-grade dysplasia with complex branching papillae and cells showing marked cytologic atypia. **E,** Well-differentiated PDA forming glands and showing mild nuclear pleomorphism. **F,** Poorly differentiated PDA with solid growth pattern and infiltration of individual cells. The neoplastic cells show marked nuclear pleomorphism.

recently, it has been observed that IPMNs with moderate dysplasia had reduced or absent pp32 nuclear expression (Brody et al, 2007). This may be functionally significant, because *ANP32A* acts as a tumor suppressor in pancreatic and other cancers, and the absence of this protein may facilitate the tumorigenesis process.

Future Perspective of Precursor Lesions

Continued surgical resection, pathologic identification, and molecular dissection of PanIN and IPMN lesions will hopefully provide molecular signatures that will enlighten us about early events that drive tumorigenesis. Further, proteomic analysis of sera and blood from patients with these precursor lesions will likely reveal early detection markers that can be used for screening purposes.

GENETICS OF PANCREATIC DUCTAL ADENOCARCINOMA

Genomic (DNA) Alterations in Pancreatic Cancer

The multitude of genetic abnormalities in pancreatic cancer have many characteristics similar to other solid tumors, thus they include point mutations in critical genes, chromosomal (copy number) aberrations, mitochondrial DNA mutations, telomeric abnormalities, and epigenetic silencing by methylation of defined promoter DNA sequences. Recently, it was estimated that an individual pancreatic tumor contains, on average, 63 genetic alterations, primarily point mutations. It is also believed that only a small subset of these mutations is required for tumorigenesis (Jones et al, 2008).

The field of analyzing the genetics of pancreatic cancer can be broken down chronologically (see Fig. 8A.1). First, landmark studies starting in the late 1980s and spanning nearly two decades are highlighted by the discovery of *KRAS* activation, *SMAD4* and *BRCA2* mutations, and *CDKN2A* silencing (see Fig. 8A.1 and Fig. 8A.2, *left*). Some of these discoveries not only opened up lines of investigation in the field of pancreatic cancer but also opened up avenues with other tumor types and specific classification of PDA subtypes (Iacobuzio-Donahue et al, 2009). Then, in 2008 and 2009, Jones and colleagues, with the help of advanced DNA sequencing technology, were able to perform high-throughput genetic analysis on various pancreatic cancer genomes (see Figs. 8A.1 and 8A.2, *right*).

Copy-Number Aberrations

Although now considered primitive, valuable cytogenetic analysis performed over a decade ago found that chromosomal aberrations occur in virtually every pancreatic cancer. Cytogenetic analyses of pancreatic cancers have shown multiple, nonrandom numerical and structural changes (Griffin et al, 1995; Sirivatanauksorn et al, 2001). The most common numerical abnormalities include losses of chromosomes 6, 12, 13, and 18 and gains of chromosomes 7 and 20. Structural abnormalities (intrachromosomal break points) frequently involve 1p and 1q, 3p, 4q, 6q, 7q, 17p, 11p, 11q, 15q, 16q, and 19q (Rigaud et al, 2000). The technical limitations of conventional cytogenetics has presented challenges for identifying genes that are affected by chromosomal breaks. Allelotyping identifies areas of gross chromosomal loss by using polymorphic microsatellite markers to determine regions of genomic loss compared with matched normal tissues, also known as *loss of heterozygosity* (LOH) analysis. Allelotyping operates on the basic principle of the two-hit hypothesis, which postulates that tumor suppressor genes require biallelic inactivation. This most commonly happens by intragenic mutation in one allele, followed by loss of genetic material in the other allele. Identifying regions of single or biallelic loss or mutation holds the potential to understand the role of neighboring novel and well-known tumor suppressor genes. A landmark allelotype analysis of pancreatic cancers was performed using approximately 80 pancreatic cancer xenografts and 386 microsatellite markers (Iacobuzio-Donahue et al, 2004). This work discovered allelic losses in chromosome regions in proximity to tumor suppressor genes *CDKN2A*, *TP53*, and *SMAD4*. Allelotype analysis of PanIN lesions also has been performed using microdissected samples, and as expected, LOH is seen in many of the same chromosomal regions as invasive cancer, including 9p, 17p, and 18q (Luttges et al, 2001b; Yamano et al, 2000). Although the changes are conserved in most synchronous precursor lesions (i.e., the same allele is lost in PanIN and associated cancers), there is occasional clonal divergence between high-grade PanIN lesions harboring genetically distinct changes from the synchronous invasive cancer (Yamano et al, 2000). These findings may have important clinical implications in regard to tumor heterogeneity and clonal cancer cell drug resistance.

CGH identifies genomic amplifications and deletions and differentially labels normal and tumor genomic sequences with different dyes. The relative ratio of the two dyes indicates regions of cancer-associated losses or gains, with a ratio of 1 : 1 consistent with no change in copy number compared with normal DNA. Conventional CGH is performed on metaphase spreads and suffers from low resolution and inability to precisely map the various regions of amplifications and deletions (Mahlamaki et al, 1997). The resolution of array CGH is significantly better than the conventional technique, ranging from 500 kb to 30 kb, permitting the precise mapping of deletion and amplicon boundaries and genes targeted therein. Array technology also provides the ability to more efficiently use probes to study amplification of a larger number of genes. Array CGH analysis of pancreatic cancers has identified numerous recurrent copy-number aberrations, including amplifications of c-*MYC* (8q), *EGFR* (7p), *KRAS* (12p), *AKT2* (19q), and *NCOA3* (20q) and deletions *of SMAD4* (18q), *CDKN2A* (9p), *FHIT* (3p), and *MAP2K4* (17p) (Aguirre et al, 2004; Calhoun et al, 2006; Holzmann et al, 2004).

Utilizing high-density single-nucleotide polymorphism arrays, Calhoun and colleagues surveyed all the commercially available pancreatic cancer cell lines. In brief, this study provided high resolution and detailed break-point mapping of these cell lines and found two subclasses of cancer cell lines, original chromosomal instability (CIN) and holey CIN genotypes (Calhoun et al, 2006). Perhaps global classification of tumor cells with high-density arrays will become part of a prognostic or predictive molecular signature panel in the future.

Specific Gene Mutations

Allelotyping provides insight into areas harboring tumor suppressor genes, but it cannot qualify areas of enhanced genomic expression as happens with oncogene activation. Simplistically, wild-type tumor suppressor genes can "put the brakes" on the speeding vehicle (the cell), but if mutated, these "brakes" become defective, and the vehicle cannot stop. Using a similar automobile analogy, protooncogenes, in a mutated form known as *oncogenes,* become the "accelerators," and these "go signals" are often critical in transforming normal cells to a malignant phenotype.

Much like other solid tumors, genes altered in pancreatic cancer include three functional classes*: oncogenes, tumor suppressor genes,* and *caretaker genes.* A family of caretaker genes recognized as being disrupted in pancreatic cancer are genes of the Fanconi anemia complementation group, which are involved in homologous recombination-based DNA damage repair (D'Andrea et al, 2003). Patients with Fanconi anemia present with a wide variety of clinical issues, including aplastic anemia and a high risk of developing cancer. *BRCA2* is a member of this DNA repair pathway and is mutated in a subset of familial pancreatic cancers (Murphy et al, 2002). This has led to the search for mutations in other Fanconi anemia genes in pancreatic cancer. Somatic mutations of two genes in the core complex, *FANCC* and *FANCG*, were discovered but are rare in sporadic pancreatic cancers (van der Heijden et al, 2003). Through other modern techniques, Jones and colleagues (2009) discovered *FANCN (PALB2)* as another mutated gene found in familial pancreatic cancers.

Mutations in this core complex and in this DNA repair mechanism have major therapeutic implications (Fig. 8A.5, Table 8A.1; see the Familial Pancreatic cancer section below) (van der Heijden et al, 2004). Unlike most in vivo experiments, xenografted mice with isogenic cell lines (*FANCC* deficient and proficient) experienced regression of tumor after a single dose of the available mitomycin C intrastrand cross-linking drug (van der Heijden et al, 2005). Although other mutations in the Fanconi complementation group have not yet been described—other than *FANN, FANCC,* and *FANCG*—and the frequency of

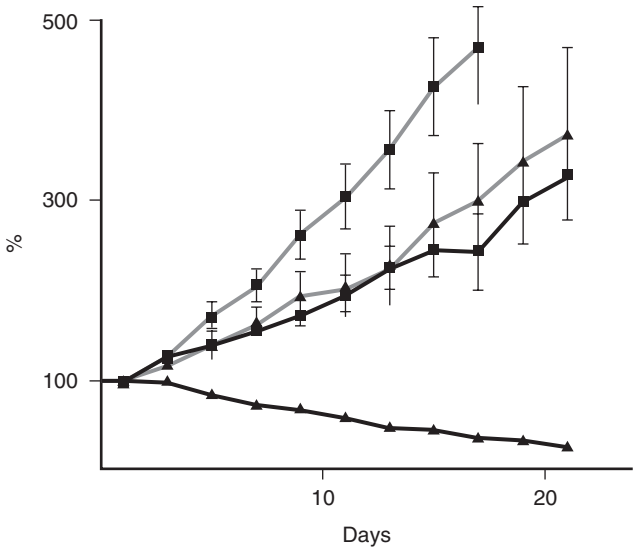


FIGURE 8A.5. Preclinical model shows an example of a successful targeted treatment strategy against a Fanconi-deficient tumor. A single-dose treatment with mitomycin C (5 mg/kg) of pancreatic cancer cell lines xenografted into nude mice. Note the hypersensitivity and tumor regression in the *FANCC*-deficient PL11 cells (*squares*) compared with the retrovirally corrected *FANC*-proficient PL11 cells (*triangles*). *Solid lines* indicate treated mice; *gray lines* indicate no treatment controls. Similar sensitivity was seen in the *BRCA2*-deficient CAPAN1 xenografted cells (van der Heijden et al, 2005).

these mutations in PDA appear to be low, it is likely that defects in other *FANC* genes yet to be thoroughly investigated (i.e., *FANCA*) are the direct cause of some familial and sporadic PDAs.

Oncogenes

Perhaps the best evidence that *KRAS* activation is an early and important event in tumorigenesis comes from decades of research on pancreatic cancer. The *KRAS2* oncogene on chromosome 12p is the most commonly altered oncogene, with up to 90% of pancreatic cancers containing mutations on codons 12, 13, and 61 (Caldas et al, 1994b). Activating mutations impairs the intrinsic GTPase activity of the *KRAS2* gene product, resulting in a protein that is constitutively active in intracellular signal transduction. Inactivation of *KRAS2* happens early in the pathway to oncogenesis, with approximately 30% of PanIN-1 lesions harboring *KRAS2* mutations (Hruban et al, 2000; Moskaluk et al, 1997). The first mouse model of pancreatic cancer was generated by constitutive overexpression of mutant *KRAS2* in the murine pancreatic ductal epithelium, underscoring its importance in pancreatic oncogenesis (Hingorani et al, 2003). This model was further developed into a powerful and useful preclinical model for PDA progression (Hingorani et al, 2005). Several good sources on mouse modeling and pancreatic cancer have been published (Frese et al, 2007; Karreth et al, 2009; Olive et al, 2006; Tuveson et al, 2005).

Rarely, pancreatic cancers with wild-type *KRAS2* genes harbor point mutations of *BRAF*, another gene in the RAS/RAF/MAP kinase signaling pathway, thereby explaining why mutations of these genes occur in mutually exclusive patterns in pancreatic cancer (Calhoun et al, 2003). This highlights the importance of identifying different molecular targets that lead to similar pathways in pancreatic cancer development and of finding a drug that can target one pathway, not one gene. Studies have shown that targeting *KRAS* may have potential in modulating angiogenesis in tumorigenesis. Matsuo and colleagues showed that oncogenic overexpression of *KRAS* increases production of angiogenesis, promoting CXC chemokines and VEGF from human pancreatic duct epithelial cells. This upregulation acts through the mitogen-activated protein kinase pathway and c-*JUN* signaling (Matsuo et al, 2009). *KRAS* mutation has been shown to be associated with increased *VEGFA* expression and poorer prognosis in pancreatic carcinoma (Ikeda et al, 2001). Yet to date, targeting KRAS activation in PDA patients has shown no success. Perhaps KRAS activation is a critical early event in pancreatic tumorigenesis, but once cells become malignant, there is no need for constitutive *KRAS* activation or for oncogenic addiction for that matter.

Other oncogenes implicated in pancreatic cancers include *MYC* and *EGFR*, which can be amplified in various subsets of cancers. Overexpression of *MYC* transcripts occurs in approximately 50% to 60% of pancreatic cancers (Aguirre et al, 2004; Han et al, 2002). Therapeutic targeting using monoclonal antibodies or small-molecule tyrosine kinase inhibitors makes use of the constitutive activation of the *EGFR* signaling pathway in pancreatic cancers via amplification of the *EGFR* gene (Holzmann et al, 2004; Li et al, 2004). Lack of a rigorous and reliable immunohistochemical assay to detect overexpression of *EGFR* has proven to be difficult and limiting.

Tumor Suppressor Genes

CDKN2A, on chromosome 9p, is the most commonly inactivated gene in pancreatic cancers, occurring in 90% of patients (Caldas et al, 1994a; Schutte et al, 1997). *CDKN2A* belongs to the cyclin-dependent kinase inhibitor family and inhibits cell-cycle progression through the G_1-S checkpoint mediated by cyclin-dependent kinases such as CDK4 and CDK6. Homozygous deletions (40%), intragenic mutation with loss of the second allele (40%), and epigenetic silencing by promoter methylation (10% to 15%) all contribute to gene inactivation. Immunolabeling for nuclear p16 protein expression is a reliable surrogate for *CDKN2A* genetic status; however, such immunolabeling does not identify specific genetic mechanisms of inactivation (Geradts et al, 2000). Loss of *CDKN2A* function occurs throughout the process of oncogenesis, with lesions appearing in different PanINs: 30% of PanIN-1A and PanIN-1B, 55% of PanIN-2, and 71% of PanIN-3 lesions show loss of nuclear p16 protein expression (Wilentz et al, 1998). The *CDKN2A* homozygous deletions encompass the *MTAP* gene in approximately 30% of pancreatic cancers, which offers potential therapeutic benefit, because targeted therapies have been developed that specifically inhibit the growth of *MTAP*-deficient cells (Chen et al, 1996).

Approximately 50% to 75% of pancreatic cancers contain an inactivation of the *TP53* gene on chromosome 17p. Such inactivation almost always occurs via intragenic mutation combined with loss of the second allele. The TP53 (*p53*) protein leads to cell-cycle arrest and activates apoptosis in the presence of DNA damage. It is believed that loss of TP53 function allows cells to survive and divide, despite the presence of damaged DNA, leading to accumulation of additional genetic

Table 8A.1

Genetic Syndromes with Inherited Predisposition to Pancreatic Cancer and Potential Targeted Therapy

Syndrome/Disease	Gene(s)	Genetic Testing Considerations	Risk of Pancreatic Adenocarcinoma	Available Targeted Therapy/Clinical Correlates
Hereditary breast/ ovarian cancer syndrome (HBOCS)	*BRCA1* *BRCA2*	NCCN test criteria require personal or family history of breast and ovarian cancer	*BRCA1*: 2.26-fold* *BRCA2*: 3- to 9-fold†	Cross-linking chemotherapeutics (mitomycin C, cisplatin, chorambucil, melphalan) PARP inhibitors
Peutz-Jeghers syndrome (PJS)	*STK11 (LKB1)*	Diagnosis of index case is generally based on clinical findings/working definition‡	132-fold; lifetime risk ~36%§	Reports of a PJS associated cancer with loss of the wild-type *STK11* allele together with a germline mutation in the other allele Some sporadic PDAs exhibit somatic mutations of *STK11*‖
Hereditary pancreatitis	*PRSS1; SPINK1, CFTR, CTRC*	Testing guidelines are based on symptoms with or without family history of pancreatitis¶	50- to 67-fold; lifetime risk 44%[a,b]	Tumor susceptibility is presumably due to mitogenic stimulation and clonal outgrowth of PDA cells as part of the normal healing responses that occur subsequent to repeated rounds of tissue destruction[b]
FAMM melanoma syndrome	*CDKN2A*	Documented patients/ families with multiple melanomas	13- to 39-fold†	Somatic p16 alterations were identified in 80% of PDAs[c]
HNPCC-Lynch Syndrome	*MLH1, MSH2, MSH6,* and *PMS2*	Bethesda Guidelines (tumor MSI/IHC) and Amsterdam Clinical Criteria II (germline studies)	<5-fold†	MSI-H pancreatic cancer may have a better prognosis after resection, possibly because of intensive immunoreaction to the tumor[d]
Familial adenomatous polyposis (FAP)	*APC*	APC is considered in individuals with ≥20 colon adenomas	Relative risk 4.46[e] Lifetime risk ~2%[f]	Some theorize that pancreaticobiliary secretions affect the development of adenomas and cancer in this area[g]
Cystic fibrosis (CF)	*CFTR*	Genotyping identifies patients with class IV and V mutations, which are likely to represent those with a functioning pancreas[h]	Relative risk 5.3[i]	Modifier genes or environmental factors may also be important in stratifying risk (e.g., mucin genes are found in both CF and PDA)[j]

*Thompson D, et al, 2002. Cancer incidence in *BRCA1* mutation carriers. J Natl Cancer Inst 94(18):1358-1365.
†Brand RE, et al, 2007. Advances in counseling and surveillance of patients at risk for pancreatic cancer. Gut 56(10):1460-1469.
‡Giardiello FM, et al, 1987. Increased risk of cancer in the Peutz-Jeghers syndrome. N Engl J Med 316(24):1511-1514.
§Giardiello FM, et al, 2000. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology 119(6):1447-1453.
‖Su GH, et al, 1999. Germline and somatic mutations of the *STK11/LKB1* Peutz-Jehgers gene in pancreatic and biliary cancers. Am J Pathol 154(6):1835-1840.
¶Ellis et al, 2001. Genetic testing for hereditary pancreatitis: guidelines for indications, counseling, consent, and privacy issues. Pancreatology 1(5):405-415.
[a]Lowenfels AB, et al, 1997. Hereditary pancreatitis and the risk of pancreatic cancer: International Hereditary Pancreatitis Study Group. J Natl Cancer Inst 89(6):442-446.
[b]Howes N, et al, 2004. Clinical and genetic characteristics of hereditary pancreatitis in Europe. Clin Gastroenterol Hepatol 2(3):252-261.
[c]Rozenblum E, et al, 1997. Tumor-suppressive pathways in pancreatic carcinoma. Cancer Res 57(9):1731-1734.
[d]Nakata B, et al, 2002. Prognostic value of microstaellite instability in resectable pancreatic cancer. Clin Cancer Res 8(8):2536-2540.
[e]Giardiello FM, et al, 1993. Increased risk of thyroid and pancreatic carcinoma in familial adenomatous polyposis. Gut 34(10):1394-1396.
[f]Burt RW, 2000. Colon cancer screening. Gastroenterology 119(3):837-853.
[g]Wallace MH, et al, 1998. Upper gastrointestinal disease in patients with familial adenomatous polyposis. Br J Sur 85(6):742-750.
[h]Krysa J, et al, 2007. Pancreas and cystic fibrosis: the implications of increased survival in cystic fibrosis. Pancreatology 7(5-6):447-450.
[i]Maisonneuve P, et al, 2007. Risk of pancreatic cancer in patients with cystic fibrosis. Gut 56(9):1327-1378.
[j]Singh AP, et al, 2007. *MUC4* expression is regulated by cystic fibrosis transmembrane conductance regulator in pancreatic adenocarcinoma cells via transcriptional and post-transcriptional mechanisms. Oncogene 26(1):30-41.
NCCN, National Comprehensive Cancer Network; *PARP,* poly (ADP-ribose) polymerase; *PDA,* pancreatic ductal adenocarcinoma; *MIS-H,* microsatellite instability; *MSI,* microsatellite instability; *H,* high frequency; *FAMM,* familial multiple mole; *HNPCC,* hereditary nonpolyposis colorectal cancer

Modified from Showalter SI, et al, 2010: Identifying pancreatic cancer patients for targeted treatment: The challenges and limitations of the current selection process and vision for the future. Expert Opin Drug Deliv 7(3):1-12.

abnormalities and eventually to neoplasia. Nuclear overexpression of the TP53 protein does not correlate well with mutation status. By immunohistochemistry, TP53 accumulation is seen only in the advanced PanIN-3 lesions, consistent with TP53 being a "late" genetic event in pancreatic cancer progression (Maitra et al, 2003). PDA cells with a mutant *TP53* have been shown to have a greater propensity for metastases (Morton et al, 2010). Of note, in an experimental model, the *BRCA2* gene could not be artificially disrupted in cancer cells with intact wild-type *TP53* status (Hucl et al, 2008; Callmeier et al, 2007). This interplay between TP53 and a genome maintenance pathway may have therapeutic value (see discussion on synthetic lethality later in this chapter).

Inactivation of the *SMAD4* gene on chromosome 18q21 occurs in approximately 55% of pancreatic cancers by homozygous deletions (30%) or by intragenic mutations and loss of the

second allele (25%). Loss of *SMAD4* function interferes with intracellular signaling cascades downstream of the transforming growth factor (TGF) family of cell surface receptors, leading to decreased growth inhibition and uncontrolled proliferation. *SMAD4* is only rarely mutated in other types of cancer (Schutte et al, 1996). Similar to *TP53,* loss of *SMAD4* function is a late genetic event in pancreatic carcinoma progression, with loss of *SMAD4* seen only in a few PanIN-3 lesions (Maitra et al, 2003). Examination of resected tumor specimens found that *SMAD4* inactivation portends a poorer prognosis and greater potential to metastasize (Iacobuzio-Donahue et al, 2009; Blackford et al, 2009). In brief, upon autospy evaluation, PDA patients died, with either locally destructive pancreatic cancer (30%) or widespread metastatic disease (70%). At autopsy, intact DPC4 staining (wild-type DPC4 status) of the tumor tissue significantly correlated with a locally advanced tumor and no detectable widespread metastatic disease phenotype (22%), although the majority of patients who had widespread metastases, numbering in the hundreds and thousands, had loss of DPC4 (78%) (Iacobuzio-Donahue et al, 2009). Identification of downstream targets might allow restoration of DPC4-dependent signaling in pancreatic cancer, yielding an improved prognosis (Cao et al, 2008).

Several tumor suppressor genes are inactivated in smaller numbers (5% to 10%) of pancreatic cancers, including *STK11* (chromosome 19p) (Sahin et al, 2003), *TGFBR1* (chromosome 9q), *TGFBR2* (chromosome 3p), *RB1* (chromosome 13q) (Jaeger et al, 1997), and *MAP2K4* (chromosome 17p) (Su et al, 1998). *MAP2K4*s function has been explored in a number of models, yet the main reason for its loss in pancreatic cancer is still unknown (Cunningham et al, 2006).

Other Caretaker Genes

In addition to classic oncogenes or tumor suppressor genes, caretaker genes (beyond Fanconi anemia–related genes) have been shown to play a role in oncogenesis. In theory, caretaker genes do not influence cell growth and proliferation directly but rather prevent the accumulation of DNA damage and cumulative mutations within key exonic sequences that make up the human genome. Loss of function of the DNA damage repair genes (*MLH1*, h*MSH2*) occurs in a small subset of pancreatic cancers in the familial setting but can also be seen in occasional, sporadic, nonfamilial cases (Ghimenti et al, 1999). Histologically, these microsatellite instability (MSI) cancers comprise poorly differentiated cancers with a syncytial growth pattern, expanding tumor margins, extensive necrosis, and intratumoral lymphocytic infiltrates. This uncommon variant has been termed *medullary cancer* to distinguish it from the more common pancreatic ductal adenocarcinoma (Wilentz et al, 2000b). Although findings in colon cancer have attempted to correlate MSI status with response to 5-fluorouracil, other studies have questioned these claims (Brody et al, 2009a).

Telomere Length Abnormalities

Telomeres are hexameric repeats of the sequence TTAGGG at the ends of chromosome arms that confer stability to chromosomes during cell division and prevent the ends from becoming "promiscuous" (Gisselsson, 2003). In other words, intact telomere structure guards against chromosomal fusion and thus may prevent chromosomal instability (Greenberg et al, 2005; Raynaud et al, 2008). In fact, telomeric dysfunction has been hypothesized to be one of the more important gateways of chromosomal instability, a signature of most solid cancers characterized by aneuploidy and extensive chromosomal rearrangements. The development of direct visualization of in situ telomere length was a breakthrough for understanding telomere length abnormalities and cancer development (Meeker et al, 2004). A study by van Heek and colleagues showed that telomere length abnormalities are one of the earliest demonstrable genetic aberrations in pancreatic cancer, with greater than 90% of the lowest grade PanIN lesions showing marked shortening of telomeres, as compared with normal duct epithelium (van Heek et al, 2002). It has been hypothesized that intact telomeres may serve as "caretakers" in the pancreatic ducts, and that the loss of telomeres in PanIN lesions sets the stage for progressive accumulation of chromosomal abnormalities, eventually culminating in neoplasia. Of note, Dr. Carol Greider, the lead investigator on a number of landmark studies involving telomerase and telomere function, recently (2009) won the Nobel prize based on her work with telomeres. This underscores the importance of this molecule's involvement in both cancer and the aging process (Harley et al, 1994).

Alternative Genetic Silencing: Epigenetic Abnormalities

Although the classic two-hit hypothesis postulated that tumor suppressor gene silencing occurs by a combination of intragenic mutations and allelic loss, it has become apparent since the 1990s that epigenetic mechanisms of silencing are probably as important in terms of frequency and prevalence in many cancers (Baylin et al, 2000). Epigenetic silencing occurs predominantly through hypermethylation of so-called *CpG islands* in the promoter region of tumor suppressor genes, leading to transcriptional abrogation. Gene silencing by promoter methylation occurs physiologically at many sites in the human genome, where it is called *imprinting.* The most basic example is the one that occurs on an X chromosome in females, known as *X inactivation,* in which one of the two X chromosomes in females becomes silenced. In cancers, preferential hypermethylation of the promoter occurs in the neoplastic cells with consequent downregulation of gene expression, but this does not occur in the corresponding normal counterpart. Epigenetic silencing is seen frequently in pancreatic cancers and tends to involve genes that function in tumor suppression or in critical homeostatic pathways (e.g., *CDKN2A,* E-cadherin, retinoic acid β, osteonectin, *SOCS1*) or in both (Sato et al, 2003a; Ueki et al, 2000).

Aberrant methylation of genes is also found in precursor lesions of pancreatic cancers and tends to occur in intermediate- or late-stage lesions (PanIN-2 and PanIN-3) (Fukushima et al, 2002). The presence of promoter hypermethylation in noninvasive precursor lesions implies that the detection of aberrantly methylated DNA sequences in clinical samples might be useful as a strategy for early detection of pancreatic cancer. Methylated proenkephalin sequences can be detected in approximately 60% of pancreatic juice samples obtained from patients with pancreatic cancer but not in patients with nonneoplastic periampullary diseases, including chronic pancreatitis (Fukushima et al, 2003). The development of tumor-specific early detection panels using aberrantly methylated DNA sequences is currently an area of active investigation for many human cancers, including pancreatic cancer.

Although there has been extensive work on the role of promoter hypermethylation in the pathogenesis of cancers, more

recent data suggest that promoter hypomethylation in candidate genes also may be important in cancer development and progression. Genes showing preferential hypomethylation in pancreatic cancers—*SERPINB5, S100P, MSLN, PSCA,* and *CLDN4*—are usually overexpressed in the cancers compared with normal pancreas, suggesting that epigenetic mechanisms can affect gene expression in either direction (Sato et al, 2003b).

Aberrant epigenetic silencing by promoter methylation also has been reported in IPMNs, including methylation of the *SOCS1* and *CDKN2A* genes (Sato et al, 2002). Global analyses of gene expression in IPMNs have revealed the overexpression of *LCN2, LGALS3, CTSE, CLDN4,* and three members of the trefoil factor family, *TFF1, TFF2,* and *TFF3* (Sato et al, 2004a; Terris et al, 2002). These global analyses also have shown that *CLDN4,* CXCR4, S100A4, and *MSLN* all are expressed at significantly higher levels in invasive IPMNs than in noninvasive IPMNs, suggesting that these proteins may contribute to the process of invasion (Sato et al, 2004b).

SECOND ERA OF MOLECULAR BIOLOGY

Core Signaling Pathways Disrupted in Pancreatic Cancer

The modern era of molecular biology has progressed to allow high-throughput surveying of the pancreatic cancer genome (Figs. 8A.1 and 8A.2, *right*), bringing some clarity to our understanding of the interactions of molecular pathways in tumorigenesis. This high-throughput analysis revealed that pancreatic cancers contain an average of 63 genes that are genetically altered (Jones et al, 2008). In this work, Jones and colleagues used a combination of modern molecular techniques to report that 67% to 100% of all pancreatic cancer genomes surveyed had a genetic abnormality in 12 core signaling pathways and processes. These pathways include apoptosis, DNA damage control, regulation of G_1–S phase transition, Hedgehog signaling, hemophilic cell adhesion, integrin signaling, c-*JUN* N-terminal kinase signaling, *KRAS* signaling, regulation of invasion, small GTPase-dependent signaling (other than *KRAS*), *TGFB* signaling, and *WNT/NOTCH* signaling.

Unlike certain subtypes of leukemia that are driven by single "targetable" oncogenes, we have learned that pancreatic cancers result from genetic alterations of large numbers of genes that function through a distinct number of pathways. The study by Jones and colleagues suggests that it may be beneficial to target the physiologic effects of disrupted pathways rather than individual target genes.[4] In fact, targeting multiple pathways or multiple points in the pathway may be in line with the early preclinical and clinical success stories of the concept of "synthetic lethality" (Ashworth, 2008). This promising direction in therapeutic development is extracted from fruit fly (*Drosophila melanogaster*) and yeast genetic studies, in which deletion of multiple genes in the same pathway was found to be deleterious to the organism, although disruption in just one gene in the pathway is not. Thus, targeting an additional gene in an already disrupted pathway in a tumor may be deleterious for tumor cells and may thus be a promising therapeutic strategy.

Future Perspective of the Genetics and the Epigenetics of Pancreatic Ductal Adenocarcinoma

Certainly the rapid advancement of whole genome sequencing should find novel genes and genomic regions that are disrupted in pancreatic cancer. These genetic alterations may be used as biomarkers not only to predict prognosis but also to direct therapies. Not too far into the future, we will use single nucleotide polymorphisms (SNPs), which may contribute not only to the disease process but also to chemotherapy metabolism. The future opportunity of cancer genetics to yield therapeutic benefit is based on our ability to distinguish the subtle *differences* between individual pancreatic cancers, not the similarities. Because, in fact, it is these differences that will generate clinical success. Finally, once we thoroughly screen the complete landscape of the pancreatic cancer genome, we will still need to perform the basic laboratory studies to understand exactly how these disrupted genes contribute to the complex tumorigenesis process and how we may take advantage of these alterations therapeutically.

FAMILIAL PANCREATIC CANCER

Approximately 10% of pancreatic cancers show familial aggregation (Petersen et al, 2003). The presence of two first-degree family members with pancreatic cancer confers a 6- to 18-fold increased risk of the disease in other first-degree relatives. This risk is increased 32- to 57-fold in families with three or more first-degree relatives with pancreatic cancer (Klein et al, 2004; Tersmette et al, 2001). Only a minority of these familial cancers is caused by a recognized cancer syndrome associated with germline mutations in known genes. Included in Table 8A.1 are possible "targeted therapies" for the genes and disorders germane to pancreatic cancer. Thus, this table underscores the significance for understanding the inherited lesion that may have contributed to the pancreatic cancers found in these families.

For example, as mentioned earlier in this chapter, Fanconi anemia is characterized as a rare, autosomally recessive cancer syndrome that results initially from a mutation in one of the multiple *FANC/BRCA* complementation groups in the *FANC/BRCA* pathway (Mathew, 2006). One gene in this pathway, *BRCA2*, is associated with a greatly increased risk of cancer when deleted via a biallelic mutation. The *BRCA* genes play a critical role in DNA repair via RAD51 repair pathways (Gudmundsdottir et al, 2006). Loss of functional *BRCA1* and *BRCA2* conveys chromosomal instability to cells by impairing the critical function of DNA double-stranded break repair (Ashworth, 2008). It has been well established that DNA damaging agents such as mitomycin c or cisplatin effectively kill cells with loss of *BRCA2* or related genes (see Fig. 8A.5) (Hussain et al, 2004).

Currently, poly (ADP-ribose) polymerase (PARP) inhibitors have similar promising results as intrastrand cross-linking agents in early phase trials in other cancer types (ovarian, breast) (Farmer et al 2005). Certainly, pancreatic cancer is a logical tumor system in which to test novel PARP inhibitors in combination with other DNA-damaging agents. Targeting the *FANC-BRCA* pathway with PARP inhibitors similarly has been shown to lead to synthetic lethality, creating a convenient and fortuitous therapeutic window (Ashworth, 2008). The makeup of this therapeutic window relies on the fact that normal cells

will have an intact DNA repair mechanism and thus will be capable of managing and repairing the damage put forth by a DNA-damaging agent. In contrast, the tumor will be unable to repair such damage due to loss of a key aspect of this repair mechanism (i.e., *BRCA2;* see Fig. 8A.5).

Identification of mutations in the *FANC-BRCA* pathway in familial cancers has the potential to shed light on the treatment of sporadic cancers as well. It has been suggested that perhaps up to 25% of sporadic breast and ovarian cancers manifest a *BRCA*-like phenotype. (Turner et al, 2004). The data have been derived from *BRCA1, FANCC, FANCG,* and *FANCF* methylation studies (Turner et al, 2004). Further studies are warranted, but future banking of sporadic pancreatic cancers to study all of the tumor characteristics—posttranscriptional modification, polymorphisms, CGH analysis—along with thorough analysis of family history may reveal a "*BRCA*ness" among certain sporadic pancreatic tumors, aiding in the personalization of therapy (Martin et al, 2010). Focused DNA repair microarray analysis may also shed light on other cancer susceptibility genes.

Of note, a recent report demonstrated that *PALB2,* formerly known as *FANCN,* is a gene inherited in a mutant form that produces a stop codon in a small percentage of familial PDAs. This gene was discovered to be mutated in three of 96 familial pancreatic cancers, each producing a different stop codon (Jones et al, 2009). Truncating mutations in *PALB2* were not found in any of the 1084 patients of similar ethnicity used as a control cohort in a similar study, thus ruling out a polymorphic sequence variant. This information suggests that next to *BRCA2*, *PALB2* is the second most commonly mutated gene in hereditary pancreatic cancer (Jones et al, 2009). Thus most familial pancreatic cancers have no known genetic bases at this time, although many believe an autosomal dominant inheritance of a rare mutant allele is the most likely cause of these cancers. Of apparently "sporadic" (nonfamilial) pancreatic cancer patients, 7% harbor germline mutations in the *BRCA2* gene, and this low-penetrance pattern is peculiar to cancers arising in the Ashkenazi Jewish population (Goggins et al, 1996). Perhaps no single gene is responsible for the other familial forms of PDA, carcinogenesis of which may be the best example that core pathways collaborate with the environment (Yeo et al, 2009); thus no single gene from one pathway will prove to be disrupted in the complex process of tumorigenesis in this familial form of pancreatic cancer.

Finding Familial Patients

Canto and colleagues published a list of arguments for and against screening patients with a family history of pancreatic cancer. Arguments for screening include the fact that once the disease is symptomatic, it is often not curable, and that high-risk patients can be identified and are often very compliant with follow-up. Arguments against screening include lack of a standard protocol on screening patients with two or fewer first-degree relatives with PDA and technical limitations in screening (Steinberg et al, 2009).

TRANSCRIPTOMIC (RNA) ABNORMALITIES IN PANCREATIC CANCER

Although the presence of clonal genomic abnormalities in some ways defines the pancreatic cancer phenotype, recent years also have seen an explosion of new data characterizing the transcriptomic (RNA) abnormalities in human cancers. This cataloging has been greatly facilitated by the development of global expression analysis platforms, such as oligonucleotide microarrays, cDNA microarrays, and serial analysis of gene expression (SAGE). Several studies have analyzed pancreatic cancers and compared their gene expression profile with normal pancreas tissue to identify differentially overexpressed and underexpressed genes (Argani et al, 2001a; Crnogorac-Jurcevic et al, 2001; Geng et al, 1998; Iacobuzio-Donahue et al, 2002, 2003a, 2003b; Ryu et al, 2001, 2002). A comprehensive analysis of pancreatic cancer using high-density oligonucleotide microarrays identified 217 genes as being overexpressed threefold or higher in cancers versus normal tissue (Iacobuzio-Donahue et al, 2003a). Of these genes, 40 were determined to be overexpressed by more than one global expression profiling platform, and six genes—keratin 19, retinoic acid–induced 3, secretory leukocyte protease inhibitor, stratifin, tetraspan 1, and transglutaminase 2—were found to be overexpressed in pancreatic cancer by all three platforms: oligonucleotide and cDNA microarrays and SAGE. The future role of one or all of these six genes in early detection or therapy remains to be elucidated.

The identification of differentially expressed genes not only serves the further understanding of the basic biology of pancreatic cancers, it also provides a fertile ground to identify markers for early diagnosis, imaging, and novel therapeutic strategies. Mesothelin (*MSLN*) was identified by SAGE as a gene overexpressed in pancreatic cancers, and it was confirmed by immunohistochemistry to be restricted to the neoplastic epithelium (Argani et al, 2001b). These data were corroborated by a number of laboratories that included surveying of tumor tissues from diverse and distinct tumor banks (Showalter et al, 2008). This identification led to the development of a pancreatic cancer vaccine targeted to the mesothelin antigen and the development of antimesothelin antibody-conjugated immunotoxins, both of which are undergoing clinical trials in pancreatic cancer (Thomas et al, 2004). Moreover, a therapeutic strategy that delivers a suicide gene, *DT-A*, to pancreatic cancer cells under the regulation of the mesothelin promoter has showed early success (Showalter et al, 2008). Hucl and colleagues were able to define the exact sequence motif within the promoter region that was responsible for driving cancer-specific transcription, termed *CanScript*. This region was critical for binding of the TEF-1 transcription factor (Hucl et al, 2007). Interestingly, in the comprehensive SAGE analysis performed in the Jones and colleagues publication (see Fig. 8A.2) (Jones et al, 2009), mesothelin was labeled as not overexpressed, because it did not exceed the arbitrary tenfold-over-normal threshold. Future bench-work studies on these proteins should elucidate the functional significance of these overexpressed genes. Moreover, better tools in the laboratory will show that haploinsufficiency and/or modestly reduced and overexpressed molecules may have important effects on tumor phenotype and invasiveness.

More recently, the misexpression of two "embryonic" signaling pathways, Notch and Hedgehog, was described in most pancreatic cancers (Berman et al, 2003; Miyamoto et al, 2003; Thayer et al, 2003). These pathways are highly expressed in multiple tissues during in utero development, hence the term "embryonic"; but these are for the most part turned off in adult somatic cells, including those of the normal pancreas. Overexpression of genes in both the *NOTCH* and *HEDGEHOG* pathways have been described in invasive cancers and PanIN lesions but not in normal pancreatic duct epithelium (Miyamoto et al,

2003; Thayer et al, 2003). The neoplasia-specific activation of these pathways makes them an attractive target for therapy using specific small-molecule inhibitors. In fact, the *HEDGEHOG* small-molecule inhibitor cyclopamine has been shown to cause regression of pancreatic cancer growth in vitro and in vivo (Berman et al, 2003).

Posttranscriptional Regulation

In recent years, strong evidence has shown that posttranscriptional regulation of genes can directly affect both the tumorigenesis process (Lopez de Silanes et al, 2003, 2005) and cancer cell susceptibility to chemotherapy (Brody et al, 2009a; Constantino et al, 2009; Gorospe, 2003). Posttranscriptional gene regulation can have the same effect on gene expression as a genetic mutation or methylation of a promoter. One potent mechanism of posttranscriptional regulation involves RNA-binding proteins. One such RNA-binding protein that has been shown to be important in a number of tumor systems is Hu antigen R (HuR), a ubiquitously expressed member of the *HU* family that mediates cellular response to stress and DNA damage by posttranscriptional regulation (Hinman et al, 2008). Elevated HuR cytoplasmic expression is detected in tumors with poor pathologic features and poor predicted outcomes (Lopez de Silanes et al, 2005). It is has been shown that during times of certain cellular stressors—brought on by agents such as ultraviolet C (UVC) irradiation, heat shock, hypoxia, tamoxifen (Hostetter et al, 2008), and actinomycin D—HuR can bind to certain apoptotic or survival mRNA transcripts by binding to AU-rich elements in the 3′ untranslated region (UTR) of these mRNAs. In regard to tumorigenesis, HuR has been shown to bind to and stabilize proteins such as p21, p53, and cyclin A (Gorospe, 2003). For instance, Gorospe and colleagues showed that HuR can enhance translation of proteins such as p53 under stress from UVC irradiation (Gorospe, 2003). Thus HuR's role in cellular stress and damage gives it a likely pivotal role in both the tumorigenesis process and in the acute cellular response to chemotherapy in pancreatic cancer cells.

As an example, Costantino and colleagues showed that pancreatic cancer cell lines that overexpressed HuR were dramatically sensitive to gemcitabine, the standard chemotherapeutic treatment for pancreatic cancer, when compared with controls (Constantino et al, 2009). Treatment of cells with gemcitabine caused an increase in cytoplasmic HuR levels, and HuR associates with deoxycytidine kinase (dCK) mRNA and in turn regulates dCK protein levels (Constantino et al, 2009). This is important, because *DCK* encodes the protein that metabolizes gemcitabine. Clinically, cytoplasmic HuR levels in pancreatic cancer patients predicted response to gemcitabine therapy. In brief, patients who had low cytoplasmic HuR levels had a sevenfold increase in mortality compared with patients who had elevated cytoplasmic HuR levels (Fig. 8A.6) (Constantino et al, 2009). Prospective studies and attempts to manipulate HuR expression levels in tumor cells to optimize gemcitabine therapy are currently being investigated.

MicroRNAs

MicroRNAs (miRNAs) are defined as short, noncoding regions of RNA sequences (22 nucleotides) that can potently regulate gene expression patterns; miRNAs have been shown to regulate a number of disease- and developmental-related genes, and they are tissue specific in expression (Rosenfeld et al, 2008). These miRNA-specific attributes make them putative, powerful, and unique candidate biomarkers (Mardin et al, 2009). Discovering the presence of miRNAs in pancreatic cancer may be extremely valuable, although understanding the significance of these miRNAs may be more difficult and tedious, as miRNAs have been shown to distinguish between various disease states and tissues including pancreatitis, PDA, IPMN, and normal specimens (Mardin et al, 2009). Further, it has been shown that a miRNA molecular signature can stratify long- and short-term survivors (Bloomstron et al, 2007).

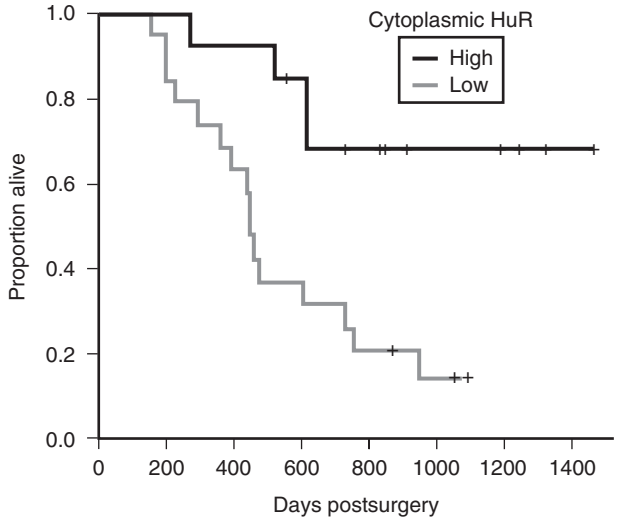


FIGURE 8A.6. Tumor human antigen R (*HuR*) cytoplasmic status can stratify pancreatic cancer patients treated with standard-of-care chemotherapy (gemcitabine) into two groups: responders (high cytoplasmic HuR) versus nonresponders (low cytoplasmic HuR) *(Constantino et al, 2009)*.

Future Perspectives on the Transcriptome

Genetic alterations have been proven over countless investigations to be critical for the development of PDA. Now that we have the technology to identify subtle mRNA expression changes, and also the ability to comprehend the complexity of numerous transcriptional regulatory mechanisms, we can begin to utilize this information for our understanding of PDA biology and therapeutic resistance mechanisms. Understanding the special plasticity of the pancreatic cancer transcriptome—not only in response to drugs (Brody et al, 2009b) but also in response to cancer-specific environmental concerns, such as hypoxia and radiation—will most likely be critical for our successful management of pancreatic cancer patients.

STROMAL CONTENT IN PANCREATIC CANCER

One of the reasons why pancreatic cancer remains such a lethal disease stems from its relative insensitivity to chemotherapeutic agents. The bulk of PDA tumor volume consists of stroma, thus identifying the signaling pathways disrupted in the stromal component adjacent to cancer cells may be extremely valuable.

A number of studies have been conducted using cell co-culturing (Sato et al, 2004b) as well as genetic evaluation (Walter et al, 2008) of the stromal component of pancreatic

cancer tissue. For example, Olive and colleagues studied the differences in gemcitabine delivery in mice that had tumors implanted in their tissue compared with mice that were genetically engineered (KPC mice) to conditionally express endogenous mutant *KRAS* and *TP53* alleles similar to pancreatic cancer cells (Olive et al, 2009). Mice with transplanted tumors showed greater tissue accumulation of the active metabolites of gemcitabine than the KPC mice. Visual microscopic studies revealed that the KPC mice had a much greater stromal content and reduced blood vessel density than the tumor-implanted mice, therefore increasing the space between neoplastic cells and blood flow. The decreased stromal content in the tumor-implanted mice apparently led to greater therapeutic efficiency of gemcitabine delivery. To pursue this issue, the investigators treated mice with IPI-926, an inhibitor of *SMO* that is normally upregulated in the *HEDGEHOG* pathway in stromal cells. Mice treated with IPI-926 exhibited depletion of desmoplastic stroma and increased tumor vascularity. In turn, the concentration of gemcitabine in KPC tumors was elevated by 60% after 10 days of pretreatment with the combined IPI-926/gemcitabine treatment. KPC mice treated with the combination therapy showed decreased tumor size and increased survival benefit when compared with mice treated with IPI-926 or gemcitabine alone (Olive et al, 2009). This study is a nice example of exploring and exploiting a potential target in stroma cells, and its results sheds light on the importance of identifying pathways (i.e., stromal development) that lead to tumorigenesis or impact drug delivery. Treating the stromal component of the tumor with IPI-926 and taking advantage of the tumor cell's HuR status is an example of how we may be able to powerfully target both the stromal and epithelial components of pancreatic cancer at the same time.

MOLECULAR GENETICS OF OTHER PANCREATIC NEOPLASMS

The discussion in this chapter has centered on precursor lesions and pancreatic ductal adenocarcinoma. Comparing the genetic changes in less common pancreatic lesions with those of ductal adenocarcinomas helps us better understand the mechanisms of carcinogenesis within different compartments of the pancreas. At the same time, many of these less common neoplasms have a significantly less ominous prognosis than conventional ductal adenocarcinomas, and histologic and molecular tools may be required to distinguish unequivocally the groups in diagnostic specimens.

FINAL THOUGHTS AND PERSPECTIVES

We are currently at an interesting and critical time in studying the molecular aspects of pancreatic cancer. The research community has incredible resources at its disposal, ranging from patient databases to complex sequencing equipment. This coming of age of pancreatic cancer research must include surgeons, pathologists, molecular biologists, and medical oncologists collaborating toward ultimately better and more personalized patient care. It is also time for the National Institutes of Health and other funding agencies to provide increased support and to step up their efforts at this exciting time in pancreatic cancer research. Hopefully, those in the field will take the time to connect the dots with all the rigorous and voluminous research that has been performed over the last few decades (see Fig. 8A.1), allowing future landmark progress. Current research will need to provide better early detection markers, so that physicians can have more opportunities to prevent cancer from forming, instead of attempting to cure it before it is too late. Our hope is that the treatment of pancreatic cancer will follow a paradigm similar to that of infectious disease specialists treating bacterial infections. Specific bacterial infections are easily cleared with specific antibiotics. Following this logical course, and based on the past decades of research, an individual pancreatic cancer patient of the future will likely benefit from personalized treatment. In the coming decade, we must translate our molecular research efforts into a better understanding of familial risk, earlier detection, and logical but innovative therapies in order to generate better outcomes for our patients.

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CHAPTER 9

Liver immunology

Zubin M. Bamboat, Venu G. Pillarisetty, and Ronald P. DeMatteo

FUNDAMENTALS OF IMMUNOLOGY

The immune system is composed of two major components: *innate* and *adaptive* immunity (Fig. 9.1; Janeway, 2001). Innate immune cells are armed with hard-wired detection systems that recognize common structures found on pathogens or changes in surface molecules of host cells that signal danger. Such pattern recognition receptors (PRRs) account for the rapid response of innate immune cells to infection or host injury. A variety of PRRs exist, of which the best characterized is the Toll-like receptor (TLR) family. In humans, 11 TLRs are currently known that recognize various structurally conserved components of bacteria and viruses in addition to endogenous intracellular ligands. Engagement of PRRs by their respective ligands causes activation of innate immune cells, such as neutrophils, monocytes, macrophages, natural killer (NK) cells, and dendritic cells (DCs). The ensuing response results in destruction of the invading pathogen or tumor via phagocytosis or release of various cytotoxic or inflammatory agents.

In contrast, adaptive immunity refers to the arm of the immune system that is involved in antigen-specific responses, which occur either later in a particular immune response or rapidly after repeat exposure to a particular pathogen. The adaptive immune system is essentially comprised of T and B cells that circulate within the blood, lymphatic tissues, and organs. These lymphocytes interact with various antigen-presenting cells (APCs) of the innate immune system, such as DCs and macrophages. Activation occurs in the presence of specific signals between APCs and T or B cells. These signals include 1) stable antigen presentation within the context of major histocompatibility complex (MHC) molecules MHC-I or MHC-II, 2) appropriate costimulation by APCs and the corresponding receptor on T or B cells, and 3) cytokine-mediated signals that can modulate the overall response (Fig. 9.2). Innate and adaptive immune responses provide protection against a vast array of pathogens, preserving normal cells and tissues from attack. Failure of the immune system's ability to correctly recognize foreign or abnormal cells may facilitate the development or spread of infection or malignancy. In contrast, inability to distinguish self from foreign antigens may result in autoimmune disease.

Modern clinical and experimental work has shown that the liver is particularly important in immunity (Fig. 9.3). First, the fact that the liver is one of the most common sites for metastatic disease suggests that it may have an increased propensity toward immunologic acceptance. Second, allogeneic liver transplantation can be accomplished in certain strains of mice without the need for immunosuppression, and in humans it often requires less immunosuppression compared with kidney or other solid organ transplants. Third, the liver is home to chronic viral infection in the form of hepatitis B and C. Additionally, oral ingestion or portal vein injection of foreign proteins can lead to tolerance in animal models. Conversely, the liver is the site of several autoimmune processes, including primary sclerosing cholangitis and primary biliary sclerosis. Despite the significant role that the liver plays in altering the balance between tolerance and immunity, the study of liver immunology remains in its infancy. This chapter discusses our current understanding of the function of liver immune cells and their role in disease.

Anatomic Considerations

Because the vascular supply of the liver derives principally from the portal venous system draining the gut, a heavy antigen load is delivered to the liver, particularly after meals. Portal venous blood flows slowly through the vast network of hepatic sinusoids, which are discontinuously lined by fenestrated endothelium lacking a basement membrane (Fig. 9.4; see also Chapter 6). The sluggish flow of blood allows for the efficient capture of antigens by leukocytes traveling in the blood within the sinusoids and by the endothelial cells lining the sinusoids. The microscopic anatomy of the liver also favors the ability of blood-borne leukocytes to interact with hepatic parenchymal cells and resident immune cells of the liver.

Tolerance Versus Immunity

One of the most intriguing aspects of liver immunology is the propensity of antigens passing through the liver to produce tolerance rather than immunity. In experimental animal models and clinical studies of humans undergoing liver transplantation, a greater propensity for graft acceptance has been noted compared with transplantation of other solid organs. A liver transplant protects a kidney allograft transplanted simultaneously from the same donor (Creput et al, 2003). Trying to decipher the reasons for the liver's inherent propensity for tolerance has been a particularly active area of research in the field of transplantation and cancer immunobiology.

Multiple competing theories to explain the cause of liver tolerance have been advanced. One postulate is that, as in central thymic tolerance, clonal deletion of antigen-specific T cells occurs in the liver. Another theory is that liver allografts release large amounts of soluble MHC class I molecules that potentially could function to neutralize donor-specific antibodies or cytolytic T cells. Kupffer cells (KCs) and natural killer (NK) T cells have been implicated as being important in the

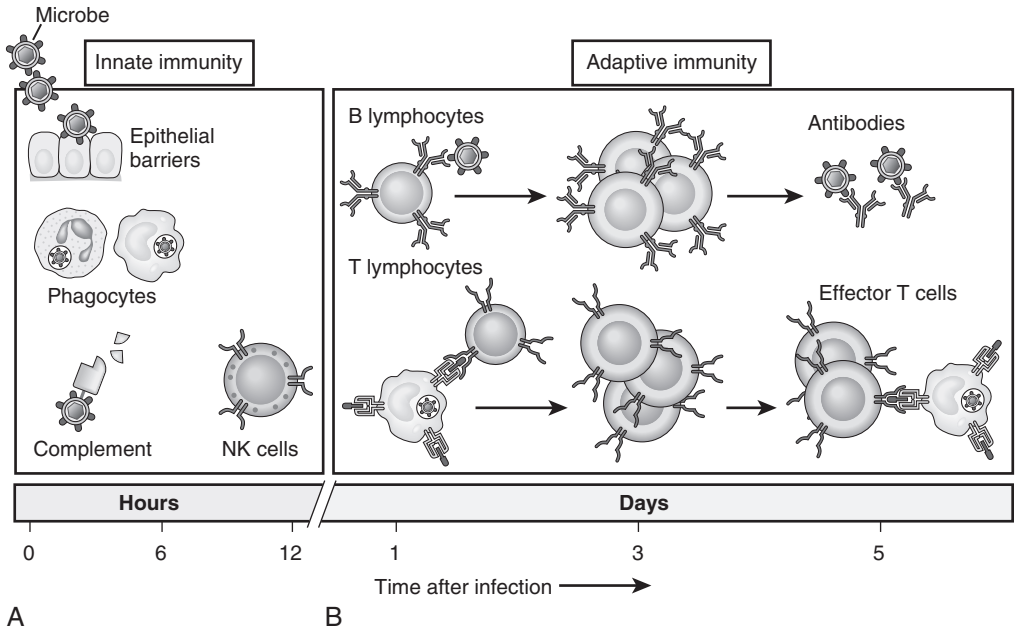


FIGURE 9.1. Innate and adaptive immunity. **A,** *Innate immunity* includes the body's initial defenses against infection. It includes certain complement proteins, epithelial defense, and phagocytes such as macrophages, natural killer (*NK*) cells, and dendritic cells (*DCs*). **B,** In contrast, *adaptive immunity* refers to the precisely targeted immune mechanisms that occur later in the immune response. The adaptive immune system has humoral (dissolved) and cellular components. B-cell secretion of antibodies functions to block infections and trigger the destruction of pathogenic organisms. T cell–mediated immunity occurs after phagocytosis and leads to direct cellular lysis. *(From Abbas AK, 2003: Cellular and Molecular Immunology. Philadelphia, Saunders.)*

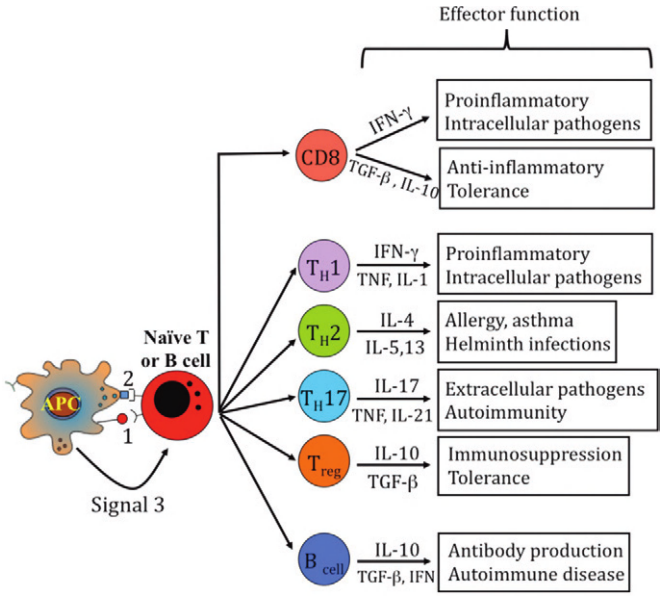


FIGURE 9.2. Antigen-presenting cell (*APC*) instruction of T and B cells. Signals 1 (antigen presentation), 2 (costimulation), and 3 (cytokine production) between APCs and naïve T or B cells govern the subsequent adaptive immune response. $CD8^+$ T cells can differentiate into either cytotoxic or regulatory cells capable of killing foreign pathogens or suppressing immune responses, respectively. Similarly, naïve $CD4^+$ T cells can differentiate into four types of T cells—Th1, Th2, Th17, and Treg—each with a distinct cytokine profile and specific effector function. B cells can also differentiate into cytokine and antibody-producing cells, which play a role in responses against tumors, pathogens, and autoimmune diseases. INF, interferon; IL, interleukin; TGF, transforming growth factor; TNF, tumor necrosis factor.

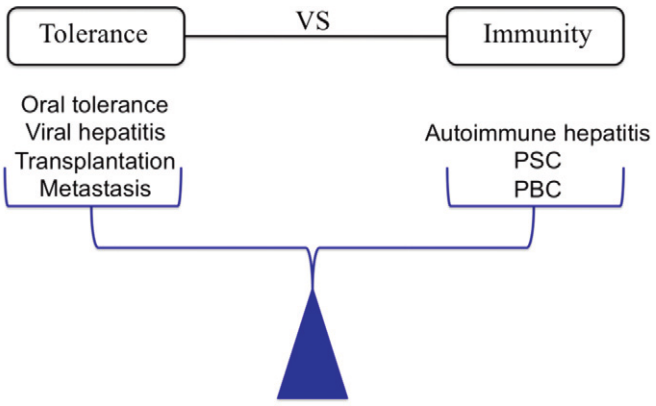


FIGURE 9.3. Role of the liver in tolerance and immunity. The liver exhibits a fine balance between the induction of tolerance and excessive immune responses. Examples of the liver as a tolerogenic organ include its role in oral tolerance, chronic hepatitis infection, and transplantation. In addition, the liver is among the most common sites of distant metastatic disease in patients with cancer. In contrast, the liver is also site of many autoimmune diseases such as autoimmune hepatitis, primary sclerosing cholangitis (*PSC*), and primary biliary cirrhosis (*PBC*).

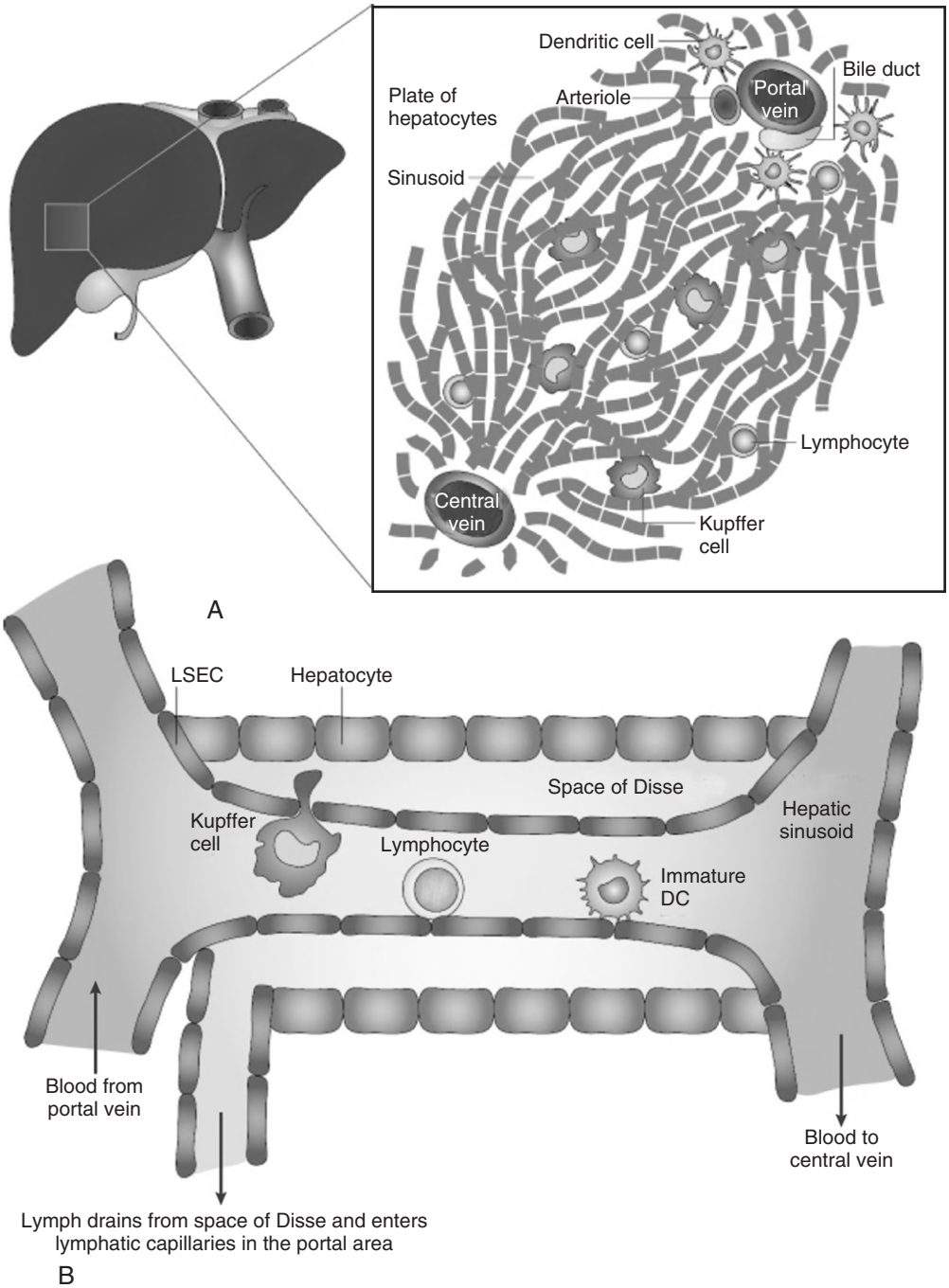


FIGURE 9.4. Microvascular hepatic anatomy. **A,** The liver is organized as lobules defined by their relation to portal vascular bundles and central veins. **B,** Liver sinusoidal endothelial cells (*LSECs*) line the hepatic sinusoids and have fenestrated membranes. A variety of immune cells exist within the sinusoids and are able to traverse the sinusoidal membrane to enter and exit the space of Disse, which is in contact with hepatocytes. *(From Crispe IN, 2003: Hepatic T cells and liver tolerance. Nat Rev Immunol 3:51-62. Copyright 2003, MacMillan Magazines Limited.)*

development of hepatic tolerance, because the depletion of either has been associated with a loss of oral tolerance. Liver DCs also have been suggested to play a role in liver tolerance, because as a group they have been shown to be less immunogenic than DCs from lymphoid organs such as the spleen (Bamboat et al, 2009). In addition, the numbers of several unusual cell types are elevated in the liver, and more recent studies have shown that multiple lineages of intrahepatic leukocytes are unique in function and phenotype compared with their counterparts from lymphoid organs. Controversy exists, however, as to whether these differences are due to de novo development, conditioning within the liver, or chemotactic signals in the liver that attract a unique population of cells. Regardless, the differences in composition and function are likely to play an important role in defining the nature of liver immunology. We devote a portion of this chapter to the major populations of liver immune cells and their role in various liver diseases.

LIVER IMMUNE CELLS

Although the liver is primarily a nonlymphoid organ, it contains numerous nonparenchymal cells (NPCs; see Chapter 6), one quarter of which are leukocytes. The composition of the intrahepatic leukocyte population is markedly different from that seen in other organs (Fig. 9.5). As in the rest of the body, however, the liver contains most of the cellular components of innate and adaptive immunity. Advances in technology have allowed for the precise delineation and isolation of cell types based on the expression of a distinct set of surface markers.

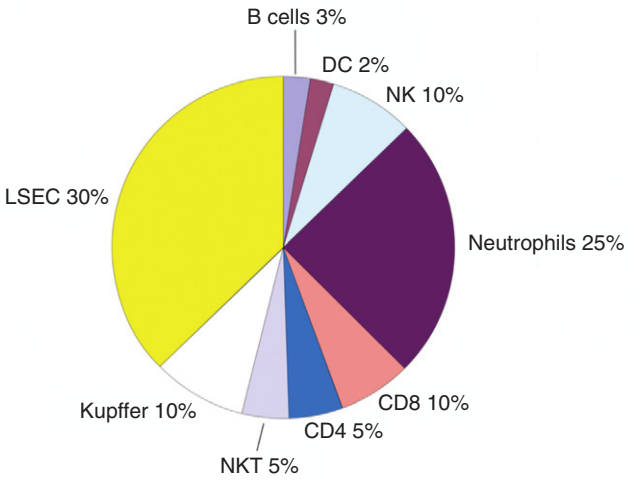


FIGURE 9.5. Human liver immune cell composition. After mehcanical and enzymatic digestion of freshly resected human liver specimens, hepatocytes were removed by centrifugation. Flow cytometry analysis was then performed on hepatic nonparenchymal cells (NPCs). Liver sinusoidal endothelial cells (*LSECs*) constitute most (~70%) of the liver NPCs. The liver has a particularly high proportion of CD8, natural killer (*NK*), NKT, and Kupffer cells. DC, dendritic cell.

Antigen-Presenting Cells

The experimental observation that antigens passing through the liver can lead to tolerance makes the understanding of antigen presentation in the liver particularly germane (Li et al, 2004). Antigen-presenting cells (APCs) play a crucial role in determining the nature of adaptive immune responses. The manner in which an APC presents any particular antigen can alter dramatically the response of antigen-specific T cells. Specifically, when antigen presentation occurs in conjunction with the appropriate costimulatory molecules, T cells proliferate and develop an immunogenic phenotypic and functional profile (Fig. 9.6). In contrast, antigens presented in the absence of costimulation lead to anergy or activation-induced T-cell death, two of the mechanisms of peripheral tolerance induction and maintenance.

Dendritic Cells

Dendritic cells (DCs) are rare, heterogeneous leukocytes that are primarily responsible for the capture of antigens in the periphery and subsequent presentation to immune effector cells. DCs are now recognized as the most potent APCs of the immune system and seem to arise from multiple hematopoietic cell lineages. Murine DCs are typically isolated based on their expression of the integrin CD11c. Immature DCs are specialized to capture antigens and then migrate to lymph nodes, where they can interact with T cells. After an encounter with pathogenic stimulus, such as bacterial lipopolysaccharide, DCs undergo phenotypic and functional changes, whereby their ability to capture antigens is diminished, but they increase their expression of MHC class II and T cell costimulatory molecules. Costimulatory molecule expression is essential in facilitating antigen presentation and efficient T cell activation. The ability of DCs to capture antigens in the periphery, translocate to areas rich in T cells, and then present antigens places DCs in a central role in immune regulation, bridging innate and adaptive immunity.

The body of literature studying the function of DCs grown in vitro from murine bone marrow progenitors or human

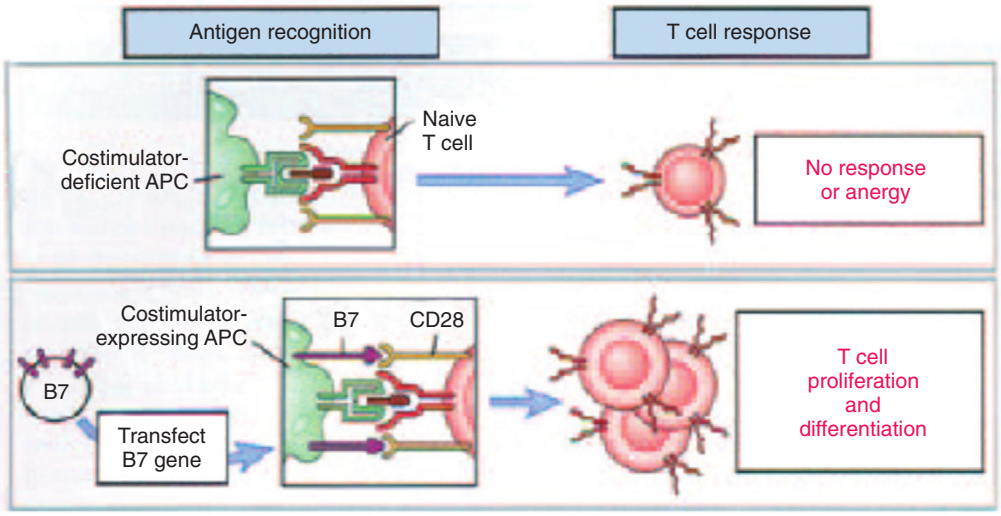


FIGURE 9.6. Antigen-presenting cells (*APCs*) and T-cell activation. The three main APCs are dendritic cells (*DCs*), macrophages, and B cells. The immune response depends on the context in which antigens are presented to T cells. The type of APC and the presence or absence of costimulatory molecules are important in determining whether a T cell has no response (anergy) or is activated. *(From Abbas AK, 2003: Cellular and Molecular Immunology. Philadelphia, Saunders.)*

peripheral blood mononuclear cells is vast. DCs isolated directly from the spleen, lymph nodes, or thymus also have been well studied. In contrast, because of the rarity of DCs in the liver, few studies have shown the phenotype or function of liver DCs. Initial studies focused on DC progenitors grown from liver nonparenchymal cells cultured with various cytokines, including granulocyte-macrophage colony-stimulating factor (GM-CSF). These early studies showed that liver DC progenitors are relatively immature cells with poor immunostimulatory ability that can promote immunologic tolerance and prolong solid organ transplants in animal models (Lu et al, 1994, 2001; Lau & Thomson, 2003).

To gain a better understanding of liver DCs as they function in situ, recent focus has been on studying freshly isolated liver DCs. In our initial studies, we wished to increase the number of liver DCs to facilitate their isolation. Because GM-CSF had been used to grow DC progenitors in culture from liver nonparenchymal cells, and because we had previously shown that in vivo GM-CSF overexpression increases the number of myeloid DCs in the spleen (Miller et al, 2002a), we suspected that it might expand liver DCs as well. We found that overexpression of GM-CSF using an adenoviral vector led to a dramatic increase in the number of highly immunostimulatory liver DCs (Pillarisetty et al, 2003). We also showed that a large proportion of the cells recruited to the liver by GM-CSF were DC precursor cells that develop into $CD11c^+$ DCs in culture, which suggests that DC development can occur in the liver. We used immunohistochemistry to locate both types of recruited cells. The liver DCs were concentrated around the central veins, whereas the DC precursors were distributed diffusely throughout the liver parenchyma.

Our experience with expanding liver DCs sheds light on in situ liver DC development, but we wished to understand the phenotype and function of liver DCs in normal, untreated mice. When our ability to isolate liver DCs from normal mice improved, we began to study them in depth. We found that compared with the relatively well-studied DCs from the spleen, $CD11c^+$ liver DCs were immature and only weakly immunostimulatory (Pillarisetty et al, 2004). We also noticed that, in contrast to spleen DCs, liver DCs are heterogeneous in their expression of MHC class II and costimulatory molecules. We further separated $CD11c^+$ liver DCs based on their expression of the myeloid marker CD11b and the lymphoid marker $CD8\alpha^+$, which have been commonly used to define murine DC subtypes. Myeloid ($CD11b^+$) and lymphoid ($CD8\alpha^+$) liver DCs, which each comprise approximately 10% of the total population of DCs in the liver, were as able to activate T cells as were their splenic counterparts. The bulk of the remaining cells, which had low to no expression of CD11b and CD8α, were only poorly immunostimulatory. This study showed that the presence of these atypical DCs was primarily responsible for the weakly activating nature of liver DCs on the whole. More recently, we discovered that despite having multiple APCs, the $CD11c^{hi}$ subset of DCs within the liver are required for effective presentation of soluble protein (Plitas et al, 2008). Using a transgenic mouse in which $CD11c^{hi}$ DCs can be depleted selectively, we found that activation of antigen-specific $CD8^+$ T cells in the liver only occurred in the presence of $CD11c^{hi}$ DCs.

Our investigation into liver DCs has now been extended into humans. We found that freshly isolated DCs from human liver exhibit tolerogenic properties when compared with autologous blood DCs. Liver DCs are weaker stimulators of T cells and favor the production of antiinflammatory IL-10, which induces the differentiation of naïve $CD4^+$ T cells into regulatory T cells with suppressive function (Fig. 9.7; Bamboat et al, 2009a).

Kupffer Cells

Liver macrophages, referred to as *Kupffer cells* (KCs), have long been believed to be the primary phagocytic cells of the liver. KCs represent the largest pool of macrophages in the body, derived from monocytic precursors in the blood. They are

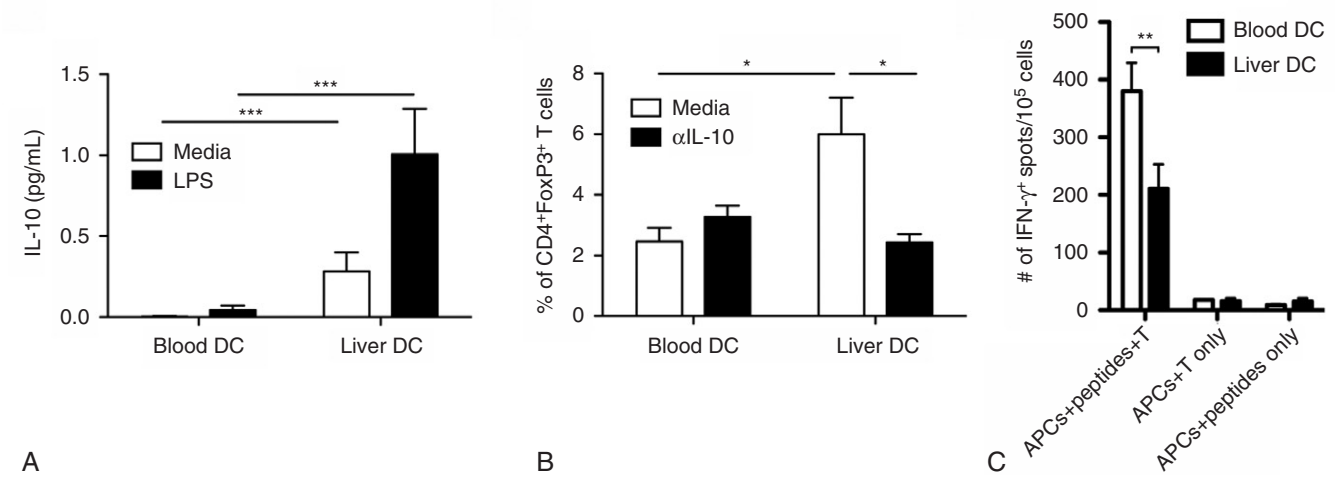


FIGURE 9.7. Human liver dendritic cells (*DCs*) are tolerogenic. **A,** Freshly isolated human liver and autologous blood DCs were cultured in media alone or in the presence of lipopolysaccharide (*LPS*). Supernatant interleukin-10 (*IL-10*) was measured 24 hours later. **B,** Liver and blood DCs were cultured with allogeneic naïve $CD4^+$ T cells in the presence or absence of an anti–IL-10 blocking antibody (αIL-10). After 5 days of culture, the T cells were restimulated using antibodies against CD3 and CD28. The percentages of $CD4^+FoxP3^+$ cells were determined 24 hours later using flow cytometry. **C,** Autologous antigen-specific $CD4^+$ T cells recognizing a pool of human leukocyte antigen (*HLA*) class II–restricted peptides (peptides) were generated by two rounds of stimulation with either liver or autologous blood DCs. The frequencies of interferon (*IFN*)-γ–producing $CD4^+$ T cells after 24 hours of culture with peptide-pulsed target cells (APCs + peptides + T) were then determined by enzyme-linked immunosorbent spot-forming analyses. Antigen-presenting cells (*APCs*) and T cells cultured alone made no detectable IFN-γ (not shown). $^*P < .05$; $^{**}P < .01$; $^{***}P < .001$.

typically found in the hepatic sinusoids; however, they also can migrate through the space of Disse to interact with hepatocytes (see Fig. 9.4). KCs have been thought to play a major role in antigen presentation and have been implicated in portal venous tolerance. Evidence also suggests that KCs may regulate T-cell responses to antigens and induce immune tolerance in the setting of liver allografts (Sun et al, 2003).

Techniques that allow for the more precise delineation of cellular subtypes have called into question some of the concepts about KCs and many other traditionally defined immune cells. Specifically, the advent of flow cytometry has allowed us to define cells by their surface marker expression, rather than simply by size or other crude physical characteristics shared by many cell types. This point is illustrated by the fact that many liver DCs express the cell surface marker CD11b, which is typically expressed by cells of monocytic lineage and has been used to define KCs in the liver. Much of the antigen-presenting ability previously attributed to KCs may be a result of DC function. The lack of consistent definitions of cells by cell surface marker expression and the continued use of less precise methods of cell isolation have led to continued ambiguity regarding KCs. An alternative explanation for the overlap in functional definitions for DCs and KCs is that DCs represent a more differentiated state of the KC lineage.

Liver Sinusoidal Endothelial Cells

Liver sinusoidal endothelial cells (LSECs) are highly specialized cells that line the hepatic sinusoids. LSECs are distinguished by the presence of fenestrations, or windows, in their cellular membranes. These fenestrations are believed to facilitate the selective passage of antigens between the sinusoid and the hepatic parenchyma. This strategic placement puts LSECs in the ideal position to interact with antigens and immune cells passing between the liver and the portal venous system.

Several studies have shown that in addition to serving as the building blocks lining the sinusoids, LSECs are immune cells with the ability to capture and present antigen and activate T cells (Knolle & Limmer, 2001). As with KCs, considerable controversy surrounds the immunologic function of LSECs. In contrast to earlier work, we have shown more recently that although LSECs are highly capable of capturing various antigens in vivo and in vitro, they lack the ability to activate T cells in the absence of exogenous costimulation (Katz et al, 2004). The differences in results may derive from the use of more specific methods of cell isolation in the latter study. The finding that LSECs are not independently capable of triggering a T cell–mediated immune response does not, however, exclude the possibility that LSECs, in concert with DCs or KCs, play an important role in antigen presentation in the liver.

Effector Cells

T Cells

As is the case for DCs, T cells are implicated in determining the liver's unique tolerogenicity. T cells are the primary effector cells of adaptive immunity. The nature of the interactions between APCs and T cells determines the overall character of the response to a particular antigen. It is difficult to know whether liver APCs or T cells are primarily responsible.

T cells are classified based on the types of antigen-recognition receptors present on their surface. Most of the T-cell subtypes in the body also have been identified in the liver. The broadest way to classify T cells is as either conventional or unconventional. *Conventional T cells* express the αβ T-cell receptor in association with either CD4 or CD8. These are the most prevalent T cells in the body and account for about one third of the murine liver T-cell population. In contrast, *unconventional T cells* expressing NK markers or the γδ T-cell receptor compose a greater proportion of liver T cells, about 50% and 10%, respectively. More recently, the discovery of the transcription factor FoxP3 has enabled the study of another family of T cells with immunosuppressive function. These $FoxP3^+$ or regulatory T cells coexpress either CD4 or CD8 and are present in the liver. Their relative contribution to liver tolerance remains to be defined.

The diversity of conventional T cells is based on their recognition of specific peptide antigen motifs within the context of MHC class I or II molecules on the surface of APCs. The αβ T-cell receptor is highly variable, and numerous T cells, each recognizing a different antigen presented by APC, are present in the immune system. $CD8^+$ T cells respond to peptides presented on MHC class I molecules, which are expressed by nearly every cell in the body, excluding erythrocytes. Activated $CD8^+$ T cells become cytolytic T lymphocytes. $CD4^+$ T cells also are called *helper T lymphocytes*; they recognize antigens presented on MHC class II molecules on the surface of professional APCs and are capable of regulating and further amplifying the immune response through the secretion of cytokines that act on nearby effector cells.

Liver T cells are divided into the same types of cells, as are the cells of lymphoid organs, however, evidence shows differences in the proportions of T-cell subtypes found within the liver. The interaction between $CD4^+$ and $CD8^+$ cells is clearly important, and more recent studies have suggested that the ratio between these two cell types—which is approximately 2:1 in the spleen, lymph nodes, and peripheral blood—is reversed in the liver (Crispe, 2003). Preliminary murine data from our laboratory, using more inclusive isolation techniques, have shown that the liver has a similar $CD4^+$ to $CD8^+$ T-cell ratio of approximately 1.5:1 as found in the spleen and node (Katz et al, 2005). Prior studies have shown that unconventional T cells are highly represented in the liver compared with the spleen or lymph nodes, and our data are in agreement with these findings.

γδ T cells

The γδ T-cell receptor is relatively invariant, but it can recognize multiple nonpeptide antigens without the need for MHC presentation. γδ T cells represent 10% of liver T cells, whereas they comprise only a small proportion (< 5%) of T cells in the blood or lymphoid organs. γδ T cells also are highly represented in the skin and at mucosal interfaces and are thought to play a regulatory role through their secretion of activating and modulatory cytokines as part of an early response to atypical bacterial and viral pathogens. They can influence the activation of γδ T cells and also have been shown to be crucial in tumor immunity through their early secretion of interferon γ (IFN-γ) (Gao et al, 2003). The high proportion of γδ T cells in the liver suggests that they have an important immunologic role, but further investigation is required. Similarly, both human and mouse livers are enriched with a large proportion of memory T cells. Although some investigators believe this is because the liver serves as a reservoir for activated T cells just before they die,

other theories include that the liver secretes chemokines that attract $CD8^+$ T cells.

Natural Killer T Cells

Natural killer (NK) T cells are a unique subset of lymphocytes that compose a small proportion of the total T-cell population throughout the body, but they are found in multiple organs. NK T cells share characteristics of conventional T cells and NK cells and are defined by the presence of several T-cell and NK-cell surface markers. Most NK T cells react against CD1d, which is a nonpolymorphic MHC class I–like glycoprotein that binds and presents glycolipid antigens. CD1d is expressed on APCs and hepatocytes. The synthetic glycolipid α-galactosylceramide, which binds CD1d and activates certain NK T cells, is the most well-studied glycolipid antigen. The complex of α-galactosylceramide bound to CD1d has been used to identify and isolate most NK T cells in mice and humans that express the invariant Vα14Jα28 T-cell receptor chain. The presence of such invariant T-cell receptor chains that are conserved across species suggests an important role for NK T cells in the innate immune response to pathogens. Activated NK T cells are capable of producing IFN-γ and interleukin-4 (IL-4), which are the prototypical helper T cell (Th1 and Th2) cytokines.

NK T cells constitute a relatively large proportion of T cells found in the liver compared with other organs. In addition, an expansion of NK T cells is seen in the liver in several models of liver injury, such as partial hepatectomy. NK T cells have been shown to play a role in the mechanisms of inflammatory diseases and clearance of infection in the liver. Depletion of NK T cells has been shown to abrogate the effects of an experimentally induced hepatitis in a mouse model, and mice lacking NK T cells are susceptible to a host of viral and bacterial infections. NK T cells are now also thought to play a part in tumor surveillance in the liver. Data from murine primary and metastatic tumor models have shown that NK T cells can mediate tumor rejection or suppression, in part because of their ability to secrete IFN-γ (Miyagawa et al, 2004).

Natural Killer Cells

NK cells are the primary respondents of innate immunity. Unlike T cells, NK cells do not possess clonotypic antigen receptors but still have the capability to respond to infected or transformed host cells. By expressing a variety of activating and inhibitory receptors, NK cells can bind ligands on their target cells. The resulting activation of NK cells causes the release of lytic granules, or cytokines such as IFN-γ, which kill the infected host of tumor cell in an MHC-unrestricted fashion. NK cells can also become activated by antibodies that are released B cells. The constant region of various antibodies bind Fc receptors on NK cells, causing antibody-dependent cytotoxicity of target cells.

NK cells have been shown to be a major component of murine and human liver lymphocytes (see Fig. 9.5) and are partially responsible for the inflammatory reactions seen in viral and autoimmune hepatitis. In addition, NK cells serve as the first line of defense against tumors in the liver. We recently discovered that bulk human liver NK cells possess weaker lytic capabilities when compared with autologous blood NK cells (Burt et al, 2009), because the liver has a greater proportion of NK cell subtypes, with weaker cytolytic function when compared with blood NK cells.

CYTOKINES

Cytokines (see also Chapter 10) are small signaling molecules produced by immune cells. They are proteins that typically act on nearby cells, but they also may have systemic effects. Cytokines can be roughly divided into two categories, those of *innate* and those of *adaptive* immunity (Table 9.1). Cytokines also can be distinguished based on whether they are *activating* or *inhibitory*, however, these distinctions are not always consistent. Additionally, the same cytokine can have different effects, depending on the setting and the particular cell on which it is acting. Although hundreds of cytokines have been described, we limit our discussion here to a select few that have been shown to be produced in, and have important effects on, the liver.

Tumor Necrosis Factor-α

Tumor necrosis factor (TNF)-α is one of the most important inflammatory cytokines. It directly regulates innate immunity; however, its effects are far reaching. TNF-α is primarily produced by macrophages in response to lipopolysaccharide present on the membranes of gram-negative bacteria. It also is secreted by T cells, mast cells, DCs, and NK cells. TNF-α was originally isolated from animals treated with lipopolysaccharide, and its name is derived from the fact that it was found to lyse tumors in vitro and in vivo. TNF-α has consistently been found to play a pathogenic role in acute liver failure in multiple animal models and in humans. TNF receptors are present on most cell types, and the TNF receptor family is a large group of proteins with myriad roles in inflammation and immunity.

Interleukin-6

Interleukin-6 (IL-6) is a pleiotropic cytokine that is highly expressed by the liver and has effects on innate and adaptive immunity. It is synthesized by DCs, macrophages, T cells, B cells, endothelial cells, fibroblasts, and keratinocytes. IL-6 is produced as an early response to TNF-α and is thought to amplify the inflammatory response in the liver through the induction of acute-phase protein production by hepatocytes. As part of its promotion of the early immune response, IL-6 also stimulates the differentiation of neutrophils from bone marrow precursors. Additionally, experimental models have shown that absence of IL-6 in cultures favors the differentiation of DCs; however, IL-6–knockout mice have normal numbers and types of DCs in their spleens and livers (Bleier et al, 2004). IL-6 also is known to play an important role in liver regeneration after trauma or hepatectomy.

Type I Interferons (Interferon-α and Interferon-β)

IFN-α refers to a family of structurally similar cytokines that are crucial in the immune system's defenses against viral infection. IFN-α is secreted by immune cells, whereas IFN-β is secreted by multiple cell types, such as fibroblasts, in response to their own viral infection. IFN-α was once thought to be produced by macrophages; however, more recent evidence has shown that plasmacytoid DCs are its primary producers (Siegal et al, 1999). Type I IFNs have direct antiviral action by triggering virally infected cells to produce enzymes that interfere with viral RNA or DNA replication. They also lead to the increased

Table 9.1

Cytokines Involved in Innate and Adaptive Immunity

Cytokine	Principal Source	Principal Target: Biologic Effects
Innate Immunity		
TNF-α	Macrophages, T cells, DCs	Endothelial cells: activation Neutrophils: activation Hypothalamus: fever Liver: synthesis of acute-phase proteins Muscle and fat: catabolism Multiple cell types: apoptosis
IL-1	Macrophages, endothelial cells	Endothelial cells: activation Hypothalamus: fever Liver: synthesis of acute-phase proteins
Chemokines	Macrophages, endothelial cells, T cells, fibroblasts, platelets	Leukocytes: chemotaxis, activation, migration into tissues
IL-12	Macrophages, DCs, NK DCs	T cells: Th1 differentiation NK DCs, NK cells, and T cells: IFN-γ synthesis, increased cytologic activity
IFN-α, IFN-β	IFN-α: macrophages, plasmacytoid DCs IFN-β: fibroblasts	All cells: antiviral state, increased inhibition of IL-12 production and expression of costimulatory and MHC class II molecules
IL-10	Macrophages, T cells (mainly Th2)	Macrophages, DCs: inhibition of IL-12 production and expression of costimulatory and MHC class II molecules
IL-6	Macrophages, DCs, endothelial cells, T cells	Liver: synthesis of acute-phase proteins
IL-15	Macrophages, others	NK cells: proliferation T cells: proliferation (memory $CD8^+$ cells)
IL-18	Macrophages	NK cells and T cells: IFN-γ synthesis
Adaptive Immunity		
IL-2	T cells	T cells; proliferation, increased cytokine synthesis; potentiates Fas-mediated apoptosis
IL-4	$CD4^+$ T cells (Th2), mast cells	B cells: isotype switching to IgE T cells: Th2 differentiation, proliferation NK DCs and NK cells: increased IFN-γ production
IL-5	$CD4^+$ T cells (Th2)	Eosinophils: activation, increased production
IFN-γ	$CD8^+$ T cells (Th1), NK DCs, NK cells	Macrophages: activation B cells: isotype switching to opsonizing and complement-fixing IgG subclasses T cells: Th1 differentiation Various cells: increased MHC class I and II expression, increased antigen processing and presentation to T cells
TGF-β	T cells (regulatory), macrophages, other cell types	T cells: inhibition of proliferation and effector functions B cells: inhibition of proliferation; IgA production Macrophages: inhibition
Lymphotoxin	T cells	Neutrophils: recruitment and activation Lymphoid organogenesis
IL-13	$CD4^+$ T cells (Th2)	B cells: isotype switching to IgE Epithelial cells: increased mucus production Macrophages: inhibition

TNF, Tumor necrosis factor; *DCs,* dendritic cells; *IL,* interleukin; *NK,* natural killer; *IFN,* interferon; *MHC,* major histocompatability complex; *Ig,* immunoglobulin.
Modified from Abbas AK, 2003: Cellular and molecular immunology. Philadelphia, Saunders Elsevier.

expression of MHC class I molecules on the surface of virally infected cells, increasing their likelihood of being killed by cytolytic CD8+ T cells. Additionally, type I IFNs inhibit cellular proliferation. IFN-α has been used clinically in the treatment of viral hepatitis for decades.

Interferon-γ

IFN-γ is a type II IFN. It activates macrophages and plays a crucial role in bridging innate and adaptive immunity by increasing antigen presentation through the MHC class I and II pathways (Schroder et al, 2004). It is produced by T cells, B cells, NK T cells, DCs, and NK DCs. IFN-γ has many functions that are desirable for tumor immunotherapy, including a direct antiproliferative effect. Although not as crucial as the type I IFNs, the production of IFN-γ also is important in the clearance of viral infections within the liver.

IMMUNE SYSTEM IN LIVER DISEASES

The importance attached to understanding the cells that compose the immune system of the liver derives from the fact that many diseases that affect the liver are believed to have

immunologic origins. The following sections highlight the role of the hepatic immune system in a variety of diseases affecting the liver.

Transplantation

Transplant immunology has shed significant insight into the unique properties of the liver as an immunologic organ (see Chapter 96). Unlike other organs, the liver can be accepted across MHC barriers in animal models of transplantation (Qian et al, 1994). In addition, allograft recipients often develop systemic, donor-specific tolerance (Kamada et al, 1981). In humans, liver transplants confer protection from other organs from the same donor (Rasmussen et al, 1995), and recipients can often be weaned off immunosuppression altogether (Mazariegos et al, 1997). The comparative immune privilege of the liver highlights its role as a tolerogenic organ.

The development of mouse models of orthotopic liver transplantation have provided an opportunity to gain mechanistic insight into the regulation of immune responses in the liver (Qian et al, 1991). Of the factors that are thought contribute to hepatic tolerance (Table 9.2), microchimerism and induction of activated T-cell apoptosis have been the most intensively studied and widely accepted. Defined as the persistence of donor cells in recipients that accept their allografts, microchimerism has been postulated to be a prerequisite for organ allograft acceptance (Starzl et al, 1992, 1996). The high antigenic load derived from the donor liver coupled with persistence of donor APCs within lymphoid tissues of the recipient may provide a continuing source of allostimulation (Suzuki et al, 1988; Sriwatanawongsa et al, 1995). The persistent activation of alloreactive recipient T cells is thought to result in exhaustive deletion and induction of systemic tolerance. The role of specific donor-derived liver APCs, such as DCs and KCs, in contributing to chimerism-induced tolerance remains unclear. Although freshly isolated liver DCs have been shown to exhibit tolerogenic potential via the production of IL-10 (Bamboat et al, 2009a), others have shown that donor-derived liver DCs migrate into recipients' circulation and prime recipient T cells to differentiate into proinflammatory subtypes that promote rejection (Bosma et al, 2009).

The immunoregulatory role of KCs has also been extensively investigated. KCs have been implicated in the induction of oral tolerance and in lymphocyte apoptosis, which has been a proposed mechanism of immunosuppression in liver transplantation (Callery et al, 1989). More recently, KCs have been shown to play a crucial role in induction of antigen-specific T-cell tolerance (Breous et al, 2009) and are thought to suppress T-cell response via the production of prostaglandins (You et al, 2008). Despite evidence of the tolerogenic potential of KCs, the use of gadolinium chloride to suppress KC function has not been shown to impact survival of liver allografts in mouse models of liver transplantation. In addition, hepatocyte transplantation-induced liver inflammation has been shown to result in cytokines and chemokines associated with KCs (Krohn et al, 2009).

Activated T cells and their subsequent apoptosis within the liver are thought to be another critical component in the induction of hepatic tolerance and the acceptance of liver allografts. Donor-derived APCs deliver normal activating signals to recipient T cells in lymphoid tissues. These activated T cells subsequently migrate to the liver, secondary to inflammatory cytokines, where they encounter a large antigenic load that causes restimulation and apoptotic cell death (Huang et al, 1994; Crispe et al, 2000). The overall bias of intrahepatic T-cell responses toward tolerance and apoptosis might account for the survival of liver allografts (Crispe, 2003).

From a more clinical perspective, patients transplanted for end-stage liver disease secondary to hepatitis B or C often experience higher viral loads after transplantation secondary to the immunosuppressive regimen required to prevent rejection. Recurrent disease in the transplanted liver is inevitable and is therefore one of the most common reasons for allograft failure (Brown, 2005). Recent work using adoptive immunotherapy of donor lymphocytes provides some encouraging insight into dealing with recurrent viral disease in transplant recipients. Lymphocytes enriched in NK and NK T cells harvested from donor livers at the time of explanation were primed ex vivo for 2 days prior to reinjection into allograft recipients. Hepatitis C viral loads were found to be significantly lower at 1 month posttransplantation in patients treated with adoptive therapy versus noninjected controls (Ohira et al, 2009). Using human-hepatocyte chimeric mice, the authors showed that adoptive transfer of activated donor lymphocytes conferred protection via the production of IFN-γ. This makes sense, as the liver is enriched in cells capable of producing IFN-γ, such as NK, NK T, and $CD8^+$ T cells. Other groups have also shown that antigen-specific $CD8^+$ T cells are thought to be important in preventing recurrence of hepatitis in transplant recipients via the production of IFN-γ (Jo et al, 2009).

Although the hepatic immune system has been shown to clearly play an important role in liver and systemic tolerance, definitive mechanisms in humans remain elusive. Understanding the mechanisms controlling the tolerogenic propensity of the liver is of great significance in transplantation, as it will permit the design of novel approaches to reduce immunosuppressive-related morbidity and mortality.

Table 9.2

Factors Contributing to Hepatic Tolerance

1. Immunosuppression via release of soluble MHC class I antigens
2. Distinct lymphocyte population with distinct functions (KCs, DCs, NK and NK T cells, LSECs)
3. Constant antigen load from the portal circulation
4. Induction of activated T-cell apoptosis
5. Microchimerism
6. Immature phenotype and tolerogenic function of resident liver APCs (DCs, KCs, LSECs)
7. Altered Th1 versus Th2 profile within the liver (favoring Th2)

MHC, Major histocompatability complex; *KCs,* Kupffer cells; *DCs,* dendritic cells; *NK,* natural killer; *LSECs,* liver sinusoidal endothelial cells; *APCs,* antigen-presenting cells

Modified from Gershwin ME, et al, 2003: Liver immunology. Philadelphia, Hanley and Belfus, Inc.

Hepatitis

The viruses hepatitis B (HBV) and hepatitis C (HCV) are noncytopathic and hepatotropic, and they cause acute and chronic liver disease (see Chapter 64). The worldwide burden of disease is immense, with an estimated 500 million people infected with either of these two viruses (World Health Organization, http://www.who.int/mediacentre/factsheets). The cost to society is

magnified when the increased risk of developing cirrhosis and liver cancer in those infected with HBV and HCV are taken into account. Immune-mediated destruction of liver parenchymal cells is a common final pathway in viral hepatitis. The presence of large numbers of KCs and DCs in the liver, which produce TNF-α in response to viral antigens, leads to high local levels of inflammatory cytokines and untoward host cell damage. Similarly, T cells, NK T cells, and NK cells in the liver produce IFN-γ, which also serves to amplify the local immune response by activating KCs and DCs. Consistent with this, chronic active hepatitis is morphologically identified by piecemeal necrosis associated with a predominantly mononuclear cell infiltrate (Ferrari et al, 1999). Therefore to achieve successful viral control and limit collateral damage, a sustained, antigen-specific immune response is necessary (Gerlach et al, 1999; Maini et al, 2000).

The tolerogenic predisposition of the liver outlined in the transplantation section may account in part for the persistence of viral infection. A number of additional host parameters have been shown in experimental models to alter the immune response to viral hepatitis infection. Age can influence the outcome of infection, as vertical transmission to neonates generally results in persistent infection throughout life. The reason for persistent infection in younger hosts is thought to be related to neonatal tolerance and inability of the immune system to mount an effective immune response early in the course of infection, when these viruses are thought to be most vulnerable. In line with this hypothesis, chronic viral infection in animal models of hepatitis occurs more often when the initial insult fails to elicit an acute inflammatory response. In woodchucks, the absence of an acute infection following viral inoculation correlated with an indolent and chronic course of disease (Nakamura et al, 2001).

The precise mechanisms that account for persistent infection in hosts who are infected during adulthood are less clear. Immune-specific parameters that correlate with control of viral load include a coordinated helper and cytotoxic T-cell response against a number of viral antigens. Recognition of multiple viral epitopes by the host is also advantageous, as it theoretically minimizes the emergence of mutants that escape the immune system. Although significant strides have been made in understanding the immunopathogenesis of viral hepatitis over the past two decades, a cure remains elusive. Emerging research tools that will undoubtedly shed more light on the immune mechanisms underlying viral persistence and resistance to treatment include the development of chimeric mice that are reconstituted with human hepatocytes and immune cells (Manz & Di Santo, 2009). The transplantation of human hepatocytes into immunodeficient mice will allow for large-scale screening therapeutics against human hepatitis viruses. In addition, chimeric murine models will enable researchers to study the in vivo effects of human hepatotropic viruses on human immune responses to infection for the first time.

Cancer

The immune response to neoplastic cells has been shown to be a potential determinant of survival in several human malignancies including hepatocellular carcinoma (HCC) (Fu et al, 2007; Gao et al, 2007; Sasaki et al, 2008). In addition, recently published landmark studies revealed that the density, location, and functional capacity of intratumoral T cells can serve as a powerful predictor of outcome in primary colorectal cancer (Pages et al, 2005; Galon et al, 2006). The high prevalence of metastatic disease to the liver is likely due to multiple factors; however, evidence suggests that particular characteristics of the liver immune system may play an important role in this propensity. As delineated earlier, the primary mediators of innate and adaptive immunity found in the liver, DCs and T cells, are unique in their function and distribution of subtypes (Pillarisetty et al, 2004; Katz et al, 2005). In addition, freshly isolated liver DCs may promote the development of tolerance to antigens and have been found to be less immunogenic overall than their splenic and peripheral blood counterparts (Bosma et al, 2006; Bamboat et al, 2009a).

Although many investigators have attempted to manipulate the immune system for the treatment of cancer (Hunder et al, 2008), few attempts have been made to directly target intrahepatic immune cells. A report by Wagner and colleagues (2008) showed that intrahepatic T cells appear to be selectively activated in patients with colorectal liver metastases. Further evidence on the importance of the hepatic immune system in malignancy comes from recent data by our group, which reveal that 1) when compared with autologous blood, human liver specimens from patients with malignancy contain a disproportionately higher percentage of NK cells with reduced antitumor function (Burt et al, 2009), and 2) the hepatic T cell infiltrate predicts survival following surgery in patients with metastatic colorectal liver cancer (Katz et al, 2009). The hepatic immune system may therefore play an important role in explaining the liver's propensity for harboring metastatic disease.

The primary goal of cancer immunotherapy, particularly for liver tumors, is to reverse the tendency toward tolerance to tumor antigens. This reversal has been accomplished in animal models by activating DCs, T cells, NK cells, and monocytes. We previously showed the importance of IL-12 production by DCs in activating NK cells toward protection against tumor in a mouse melanoma liver metastasis model (Miller et al, 2002b). Since then, work by others has revealed that patients with low numbers of mature DCs within metastatic liver tumors have a worse prognosis (Miyagawa et al, 2004). Despite having less lytic potential than blood NK cells, we found that human liver NK cells do have the capacity to become potent antitumor cells when activated in the presence of KCs and TLR3 ligands (Burt et al, 2009).

In addition to DCs, recent work on the role of peritumoral monocytes in patients with HCC has garnered much attention among immunologists and hepatologists alike. Activated monocytes in the peritumoral stroma of HCC have been shown to foster a state of tolerance and promote tumor progression via the expression of an immunosuppressive antigen, programmed death ligand 1 (PDL-1) (Kuang et al, 2009). In addition, tumor expression of PDL-1 was recently shown to serve as a predictor of recurrence in patients with resected HCC (Gao et al, 2009). Blocking antibodies to molecules such as PDL-1 are currently in development for human use. Modulating the peritumoral interface may be a key step in harnessing the immune system to fight hepatic malignancies.

Autoimmune Hepatitis

Autoimmune hepatitis is an idiopathic disorder that leads to cirrhosis. In contrast to the preceding sections that highlighted disease states associated with hepatic tolerance, autoimmune

hepatitis is a manifestation of an overactive hepatic immune system. It has a female predominance and is characterized by elevated levels of immunoglobulin G (IgG) autoantibodies and increased responsiveness to immunosuppression (Obermayer-Straub et al, 2000). An experimental model of autoimmune hepatitis is based on the treatment of mice with concanavalin A (ConA), a plant lectin known to activate T cells in vitro. A single intravenous injection of ConA leads to severe liver damage and is associated with the activation of $CD4^+$ T cells and the production of TNF-α and IFN-γ. Further studies showed that NK T cells are the most important subset of $CD4^+$ T cells involved in mediating ConA hepatitis. The early activation of NK T cells also is associated with IL-4 production, which contributes to triggering autoimmune hepatitis. The importance of NK T cells in mediating autoimmune liver damage also is supported by the observation that injection of α-galactosylceramide, an activator of NK T cells through CD1d binding, leads to a similar form of injury as that seen in ConA hepatitis.

Primary Biliary Cirrhosis

Primary biliary cirrhosis is an autoimmune liver disease that leads to the destruction of intrahepatic bile ducts and subsequent cholestasis and cirrhosis (Bergasa et al, 2004; Lindor et al, 2009). Most cases of primary biliary cirrhosis (95%) are associated with antimitochondrial antibodies directed against specific enzymes located on the inner mitochondrial membrane. Antinuclear antibodies—usually associated with systemic lupus erythematosus, rheumatoid arthritis, and several other autoimmune diseases—are present in 50% of patients with primary biliary cirrhosis. Helper T cells and cytolytic T lymphocytes also are thought to be important in the pathogenesis of primary biliary cirrhosis. This is supported by the findings of lymphoid infiltration of the portal tracts and aberrant expression of MHC class II on biliary epithelial cells. Because biliary epithelial cells are the primary target of injury in primary biliary cirrhosis, their expression of MHC molecules and cytokines is likely to play an important role in the pathogenesis of this disease. In addition to increased MHC class II molecules, biliary epithelial cells from patients with primary biliary cirrhosis have elevated levels of intercellular adhesion molecule (ICAM) 1, and they attract mononuclear cells via the chemokine CX3CL-1 and overexpress the inflammatory cytokines IL-6 and TNF-α (Shimoda et al, 2009).

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) results from fibrosis of the intrahepatic and extrahepatic bile ducts (Lee & Jonas, 2007; see Chapter 41). The pathogenesis is thought to result from immune activation within the liver after bacteria gain access to the portal circulation via a diseased colon. The end result is biliary cirrhosis and a high risk of developing cholangiocarcinoma. Most cases of PSC are associated with underlying inflammatory bowel disease, specifically ulcerative colitis. In contrast to most autoimmune diseases, which predominantly affect women, PSC affects men twice as often as it does women. PSC is also associated with a particular MHC class II haplotype associated with other autoimmune disorders believed to be mediated by T cells. Although specific evidence that PSC is an autoimmune disorder remains to be elucidated, the disease is associated with T cells infiltrating the portal tracts. In addition, an increase in production of circulating proinflammatory cytokines has been shown to correlate with disease progression.

Ischemia/Reperfusion Injury

Liver ischemia/reperfusion (I/R) injury is a well-recognized consequence of trauma, circulatory shock, partial hepatectomy, and liver transplantation. It contributes to the shortage of organs available for transplantation and is a major determinant of postoperative allograft dysfunction and morbidity (Clavien et al, 1992). During liver I/R, the release of endogenous molecules signal danger to the host by activating innate immune cells through their interaction with TLRs (Lotze et al, 2007). Such "danger signals," or *danger-associated molecular patterns* (DAMPs), can be classified as intracellular proteins, nucleic acids, or components of the extracellular matrix that are released following host cell injury. The ensuing host immune response results in untoward collateral tissue damage that culminates in hepatocyte death and a systemic inflammatory response. The injury stems from the inability of TLRs on innate immune cells to distinguish infectious ligands from DAMPs released by autologous tissue. The need for effective approaches to manage patients with I/R-induced organ damage is highlighted by the fact that current treatment is merely supportive care.

Using a murine model of segmental liver I/R, we have recently discovered that hepatic DCs and TLR-9 play critical roles in modulating the host immune response during liver I/R (Bamboat et al, 2009b). Hepatocyte DNA released during ischemia binds TLR-9 on a variety of liver immune cells that cause liver damage. Using TLR-9–knockout mice, we found that the global absence of TLR-9 signaling confers protection from liver I/R injury (Fig. 9.8). Interestingly, the immune effects of TLR-9 activation appear to be cell specific. In neutrophils, host DNA binds TLR-9 and exacerbates injury through production of inflammatory cytokines and reactive oxygen species (ROS). In contrast, DCs respond to host DNA by curtailing injury via production of antiinflammatory IL-10, which confers protection by suppressing the function of inflammatory monocytes that migrate to the liver from the bone marrow (Fig 9.9).

Identifying mechanisms by which DCs and TLR-9 function as important regulators of the inflammatory response in liver I/R will enable development of novel strategies to limit untoward tissue injury. Extension of our murine I/R findings to humans have thus far revealed that freshly isolated human liver NPCs respond to ischemia- and hepatocyte-derived proteins by producing inflammatory cytokines (unpublished data). In addition, freshly isolated human liver DCs also have a propensity to secrete large amounts of IL-10 at baseline and after TLR activation (Bamboat et al, 2009a). Improved understanding of the complex interactions between DAMPs and PRRs on immune cells will promote the development of rational, more effective approaches to limit liver I/R injury.

Partial Hepatectomy

Unlike most other mammalian organs, the liver has the capacity to regenerate after resection or traumatic injury (see Chapter 90A). This unique property not only allows for partial liver transplantation from live donors but also enables surgeons to perform major hepatic resections for malignancy. The early response to hepatectomy involves the activation of NF-κB in liver NPCs and hepatocytes, which causes additional injury

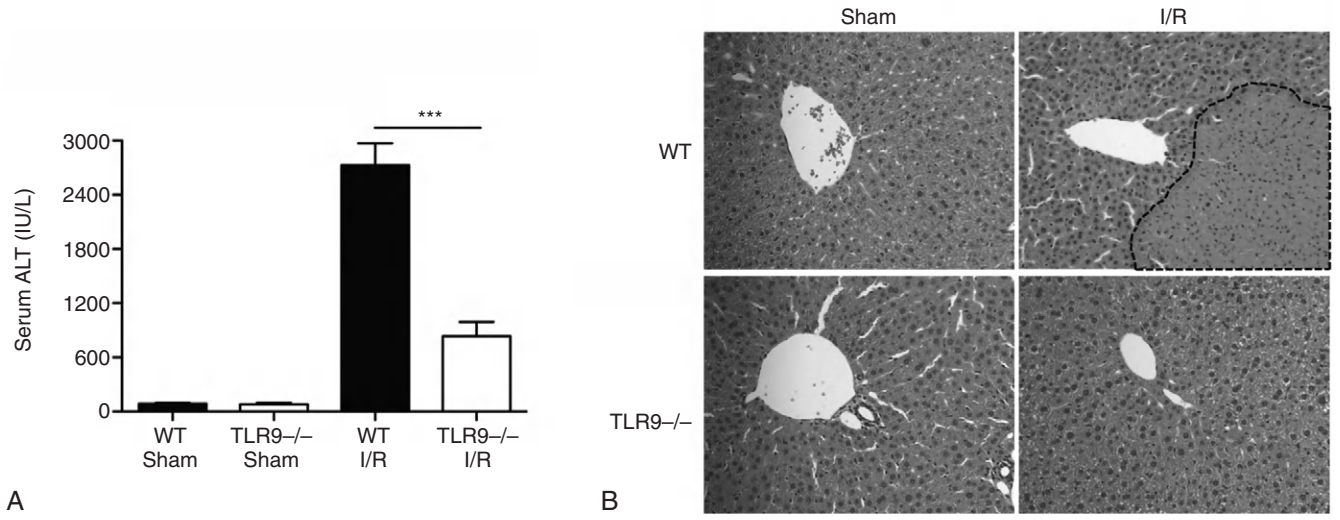


FIGURE 9.8. TLR9–/– mice are protected from liver I/R injury. **A,** Wild-type (WT) and TLR9–/– mice were subjected to sham laparotomy (Sham) or 1 hour of liver ischemia followed by 12 hours of reperfusion (I/R). Serum ALT was then measured. **B,** Hematoxylin and eosin–stained liver sections from the ischemic lobes of WT and TLR9–/– mice after sham procedure and 12 hours of liver I/R (original magnification ×200). Nonviable tissue is demarcated by the *dashed lines*. ***$P < .001$. *(From Wiley InterScience. Bamboat ZM, et al, 2009: Toll-like receptor 9 inhibition confers protection from liver ischemia-reperfusion injury. Hepatology 51[2]:621-632.)*

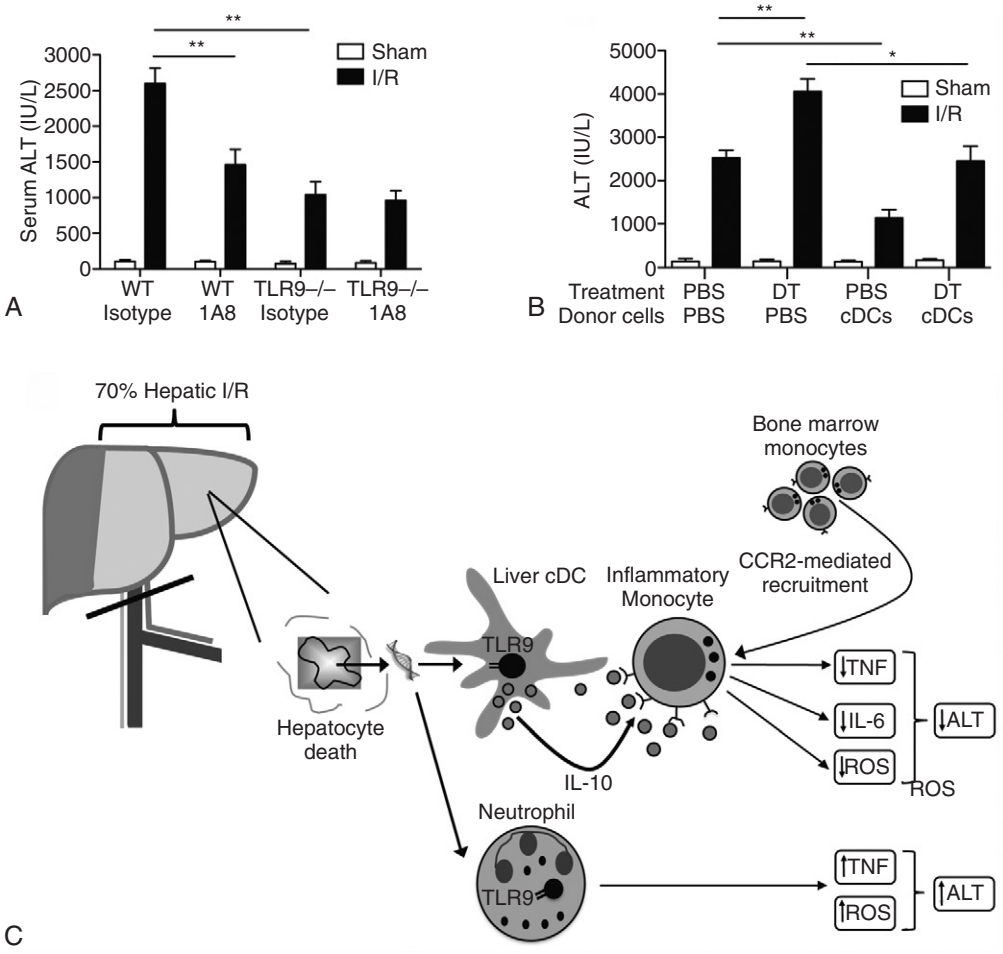


FIGURE 9.9. The role of Toll-like receptor 9 (*TLR9*) in neutrophils and dendritic cells (*DCs*) during liver ischemia/reperfusion (*I/R*). **A,** Wild-type (*WT*) and TLR9–/– mice were depleted of neutrophils using an antibody (*1A8*) or isotype control (*Isotype*). Mice then underwent sham laparotomy (*Sham*) or 1 hour of segmental ischemia followed by 12 hours of reperfusion (*I/R*). Serum alanine aminotransferase (*ALT*) was then measured. **B,** Conventional DCs (*cDCs*) were depleted selectively in transgenic mice via a single injection of diphtheria toxin (*DT*). Control mice were injected with saline (*PBS*). 12 hours later, mice were injected intravenously with cDCs or PBS just prior to sham or I/R. Serum ALT was measured 12 hours later. **C,** After segmental liver I/R (70% ischemia), the resultant hepatocyte death causes release of host DNA that activates cDCs and neutrophils via TLR9. cDCs produce interleukin-10 (*IL-10*), which suppresses the function of inflammatory monocytes. As a result, less inflammatory cytokines (tumor necrosis factor [*TNF*], IL-6) and reactive oxygen species (*ROS*) are produced, causing less liver injury. In contrast, neutrophil TLR9 activation causes an increase in TNF and ROS production, which increases ALT. *$P < .05$; **$P < .01$. *(**A,** From Wiley InterScience. Bamboat ZM, et al, 2009. Toll-like receptor 9 inhibition confers protection from liver ischemia-reperfusion injury. Hepatology 51[2]:621-632. **B** and **C,** Modified from the American Society for Clinical Investigation. Bamboat ZM, et al, 2010. Conventional dendritic cells reduce ischemia/reperfusion injury in mice via IL-10. J Clin Invest 120[2]:559-569.)*

through the production of ROS, TNF, and other inflammatory cytokines. Over time, IL-6 and IL-10 production increases, favoring a more antiinflammatory state that limits immune-mediated damage and promotes hepatocyte regeneration. Liver DCs have been reported to increase in number and function after partial hepatectomy in mouse models (Castellaneta et al, 2006). DCs produce more IL-10 and promote the development of antiinflammatory T cells from naïve precursors. In addition, increasing DC numbers via the administration of the growth factor fms-like tyrosine kinase 3 ligand (Flt3L) enhanced liver regeneration after partial hepatectomy. These data suggest that inherent tolerogenic properties of hepatic DCs may serve to promote hepatocyte regeneration after hepatectomy.

Like liver I/R, partial hepatectomy results in the release of a variety of danger signals that bind PRRs on innate immune cells, triggering a cascade of signaling events that modulate the rate of parenchymal regeneration. Deficiency in the intracellular signaling molecule, MyD88, which acts downstream of almost all TLRs (except TLR3), results in poorer outcome in mouse models of partial hepatectomy (Seki et al, 2005). In contrast, the absence of TLR3, which signals in a MyD88-independent manner, or blocking signaling of another PRR, the receptor for advanced glycation end products (RAGE), promotes liver regeneration and survival after massive hepatectomy (Cataldegirmen et al, 2005; Zorde-Khvalevsky et al, 2009). These data suggest that a balance exists between various TLRs and RAGE that governs the net effect of partial hepatectomy. Identification of mechanisms that limit regeneration after massive injury holds the key to expanding the limits of liver transplantation and salvaging livers and hosts overwhelmed by carcinoma and toxic insults.

Drug-Induced Liver Disease

The prevalence of liver failure as a result of drug-induced toxicity is increasing at an alarming rate and is the most common cause of acute liver failure in the developed world (Lee, 2007). The injury is characterized by toxin-induced hepatocyte death and activation of the innate immune system. This triggers a cascade of proinflammatory signals that result in further hepatocyte death and ultimately in liver failure. Through the use of mouse models of acetaminophen-induced liver injury, the roles of various components of the hepatic immune system have been well characterized. LSECs are thought to mediate liver injury by detecting hepatocyte DNA via TLR-9, resulting in production of pro–IL-1 and pro–IL-18, which are cleaved into their active forms by an intracellular protein complex called the *inflammasome* (Imaeda et al, 2009). Widespread inflammation ensues, resulting in additional parenchymal injury. The authors went on to show that administration of aspirin blocks inflammasome activation and the generation of active IL-1 and IL-18 and limits acetaminophen-induced liver injury.

In another set of elegant experiments using the same mouse model of liver injury, Chen and colleagues discovered how immune cells differentiate host danger signals from pathogenic ligands (Chen et al, 2009). An immune cell antigen, CD24, limits pathologic tissue damage by blocking PRR signaling from ligands released during sterile host cell damage. It fails, however, to block signaling from pathologic ligands that bind to the same PRR during infection. By understanding how immune cells distinguish between ligands released during infection and those encountered during sterile inflammation, researchers can develop approaches to curtail the progression of autoimmune diseases that are triggered by the release of host-derived danger signals.

Bacterial and Parasitic Liver Disease

Hepatic tolerance not only appears to be involved in the hyporesponsiveness to liver allografts but may also play a role in the vulnerability of the liver to various bacterial and parasitic infections (see Chapters 11, 66, 67, and 68). Pyogenic liver abscesses have increased in incidence as a result of more aggressive management of hepatobiliary diseases. The placement of stents for malignant biliary obstruction is the most common cause of hepatic abscesses. The host response to bacteria within the liver results in formation of an abscess in an effort to curtail the spread of infection. Neutrophils are recruited to the site of infection via chemoattractant signals released by the invading bacteria and activation of complement. Neutrophils then release cytokines and reactive oxygen species that promote inflammation and kill bacteria.

Helminthic infections of the liver such as schistosomiasis, echinococcus, and ascariasis have a hepatic phase in their life cycles. Animal models of schistosomiasis have helped in understanding the relationship between the hepatic immune system and the parasite. Eggs that are laid by adult worms in the portal vein get trapped within the hepatic sinusoids and trigger an immune response that results in granuloma formation. The early immune response mediated by eosinophils and neutrophils is proinflammatory. Later on, the cytokine profile within the liver becomes antiinflammatory and continues for the course of disease, ultimately resulting in liver fibrosis (Burke et al, 2009). KCs, IL-4, and IL-13 are thought to play a major role in shifting the cytokine profile during the course of schistosomiasis infection (Hayashi et al, 1999).

SUMMARY

The liver is an important immunologic organ with several unique features. It is constantly faced with the task of differentiating between nontoxic foreign antigens from the gut and those that may pose a significant threat to the host. Its propensity toward tolerogenicity in the setting of transplantation, infection, and malignancy is consistent with the finding that oral ingestion or portal vein injection can lead to antigen-specific tolerance. The liver contains a unique subset of immune cells that are, on the whole, less immunogenic than their counterparts found in lymphoid organs. Our understanding of the liver's immune system and how it relates to the immune system at large remains rudimentary, however, scientific investigation into this fascinating aspect of liver biology is rapidly accelerating, and it is hoped that this research will provide insight into how to modulate the immune system to treat the diverse array of liver diseases.

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CHAPTER 10

Cytokines in liver, biliary, and pancreatic disease

Matthew J. Weiss

OVERVIEW

Cytokines are small, nonstructural proteins that are key regulators of the human response to noxious stimuli. Cytokines can be proinflammatory, antiinflammatory, or both depending on the timing and context in which they are secreted. Nearly all nucleated cells are capable of both synthesizing and responding to cytokines, but most cytokine genes are not expressed unless stimulated by a specific stressor. This chapter reviews the roles that specific stimuli—including endotoxin, microbial products, and cytokines—play in both the normal physiology and pathophysiology of liver, biliary, and pancreatic disease, with particular attention to surgical problems. Both a metabolic and immunologic organ, the liver has been the subject of extensive research, but cytokines undoubtedly play a role in pancreatic pathophysiology as well. The entire field of cytokine research has continued to grow exponentially since the last version of this text, with several key discoveries that are directly applicable to surgical practice. Exciting areas of therapeutics based on this new knowledge are also discussed.

MICROBIOLOGIC RECOGNITION AND TOLL-LIKE RECEPTORS

In mounting an immune response, the challenge to the host is to identify the presence of an infectious process early and to coordinate its considerable resources to eradicate the pathogen, while minimizing tissue damage and chronic inflammation. The recognition of microbial pathogens and the ability to distinguish self from nonself relies heavily on the innate immunity and cell surface receptors present on antigen-presenting cells in the liver (Akira & Hemmi, 2003). Antigen-rich blood from the portal circulation has the potential to activate either the innate and adaptive immune responses against infections or to maintain immunologic tolerance of harmless antigens (Tacke et al, 2009). In addition, the infiltration of monocytes during liver injury is an important adaptive mechanism leading to chronic infammation (Karlmark et al, 2009). The immune response to a biologic insult is a highly organized process that involves pattern-recognition receptors (PRRs) that identify preserved structures of different pathogens. Toll-like receptors (TLRs) are an important family of at least 10 PRRs that are ubiquitously expressed in humans (Akira & Takeda, 2004). Current evidence demonstrates crucial roles for TLRs in alcoholic liver disease, nonalcoholic steatoheaptitis, hepatitis B, hepatitis C, hepatic fibrosis and cirrhosis, hepatocellular carcinoma, primary biliary cirrhosis, acetaminophen-induced hepatotoxicity, and ischemia-reperfusion (I/R) liver injury, all of which are potential therapeutic targets (Pimental-Nunes et al, 2010; Table 10.1).

ENDOTOXIN STRUCTURE AND BIOLOGIC ACTIVITY

Lipopolysaccharides (LPSs) from gram-negative bacteria have a wide range of harmful biologic activities and are therefore also considered endotoxins (Dinarello, 2004). Research over the past decade has elucidated the mechanisms by which the host recognizes endotoxin and the innate immune response is initiated. Much more is known about the cell surface receptors and signaling pathways involved in the host response to endotoxin than is known about several other microbial products and TLRs. Although endotoxin has been implicated in the beneficial and injurious host responses to gram-negative infections, the exact role of endotoxin in the pathogenesis of human disease remains unclear. Similarities in host responses to various microbial products, including LPSs from gram-negative bacteria and the glycoconjugates of gram-positive bacterial and fungal infections, suggest that the host innate immune system has evolved to respond consistently to microbial invasion, regardless of its antigenic source (Fearon & Locksley, 1996).

Endotoxin is the major constituent of the outer cell wall of gram-negative bacteria and can comprise 65% by weight of the total bacterium. Endotoxin is shed spontaneously from the cell walls of living bacteria and is released in copious amounts upon cell death and cell lysis. Endotoxin comprises three major components: an inner lipid A, an intermediate R-core oligosaccharide, and an outer O-polysaccharide (Fig. 10.1). The inner lipid A portion and the R-core oligosaccharide generally are conserved, whereas the structure of the O-polysaccharide is unique for each strain of bacteria. The R-core oligosaccharide is exposed in rough forms of gram-negative bacteria. The internal lipid A moiety is poorly antigenic but seems to be a primary factor in inducing most of the biologic effects of LPS. Binding of endotoxin to serum proteins and its activation of host immunity through its cellular receptor are mediated predominantly via the lipid A moiety; the O-antigen is primarily immunogenic (Ulevitch & Tobias, 1999).

The host response to endotoxin is immediate (within minutes), is dose dependent, and affects all organ and tissue systems (Table 10.2). High-dose endotoxin exposure in rodents and primates reproduces the toxic effects of gram-negative bacteremia, characterized by hemodynamic collapse, shock, organ failure, and death (Beutler et al, 1985). Low-dose administration of endotoxin to human volunteers (Fong et al, 1990; Michie et al, 1988) produces a variety of constitutional

Table 10.1

Toll-like Receptors and Their Potential Targets for Gastrointestinal Diseases

Organ	Disease	Target
Stomach	*Helicobacter pylori* infection	2, 4, 9
	Adenocarcinoma	2, 4, 9
Pancreas	Acute pancreatitis	2, 4, 9
	Chronic pancreatitis	3
	Pancreatic cancer	2, 3, 6, 9
Liver	Alcoholic liver disease	4
	Nonalcoholic steatohepatitis	4
	Hepatitis B	3, 7, 8, 9
	Hepatitis C	3, 7, 9
	Fibrosis/cirrhosis	4, 9
	Hepatocellular carcinoma	3, 4
	Ischemia/reperfusion	2, 4
Colon	Inflammatory bowel disease	2, 4, 5, 9
	Adenocarcinoma	2, 4, 5, 9

symptoms consistent with a milder infectious process, including fever, myalgia, tachycardia, occasional hypotension, transient leukopenia followed by neutrophilia, and a hepatic acute-phase response (Table 10.3).

Although the host responses to endotoxin are likely to be dose dependent, there is now general acceptance that the clinical sequelae associated with systemic endotoxin administration are probably secondary to the host innate immune response rather than a result of direct interactions between endotoxin and cell membranes or secretory proteins (Fearon & Locksley, 1996; Ulevitch & Tobias, 1999). At high doses, endotoxin can produce direct endothelial injury, but most host responses to endotoxin are mediated by complement activation and the release of humoral factors, including proinflammatory cytokines, nitric oxide (NO), and prostaglandins.

IMMUNE REGULATION AND RESPONSE TO ENDOTOXIN (SEE CHAPTER 9)

The host defense against many gram-negative bacteria is dependent on the innate immune recognition of endotoxin, and this response must be highly sensitive and self-limited. The sensitivity of this system is crucial for prompt mobilization to combat infection, but a risk of severe immune-mediated pathology exists if this response not self-limited. Optimal sensitivity is achieved by the strictly ordered interactions of endotoxin with different extracellular and cell surface proteins, including lipopolysaccharide (LPS)-binding protein (LBP), cluster of differentiation (CD)14, MD-2, and Toll-like receptor 4 (TLR-4) (Gioannini & Weiss, 2007). The presence of endotoxin in the plasma and lymphatic system is initially recognized by serum proteins and lipoproteins, and this recognition initiates the activation of the innate immune response (Beutler et al, 2003). Redundancy is the hallmark of this activation process, as proteins, glycoproteins, lipids, and nucleic acids of prokaryotic origins are recognized by different TLRs and other components of innate immunity. For the most part, the innate immune system relies on cell surface receptors and hepatic secretory proteins, primarily opsonins, to recognize carbohydrate and lipid, protein, and DNA structures indicative of a microbial infection.

Different constituents of specific microbial products, including endotoxin, are recognized by different aspects of the innate immune system (Ulevitch & Tobias, 1999). The first step in the recognition of endotoxin by the innate immune system is its binding to a hepatic secretory protein, LBP, to form the LPS-LBP complex (Fig. 10.2). LBP is a member of a group of homologous lipid-binding proteins that function as lipid-transfer proteins (Tobias et al, 1986, 1989; Wright et al, 1989). Secreted by the liver and found in human blood in 2 to 20 mg/mL concentrations, LBP binds avidly to the lipid A moiety of endotoxin and mediates its transfer to the cell surface endotoxin receptor, CD14. Although CD14 functions as a ligand-binding protein for endotoxin-LBP complexes, CD14 is bound to the cell membrane through a glycosyl–phosphatidylinositol anchor, and it lacks an intracellular domain capable of transducing a

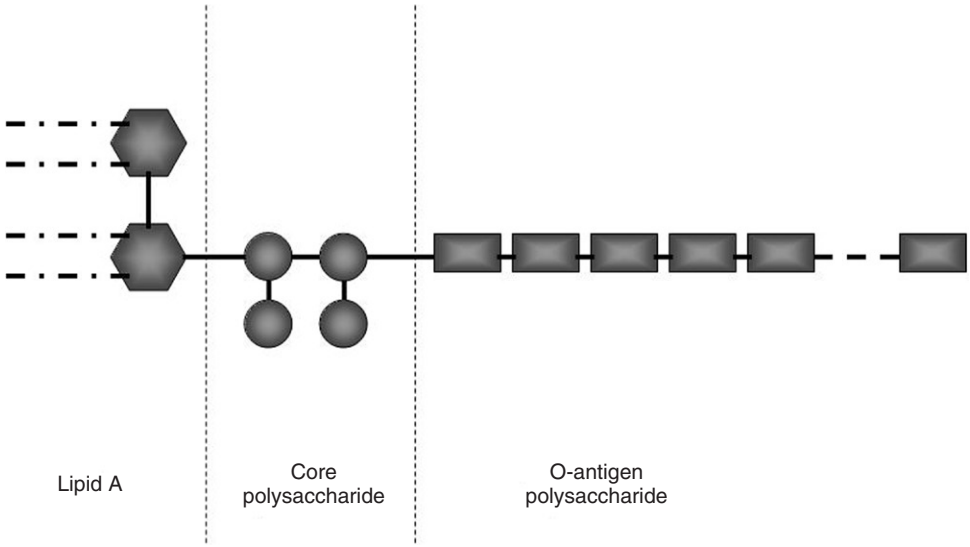


FIGURE 10.1. Schematic representation of the structure of endotoxin.

Table 10.2

Biologic Actions of Endotoxin

Fever

Direct effect on hypothalamus via prostaglandins
Indirect effect mediated by local interleukin production (IL-1, IL-6)

Hemodynamic Effects

Vasoconstriction
Direct effect
Secondary to sympathetic neurogenic activity
Indirectly caused by catecholamine and prostaglandin release
Vasodilation
Secondary to tissue hypoperfusion caused by vasoconstriction, endothelial injury, and reduced cardiac output
Indirectly caused by complement activation, neutrophil degranulation, prostacyclin and prostaglandin release, nitric oxide production
Produces pooling of blood in pulmonary and splanchnic vascular beds with hypotensive shock

Endothelial Cell Injury

Probable direct cell membrane damage by endotoxin at high concentrations
Prostaglandins, prostacyclin, procoagulants (e.g., tissue factor, factor V) and plasminogen activator inhibitor-1 release
Upregulation of adherence molecules with neutrophil adherence
Indirectly caused by TNF-α release

Intravascular Coagulation

Direct activation of the intrinsic and extrinsic pathways
Indirectly caused by release of tissue factor from monocytes and endothelial cells

Complement Activation (Antibody Independent)

Classical pathway activation (lipid A)
Alternative pathway activation (polysaccharide fraction)

White Blood Cell Effects

Transient leukocytopenia followed by leukocytosis, primarily a neutrophilia
Sustained monocytopenia and lymphopenia
Direct and indirect neutrophil activation and cytokine release, including TNF-α, IL-1α, IL-1β, IL-6, IL-8, CSF, PAF, procoagulants, prostanoids, and leukotrienes

Platelet Effects

Platelet aggregation and release of active constituents, direct effect of endotoxin and indirectly caused by release of PAF from monocytes/macrophages
Thrombocytopenia, probably secondary to platelet aggregation and intravascular coagulation

Activation of Reticuloendothelial System

Direct effect on tissue macrophages with release of secondary inflammatory mediators
Indirectly caused by proinflammatory cytokine release

Immunologic Effects

Specific B-cell antibody response to endotoxin antigens, especially potent O-antigen
Nonspecific polyclonal B-cell stimulation, indirectly caused by cytokines in response to IL-6 and IL-11 release
T-cell/macrophage regulation of antibody responses
B-cell release of CSF

Endocrine and Metabolic Responses

Increased resting energy expenditure
Increased plasma growth hormone, corticotropin, and cortisol
Increased lipolysis with raised plasma free fatty acid levels
Alterations in carbohydrate metabolism, increased gluconeogenesis, and glycogenolysis
Decreased albumin synthesis, increased acute-phase response protein production mediated by IL-6 and, to a lesser extent, TNF-α and IL-1

Organ-Specific Injury

Primarily lung, liver, and kidney
Secondary to microvascular effects and secondary cytokine release by infiltrating inflammatory cells

IL, interleukin; TNF, tumor necrosis factor; CSF, colony-stimulating factor; PAF, platelet activating factor

Table 10.3

Biologic Responses to Low-Dose Endotoxin in Human Volunteers

Constitutional Responses*

Fever (38° C to 39.8° C)
Headache
Chills
Myalgia
Photophobia
Nausea, vomiting

Cytokine/Hormone Responses

TNF-α (50 to 200 pg/mL)*
IL-6 (100 to 500 pg/mL)*
IL-1Ra (100 ng/mL)†
sTNFR (5 to 10 ng/mL)†
Corticotropin (80 to 120 pg/mL)*
Cortisol (350 to 500 ng/mL)‡
Epinephrine (50 to 60 pg/mL)*
Norepinephrine (375 to 450 pg/mL)*

Hemodynamic Responses

Tachycardia (90 to 105 beats/min)‡
Transient hypertension (increasing to 90 to 100 mm Hg)*

Leukocyte Responses

Transient neutropenia (<2000 cells/μL)*
Sustained delayed neutrophilia (>8000 cells/μL)†
Sustained lymphopenia and monocytopenia†

Metabolic Responses

Resting energy expenditure (20% increase)*
Increased free fatty acid concentration and appearance
Increased amino acid release and splanchnic uptake
Increased whole body and skeletal muscle protein breakdown
Increased gluconeogenesis and glucose oxidation

*≤4 hours' duration
†6 to 24 hours' duration
‡6 to 12 hours' duration
TNF-α, tumor necrosis factor α; IL, interleukin; s-TNFR, soluble TNF receptor

Data from Fong et al, 1990: The acute splanchnic and peripheral tissue metabolic response to endotoxin in humans. J Clin Invest 85:1896-1904.

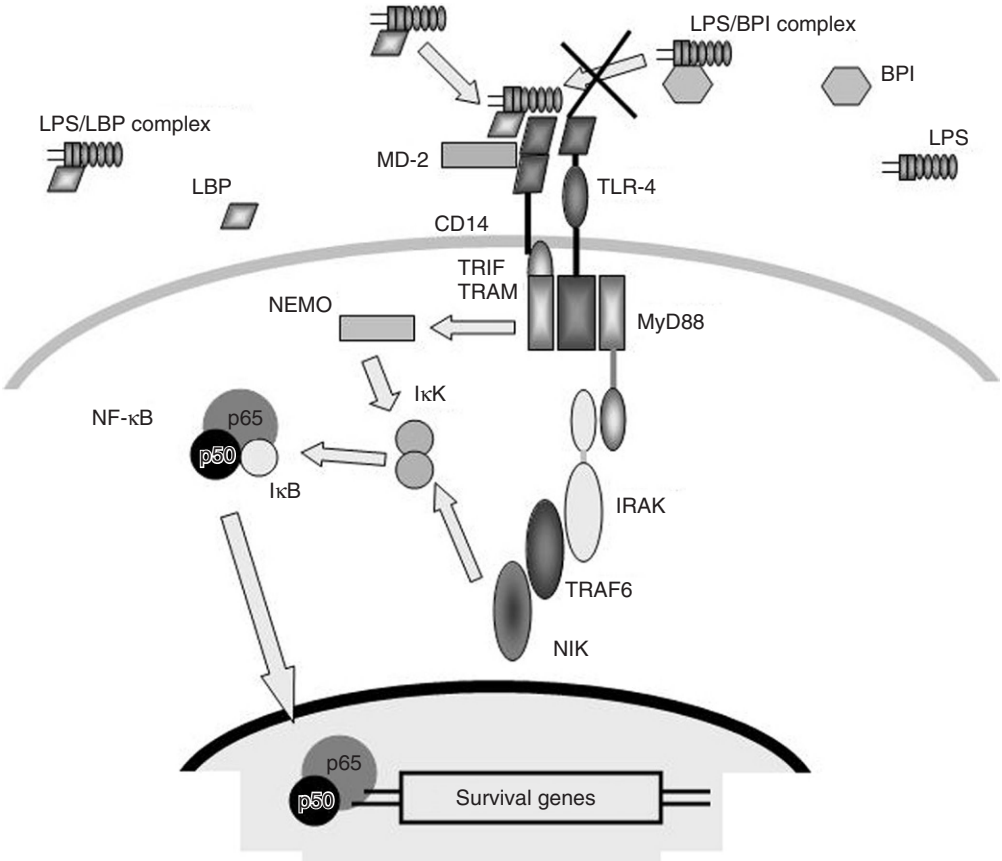


FIGURE 10.2. Endotoxin-binding proteins and signal transduction. Endotoxin in body fluids is rapidly recognized by endotoxin-binding proteins and lipoproteins. The balance between lipopolysaccharide binding protein (*LBP*) and bactericidal permeability–increasing protein (*BPI*) or high-density lipoprotein or both determines whether endotoxin in body fluids is detected by macrophages and other effector cells of the innate immune system. LBP-endotoxin complexes bind to CD14 and interact with Toll-like receptor-4 (*TLR-4*) and MD-2 membrane proteins, which activates intracellular myeloid differentiation response gene (88) (*MyD88*) dependent and independent pathways that ultimately lead to nuclear factor (NF)-κB activation and type I interferon production. IkB, inhibitor of NF-κB; IkK, inhibitor of NF-κB kinase; IRAK, interleukin-1 receptor–associated kinase; LPS, lipopolysaccharide; NIK, NF-κB–inducing kinase; NEMO, NF-κB essential modulator; TRAF, tumor necrosis factor receptor–associated factor; TRAM, Toll receptor–associated molecule; TRIF, Toll receptor–associated activator of interferon.

signal. LPS-LBP complex binding to CD14 alone is insufficient to transduce a signal.

The signal-transducing component of the CD14 bipartite complex protein has been identified as a member of the family of TLRs, specifically TLR-4 (Beutler, 2002). Although TLR-4 is expressed in several cells of healthy liver, signs of inflammation are absent because of low expression levels of TLR-4 and modulation of TLR-4 signaling. Mounting evidence suggests that altered LPS–TLR-4 signaling plays a role in the pathogenesis of chronic liver disease (Soares, 2010). TLR-4 seems to interact with CD14, the LBP-endotoxin complex, and a third protein, MD-2 (Viriyakosol et al, 2001).

Defining the complex role of CD14 in endotoxin-induced activation of TLR-4 is a challenge, and whether this role is obligatory remains unclear (Beutler et al, 2006; Jiang et al, 2005). However, the activation of TLR-4 by endotoxin does appear to require the simultaneous binding of endotoxin and TLR-4 by MD-2 (Gioannini et al, 2004). TLR-4 signaling can occur via a Toll-like and interleukin (IL)-1 receptor (TIR) domain and the formation of a scaffold composed of members of myeloid differentiation factor 88 (MyD88) adaptor proteins. At the same time, TLR-4 signaling also occurs through a MyD88-independent pathway that involves the adaptor protein TIR domain–containing adaptor inducing interferon-β (TRIF). This latter pathway seems to be more essential for the expression of type I interferons (IFNs) and IFN-dependent proteins in response to endotoxin exposure (Yamamoto et al, 2003). Although it is presently unknown how CD14-dependent signaling is integrated from the cell surface via TLR-4, the confirmation of TLR-4 as the signaling complex is important, because it identifies a signal transduction pathway and potential therapeutic targets.

The presence of LBP in the plasma increases the sensitivity of cells bearing CD14 to endotoxin by at least 1000-fold. From a teleologic standpoint, this has distinct advantages, because endotoxin can be detected, and innate immunity activated early, in response to gram-negative infection. However, increasing the sensitivity of the innate immune response to endotoxin can have devastating pathologic consequences, as may occur during sepsis or when gastrointestinal integrity is lost. These pathologic consequences include loss of vascular integrity, shock, organ failure, and death. Hosts have evolved several mechanisms to reduce the likelihood of an exaggerated endotoxin-induced signal.

High-density lipoproteins can bind endotoxin in serum and may play a role in protecting against endotoxemia (Cue et al, 1994). An additional endogenous mechanism to suppress

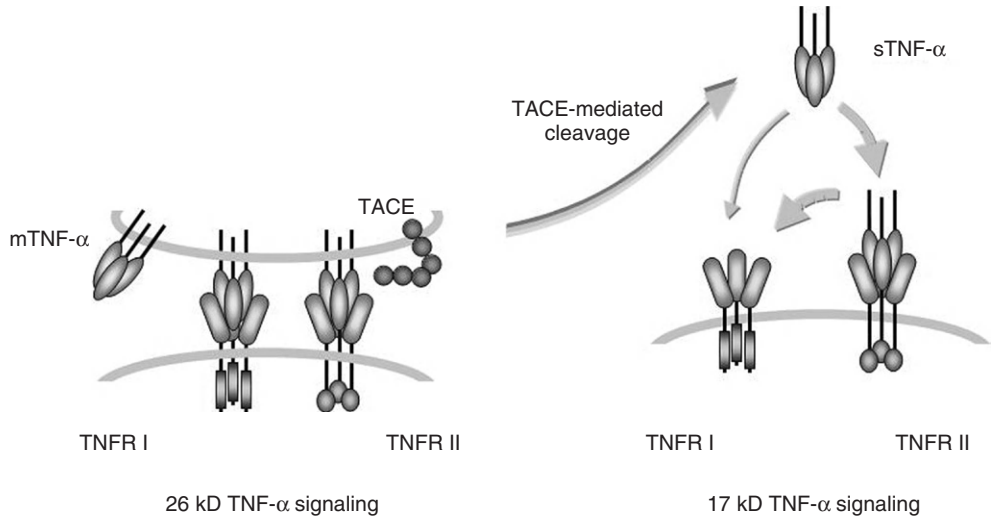


FIGURE 10.3. Processing of tumor necrosis factor (*TNF*)-α, which is initially synthesized as a 26-kD membrane-associated protein that is processed by TNF-α converting enzyme (*TACE*) to a secreted 17-kD homotrimer. Cell-associated and secreted molecules can bind and transduce a signal through two TNF receptors (*TNFRs*; p55 [type I] and p75 [type II]). mTNF, membrane TNF; sTNF, soluble TNF.

endotoxin responsiveness is through the release of an LBP-homologous protein, bactericidal/permeability-increasing protein (BPI; see Fig. 10.2). BPI is a 55- to 60-kD protein structurally similar to LBP, which binds endotoxin through its lipid A moiety. However, the resulting BPI-endotoxin complexes do not bind to CD14 or transduce a signal (Elsbach, 1998). BPI acts as an endogenous endotoxin inhibitor and has shown some modest beneficial effects in patients with meningococcal sepsis (Levin et al, 2000). In addition, BPI released from activated neutrophils can bind directly to endotoxin being expressed on the surface of gram-negative bacteria, and it is growth arresting and cytolytic for the bacteria (von der Mohlen et al, 1996).

BPI is stored in the granules of neutrophils and is released on neutrophil activation and degranulation. In a healthy adult, BPI levels in the serum are very low (15 to 50 ng/mL), but concentrations increase in response to an inflammatory or endotoxemic challenge (Calvano et al, 1994). In contrast, LBP concentrations are several logs higher in patients in the surgical ICU (2 to 20 mg/mL) and increase only modestly in response to inflammation. During infection, the ratio of LBP to BPI concentrations in the plasma approaches 1000:1, and this ratio favors endotoxin signaling. In closed-space infections infiltrated with neutrophils, however, BPI exceeds LBP concentrations, and BPI concentrations are directly proportional to neutrophil counts. These findings suggest that in the normal healthy adult and in patients with sepsis, the relationship between plasma LBP and BPI concentrations favors the recognition of endotoxin and activation of the innate immune response. In local infectious sites, where neutrophil and inflammatory cell recruitment has occurred, the increased BPI response is presumably compensatory and aimed at the continued activation of the immune system and reduction of bacterial growth.

Endotoxin signaling via the CD14 receptor and TLR-4 involves a novel IL-1 receptor-associated kinase, which activates a secondary kinase, NF-κB–inducing kinase (NIK) (Yang et al, 1999). Activation of this cascade rapidly induces the phosphorylation of additional kinases, which results in NF-κB translocation and the transcription of NF-κB–dependent genes (see Fig. 10.2). Genes containing NF-κB response elements are numerous and include most of the proinflammatory cytokines, including tumor necrosis factor (TNF)-α, IL-1, IL-6, IL-8, IL-12, IL-18, and IFN-γ (Blackwell & Christman, 1997).

Most of the systemic inflammatory responses to endotoxin are mediated by the release of proinflammatory cytokines and other humoral factors, predominantly TNF-α, IL-1, and IL-6 and, to a lesser extent, Fas ligand (FasL) (Suffredini et al, 1999). These proinflammatory cytokines not only globally regulate the inflammatory response to endotoxin, they also play a crucial role in reprogramming the metabolic and protein synthetic responses by the liver. As we will discuss in greater detail, TNF-α and IL-6 in particular play unique roles in regulating not only the hepatocyte acute-phase response to endotoxin but also hepatocyte proliferation versus apoptosis in liver regeneration (Michalopoulos & DeFrances, 1997; see Chapter 5), viral hepatitis (Hayashi & Mita, 1997; see Chapter 64), and toxic liver injury (Batey et al, 1999; Bradham et al, 1998; McClain et al, 1999). In contrast, FasL is a potent inducer of hepatocyte apoptosis and has been implicated in the pathogenesis of viral hepatitis (Kondo et al, 1997; Hayashi & Mita, 1997).

TUMOR NECROSIS FACTOR SUPERFAMILY

Since the discovery of TNF-α 35 years ago, the TNF superfamily has grown to comprise at least 20 related proteins that signal through greater than 30 receptors (Grewal, 2009). Members of the TNF superfamily are primarily homotrimeric proteins, with the exception of lymphotoxin, and they exist primarily in a membrane-associated form (Bazzoni & Beutler, 1996). As a general rule, members of the TNF family are primarily involved in the regulation of cell proliferation and apoptosis, although several of the members—including TNF-α, TNF-β, FasL, CD30L, and CD40L—also have proinflammatory properties.

TNF-α is synthesized as a bioactive cell-associated protein that is primarily involved in juxtacrine signaling of cytotoxicity. This 26-kD intermediate is enzymatically cleaved by a matrix metalloproteinase to a 17-kD secreted form that acts in a paracrine or endocrine fashion (Fig. 10.3). TNF-α originally was characterized as a factor that produced necrosis of solid tumors

Table 10.4

Biologic Activities of Tumor Necrosis Factor-α

Immune Cells	Nonimmune Cells	In Vivo
Monocytes-Macrophages	**Vascular Endothelial Cells**	**Central Nervous System**
Activate/autoinduce TNF	Modulate angiogenesis	Fever
Induce cytokines and prostaglandins	Increase permeability	Anorexia
Chemotaxis and transmigration	Prevent fibrinolysis	Altered pituitary hormone secretion
Stimulate metabolism	Increase coagulation	**Cardiovascular**
Inhibit differentiation	Suppress proliferation	Shock
Suppress proliferation	Rearrange cytoskeleton	Capillary leakage
Polymorphonuclear Leukocytes	Induce NO synthase	**Gastrointestinal**
Prime integrin response	Induce cytokines IL-1, IL-3R, G-CSF, GM-CSF	Ischemia
Increase phagocytic capacity	Induce prostacyclin	Colitis
Enhance production of superoxide	Induce E-selectin, ICAM, VCAM	Hepatic necrosis
Increase adherence to extracellular matrix	**Fibroblasts**	Inhibit albumin expression
Lymphocytes	Induce proliferation	Decrease hepatic catalase
Induce T-cell colony formation	Induce cytokines IL-1, IL-6, LIF	**Metabolic**
Induce superoxide in B cells	Induce metalloproteinases	Net lipid catabolism
Induce apoptosis in mature T cells	Suppress respiratory activity	Net protein catabolism
Activate cytotoxic T-cell invasiveness	Inhibit collagen synthesis	Release stress hormone
	Adipocytes	Insulin resistance
	Enhance release of free fatty acids	**Inflammatory**
	Suppress lipoprotein lipase	Activate cytotoxicity
	Endocrine System	Enhance natural killer cell function
	Stimulate corticotropin, prolactin	Mediate IL-2 tumor toxicity
	Inhibit TSH, FSH, GH	
	Enhance IL-1 inhibition of steroidogenesis	

FSH, follicle-stimulating hormone; G-CSF, granulocyte colony-stimulating factor; GH, growth hormone; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICAM, intercellular adhesion molecule; IL, interleukin; LIF, leukemia inhibitory factor; TSH, thyroid-stimulating hormone; VCAM, vascular cell adhesion molecule

in vivo (Carswell et al, 1975). It subsequently was recognized that TNF-α modulates growth, differentiation, and metabolism in a variety of cell types; it can produce cachexia by stimulating lipolysis, inhibiting lipoprotein lipase activity in adipocytes, and stimulating hepatic lipogenesis; and it can initiate apoptosis in hepatocytes and lymphoid cells (Table 10.4; Ksontini et al, 1998).

TNF-α is a powerful inducer of the inflammatory response both directly and through stimulation of numerous downstream proinflammatory mediators. Secondary mediators that are known to be induced by systemically administered TNF-α include cytokines (IL-1, IL-2, IL-4, IL-6, IL-10, IL-12, IL-18, IL-23, type I and type II IFN, transforming growth factor-β, leukemia inhibitory factor [LIF], and macrophage migration inhibitory factor [MIF]), hormones (cortisol, epinephrine, glucagon, insulin, and norepinephrine), and assorted other molecules (acute-phase proteins, IL-1 receptor antagonist [IL-1Ra], leukotrienes, oxygen free radicals, NO, platelet-activating factor, and prostaglandins; Tracey & Cerami, 1994). Other principal biologic effects of TNF-α are listed in Table 10.4 (see Chapter 9).

Not only is TNF-α involved in tissue inflammation, but there is a growing recognition that it is also a prominent ligand for the activation of programmed cell death. Apoptosis occurs naturally during growth and development, but it may also result from certain pathologic conditions in which local and systemic production of TNF-α is increased. Hepatocytes are particularly sensitive to TNF-α–induced apoptosis, especially during simultaneous transcriptional inhibition (Leist et al, 1994).

TNF-α has been administered systemically in low doses to human volunteers and regionally in higher doses to sarcomas and melanomas. The physiologic responses to low-dose (50 mg/m^2) TNF-α administration were remarkably similar to the responses seen with low-dose endotoxin administration: fever and constitutional symptoms of pain, headache, myalgia, and nausea. Hematologically, the volunteers developed a rapid leukopenia, followed by neutrophilia with sustained lymphopenia and monocytopenia (van der Poll et al, 1992). Plasma IL-6 levels increased 40-fold, and the volunteers developed an acute-phase protein response. Prostaglandin (6-keto prostaglandin [PG] F_{1a}) production also was markedly increased. Metabolically, the patients exhibited increased lipolysis and glucose turnover (van der Poll et al, 1991b). There also were significant effects on the vascular endothelium. Within 1 hour, TNF-α administration induced activation of the fibrinolytic pathway, followed by activation of the coagulation cascade (van der Poll et al, 1991a).

At higher doses of TNF-α, as achieved with regional perfusion of limbs, the systemic release of large quantities of protein occasionally occurs, and the effects on the vascular endothelium are profound. Under these conditions, activation of the endothelium is evident by increased release of soluble selectins and integrins, and hemodynamic instability is common (Aderka et al, 1998; Zwaveling et al, 1996); therefore continuous monitoring for systemic leakage is required.

INTERLEUKIN-1 FAMILY

The IL-1 family of ligands and cytokines are similar to the TNF superfamily in that they are also primarily associated with inflammation. IL-1 possesses several biologic properties that result in increased expression of downstream proinflammatory genes. The most salient and relevant is the ability of

IL-1 to initiate and sustain the expression of cyclooxygenase type 2 and inducible NO synthase (Dinarello, 1996). This property accounts for the large amount of PGE_2 and NO produced by cells exposed to IL-1 or in subjects injected with IL-1. Other important proinflammatory properties of IL-1 are its ability to increase IL-8 synthesis and to express adhesion molecules on endothelial cell surfaces, which accounts for the infiltration of inflammatory cells into the extravascular space. IL-1 also potentiates the biologic activities of TNF-α, and modest doses of the two in combination can be lethal in experimental animals.

The original IL-1 superfamily consisted of two members: IL-1α and IL-1β. Currently, the IL-1 superfamily also contains IL-1Ra, IL-16, IL-17, IL-18, IL-33, and at least six other homologues in the IL-1 family (Schmitz et al, 2005). IL-1α and IL-1β are agonists, and IL-1Ra is a specific receptor antagonist for the IL-1 receptor family. The naturally occurring IL-1Ra seems to be unique in cytokine biology (Arend, 1993). The intron–exon organization of three primary IL-1 genes suggests the duplication of a common gene some 350 million years ago. Processing of IL-1α or IL-1β to "mature" forms requires specific cellular proteases. In contrast, IL-1Ra evolved with a signal peptide and is readily transported out of the cell and is termed *secreted IL-1Ra*.

Even under conditions of cell stimulation, human blood monocytes do not process or readily secrete mature IL-1α, which is probably only released by dying cells, as it is a key factor released by necrotic cells that promotes inflammation (Chen, 2007). The IL-1α precursor proIL-1α is synthesized in association with cytoskeletal structures (microtubules), which is in contrast to most proteins translated in the endoplasmic reticulum. ProIL-1α is fully active as a precursor and remains intracellular. The opposite is the case with the IL-1β precursor proIL-1β, which is not fully active, and a considerable amount is secreted after cleavage by a specific, intracellular cysteine protease, IL-1β–converting enzyme, or caspase-1. Caspase-1 plays a central role in the biology of IL-1β, IL-18, and IL-33 and has become a therapeutic target for modulating IL-1–based diseases (Martinon & Tschopp, 2004). IL-33 is an activator of Th2 cells and has recently been shown to play a protective role in the development of atherosclerosis (Miller et al, 2008; Sanada et al, 2007) and is thought to be released by cell death (Carriere et al, 2007).

Nearly all microbes and microbial products induce production of the three IL-1 family proteins, but stimulants of nonmicrobial origin also can elicit transcription and synthesis. Stimulants such as the complement component C5a, hypoxia, adherence to surfaces, and clotting of blood induce the synthesis of large amounts of IL-1 mRNA in monocytic cells without significant translation into the IL-1 protein.

Although animal experiments revealed that IL-1 was proinflammatory, a great deal of information has been gathered from studies in which humans have been injected with recombinant IL-1α or IL-1β. Humans have received IL-1α infusions as part of clinical trials following bone marrow transplantation because of its hematopoietic properties. Although the duration of leukopenia and thrombocytopenia were reduced, patients had serious signs of systemic inflammation that included fever, hypotension, and flulike symptoms, similar to endotoxemia (Smith et al, 1993). Interestingly, the exquisite sensitivity of humans to IL-1 given systemically was not appreciated from animal studies.

Table 10.5

Overlapping Biologic Activities of IL-1, TNF-α, and IL-6

	IL-1	TNF-α	IL-6
Endogenous pyrogen	Strong	Yes	Weak
Hepatic acute-phase inducer	Yes	Weak	Strong
Anorexia and cachexia	Yes	Yes	Yes
Induction of hypothalamic-pituitary-adrenal axis	Yes	Weak	Yes
Prostaglandin and NO synthesis induction	Strong	Strong	Weak
Shock producing	Yes*	Strong	No
NF-κB induction	Yes	Yes	No
Induction of hepatocyte apoptosis	Inhibitor	Yes†	No/inhibitor
Hepatic regeneration	Weak	Strong	Strong

The terms *weak* and *strong* are relative to the other two cytokines.
*Shock is not irreversible with IL-1.
†In the presence of transcriptional inhibition.
IL, interleukin, TNF, tumor necrosis factor; NO, nitric oxide; NF-κB, nuclear factor kappa B

INTERLEUKIN-6

IL-6 is another pleiotropic cytokine produced by a wide variety of cells, including T cells, B cells, endothelial cells, fibroblasts, monocytes, and macrophages. The biologic activities of IL-6 include immune regulation, hematopoiesis, inflammation, and oncogenesis (see Chapter 9). The IL-6 gene has been mapped to chromosome 7, and its product varies from 21 to 28 KD, depending on posttranslational modifications. IL-6 belongs to a much larger superfamily of related cytokines, including leukemia inhibitory factor, oncostatin M, ciliary neurotrophic factor, cardiotrophin-1, and IL-11. All members of this superfamily share a modest degree of structural homology, but more importantly, all these related cytokines use a common signal transduction pathway through heterocomplexes composed of gp130. Each ligand has its own receptor, which combines in a duplex to transduce its signal through the JAK/Stat signaling cascade.

Although microbial products are potent inducers of IL-6, the synthesis of IL-6 seems to depend on the release of more proximal cytokines, primarily TNF-α and IL-1. The biologic activities of IL-6 are numerous and can be divided into those involved in the regulation of the hematopoietic system and those involved in activation of the innate immunity. Recent studies have elucidated a crucial role for IL-6 in regulating the balance between T-regulatory cells and a new subset of T-helper cells that produce IL-17 (Kimura & Kishimoto, 2010). In the liver, IL-6 is secreted by Kupffer cells and is an important regulator of innate immune response and a stimulator of hepatocyte proliferation. Although IL-6 shares several biologic responses with TNF-α and IL-1, IL-6 is the predominant regulator of the hepatic acute-phase response and induces hepatocyte proliferation during liver regeneration (Table 10.5).

FAS LIGAND

FasL is another member of the TNF superfamily. Similar to TNF-α, FasL is synthesized and expressed first as a 40-kD membrane–associated protein and is then processed further by

matrix metalloproteinases to a homotrimeric 26-kD secreted form (Nagata & Golstein, 1995). Historically, FasL was presumed to have predominantly proapoptotic properties, especially for hepatocytes, and these were associated primarily with its membrane-associated form. Although it was noted that secreted FasL formed trimeric structures and retained its ability to ligate the Fas receptor, it was unclear whether soluble FasL could induce apoptosis (Schneider et al, 1998). A model of Fas activation has recently been proposed that distinguishes five separate stages (Lee et al, 2006). FasL occurs in a membrane-bound found and in a soluble form that is the result of splicing of the membrane-bound form. Studies in mice in particular suggested that the soluble forms of FasL may be receptor antagonists of Fas, which inhibit cell-associated FasL-mediated apoptosis.

The hypothesis that soluble FasL is strictly an inducer of apoptosis has been dispelled by several groups, who reported that soluble FasL also has proinflammatory properties. FasL can induce NF-κB through NF-κB–inducing kinase (NIK) signaling (Malanin et al, 1997). Ottonello and colleagues (1999) showed that soluble FasL in humans is endowed with potent chemotactic properties for neutrophils at concentrations incapable of producing apoptosis. FasL does not seem to activate neutrophils, only to recruit them; neutrophil calcium flux, superoxide production, and degranulation are not affected. Other investigators have come to similar conclusions (Chen et al, 1998; Seino et al, 1998). In addition, Park and colleagues (2003) suggested that FasL can activate blood monocytes. These authors showed that these inflammatory properties are separate and distinct from the proapoptotic properties of FasL. This observation is significant in part because it suggests that FasL, similar to TNF-α and other members of the TNF superfamily, may contribute to neutrophil and monocyte infiltration and recruitment as part of the host inflammatory response. This observation is particularly relevant in viral hepatitis, in which increased FasL expression and neutrophil infiltration have been observed.

Although FasL was originally thought to be expressed only by cells of the lymphoid or myeloid lineage—including predominantly T and B cells, phagocytes, and natural killer cells—it is now recognized that FasL frequently is expressed by nonlymphoid cells (Kiener et al, 1997; Liles et al, 1996). The Fas receptor, also called CD95 or Apo1, is widely expressed on a variety of cell types, including hepatocytes. The Fas receptor shares structural homology with the TNF receptor I (Fig. 10.4), and Fas signaling can also lead to proinflammatory events through the activation of NF-κB–dependent pathways, which may be responsible for some its chemotactic properties.

TRANSFORMING GROWTH FACTOR-β

TGF-β is another ubiquitously expressed cytokine that plays a role in several cellular functions, including apoptosis, cell cycle regulation, immune regulation, and inflammation (Massague, 2008; Bierie & Moses, 2006). TGF-β is produced in an inactive form that requires activation by proteases such as matrix metalloproteinase (MMP)2 and MMP9. Interestingly, TGF-β and its proteases are present at high levels in the periphery of certain tumors (Reiss & Barcellos-Hoff, 1997), and TGF-β also seems to be a potent inducer of fibrosis (see Chapter 6) and eventually of carcinogensis of the liver (see Chapter 8C). TGF-β signaling is via phosphorylation of Smad3, but the location of phosphorylation determines whether the effect will be oncogenic or tumor suppressive. Phosphorylation at the C-terminal region of Smad3 transmits a tumor-suppressor signal, and phosphorylation at the linker region initiates oncogenic sequelae. Therefore TGF-β signaling appears to play a role in chronic liver disease progressing to cancer. In addition, mutations in the genes encoding the receptors for TGF-β and decreased expression of downstream Smad proteins have been reported in pancreatic cancer (Derynck et al, 2001).

CYTOKINES IN THE LIVER AND PANCREAS

Regulation of Cytokine Expression in the Liver

Cytokine production by resident cell populations in the liver contributes significantly, not only to local cytokine appearance and organ homeostasis but also to the cytokines' emergence into the systemic circulation. Fong and colleagues (1990) cannulated the hepatic vein of human volunteers and examined the efflux of TNF-α and IL-6 from the splanchnic bed after intravenous endotoxin administration. Almost 40% of the TNF-α that appeared in the systemic circulation was derived from the splanchnic bed. Not only are Kupffer cells a potential source of proinflammatory cytokines in the liver, biliary epithelial cells and venous endothelial cells can also make significant quantities of cytokines, especially TNF-α, during liver regeneration (Bradham et al, 1998). In addition, resident and infiltrating T cells and natural killer cells can contribute significantly to TNF-α and FasL production, especially during viral-induced hepatic injury (Hayashi & Mita, 1997). There is some evidence that virally infected hepatocytes themselves can express TNF-α directly (Gonzalez-Amaro et al, 1994). TNF-α, IL-1, IL-6, and FasL expression is increased in the liver in response to intravenous endotoxin administration, generalized peritonitis, hepatic I/R injury, infected burn injury, and concanavalin A–induced hepatitis and during liver regeneration (Solorzano et al, 1997; Tannahill et al, 1999).

Cytokines and the Hepatic Acute-Phase Response

The local and systemic release of TNF-α, IL-1, and IL-6 provide anabolic signals to the liver that direct the increased synthesis of hepatic acute-phase reactant proteins (Table 10.6). IL-1 and IL-6 in particular act on the hypothalamic–pituitary axis to stimulate the release of corticotropin-releasing hormone, corticotropin, and cortisol, and these serve to facilitate the mobilization of free amino acids from skeletal muscle, connective tissue, and gut to the liver, where amino acid uptake is enhanced. These free amino acids become the precursors for increased protein synthesis and the altered protein synthetic pattern seen in patients with chronic inflammation and mediated directly by IL-6, IL-1, and to a lesser extent TNF-α.

These three cytokines transcriptionally suppress albumin synthesis, the primary protein secretory product of the liver in the healthy adult. Decreased albumin synthesis and hypoalbuminemia are well-described consequences of chronic liver disease, and the patient's plasma albumin concentration often has been predictive of adverse outcome in a variety of hospitalized patients. In addition, IL-6, IL-1, and TNF-α induce the transcription of a class of heavily glycosylated secretory proteins, termed *acute-phase reactants*. The number of acute-phase reactants synthesized by the liver in response to these cytokines

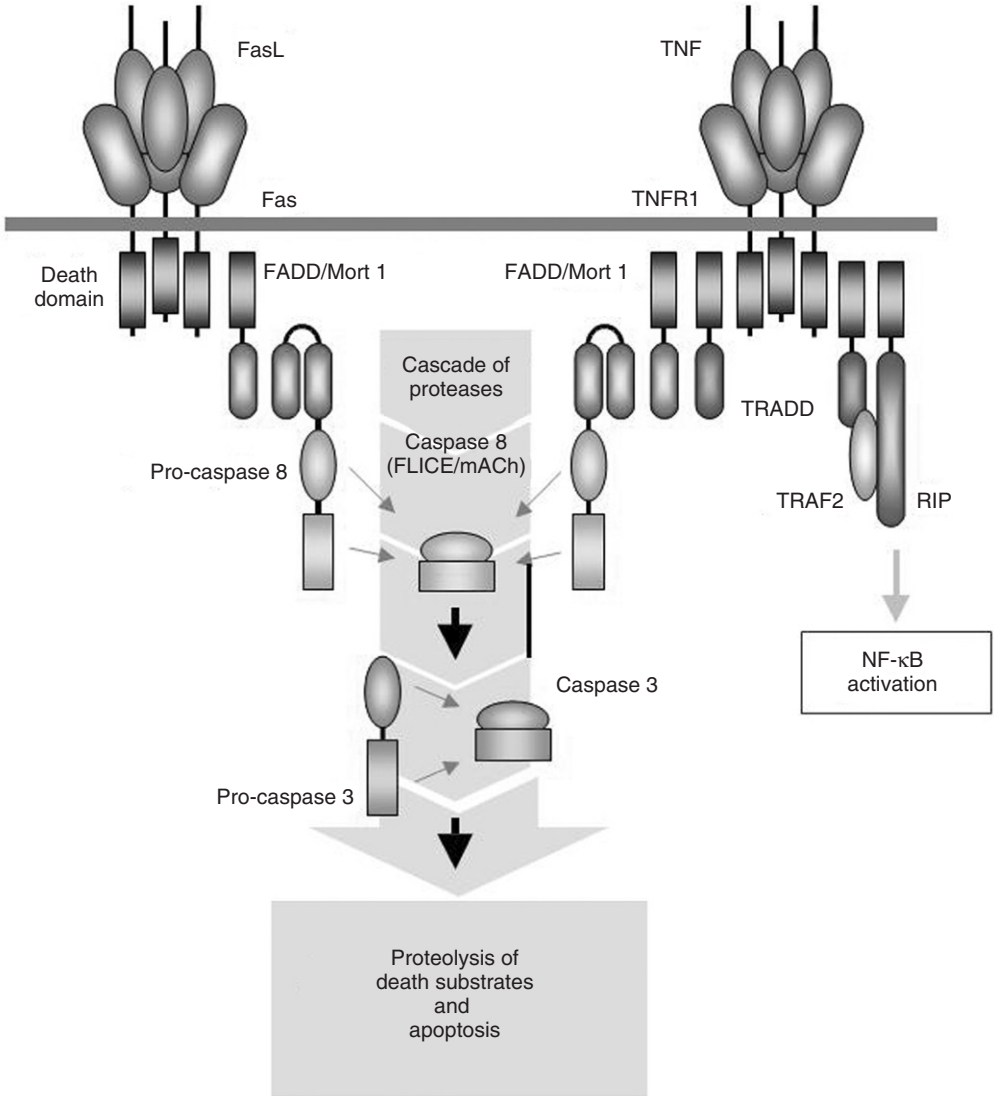


FIGURE 10.4. Tumor necrosis factor (TNF) receptor I and Fas signaling of apoptosis and nuclear factor (*NF*)-κB activation. TNF type I and Fas signaling share a common signal transduction pathway, leading to apoptosis through caspase-8 and caspase-3. TNF type I receptor signaling leads directly to NF-κB activation through a divergent tumor necrosis factor receptor–associated factor (*TRAF2*)-dependent pathway. Fas signaling also can induce NF-κB through NF-κB–inducing kinase (NIK) activation, but under in vivo conditions, Fas signaling is a weaker inducer of NF-κB than TNF type I receptor. FADD/Mort1, Fas-associated death domain; FLICE, FADD-like interleukin-1β–converting enzyme; mACh, muscarinic acetylcholine; RIP, receptor interacting protein; TNFR, TNF receptor; TRADD, TNFR type 1–associated death domain.

Table 10.6

Hepatic Acute-Phase Reactant and LPS Recognition Molecules

Molecule	Synthesis	Ligand	Function
C-reactive protein	Hepatic acute-phase reactant	Microbial polysaccharides	Complement activation, increased phagocytosis
Serum amyloid P	Hepatic acute-phase reactant	Microbial cell wall polysaccharides, extracellular matrix proteins	Increased phagocytosis, stabilizes extracellular matrix proteins and mannose binding
Hepatic secretory protein	Microbial cell wall polysaccharides	Binds collectin receptor and protein	Activates complement, increased phagocytosis
LPS-binding protein	Hepatic acute-phase reactant	Transfers LPS to CD14 and serum lipoproteins	Macrophage activation, enhances sensitivity to LPS
BPI	Neutrophil granules	Binds LPS and prevents transfer to LBP/CD14	Prevents LPS-induced actions
Soluble CD14	Plasma-protein derived, shed from monocytic cells	LPS and other microbial cell wall fragments	Enhances sensititvity to LPS, particularly in cells lacking CD14 but possessing TLRs
C3	Hepatic acute-phase reactant	Forms ester linkages with OH groups	Ligand attachment for CD21 and on proteins CD35

LPS, lipopolysaccharide; BPI, bactericidal permeability-inducing protein; LBP, lipopolysaccharide-bindng protein; TLRs, Toll-like receptors; CD, cluster of differentiation.

Modified from Fearon DT, Locksley RM, 1996: The instructive role of innate immunity in the acquired immune response. Science 272:50-53.

Table 10.7

Acute-Phase Reactants and Their Responses

Acute-Phase Proteins Whose Plasma Concentrations Increase

Complement System

C3
C4
C9
Factor B
C1 inhibitor
C4b-binding protein
Mannose-binding lectin

Coagulation and Fibrinolytic System

Fibrinogen
Plasminogen
Tissue plasminogen activator
Urokinase
Protein S
Vitronectin
Plasminogen activator inhibitor 1
Antiproteases
α_1-Protease inhibitor
α_1-Antichymotrypsin
Pancreatic secretory trypsin inhibitor
Inter-α-trypsin inhibitor

Transport Proteins

Ceruloplasmin
Haptoglobin
Hemopexin

Participants in Inflammatory Responses

Secreted phospholipase A_2
LPS-binding protein
IL-1–receptor antagonist
Granulocyte colony-stimulating factor

Others

C-reactive protein
Serum amyloid A
α_1-acid glycoprotein
Fibronectin
Ferritin
Angiotensinogen

Plasma Proteins Whose Plasma Concentrations Decrease

Albumin
Transferrin
Transthyretin
α_2-HS glycoprotein
α-Fetoprotein
Thyroxin-binding globulin
Insulin-like growth factor I
Factor XII

LPS, lipopolysaccharide; IL, interleukin.

Modified from Gabay C, Kushner I, 1999: Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 340:448-454.

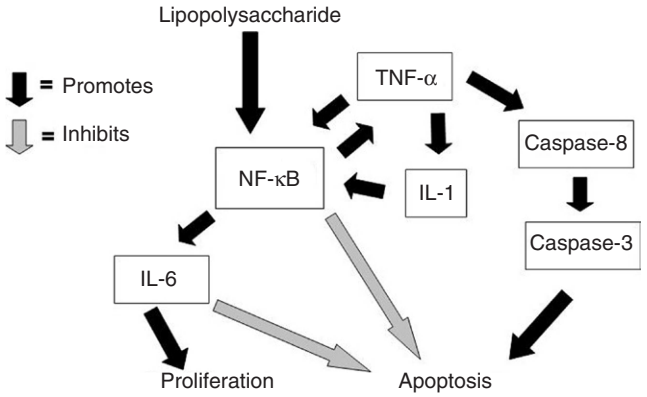


FIGURE 10.5. Hepatocyte fate is determined by the balance between tumor necrosis factor-α (*TNF-α*)–mediated nuclear factor (NF)-κB activation and apoptosis. TNF-α signaling simultaneously activates pathways that induce and antagonize capase-dependent apoptosis. Drugs or agents that inhibit NF-κB activation promote apoptosis, whereas cytokines that induce NF-κB protect against TNF-α–mediated apoptosis. IL, interleukin.

is quite large and has already been reviewed (Gabay & Kushner, 1999). As a class, the acute-phase proteins have diverse biologic functions (Table 10.7), but many of these proteins are recognition molecules of the innate immune system, including C-reactive protein, MBP (collectin), LBP, amyloid A, and amyloid P (Fearon & Locksley, 1996). These proteins bind microbial polysaccharides or LPS and either activate complement or enhance phagocytosis. Other acute-phase reactants—such as α_1-antitrypsin, α_1-antichymotrypsin, and tissue inhibitors of metalloproteinases—are protease inhibitors, whereas some, such as haptoglobin and hemopexin, are antioxidants. The function of these latter two groups of acute-phase reactants is to reduce local tissue damage secondary to activation of the innate immune response.

Cytokines and the Pancreas

Many pathways that regulate pancreatic development have already been identified and include TGF-β, Notch, Hedgehog, fibroblast growth factor, and epidermal growth factor (EGF) (Rane, 2006; see Chapter 1A). Dysregulation of these pathways appears to be important in many pancreatic disease states.

Much of the current data pertaining to the role of cytokines in the pancreas comes from the diabetes, pancreatitis, and adenocarcinoma literature. It is known that islet cells produce a variety of cytokines in response to both physiologic and pathologic exposure to nutrients (Donath et al, 2010). The inflammatory mediators of cytokine production are produced by α, β, endothelial, ductal, and immune cells. A chronic state of metabolic stress is believed to induce an inflammatory state that leads to islet cell dysfunction and insulin secretion failure. A significant role for TGF-β in the progression of type 1 diabetes has been demonstrated in mice (Baxter et al, 1995).

TGF-β proteins are regulators of pancreatic cell function and appear to have key roles in the development of nondiabetic pancreatic disease as well. The first model of pancreatic adenocarcinoma was generated with overexpression of TGF-β (Greten et al, 2001). These mice developed fibrosis and then pancreatic adenocarcinoma. Additionally, TGF-β2 subset levels appear to be associated with advanced tumor stage (Friess et al, 1993). Patients with long-standing pancreatitis are thought to be at increased risk of developing adenocarcinoma. TGF-β levels are elevated in patients with chronic pancreatitis, and this appears to correlate with both fibrosis and hyperglycemia (Fogar et al, 1998).

Cytokines and Apoptosis

TNF-α seems to be a prominent ligand for the activation of cellular apoptosis, but how TNF-α induces apoptosis in hepatocytes remains unclear. Although hepatocytes are particularly sensitive to TNF-α–mediated apoptosis, the cells first must be exposed to transcriptional inhibition. Incubating cultured hepatocytes with TNF-α or administering TNF-α does not produce hepatocyte apoptosis unless D-galactosamine or actinomycin D is coadministered. The requirement for transcriptional inhibition is likely explained by TNF-α simultaneously activating signaling pathways in hepatocytes that both induce and antagonize apoptosis, suggesting a delicate balance among TNF-α signaling pathways (Fig. 10.5; Beg & Baltimore, 1996; Van Antwerp et al, 1996). Induction of the proinflammatory properties of TNF-α, induced in part through activation of NF-κB–dependent "survival genes," seems to inhibit apoptosis directly (Baker & Reddy, 1998). NF-κB is a ubiquitous transcription factor that plays a crucial role in the cellular response to signal transduction by TNF-α and IL-6. All members of this family (NF-κB) share a conserved region of approximately 300 amino

acids important for their dimerization, nuclear translocation, and DNA binding (Baeuerle, 1998). These NF-κB proteins form homodimers and heterodimers, and their activity is modulated by interactions with inhibitory proteins of the I-κB family.

These findings have several clinical implications. The role of NF-κB in the development of type 1 diabetes and its effect on β cells is still unclear, but both antiapoptotic and proapoptotic effects have been described (Donath et al, 2008). Recent studies suggest that enhanced activation of the NF-κB pathway via NIK overexpression may exist in pancreatic adenocarcinoma (Nishina et al, 2009). Robin and colleagues (2005) showed that alcohol abuse increases the sensitivity of hepatocytes to TNF-α–mediated apoptosis and hepatotoxicity. This increased sensitivity seems to be secondary to the failure of TNF-α to induce NF-κB activation in the livers of animals after alcohol abuse. Similarly, radiation to hepatocytes prevents induction of survival genes and increases the apoptotic response to TNF-α (Christiansen et al, 2004). In contrast, ischemic preconditioning seems to protect livers from subsequent apoptotic cell death secondary to induction of NF-κB and IL-6 (Iwasaki et al, 2002). In contrast, activation of TNF-α signaling of caspase-8 and caspase-3 via tumor necrosis factor receptor type 1–associated death domin/Fas-associated death domain (TRADD/FADD) leads to apoptosis through pathways shared by FasL signaling. The balance between these two pathways ultimately determines whether a cell responds to TNF-α by proliferating or undergoing apoptosis (Beg & Baltimore, 1996;Van Antwerp et al, 1996).

The role that specific cytokines play in apoptotic liver injury secondary to endotoxin administration has been well characterized. Similar to high-dose TNF-α in the absence of transcriptional inhibitors, high-dose endotoxin administration results in significant liver injury secondary to hepatocyte necrosis, although hepatocyte apoptosis is minimal (Bohlinger et al, 1996). Simultaneous inhibition of transcription, either by depleting hepatocyte nucleotides with D-galactosamine or by blocking transcription with actinomycin D, results in a 1000-fold increased sensitivity to endotoxin-induced lethality, and the hepatic injury is characterized by massive liver apoptosis (Solorzano et al, 1997). The liver injury seems to depend primarily on TNF-α expression, although FasL, interferon-γ, IL-12, IL-18, and IL-23 probably also contribute. Mice lacking either TNF-α or the TNF type I receptor are completely protected from endotoxin and D-galactosamine–induced hepatocyte apoptosis and mortality, whereas they are still susceptible to high-dose endotoxin-induced lethality. Fas agonists differ from TNF-α in that they apparently can induce massive hepatocyte apoptosis in the absence of transcriptional inhibition. The differential response to apoptosis mediated by TNF-α and FasL seems to be related to the observation that FasL is a significantly weaker inducer of NF-κB than is TNF-α. IL-1 and NO protect hepatocytes from TNF-α–mediated apoptosis, presumably by stimulating NF-κB activation and inhibiting caspase activities (Bohlinger et al, 1996). Caspases play central roles as the "suicide effectors" of hepatocyte apoptosis, demonstrated by the treatment of mice with broad-acting caspase inhibitors to prevent apoptotic liver injury and mortality (Kunstle et al, 1997; Mignon et al, 1999).

Nitric Oxide

Oxidative stress has been implicated in the pathogenesis of apoptosis, cancer, diabetes, hypertension, and inflammation. This implies that it may be a final common pathway by which numerous diseases exert their harmful effects. The contribution of NO to liver injury and apoptosis is complex. NO is a lipophilic, short-lived molecule (with a half-life of seconds) that physiologically seems to have roles in vasodilation, immune response, apoptosis, and protection of cells from oxidative killing (Wink et al, 1999). NO derived from NO synthase originating in endothelial cells and other nonparenchymal liver cells seems to be hepatoprotective in most cases (Ou et al, 1997). NO from inducible NO synthase (iNOS) in hepatic parenchymal cells can either damage or protect hepatocytes. Upregulation of iNOS occurs after stimulation by endotoxin and by cytokines such as IL-1b (Kitade et al, 1996; Zamora et al, 2000). Depending on the level of redox stress, iNOS can cause detrimental effects, such as direct cytotoxicity and suppression of hepatic protein synthesis, in a manner similar to the septic state (Taylor et al, 1998; Chen et al, 2003). After resuscitation from profound hemorrhagic shock, iNOS can also mediate activation of NF-κB and increases in IL-6 expression, which leads to acute liver injury followed by recovery (Hierholzer et al, 1998).

Alternatively, with lower redox states, NO plays a cytoprotective role by suppressing apoptosis in hepatocytes and reducing mitochondrial dysfunction to limit liver injury (Brookes et al, 2000; Wang et al, 2002; Chen et al, 2003). NO exerts its cytoprotective effect during acute inflammation by suppressing caspase activation, inducing heat shock proteins (Kim et al, 1997), upregulating hemoxygenase-1 (Zamora et al, 2000), and activating the cyclic guanosine monophosphate signal pathway to interrupt apoptosis (Kim et al, 1997; Wang et al, 2002; Chen et al, 2003). NO can act as an electron acceptor for S-nitrosylation, which can alter the catalytic site of caspases and render them inactive (Li et al, 1997). NO also can induce the expression of heat shock proteins 70 and 32 (Kim et al, 1995; Li et al, 2000). These proteins may function by refolding damaged proteins in the liver, modulating caspase activation, and regulating expression of hemoxygenase-1, an inducible enzyme that catalyzes the degradation of heme into biliverdin, releasing carbon monoxide as a by product, which is thought to confer local antiinflammatory effects (Otterbein et al, 2000). NO also can bind soluble guanylyl cyclase, which can increase intracellular cyclic guanosine monophosphate, suppressing apoptosis and caspase activity (Lucas et al, 2000). Which particular mechanism predominates likely depends on the specific circumstances (Chen et al, 2003). To delineate further the effect of NO on hepatocytes, Wang and others (2002) are continuing to evaluate genetic changes using DNA microarray and large-scale proteomic analysis.

Liver Regeneration

The liver's ability to regenerate is a unique quality that is essential for its functions of controlling metabolism and detoxification (see Chapter 5). This capability to fully regenerate after insult differs significantly from other organs, which heal with scar (Fausto et al, 2006; Michalopoulos et al, 2007). However, in certain chronic liver injury states, the liver's regenerative capacity can be insufficient, leading to the replacement of functional epithelial tissue with connective tissue and to development of cirrhosis. A thorough understanding of the mechanisms and factors by which liver regeneration takes place is important in developing therapies to enhance regenerative capacity and prevent cirrhosis.

It has been shown that humoral factors are required, because hepatectomy in a rodent joined in parabiotic circulation results in proliferation and regeneration of the intact liver from the other member of the pair (Moolten & Bucher, 1967). This work provides convincing evidence that some mitogenic factor or factors are released into the peritoneal or systemic circulation during liver regeneration. Studies with recombinant proteins, cytokine inhibitors, and transgenic mice have convincingly shown that at least three cytokines—TNF-α, IL-6, and hepatocyte growth factor—play crucial roles in this regenerative process (Michalopoulos & DeFrances, 1997). The regenerative process of the liver can be divided into three phases: 1) initiation, 2) expansion, and 3) termination (Zimmermann et al, 2004) and is discussed elsewhere (Chapter 5). However, cytokines and growth factors play a significant role. The initiation phase is regulated by cytokines such as IL-6 and TNF-α, the expansion stage is regulated by mitogenic factors such as hepatocyte growth factor, and the termination phase is where mitosis stops, and sometimes apoptosis begins to control overgrowth. Additional cytokines, TGF-β and EGF, also may have roles. The TGF-β superfamily of cytokines appears to play a significant role in maintaining embryonic stem cell identity, and the differentiation of pancreas and liver progenitor cells is restricted by this pathway (Wandzioch & Zaret, 2009).

Several converging lines of evidence suggest that TNF-α, and particularly its signaling through the type I receptor, is essential for liver regeneration. Treatment of animals with neutralizing antibodies against TNF-α delays regeneration and decreases DNA synthesis (Yamada et al, 1997). DNA synthesis is also impaired after partial hepatectomy in TNF-receptor type I knockout mice. Whether these defects are due directly to the effects of TNF-α or are mediated through TNF-α–dependent expression of other mediators, including IL-6, is not fully understood, because treating TNF-receptor type I knockout mice with exogenous IL-6 corrects this delay in regeneration.

The role of IL-6 in hepatic regeneration also has been established (Drucker et al, 2010). Plasma IL-6 concentrations increase after partial hepatectomy, peaking within 24 to 48 hours (Matsunami et al, 1992; Rai et al, 1996). Although it is controversial whether IL-6 is directly mitogenic for hepatocytes in culture, it is clear that IL-6 is mitogenic for biliary epithelial cells (Matsumoto et al, 1994), and the absence of IL-6 delays regeneration in vivo (Cressman et al, 1996). Hepatocyte DNA synthesis after a partial hepatectomy is suppressed in IL-6 knockout mice. A recent randomized trial suggested a beneficial effect of pentoxifylline, a TNF-α inhibitor, on liver regeneration that seems to be IL-6 mediated (Petrowsky et al, 2010). IL-6 expression required for a normal regenerative response seems to depend on NF-κB translocation. NF-κB–dependent pathways are required to protect hepatocytes from TNF-α–mediated apoptosis. Studies from several groups have shown that inhibition of TNF-α–mediated NF-κB activation exaggerates apoptotic pathways initiated by TNF-α and FasL. Xu and colleagues (1998) noted that blocking NF-κB in RALA hepatocytes resulted in TNF-α–mediated apoptosis. Actinomycin D pretreatment of the same cells also promoted TNF-α apoptosis but did not prevent NF-κB translocation. Actinomycin D prevented the transcription of NF-κB–induced genes in response to TNF-α. In addition, inhibition of NF-κB using an inhibitory adenoviral vector in the livers of mice after hepatic resection produces massive apoptosis and liver failure (Iimuro et al, 1998). Taken together, these findings suggest that blockade of NF-κB–dependent transcription of certain genes in hepatocytes during liver regeneration results in TNF-α–mediated apoptosis.

PATHOGENESIS OF ENDOTOXIN AND CYTOKINES IN LIVER, BILIARY, AND PANCREATIC DISEASE

Endotoxemia and Bacterial Translocation

Bacterial translocation has been defined as the process by which viable enteric bacteria cross the intestinal mucosal barrier to mesenteric lymph nodes and remote organs and tissues (Lemaire et al, 1997; MacFie, 1997). Because the bowel contains massive amounts of viable, pathogenic bacteria and endotoxin, several physiologic mechanisms must be disrupted for bacterial translocation to occur.

The exact mechanisms by which bacterial translocation occurs through the intestinal mucosa are not fully known. Electron microscopy has revealed bacteria penetrating epithelial cells. Most of the bacteria are phagocytosed by macrophages, but free bacteria can be recovered from the portal circulation and the lymphatics. Nonpathogenic obligate anaerobic organisms, the mucosal barrier, and an efficient reticuloendothelial system all act in concert to reduce the frequency of pathogenic bacterial translocation.

For bacterial translocation to occur, several perturbations must take place simultaneously. Alterations in the composition of the gut flora as a result of malnutrition, antibiotic use, changes in bile production, or intestinal stasis all predispose the patient to bacterial translocation. Similarly, drugs or diseases that alter the integrity of the mucosal barrier increase the risk of bacterial translocation. Chemotherapeutic agents can reduce secretory IgA levels by inhibiting the antimicrobial function of immune cells. Total parenteral nutrition, chemotherapeutic agents, direct injury secondary to shock, and reperfusion injury can all increase bacterial translocation.

Endotoxemia itself can further promote bacterial translocation, possibly suggesting an amplification cascade. Endotoxemia frequently produces hypoperfusion of the splanchnic bed, leading to decreased perfusion of the distal ileum and cecum and increased intestinal permeability. In mice, administration of endotoxin induced bacterial translocation, which could be blocked by inhibitors of xanthine oxidase activity (Deitch et al, 1989a, 1989b, 1989c). In humans, low-dose endotoxin administration increases urinary excretion of orally administered D-mannitol, suggesting a reduction in gut barrier function (O'Dwyer et al, 1988).

Bacterial translocation has been proposed to occur in acute necrotizing pancreatitis (Fritz et al, 2010) and numerous biliary diseases, including obstructive jaundice, cirrhosis, portal hypertension, and alcoholic hepatitis (Nehez & Andersson, 2002; Wiest & Garcia-Tsao, 2005). Although the measurement of endotoxin in the blood of patients using current assays is problematic, increased appearance of endotoxin in the systemic circulation is a reproducible event. Several investigators have postulated that endotoxemia and bacterial translocation are the "engines" that drive the systemic inflammatory response syndrome in liver disease (Szabo et al, 2002).

Systemic endotoxemia rarely occurs in patients without liver disease or sepsis. In patients with cirrhosis, alcoholic hepatitis,

or obstructive jaundice, systemic appearance of endotoxin has been reported in as many as 70% of patients. Increased levels are also associated with adverse outcomes (Hanck et al, 1998; Kimmings et al, 1995). One hypothesis for obstructive jaundice is that the absence of bile secretion leads to endotoxemia, because enteric biliary drainage of bile salts reduces the absorption of endotoxin (Kimmings et al, 1995, 2000).

The liver is the primary site of endotoxin uptake and detoxification from the blood. Clearance of endotoxin by the liver is greater from the portal enteric drainage than from the hepatic artery. Considerable experimental and clinical evidence suggests that the increased systemic appearance of endotoxin seen in patients with liver and biliary tract disease is the result of increased enteric absorption and reduced clearance from the hepatic reticuloendothelial system (Kimmings et al, 1995). Increased endotoxemia has been reported in patients with cirrhosis, acute hepatic failure, severe hepatitis B and C infections, and obstructive jaundice. In many cases, the appearance of endotoxemia in fulminant hepatic failure correlates strongly with liver disease severity, coexisting renal failure, and mortality. Endotoxin is detected at a higher frequency in the circulation of patients with cirrhosis who exhibit ascites, renal dysfunction, and portocaval shunting, and endotoxemia is a predictor of adverse outcome (Kimmings et al, 1995), although endotoxin can bypass the liver directly via the lymphatics. In rats subjected to a cecal ligation and puncture, endotoxin appearance in the thoracic lymph duct was higher by a factor of several hundred than in the portal blood, suggesting that lymphatic flow may represent a significant source for the systemic circulation (Olofsson et al, 1986).

Pathogenesis of Proinflammatory Cytokines

Convincing circumstantial evidence shows that increased TNF-α–mediated and FasL-mediated apoptosis contributes to hepatocyte injury in chronic hepatitis C infections and in alcoholic hepatitis. Increased TNF-α and FasL expression has been detected in liver biopsy specimens from patients with hepatitis C infections (Fukuda et al, 1995; Larrea et al, 1996), presumably localized to infiltrating inflammatory cells (Kupffer, T, and natural killer cells). In addition, patients with chronic hepatitis B and C often have elevated plasma TNF-α concentrations and occasionally have increased soluble Fas and FasL concentrations. Plasma concentrations of the shed TNF receptors are commonly elevated in chronic hepatitis B and C infections, and levels frequently correlate with the extent of inflammation and hepatocyte death.

Increased hepatocyte apoptosis also has been detected in livers from patients with chronic hepatitis C (Bantel et al, 2004; McPartland et al, 2005). Anti–TNF-α agents administered to mice infected with chronic hepatitis C appear to be antiviral by promoting apoptosis and preventing regeneration of hepatocytes (Brenndorfer et al, 2010). Similarly to plasma TNF-α levels, IL-6 and endotoxin levels are both increased in patients with alcoholic hepatitis, and concentrations often correlate with mortality (Bird et al, 1990; Khoruts et al, 1991; Naveau et al, 1998; Sheron et al, 1991). Peripheral blood monocytes from patients with alcoholic cirrhosis spontaneously release more TNF-α and IL-6 than monocytes from healthy adults, and they do so in response to ex vivo endotoxin stimulation (Schafer et al, 1995). One explanation for this increased endotoxemia and TNF-α expression is that ethanol consumption increases the permeability of the gut to bacterial products such as endotoxin, potentially inducing TNF-α and FasL expression in the liver.

Several reports have shown elevated levels of TNF-α, its shed receptors, and IL-6 in animals and patients with obstructive jaundice (Kimmings et al, 1995). In animal models of experimental biliary obstruction, TNF mRNA expression in the liver is increased, and plasma concentrations rise (Beierle et al, 1996). These animals produce more TNF-α after a surgical injury than do healthy mice, and the increased production correlates with an adverse outcome (Bemelmans et al, 1992, 1993). In patients with obstructive jaundice, elevated TNF-α production by peripheral blood mononuclear cells also has been detected (Kimura et al, 1998; Puntis & Jiang, 1996).

There is considerable controversy regarding the increased level of circulating TNF-α and whether it is biologically active, because many assays only detect total TNF-α. The shed receptors of TNF-α are natural inhibitors of TNF-α bioactivity, and their concentrations also increase in patients with obstructive jaundice. Shedding of the TNF receptors may represent a protective mechanism to reduce the pathologic responses to TNF-α by binding and blocking their interaction with cellular receptors, and binding of TNF-α to its shed receptor may facilitate its clearance by the kidneys. In mice with jaundice, the concentrations of the shed receptors are increased (Bemelmans et al, 1996), and similar findings are seen in patients with obstructive liver disease (Kimmings et al, 1995).

Serum IL-6 levels are significantly higher in patients with biliary obstruction compared with control subjects (Akiyama et al, 1998; Kimura et al, 1999; Puntis & Jiang, 1996; Yamashiki et al, 1998). In one study, serum IL-6 levels decreased significantly after drainage (Akiyama et al, 1998). Patients with elevated serum IL-6 levels had lower serum levels of total protein and albumin, higher mean age, and more frequent positive cultures of bile compared with patients with lower serum IL-6 levels.

Cytokines in Ischemia-Reperfusion Injury

Visceral ischemia and reperfusion are frequent occurrences during hepatobiliary surgery, liver transplantation, trauma surgery, aortic surgery, and mesenteric vascular surgery and can lead to pulmonary and hepatic injury and multiorgan failure. Elective hepatic resection in particular is often performed using portal inflow occlusion with intermittent periods of reperfusion, which potentially reduces blood loss during the resection but can result in hepatocellular damage. I/R injury is associated with release of TNF-α and other proinflammatory cytokines (Colletti et al, 1996; Liu et al, 2000). In rats, intestinal ischemia of 120 minutes followed by reperfusion for 30 minutes was associated with 10-fold increases in circulating TNF-α over controls, which were transient and cleared by 60 minutes of reperfusion (Caty et al, 1990). Blocking TNF-α or IL-1 could mitigate the degree of organ damage (Welborn et al, 1996). After ischemia, gut-derived endotoxin was detected in the portal vein, which preceded the appearance of TNF-α in systemic plasma (Caty et al, 1990). I/R injury is also associated with activation of the oxidant-sensitive TNF transcription factor, NF-κB (Donnahoo et al, 2000; Yoshidome et al, 1999). Studies in mice demonstrate that reperfusion of ischemic liver tissue causes a series of events that include superoxide anion generation and NF-κB–mediated expression of injurious and

protective mediators that favor injury (Abe et al, 2009). IL-10 seems to protect against acute lung injury that can occur after hepatic I/R injury (Huber et al, 2000; Welborn et al, 2003; Yoshidome et al, 1999). Hemoxygenase-1 also has been shown to reduce I/R injury in an ex vivo liver transplant model in rats (Amersi et al, 1999), and low-dose carbon monoxide has been shown to be hepatoprotective (Amersi et al, 2002).

In humans, thoracoabdominal aortic aneurysm repair necessitates complete occlusion of the thoracic aorta above the celiac artery for 20 minutes to more than 1 hour, which is associated with pulmonary and renal dysfunction, consumptive coagulopathies, and mortality of 15% (Derrow et al, 2001; Rectenwald et al, 2002). For patients undergoing thoracoabdominal aortic aneurysm repair, visceral I/R is also associated with proinflammatory cytokine release (Welborn et al, 2000). Compared with patients undergoing infrarenal abdominal aortic aneurysm repair, in which the viscera remain perfused, patients undergoing thoracoabdominal aortic aneurysm repair had elevated levels of TNF-α, IL-6, IL-8, and IL-10 and the TNF receptors p55 and p75 (Welborn et al, 2000). The postoperative cytokine response was associated with the duration of visceral ischemia, and when left atrial femoral bypass was used to reduce ischemia time, the systemic TNF-α, p75, and IL-10 responses were attenuated. Patients with early and sustained peaks of IL-6 and TNF-α were more likely to develop multisystem organ failure.

Microarray technology and multiplex protein analyses were used on blood leukocytes and plasma in 10 patients to identify adverse clinical outcomes after thoracoabdominal aortic aneurysm repair with its requisite I/R injury (Feezor et al, 2004). From roughly 30,000 genes, changes in 146 correlated with an adverse clinical outcome. Several—such as monocyte-to-macrophage differentiation-associated factor, matrix metalloproteinase-8, and platelet factor 4—are involved in the innate immune response. Others are associated with a general stress response and cytoprotection, such as the upregulation of heat shock proteins; several genes involved with major histocompatability complex (MHC) class I were downregulated. Many of the differences seen in patients who eventually would develop multiorgan dysfunction were evident preoperatively, suggesting a preexisting proinflammatory state in these patients with diseased vasculature (Feezor et al, 2004).

Cytokines in Ablation of Hepatic Tumors (See Chapters 83 and 85)

For resectable primary and metastatic tumors, resection remains the standard of care (Blumgart & Fong, 1995; DeMatteo et al, 1999). However, several ablative techniques have been described, which by definition leave tumor debris in situ and can elicit a complex immunologic response. Cryoablation entails the use of metallic probes cooled with liquid nitrogen and placed into the tumor or on the liver surface (Chapman et al, 2000). Freezing of the tumor tissue results in obliteration of small vessels and disruption of hepatocyte plasma membranes (Chapman et al, 2000). In early clinical series, approximately 1% of patients treated with cryoablation developed "cryoshock," a syndrome characterized by acute respiratory distress syndrome, multiorgan failure, and disseminated intravascular coagulation; it results in death in nearly 20% of patients who develop it (Seifert & Morris, 1999). This complication, now rarely seen, was noted to be dose dependent, such that the risk increases proportionately with the volume of treated liver, and especially when more than 30% of the total hepatic volume is cryoablated (Chapman et al, 2000; Sarantou et al, 1998). This process seems to be mediated by NF-κB, which becomes activated, and transcription of TNF-α and other cytokines is increased (Barnes & Karin, 1997; Blackwell et al, 1999; Chapman et al, 2000; Seifert et al, 2002).

Radiofrequency ablation (RFA) involves the dispersal of heat around a needle passed into a tumor to cause coagulative necrosis. The technology behind this technique is limited by a smaller zone of ablation, which prevents its use in larger tumors (Chapman et al, 2000). In contrast to cryoablation, after treatment with RFA, liver cell organelles undergo thermal coagulative destruction, but the plasma membrane stays intact (Chapman et al, 2000). In rodent models in which the size of the ablation was controlled, rats treated with RFA had markedly diminished lung inflammation and lower TNF-α and macrophage inhibitory protein-2 levels (analogous to human IL-8) compared with rats treated with cryoablation (Chapman et al, 2000; Ng et al, 2004). In a study of 17 patients undergoing RFA, production of cytokines (TNF-α, IL-1b, IL-1Ra, IL-6, IL-8, and IL-10) and the TNF cytokine receptors (p55 and p75) was not altered at any time within the first 48 hours after the procedure (Schell et al, 2002). When stimulated with endotoxin (LPS), blood samples from the same patients showed normal ability to elaborate cytokines, suggesting that the absence of cytokine production after RFA was not related to the patients' underlying disease or inability to produce cytokines but rather was due to thermal coagulation of hepatocytes (Schell et al, 2002).

Microwave ablation is a more recently developed technology that is being used with increasing frequency to treat liver tumors. Microwave ablation involves application of microwaves directly to liver tissue to produce rapid temperature elevations and cause coagulative necrosis. Zhang and colleagues (2002) demonstrated a significant increase in T cells, NK cells, and monocytes in microwave-ablated hepatocellular patients. This response was maximal at day 3 but persisted to day 30. Interestingly, patients with a higher degree of immune cell infiltration had lower recurrence rates, similar to RFA patients (Hansler et al, 2006).

FUTURE DIRECTIONS

Over the past two decades, cytokines have been the subject of intense research, particularly from pharmaceutical companies. As a result of both academic and industrial interest, several agents are currently available that either stimulate cytokine activity or block their effects to treat cancer, infectious disease, inflammatory disorders, and autoimmunity.

Although it is clearly premature to celebrate the widespread use of cytokine or anticytokine therapies for patients with liver, biliary, or pancreatic disease, research is certainly heading in that direction. Several treatment modalities that offer the opportunity to interrupt endotoxin and the proinflammatory cytokine responses in liver disease remain of considerable interest. Antiendotoxin therapies are of particular interest in obstructive jaundice and acute alcoholic hepatitis. In chronic viral hepatitis, in which increased TNF-α–mediated and FasL-mediated apoptosis are presumed to occur, enthusiasm remains for the opportunity to intervene with either immunoadhesins or antibodies. The clinical use of antiinflammatory cytokines, such

as IL-10, is likely to occur at some point in the near future, although the risk of added immunosuppression remains a concern. The pegylated form of IFN-α, which has greater stability and in vivo activity than IFN-α alone, has substantially improved viral response rates in hepatitis C patients (see Chapter 64). As a result, it is now considered the standard of care for treatment of hepatitis C and may also have some efficacy in hepatitis B patients.

The greatest excitement, however, has been focused on the availability of antiendotoxin and cytokine therapies currently being used for other disease states that may eventually be utilized for diseases of the liver, biliary system, or pancreas.

Antiendotoxin antibodies have been evaluated in patients with sepsis, generally with disappointing results. Although concerns have been raised about the neutralizing capacity and specificity of some of these antibodies, the lack of efficacy could be explained in part by the inadequate selection of patients and the timing of administration. Only a fraction of the patients receiving antiendotoxin therapies were actually endotoxemic, and the administration of the antibody usually occurred 12 to 24 hours after the onset of symptoms. Recently, focus has been placed on the development of antiendotoxin vaccines, which likely will be tested in Phase I human trials soon (Cross, 2010). An alternative approach is recombinant BPI. In human volunteers treated with low-dose endotoxin, recombinant BPI administration reduced the proinflammatory cytokine responses and activation of the fibrinolytic and coagulation pathways (von der Mohlen et al, 1995). Recombinant BPI continues to be under U.S. Food and Drug Administration (FDA) investigation for its potential use in children with meningococcal sepsis (Levin et al, 2000). Although the results of this trial indicated a trend toward a survival benefit, this study was underpowered to detect significant differences in mortality. In rats subjected to a partial hepatectomy, recombinant BPI reduced liver injury and the magnitude of the inflammatory response (Kimmings et al, 1999).

Another group of cytokine modulators being utilized to treat other diseases are TNF-α blockers. Three TNF-α blocking agents—etanercept (Enbrel), adalimumab (Humira), and infliximab (Remicade)—have received FDA approval for rheumatoid arthritis. TNF-α blockers are also currently the cornerstone of therapy for inflammatory bowel disorders, particularly infliximab and adalimumab. Recombinant human IL-1Ra, anakinra (Kineret), a potent inhibitor of IL-1, is currently approved for the treatment of rheumatoid arthritis.

Although most of the cytokine and anticytokine therapies currently in use are not specifically indicated for liver, biliary, or pancreatic disease, much information about their effects will be learned in the coming years, and some of these therapies may well emerge as effective therapies in patients with inflammatory, neoplastic, or other hepatopancreatobiliary disorders. A recent phase I/II trial of intratumoral injections of TLR-2 and TLR-6 antagonists for R2 resected pancreatic adenocarcinoma shows a possible increased survival, but larger trials will be needed (Schmidt et al, 2007). Preclinical studies indicate that TLR-3 antagonists may delay the development of pancreatic cancer (Schwartz et al, 2009). The now common use of TNF-α and pegylated IFN demonstrate the potential application of cytokine therapy to liver disease. The liver's complex interplay of metabolism, immunology, cytokine productivity, and regenerative capacity make it ideally suited for the development of cytokine-directed therapies.

References are available at expertconsult.com.

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CHAPTER 11

Infections in liver, biliary, and pancreatic surgery

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INFECTION

Infection is defined as a pathologic state resulting from invasion of the body by pathogenic microorganisms—bacteria, yeast, parasites, or viruses. These agents can challenge host defense mechanisms because of either an infectious organism's virulence or a weakness in host defenses. In most instances, infection results when normal host defense mechanisms fail to prevent tissue penetration and the subsequent local propagation and/or systemic dissemination of the injurious agent. All infections can be complicated by sepsis, which is the invasion of a micoorganism or its toxins into the bloodstream, coupled with the host response to that invasion. More specifically, *sepsis* is a systemic inflammatory response syndrome caused by infection (American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee, 1992). When sepsis remains untreated, altered host inflammatory and coagulation cascades—intracellular homeostasis, cellular hypoxia, endothelial dysfunction, apoptosis, and eventually cardiovascular collapse—lead to multiorgan failure and death. Despite recent advances in treatment (Rivers et al, 2001), the incidence of sepsis and septic shock has been increasing (Angus et al, 2001). Furthermore, the associated mortality rate remains at 30% among all septic patients, with rates increasing to 85% in the setting of multiple organ failure (Angus et al, 2001).

Patients undergoing hepatopancreatobiliary surgery are at particular risk for infection and sepsis because of the severity of their disease process, often complicated by comorbid medical conditions and exacerbated by the stress of the surgical treatment itself. Hepatopancreatobiliary diseases that place patients at particular risk include infected necrotizing pancreatitis and sepsis associated with uncontrolled leakage from pancreatic–enteric anastamosis following pancreatoduodenectomy (Howard et al, 2007; Adams, 2009). This chapter reviews the applicable host defense mechanisms as well as their alteration by hepatopancreatobiliary diseases and operations.

HOST DEFENSES

The host defense mechanisms preventing the entry of infectious organisms into the liver, biliary tract, and pancreas can be organized into three broad categories (Krige & Bornman, 2000): *physical, chemical,* and *immunologic* (Table 11.1). Although these mechanisms are distinct, significant overlap occurs. Furthermore, optimal defense often requires coordination of all three systems.

Infectious microorganisms can enter the liver either hematogenously or retrograde via the biliary ductal system. The most common hematogenous route of infectious entry is the portal venous system. Under normal circumstances, the portal system drains all abdominal gastrointestinal venous blood directly into the liver before it enters the systemic circulation. As a result, portal venous blood typically contains enteric pathogens and toxins, which are cleared and neutralized by the liver (see Chapter 9). This activity is primarily regulated by Kupffer cells, which act as the resident hepatic macrophages. Consequently, Kupffer cells are not only important determinants of normal hepatic physiology and hemostasis but also of any inflammatory response. The liver therefore acts as the ultimate barrier to infection for all gastrointestinal tract and peritoneal cavity microorganisms attempting to access the systemic circulation. Perturbation of this flow, in particular portal venous obstruction, may occur from causes that are *presinusoidal* (portal vein thrombosis, surgery, trauma, cancer), *sinusoidal* (hepatitis, cirrhosis), or *postsinusoidal* (Budd-Chiari syndrome, right heart failure). Such obstructions often lead to portal hypertension with subsequent portosystemic shunting (see Chapter 70A). This new access to the systemic circulation allows a bypass of the liver's defenses against enteric pathogens and toxins, thereby increasing the risk of bacteremia and sepsis. Although less common, direct hematogenous spread of microorganisms to the liver may also occur via the hepatic arterial system (e.g., bacterial endocarditis, intravenous drug use).

Under normal circumstances, an intact sphincter of Oddi provides an effective mechanical barrier that prevents bacteria and other enteric organisms from entering the liver (retrograde) via the biliary system (see Chapter 1B). Ascending infection from the intestine can access the biliary tree when the sphincter mechanism is destroyed, endoscopically or surgically; bypassed, as in a biliary-enteric anastomosis; or violated, such as via a transsphincteric stent. The biliary system can also be directly contaminated by percutaneous access via either the transhepatic route or with operatively placed drains (e.g., T-tubes). Fortunately, the presence of bacteria within bile does not uniformly result in an ascending biliary infection, because the main physical barrier to biliary sepsis remains: intrahepatic tight junctions (Fig. 11.1), which form a barrier between bile canaliculi and hepatic sinusoids and act to keep bile separated from the bloodstream. Under pathologic conditions, mixing of these two compartments can result in seeding of biliary organisms into the hepatic blood supply. Another physical hepatic defense mechanism is the flow of bile itself. Bile is produced by hepatocytes and excreted into bile canaliculi, which then coalesce to form larger ductules, major sectoral ducts, and ultimately extrahepatic biliary ducts. Bile flow out of the liver helps prevent ascending infection by its mechanical flushing action; however, interruption of flow via obstruction or stasis reduces this protective mechanism (see Chapter 43).

Table 11.1

Hepatobiliary and Pancreatic Host Defense Mechanisms

	Hepatobiliary	Pancreatic
Physical	Biliary sphincter	Pancreatic sphincter
	Hepatic tight junctions	Pancreatic tight junctions
	Bile flow	Pancreatic juice flow
	Mucus	Mucus
	Cilia	Cilia
Chemical	Bile salts	Pancreatic fluid
Immunologic	Kupffer cells	—
	Immunoglobulin A	Immunoglobulin A
	Fibronectin	—
	Complement	Complement
	CD40 receptor	CD40 receptor
	Blood supply	Blood supply

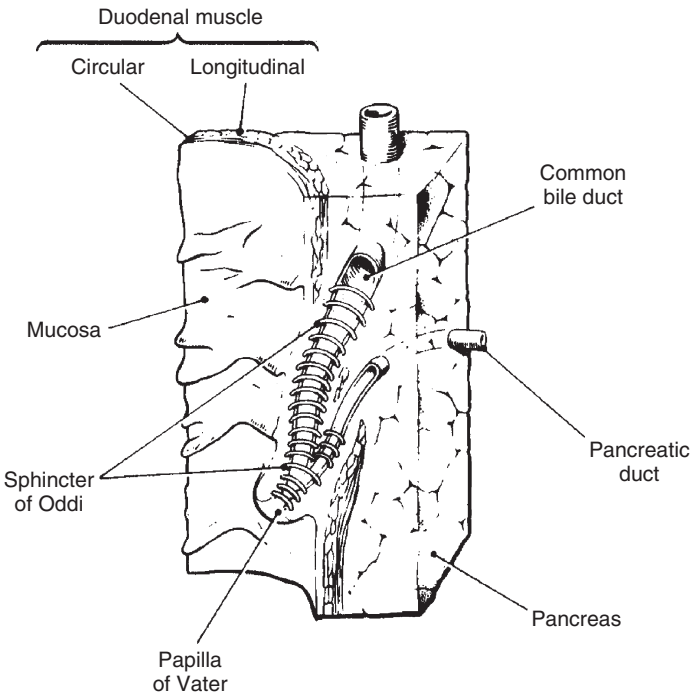


FIGURE 11.2. Schematic representation of the sphincter of Oddi in the human, showing the circular muscle (sphincter) that surrounds the termination of the common bile duct and pancreatic duct. The pancreatic duct has a shorter sphincter than the bile duct; most of the sphincter lies within the wall of the duodenum. *(From Touli J, 1984: Sphincter of Oddi Motility. Br J Surg 71:251.)*

As previously discussed, the main physical host defense against the reflux of enteric contents, and adherent bacteria, into the biliary system is the biliary sphincter within the sphincter of Oddi (Fig. 11.2; see Chapter 1). Similar to the liver, bile flow also assists the biliary system by flushing and helping prevent free reflux of duodenal contents into the extrahepatic ducts. The bile duct epithelium within the ductules has a single cilium, which facilitates propulsion of bile toward the extrahepatic biliary ducts (Gilroy et al, 1995; Itoshima et al, 1977). Bile flow is further propelled toward the duodenum by gallbladder contraction. A final physical barrier within the biliary tract is mucus produced by the epithelial cells throughout the extrahepatic bile ducts. Mucus promotes distal flow by preventing adherence of bacteria and debris to the epithelial cell membrane (see Chapter 7).

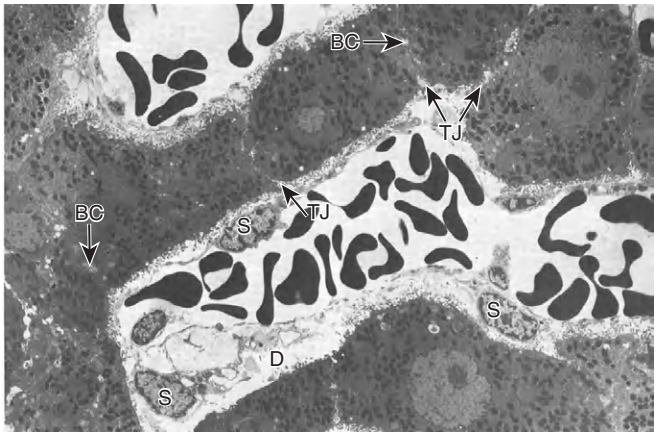


FIGURE 11.1. Electron micrograph shows the main ultrastructural features of the liver. Each hepatocyte is bathed on at least two sides by blood in the sinusoids, which are lined by a discontinuous layer of sinusoid lining cells (*S*) supported by the fine reticular framework of the liver such that a space, *the space of Disse* (*D*), remains between the lining cells and the hepatocyte surface. Because the sinusoid lining cells form a discontinuous layer, the space of Disse is continuous with the sinusoid lumen, and numerous irregular microvilli extend into it from the hepatocyte surface, greatly increasing the plasma membrane surface available for bidirectional exchange of metabolites between liver and blood. Bile canaliculi (*BC*) are formed from the plasma membranes of adjacent hepatocytes; these membranes are bound by tight junctions *(TJ)*; small microvilli project into the canaliculi. *(From Wheater PR, et al, 1985: Functional Histology. New York, Churchill Livingstone, p 206.)*

Similar to the biliary system, the main physical host defense mechanism for the pancreas is the pancreatic sphincter within the sphincter of Oddi. Although a true anatomic pancreatic sphincter is present in only one third of patients, all normal glands have a pressure zone at the end of the pancreatic duct that relaxes in response to secretin (Carr-Locke et al, 1985). This pressure zone prevents reflux of enteric contents into the pancreatic ductal system. Similar to the liver, the pancreas also contains paracellular seals or tight junctions between acinar and intralobular ductal epithelial cells. The integrity of the pancreatic tight junctions can be compromised, however, in experimental states of inflammation or pancreatitis, and possibly when ductal pressures are elevated (Fallon et al, 1995; Schmitt et al, 2004). The pancreatic ductal system is also aided by the flow of pancreatic duct fluid (flushing) to prevent reflux of duodenal contents. To facilitate this flow, the epithelium in the secondary ducts has a single cilium (Fig. 11.3) that propels secretion into the main pancreatic ductal system. Similar to the biliary system, the pancreatic ductal epithelium also secretes mucus, which acts as a barrier to the adherence of bacteria and debris (Moniaux et al, 2004; Trede & Carter, 1997).

Chemical host defense mechanisms also exist in the hepatic and pancreatobiliary systems. Bile salts within the biliary ducts have been shown to have bacteriostatic and bactericidal properties (Stewart et al, 1986; Sung et al, 1993). The maintenance of intestinal flora by bile salts is also crucial to host defenses,

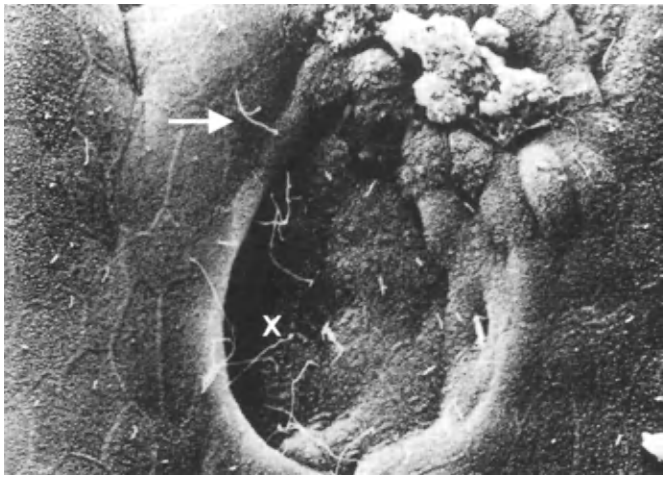


FIGURE 11.3. Electron micrograph of cat pancreatic duct showing surface contours of individual epithelial cells, some of which possess a solitary cilium (*arrow*) that protrudes into the lemen of the duct. The point of entry (*X*) of a tributary duct is shown. *(From Trede M, Carter DC, 1997: Surgery of the Pancreas, 2nd ed. New York, Churchill Livingstone.)*

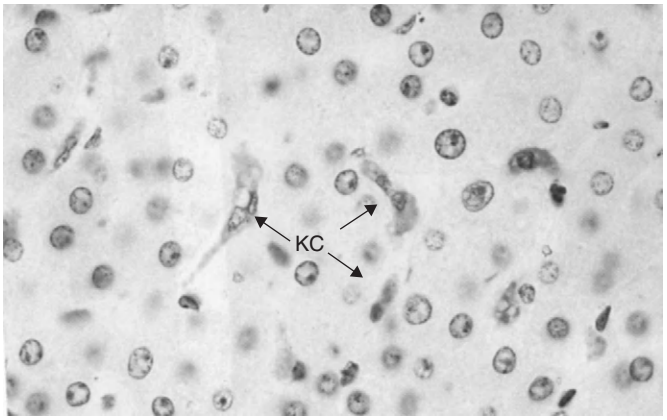


FIGURE 11.4. The sinusoidal macrophages can be distinguished from endothelial cells by the presence of histiocyte markers. This immunostain for lysozyme shows the positive Kupffer cells (*KC*). *(From Ishak KG, et al [eds], 2001: Tumors of the Liver and Intrahepatic Bile Ducts. Washington, DC, Armed Forces Institute of Pathology, p 4.)*

because bile salts have the ability to suppress pathogenic bacteria that threaten the integrity of the mucosal barrier, and they promote translocation of bacteria into the portal circulation (Bradfield, 1974; Clements et al, 1993; Deitch et al, 1990). Conditions of either bile salt loss or administration of prolonged courses of antibiotics may interfere with the balance of the intestinal flora and weaken this important host defense. Bile salts have also been shown to have antifungal effects, particularly against *Candida albicans* (Marshall et al, 1987). Furthermore, their trophic impact on epithelial cells increases both their integrity and ability to withstand insult from infectious pathogens (Stewart et al, 1986). Finally, bile salts posses an antiendotoxin effect (Stewart et al, 1986).

Pancreatic ductal fluid also contains inherent antibacterial properties (Rubinstein et al, 1985) independent of its enzymatic activity. Data suggest this fluid is bactericidal against multiple bacteria, including *Escherichia coli, Shigella* and *Salmonella* species, and *Klebsiella pneumoniae* (Kruszewska et al, 2004). Pancreatic fluid is also bacteriostatic against *Staphylococcus aureus, S. epidermidis,* and *Pseudomonas aeruginosa;* however, *Bacteroides fragilis* and *Streptococcus faecalis* are resistant to effects of pancreatic ductal fluid (Rubinstein et al, 1985). According to studies in swine, the antibacterial activity of pancreatic fluid appears to be independent of digestive enzymes. It is highest before eating and lowest during digestion of food, suggesting regulation through alternative signaling pathways (Holowachuk et al, 2004). By virtue of its antibacterial properties, pancreatic ductal fluid also regulates the colonization of enteric bacteria throughout the intestine by allowing the flora to maintain a normal homeostatic balance (Kruszewska et al, 2004).

In addition to its antibacterial effects, pancreatic ductal fluid appears to enhance the inherent action of certain bactericidal antibiotics (e.g., quinolones, trimethoprim, chloramphenicol, tetracycline) in studies comparing microbiologic media with those containing pancreatic ductal fluid (Mett et al, 1984). This enhanced activity has been shown toward many species of bacteria, including *E. coli, Salmonella, Serratia, Proteus,* and *Staphylococcus.* An unidentified, low-molecular-weight factor (independent of complement or lysozyme) in the pancreatic ductal fluid has been implicated (Mett et al, 1984). Although this factor is unknown, reproducible data show enhanced antibacterial activity in combination with commonly employed antibiotics, such as mezlocillin, ceftriaxone, gentamicin, ciprofloxacin, ofloxacin, and imipenem (Minelli et al, 1996). The relative degree of enhanced activity from pancreatic juice also depends on the specific bacteria (Minelli et al, 1996). Pancreatic ductal fluid contains fungistatic properties, in particular toward *C. albicans* (Kruszewska et al, 2004; Rubinstein et al, 1985), as well as growth factors (e.g., epidermal growth factor) that have a trophic effect on pancreatic epithelial cells. This helps preserve their integrity to pathogens (Alvarez et al, 1997). It is unknown whether pancreatic ductal fluid offers any antiendotoxin effects.

Immunologic host defense mechanisms also exist in the hepatic and pancreatobiliary systems. Hepatic cellular defense is provided by a large phagocyte population termed *Kupffer cells* (Fig. 11.4) as well as a plethora of other immunologically active cells (see Chapters 9 and 10). Kupffer cells are strategically located in the sinusoids of the liver, where they filter endotoxins from the gut, phagocytose bacteria, regulate sinusoidal vascular responsiveness, process and present antigens to T cells, and secrete cytokines, such as interleukins (ILs), interferons (INFs), and tumor necrosis factor (TNF) (Laskin, 1990). Kupffer cells represent one third of all nonparenchymal liver cells and 85% of all mononuclear phagocytes in the body (Kimmings et al, 1995; Wang et al, 1993). With the exception of circulating mononuclear cells, there is no evidence of a functionally equivalent resident phagocyte population in the pancreas.

Humoral defenses also exist within the hepatic and pancreatobiliary systems. Immunoglobulin (IG) A is secreted into the bile from the gallbladder and intrahepatic/extrahepatic biliary epithelium and plays an important role in barrier protection from infectious pathogens (Emmrich et al, 1998; Scott-Conner & Grogan, 1994) and is also present in pancreatic ductal fluid. The concentration of IgA is inversely related to pancreatic ductal fluid volume (Ohshio et al, 2001). In disease states characterized by exocrine insufficiency (e.g., chronic pancreatitis), a

higher concentration of IgA is also observed in the remaining human pancreatic ductal fluid (Emmrich et al, 1998).

Other immunologic molecules in the bile include fibronectin, which opsonizes pathogens and facilitates biliary epithelial defense against bacteria (Wilton et al, 1987). Complement—in particular, C3, C4, and factor B—is also present and functionally active in the bile at levels similar to serum (Sumiyoshi et al, 1997). As expected, clinical conditions of C3 deficiency are associated with increased susceptibility to infection in the biliary system and elsewhere (Homann et al, 1997). Complement is also present in pancreatic ductal fluid (Andoh et al, 1996; Sumiyoshi et al, 1997). Specifically, C3, C4, and factor B are synthesized in the pancreatic ductal epithelium and secreted in response to proinflammatory cytokines IL-1β, TNF-α, and INF-γ (Andoh et al, 1996; Sumiyoshi et al, 1997). These cytokines act as the primary drivers for sepsis (Cohen, 2002).

The biliary and pancreatic epithelium also may have some inherent immunologic ability. Normally, the CD40 receptor is expressed on regenerating or inflamed bile duct epithelium. CD40-CD40 ligand interactions may be responsible for immunity to certain pathogens. CD40 is also expressed on pancreatic ductal epithelial cells and may play a similar role (Vosters et al, 2004). Patients with deficient CD40 ligand (X-linked immunodeficiency with hyper-IgM) show a higher incidence of hepatopancreatobiliary infections, inflammation, and carcinoma (Hayward et al, 1997).

A final common immunologic host defense to liver, biliary, and pancreatic systems is the rich blood supply. An efficient and uninterrupted blood supply prevents tissue ischemia and allows for a microorganism challenge to be fully mounted by all elements of the host's immune system.

Host Defenses Challenged by Underlying Hepatopancreatobiliary Conditions in Surgical Patients

Numerous conditions—those both generalized and specific to the liver, biliary tree, and pancreas—may interfere with the host defenses in patients with hepatopancreatobiliary disease. Patients can be systemically immunosuppressed secondary to either exogenous medications or autoimmune diseases. Underlying hepatopancreatobiliary cancers themselves also have depressive effects on host defense. Malnutrition, obesity, smoking, age, and major organ system dysfunction are further important risk factors in this population.

Liver

Underlying hepatic conditions that may challenge host defenses in a surgical patient include hepatitis, cirrhosis, liver failure, portal hypertension, and hepatocellular toxin–induced dysfunction (see Chapters 64 and 70A). Hepatitis, cirrhosis, and liver failure all represent relative degrees of hepatic dysfunction, insufficiency, and compromise. As hepatic function deteriorates and ultimately leads to liver failure, physical, chemical, and immunologic hepatic host defenses also become compromised. With decreased bile production capacity, the physical defense of flushing bile flow is less efficient. The effect of primary liver cell dysfunction on hepatic tight junction integrity is unknown, but these junctions are altered in biliary obstructive causes of liver dysfunction. Bile salt deficiency associated with liver dysfunction leads to inadequate chemical defenses of bile salt–mediated antibacterial and antiendotoxin effects, as well as epithelial tropism, which results in reduced integrity of the epithelial barrier. The bacteriologic flora of the intestine is also altered, which may increase the quantity and change the type of bacteria that translocate into the portal system (Clements et al, 1993; Deitch et al, 1990). Liver dysfunction also leads to primary and secondary decreases in Kupffer cell function and to depressed synthesis of immunologically active proteins, which impairs cellular and humoral immunologic defense. Finally, cellular immunity may also be affected by the altered number and type of T cells present within the liver in hepatitis and cirrhosis (Deignan et al, 2002).

Portal hypertension is responsible for secondary decreases in Kupffer cell function. Resultant portosystemic shunting in patients with cirrhosis may compromise reticuloendothelial cell function by allowing enteric pathogens to be moved away from Kupffer cells. Portal hypertension therefore contributes to an increased risk of infection in animals with liver dysfunction (Basista et al, 1994). Local blood flow is also substantially altered in portal hypertension and cirrhosis, as intrahepatic sinusoidal resistance is increased. Sinusoidal responsiveness to endogenous vasodilators is depressed, whereas responsiveness to endogenous vasoconstrictors is increased (Birney et al, 2003). Endothelin and nitric oxide are two significant endogenous mediators of stellate cell contractility that modulate the local intrahepatic resistance in portal hypertension (Rockey, 2001).

Biliary System

The most well-studied underlying biliary condition that can interfere with host defenses in a surgical patient is biliary obstruction (see Chapter 7). This condition may occur from causes that are *intrinsic* (tumors, stones, strictures), *extrinsic* (pancreatitis, tumors), or *functional* (sphincter of Oddi dysfunction). The increased pressure within the biliary system as a consequence of biliary obstruction leads to weakened hepatic tight junctions. This effect is even more dramatic when pressure increases rapidly, such as with biliary tract manipulation (Raper et al, 1989). Leaky tight junctions result in bile reflux into the hepatic sinusoids (i.e., cholangiovenous reflux). Other studies suggest that cholangiovenous reflux may occur directly from bile ductules, through the spaces of Mall and Disse (see Fig. 11.1), into the hepatic sinusoids. This pathway measures 1.7 to 10 μm and offers less resistance to bacteria and toxins than higher resistance pathways such as hepatic tight junctions, biliary canaliculi, or hepatocytes (Stewart et al, 1988). During states of biliary obstruction, the reduced flow of bile also diminishes the physical barrier of the flushing action of bile. Obstruction causes decreased bile salt delivery to the intestine, resulting in reduced bile salt–mediated bacteriostatic and bactericidal activity and therefore colonic bacterial overgrowth. This overgrowth disturbs the protective bacterial flora and promotes local inflammation, injury, and subsequent increased rates of translocation into the portal circulation (Clements et al, 1993; Deitch et al, 1990). The increased bacterial load is not adequately cleared in the liver, allowing entry into the systemic circulation (Bradfield, 1974).

In addition to the direct local effect, jaundice associated with biliary obstruction can substantially alter host defenses. It causes depressed Kupffer cell function by reducing clearance capacity. This results in an increased bacterial load, which overwhelms the hepatic sinusoids and increases bacterial entry into the bloodstream (Clements et al, 1993; Ding et al, 1992; Katz et al, 1991; Megison et al, 1991; Pain et al, 1987).

The cause of Kupffer cell dysfunction in biliary obstruction and jaundice is unclear. One plausible theory relates increased bacterial translocation from the ileum and colon into the portal venous system, thereby directly overwhelming Kupffer cell clearance. Other theories include direct effects of bile salts on Kupffer cell membranes (Takiguchi & Koga, 1988), ineffective opsonins (e.g., fibronectin), decreased sinusoidal size and blood flow, and reduced major histocompatibility complex expression (Clements et al, 1994a, 1994b; Ding et al, 1992; Takiguchi & Koga, 1988).

The role of endotoxins on Kupffer cell function is also poorly understood, and animal studies suggest that biliary obstruction and portal vein endotoxinemia may generate oxygen free radicals in the liver that reduce the ability of Kupffer cells to clear toxins (Ogura et al, 1996; Takahashi et al, 1996). The use of oxygen free-radical scavengers, such as coenzyme Q10 or styrene-co-maleic acid superoxide dismutase in animal models, has been shown to interrupt the detrimental effects of endotoxin on Kupffer cell clearance and hepatic immunologic reserve (Ogura et al, 1996; Takahashi et al, 1996). Biliary obstruction results in less IgA production by the liver and lowers bile IgA levels. Endoscopic drainage of patients with biliary obstruction resolves this IgA deficiency in the bile (Sung et al, 1995); however, prolonged biliary obstruction eventually leads to hepatocyte dysfunction and necrosis, impairing liver synthetic function. Many proteins with immunologic importance are produced less efficiently, resulting in an increased susceptibility to infection.

Clinical relevance of the host challenge associated with biliary obstruction is evident in the higher probability of morbidity and mortality in patients with obstructive jaundice who undergo invasive procedures (Blamey et al, 1983; Pitt et al, 1981; Povoski et al, 1999; Schmidt et al, 2004).

Numerous controlled studies have suggested that preoperative external biliary drainage is associated with increased infectious morbidity. This is likely related to bile loss and the risk of infection and inflammation with catheterization of the biliary tree (Hatfield et al, 1982; Hochwald et al, 1999; Kimmings et al, 2000; McPherson et al, 1984; Pitt et al, 1985; Povoski et al, 1999; Smith et al, 1984; Sohn et al, 2000; van der Gaag et al, 2009). Internal stenting offers a theoretic benefit, with avoidance of external catheters and a return of bile to the gastrointestinal tract (eneterohepatic cycle). Unfortunately, multiple retrospective studies have reported mixed results (Trede & Schwall, 1988; Sohn et al, 2000; Schmidt et al, 2004), and four prospective randomized controlled trials provide conflicting data. These trials typically include patients undergoing pancreaticoduodenectomy (periampullary or pancreatic head adenocarcinoma), randomized to either preoperative endoscopic biliary drainage or surgery without drainage (see Chapters 50B, 50C, 62A, 90B, and 90C). Because of varied findings, however, the authors' conclusions have ranged from recommending routine preoperative endoscopic biliary drainage for patients with biliary obstruction (Lygidakis et al, 1987) to suggesting that although liver function improves with internal stenting, there is no difference in infectious outcomes (Lai et al, 1994). The most recent and methodologically sound trial reports that routine preoperative biliary drainage actually increases the rate of complications related to surgery (van der Gaag et al, 2010). Finally, a Cochrane review, as well as a meta-analysis, concluded no positive effect was seen from preoperative endoscopic biliary stenting in obstructed patients (Saleh et al, 2002; Wang et al, 2008).

Differences in the perioperative risk of pancreatectomy and major partial hepatectomy in jaundiced patients must be recognized. Contrary to the results in pancreas, some evidence shows improved outcome with decompressing the future liver remnant in patients with proximal biliary tumors (see Chapters 50C and 90C).

Theoretically, internal biliary stenting is advantageous over externalized stents, because it avoids the loss of bile and may reduce bacterial contamination. In animal models of obstructive jaundice, biliary decompression via internal stenting promotes Kupffer cell recovery (Clements et al, 1996), as evidenced by increased cell clearance capacity and normalization of endotoxin and anti–core glycolipid antibody concentrations (Greve et al, 1992). It has been suggested that the inconsistent results of clinical trials may be due to inadequate time allowed for liver recovery. The duration of biliary decompression needed to affect these parameters is unknown (van der Gaag et al, 2009). Some animal studies suggest several weeks (Katz et al, 1991; Megison et al, 1991; Parks et al, 1996; Roughneen et al, 1986; Scott-Conner & Grogan, 1994; Thompson et al, 1990), which may not be feasible in the clinical setting for cancer patients. In contrast, studies of limited duration in bile duct ligation models suggest Kupffer cell clearance recovers within days (Ding et al, 1992).

In addition to the effects of biliary obstruction on hepatic tight junctions, bile salt loss, bacterial overgrowth, and Kupffer cell dysfunction as described earlier, it may also be associated with the development of cholangitis. Although bacteria may colonize the biliary tract without producing clinically significant cholangitis, the risk of subsequent infection is directly related to the pressure within the biliary system. More specifically, greater degrees of obstruction lead to higher pressures (Pitt et al, 1990). This increase has a more dramatic effect when pressure increases quickly, as with biliary tract manipulation or common bile duct stone obstruction (Raper et al, 1989). In addition, specific virulence factors may explain how some bacteria species colonize and others cause sepsis. Slime production, for example, is necessary for some bacteria to colonize, but too much prevents cholangiovenous reflux and sepsis (Stewart et al, 2003). Bacteria that create complement are thought to induce an enhanced cholangiovenous reflux from resulting TNF-α production (Stewart et al, 2002). P1 fimbriae, α-galactosyl residues, and the absence of mannose-specific fimbriae also have been cited as distinguishing pathogenic bacteria from colonizing bacteria (Wetter et al, 1994). As a result, the degree and rapidity of obstruction and bacterial virulence play important roles in determining whether biliary pathogens will promote cholangitis.

Pancreas

The underlying pancreatic conditions that interfere with host defenses in surgical patients are pancreatic ductal obstruction, pancreatitis, and chronic pancreatic insufficiency. Ductal obstruction can be due to pancreatitis, tumor, a stone, or mucus (intraductal papillary mucinous neoplasm). This obstruction results in the loss of pancreatic ductal flow with its associated flushing, antibacterial, and immunologic actions. The treatment of some pancreatic diseases involves pancreatic duct stenting, but this leads to subsequent disruption of the pancreatic sphincter/pressure zone barrier between the intestine and

pancreas, which makes the pancreas susceptible to bacterial colonization, infection, and scarring. Stenting can also cause subsequent pancreatitis or can exacerbate previously existing pancreatitis.

In acute and chronic pancreatitis, host defenses can also be affected by obstruction of the biliary duct, duodenum, or mesenteric vasculature. Obstruction of bile flow to the intestine can depress host defense, as previously discussed. Duodenal obstruction can ultimately lead to poor nutrition with subsequent effects on patient immunologic reserve. Mesenteric vascular obstruction can result in liver or intestinal ischemia, insufficiency, or failure, which depresses the host's functional reserve. Ultimately, patients with chronic pancreatitis may develop pancreatic failure manifested as exocrine and endocrine insufficiency. Exocrine insufficiency can lead to poor absorption of fats, protein, and carbohydrates. If undertreated, this may cause malnutrition, weight loss, and decreased functional and immunologic reserve. Endocrine insufficiency (diabetes) has well-established risks to host defenses that include glycosylation of tissues and a general predisposition to infections.

Patients who present with acute necrotizing pancreatitis are at significant risk of developing a pancreatic infection. Translocation of bacteria and endotoxin is thought to play a major role in the cause of these infectious complications, both before and after operative debridements. This theory is based on experimental (Foitzik et al, 1995; Medich et al, 1993; Widdison et al, 1994) and clinical data (Buchler et al, 1992). Interestingly, the bacteriology of infected pancreatic tissue has changed substantially in recent years from predominantly gut flora to a greater emphasis on gram-positive microorganisms as well as on fungus (Kochhar et al, 2009; Besselink et al, 2009). This is presumed to be a consequence of improved therapies with a resultant increase in the microorganisms (gram-positive and fungal) associated with advanced/prolonged critical care treatments (central line infections). Finally, bacteria may exist within pancreatic pseudocysts, which if drained ineffectively can result in pancreatic abscess that may progress to systemic infection.

Numerous prospective randomized controlled trials have attempted to address the role of prophylactic antibiotics in preventing pancreatic infection during acute pancreatitis. The methodologic heterogeneity in these studies is striking, given their variations in patient numbers (underpowered), entry criteria, antibiotic selection, outcome measures, and lack of appropriate controls. They have also often ignored patients with significant necrosis, who are at greatest risk for infection. Although older trials employing prophylactic antibiotics (Foitzik et al, 1995; Luiten et al, 1995; Pederzoli et al, 1993; Sainio et al, 1995) reported reductions in the incidence of infectious complications, subsequent operations, and mortality, two larger contemporary trials found no significant benefit to the early use of prophylactic antibiotics in patients with severe acute pancreatitis (Dillinger et al, 2007; Isenmann et al, 2004). These data highlight the impact of proinflammatory mediators (cytokines) in inducing a systemic inflammatory response syndrome during the early phase (onset to 2 weeks) of pancreatitis and therefore a shift in philosophy from previous reviews and meta-analyses (Bassi et al, 2003; Nathens et al, 2008). As a result, currently no compelling evidence supports the use of early prophylactic antibiotics in these patients (Howard, 2007).

Host Defenses Challenged by Hepatopancreatobiliary Surgery

Any invasive or surgical procedure on the hepatopancreatobiliary system affects the host defense mechanisms. These include the introduction of foreign bodies, removal of functional tissue mass, rerouting of normal flow of fluids (bile, pancreatic fluid, succus entericus), mixing of normal barriers (sphincters), reduction of blood supply (ischemia, necrosis, shock), blood transfusion (immunosuppression), and microbiologic contamination of sterile fluid and tissue.

Liver

SURGERY. The main surgical procedures of the liver involve resections of various extents in patients with variable degrees of hepatic reserve. Liver resection may be accompanied by biliary–enteric reconstructive procedures, such as with proximal cholangiocarcinomas (see Chapter 50B). Various hepatic ablative techniques are also being increasingly utilized, such as radiofrequency ablation, cryoablation, and microwave ablation (see Chapter 85).

HOST DEFENSE. The main effect of liver resection on host defense is the removal of functional liver mass, which results in hepatocyte loss, disruption of the biliary drainage system, and reduced portal venous drainage (increased portal pressure, reduced portal outflow). Loss of functional liver mass has a direct and proportional effect on the capacity of the reticuloendothelial system to respond to infection. Bacterial and endotoxin clearance is also suppressed after hepatectomy. Normally, the existing reserve of a healthy liver can accommodate this loss, however, a patient with impaired liver function may not be able to compensate. In recent years, the role of preoperative portal vein embolization (PVE) of the hepatic lobe to be resected has been increasing (see Chapter 93). This allows preoperative hypertrophy of the remaining lobe, which can be beneficial in patients with limited hepatic reserve.

Despite the overall loss of Kupffer cell quantity, function of the remaining liver is not depressed (Andersson & Foss, 1991; Gross et al, 1985; Vo & Chi, 1988). Loss of functional liver mass also results in less overall production of bile and bile salts with their trophic (Borghi et al, 1991), antibacterial, antiendotoxin, and immunologic effects (Cahill et al, 1987; Dahlgren et al, 1986). Loss of reticuloendothelial system capacity, portal venous drainage, and protective effects of bile salts presents significant challenges to host defenses. Preexisting liver dysfunction and postoperative liver failure further exacerbate these challenges.

Although ablative procedures may preserve more hepatic mass than formal resections, the loss of functional volume remains important. More specifically, ablative techniques can result in two distinct challenges to host defenses: First, they create necrotic tissue, which is not surgically removed. Cryoablation causes hepatocellular necrosis by inducing formation of ice crystals, whereas radiofrequency and microwave ablation result in necrosis via heat-induced coagulation. Necrotic tissue from either source can act as a nidus for infection. Second, ablative techniques may have systemic effects, as cryotherapy has been shown to induce "cryoshock" in 1% of patients (Seifert & Morris, 1999). This can result in a systemic inflammatory response, coagulopathy, and multiorgan dysfunction or failure, particularly of the renal and pulmonary systems. More recent

studies have suggested that patients undergoing radiofrequency ablation do not display the systemic inflammatory responses with Kupffer cell–mediated cytokine release of proinflammatory cytokines (TNF-α, IL-1) characteristic of cryoablation (Schell et al, 2002; Jansen et al, 2010). Other authors have confirmed a reduced cytokine response after radiofrequency ablation but suggest that it still has a significant response compared with resection alone. This group also reported that the renal and lung dysfunction characteristic of cryoablation does not occur in swine treated with radiofrequency ablation (Ng et al, 2004). In contrast, other authors have suggested the systemic inflammatory response characteristic of cryoablation is not detrimental but rather leads to inhibition of tumor growth (Joosten et al, 2001, 2003).

Although the acceptance of laparoscopic techniques for hepatic resection is rapidly increasing, data outlining the immune host response to this approach are minimal. Porcine models suggest that open procedures may be associated with more immune suppression than laparoscopic approaches (Burpee et al, 2002), but to date no studies have evaluated differences in relevant clinical end points, such as postoperative infection.

INFECTIONS. Septic complications represent the most frequent cause of morbidity after liver resection (D'Amico & Cillo, 1999; Melendez et al, 1998) with the most common issue being intraabdominal abscesses (D'Amico & Cillo, 1999; Melendez et al, 1998). Intraabdominal infection can lead to sepsis and organ failure. Mortality from infectious complications after liver resection is significant and depends on age, comorbidities, hepatic reserve, and extent of liver resection (Garwood et al, 2004).

Pathophysiology of Infection. Translocation of bacteria and endotoxin is thought to play a major role in the cause of sepsis after liver resection. Bacteria are present in the mesenteric lymph nodes, portal venous system, and systemic vasculature after resection, regardless of whether a biliary–enteric drainage is constructed (Wang et al, 1992, 1994, 1995; Yeh et al, 2003). Decreased bile flow through the intestine, bacterial overgrowth with preference for *E. coli* (Wang et al, 1993), and postoperative ileus associated stasis, overgrowth, and bacterial adherence to the intestine appear to be important factors. Finally, experimental evidence indicates that decreased blood flow to the intestine results in enterocyte protein loss, mucosal atrophy, and loss of villous height (Wang et al, 1993). This combination is thought to promote bacterial and endotoxin translocation in the setting of decreased functional Kupffer cell mass. As noted earlier, ablative therapies may also promote infection through the formation of necrotic liver tissue and its effects on systemic immunity and end-organ function. All of these factors combine to promote infection in patients following liver surgery.

Risk Factors. One of the risk factors for infection in patients undergoing hepatic resection may relate to the amount of ischemic/necrotic liver at the resection margin (Yanaga et al, 1986) or ablation site. Intraperitoneal blood and bile, which accumulate in the surgical field, also inhibit peritoneal macrophage function (Andersson et al, 1989, 1990a, 1990b). Other risk factors relate to the extent of hepatic resection—specifically, the loss of functional liver mass—patient functional reserve, preoperative liver sepsis, iatrogenic introduction of bacteria (stenting, biliary-enteric anastomosis), blood transfusion, and shock (Andersson et al, 1990a, 1990b; Hochwald et al, 1999; Pace et al, 1989; Yanaga et al, 1986).

Causative Organisms. Most organisms isolated from intraabdominal sepsis after liver resection are enteric gram-negative aerobes, most commonly *E. coli*, and *Enterococcus*. Multiple bacterial isolates are present in 50% to 75% of cases (Pace et al, 1989; Wang et al, 1992). Common isolates associated with higher mortality in current studies also include fungus and gram-positive organisms, particularly methicillin-resistant *S. aureus* (Garwood et al, 2004).

Prevention and Treatment. Prophylactic antibiotics that cover enteric organisms—gram-negative aerobes, anaerobes, and enterococci—should be administered prior to any hepatobiliary manipulation. In addition, prophylactic antibiotics to cover skin flora should be included. Minimizing the amount of necrotic tissue at the margin of resection is optimal, and methods of sparing functional liver mass (parenchymal-sparing segmental resections) can be preventive (Jarnagin et al, 2002). Techniques using low central venous pressure and intermittent Pringle maneuvers reduce blood loss and thereby decrease the subsequent need for transfusion. Meticulous hemostasis, intraoperative identification of bile leaks, and judicious use of saline irrigation to remove bile, blood, and succus entericus from the peritoneal cavity and wound at the time of surgery are also essential.

After liver resection, early enteral feeding has been shown to reduce the rate of all infectious complications (Shirabe et al, 1997). It is thought to preserve and promote the gut mucosal integrity by maintaining nutrition and normal microbiologic flora. Animal studies have also shown that ethylhydroxyethyl cellulose (Wang et al, 1993, 1995), dextran 70 (Wang et al, 1997), and probiotics (Seehofer et al, 2004) can reduce bacterial translocation after liver resection. Ethylhydroxyethyl cellulose and dextran 70 act as cellular surfactants that may enhance endothelial cell resistance (Wang et al, 1995, 1997). Probiotics are bacterial cultures (e.g., lactic acid bacteria) that promote the normal microbiologic flora (Seehofer et al, 2004). Proper validation of these interventions still await human trials (Rayes et al, 2009).

Abdominal drains after liver resection do not prevent infection and may be associated with greater infectious complications based on randomized prospective studies (Belghiti et al, 1993; Burt et al, 2002; Fong et al, 1996; Liu et al, 2004). Techniques of preoperative PVE and hepatic arterial embolization may be employed to promote hypertrophy of the existing functional liver mass before resection. A prospective trial in 55 patients undergoing right hepatectomy showed that PVE significantly decreased postoperative complications in patients with chronic liver disease. Notably, a trend was seen ($P < .08$) toward decreased septic complications (Farges et al, 2003).

By creating a greater functional liver volume, the remaining mass after resection may better support any infectious challenge to host defenses. A study comprising 181 patients in whom mesenteric lymph nodes were cultured before and after liver resection showed that the only factor associated with bacterial translocation and subsequent postoperative infection was intraoperative blood transfusion (Yeh et al, 2003). Avoidance of blood-product transfusion during liver resection deserves strong consideration based on data indicating higher complication

rates, longer hospital stays, and early mortality (Kooby et al, 2003; Dixon et al, 2009).

Biliary System

SURGERY. Surgery on the biliary system typically involves resection (gallbladder, biliary tree) and/or biliary drainage. The most common biliary procedure is laparoscopic cholecystectomy.

HOST DEFENSE. With resection of the gallbladder, the patient loses the protective effects of gallbladder contraction and therefore the propulsion of bile toward the duodenum. As previously noted, bile flow helps prevent ascending infection by its flushing action. Resection, bypass, manipulation, and disruption of the biliary sphincter may also interfere with its ability to prevent reflux of enteric contents and adherent bacteria from the duodenum into the common bile duct. Resection of the extrahepatic biliary tract with a hepaticojejunostomy eliminates protective mechanisms of the biliary epithelium. Mucus, IgA, and complement produced by the biliary epithelium are also lost with resection.

In comparison to laparoscopic techniques, data suggest that open procedures may be associated with significant suppression of cell-mediated immune response, such as delayed-type hypersensitivity (Altamura et al, 2002; Whelan et al, 2003; Boo YJ et al, 2007). Additionally, the degree of intraabdominal pressure during laparoscopic cholecystectomy may regulate interleukin release (Basgul et al, 2004). To date, few trials have shown differences in immunologic parameters and relevant clinical end points, such as postoperative infection (Jacobi et al, 2002; Kooby, 2006).

INFECTIONS. The most common significant postoperative infection is the intraabdominal abscess; however, cholangitis may also occur when indwelling stents are introduced into the biliary ductal system. Wound infection may comprise skin flora, but more commonly, it involves enteric organisms when bile is infected, or when a biliary-enteric anastomosis has been performed (Lewis et al, 1987; Wells et al, 1989).

Pathophysiology of Infection. Infection occurs from two main sources: First, bacteria invade the biliary tract and liver locally by ascending from the duodenum. This invasion is facilitated by indwelling stents, sludge, or various degrees of biliary obstruction. Second, enteric bacteria translocate from the intestine and are introduced hematogenously into the liver through the hepatic portal vein. If the bacterial or endotoxin load exceeds the liver's clearance capacity, bacteremia and sepsis result.

Risk Factors. Bactibilia is an important risk factor for infectious complications in biliary surgery. The presence of bacteria in the bile does not predict a patient's risk of infection; however, evidence of bactibilia was found in 10% to 15% of patients at low risk for positive gallbladder bile cultures, for example, patients undergoing elective open cholecystectomy (Lewis et al, 1987; Reiss et al, 1982; Wells et al, 1989). Bactibilia is present in more than 80% of patients at high risk for positive cultures, such as those with acute cholecystitis (Claesson, 1986).

In patients undergoing laparoscopic cholecystectomy with positive gallbladder bile cultures, no significant difference in postoperative infectious complications were seen when a several-day course of preoperative antibiotics was employed for those at high risk (Al-Abassi et al, 2001). In contrast, the presence of bactibilia in the setting of common bile duct disease, and specifically increased biliary pressure and biliary obstruction, does predispose patients to postoperative infectious complications (Cox et al, 1978; Pitt & Couse, 1990). The greater the concentration of bacteria and the higher the degree and rapidity of obstruction, the more severe the septic complications (Pitt & Couse, 1990; Raper et al, 1989). As expected, in patients with acute suppurative cholangitis, bactibilia is present in nearly 100% of cases. This translates into a high risk of postoperative infection (Lee & Chung, 1997). Other risk factors for infection include the patient's functional reserve, preoperative sepsis, introduction of foreign bodies (stents, drains), disruption of efficient blood supply, blood transfusion, and shock.

Causative Organisms. Bile is normally sterile, so the type and concentration of biliary bacteria depend on the degree of obstruction or stasis, the presence of foreign bodies, and whether the obstruction is related to malignant or benign causes. The most common biliary pathogens are enteric gram-negative aerobes (Lee & Chung, 1997). Polymicrobial cultures are present in 67% of infected bile cultures (Leung et al, 1994). In patients with previous biliary instrumentation, and particularly after long-term antibiotic treatment, *Pseudomonas, Serratia, Streptococcus, Enterococcus,* and *Enterobacter* species may be present (Lipsett & Pitt, 1990; Nomura et al, 2000; Thompson et al, 1994). Gram-positive organisms, especially *Enterococcus faecalis,* are more common in patients who have undergone percutaneous instrumentation of the biliary tree. Anaerobes are present only occasionally but typically are found in patients with poor functional reserve, complex biliary problems, or long-term biliary stenting (Doty & Pitt, 1986; Krige et al, 1992; van den Hazel et al, 1994a, 1994b). Bile cultures in patients with malignant causes of biliary obstruction more commonly display *Klebsiella, Enterobacter, Streptococcus, Enterococcus,* and *Candida* species compared with benign biliary obstruction (Nomura et al, 2000; Thompson et al, 1994). Whether *E. faecalis* is truly a biliary pathogen is unclear. Antibiotic use is known to destabilize *E. faecalis* in the enteric flora by killing susceptible strains. Multiple antibiotic-resistant enterococcal strains, such as *E. faecalis* strain V583, are able to colonize the gut (Gilmore & Ferretti, 2003). In a study of patients with biliary malignancy undergoing preoperative biliary decompression, only the incidence of enterococcal bactibilia increased after antibiotic use (16% before and 63% after antibiotic use). When analyzing the correlation between preoperative bile bacteria and postoperative complications, only *Enterococcus* species were associated with the occurrence of complications (Nomura et al, 2000). Whether *E. faecalis* works independently or synergistically with other biliary bacteria as a primary pathogenic mechanism is unknown.

Prevention and Treatment. In patients undergoing biliary surgery, preoperative obstruction and jaundice—with their physical, chemical, and immunologic consequences—increase the risk of perioperative infectious complications. Prophylactic antibiotics treating enteric gram-negative aerobes, anaerobes, and skin flora should be used. If the patient has an indwelling biliary catheter, bile cultures should be taken, and antibiotics should be tailored to the particular bacteria and their

corresponding sensitivities. Oral bile salts may be employed to replenish stores in patients with obstructive jaundice.

The role of biliary stenting is controversial. External stenting to relieve biliary obstruction has been shown consistently to increase the complication rate in patients undergoing pancreatobiliary surgery, secondary to the introduction of bacteria directly into the biliary tree. External stenting is reserved for cases of cholangitis that cannot be relieved by internal stenting and for nonsurgical palliation of high biliary obstruction. Preoperative internal stenting to relieve biliary obstruction in patients undergoing pancreatobiliary surgery is more controversial. Theoretically, internal stenting avoids the introduction of exogenous bacteria characteristic of external stenting and corrects the detrimental effects of biliary obstruction and reduced bile salt delivery into the gut. Clinical trials have yet to establish the role of internal stenting in this setting.

Pancreas

SURGERY. Surgery on the pancreas typically involves resection (distal pancreatectomy, pancreaticoduodenectomy, debridement) and/or drainage (pancreaticoenteric) procedures.

HOST DEFENSE. The main effect of resection on host defense is the removal of functional pancreatic tissue mass. Pancreatectomy results in less production of pancreatic ductal fluid with its trophic, antibacterial, and immunologic effects. Pancreatic exocrine insufficiency following resection can also cause malnutrition and result in long-term depressed immunity without sufficient supplementation of exogenous pancreatic enzymes. In patients with preexisting pancreatic exocrine insufficiency, these host defenses are suppressed even further. Pancreatectomy may also result in pancreatic endocrine dysfunction secondary to loss of islet cell mass or in patients with inadequate islet cell function. Although the precise target range is somewhat controversial, uncontrolled perioperative hyperglycemia is a significant predisposing factor for postoperative infection and mortality (Capes et al, 2000; Grey & Perdrizet, 2004; Lipshutz & Gropper, 2009). Also, when pancreatic surgery involves enteric drainage, the effect on host defense results from exposure to enteric pathogens via biliary–enteric or pancreaticoenteric anastomoses. Finally, the impact of laparoscopic techniques for pancreatic resection on host immune status is unclear. In dog models, however, laparoscopic distal pancreatectomy results in significantly less stress as measured by both IL-1 and serum cortisol levels, when compared with conventional open procedures (Naitoh et al, 2002).

INFECTIONS. The most common cause of intraabdominal sepsis in pancreatic surgery is intraabdominal abscess with or without pancreatic fistula or pancreaticoenteric anastomotic leak. Wound infection may occur with skin flora or enteric flora when bile is infected, or when an enteric anastomosis is performed (Lewis et al, 1987; Wells et al, 1989). Surgical procedures to address the complications of acute necrotizing pancreatitis, infected pancreatic necrosis, or pancreatic abscess are frequently accompanied by sepsis and the systemic inflammatory response syndrome.

Pathophysiology of Infection. The pathophysiology of infection in pancreatic resection without enteric drainage is due to pancreatic fistula and bacteria in the pancreatic ductal fluid. Intraabdominal abscess occurs in these patients when the pancreatic duct leaks fluid that is contaminated with bacteria. Preexisting bacteria in the pancreatic duct are typically a result of endoscopic, radiologic, or surgical instrumentation of the duct itself.

The pathophysiology of pancreatic resection with enteric drainage is similar. In this scenario, the direct communication of the duct with the intestine allows for enteric bacteria to invade the pancreatic ducts and contaminate the ductal fluid because of the absence of a functional sphincter. If an anastomotic leak occurs after pancreaticoenteric anastomosis, the pancreatic ductal fluid contains enteric bacteria. With adequate drainage, the patient may avoid local or systemic signs of sepsis, unless bacterial antibiotic resistance develops. Translocation of bacteria and endotoxin is thought to play a major role in the cause of infectious complications in necrotizing pancreatitis.

Risk Factors. Risk factors include the extent of the pancreatic resection and corresponding loss of functional mass, general functional reserve of the patient, underlying sepsis, pancreatitis, ischemic necrosis, disruption of efficient blood supply, blood transfusion, shock, and use of stenting, instrumentation, and drains. Biliary obstruction, as seen in many patients undergoing pancreaticoduodenectomy, is also a significant risk factor.

Causative Organisms. Enteric gram-negative aerobes arising in the pancreatic ductal fluid, either from instrumentation or via biliary-enteric or pancreaticoenteric drainage, are the main source of bacterial contamination. In acute necrotizing pancreatitis, gram-negative organisms are more commonly isolated in patients with biliary pancreatitis, whereas gram-positive organisms are more frequent in those with alcoholic pancreatitis (Raty et al, 1998). The incidence of gram-positive organisms may also be higher in necrotizing cases, when sampling of fluid collections or necrosis is performed. *Candida* and *Pseudomonas*, as in biliary bacteriology, occur during long hospital and intensive care unit stays and are typically associated with prolonged courses of antibiotics and subsequent increased mortality (Bittner et al, 1987; Kochhar et al, 2009; Agvald-Ohman C, 2008).

Prevention and Treatment. Prevention of the infectious risks associated with pancreatic surgery entails counteracting the loss of functional pancreatic tissue. For pancreatic exocrine insufficiency, adequate exogenous pancreatic enzyme supplementation should begin postoperatively with initiation of diet. Early feeding prevents the breakdown of gut integrity (Kimmings et al, 1995), and for pancreatic endocrine insufficiency (diabetes), reasonable perioperative control of hyperglycemia with insulin should be routine. Appropriate prophylactic antibiotics must be employed that address enteric gram-negative aerobes, anaerobes, and skin flora. Prophylactic antibiotics that address translocation flora and penetrate pancreatic tissue (e.g., imipenem, cilastatin, piperacillin/tazobactam) remain important preventive measures, particularly in patients with underlying pancreatic necrosis.

CONCLUSION

This chapter provides a basic understanding of the pathophysiology of sepsis and the host defense mechanism's ability to

mount an effective response following hepatopancreatobiliary surgery. Physical, chemical, and immunologic host defense mechanisms in the liver, biliary, and pancreatic systems can be profoundly altered by the patient's underlying health status (comorbid conditions), hepatic or pancreatobiliary disease, and specific surgical therapy. Important preventive measures should be instituted to minimize the risk of infectious complications from hepatopancreatobiliary surgery.

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CHAPTER 12

Clinical investigation of hepatopancreaticobiliary disease

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Despite the rapid increase in diagnostic modalities available to the clinician dealing with hepatobiliary disease, a detailed history and clinical examination are crucial if an accurate overall assessment is to be made. With advances in technology, an array of diagnostic modalities is at the disposal of the physician. These include better availability of tumor markers and more sensitive and specific imaging. A systematic approach is important to rationalize the use of these techniques. Multidisciplinary assessment allows more accurate diagnosis and disease staging, while avoiding unnecessary and expensive investigations. This chapter addresses the specific features in the history and clinical examination that are of particular importance in hepatobiliary and pancreatic disease.

CLINICAL HISTORY AND PHYSICAL EXAMINATION

The clinical investigation of patients with hepatobiliary and pancreatic disease begins with a detailed history and physical examination that will direct the sequence of subsequent investigations. The history should begin with the presenting complaint and then proceed with a systematic inquiry into hepatopancreatobiliary symptoms. The history should include details of gastrointestinal symptoms including anorexia, nausea, vomiting, and any alteration of bowel habit, because this may indicate the source of a liver mass (e.g., colorectal metastasis to the liver). The history also should include a careful assessment of pain, itching, or jaundice and a comprehensive past medical history, family history, foreign travel history, and drug history, including alcohol intake and smoking. The general symptoms of liver dysfunction include weakness, fatigue, anorexia, nausea and vomiting, weight loss or gain (related to ascites), disordered taste and smell, muscle cramps, and impotence. Specific symptoms of liver dysfunction relate to ascites (abdominal distension and oliguria), coagulopathy (excessive bruising or bleeding), cholestasis (itching), and jaundice.

Examination should assess the presence or absence of the stigmata of chronic liver and biliary disease (see Chapter 7), including jaundice, pruritus, spider nevi (Fig. 12.1), hepatosplenomegaly (Fig. 12.2), ascites (Fig. 12.3), and caput medusae. Abnormal abdominal masses should also be noted. The circulation in patients with liver failure is hyperdynamic with flushed extremities and a bounding pulse, and peripheral cyanosis may be evident. Fetor hepaticus—a sweet, musty odor of the breath—is associated with hepatocellular failure and is thought to be related to changes in the gut flora (Challenger & Walsh, 1995). Spider nevi are angiomata that occur in the vasculature of the superior vena cava, and their disappearance and reappearance vary with liver function and are thought to be associated with estrogen excess (Bean, 1959). Palmar erythema (Fig. 12.4) affects the thenar and hypothenar eminences and is associated with the hyperdynamic state. Other changes include loss of axillary and pubic hair and whitening of the nails (Lloyd & Williams, 1948). Gynecomastia (Fig. 12.5) and testicular atrophy can also occur.

Chronic encephalopathy associated with portal hypertension and portosystemic shunting varies in severity, producing symptoms that range from mild confusion and a shortened attention span to marked intellectual deterioration that may end in coma. Psychomotor tests have been devised to quantify the intellectual deterioration and allow monitoring (Sherlock & Dooley, 2002). A flapping tremor of the extended wrist ("liver flap") and later cogwheel rigidity and ankle clonus may be present. Acute liver failure is associated with jaundice, confusion, delirium, and renal failure. These features may occur on a background of cirrhosis, and the precipitating cause may be treatable (e.g., infection).

Patients also may be seen with acute abdominal pain or jaundice. Examination may reveal localized peritonism in the right upper quadrant or epigastrium with a tender mass or generalized peritonitis in cases of gallbladder perforation or severe pancreatitis. A Murphy sign is a "catch" in the breath elicited by gently pressing on the right upper quadrant and asking the patient to take a deep breath. A Boas sign is hyperesthesia of the skin over the lower right ribs posteriorly. One or both of these signs may be found in acute cholecystitis. Erythema ab igne is caused by prolonged local application of heat and may be evident in the right upper quadrant in patients with chronic gallbladder disease or, more commonly, on the back in patients with chronic pancreatitis (Fig. 12.6). In Asia, bleeding from a ruptured hepatocellular carcinoma is a common acute presentation. Patients with severe acute pancreatitis may develop a bluish discoloration of the flanks as a result of retroperitoneal bleeding (Turner sign) or in the periumbilical area (Cullen sign; Fig. 12.7).

EXAMINATION OF THE LIVER

The liver is examined using a combination of palpation and percussion from above and below to delineate its borders. Dullness to percussion of the upper border extends as far as the fifth intercostal space. Auscultation is also important, because a venous hum may be heard with portal hypertension, and a bruit may be heard in association with hepatocellular carcinomas.



FIGURE 12.1. Spider nevus in a patient with cirrhosis.



FIGURE 12.2. Hepatomegaly and Dupuytren contracture in a patient with extensive cirrhosis.

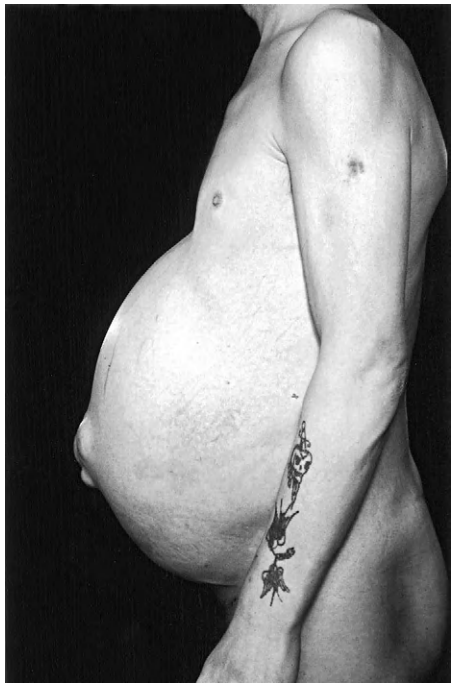


FIGURE 12.3. Ascites with an everted umbilicus and venous distension in a patient with cirrhosis.



FIGURE 12.4. Palmar erythema affecting the thenar and hypothenar eminences.

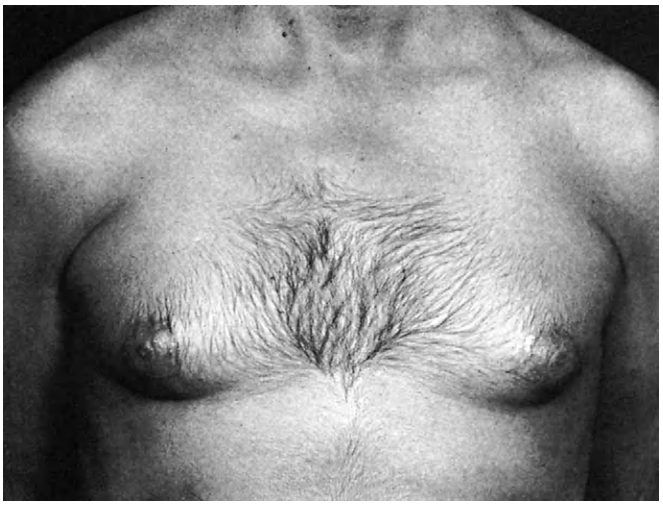


FIGURE 12.5. Bilateral gynecomastia in a patient with alcoholic liver disease.



FIGURE 12.6. This patient has long-standing chronic pancreatitis that affects the entire length of the pancreas with severe flank and back pain on the left side. Prolonged application of local heat has resulted in marked rash of erythema ab igne.

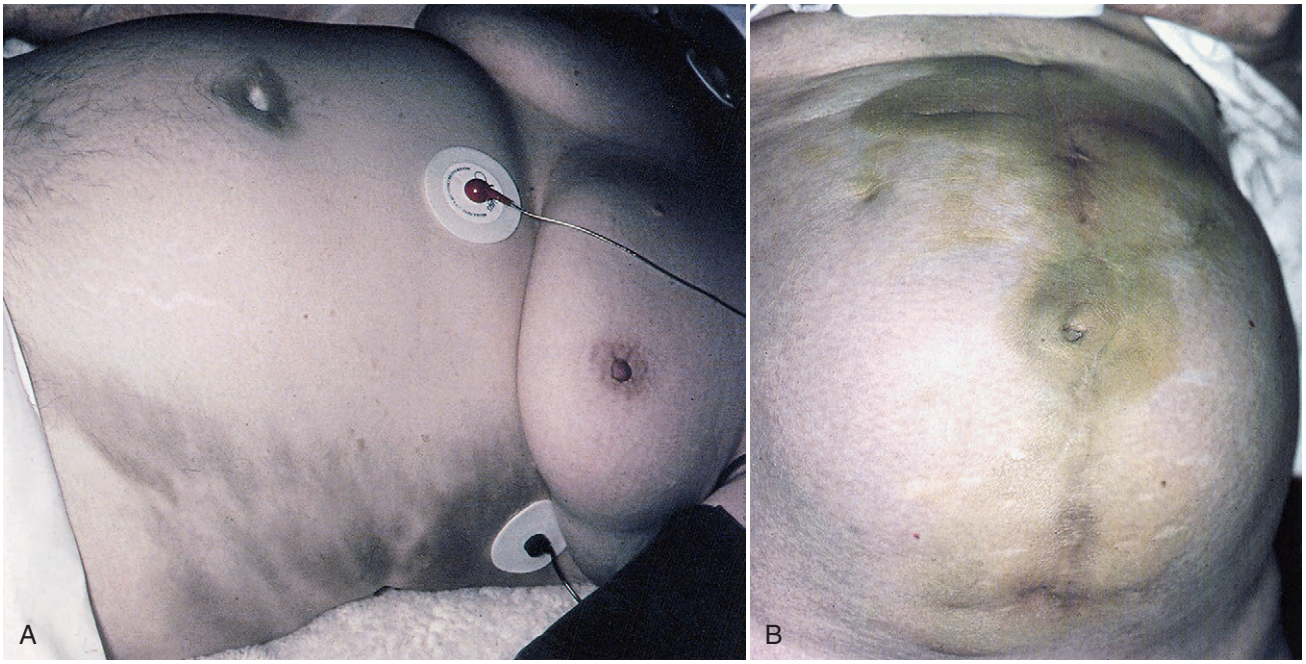


FIGURE 12.7. Turner sign (**A**) and Cullen sign (**B**) in patients with acute pancreatitis.

The normal liver is usually impalpable; however, in asthenic individuals, the anterior edge may be palpable. Enlargement of the liver occurs in many pathologic states, although a tonguelike extension from the right lobe—a *Riedel lobe*, which is of no pathologic significance—may be mistaken for a tumor (Fig. 12.8). Causes of hepatomegaly are listed in Table 12.1. A lobe may undergo hypertrophy and become palpable, and this may occur in the presence of liver atrophy or after liver resection. Reduction in liver size also is important, because this may occur in cirrhosis and certain types of hepatitis. Consistency also is relevant; a hard, knobbly liver often represents the presence of metastases, whereas smooth enlargement may be due to cirrhosis.

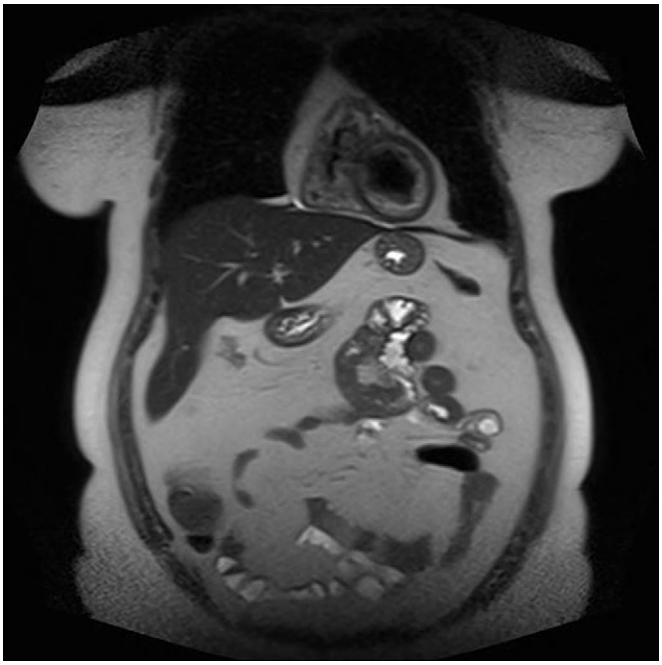


FIGURE 12.8. Coronal magnetic resonance image of a Riedel lobe of liver. This normal variant, a tonguelike extension from the right lobe, may be mistaken for a mass or an enlarged liver on physical examination.

EXAMINATION OF THE SPLEEN

Examination of the spleen should begin in the right iliac fossa and proceed toward the left subcostal region, because this is the direction in which splenomegaly occurs. Rotation of the patient 45 degrees to the right may aid palpation, because the spleen then falls onto the examining right hand. During this maneuver,

Table 12.1

Causes of Hepatomegaly

Variant Anatomy
Riedel lobe
Low-lying diaphragm

Inflammatory
Hepatitis
Abscesses, amebic and pyogenic
Schistosomiasis
Cirrhosis, early
Sarcoid
Biliary obstruction, especially extrahepatic

Metabolic
Amyloid
Steatohepatitis
Glycogen storage disease

Hematologic
Leukemias
Lymphomas
Myeloproliferative disorders
Sickle cell disease
Porphyrias

Tumors
Primary, benign and malignant
Secondary

Cardiovascular
Cardiac failure
Hepatic vein obstruction

Table 12.2

Causes of Splenomegaly

Infection

Acute: viral, bacterial
Chronic: tuberculosis, brucellosis
Parasitic: malaria, schistosomiasis

Hematologic

Leukemias
Hemolytic anemias
Hemoglobinopathies
Portal hypertension, especially extrahepatic

Neoplastic

Lymphomas
Myeloproliferative disorders
Secondary deposits

Inflammatory

Rheumatoid
Systemic lupus
Amyloidosis

the left hand should support the rib cage and relax the skin and abdominal musculature by drawing these down to the right. Percussion may be useful, and if ascites is present, the spleen may be ballotable. If the spleen is sufficiently enlarged, the notch on its anterior border may become palpable. Causes of splenomegaly are listed in Table 12.2.

SIGNS OF PORTAL HYPERTENSION

Portal hypertension (see Chapter 70A and 74) is due to either intrahepatic or extrahepatic portal venous obstruction. Intrahepatic portal hypertension usually is associated with hepatomegaly and may be accompanied by splenomegaly and ascites. Dilated abdominal wall veins also may be found secondary to portosystemic anastomosis, giving rise to a caput medusae. The more common clinical site of portosystemic anastomosis is at the gastroesophageal junction, leading to esophageal varices; any evidence of upper gastrointestinal blood loss, whether hematemesis or melena, should be investigated with urgent endoscopy (see Chapter 75A). Rarely, these patients may develop hemorrhoidal varices around the anus as a result of portosystemic anastomosis.

Extrahepatic portal hypertension is usually due to portal vein thrombosis, and as such it is important to identify any history of neonatal infection around the umbilicus, major intraabdominal sepsis, pancreatic cancer, or a blood disorder that might lead to hypercoagulability. These patients almost invariably have splenomegaly, often associated with pancytopenia. In such cases, the liver is normal, but ascites may be present. A palpable spleen in the upper left abdomen associated with portal hypertension may be found in the event of splenic occlusion caused by tumor or chronic pancreatitis.

CLINICAL FEATURES OF ALCOHOLIC LIVER DISEASE

The symptoms and signs of alcoholic liver disease may be related directly to alcoholism or to secondary hepatocellular dysfunction. Patients commonly experience repeated falls while inebriated and may have signs of trauma and bruising. Multiple "old" rib fractures are common findings on chest radiographs and are related to such behavior. Alcoholic neuropathy also may be present, especially given the malnourished state of many patients. Acute alcoholic hepatitis usually occurs after a bout of drinking and may be associated with liver tenderness, jaundice, pyrexia, and leukocytosis. Advanced alcoholic liver disease may be associated with other manifestations of hepatic impairment (e.g., portal hypertension, ascites, hepatomegaly, liver failure).

CLINICAL FEATURES OF OTHER TYPES OF LIVER DISEASE

Primary Biliary Cirrhosis

Primary biliary cirrhosis, or *chronic nonsuppurative destructive cholangitis*, usually affects middle-aged women. Asymptomatic individuals may be diagnosed during routine examination, where they are found to have hepatomegaly, elevated autoantibodies, or elevated plasma alkaline phosphatase. The earliest symptom is usually pruritus, even before clinical jaundice is apparent, but later the patient may develop overt jaundice; hepatosplenomegaly; xanthelasma, especially in the palms and around the eyes; vitiligo; and arthritis. Primary biliary cirrhosis often is found in association with connective tissue disease.

Ulcerative Colitis and Crohn Disease

Ulcerative colitis and Crohn disease are associated with hepatobiliary disorders, especially primary sclerosing cholangitis (see Chapter 41). It is important to include a detailed gastrointestinal systems review and investigations in any patient with unexplained liver disease.

Budd-Chiari Syndrome

This syndrome is characterized by venous outflow obstruction to the liver, which could be intrahepatic or extrahepatic (see Chapter 77). Acute venous obstruction is usually secondary to another pathologic process and presents with abdominal pain, vomiting, hepatomegaly, ascites, and jaundice, which may be mild. Hepatocellular failure leading to death is usually rapid. Chronic venous obstruction of the liver usually presents with ascites and hepatomegaly. If the inferior vena cava (IVC) is blocked with tumor or thrombus, gross edema of the legs and superficial venous distension of the abdominal veins is apparent. Diagnosis is made on imaging.

Hemochromatosis

Hemachromatosis is an iron overload state in which the liver is usually affected. Excess iron deposition leads to fibrosis and cirrhosis with an increased risk of developing hepatocellular carcinoma. Clinically, hemochromatosis usually presents between the ages of 40 and 60 years. Symptoms are usually nonspecific with lethargy, increased pigmentation, loss of body hair, loss of libido, arthralgia, and diabetes, usually due to the involvement of the pancreas. Clinical examination may show hepatomegaly and hyperpigmentation in the axillae, groins, and genitalia as well as testicular atrophy. Diagnosis is made by hematologic tests including serum iron, serum ferritin, and serum transferrin; liver damage can be assessed with a liver biopsy.

Polycystic Disease

Symptoms of polycystic disease are usually caused by the mass effect of the enlarged liver (see Chapter 69A). Abdominal

distention and breathlessness are common. Early satiety and vomiting can occur because of pressure on the stomach. Acute abdominal pain is usually due to infection or bleeding into a cyst.

Acute Liver Failure

Acute liver failure (ALF) is characterized by massive cellular injury to a previously healthy liver, and it is associated with the development of hepatic encephalopathy (see Chapter 72). This can occur as a result of paracetamol (acetaminophen) toxicity, usually caused by overdosage, or from a massive viral infection. ALF is associated with a high mortality and requires careful monitoring. Orthotopic liver transplantation is the only effective treatment for this condition, although some cases of ALF can recover spontaneously. Donor organ shortage has dictated the development of criteria that can help to predict whether a patient with ALF has a potential to recover or whether a liver transplant is required. More recently, these criteria have also been used to predict the prognosis of patients with cirrhosis undergoing surgery for hepatocellular carcinoma (Kuang et al, 2009). Various sets of criteria have been proposed, of which the Model for End-Stage Liver Disease (MELD) and the King's College Hospital (KCH) criteria are the best known. Most criteria utilize prothrombin time/INR, serum bilirubin, serum creatinine, arterial blood pH, and hepatic encephalopathy in categorizing patients' disease severity.

Liver Masses

Patients with large liver masses may be seen initially with right upper quadrant discomfort or a palpable mass in the upper abdomen. More often, liver masses are discovered during imaging as part of the investigation of jaundice, nonspecific abdominal symptoms, or follow-up of malignancy. If the liver mass is discovered incidentally, a full clinical history should be obtained with particular attention to gastrointestinal and respiratory symptoms. Details and duration of oral contraceptive and anabolic steroid use should be recorded. Relevant past history, especially of other malignancies, should be obtained, and the possibility of viral hepatitis should be considered. A thorough abdominal examination should be performed, especially for abnormal masses and ascites, and a digital rectal examination is mandatory at the initial assessment. Signs of jaundice, liver insufficiency, and development of collateral circulation should be sought. A comprehensive hematologic and biochemical screening (Table 12.3) should include an assessment of coagulation factors and of common tumor markers (α-fetoprotein, carcinoembryonic antigen (CEA), CA 19-9, CA 125). Cross-sectional imaging evaluation of liver masses is discussed later in this chapter (see Investigation of Hepatobiliary Disease; see also Chapters 16 and 17).

Table 12.3

Laboratory Investigations in Hepatopancreatobiliary Disease

Hematologic Tests

Complete blood count: erythrocyte sedimentation rate, reticulocyte count, haptoglobulin levels, Coombs test
Coagulation profile (prothrombin time)

Liver Function Tests

Conjugated and unconjugated bilirubin levels, aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, alkaline phosphatase
Proteins (albumin, globulin)

Immunologic and Serologic Tests

Mitochondrial antibodies
Smooth muscle and antinuclear antibody
Immunoglobulins
Hepatitis B surface antigens
Immunoglobulin M antibody to hepatitis A
Hepatitis C antibodies
Cytomegalovirus antibodies
Epstein-Barr virus antibody
Leptospiral agglutinins
Fasciola complement fixation test
Amebic complement fixation test
Hydatid complement fixation test
Wasserman reaction and other serologic tests for syphilis

Tumor Markers

Carcinoembryonic antigen
α-Fetoprotein
CA 19-9
α_1-Antitrypsin levels

Other Tests

Serum amylase
Plasma ceruloplasmin levels
Iron and iron-binding capacity
Spot blood alcohol
Urine (urobilinogen, hemosiderin)
Stools (ova and parasites)

GALLBLADDER AND BILIARY TRACT DISEASE

Gallbladder

Tenderness and guarding in the right hypochondrium exacerbated by inspiration (Murphy sign) suggests cholecystitis. If the gallbladder is palpable in the presence of obstructive jaundice, this suggests malignant obstruction of the biliary tree (Couvoisier's law), which is commonly due to carcinoma in the head of the pancreas. Failure to palpate the gallbladder does not exclude malignant disease, however, and a nonpalpable gallbladder is the rule in malignant obstruction at the hilus of the liver. A gallbladder that is intermittently palpable suggests the presence of a periampullary carcinoma (Kennedy & Blumgart, 1971). Gallbladder distension and signs of sepsis in the presence of gallstones may indicate empyema of the gallbladder. In such instances, initial treatment consists of percutaneous aspiration and drainage, with a cholecystectomy delayed for some time.

Acute Cholecystitis

Acute cholecystitis may begin with a constant dull ache that slowly increases in severity over time, usually a couple of days, and may be associated with anorexia, nausea and vomiting, and pyrexia. It arises as the result of acute inflammation of a distended, obstructed, and usually infected gallbladder (see Chapter 31). Patients may be more comfortable lying still because of the associated localized peritonitis, and coughing or sneezing may exacerbate the pain. Acute cholecystitis is often associated with tenderness (peritoneal irritation) in the right upper quadrant and signs of systemic infection (pyrexia, raised leukocyte count,

raised C-reactive protein), and it requires antibiotic therapy to settle the infection. An infected, obstructed gallbladder sometimes ruptures and causes generalized peritonitis or a liver abscess. It is important to examine patients with acute cholecystitis regularly, and if the pain and tenderness do not settle rapidly with antibiotic therapy, percutaneous drainage of the gallbladder or an emergency cholecystectomy may be required.

Biliary *colic*, which is a clinical entity distinct from acute cholecystitis, usually has a crescendo-decrescendo pattern, with the pain slowly building up to a peak over a few hours; this peak is often associated with vomiting, and the pain then gradually subsides over the ensuing few hours. Often the pain radiates to the back (Berhane et al, 2006), and this pattern of gallbladder pain is thought to arise from gallbladder nociceptors, in response to a rise in intracholecystic pressure caused by strong contraction of the gallbladder against an obstructed neck. Biliary colic usually settles spontaneously, leaving some residual soreness in the right upper quadrant. These attacks of pain can be widely variable in their occurrence, and some patients may have an interval of many years between attacks; others may have almost constant discomfort. Some patients report that the pain is triggered by certain foods, usually fatty foods, and some patients are afraid of eating for fear of triggering an attack of pain (sitophobia).

Cholelithiasis

Symptomatic cholelithiasis is the commonest indication for cholecystectomy. Unfortunately, the symptomatology of gallbladder stone disease has been hard to define despite research spanning decades (Johnson & Jenkins, 1975; see Chapter 30). A large epidemiologic investigation in Denmark into the relationship between abdominal symptoms and gallstones concluded that the predictive values of various abdominal symptoms for gallstones were very low. In patients with gallstones, the prevalence of right upper quadrant abdominal pain was similar to patients without gallstones but was higher in patients who had previously undergone cholecystectomy (Jorgensen, 1989). A larger, multicenter Italian study, MICOL, showed that in an Italian population, the presence of epigastric or right upper quadrant pain radiating to the right shoulder that forced the patient to rest and intolerance to fried or fatty food were good predictors of gallstones (Corazziari et al, 2008). A recent Swedish study that followed up 503 patients without gallstones for 5 years reported that the incidence of gallstone formation was 1.39 per 100 person-years, and that no change was seen in the symptoms of these patients before and after development of gallstones (Halldestam et al, 2009).

Studies examining the relief of symptoms after cholecystectomy suggest that approximately one quarter of patients undergoing cholecystectomy will not experience relief of symptoms, and that dyspeptic symptoms are least likely to be cured by cholecystectomy (Weinert et al, 2000; Jorgensen et al, 1991). A study comparing the symptomatic outcomes after cholecystectomy for functioning and nonfunctioning gallbladders showed no difference in outcome (Larsen et al, 2007). An important study outlined the variation in perceptions of what was considered a valid indication for cholecystectomy (Scott & Black, 1991). These authors showed the case histories of 252 patients to two panels, one comprising surgeons and the other a mixed panel of doctors. The mixed panel considered 41% of the operations appropriate for the indications and 30% inappropriate, but the surgeons considered 52% appropriate and 2% inappropriate but could not agree on the other 46%. It is therefore important that an accurate documentation of dyspeptic or atypical symptoms be made, and patients should be counseled that cholecystectomy may not relieve any of their symptoms.

Biliary Obstruction

Classically, pain is a discriminating feature in jaundiced patients. Patients with biliary tract obstruction resulting from tumor usually have painless jaundice (see Chapters 50A through 50D and Chapter 58B), whereas patients with an acute attack of pain or a long history of intermittent episodes of jaundice accompanied by pain frequently have gallstone disease (see Chapter 35). In the event of cholangitis, rigors and fever also are present. Jaundice unaccompanied by pain, and especially if the gallbladder is palpable, almost always indicates malignancy. Back pain usually indicates a pancreatic lesion; chronic pancreatitis and tumors of the pancreas can manifest in this manner. Patients with chronic pancreatitis occasionally are seen with jaundice, especially during an acute-on-chronic attack, and the jaundice may be accompanied by symptoms of endocrine and exocrine deficiency (diabetes, steatorrhea, malabsorption; see Chapter 55A).

Malignant disease affecting the hepatic ducts at the biliary confluence in the hilus of the liver often presents with jaundice (Fig. 12.9), but in such instances, the gallbladder is not palpable (see Chapter 50B). Itching can be an initial feature of biliary obstruction (Fig. 12.10), but in prolonged cholestasis, itching may occur in association with partial biliary obstruction and significantly in primary biliary cirrhosis. Alkaline phosphatase often is markedly increased in partial biliary obstruction, even though the bilirubin may be only marginally elevated. A markedly increased or increasing alkaline phosphatase level may be the only sign of an early malignant or benign biliary stricture.

The distinction between obstructive (surgical) jaundice and hepatocellular (medical) jaundice is seldom the problem it was in the past. Hematologic and biochemical tests of liver function (Table 12.4) usually indicate whether the jaundice is obstructive, but this is not always the case. Identification of the cause and level of biliary obstruction is essential. Ultrasound (Chapter 13) is the preferred initial imaging test for diagnosis of biliary obstruction and to determine the etiology and level of obstruction. Computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP; see Chapters 16 and 17) are also extremely useful for evaluation of biliary obstruction.

Bile Duct Stones

The human bile duct is sensitive to acute distension, and obstruction of the lower end of the bile duct by a gallstone may cause epigastric pain that may radiate to the chest and back. Cholesterol bile duct stones are lighter than bile, and any distension of the bile duct may cause these stones to float proximally, releasing the obstruction. The symptoms of bile duct stones are typically intermittent jaundice associated with upper abdominal pain.

Acalculous Biliary Pain

Acalculous biliary pain is considered to be the result of a "functional" motor disorder of the gallbladder and/or sphincter of Oddi (Behar et al, 2006). Gallbladder motor dysfunction giving

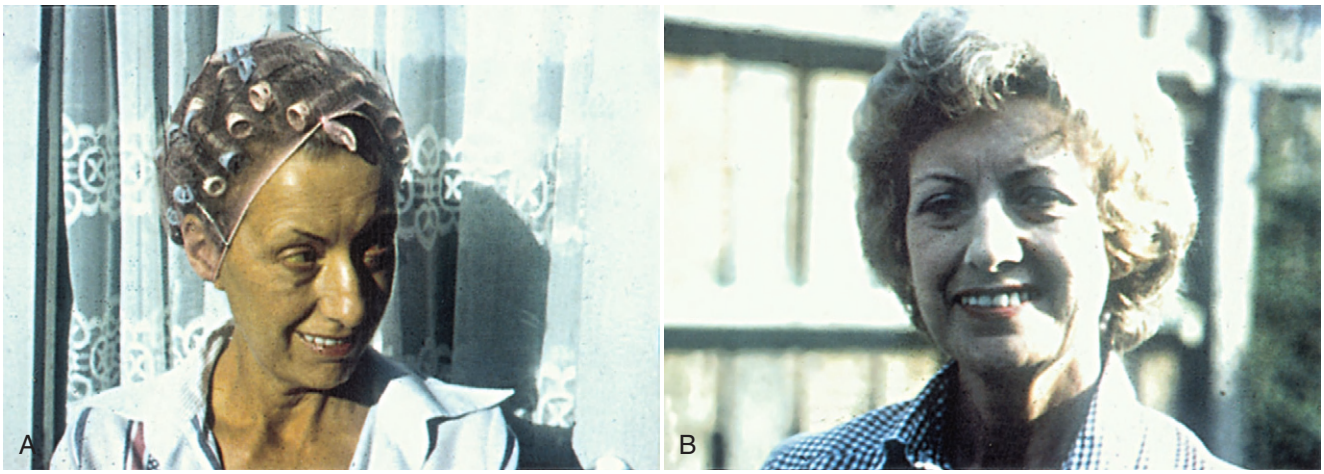


FIGURE 12.9. This patient initially presented with obstructive jaundice resulting from hilar cholangiocarcinoma. She had lost a great deal of weight and was anorexic and had intermittent attacks of cholangitis. Treatment was extended right hepatic lobectomy with excision of the biliary confluence and hepaticojejunostomy with Roux-en-Y to the left hepatic ducts. Four years later, she shows an excellent result: no tumor recurrence, normal liver function tests, and the patient has gained weight.



FIGURE 12.10. **A,** Patient with severe itching associated with primary biliary cirrhosis. She is scratching her back with a wooden back scratcher. **B,** Severe excoriation of the legs caused by scratching in a woman with severe itching resulting from primary biliary cirrhosis.

Table 12.4

Liver Function Aberrations in Obstructive and Hepatocellular Jaundice*

Parameter	Value	Obstructive Jaundice	Hepatocellular Jaundice
Bilirubin	Assesses severity; unconjugated bilirubin increases in hemolysis	↑↑↑↑	↑↑
Alkaline phosphatase	Marker of cholestasis	↑↑↑↑	↑↑
Alanine aminotransferase	Marker of hepatocellular damage	↑↑	↑↑↑↑
Aspartate aminotransferase	Marker of hepatocellular damage	↑↑↑	↑↑↑↑
γ-Glutamyltransferase	Marker of alcohol abuse and biliary stasis	↑	↑↑↑
Albumin	Marker of synthetic function	↓ or normal	Usually ↓↓
Prothrombin time†	Marker of synthetic function	↑↑↑	↑↑↑↑

*Prolonged biliary obstruction causes hepatocellular damage.
†Coagulopathy associated with biliary obstruction can be rapidly reversed with vitamin K, but not so in hepatocellular damage.

rise to abdominal pain has been defined by the Rome II Committee on Functional Biliary and Pancreatic Disorders as episodes of severe, steady pain located in the epigastrium and right upper quadrant and all of the following: episodes last 30 minutes or more, symptoms have occurred on one or more occasions in the previous 12 months, the pain is steady and interrupts daily activities or requires consultation with a physician, no evidence of structural abnormalities explains the symptoms, and gallbladder function is abnormal with regard to emptying. To eliminate calculous disease from the differential diagnosis, the Rome II Committee recommendations in the evaluation of these patients includes screening tests: upper gastrointestinal endoscopy, liver biochemisty, pancreatic function tests, and ultrasound of the gallbladder should be normal, and microlithiasis of bile should be excluded by endoscopic aspiration at endoscopic retrograde cholangiopancreatography (ERCP) or by aspiration of bile from the duodenum after stimulation by cholecystokinin (CCK) or magnesium sulfate. The recommended tests for gallbladder function are CCK cholescintigraphy assessment of gallbladder emptying, CCK- or meal-stimulated ultrasonographic volumetry of the gallbladder, and CCK-induced pain provocation tests. The Committee recommended that abnormal gallbladder emptying after CCK stimulation (<40% ejection) is an acceptable indication for cholecystectomy, as medical therapies are usually not effective (Corazziari et al, 1999).

Unfortunately, no consensus exists regarding the infusion rate of CCK that in turn can directly influence gallbladder emptying. Delgado-Aros and colleagues (2003) and DiBaise and Oleynikov and colleagues (2003) reported meta-anlayses of studies examining the symptomatic benefit from cholecystectomy based on abnormal CCK-stimulated gallbladder emptying. They found no good evidence to support the use of CCK-stimulated gallbladder ejection fraction to select patients for cholecystectomy. Similar findings were reported by Rastogi and colleagues (2005). Smythe and colleagues (1998) conducted a critical evaluation of CCK-provoked gallbladder pain and concluded that this test was not a predictor of symptomatic relief after cholecystectomy. It is interesting to note that in a prospective randomized study examining the development of symptoms in patients with uncomplicated gallbladder stones, a CCK-stimulated ejection fraction greater than 60% was independently associated with the development of symptoms.

The etiology and pathogenesis of calculous and acalculous gallbladder pain are poorly understood despite some recent insights by mathematical modeling (Li et al, 2007, 2008; Bird et al, 2006; Wegstapel et al, 1999; Ooi et al, 2004; Ahmed et al, 2000). We would therefore currently recommend that patients experiencing recurrent and severe symptoms as defined by the Rome II criteria should be offered cholecystectomy but should be carefully counseled regarding the uncertainty of its outcome, and this counseling should be clearly documented.

Sphincter of Oddi Dysfunction

Sphincter of Oddi (SO) dysfunction may be present in patients with an intact biliary tree, but it usually comes to light as a potential diagnosis when symptoms continue after a cholecystectomy. SO dysfunction has been subclassified into a biliary or pancreatic type. *Biliary type* SO dysfunction in postcholecystectomy patients has been arbitrarily subclassified into types I, II, and III. *Type I SO dysfunction* is defined as pain, elevated liver function tests documented on two or more occasions, delayed contrast drainage, and a dilated common bile duct with a corrected diameter of 12 mm or more at endoscopic retrograde cholangiopancreatography (ERCP). *Type II SO dysfunction* is characterized as pain only with one or two of the criteria in Type I. *Type III SO dysfunction* is defined as recurrent biliary-type pain with none of the criteria from type I. Toouli (2009) concluded that accurate sphincter manometric data is crucial to establish a diagnosis of SO dysfunction. Invasive investigation of sphincter dysfunction and/or sphincterotomy is associated with a risk of pancreatitis in up to 30% of patients. Insertion of prophylactic pancreatic stents are advocated as a means of reducing this risk, and some evidence exists to support this practice. Injection of botulinum toxin into the sphincter also has been advocated as a "therapeutic test" before a sphincterotomy is performed. In a literature review, Sgouros and Pereira (2006) concluded that biliary sphincterotomy reliably treats symptoms in 85%, 69%, and 37% of patients with types I, II, and III SO dysfunction, and pancreatic sphincterotomy may benefit up to 75% of patients. They state that sphincter manometry is the gold standard in the investigation. *Pancreatic type* SO dysfunction is also subclassified into types I, II, and III according to whether pancreatic enzymes are elevated soon after an attack of pain and whether the pancreatic duct is dilated greater than 5 mm.

Iatrogenic Biliary Injury

Patients with iatrogenic damage to the biliary tract (see Chapter 102) may not only present with jaundice because of biliary stricture but also may present with biliary leakage, resulting in biliary peritonitis or fistula. In such patients it is important to obtain a good history that includes a copy of the original operative report, which may offer an indication as to the level and nature of the injury and may provide a baseline for comparison with further investigations. Many patients may present with biliary and abdominal sepsis, and blood and bile cultures should be obtained. If a biliary fistula is present, or if the patient is deeply jaundiced, coagulation may be deranged. Liver function tests may show biochemical evidence of biliary obstruction or of liver damage, and patients are often nutritionally depleted and may be anemic. Ongoing liver damage may be present, resulting from a combination of sepsis and biliary obstruction.

Imaging with CT and MRCP may yield valuable information in these patients. MRCP can accurately depict areas of stricture and fistula formation, and CT can be used to guide intervention and drainage. The key question is whether the biliary tract is intact and in continuity. In patients with a biliary fistula, fistulography may outline the problem; but ERCP and percutaneous transhepatic cholangiography are more useful, because they provide a dynamic view of the site and show the severity of leakage, which may allow a stent to be placed across the site of the leak. Associated vascular injuries should be suspected and may be suggested at imaging. Extensive bleeding at the time of cholecystectomy should lead to a high index of suspicion for vascular injury. Hepatic arterial injury is usually well compensated, and portal venous injury may be revealed by the presence of liver atrophy, usually best seen on CT. Occasionally, long-standing biliary strictures result in secondary biliary cirrhosis, and liver biopsy may be necessary.

PANCREAS

Acute Pancreatitis

Acute pancreatitis is usually accompanied with severe upper abdominal pain that develops rapidly, becomes constant, and persists for several hours (see Chapter 53). The pain typically starts in the epigastrium but may soon spread throughout the abdomen and radiate into the back. Sometimes the patient may find relief by sitting forward, but usually they lie still and curled up in bed. The pain can be so sudden in onset that at times, it can simulate a perforated peptic ulcer, and indeed acute pancreatitis can mimic almost every cause of acute abdominal pain and may even produce chest pain that simulates myocardial infarction, pneumonia, or pleurisy. Frequent vomiting and sequestered fluid in the small bowel may lead to rapid and severe dehydration. Even keeping the stomach empty with a nasogastric tube may not prevent the patient from retching, and marked nausea is almost a constant feature. Hiccoughs can also occur due to diaphragmatic irritation secondary to extension of the inflammatory process tracking up via the retroperitoneum.

Patients with acute pancreatitis may exhibit signs of profound shock with tachycardia, tachypnea, hypotension, and confusion. At the other extreme, patients may appear well, with little in the way of physical signs. The patient may be afebrile on admission, but progression of the inflammatory process leads to fever, facial flushing, and mild jaundice. Abdominal examination usually reveals marked tenderness in the epigastrium with guarding, but marked rigidity as seen in a perforated ulcer is often lacking. The presence of a paralytic ileus may result in abdominal distension with a tympanitic percussion note and diminished bowel sounds. Later features may include a discoloration around the umbilicus (Cullen sign) or in the flanks (Grey-Turner sign) as a result of bruising within the fascial planes, pancreatic ascites, and a pleural effusion. A mass is rarely present, unless the inflammatory process has resulted in a pancreatic abscess or sizeable pseudocyst. General features of acute pancreatitis may include confusion, disorientation, hypoxemia, and even adult respiratory distress syndrome. The associated hypocalcemia rarely results in clinical signs of neuromuscular irritability.

Rarely, acute pancreatitis can occur without severe pain, and in these cases, the diagnosis can be missed, and such failure may be associated with a poor prognosis (Lankisch et al, 1991). It is important to be aware of the condition and consider it in any patient who develops sudden shock or anuria, especially if it follows biliary surgery, ERCP, coronary artery bypass, or trauma. A detailed history is therefore vital, particularly inquiring as to the past medical history and family history, especially in children. Any history of alcohol abuse, bilary colic, jaundice, recent surgery, or ERCP should be actively sought.

Most cases of acute pancreatitis are associated with alcohol abuse or biliary disease but can also follow ERCP; abdominal surgery, especially to the stomach, duodenum, and biliary tree; coronary artery bypass surgery; trauma; and certain viral illnesses, especially mumps. The association with alcohol abuse varies according to country and urbanization, being as high as 65% in parts of urban America. Biliary disease is responsible for over 30% of cases in a general population, and sieving the feces of patients with gallstone-associated pancreatitis shows gallstones present in a high proportion of them (Kelly, 1976), prompting many to speculate that the pancreatitis resulted from the temporary lodging of a stone in the ampulla of Vater. Postoperative pancreatitis accounts for 5% to 10% of cases (Thompson et al, 1988), and hyperamylasemia can occur in about 10% of patients undergoing ERCP, although only 1% will develop severe acute pancreatitis. The cause of traumatic pancreatitis is again subject to geographical variation (Jones, 1985); penetrating trauma is more common in the United States and blunt trauma and injury as a result of traffic accidents are more common in the United Kingdom. Other rare causes include hyperparathyroidism, hyperlipidemia, and certain drugs including steroids, azothiaprine, and diuretics (Nakashima & Howard, 1977). However, once all these causes have been excluded, for about 25% of patients, no clear etiology is identified. The sex ratio for acute pancreatitis is virtually equal but tends to have a higher peak age incidence in women, reflecting the higher incidence of gallstones; in men the lower peak age reflects their propensity to alcohol abuse.

Chronic Pancreatitis

There are few pathognomonic or diagnostic signs for chronic pancreatitis, and diagnosis usually depends on the history and special investigations (see Chapter 55A). The patient may appear malnourished with signs of weight loss, they may be icteric as a result of compression of the common bile duct by the fibrotic process in the head of the pancreas, and erythema

ab igne may be present on the back or abdomen. Uncommonly, a palpable mass, pseudocyst, or splenomegaly may be evident, and occasionally pancreatic ascites, if there has been rupture of a pseudocyst or of the duct system.

Chronic pancreatitis is a difficult condition both to diagnose and to treat. It is crucial to exclude other associated conditions, such as pancreatic cancer; but once the diagnosis is established, it is important to 1) identify any predisposing cause, 2) stage the severity of the disease, and 3) document any morphologic and functional changes against which any progression can be assessed. One of the commonest predisposing factors is alcohol abuse, although chronic pancreatitis is also associated with biliary disease, congenital abnormalities such as an annular pancreas (Dowsett et al, 1989), ductal abnormalities, and rarely with hyperparathyroidism. An autosomal dominant hereditary form of the condition may also be a factor, so a family history is crucial (Teich, 2008). Rarely is any specific drug or dietary factor implicated.

Pain is the commonest presenting symptom of chronic pancreatitis and is often the most difficult to control. The pain is usually situated in the epigastrium and subcostal regions and commonly radiates through to the back. Pain can be severe and penetrating in nature, and often the patient will lean forward or curl up to relieve the discomfort. In severe cases, the patient may even kneel on all fours to gain relief. Occasionally, the pain may radiate to the left shoulder tip. Variation in the pattern of pain in these patients is enormous, and some are never free of discomfort, but others may simply complain of intermittent attacks. In some, these severe bouts may be brought on by eating or ingesting alcohol, although often no clear association is made between attacks and oral intake. In many the pain is so debilitating that it interferes with the patient's domestic, social, and occupational activities and can have a devastating impact on the quality of life. Indeed, in many it results in a change in personality with a manipulative tendency often associated with an addiction to opiates. These patients can be particularly difficult to assess, especially if they are already addicted to alcohol.

Other presenting symptoms include marked steatorrhoea resulting from diminished lipase production and inadequate fat absorption (Di Magno, 1982). The stool frequency may be increased up to six times a day, and the stools themselves become pale and bulky with an offensive odor, and they float, making them difficult to flush away. However, this is not a constant feature of chronic pancreatitis; some patients may even suffer from constipation as a result of the increased use of opiate analgesia.

The incidence of diabetes mellitus is a variable and often late feature. As chronic pancreatitis progresses, there may be loss of endocrine function, initially requiring dietary control and subsequently oral hypoglycemic agents or even insulin. Other more general features of chronic pancreatitis may include weight loss, nausea and vomiting, jaundice, and even gastrointestinal bleeding as a result of splenic vein thrombosis, although this is rare.

Pancreatic Cancer

Regretfully, physical signs of pancreatic cancer are often absent or infrequent, until the lesion is unresectable (see Chapter 58B). The patient may be symptomatic with weight loss, but unless the lesion is situated in the head of the pancreas such that it obstructs the common bile duct early, causing obstructive jaundice, few other signs may be evident. With distal bile duct obstruction, the gallbladder may become distended (Courvoisier gallbladder). An abdominal mass and ascites are late signs and usually herald inoperability. Systemic signs such as flitting thrombophlebitis migrans may be apparent, but this is uncommon and nonspecific. All too often cachexia is the only physical finding.

Later clinical features of pancreatic cancer are pain, weight loss, and jaundice. The pain is often severe and gnawing and radiates to the back. It is often worse at night, when the patient is lying flat, which usually indicates tumor extension to the retroperitoneum, often signifying irresectability. Weight loss may be marked, and in many cases of tumors in the body of the pancreas, weight loss may be the only symptom, until pain indicates invasion of the peripancreatic tissue. The more rapid the weight loss, the less likely the lesion is to be resectable (Bakkevold et al, 1992). Jaundice can be associated with severe pruritus, but this classical presentation only occurs when the lesion is in the head of the pancreas; when jaundice occurs with tumors of the body or tail of the pancreas, it usually signifies hilar liver or nodal metastases.

About 5% of patients with pancreatic cancer will have developed diabetes mellitus within the 2 years prior to diagnosis (Pannala et al, 2009). Other signs such as ascites, an epigastric mass, or enlarged supraclavicular nodes (Virchow sign) are indications of inoperability. Because of the lack of specific signs and symptoms, very commonly a diagnostic dilemma arises as to whether a lesion is chronic pancreatitis or pancreatic cancer. Frequently, diagnostic imaging cannot provide the answer, and even at operation it may not be apparent which condition the surgeon is facing; this occured in up to 15% of cases in some series (Mao et al, 1995).

INVESTIGATION OF HEPATOBILIARY DISEASE

All patients with suspected hepatobiliary and pancreatic disease should undergo a comprehensive hematologic and biochemical screening, including an assessment of clotting capability. The history may dictate additional serologic tests—tumor markers such as α-fetoprotein, CA 19-9, CEA—and immunologic tests, such as a viral hepatitis screening. Particular attention needs to be paid to the platelet count, coagulation profile, and liver function tests (see Tables 12.3 and 12.4).

Imaging of incidentally discovered liver masses should be directed toward characterizing the liver lesions. Magnetic resonance imaging (MRI) is usually highly specific in characterizing liver masses (Seneterre et al, 1996), and it can be used to differentiate between benign and malignant lesions (see Chapter 17). Contrast-enhanced CT scan of the chest, abdomen, and pelvis is mandatory in patients with suspected malignancy of the liver to exclude extrahepatic disease and to determine resectability (see Chapter 16). In the presence of resectable disease, liver biopsy is seldom indicated, because many lesions can be characterized by imaging and clinical features; biopsy is generally reserved for patients with nonresectable tumors that require histopathologic confirmation prior to instituting therapy (Thompson et al, 1985).

It is important to assess the patient in terms of fitness for surgery, nutritional status, cardiorespiratory and renal function, and parenchymal liver disease. It is vital to be aware of the Child-Pugh stage of the liver disease before planning any

treatment of hepatocellular cancer (see Chapter 80). An array of autoantibodies is used to diagnose autoimmune hepatobiliary disorders, and some of these are listed in Table 12.3.

Cardiorespiratory disease and fitness for surgery are assessed during history taking and may indicate the need for further detailed study. These additional investigations are often conducted with advice from anesthesiologists, in the event a major surgical procedure is contemplated. Nutritional status can be determined crudely by hemoglobin, protein, and albumin levels and is often abnormal, especially if liver function has been compromised for a long time. Continuous fine-bore enteral tube feeding may be instituted in these patients to try to optimize nutritional status before surgery (Allison, 2004; Lidder & Lewis, 2004). If renal function is abnormal, creatinine clearance quantifies the problem and may indicate the need for renal support in the perioperative period (Thompson et al, 1987).

Many patients with hepatobiliary and pancreatic disease may have undergone instrumentation of the biliary tract. ERCP or percutaneous transhepatic cholangiography may have been employed. Biliary sepsis is extremely common after these procedures (Brody et al, 1998; Heslin et al, 1998; Povoski et al, 1999). If external biliary drainage has been used, it is important to culture the biliary output, even if no evidence of systemic sepsis is present. In such cases, no immediate indication for antimicrobial therapy is apparent, but culture and sensitivity will guide future therapy. In particular, perioperative antibiotic therapy is indicated in these patients. Systemic sepsis requires urgent broad-spectrum antibiotic therapy, subsequently guided by the results of blood culture and sensitivity tests. Patients with long-standing partial biliary obstruction and sepsis have a high likelihood of fungal infections.

Colorectal Liver Metastases

Liver metastases from primary colorectal cancer are frequently discovered at the time of diagnosis on the staging CT scan (see Chapter 81A). Metastases may occasionally be detected during operation on the primary tumor, especially if this is done as an emergency procedure. They are also frequently discovered as metachronous tumors during follow-up after resection of primary colorectal cancer. Follow-up strategies in patients with colorectal cancer are a subject of much debate, and no clear consensus exists. In patients with no perioperatively detected metastatic disease and an R_0 colonic resection, it is advisable to image the chest, abdomen, and pelvis with contrast-enhanced CT scan at 9 months and 2 years postresection. If metachronous liver metastases are detected, resectability is determined by the patient's ability to undergo potentially major liver surgery by the location and segmental distribution of the hepatic metastases and by the presence of extrahepatic disease. Positron emission tomography (PET) and CT scan can be most useful in this regard (see Chapter 15). Recent reports have shown added benefit of contrast-enhanced MRI scan to determine resectability (Blyth et al, 2008; Hekimoglu et al, 2009). Synchronously detected liver metastases may be resected at the time of the resection of the primary lesion or as a second procedure, sometimes after the administration of neoadjuvant chemotherapy.

It is important to note that metastatic disease in the liver, especially in its early stages, may not give rise to symptoms and can only be detected by screening these patients. Regular serum CEA levels are useful in the follow-up of these patients, and combined with interval CT scanning, this should detect the majority of colorectal liver metastases.

INVESTIGATION OF PATIENTS WITH PANCREATIC DISEASE

In patients with acute pancreatitis (see Chapters 53 and 54), diagnosis usually is made based on the history and the serum amylase and lipase levels. An elevated serum amylase can fall quite rapidly, and it may be normal if measured 2 to 3 days after the onset of the attack. Urinary amylase may be elevated in these patients, however, a contrast-enhanced CT scan often confirms the diagnosis but is particularly poor at identifying gallstones. An ultrasound scan is usually the first investigation of choice, because it detects gallstones and allows the patient to proceed to endoscopy and endoscopic sphincterotomy when appropriate. In patients with acute pancreatitis, the duodenum and small bowel often are filled with gas, and detection of common bile duct stones is less reliable.

Serum amylase is of no value in predicting the severity of an attack, and scoring systems have been developed, such as the Ranson and Glasgow scores. Scoring systems are accurate in predicting outcome only after 48 hours. Inflammatory markers such as C-reactive protein are also are valuable, but similarly to the Ranson and Glasgow scores, such markers may not assess severity accurately until 48 hours after onset. The Acute Physiology, Age, and Chronic Health Evaluation (APACHE II) is a more accurate predictor of severity at admission, but its complexity limits its routine clinical use.

In patients who remain unwell 1 week after onset, or in those who deteriorate after initial improvement, pancreatic necrosis should be suspected, and a contrast-enhanced CT scan should be performed (British Society of Gastroenterology, 2005). Patients judged to have a severe attack of pancreatitis at onset are at high risk of developing a systemic inflammatory response syndrome and require very careful and repeated observation with attention to fluid balance, nutrition, and sepsis. Prophylactic antibiotic therapy in this group of patients is useful and may prevent the development of infected pancreatic necrosis. Patients with clinically and biochemically severe pancreatitis should be managed in conjunction with critical care physicians in a suitable environment. Patients may go on to develop pancreatic pseudocysts that may cause pain or other effects as a result of pressure on neighboring organs, especially the stomach. Nausea, vomiting, or early satiety should alert the physician, as these pseudocysts are easily detectable on CT scanning. Continuing evidence of systemic sepsis usually indicates the presence of infected pancreatic necrosis, which can be confirmed by fine needle aspiration.

In patients with chronic pancreatitis, serologic blood tests such as amylase, lipase, and elastase are not helpful, but C-reactive protein may indicate active inflammation. Fecal elastase may indicate exocrine deficiency, whereas routine hematologic and biochemical tests, including glycosylated hemoglobin, are important to provide a baseline for endocrine assessment.

It may be difficult to differentiate between pancreatic carcinoma and some cases of chronic pancreatitis, as there are no clear-cut markers for this, although lymphoplasmacytic sclerosing pancreatitis is usually accompanied by an elevated serum IgG. The tumor marker CA 19-9 has a sensitivity of 80% and a specificity of 75% for pancreatic cancer (Kim et al, 1999), but

as the level tends to correspond with tumor volume, potentially curative tumors may be associated with normal levels (Eloubeidi et al, 2004; Schlieman et al, 2003), which limits its use as a screening tool. Very high levels of CA 19-9 are associated with a higher incidence of metastatic disease (Maithel et al, 2008), and laparoscopy is advocated to determine the presence of subradiological metastatic disease in patients with a CA 19-9 level above 150 kU/L (nonjaundiced patients) and above 300 kU/L in jaundiced patients (Halloran et al, 2008).

A contrast-enhanced spiral CT scan using thin (3 to 5 mm) slices provides information as to the extent and nature of any mass and in particular helps differentiate solid from cystic lesions, vascular involvement or encasement, and lymph node metastases. No significant advantage of gadolinium-enhanced MRI over multidetector CT has been seen in the staging of pancreatic cancer (Park et al, 2009), but multidetector CT has a better diagnostic yield (Satoi et al, 2009). MRCP can be useful in the differential diagnosis of pancreatic cystic masses and duct delineation, and endoscopic ultrasound may contribute substantially to the assessment of ampullary tumors (Kahaleh et al, 2004), for image-guided aspiration of pancreatic cysts, and to obtain biopsies of intrapancreatic tumors.

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CHAPTER 13

Ultrasound of the liver, biliary tract, and pancreas

Terry S. Desser and Lucy E. Hann

ULTRASOUND TECHNOLOGY

Ultrasound is a high-resolution, low-cost imaging technique that uses no ionizing radiation. Its versatility and real-time imaging capability are also major advantages. Another unique advantage is Doppler ultrasound, which allows visualization of blood flow and assessment of flow dynamics. Ultrasound units are now smaller and more portable, so they are widely used in multiple medical settings, including the bedside, operative suite, emergency room, and in diagnostic and interventional radiology suites. Miniaturized high-resolution transducers also facilitate laparoscopic and endoscopic procedures (Berber et al, 2004; Machi et al, 2004).

Despite these broad applications for ultrasound, certain limitations influence its applicability. Ultrasound is not transmitted past bone or air interfaces with soft tissue, so some areas may be obscured or imaging access limited. Another factor is that ultrasound has a limited field of view compared to computed tomography (CT) or magnetic resonance (MR) imaging; this may pose some difficulty for localization and follow-up of lesions. Lastly, ultrasound is very operator dependent; quality of ultrasound imaging and diagnosis is influenced greatly by the experience of the examiner.

Principles of Ultrasound Interpretation

Gray-scale sonography employs a pulse-echo technique to generate a two-dimensional display of the backscattered signal from insonated tissue. The intensity of the received echoes is recorded as brightness in the image. The strength of the echo at a tissue boundary is determined by *acoustic impedence*, defined as the product of tissue density and the speed of sound in the tissue. Sonographic scanners assume a uniform velocity of sound (1540 m/s) to compute the depth from which the received echo originated. Higher frequency sound has a shorter wavelength and therefore better spatial resolution, but a high-frequency sound beam attenuates more and has less tissue penetration. For this reason, lower frequency transducers are used to image structures deep within the abdomen, and higher frequencies are used to image more superficial structures (Zagzebski, 1996).

Gray-Scale Ultrasound Terminology and Artifacts

Lesions that appear dark relative to the background tissue are termed *hypoechoic*; those that are brighter than background are *hyperechoic* or *echogenic* (Fig. 13.1). Spaces that contain fluid do not contain internal interfaces, so no sound is reflected from within them; they appear uniformly black or *anechoic*. The ultrasound scanner normally compensates for the attenuation of sound that occurs with increasing depth within the tissue by amplifying echoes that return later from the far field. This is called *time-gain compensation* (TGC) or *depth-gain compensation*. TGC results in needless amplification of echoes from areas deep to pure fluid structures, because the acoustic pulse is attenuated to a lesser extent by fluid than by tissue. Such artificially bright areas beyond the fluid represent *increased through transmission*, or *acoustic enhancement* (Fig. 13.2). Although technically an artifact, acoustic enhancement is useful to characterize structures as cystic if they also lack internal flow on color Doppler.

Several other ultrasound artifacts also are used for diagnosis. At boundaries with large acoustic impedance mismatches, such as between tissue and air or tissue and bone, nearly all the energy in the incident beam is reflected; because none is transmitted, areas beyond the interface will not be visualized. A black *acoustic shadow* is thereby produced behind the object in the image (Fig. 13.3). Shadowing is characteristic of virtually all gallstones and greatly aids in distinction of gallstones from gallbladder polyps.

Within fluid-filled structures such as the gallbladder, faint echoes are often seen paralleling the anterior surface. These echoes represent *reverberation* artifact, which occurs as the sound is repeatedly reflected between the highly echogenic anterior gallbladder wall and the transducer. Reverberation also accounts for *comet tail artifact*, a streak of tiny, bright, parallel bands tapering behind a punctate crystalline reflector, generated by sound echoing within the crystal itself. Comet tail artifact is a feature of adenomyomatosis of the gallbladder and emanates from cholesterol crystals trapped in dilated Rokitansky-Aschoff sinuses in the gallbladder wall (Fig. 13.4). Fluid-filled structures may also have artifactual echoes along the dependent wall that originate from off-axis portions of the ultrasound beam. This is termed *side lobe artifact* and may be distinguished from true debris by changing the angle of insonation or repositioning the patient (Feldman et al, 2009; Zagzebski, 1996).

Doppler Ultrasound

Doppler techniques offer unique capability for imaging blood flow. When transmitted sound strikes a moving object, the reflected signal changes frequency; this phenomenon is defined by the Doppler equation. Doppler imaging allows assessment of 1) vessel patency, 2) direction of blood flow, 3) flow velocity, and 4) spectral waveforms.

Three different Doppler displays are available (Fig. 13.5). Color Doppler displays show flow velocity and direction of flow



FIGURE 13.1. Transverse gray-scale ultrasound image of the liver shows the right hepatic vein (*hv*) as a black (anechoic) fluid-containing structure. Note that the walls of the veins are bright (echogenic). The echogenic *curved line* posteriorly represents the diaphragm.

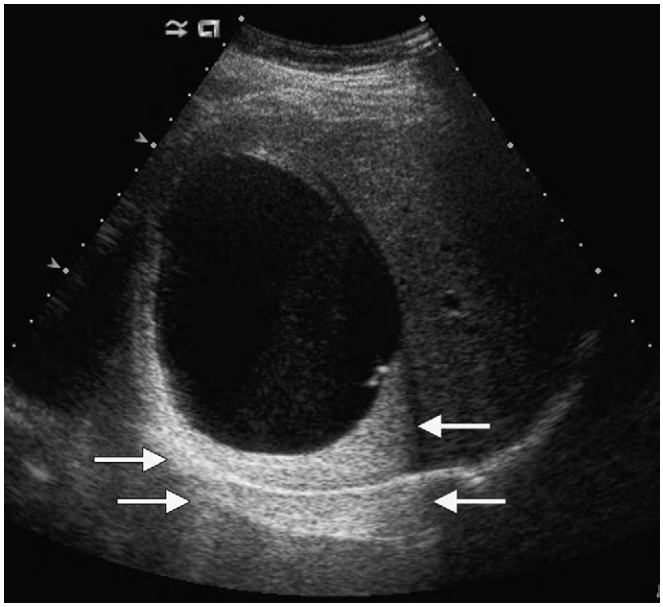


FIGURE 13.2. Simple hepatic cyst has no internal echoes and a thin smooth wall. Note the bright posterior acoustic enhancement (*arrows*) that is a characteristic feature of a cystic lesion.

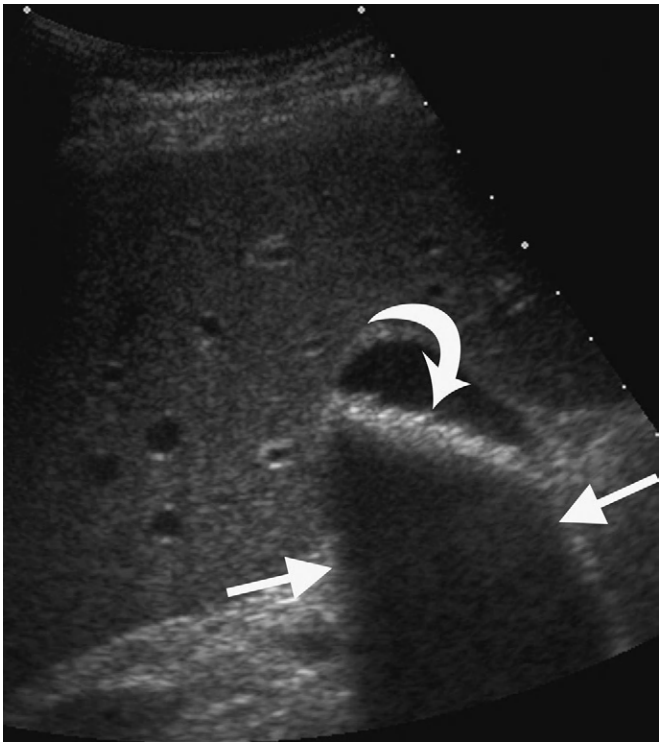


FIGURE 13.3. Gallstones (*curved arrow*) layering in the gallbladder produce an acoustic shadow (*straight arrows*).

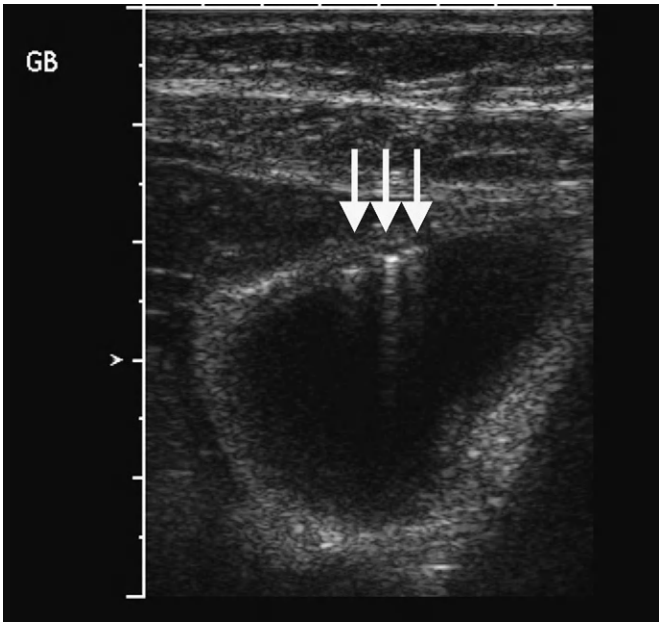


FIGURE 13.4. Bright reflectors in the gallbladder wall (*arrows*) produce comet tail, or ring-down, artifacts secondary to sound reverberation. This appearance is characteristic of gallbladder adenomyomatosis.

toward or away from the transducer. A graphic or bar on the color Doppler image indicates the colors designated for flow toward and away from the transducer and the range of displayed velocities. Focal areas of high velocity that exceed the highest value on the Doppler setting produce a disorganized color signal; this is an artifact termed *color aliasing* that is useful to identify high-velocity flow, which may indicate vascular stenosis or encasement. Power Doppler displays amplitude of flow but not flow direction, and the signal is not dependent on the angle of insonation. Power Doppler is most useful to show areas of low flow and to demonstrate intralesional vascular patterns.

Spectral Doppler displays a graph of the entire range of velocities over time, rather than the mean velocity, as in a color Doppler image. When combined with gray-scale and/or color

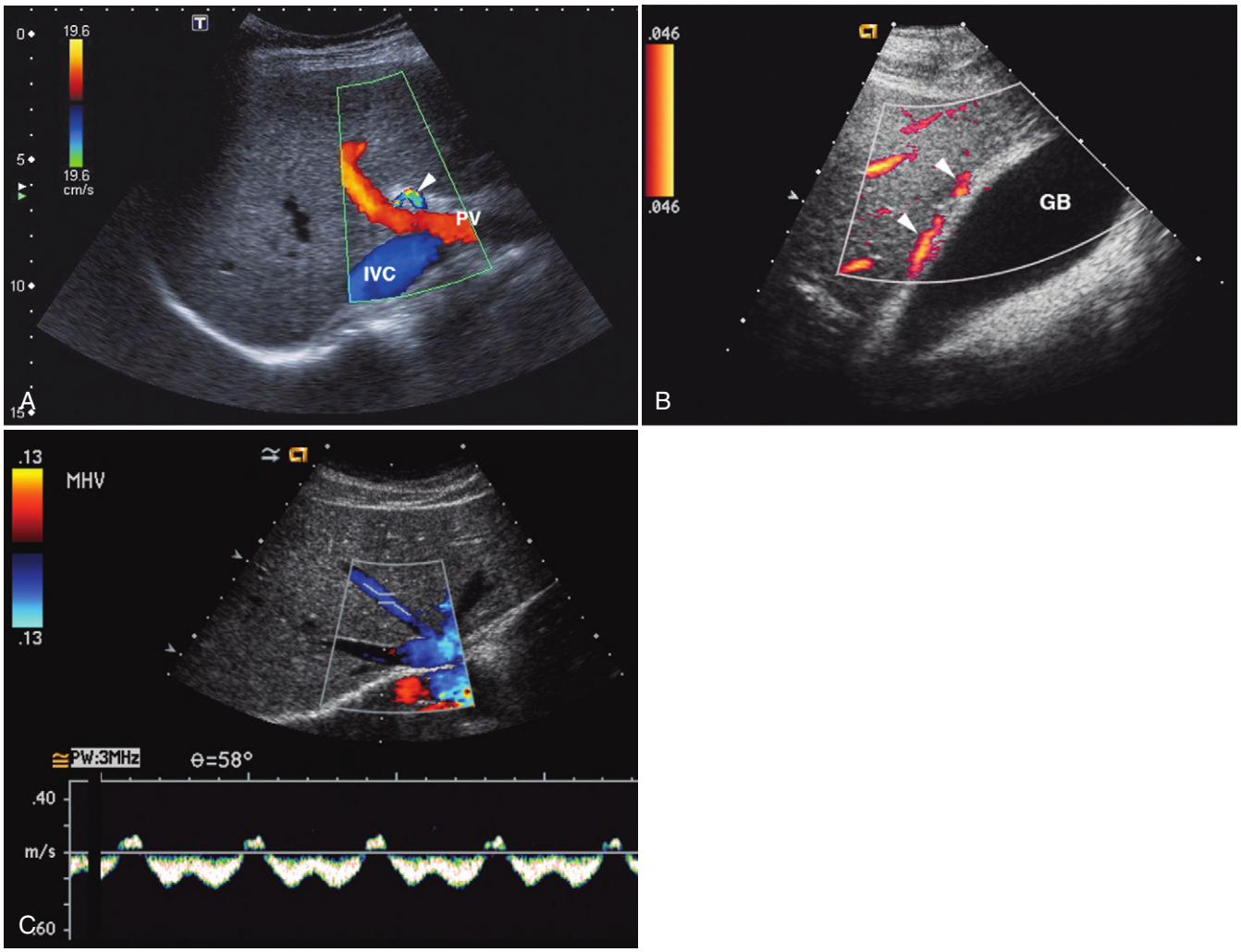


FIGURE 13.5. Doppler ultrasound of the liver. **A,** Color Doppler mode shows mean flow velocity and direction of flow toward or away from the transducer, as indicated in the *bar display at left* of the image. The portal vein (*PV*) indicates hepatopetal flow. The inferior vena cava (*IVC*) shows flow away from the transducer. The hepatic artery (*arrowhead*) has mixed signals due to high-velocity flow and aliasing. **B,** Power Doppler shows amplitude flow but not direction. It is useful for small vessels and low flow, as shown in this image of vessels in the gallbladder (*GB*) wall (*arrowheads*). **C,** Spectral Doppler shows flow pattern over time; when angle corrected, it can measure true velocity. A sample cursor is placed within the vessel, as shown in this transverse image of the middle hepatic vein. Flow variations are due to changes in right atrial pressure.

Doppler imaging in real time, it is possible to sample flow in specific blood vessels. For arterial flow, the peak systolic velocity and end-diastolic velocity indicate the strength of the inflow pressure and the downstream resistance. A useful metric for arterial waveform evaluation is the *resistive index*, defined as the difference between the peak systolic and end-diastolic velocities divided by the peak systolic velocity. A resistive index close to 1 implies nearly absent diastolic flow and high-resistance downstream. A lower than normal resistive index generally results from decreased systolic velocity and indicates impaired inflow to the region of interest. Hepatic venous waveform is usually phasic, with transmitted cardiac pulsation (see Fig. 13.5). When the hepatic veins or inferior vena cava (IVC) are narrowed, the waveform becomes flattened; this is a sensitive sign for venous compromise. Normal portal venous flow also has a phasic pattern that is decreased in conditions such cirrhosis and fatty infiltration (Colli et al, 1994).

Recent Technologic Advances

New techniques have been developed to coregister ultrasound, CT, and MRI images to facilitate lesion localization and to guide intervention or biopsy. Electromagnetic sensors placed near the scanning area and sensors attached to the ultrasound probe allow tracking of transducer position and orientation. Anatomic landmarks are identified on initial scanning and with navigation software, and these landmarks are coregistered with CT or MR images that have been downloaded into the ultrasound unit (Ewertsen et al, 2008). As the ultrasound scan is being performed in real time, the CT or MR images are reconstructed into a similar orientation plane (Fig. 13.6). Images may be displayed side by side or in a blended, overlapped format. In a study of contrast-enhanced ultrasound fused real time with CT, Jung and colleagues found that more lesions were identified with image fusion than with CT alone (Jung et al, 2009). Similar instrumentation allows global positioning system (GPS)

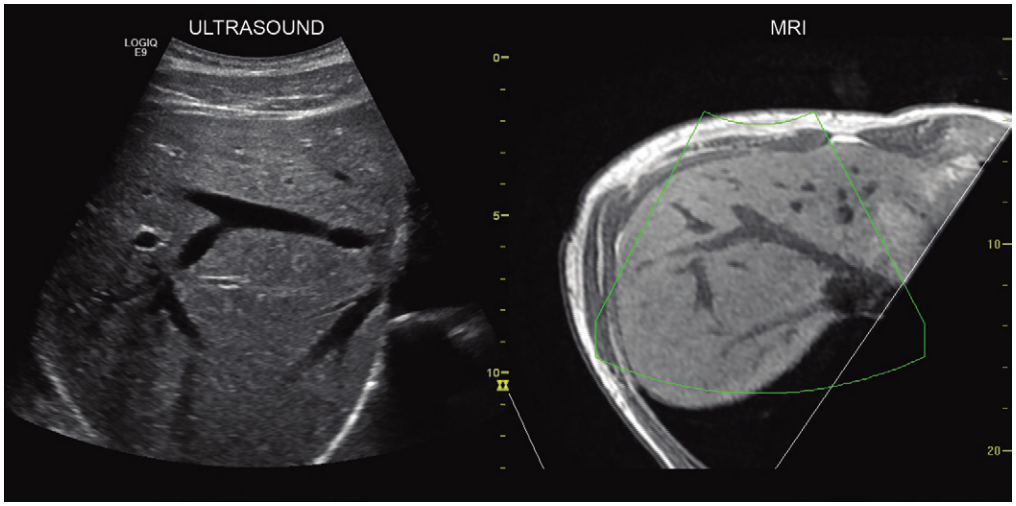


FIGURE 13.6. Coregistration technology shows a transverse ultrasound image of the liver and a magnetic resonance image that have been coregistered to display identical orientation and plane of section. *(Courtesy GE Healthcare, Little Chalfont, United Kingdom.)*

navigation for needle tracking and volume acquisition. Acoustic force imaging to assess liver stiffness is another recent advance in development (see Songraphy of Diffuse Liver Disease below), and contrast-enhanced ultrasound is discussed in various sections on liver masses, detection, and characterization that follow.

LIVER ULTRASOUND

Normal Liver Anatomy

The normal liver (see Chapter 1B) has a smooth surface and is uniform in echogenicity. Compared to adjacent organs, the liver is similar to or more echogenic than the kidneys and less echogenic than the spleen and pancreas. The superior aspect of the liver may have thin, linear indentations from diaphragmatic leaflets. Hepatic shape is variable. For example, a Riedel lobe may cause tonguelike inferior extension of the right lobe that may present as a palpable mass. Estimates of hepatic volume may be done with volumetric analysis (Treece et al, 2001; Wilson et al, 2009), but liver size is most commonly determined by a longitudinal image in the right midaxillary line. Normal liver length is reported to be less than 15.5 cm (Gosink et al, 1981). Others have used the right midclavicular longitudinal measurement with normal mean length of 10 cm (Niederau et al, 1983).

The Couinaud segmental anatomy of the liver is shown in Figures 13.7 and 13.8 (Couinaud, 1957; see Chapter 1B). Ultrasound images are obtained through available acoustic windows that avoid bone and air; this may vary the appearance of the liver compared with the standard axial, sagittal, and coronal planes of CT and MR, but the vascular landmarks that define the Couinaud segmental anatomy are well seen by ultrasound (Lafortune et al, 1991; Soyer et al, 1994). The hepatic veins and portal vein bifurcation are visualized with a subcostal transverse view; longitudinal images of the main portal vein, portal bifurcation, and hepatic artery are obtained best by intercostal approach, with the patient in the left lateral decubitus position. Transverse images of the portal confluence show the right portal vein and its bifurcation. The left portal vein in this plane courses transversely in the hilar plate for 3 to 4 cm before it extends into the umbilical fissure and gives off branches to the left hepatic segments. It is important to note that the horizontal portion of the left portal vein is extrahepatic and more readily available to the surgeon than the right portal vein.

Detection and Characterization of Focal Liver Masses

Gray-Scale Ultrasound of Focal Liver Masses

Conspicuity of liver lesions by gray-scale ultrasound is determined by lesion echogenicity relative to the liver. Small, markedly hypoechoic or hyperechoic lesions may be readily detected and characterized by ultrasound (Eberhardt et al, 2003), but masses that have echogenicity similar to adjacent liver may be more difficult to appreciate. On gray-scale ultrasound, liver masses are differentiated by internal architecture and are described as cystic, hypoechoic, and hyperechoic relative to the liver. Table 13.1 shows the common differential diagnoses within each of these categories (Charboneau, 2002; Middleton, 2002). The majority of cystic masses are benign, whereas most hypoechoic masses, with the exception of focal fatty sparing, are suspicious for neoplasm and require further evaluation, as they are clinically significant. Focal sparing often has geographic margins, typically is located in segment IV anterior to the portal bifurcation or adjacent to the gallbladder, and vessels are undisturbed. These distinctive features allow confident diagnosis (Fig. 13.9).

Hyperechoic masses include benign hemangioma, focal fat, and hepatic neoplasms such as hepatocellular carcinoma (HCC), adenoma, and metastases. Hemangiomas are brightly echogenic in the majority of cases and are sharply circumscribed. This appearance differs from malignant hyperechoic masses, which often have a hypoechoic halo. Any liver mass with a hypoechoic halo is suspicious for malignancy, and this sign has 86% positive predictive value and 89% negative predictive value for diagnosis of malignancy (Wernecke et al, 1992b).

Ultrasound Microbubble Contrast Agents for Evaluation of Liver Masses

Ultrasound microbubble contrast agents improve both detection and characterization of focal liver masses (Albrecht et al,

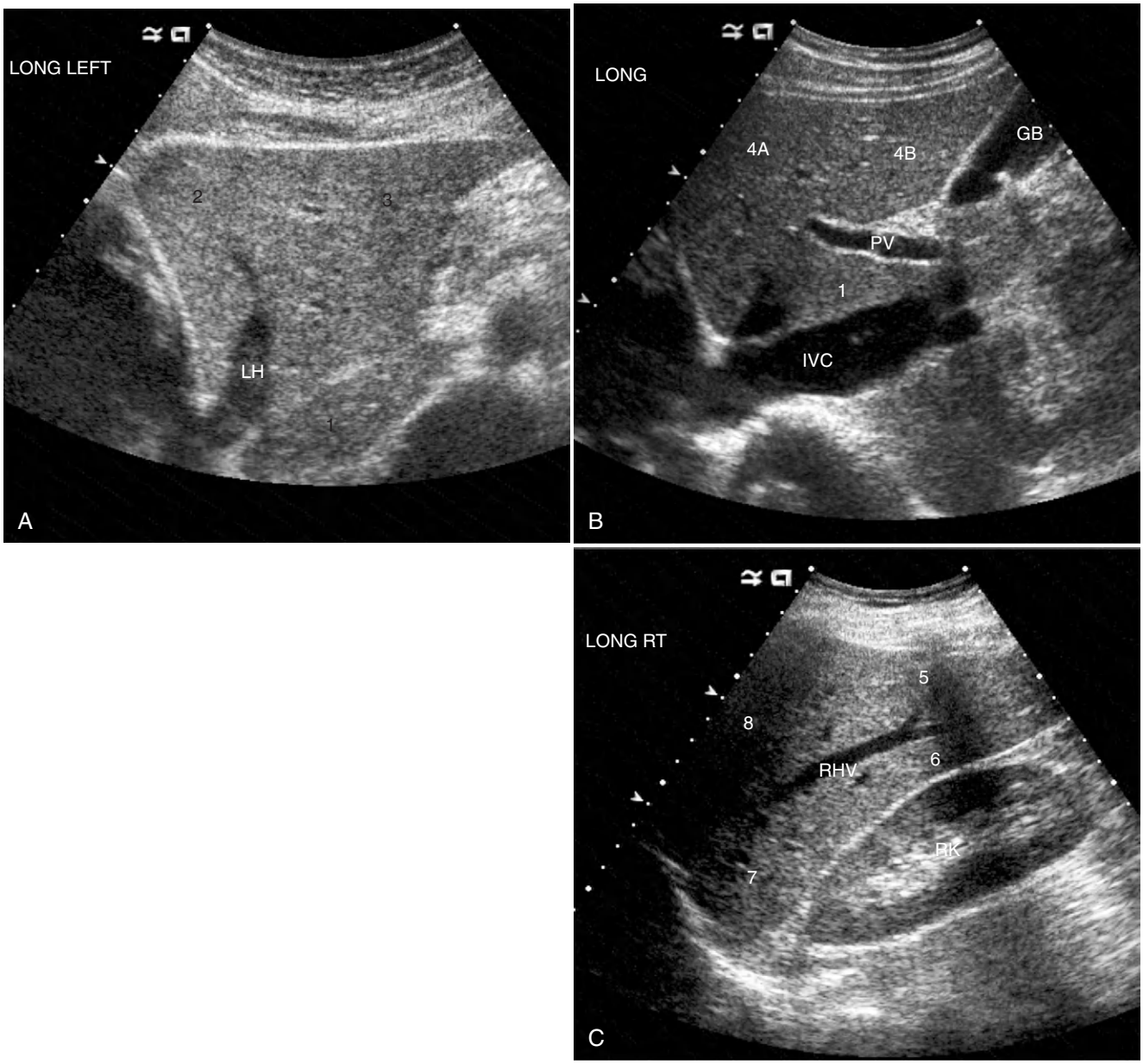


FIGURE 13.7. Normal liver longitudinal ultrasound images. **A,** Left hepatic lobe. Segments are numbered. LH, Left hepatic vein. **B,** Left lobe segment IV. PV, portal vein; GB, gallbladder; IVC, inferior vena cava. **C,** Right lobe. Segments are numbered. RHV, right hepatic vein; RK, right kidney.

2003, 2004; Blomley et al, 1999; Bryant et al, 2004; Harvey et al, 2000; Quaia et al, 2004). First-generation contrast agents, such as SHU 508A (Levovist; Schering, Berlin), remain within the Kupffer cells after the vascular phase; when high mechanical index is applied to burst the bubbles, the liver enhances brightly, but metastases and other lesions without Kupffer cells appear dark. A multicenter study showed improved detection of individual metastases from 71% to 87%, and in seven of 80 patients, contrast-enhanced ultrasound showed more metastases than CT (Albrecht et al, 2003).

More recently, second-generation contrast agents and low mechanical index (LMI) scanning techniques have become available. At LMI settings, the microbubbles emit acoustic signals as they expand and contract in response to the ultrasound pulse, but they do not burst. Because the microbubbles stay in circulation, it is possible to image throughout arterial and portal phases. With LMI scanning, hypervascular tumors that enhance in the arterial phase are more easily detected. Lesion detection is also improved in the portal phase, because hepatic malignancies are hypoechoic during this phase (Wilson et al, 2006).

Contrast-enhanced ultrasound with second-generation contrast agents and LMI techniques allow assessment of vascular morphology, arterial enhancement relative to the liver, and duration of enhancement or "washout" during the portal venous phase (Wilson et al, 2006). These patterns of enhancement can be used to differentiate benign from malignant focal hepatic lesions as shown in the algorithm presented

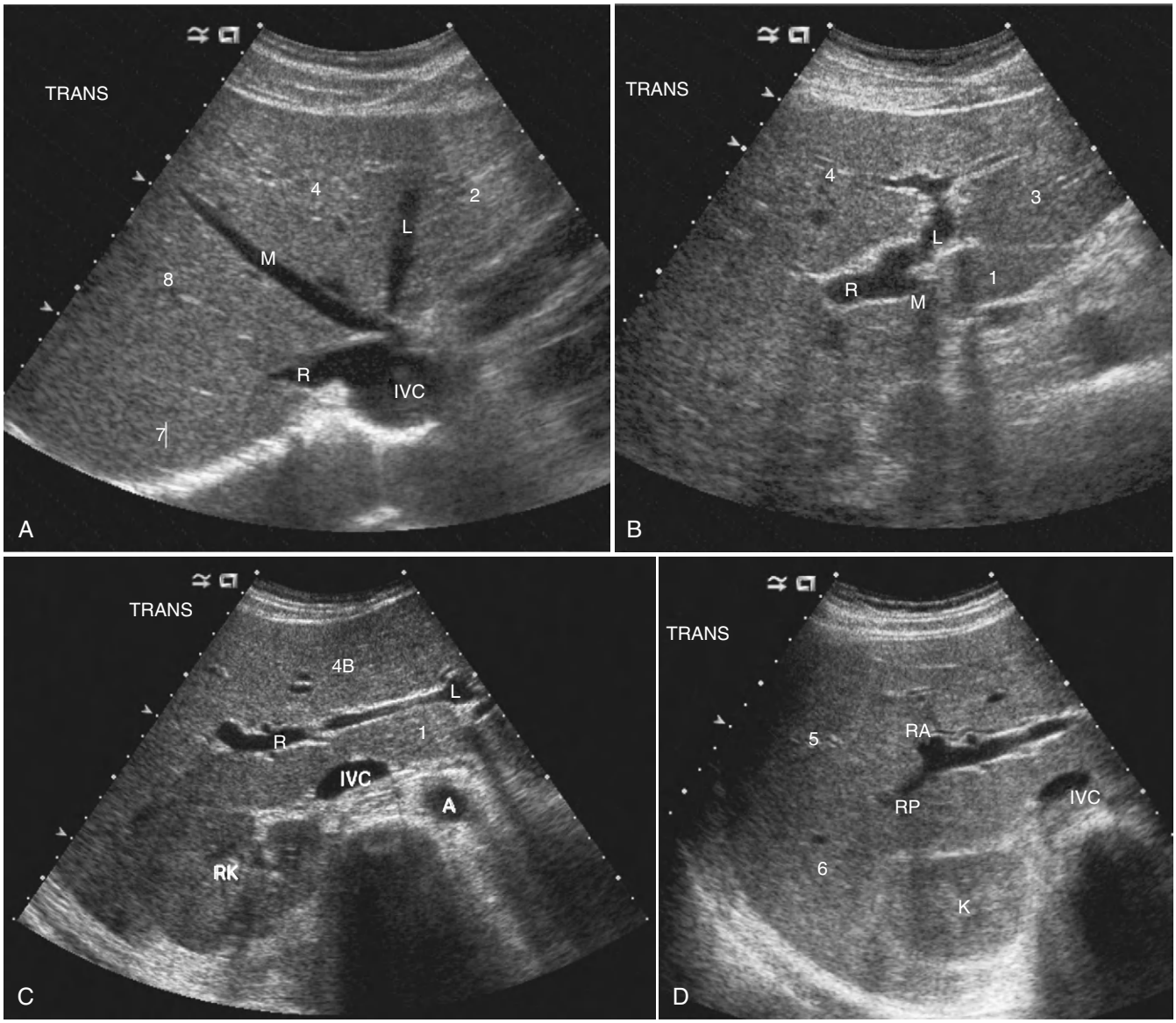


FIGURE 13.8. Transverse images of the liver. **A,** Transverse sonogram at the level of the hepatic veins. Segments are numbered. R, right hepatic vein; M, middle hepatic vein; L, left hepatic vein; IVC, inferior vena cava. **B,** Transverse section of the left lobe at the level of the portal vein bifurcation. M, uppermost main portal vein; R, right portal vein; L, left portal vein. **C,** Transverse image of the left portal vein (*LPV*) and right portal vein (RPV) at the bifurcation. Segments IVB and I are indicated. RK, right kidney; A, aorta. **D,** Transverse image of the inferior right lobe segments V and VI. K, right kidney; RA, anterior right portal vein; RP, posterior right portal vein.

in Figure 13.10 (Brannigan et al, 2004; Ding et al, 2005; Wilson et al, 2006). Washout during the portal venous phase is highly correlated with malignant histology (von Herbay et al, 2009). In the portal phase, metastases and HCC are unenhanced relative to the liver, whereas benign hemangiomas and focal nodular hyperplasia (FNH) have sustained enhancement equal to or greater than the liver (Wilson et al, 2009; Quaia et al, 2004; Brannigan et al, 2004).

In a study of 452 liver lesions, contrast-enhanced ultrasound improved diagnostic accuracy for two readers from 49% to 85% and from 51% to 88%, and diagnostic confidence was increased from 0.82 to 0.97 and from 0.83 to 0.98, respectively (Quaia et al, 2004). A multiinstitutional study of 1349 patients with hepatic masses found that contrast-enhanced ultrasound had a diagnostic accuracy of 83% for all benign lesions, 82% for hemangiomas, and 87% for FNH. Diagnostic accuracy for malignant lesions was 96% overall, 91% for hepatic metastases, and 85% for HCC (Strobel et al, 2009).

Diagnostic performance of contrast-enhanced ultrasound has been compared to that of CT and MRI in several studies. There is high concordance for appearance in arterial phase imaging but less so in the portal phase, probably due to the fact the ultrasound contrast remains intravascular, but CT and MR contrast agents diffuse into the interstitium (Wilson et al, 2006). A multicenter study of 134 patients found that in comparison to CT and MRI, contrast-enhanced ultrasound was 30% more sensitive in recognition of malignancy, 16% more specific in exclusion of malignancy, and 23% more accurate (Trillaud et al, 2009).

Table 13.1

Differential Diagnosis of Focal Liver Lesions by Gray-Scale Ultrasound Appearance

Cystic	Isoechoic	Hyperechoic	Hypoechoic
Benign			
Cyst	FNH	Hemangioma	Focal fatty sparing
Hematoma		Focal fat	
Abscess			
Clinically Significant			
		HCC	HCC
		Adenoma	Adenoma
		Metastases	Metastases
			Lymphoma

FNH, Focal nodular hyperplasia; *HCC*, hepatocellular carcinoma.

Modified from Charboneau JW, 2002: There is a hyperechoic mass in the liver: what does that mean? In Cooperberg PL (ed): Categorical Course in Diagnostic Radiology: Findings at Ultrasound—What do they Mean? Chicago, Radiological Society of North America, pp 73-78; and Middleton WD, 2002: There are nonhyperechoic lesions in the liver: what does that mean? In Cooperberg PL (ed): Categorical Course in Diagnostic Radiology: Findings at Ultrasound—What do they Mean? Chicago, Radiological Society of North America, pp 79-90.

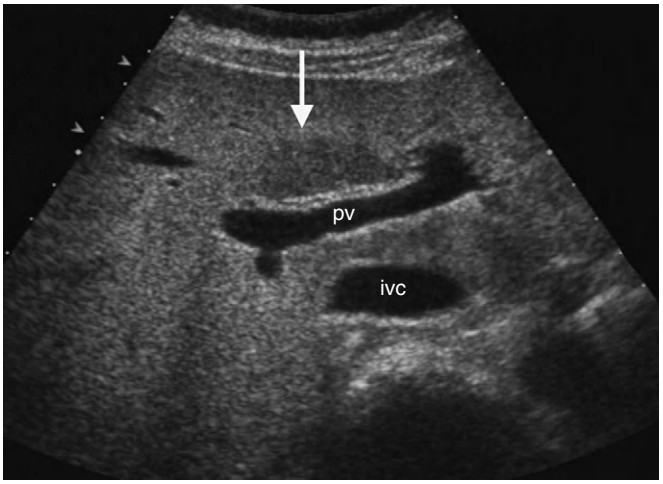


FIGURE 13.9. Focal sparing in an otherwise fatty liver. Transverse image shows a hypoechoic region (*arrow*) in segment IV anterior to the porta. pv, portal vein; ivc, inferior vena cava.

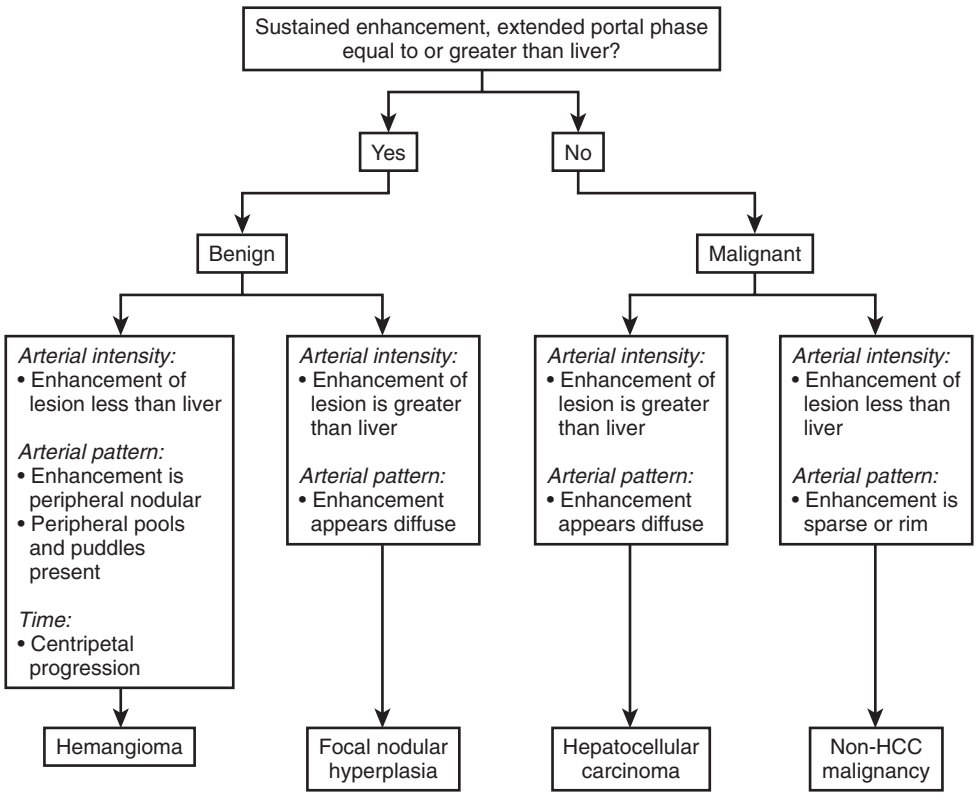


FIGURE 13.10. Algorithm for diagnosis of focal liver lesions based on ultrasound contrast enhancement patterns. HCC, hepatocellular carcinoma. *(Modified from Wilson SR, et al, 2006: An algorithm for the diagnosis of focal liver masses using microbubble contrast-enhanced pulse-inversion sonography. Am J Roentgenol 186:1401-1412.)*

Benign Liver Lesions

Cystic Masses

Benign hepatic cysts have smooth, thin walls, posterior acoustic enhancement, and no internal echoes (see Fig. 13.2). A partial, thin septum or puckered wall may be present. A confident diagnosis of simple hepatic cyst can be made on gray-scale ultrasound, and no further evaluation is required. Blood vessels and arteriovenous fistulas or aneurysms may appear cystic on gray-scale ultrasound, but these can be differentiated from simple cysts, because they will have internal flow on Doppler imaging. Lymphoma, which is very hypoechoic, may mimic a

cyst rarely, but internal vascularity will be present on Doppler imaging. When cysts are innumerable and also present in the kidneys or pancreas, polycystic disease should be considered (see Chapter 69B).

Complex masses that contain fluid have internal echoes within the fluid, irregular or thickened walls, mural nodularity, and solid areas or calcification (Middleton, 2002). Hemorrhage, infection, and neoplasm should be considered in the differential diagnosis. Hemorrhagic cysts may have internal solid components, septations, and or debris layering in the dependent portion of the cyst, but on Doppler imaging, no internal vascularity is evident. Hepatic hematomas from trauma have variable appearance in the acute phase but become hypoechoic and cystic as they evolve (Korner et al, 2008; McGahan et al, 2006).

Abscess may be solid in appearance initially, but it then becomes cystic with debris; the wall is usually vascular (Fig. 13.11). Echinococcal cysts have variable appearance; they may be simple fluid-filled cysts, they may have undulated membranes from a rupture and detached endocyst, they may contain daughter cysts and/or echogenic material, and they may show calcification (Lewall et al, 1985). When hydatid cysts are infected, they lose their characteristic sonographic appearance and become diffusely hyperechoic.

Cystic neoplasms, such as biliary cystadenoma and cystadenocarcinoma, may be multiloculated or may have a nodular wall. Cystic metastases from sarcomas undergo necrosis and have a thick wall as a result of central liquefaction within a solid mass. Ovarian cystic metastases characteristically are located peripherally, secondary to tumor implants on the hepatic surface.

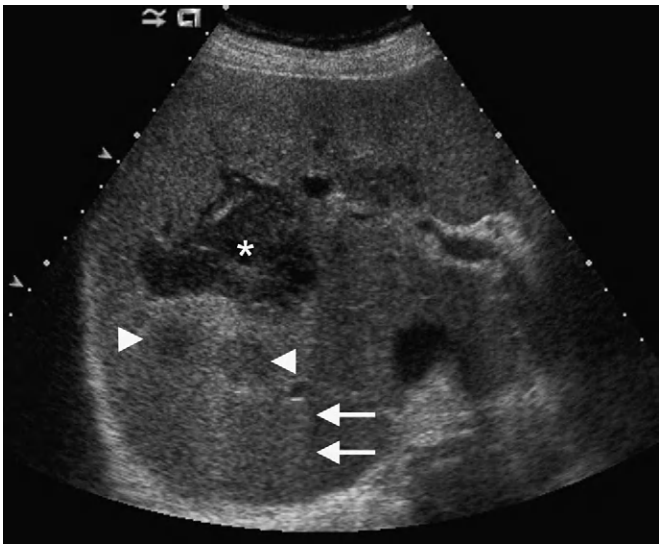


FIGURE 13.11. Hepatic abscess in a patient after embolization for hepatic neuroendocrine metastases (*arrowheads*). The abscess (*asterisk*) contains complex fluid and has posterior acoustic enhancement (*arrows*).

Cavernous Hemangioma

Typical cavernous hemangioma, seen in 80% of cases, is a brightly echogenic homogeneous mass with a sharp margin (Fig. 13.12). Approximately 10% to 20% of hemangiomas are multiple (Charboneau, 2002). Multiple vascular interfaces within hemangiomas cause the increased echogenicity; the

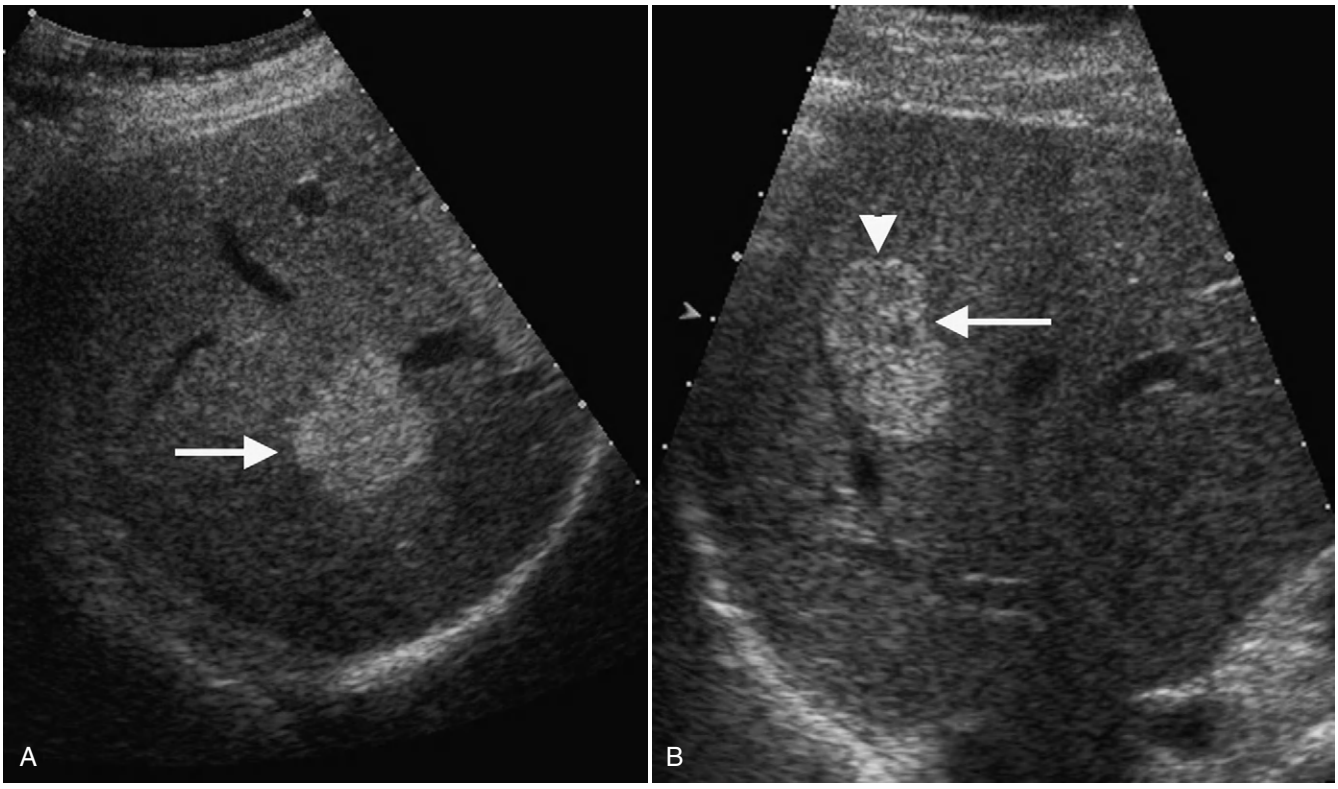


FIGURE 13.12. Hemangiomas. **A,** Longitudinal sonogram of the right lobe shows a brightly echogenic hemangioma (*arrow*) with a sharp border. **B,** Atypical hemangioma (*arrow*) seen in 20% of patients may have areas of internal heterogeneity, a result of fibrosis or myxomatous degeneration, and may demonstrate a thin echogenic rim (*arrowhead*).

margins are well demarcated because histopathologically, only one cell layer is present at the junction with adjacent liver (Charboneau, 2002). Although hemangiomas are vascular, flow is extremely slow, and usually no Doppler signals are evident. Atypical hemangiomas, seen in 20% of cases, may have a thin echogenic rim and a lacy or granular central appearance from foci of collagen (see Fig. 13.12). Hemangiomas are often smaller than 3 cm, but some are giant hemangiomas that become symptomatic as a result of mass effect. Giant hemangiomas, those greater than 5 cm, often lack the characteristic ultrasound features because of central fibrosis, necrosis, and myxomatous degeneration. When the background liver becomes hyperechoic as a result of fatty infiltration, hemangiomas also may appear atypical and less echogenic than the liver. In such cases, contrast-enhanced ultrasound or CT may be useful (Bartolotta et al, 2007; Liu et al, 2009; see Chapter 79A).

With ultrasound contrast imaging at LMI settings, hemangiomas have sustained enhancement in the portal phase and on the arterial phase, enhancement intensity is usually less than the liver, and the pattern of enhancement is peripheral and nodular with puddling of contrast and centripetal progression, similar to CT (Wilson et al, 2006; Quaia et al, 2004; Brannigan et al, 2004; Fig. 13.13).

If the ultrasound shows the classic appearance of hemangioma, and the patient has no history of underlying liver disease or malignancy, then no further investigation is required (Leifer et al, 2000). A study of 213 patients with ultrasounds that showed a typical hemangioma appearance and without risk for hepatic malignancy found only one patient with malignancy on long-term follow-up and concluded that typical hemangiomas in low-risk patients do not require follow-up. This rule does not apply to patients with cirrhosis, hepatitis, or chronic liver disease who are at increased risk for HCC, nor does it apply to patients who already have malignancies. In a study of 2000 patients with cirrhosis, 44 had hemangioma-like lesions; on follow-up, half of these proved to be HCCs, and half were hemangiomas (Caturelli et al, 2001). Thus, in patients at risk for HCC, any echogenic lesion merits further evaluation and follow-up.

Focal Nodular Hyperplasia

The second most common benign hepatic neoplasm, FNH may be difficult to detect on gray-scale ultrasound, because it often has similar echogenicity to the liver, but subtle vascular displacement or contour abnormalities may draw attention to the lesion (Buetow et al, 1996; Hussain et al, 2004; Wilson et al, 2005; Fig. 13.14). FNH typically occurs in asymptomatic patients and is more common in women. Approximately 20% are multiple, and they may occur in association with hemangiomas (Nguyen et al, 1999; see Chapter 79A). FNH contains Kupffer cells, hepatocytes, and biliary structures but without portal triads and central veins found in normal hepatic lobules (Hussain et al, 2004). FNH is considered to be secondary to vascular malformation; fibrous septa radiate from a central scar, and tortuous feeding arteries are present.

On gray-scale ultrasound, FNH has variable echogenicity and lobulated smooth contour (see Fig. 13.14). A central scar may be evident, but it is usually better depicted on CT, MRI, or contrast-enhanced ultrasound. A key to ultrasound diagnosis of FNH is the characteristic power Doppler appearance of the tortuous feeding artery and spoke-wheel vascularity within the lesion. With ultrasound contrast imaging, the central scar is better seen, and the vascular pattern can be diagnostic. FNH is hypervascular on early arterial phase imaging with diffuse enhancement that is sustained into the early portal phase (Wilson et al, 2006; Kamaya et al, 2009; Dietrich et al, 2005; Ungermann et al, 2007; Brannigan et al, 2004; Quaia et al, 2004). Persistent portal phase enhancement differentiates FNH from malignant liver lesions (Kim et al, 2009; von Herbay et al, 2009; Fig. 13.15)

Hepatic Adenoma

Hepatic adenomas are rare benign tumors that usually occur in young women with a history of oral contraceptive use, but they can also be seen in men using anabolic steroids (see Chapter 79A). They are usually solitary (80%) but can be multiple in patients with type 1 glycogen storage disease or liver adenomatosis. Adenomas lack portal venous supply and bile ductules; they have disorganized plates of cells separated by dilated sinusoids that are perfused by arterial pressure, which predisposes to hemorrhage (Grazioli et al, 2001). On gray-scale ultrasound, adenomas appear echogenic, because adenoma cells have a high lipid content. Internal hemorrhage within adenomas may produce cystic areas, and calcification may also be present (Grazioli et al, 2001). Spectral Doppler flow may have a continuous waveform (Golli et al, 1994; Bartolozzi et al, 1997). Contrast ultrasound of hepatic adenomas more often shows centripetal or mixed filling during the arterial phase; this pattern differs from FNH, which has spoke-wheel vascularity. On portal phase imaging, adenomas are variable, but most commonly they are isoechoic or slightly hypoechoic relative to the liver (Bartolotta et al, 2007; Kim et al, 2006, 2008; Ricci et al, 2008).

Malignant Liver Neoplasms

Hepatocellular Carcinoma

HCC (see Chapter 80), one of the most common malignancies worldwide, usually arises in the background of cirrhosis and has poor survival (Collier et al, 1998; El-Serag et al, 1999). Chronic hepatitis B and C infection accounts for the high prevalence of HCC in Southeast Asia, sub-Saharan Africa, and the Mediterranean, and the increased prevalence of these viral infections has contributed to rising incidence of HCC in the United States (Caturelli et al, 2003; El-Serag et al, 1999).

Ultrasound in combination with serum α-fetoprotein (AFP) is used to screen for HCC in high-risk patients, and ultrasound-guided biopsy can be used for diagnosis with 90% accuracy (Caturelli et al, 2004; Collier et al, 1998; Sato et al, 2009; Tong et al, 2001). In patients with elevated AFP, ultrasound was found to have 86% sensitivity, 82% specificity, 55% positive predictive value, and a false-negative rate of only 4% (Mok et al, 2004). A study comparing screened versus unscreened patients with cirrhosis showed improved median survival (17 months vs. 12 months) and improved survival rates at 1, 3, and 5 years for HCC arising in the screened Child-Pugh class B patients, but not in the class C patients (Trevisani et al, 2007). Chan and colleagues (2008) compared survival of HCC arising in screened versus unscreened groups during two different 7-year time periods ending in 1997 and 2004. Long-term survival was better in the screened group and, as a result of improved surgical treatment, the proportion of patients undergoing curative resection increased from 51% to 68% in those two time periods.

On gray-scale ultrasound, HCC may be solitary, multiple, or diffuse, and it has a propensity for venous and bile duct

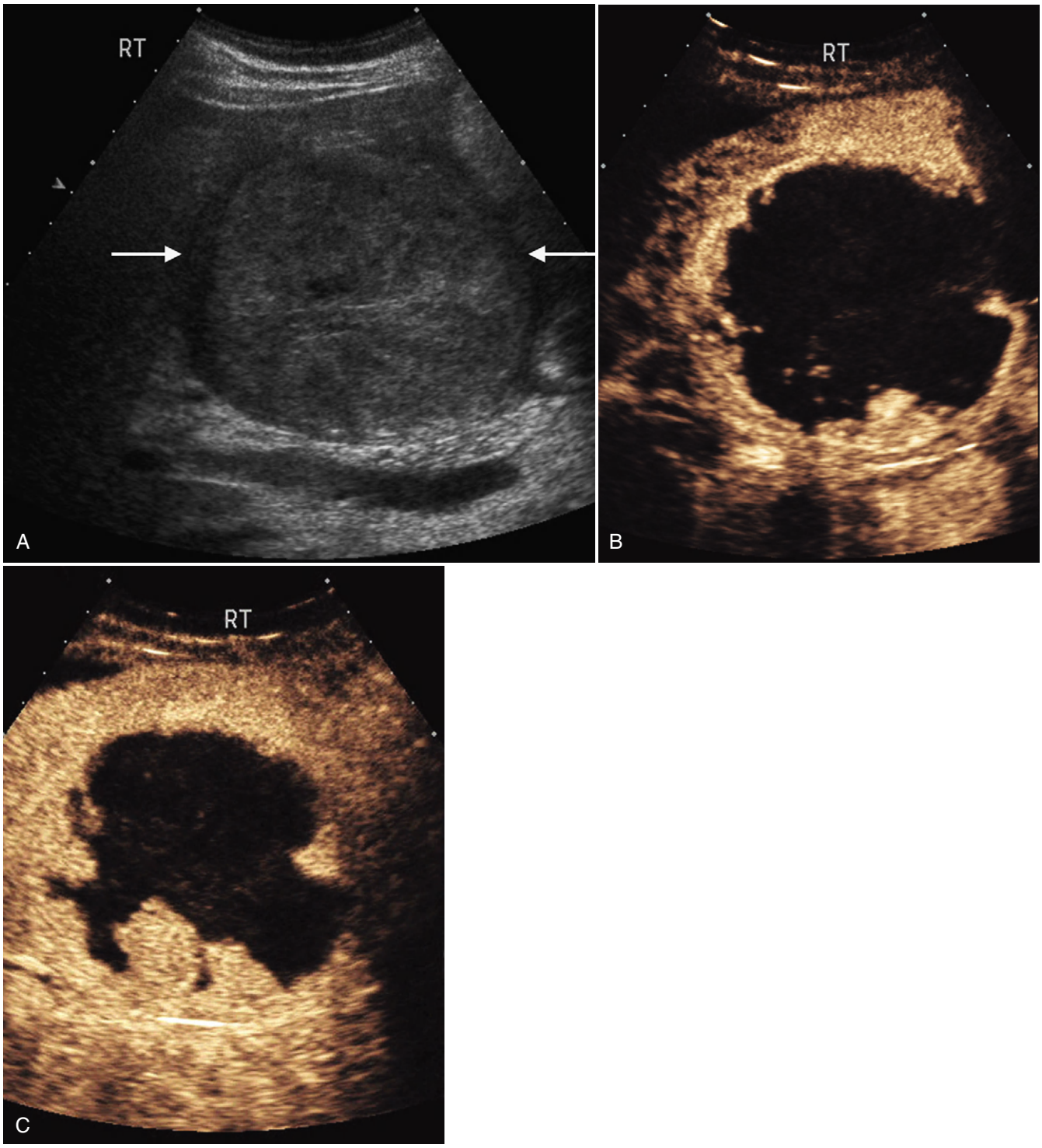


FIGURE 13.13. Giant atypical hemangioma. **A,** Baseline gray-scale image demonstrates a large, mainly isoechoic left lobe mass (*arrows*) found in a patient with abdominal pain. **B,** Contrast-enhanced ultrasound in early arterial phase (19 seconds) demonstrates that the mass has globular peripheral enhancement but no central enhancement. **C,** In the portal venous phase (56 seconds), the mass demonstrates more marked peripheral globular enhancement consistent with hemangioma. *(Courtesy Paul S. Sidhu, King's College Hospital, London.)*

involvement (Wilson et al, 2005). Small HCC tumors (<5 cm) are often hypoechoic but may be hyperechoic from fatty metamorphosis (Choi et al, 1993; Caturelli et al, 2001). Larger HCC tumors are often inhomogeneous because of liquefaction necrosis and fibrosis (Tanaka et al, 1983), and sonographic depiction of HCC may be limited in the setting of severe cirrhosis (Bennett et al, 2002). Thrombosis of portal and/or hepatic veins is frequent, seen in 30% to 60% of patients (Wilson et al, 2005; Fig. 13.16). Tumor thrombus usually expands the vein, and Doppler interrogation may reveal hepatofugal arterial flow within the



FIGURE 13.14. Focal nodular hyperplasia (FNH). As shown in this longitudinal gray-scale image of the right lobe, FNH (*crosses*) has similar echogenicity to the liver, and lesions are often subtle.

thrombus, a pathognomonic finding (Shah et al, 2007; Lencioni et al, 1995; Giorgio et al, 2004; Tanaka et al, 1993). HCC may also extend into the bile ducts and cause biliary obstruction or hemobilia (Kojiro et al, 1982).

HCC is hypervascular with dysmorphic arteries and high-velocity flow on Doppler imaging (Koito et al, 1998; Tanaka et al, 1990). Microbubble ultrasound contrast imaging improves HCC characterization and is highly concordant with CT findings, but contrast-enhanced ultrasound is best at identifying lesions greater than 2 cm (Quaia et al, 2007; Giorgio et al, 2004; Inoue et al, 2009; Jang et al, 2008). Moderately differentiated HCC is hypervascular in the arterial phase, whereas well-differentiated and poorly differentiated HCC may have a more variable appearance. Observation during the portal phase should be extended, as many HCCs have delayed washout for up to 300 seconds (Jang et al, 2007; Fig. 13.17)

Fibrolamellar Carcinoma

Fibrolamellar HCC, a variant of HCC with better prognosis, characteristically presents as a large solitary mass in an adolescent or young adult without liver disease, and AFP levels are usually normal. On ultrasound, fibrolamellar HCC is well defined, lobulated, and has variable echogenicity. Calcification may also be present (Chung et al, 2009). A central scar may be visible on gray-scale ultrasound in a third to two thirds of patients, but scars are better seen with contrast-enhanced ultrasound (Smith et al, 2008; McLarney et al, 1999). Regional lymphadenopathy is common.

Liver Metastases

Liver metastases (see Chapter 81C) are multiple in 98% of patients and are found in up to 50% of cancer patients at autopsy (Wilson et al, 2005; Middleton, 2002). Liver metastases are frequently detected by gray-scale ultrasound, but CT is the preferred modality to determine extent of disease, number of hepatic lesions, and extrahepatic disease. Response to therapy is also better evaluated by CT, because treatment-related fatty infiltration may obscure lesions that have diminished in size or changed echogenicity as a result of chemotherapy.

On ultrasound, hepatic metastases frequently have a hypoechoic halo that corresponds to fibrosis, compressed sinusoids, and tumor neovascularity surrounding the metastatic deposit (Wernecke et al, 1992a; Kruskal et al, 2000; Fig. 13.18). Uniformly hypoechoic lesions are the second most frequent sonographic appearance of metastases (Middleton, 2002; Fig. 13.19) Hypoechoic appearance and hypoechoic halo are highly suggestive of malignancy. In addition to metastases, lymphoma and HCC should be considered in the differential diagnosis. Contrast-enhanced ultrasound improves detection of individual metastases compared with gray-scale ultrasound, and in some cases, contrast-enhanced ultrasound may reveal more lesions than are evident on CT (Albrecht et al, 2003; see Fig. 13.19).

The ultrasound appearance of metastases may vary according to the primary origin. Echogenic lesions tend to arise from HCC or gastrointestinal primaries. Vascular metastases, such as those from renal cell carcinoma, islet cell tumors, carcinoids, and choriocarcinoma, also are typically hyperechoic (Tanaka et al, 1990; Marchal et al, 1985; Rubaltelli et al, 1980). Hypoechoic metastases are commonly due to untreated metastatic breast, lung, pancreatic, gastric, and esophageal carcinoma. Lymphoma, which is also hypoechoic because of its uniform cellularity, may be diffusely infiltrative or may have multiple masses; this latter pattern is more common in non-Hodgkin lymphoma or AIDS-related lymphoma (Townsend et al, 1989). Calcified metastases may be found with mucinous adenocarcinoma of the colon as well as other primaries. Cystic hepatic metastases are seen in ovarian and pancreatic cystadenocarcinomas and mucinous colon carcinomas. Metastases undergoing central necrosis, such as sarcomas, also may appear cystic, but the thick surrounding tumor wall is usually evident. When metastases are diffusely infiltrative, such as in breast or lung carcinoma, it can be difficult to detect individual lesions, and the liver may have a pseudocirrhotic appearance (Fennessy et al, 2004; Young et al, 1994).

Sonography of Diffuse Liver Disease

Steatohepatitis

Fatty liver (see Chapter 65) is commonly encountered incidentally on sonograms of the liver and in patients referred for imaging evaluation of abnormal values on liver function tests. The fat deposition within hepatocytes results in increased echogenicity of the liver relative to the kidney and in decreased acoustic penetration (Fig. 13.20). Because echogenicity is not a quantitative measure, one useful objective sign of fatty infiltration is loss of the echogenic borders of the portal vessels. To reduce subjectivity in fatty liver diagnosis, some investigators advocate comparing the relative echogenicity between the liver and right kidney to that between the spleen and left kidney. Because the normal spleen is more echogenic than liver, if the difference in echogenicity between the liver and right kidney is greater than the difference between the left kidney and spleen, then the liver is abnormally echogenic (Tchelepi et al, 2002).

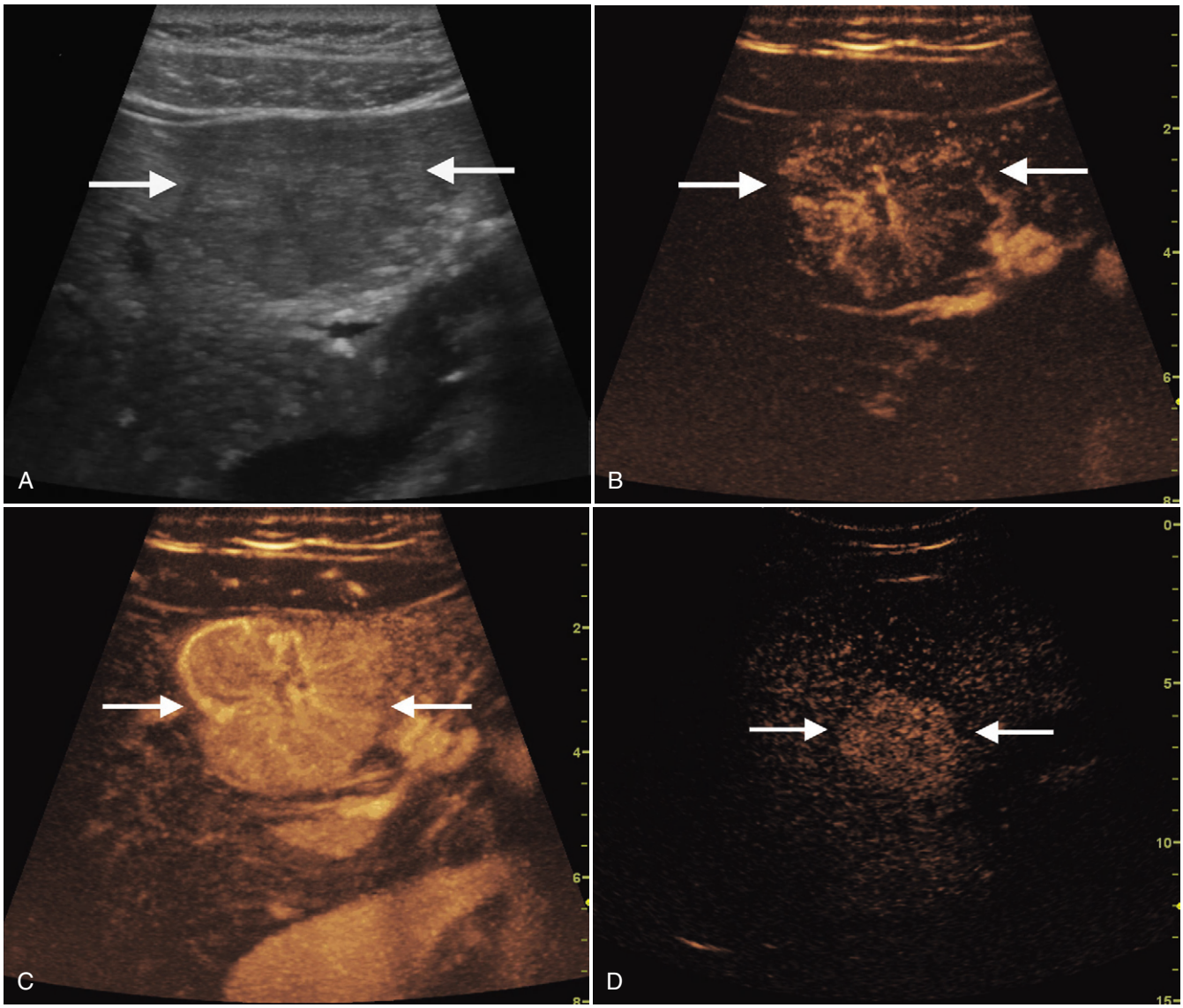


FIGURE 13.15. Focal nodular hyperplasia (FNH) on contrast-enhanced ultrasound. **A,** An isoechoic mass (*arrows*) is seen in the left hepatic lobe on gray-scale imaging. **B,** Twelve seconds after contrast injection, the FNH (*arrows*) shows enhancement in a central scar and a characteristic spoke-wheel vascular pattern. **C,** The FNH (*arrows*) enhances brightly at 18 seconds. **D,** Five minutes after contrast injection, the FNH (*arrows*) is still enhanced and is echogenic relative to the liver. *(Courtesy GE Healthcare, Little Chalfont, United Kingdom.)*

In fatty liver disease, the liver edge remains smooth. In severe cases, hepatomegaly may be present. The presence of a fatty liver degrades the quality of sonographic evaluation of the hepatic parenchyma because of decreased acoustic penetration, and focal lesions may escape detection. In addition, lesions that typically appear echogenic against a background of normal liver, such as hemangiomas, may appear hypoechoic in the fatty liver.

A fatty liver may be diffuse and uniform, patchy, or focal. Areas of focal fat deposition are commonly wedge-shaped and echogenic and occur in characteristic locations, such as along the ventral surface of segment IV and adjacent to the falciform ligament. Focal fat deposition may also be lobar, rounded, and masslike or perivascular in distribution. In the latter two cases, magnetic resonance imaging (MRI) with in-phase and opposed-phase sequences is highly useful to confirm that the focal abnormality truly represents intracellular fat deposition and not a mass lesion. Focal fat deposition should not have mass effect, and therefore intrahepatic vessels should traverse these areas of increased echogenicity without displacement. However, this finding is not entirely specific, as occasionally some mass lesions may likewise fail to displace vessels. Finally, within the diffusely fatty liver, certain regions may be spared (see Fig. 13.9). These are typically areas of nonportal venous inflow, such as around the gallbladder (cystic veins) and in the region of the porta hepatis.

Acute Hepatitis

Most imaging modalities, including sonography, are neither sensitive nor specific for the diagnosis of acute hepatitis. Definitive diagnosis of hepatitis is usually made based on clinical and laboratory grounds, with imaging useful for excluding other diagnoses, such as biliary obstruction or hepatic mass lesions

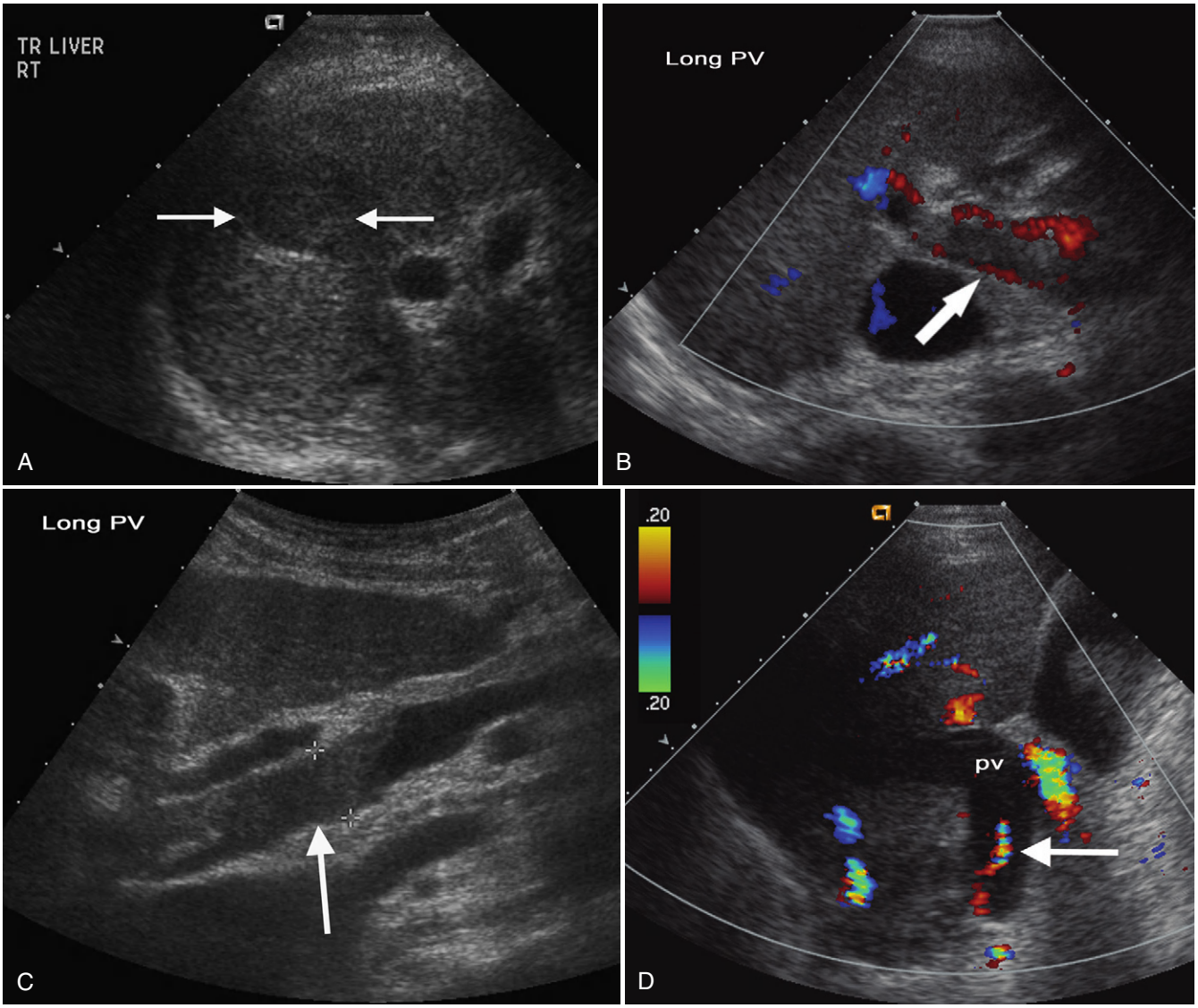


FIGURE 13.16. Hepatocellular carcinoma with portal vein thrombosis. **A,** Transverse image shows a hypoechoic right hepatic hepatocellular carcinoma (*arrows*). **B,** Transverse image of the main portal vein reveals only a trickle of blood flow (*arrow*), and the lumen is filled with echogenic thrombus. **C,** Longitudinal image of the main portal vein shows the long area of thrombus (*arrow*). **D,** Color Doppler image of the main portal vein confirms arterial flow (*arrow*) within the hypoechoic thrombus; this is pathognomonic for tumor thrombus. *pv*, Portal vein.

(Mortele et al, 2001). The most common sonographic abnormality in hepatitis is hepatomegaly. Periportal edema may be appreciated sonographically, but it is better seen on CT or MRI. Occasionally, sonography may demonstrate very low hepatic parenchymal echogenicity, producing an appearance known as the "starry night" liver for the striking prominence of the periportal echoes against the abnormally dark background liver (Mortele et al, 2001; Tchelepi et al, 2002). Hepatitis may also produce secondary changes in the gallbladder, with irregular lamellated thickening of the gallbladder wall noted, especially in hepatitis A (Tchelepi et al, 2002).

Cirrhosis

Cirrhosis (see Chapter 70A) is a diagnosed histologically by the presence of bridging fibrosis and regenerative nodule formation. Although sonographic findings are neither sensitive nor specific for the diagnosis, certain findings may suggest that cirrhosis is present (Tchelepi et al, 2002). Surface nodularity is the most reliable sign of cirrhosis, and nodularity along the deep surfaces of the liver has been found to be a more sensitive sign of cirrhosis than superficial nodularity (Filly et al, 2002; Fig. 13.20). Surface nodularity may be better appreciated in the presence of ascites. Other sonographic features of cirrhosis include coarsening and inhomogeneity of the parenchymal echo texture and volume loss in the right lobe with relative hypertrophy of the left lobe and caudate.

Stigmata of portal hypertension—such as splenomegaly, ascites, reversal of portal venous flow direction, and varices—indicate that severe parenchymal disease is present. The portal vein diameter may exceed 13 mm, although this is not invariably the case. Enlarged, tortuous hepatic arteries are often present in cirrhotic livers and should not be mistaken for dilated

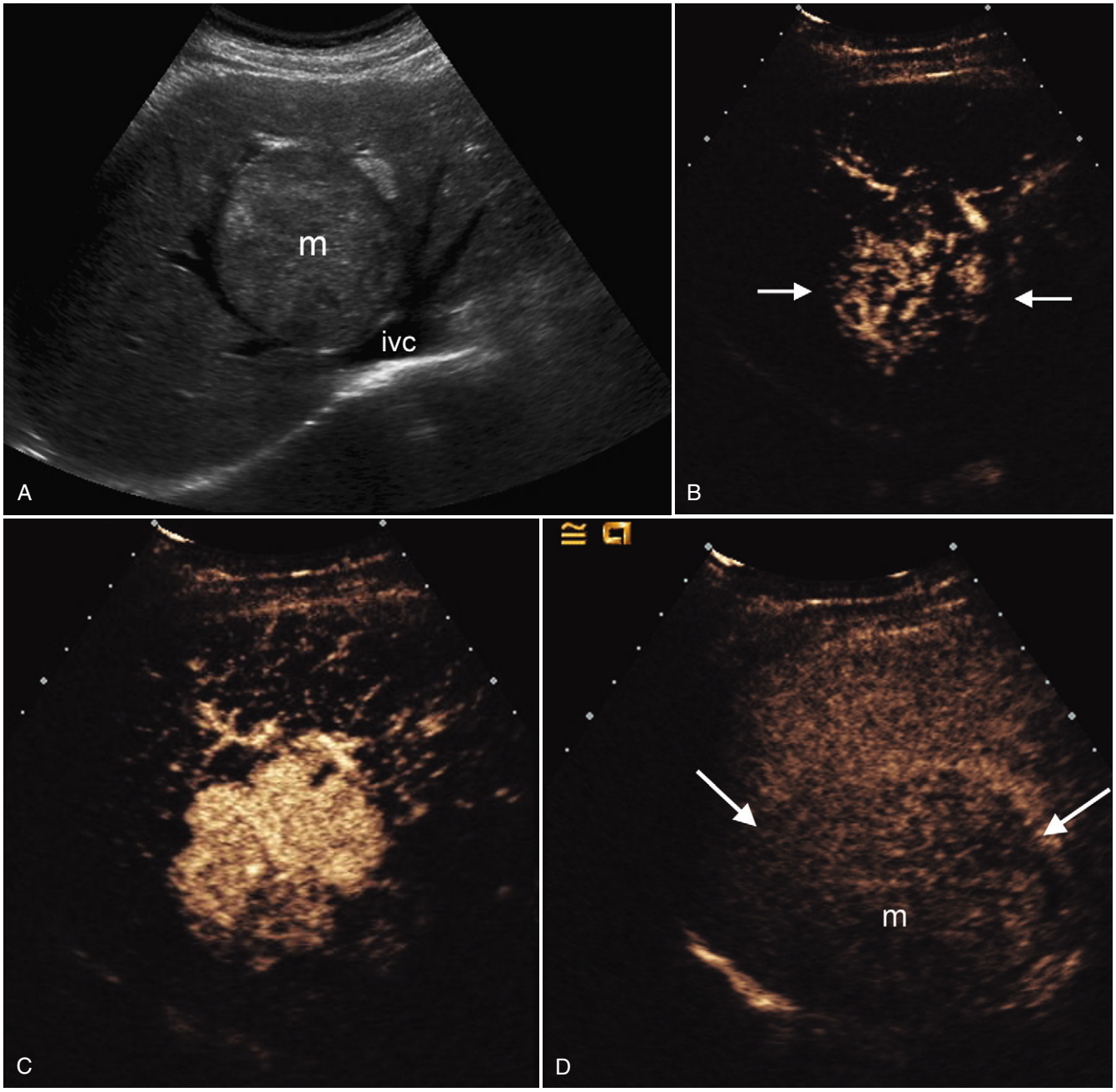


FIGURE 13.17. Hepatocellular carcinoma. **A,** Transverse gray-scale image reveals a large hepatocellular carcinoma (HCC); the mass (*m*) splays the hepatic veins. ivc, inferior vena cava. **B,** Contrast-enhanced ultrasound, early arterial portal venous phase, shows dysmorphic vessels in the hypervascular hepatocellular carcinoma (HCC) (*arrows*). **C,** Peak arterial portal phase image shows brightly enhancing HCC. **D,** The HCC (*arrows*) has very slow and weak washout, not shown until more than 4 minutes from the end of the saline flush. *(Courtesy Stephanie R. Wilson.)*

bile ducts or venous collaterals; color and spectral Doppler are useful for making this distinction. Although not widely used, a scoring system has been developed for cirrhosis based on four ultrasound criteria: 1) *surface appearance*, either normal, irregular, undulated; 2) *parenchymal echo texture*, either normal, heterogeneous, or coarse; 3) *intrahepatic vessel caliber*, either normal, obscure, or narrowed; and 4) *spleen size*, which has been proposed with scores above 7 or 8 having relatively high sensitivity and specificity (Lin et al, 1993).

Elastography is a relative new sonographic technique that has shown great promise for noninvasive quantification of hepatic fibrosis in patients with cirrhosis or chronic hepatitis. Two primary methods for performing elastography with ultrasound have been devised. Transient elastography (TE, FibroScan) uses an ultrasound transducer mounted on the axis of a vibrator. A vibration sent into the tissue induces an elastic shear wave, the velocity of which is directly related to tissue stiffness. The harder the tissue, the faster the shear wave

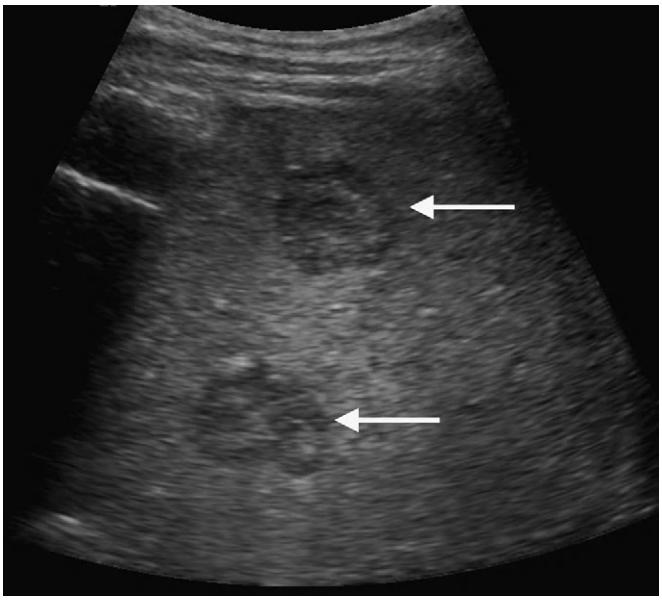


FIGURE 13.18. Liver metastases with hypoechoic halo. Metastatic neuroendocrine tumors (*arrows*) in the liver have a hypoechoic halo peripherally and a target appearance. A hypoechoic halo usually indicates malignant lesion or, less commonly, an infectious etiology.

propagates. The TE technique is rapid, operator independent, feasible with nonfasting patients, and it yields results that are reproducible and immediately available (Goyal et al, 2009). A recent trial of the technique in 711 patients with chronic liver disease found that a cutoff value of 17.6 kPa for liver stiffness had 90% positive and negative predictive values for the presence of cirrhosis (Foucher et al, 2006). More recently, the technique of real-time elastography was studied in 79 patients with chronic viral hepatitis and known fibrosis and in 20 healthy, normal volunteers. Unlike TE, real-time elastography uses conventional ultrasound probes and can be performed with modified conventional real-time sonography equipment. Results were promising, with areas under the receiver operating characteristic curve 0.75 for significant fibrosis, 0.73 for severe fibrosis, and 0.69 for cirrhosis (Friedrich-Rust et al, 2007).

Liver Transplantation (see Chapter 100)

Ultrasound is the modality of choice for the evaluation of the postoperative liver transplant recipient. Both gray-scale and Doppler imaging modes are required—the former for evaluation of the biliary tree and posttransplant fluid collections and the latter for evaluation of the status of the hepatic vasculature. Early detection of transplant complications is essential for preservation of graft function; therefore sonographic expertise must be readily available in any transplant setting (see Chapter 100). The frequency of sonographic surveillance varies by institution, although initial assessment of vascular patency is generally performed in the immediate (<24 hours) posttransplant period.

The overall incidence of vascular complications following liver transplantation is approximately 9% (Caiado et al, 2007; Quiroga et al, 2001), and Doppler ultrasound is the mainstay of evaluation. Among vascular complications, hepatic arterial thrombosis is the most feared, because it impairs the viability of the transplant bile ducts. In the native liver, arterial collaterals, primarily from the phrenic arteries, can sustain bile ducts following hepatic artery ligation (Bekker et al, 2009), but in the transplanted liver, such collaterals are initially absent, requiring at least 2 weeks to develop. Therefore in the early posttransplant period, bile ducts are supplied solely by the hepatic artery.

The frequency of early hepatic arterial thrombosis is higher in children (see Chapter 98C) than adults and has been decreasing over the past two decades with improvements in perioperative care. A recent review of 71 clinical studies of early hepatic arterial thrombosis published between 1990 and 2007 found an overall incidence of 4.4%, with a rate of 8.3% in children and 2.9% in adults (Bekker et al, 2009). Causes of hepatic arterial thrombosis include technical surgical problems (kinking, stenotic anastomosis) and nonsurgical causes such as immunologic factors, clotting abnormalities, and infections, especially cytomegalovirus (Pastacaldi et al, 2001). The median time to detection of hepatic arterial thrombosis is approximately 7 days (Bekker et al, 2009). Most cases of hepatic artery thrombosis are identified through routine sonographic surveillance, when patients are either asymptomatic or have only mild elevation of values on liver function tests. Fulminant hepatic necrosis is decidedly unusual. More commonly, undiagnosed bile duct ischemia as a result of hepatic artery thrombosis results in recurrent cholangitis, intrahepatic abscess, bile duct stenosis, or bile leak (Garcia-Criado et al, 2002).

On sonographic evaluation, the normal hepatic artery waveform shows a brisk upstroke in systole and continuous forward flow in diastole, with a resistive index between 0.5 and 0.8. The normal acceleration time, measured from end diastole to the first systolic peak, should be less than 0.08 seconds. Hepatic artery thrombosis is diagnosed on ultrasound when flow is absent in the proper hepatic artery and intrahepatic arteries on color and spectral Doppler.

Stenosis of the hepatic artery occurs in an estimated 5% to 11% of transplant recipients and usually develops at the anastomotic site within 3 months of transplantation (Caiado et al, 2007). If the anastomotic site can be visualized directly, color Doppler may show focal aliasing, and spectral Doppler will demonstrate elevated velocities. More commonly, though, the hepatic artery can only be visualized in the porta hepatis downstream of the anastomosis. With anastomotic stenosis, there will be a tardus-parvus waveform in the downstream proper hepatic and intrahepatic arteries (Fig. 13.21). This waveform is characterized by a blunted, delayed peak systolic velocity with resistive index below 0.5 and a prolonged acceleration time in excess of 0.08 seconds (Caiado et al, 2007; Tamsel et al, 2007). Occasionally a tardus-parvus waveform may be present in the intrahepatic arteries in the setting of chronic hepatic artery thrombosis. This implies that a collateral arterial supply has developed, and its dampened flow resembles the waveform seen in hepatic artery stenosis (Caiado et al, 2007). Therefore both the main hepatic artery in the porta hepatis and the intrahepatic right and left hepatic arteries must be interrogated on all Doppler studies of transplanted livers. In the early postoperative period, the hepatic artery resistive index may be elevated, but this finding is generally of no clinical consequence and is often associated with an older donor age or prolonged cold ischemia time (Caiado et al, 2007; Shaw et al, 2003).

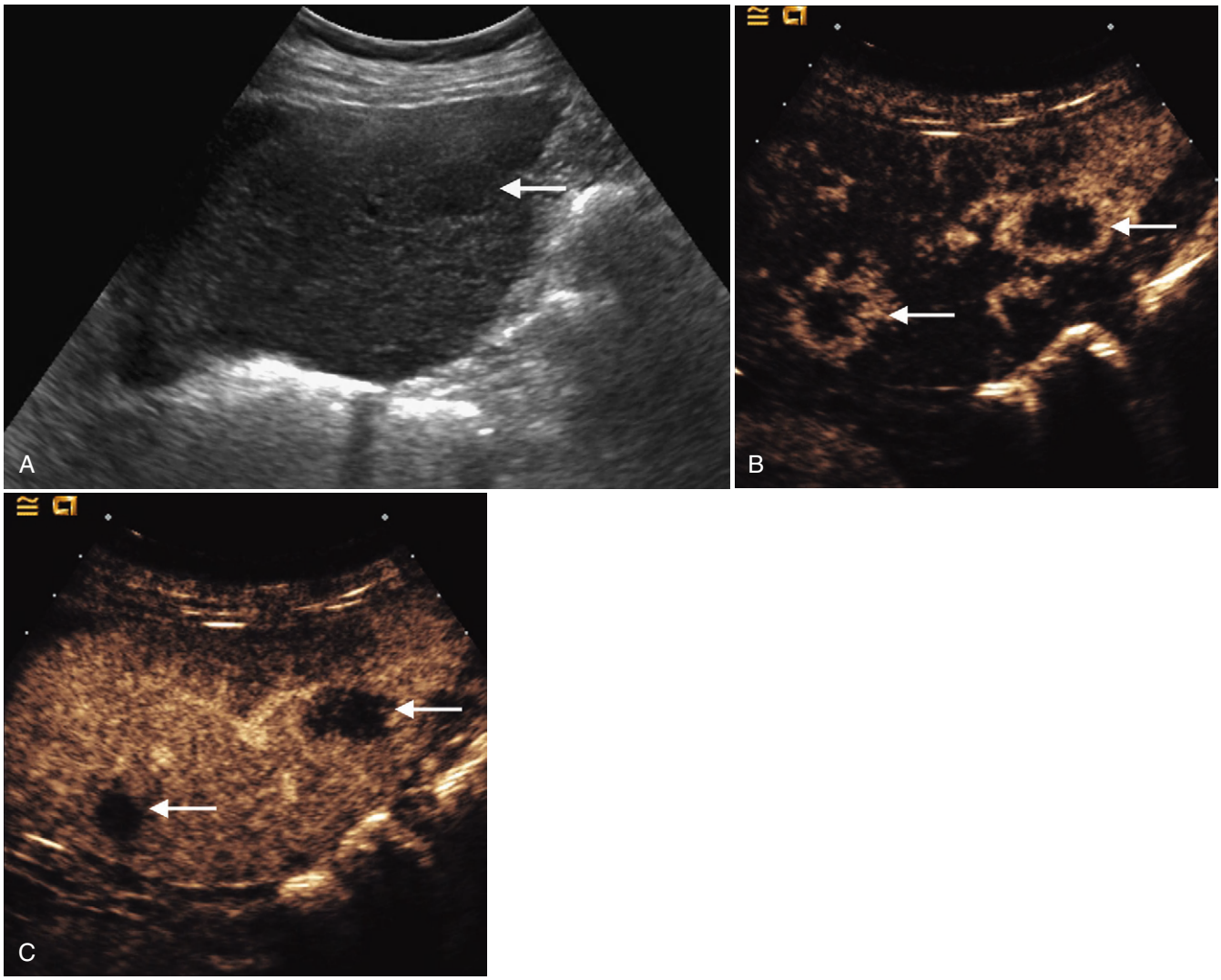


FIGURE 13.19. Hepatic metastases evaluated with contrast-enhanced ultrasound. **A,** Gray-scale image reveals a hypoechoic mass (*arrow*) consistent with metastasis. **B,** In the arterial portal phase after contrast injection, the liver metastases (*arrows*) have peripheral rim enhancement, and an additional lesion is now evident. **C,** The metastases show complete washout of contrast in less than a minute; image taken at 54 seconds. *(Courtesy Stephanie R. Wilson.)*

On the venous side, portal and hepatic vein transplant complications are relatively rare (see Fig. 13.21). Portal vein stenosis and thrombosis each have an incidence of approximately 1% to 2% (Caiado et al, 2007; Tamsel et al, 2007). Portal vein thrombosis may result from technical problems at surgery, previous portal vein thrombosis, increased downstream resistance from hepatic venous outflow impairment, sluggish portal vein inflow, or hypercoagulable states. Diagnosis is made when flow is absent in the various Doppler modes, or an echogenic thrombus is visualized on gray-scale ultrasound. Very slow flow may be undetected by sonography; so, suspected thrombosis should be confirmed with another modality, such as CT or MRI.

Vascular Disorders of the Liver

Portal Vein Thrombosis and Cavernous Transformation

Portal vein thrombosis may be caused by hypercoagulable states; inflammatory diseases; sepsis; myeloproliferative disorders; neoplasms, especially HCC; and most commonly, portal hypertension (Rossi et al, 2006; Wilson, 2005). Gray-scale findings include solid material within the portal vein lumen that may be anechoic, hypoechoic, isoechoic, or hyperechoic. The portal vein diameter may be normal, or it may be expanded. Doppler imaging may show absent color flow or areas in the vessel that do not fill with color completely. Tumor thrombus may be distinguished from bland thrombus by the presence of arterial waveforms within the thrombus, a finding that is specific but not very sensitive (Rossi et al, 2006; see Fig. 13.16). Recent work with microbubble sonographic contrast media suggests that contrast administration improves both detection and characterization of thrombi in the portal system (Rossi et al, 2006). Very slow flow in the portal venous system may result in a false-positive sonographic diagnosis; therefore CT or MRI can be useful for confirmation, especially in the evaluation of patients prior to liver transplantation.

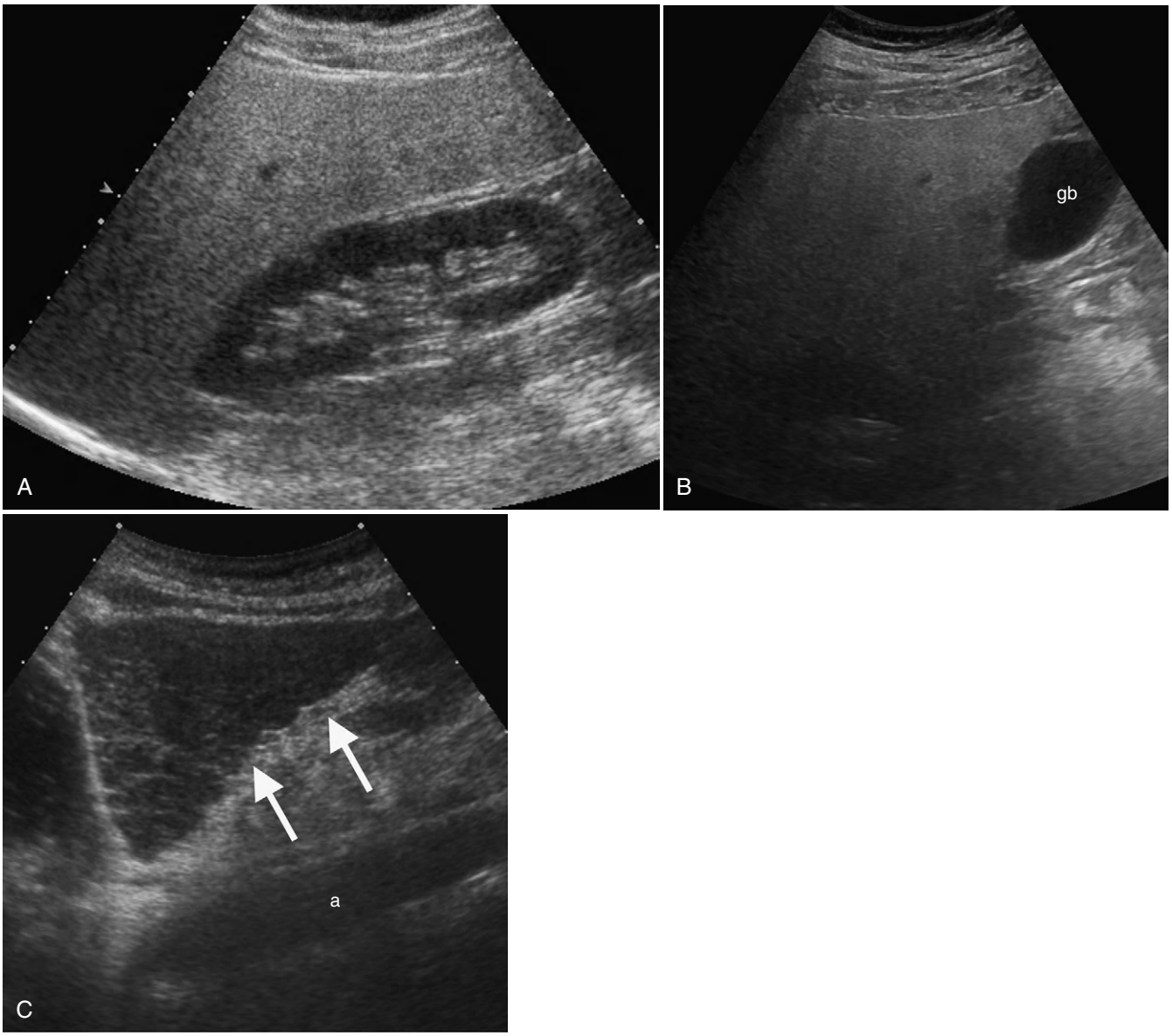


FIGURE 13.20. Diffuse liver disease. **A,** Hepatic steatosis, longitudinal right lobe. Fatty liver is very echogenic relative to the right kidney. **B,** Severe fatty infiltration. There is such marked attenuation of sound that the posterior liver is not visualized. gb, gallbladder. **C,** Cirrhosis. The left lobe is small, with coarsened echogenicity and a nodular surface (*arrows*). a, aorta.

In the setting of long-standing portal vein thrombosis, a collateral hepatopetal venous circulation develops in the hepatic hilum through recanalization of the thrombus and enlargement of collateral veins (de Groen et al, 1999). This phenomenon is known as *cavernous transformation* of the portal vein, and it manifests on sonography as numerous serpiginous vessels in the periportal region and nonvisualization of the main portal trunk (Wilson, 2005; Fig. 13.22) In patients with cirrhosis, spectral Doppler should be used to confirm the venous character of the varicosities, because enlarged and tortuous hepatic arteries may have a similar appearance on color Doppler. In chronic portal vein thrombosis and cavernous transformation, the morphology of the liver may become distorted, with enlargement of the caudate lobe and segment IV and atrophy of the left lateral segment and/or periphery of the liver (Vilgrain, 2001; Vilgrain et al, 2006; Tublin et al, 2008).

Transjugular Intrahepatic Portosystemic Shunt Evaluation

Transjugular intrahepatic portosystemic shunts (TIPS; see Chapter 76E) are often placed for management of the complications of portal hypertension, such as variceal bleeding, or as a bridge to liver transplantation. Color and spectral Doppler ultrasound is essential for evaluation of these shunts, which typically extend from the right portal vein to the right hepatic vein. In normally functioning TIPS, flow in the portal veins should be directed toward the TIPS rather than antegrade into the liver parenchyma. Color Doppler should therefore show reversed flow direction in the left and right portal veins. The

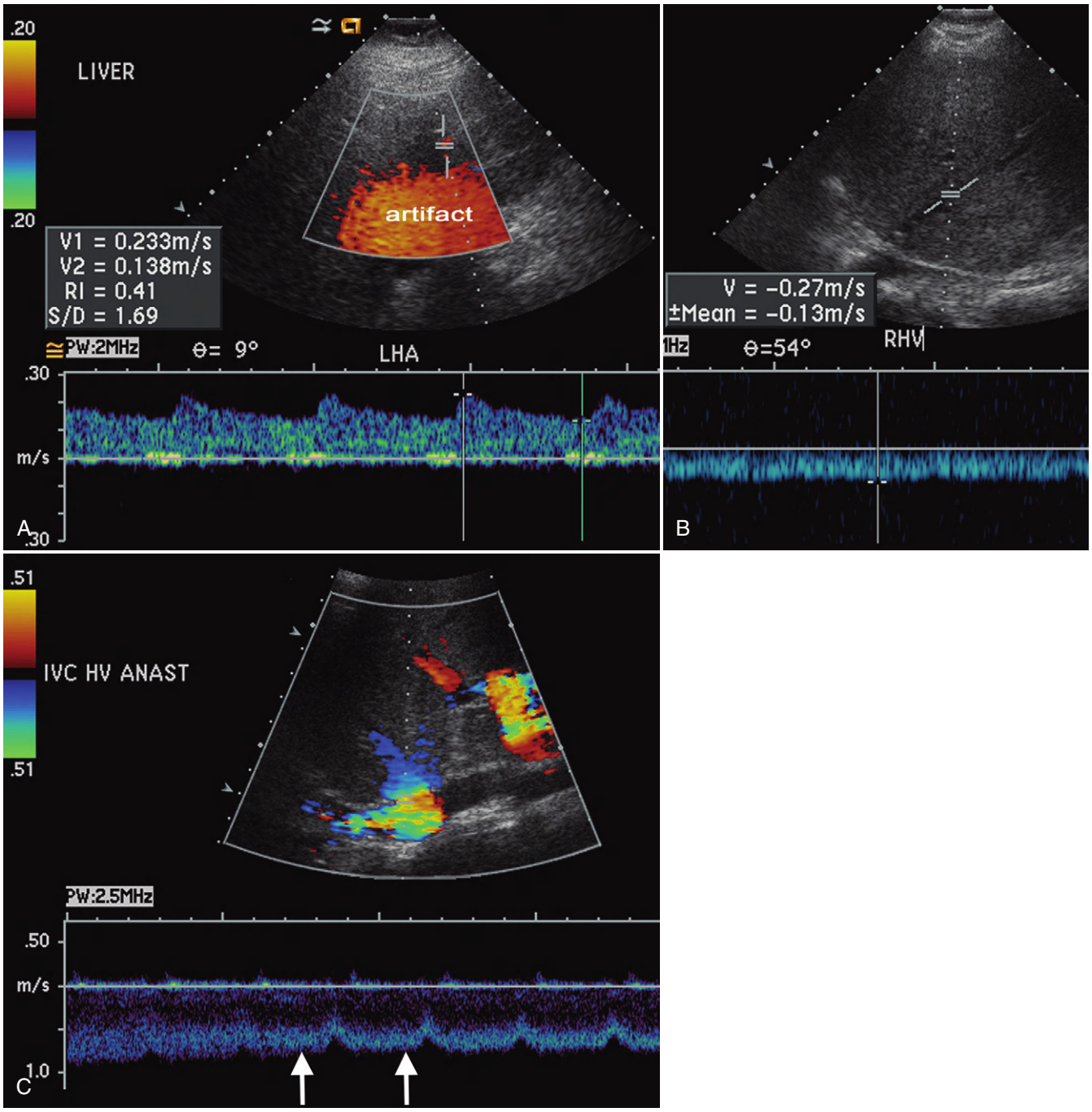


FIGURE 13.21. Vascular complications after liver transplantation. **A,** Left hepatic artery (*LHA*) tardus-parvus waveform indicates hepatic artery stenosis or thrombosis. The waveform has blunted arterial upstroke and high diastolic flow with resistive index <0.5. **B,** Duplex spectral Doppler image of the right hepatic vein (*RHV*) in a patient after orthotopic liver transplant with piggyback anastomosis (*ANAST*) shows monophasic flattened flow, indicating anastomotic stricture. **C,** Duplex Doppler with the sample placed over the area of flow aliasing shows high-velocity turbulent flow (*arrows*) at the stenotic venous anastomosis, localizing the area of focal narrowing. IVC, inferior vena cava.

flow velocity within the mid and distal segments of the shunt should range from 90 to 200 cm/s (Abbitt, 2002; Tchelepi et al, 2002). TIPS evaluation with ultrasound is usually performed immediately after shunt placement to obtain baseline velocity values and at 3-month intervals thereafter to monitor for dysfunction that could indicate developing stenosis. Absent flow on color and spectral Doppler is 100% sensitive and 96% specific for shunt thrombosis (Abbitt, 2002). Doppler sonography can also detect stenosis of the hepatic vein receiving the shunt. An angle-corrected peak velocity below 50 cm/s or reversal of flow in the proximal portion of the hepatic vein suggests stenosis (Abbitt, 2002; Dodd et al, 1995). Other authors have found that an increase or decrease in peak stent velocity of more than 50 cm/s compared with baseline is

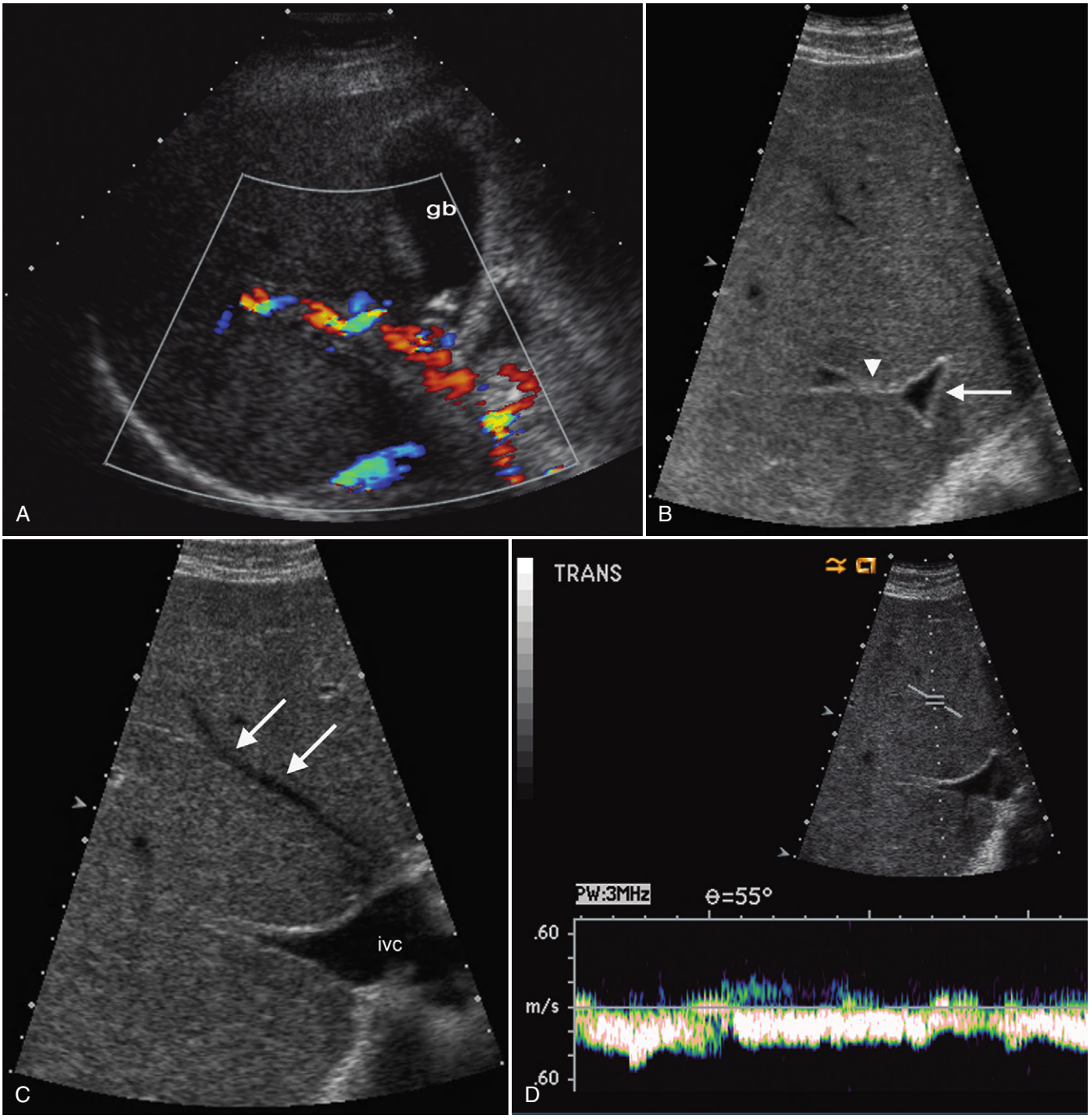


FIGURE 13.22. Vascular disorders of the liver. **A,** Cavernous transformation of the portal vein. The portal supply has a serpiginous appearance because of numerous collaterals. gb, gallbladder. **B,** Outflow obstruction in a patient with venoocclusive disease. On transverse view, the intrahepatic inferior vena cava (*arrow*) is markedly narrowed, and portions of the right hepatic vein (*arrowhead*) are obliterated. **C,** The middle hepatic vein (*arrows*) is narrowed. ivc, inferior vena cava. **D,** The middle hepatic vein shows flattened Doppler flow consistent with partial venous obstruction.

93% sensitive and 77% specific for shunt stenosis (Dodd et al, 1995).

Budd-Chiari Syndrome and Venoocclusive Disease (See Chapter 77)

Hepatic venous outflow obstruction may be secondary to obstruction of the inferior vena cava, hepatic veins, or hepatic venules. Etiologies include venous thrombosis, venous webs, venous obstruction by intrahepatic tumor, or injury to hepatic venules from irradiation and chemotherapy (Cura et al, 2009). The liver becomes enlarged and heterogeneous in echogenicity, but the caudate is typically spared and hypertrophied because of its unique venous drainage (Bargallo et al, 2003). Venous obstruction and ascites are key features of Budd-Chiari

syndrome in the acute phase; in the more chronic phase, intrahepatic venous collaterals and regenerating nodules are also present (Brancatelli et al, 2002, 2007).

Ultrasound is a primary imaging method for evaluation of Budd-Chiari syndrome (Kane & Eustace, 1995). Gray-scale imaging of the hepatic vein confluence may show narrowed hepatic veins, tumor encasement, or intraluminal thrombus. On color Doppler imaging the hepatic vein flow alterations and venous collaterals are readily evident, and spectral Doppler analysis shows flattened waveforms or areas of high velocity flow because of the more central venous obstruction (Grant et al, 1989; Ralls et al, 1992; see Fig. 13.22).

ULTRASOUND OF THE GALLBLADDER AND BILE DUCTS

Normal Anatomy of the Gallbladder and Bile Ducts (See Chapter 1B)

The gallbladder lies on the undersurface of the liver in the plane between the right and left lobes as defined by the middle hepatic vein superiorly and inferiorly by the interlobar fissure, which extends from the right portal vein to the gallbladder fossa. The fundus, body, and neck of the gallbladder are best visualized sonographically from the right intercostal approach with the patient in the left posterior oblique position (Fig. 13.23). At the junction with the cystic duct, the spiral valves of Heister are often visualized. The gallbladder may fold upon itself or may have a phrygian cap appearance at the fundus.

The main bile duct is demarcated into two sections defined by the cystic duct insertion: the common hepatic duct is above; the common bile duct, which traverses the pancreas and enters the duodenum via the sphincter of Oddi, is below the cystic duct insertion. The common bile duct, best seen from the right intercostal approach, normally measures 6 mm in diameter or less. There may be no change or only a slight increase in diameter after cholecystectomy (Mueller et al, 1981; Abbitt, 2002; Feng et al, 1995). The effect of age is controversial, but even in the elderly, the common duct diameter usually does not exceed 7 mm. (Bachar et al, 2003; Horrow et al, 2001; Perret et al, 2000). The right and left main bile ducts are anterior to the portal vein confluence and are best visualized on transverse subcostal ultrasound images. Second order branches may also be seen adjacent to the segmental portal vein branches. The several variant patterns of biliary branching are described in Chapter 1B.

Gallbladder

Cholelithiasis (See Chapter 30)

Ultrasound is the procedure of choice for detection of gallstones, which are highly echogenic and have posterior acoustic shadowing because of the difference in the acoustic impedance between stones and bile (Fig. 13.24; also see Fig. 13.3). It is important to scan patients in different positions, as gallstones are mobile, whereas polyps are fixed. Tumefactive sludge or thick bile may also change with positional variation, but sludge is thick and moves slowly, whereas gallstones roll quickly on real-time ultrasound. Stones in the gallbladder neck may be difficult to visualize, but when the patient is examined in the left lateral decubitus position, they may roll into the gallbladder body or fundus. Fixed stones impacted in the gallbladder neck are frequently associated with cholecystitis. There may be little surrounding bile if large stones or multiple stones fill the entire gallbladder lumen; when this occurs, gallstones are diagnosed by the "wall echo shadow" sign produced by echoes from the anterior gallbladder wall, anterior surface of the stone, and posterior acoustic shadowing.

Cholecystitis (See Chapter 31)

Acute cholecystitis is associated with cystic duct or gallbladder neck obstruction from cholelithiasis in approximately 90% to 95% of cases (Bennett et al, 2003). Ultrasound has 80% to 100% sensitivity, 60% to 100% specificity, and positive predictive value of 94% for the diagnosis (Harvey et al, 1999; Ralls et al, 1985; van Breda Vriesman et al, 2007). Ultrasound findings include gallstones, gallbladder wall thickening greater than 3 mm, pericholecystic fluid, and a positive sonographic Murphy sign (Smith et al, 2009; Teefey et al, 1991; Fig. 13.25).

Gangrenous cholecystitis occurs more often in patients with diabetes mellitus or a white blood cell count greater than 15,000 cells/mL (Fagan et al, 2003). Ultrasound features include floating intraluminal membranes from sloughed mucosa, shadowing foci from air in the gallbladder wall, disrupted gallbladder wall, and pericholecystic abscess formation (Jeffrey et al, 1983). When emphysematous cholecystitis is present, air in the gallbladder wall produces acoustic shadowing and reverberation artifact. This may be diagnosed sonographically, but CT is more sensitive for the presence of air in the gallbladder wall (Gill et al, 1997).

Gallbladder wall thickening may be seen in acalculous cholecystitis and in other conditions that cause edema in the pericholecystic space such as hypoalbuminemia, congestive heart failure, hepatitis, and pancreatitis.

Gallbladder Polyps and Adenomyomatosis (See Chapter 48)

The spectrum of hyperplastic cholecystosis includes benign cholesterol polyps and adenomyomatosis. Cholesterol polyps are usually numerous, small (2 to 10 mm), nonshadowing, and fixed in position (see Fig. 13.23). These are benign with no malignant potential (Ito et al, 2009; Levy et al, 2002). Adenomyomatosis results from hypertrophy of the smooth muscle in the gallbladder wall with prominent Rokitansky-Aschoff sinuses, which may appear as cystic spaces in the gallbladder wall with a characteristic ring-down or comet tail artifact (see Fig. 13.4). The gallbladder wall thickening may be focal, segmental, or diffuse. Focal thickening is most often seen in the fundus, but when it occurs in the middle region, it produces an hourglass-shaped gallbladder.

Gallbladder Carcinoma

Carcinoma of the gallbladder (see Chapter 49) may appear as a focal mass, thickened gallbladder wall, or infiltrative mass that fills the gallbladder lumen and extends into the adjacent liver and bile ducts (Wibbenmeyer et al, 1995; see Fig. 13.24). When the mass occupies the gallbladder lumen, it can result in a displaced or "trapped" stone that is fixed in position because of an intraluminal tumor (Khalili & Wilson, 2005). Mucosal plaque and wall irregularity of gallbladder carcinoma can be differentiated from other causes of gallbladder wall thickening when tumor vessels are demonstrated on Doppler imaging. Contiguous hepatic involvement in segments IV and V is common. Gallbladder carcinoma also frequently extends into the hepatic hilus and causes biliary obstruction secondary to direct involvement

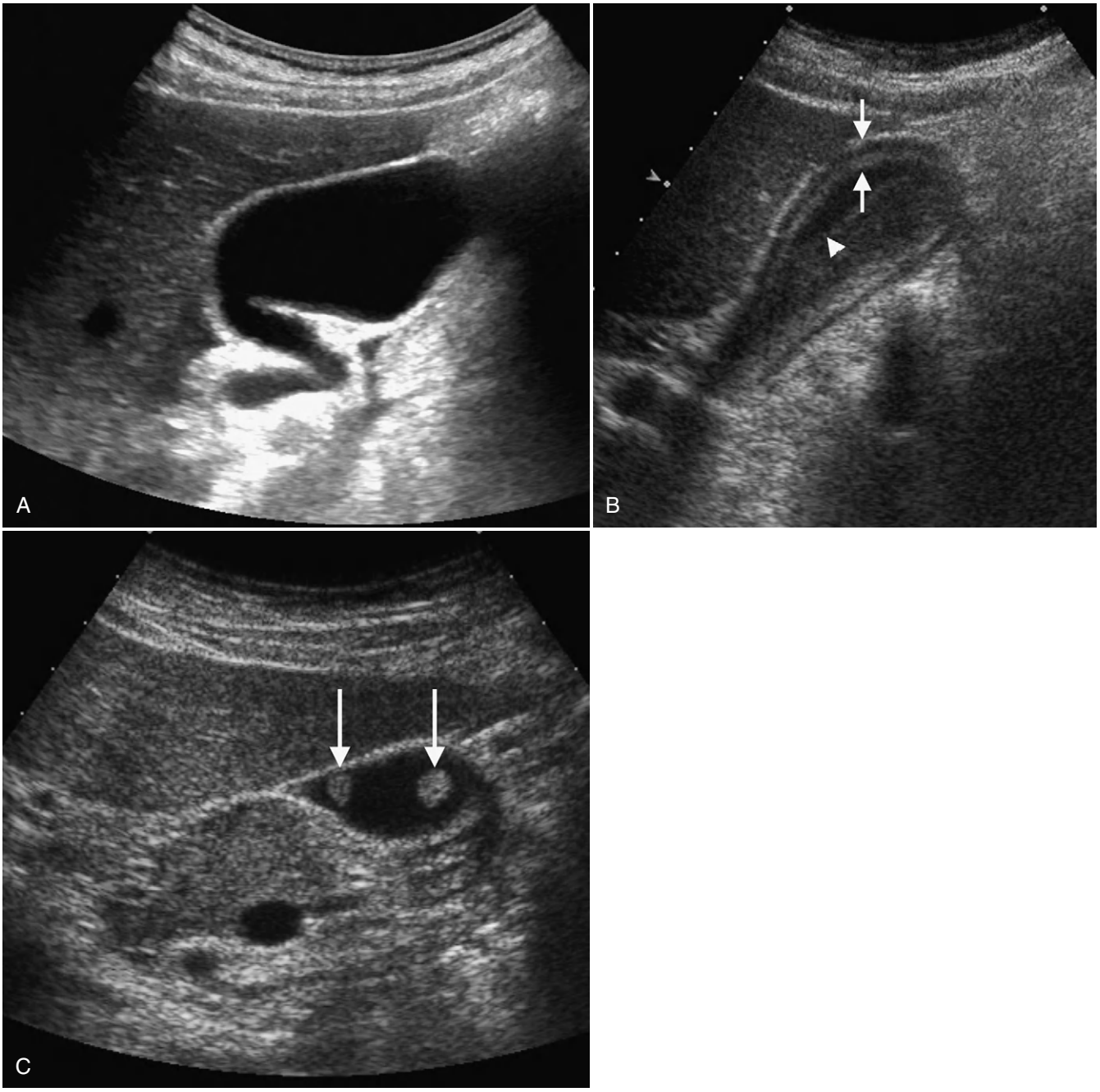


FIGURE 13.23. Gallbladder. **A,** Normal longitudinal gallbladder image with visualization of the gallbladder neck. **B,** Thickened gallbladder wall resulting from inflammation. Sludge (*arrowheads*) layers posteriorly. **C,** Gallbladder polyps (*arrows*). Note the lack of acoustic shadowing.

of the common hepatic duct. Adjacent adenopathy may also be present. Ultrasound performs well for detection of the gallbladder primary and local tumor spread, but CT is necessary to more accurately determine resectability, distant disease spread, and peritoneal metastases (Bach et al, 1998).

In the era of laparoscopic surgery for gallstone disease, it is especially important to assess the gallbladder carefully on preoperative ultrasound to exclude occult gallbladder cancer and to plan an appropriate surgical approach. Unfortunately, approximately 47% of gallbladder carcinomas are detected incidentally at laparoscopic cholecystectomy (Duffy et al, 2008). For these patients, reexploration with definitive resection to clear disease and reexcision of laparoscopic port sites is required (D'Angelica et al, 2009; Duffy et al, 2008; Winston et al, 1999).

Biliary Ducts

Congenital Anomalies

Choledochal cysts (see Chapter 46) are classified according to the location of the dilated ductal segment: *type 1* is fusiform common duct dilation, *type II* is diverticulum of the duct, *type*

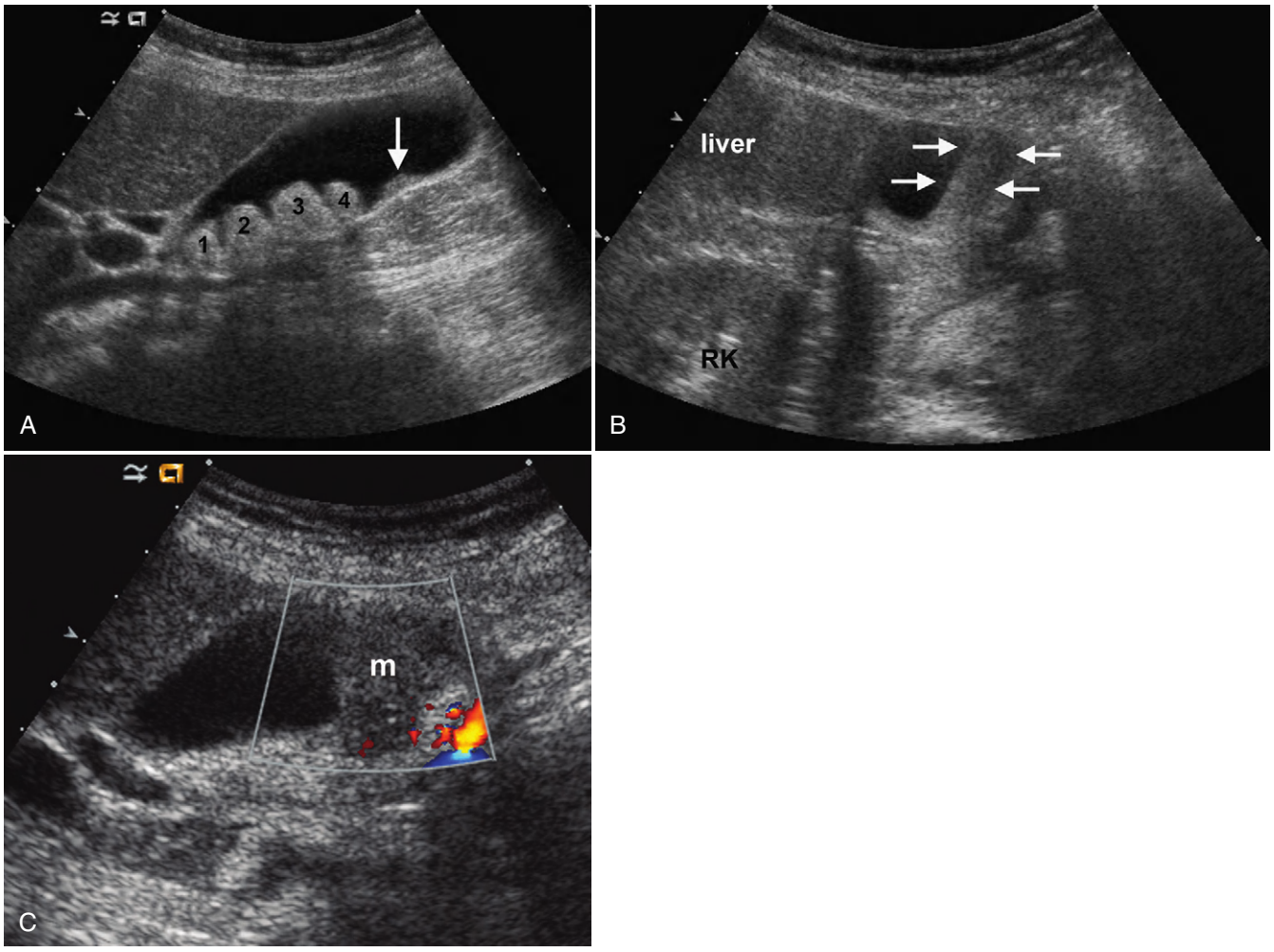


FIGURE 13.24. Gallstones and gallbladder carcinoma. **A,** Longitudinal view of the gallbladder shows layering stones (*numbered*) with acoustic shadow. A small amount of sludge (*arrow*) is also seen in the dependent portion of the gallbladder. **B,** Views of the fundus show focal mural thickening (*arrows*) suspicious for tumor. RK, right kidney. **C,** Flow is seen within the mass (*m*) on color Doppler imaging.

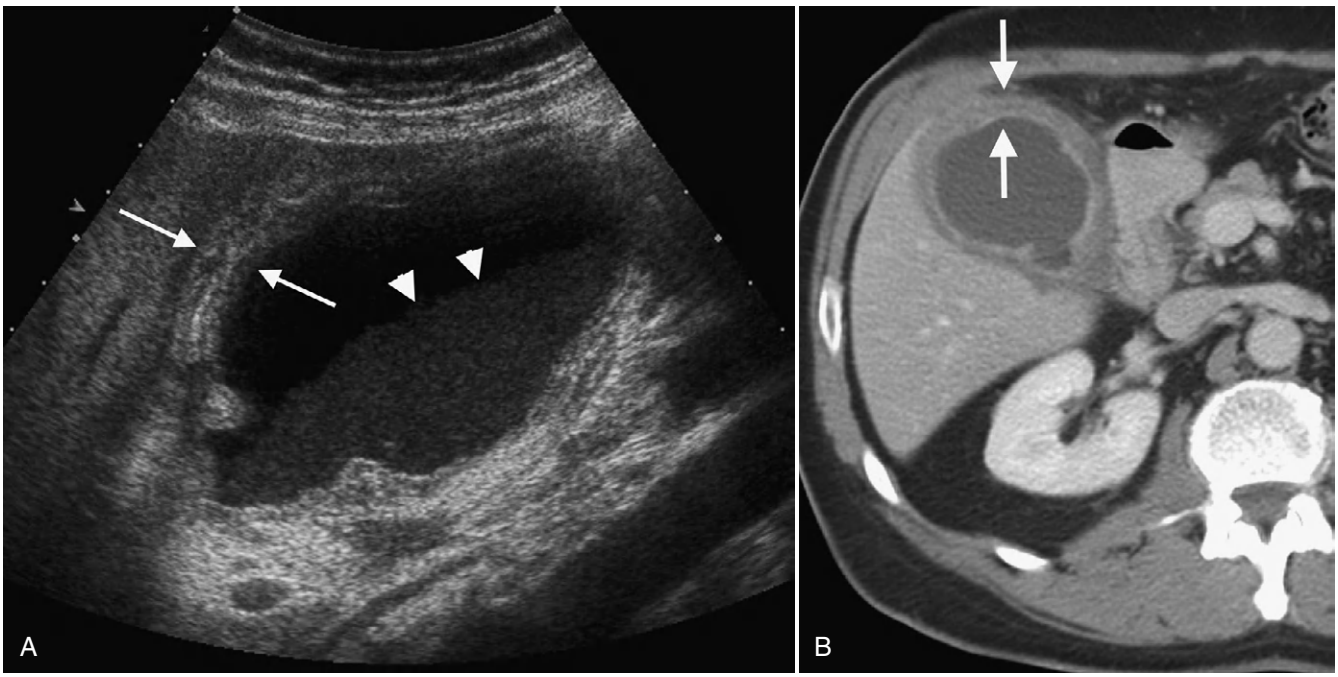


FIGURE 13.25. Acute cholecystitis. **A,** Longitudinal sonogram shows a distended gallbladder with thickened irregular wall (*arrows*) and layering sludge (*arrowheads*). **B,** Computed tomographic scan shows gallbladder wall thickening (*arrows*).

III is a choledochocele from a dilated terminal portion of the common bile duct, and *type IV* is multifocal dilation (Todani et al, 1977). The cysts may be large, and the connection with the bile duct is not always evident sonographically (Khalili & Wilson, 2005). Caroli disease is cystic bile duct malformation that results in multiple diverticulum-like outpouchings from the intrahepatic ducts. On imaging, it is important to demonstrate the connection with the bile ducts to differentiate this condition from polycystic disease. Arterial signals from the fibrovascular bundle at the margin of the saccules may also aid in diagnosis (Miller et al, 1995).

Biliary Obstruction

Ultrasound is the preferred initial imaging study to diagnose biliary obstruction and to determine the level of obstruction (Gibson et al, 1986). Signs of intrahepatic biliary obstruction include the "double track" sign and the "too many tubes" sign caused by dilated bile ducts parallel to the portal vein branches (Fig. 13.26). Bile duct dilation is best appreciated in transverse images of the left hepatic lobe. The pattern of bile duct dilation should be assessed to determine whether it is symmetric in both lobes or localized to one portion of the liver. To determine the level of obstruction, the left and right main ducts are followed transversely to their junction, and transverse views of the common hepatic and common bile ducts are obtained. With this approach it is possible to differentiate intrahepatic from extrahepatic obstruction, and usually the etiology of the obstruction can be determined (Fig. 13.27).

Bile duct calculi (see Chapters 35 and 39) appear as intraluminal filling defects (see Fig. 13.26). Because there is little bile surrounding the ductal calculi, acoustic shadowing may not always be elicited. Debris or thick bile within the ducts may cause internal echoes within ducts and fluid levels, but debris does not shadow, and it shifts with positional variation. Hemobilia (see Chapter 105) may layer or appear echogenic and masslike if the clot is organized. Intraductal tumor from colorectal metastases or HCC may also appear as an intraductal mass, but tumor often expands the duct, and it does not produce acoustic shadowing (Ghittoni et al, 2009; Jhaveri et al, 2009). Obstruction as a result of biliary ascariasis is associated with tubular structures within the bile duct, and movement of the worms is pathognomonic (Lim, 1990; see Chapter 45).

The pattern of biliary obstruction and the appearance of the duct wall are also useful for diagnosis. Recurrent pyogenic cholangitis (see Chapter 44) is evidenced by dilated ducts with intraductal calculi, but dilation is often segmental, frequently in the left lobe. Lobar atrophy may also be present. Primary sclerosing cholangitis (see Chapter 41) causes a beaded appearance of the ducts with wall thickening, strictures, and discontinuous areas of dilation. Mural thickening of the ducts also is seen with AIDS-associated cholangitis. For tumors adjacent to the umbilical portion of the left portal vein, subtle bile duct dilation or wall thickening may be a clue to biliary ductal involvement.

In patients with biliary obstruction who are being considered for surgical resection or palliative biliary drainage, the distribution of biliary ductal dilation should be carefully evaluated to determine management. For example, if surgery is being considered for a mass or vascular or biliary ductal involvement in one lobe, and main biliary duct obstruction is in a contralateral lobe, the disease is not resectable (Jarnagin et al, 2001). Any isolated biliary ductal segments that do not communicate with the main ducts should be noted, as isolated segments may alter surgical approach, and biliary drainage may require placement of multiple catheters.

Primary Bile Duct Neoplasms

INTRAHEPATIC CHOLANGIOCARCINOMA. Cholangiocarcinoma is the second most common primary hepatic neoplasm after HCC. The peripheral intrahepatic form arises from the intralobular ducts and presents as a focal hepatic mass that is usually solitary, but satellites may occur. Intrahepatic cholangiocarcinoma (see Chapter 50A) has associated peripheral biliary ductal dilation in 25%, may have capsular retraction, and lacks venous thrombosis; these features help differentiate

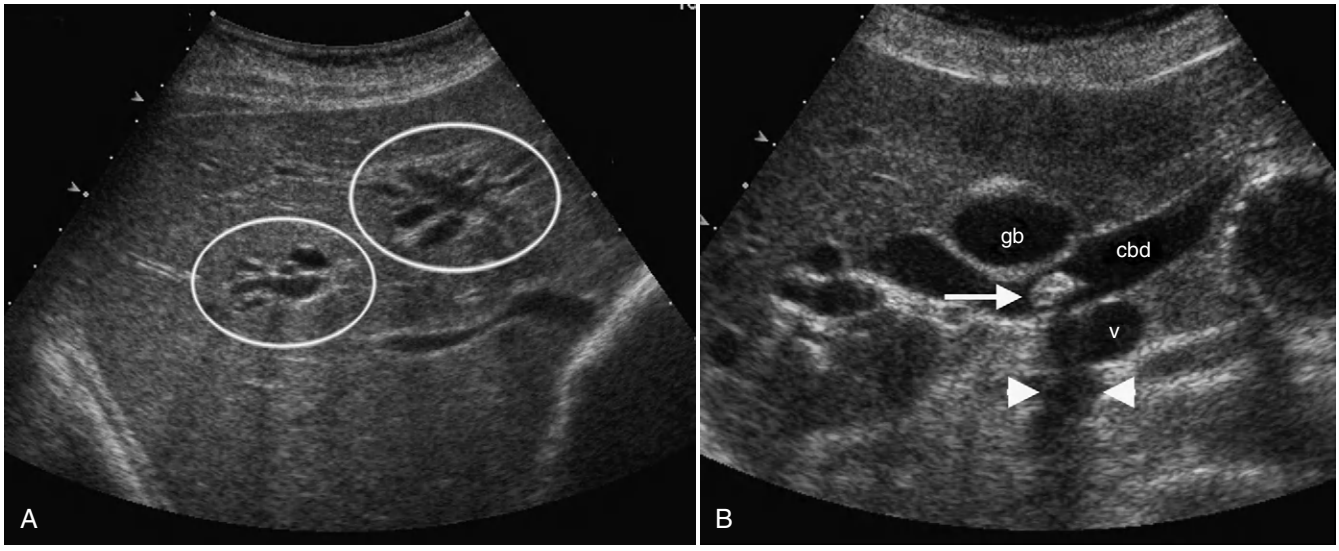


FIGURE 13.26. Biliary obstruction from choledocholithiasis. **A,** Transverse sonogram of the liver reveals "too many tubes" (*circled areas*), consistent with intrahepatic biliary dilation. **B,** Longitudinal view of the common bile duct (*cbd*) shows an echogenic stone (*arrow*) that produces acoustic shadowing (*arrowheads*). gb, gallbladder; v, portal vein.

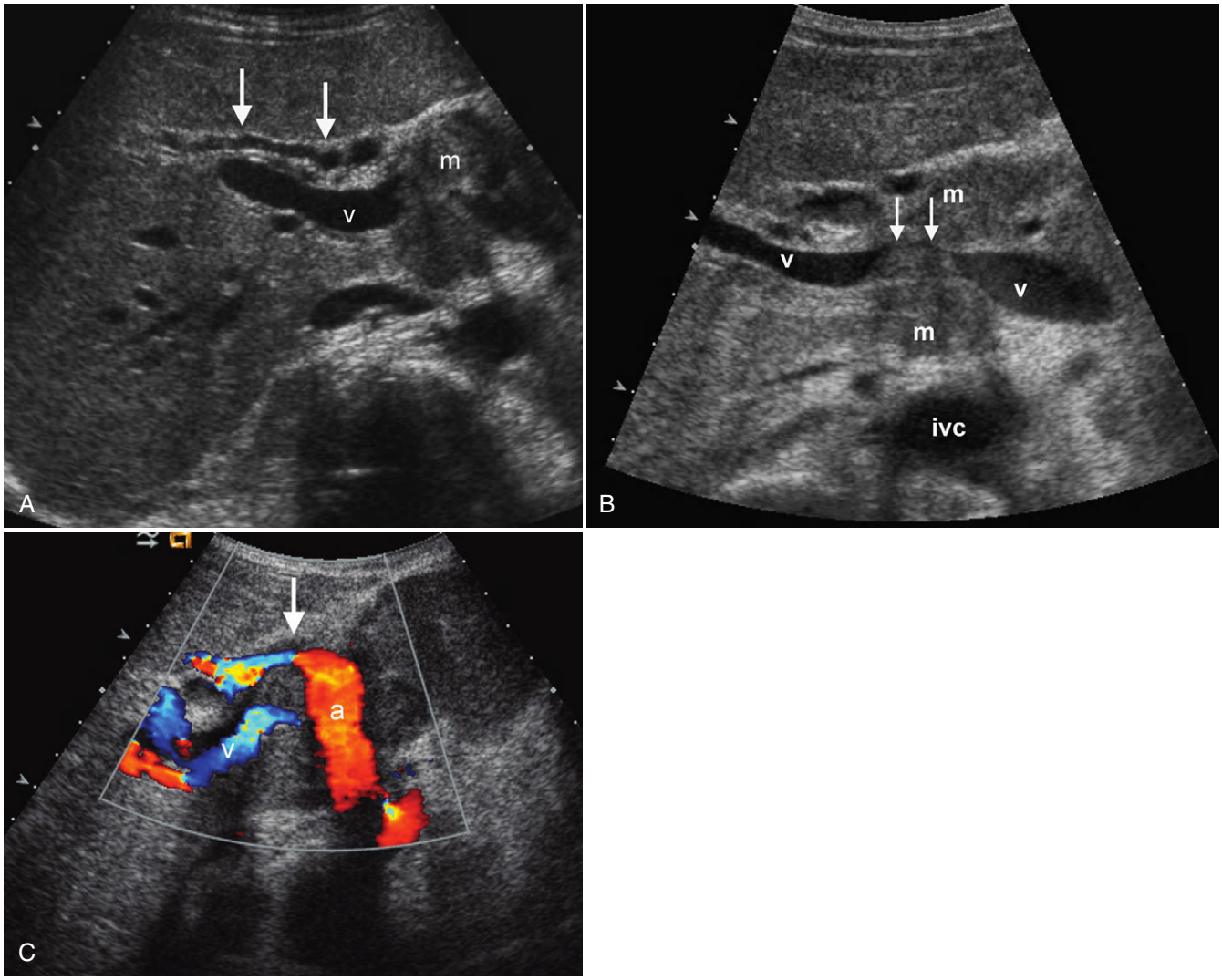


FIGURE 13.27. Biliary obstruction and vascular encasement from adenopathy at the porta hepatis. **A,** Mass (*m*) obstructs a mildly dilated common bile duct (*arrows*) and involves the main portal vein (*v*). **B,** Nodal masses (*m*) encase the portal vein (*v*) that is markedly narrowed (*arrows*). ivc, inferior vena cava. **C,** Color Doppler image shows narrowed hepatic artery (*a*; *arrow*) with dilation proximal to the encased segment.

peripheral cholangiocarcinoma from HCC (Soyer et al, 1995; Chung et al, 2009).

HILAR AND DISTAL CHOLANGIOCARCINOMA. Hilar cholangiocarcinoma or Klatskin tumor (see Chapter 50C), occurs at the biliary confluence. It is best evaluated by ultrasound prior to placement of biliary drainage catheters, as pneumobilia or stent artifact may obscure tumor margins, and the pattern of biliary obstruction may not be evident after decompression. Hilar cholangiocarcinoma is classified by extent of tumor along the duct, and some staging systems also include the status of the portal vein, because direct encasement of the adjacent vessels is common; surgical approach is determined by both portal vein status and ductal spread (de Groen et al, 1999; Jarnagin et al, 2001; Fig. 13.28).

On ultrasound, extrahepatic cholangiocarcinoma (see Chapter 50B) may be infiltrating, nodular, or papillary (Hann et al, 1997). The papillary form, which is expansile, has a better prognosis and surgical outcome (Jarnagin et al, 2005). With experienced operators, ultrasound can correctly identify 96% of extrahepatic cholangiocarcinomas and can demonstrate tumor infiltration along the duct wall (Lim, 2003; Robledo et al, 1996). Ultrasound contrast agents aid diagnosis and staging (Lim et al, 2006). Khalili and colleagues (2003) reported that correct prediction of resectability improved from 69% on noncontrast ultrasound to 96% after contrast.

ULTRASOUND OF THE PANCREAS

Anatomy and Technique

The pancreas is oriented transversely in the epigastrium (see Chapter 1) and is situated immediately ventral to the splenic vein (Fig. 13.29). The latter serves as a useful landmark for locating the pancreas because the organ may sometimes appear isoechoic with the surrounding fat. The splenic vein unites with the superior mesenteric vein (SMV) just posterior to the neck of the pancreas, so that the SMV is a useful anatomic landmark

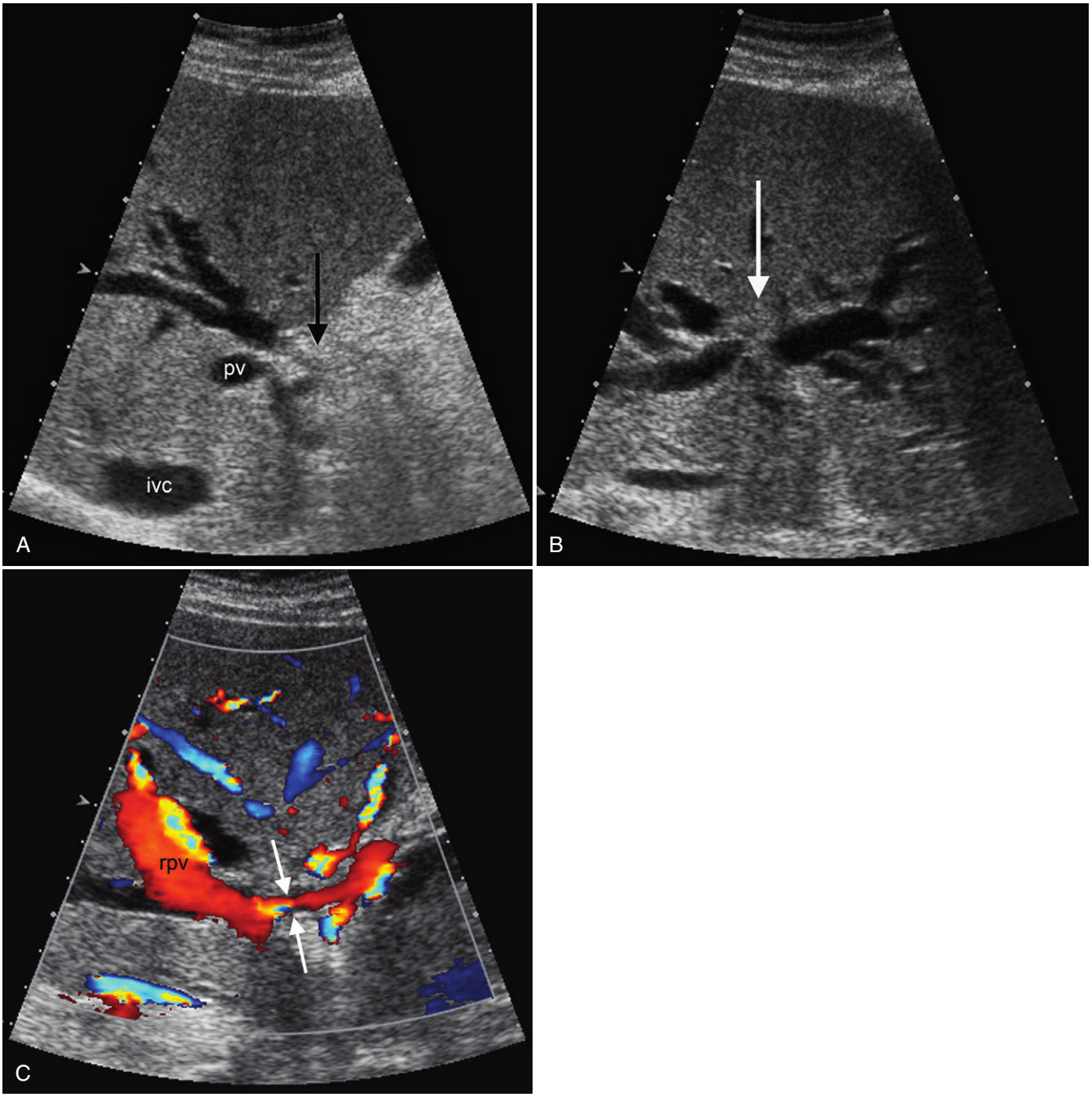


FIGURE 13.28. Klatskin tumor. **A,** Longitudinal view of the common hepatic duct shows a tapered segment (*arrow*) consistent with tumor stricture. pv, portal vein; ivc, inferior vena cava. **B,** Transverse image at the biliary confluence reveals an echogenic mass (*arrow*) at the bifurcation and dilated bile ducts in both lobes. **C,** The left portal vein is narrowed and encased (*arrows*), as shown on color Doppler transverse image. rpv, right portal vein.

that separates the head from the neck of the pancreas. Normal pancreas is homogeneously echogenic and generally of higher echogenicity than the normal liver. In thin patients, the normal pancreatic duct may be visible as an anechoic tubular structure oriented along the long axis of the pancreas. The normal pancreatic duct in young patients should measure no larger than 2 mm in diameter. On transverse images, the common bile duct can usually be visualized in cross section in the posterior aspect of the head of the pancreas (see Fig. 13.29). The gastroduodenal artery can often be seen in cross section along the right anterior aspect of the pancreatic head.

Because of its midline and posterior location, the pancreas is often partially obscured by overlying gas in the stomach. Therefore when primary pancreatic pathology is suspected, CT is the preferred imaging modality (see Chapter 16). Nevertheless, routine abdominal sonograms should include the pancreas, and when sonography is performed for biliary colic or suspected biliary dilation, every attempt must be made to

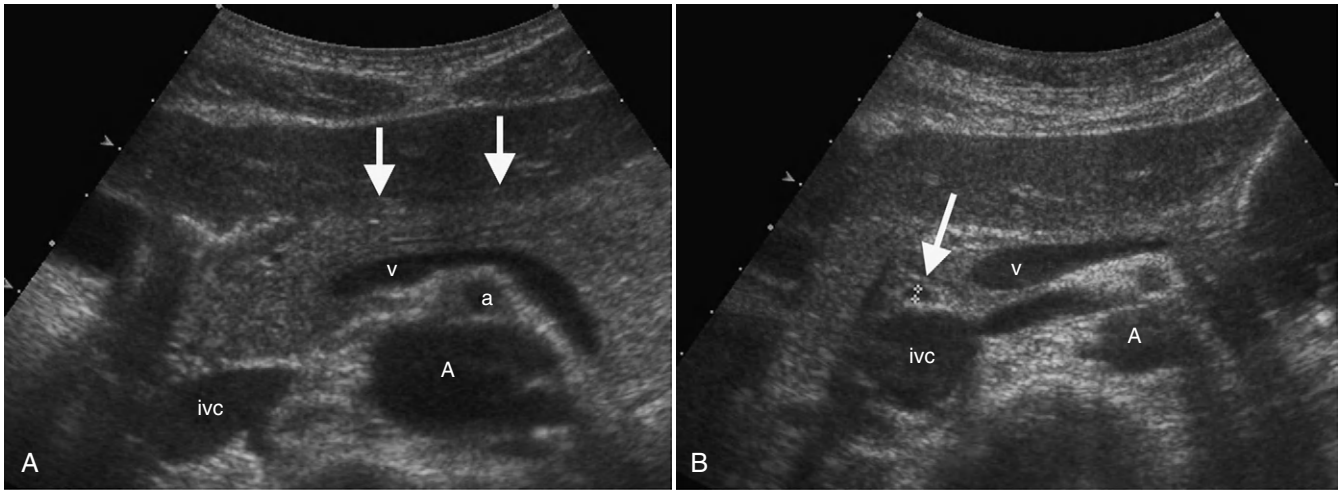


FIGURE 13.29. Normal pancreas. **A,** Transverse image of the normal pancreas and adjacent vascular anatomy. Pancreatic body (*arrows*) is shown. v, splenic vein; a, superior mesenteric artery; A, aorta; ivc, inferior vena cava. **B,** Common bile duct (*cursors; arrow*) in the head of the pancreas.

visualize at least the pancreatic head. It is usually best to begin scans of the abdomen by obtaining images of the pancreas, because the deep inspiratory scans used to image the liver lead to aerophagia and diminish the likelihood of pancreatic visualization. Positional maneuvers, such as sitting the patient upright to displace the stomach gas into the fundus, may help with pancreatic visualization if overlying gas is present in the supine position.

Pancreatitis

Acute pancreatitis (see Chapters 52 and 53) is a common cause of abdominal pain and is usually diagnosed clinically and with laboratory examination findings. Although CT is the preferred technique for gauging the severity and extent of acute pancreatitis, sonography in this setting is useful to determine whether the disease was triggered by gallstones, because the sensitivity of CT for detection of gallstones has been reported to be as low as 25% (Chan et al, 2006). Direct visualization of the pancreas itself on ultrasound may be impaired by gas from an overlying paralytic ileus at initial presentation. In mild pancreatitis, no sonographic abnormalities may be appreciable. If the inflammation is diffuse and more severe, the pancreas may be uniformly hypoechoic. The presence of pancreatic necrosis or hemorrhage cannot be determined reliably with ultrasound; CT is therefore necessary for accurate evaluation.

Other complications of acute pancreatitis, such as extrapancreatic and intrapancreatic fluid collections and pseudocysts, may be readily seen with sonography (see Chapter 54). Pseudocysts form in approximately 10% to 20% of patients with acute pancreatitis (Atri & Finnegan, 2005). They are loculated fluid collections contained within a wall of collagen and granulation tissue, and they generally take 4 to 6 weeks to form following an acute episode of pancreatitis (Atri & Finnegan, 2005; Balthazar, 2002). On sonography, pseudocysts are typically well-marginated ovoid or spherical anechoic masses with posterior acoustic enhancement (Fig. 13.30). Internal echoes representing hemorrhage or debris may be present in the early stages, and

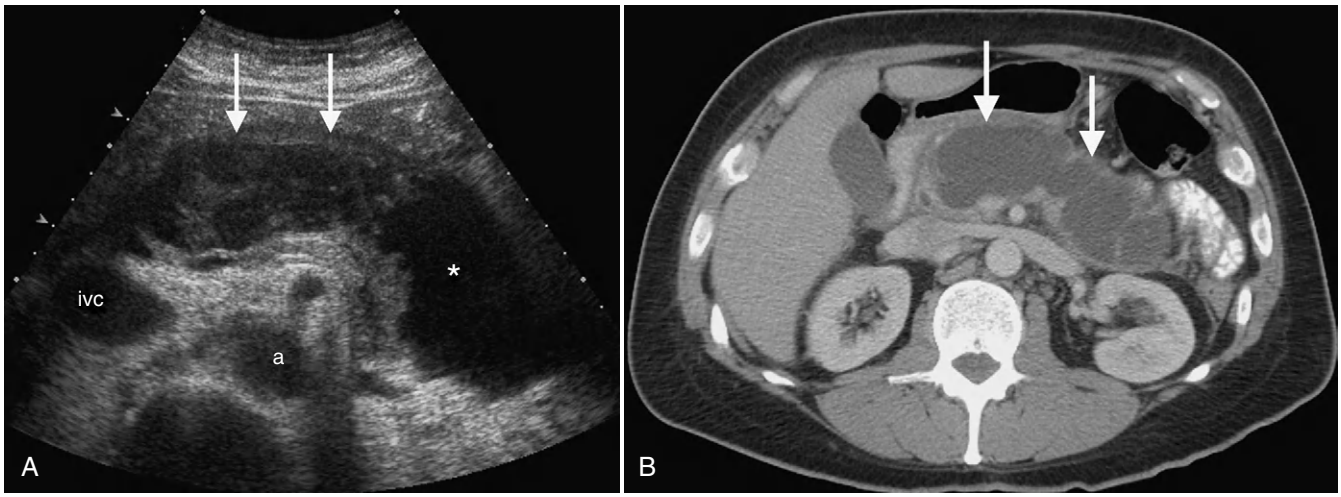


FIGURE 13.30. Pancreatic pseudocyst. **A,** Transverse sonogram of the pancreas reveals a cyst (*asterisk*) in the tail and extension into the body (*arrows*). ivc, inferior vena cava; a, aorta. **B,** Computed tomographic scan confirms extensive pseudocyst (*arrows*).

calcification of the pseudocyst wall may occur. Color Doppler should always be used to evaluate any epigastric cystic mass, including those seen in the setting of pancreatitis, to distinguish these fluid collections from other complications of pancreatitis such as pseudoaneurysms. Color Doppler will also enable detection of splenic vein thrombosis, which occurs in 1% to 3% of patients following acute pancreatitis (Balthazar, 2002).

With repeated episodes of mild acute or subclinical pancreatitis, chronic inflammation with scarring and destruction of pancreatic parenchyma occurs. The changes of chronic pancreatitis seen on sonography include dilation and irregularity of the main pancreatic duct, intraductal calcifications, and focal inflammatory masses (Atri & Finnegan, 2005; see Chapter 55A). The latter may be especially problematic, because these hypoechoic focal regions mimic the ultrasound appearance of pancreatic carcinoma. The finding of calcifications within a hypoechoic focal mass is helpful for differentiating the two entities and suggests chronic pancreatitis, rather than carcinoma, as the etiology. Common duct dilation can be seen in 5% to 10% of patients with chronic pancreatitis (Bolondi et al, 1989), although again, other etiologies—including a downstream obstructing adenocarcinoma or intraductal papillary mucinous neoplasm—should also be considered in the differential diagnosis of main pancreatic duct dilation. Again, calcification visible within the pancreas makes chronic pancreatitis more likely.

Autoimmune lymphoplasmacytic pancreatitis is an unusual type of chronic pancreatitis characterized by fibrotic change with lymphocytic infiltration (Fig. 13.31). On imaging studies, the gland is diffusely or focally swollen, and the main duct is irregularly narrowed (Araki et al, 2006; Sahani et al, 2004). This type of pancreatitis is highly responsive to steroids, and recent studies of contrast-enhanced sonography suggest that the degree of vascularity evident following contrast injection correlates directly with the pathologic grade of inflammation and inversely with the grade of fibrosis (Numata et al, 2004).

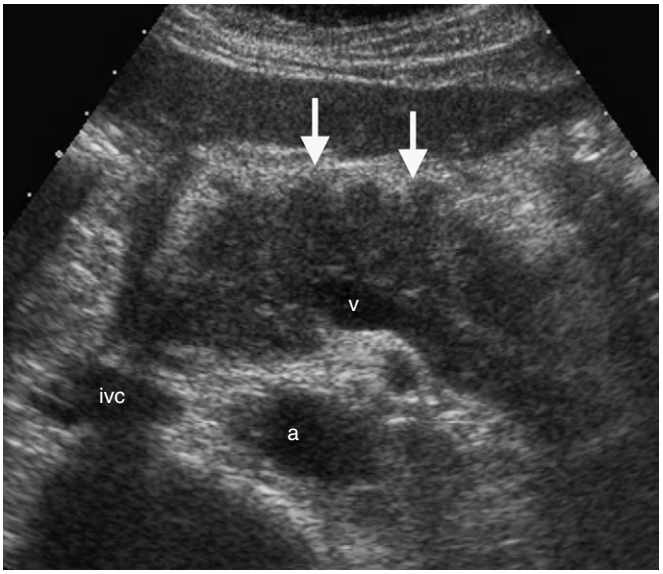


FIGURE 13.31. Lymphoplasmacytic pancreatitis. Transverse image of the pancreas shows diffuse pancreatic enlargement, well-defined margins, and lobulated appearance (*arrows*). ivc, inferior vena cava; a, aorta; v, splenic vein.

Pancreatic Neoplasms

Solid Neoplasms of the Pancreas

Although best staged by CT, adenocarcinoma of the pancreatic head is often detected on sonography, because ultrasound is typically the initial imaging study for evaluation of jaundice, right upper quadrant pain, and epigastric pain (see Chapter 58B). The typical pancreatic adenocarcinoma is an ill-defined hypoechoic mass associated with abrupt dilation of the upstream pancreatic duct and atrophy of the more distal pancreas (Fig. 13.32). Carcinomas of the pancreatic head typically also cause biliary dilation and a "Courvoisier gallbladder." Dilation of both the pancreatic duct and common bile duct, the "double-duct sign," is always a suspicious imaging finding for pancreatic adenocarcinoma, with any imaging modality. Adenocarcinoma in the body or tail of the pancreas is inconsistently visualized on sonography because of variables such as patient body habitus and overlying gastric or bowel gas. Color Doppler sonography typically does not show increased vascularity within pancreatic adenocarcinoma. Nevertheless, this mode can be useful to

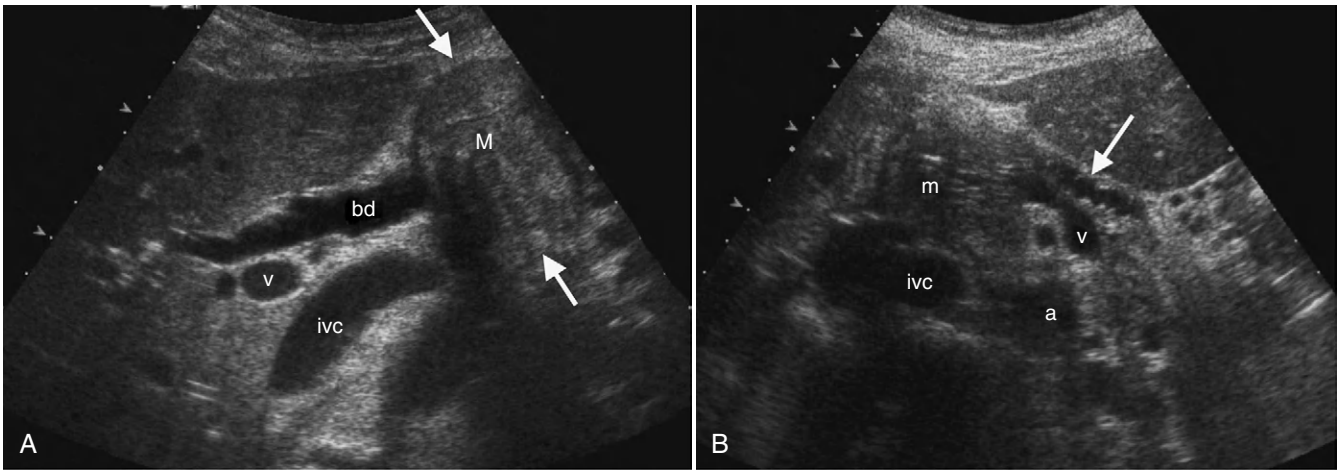


FIGURE 13.32. Pancreatic adenocarcinoma. **A,** Longitudinal view reveals a mildly dilated common bile duct that terminates in a pancreatic head mass (*M; arrows*). v, Portal vein; ivc, inferior vena cava; bd, bile duct. **B,** On transverse view, the pancreatic duct (*arrow*) is dilated. m, Pancreatic head mass; v, splenic vein; a, aorta.

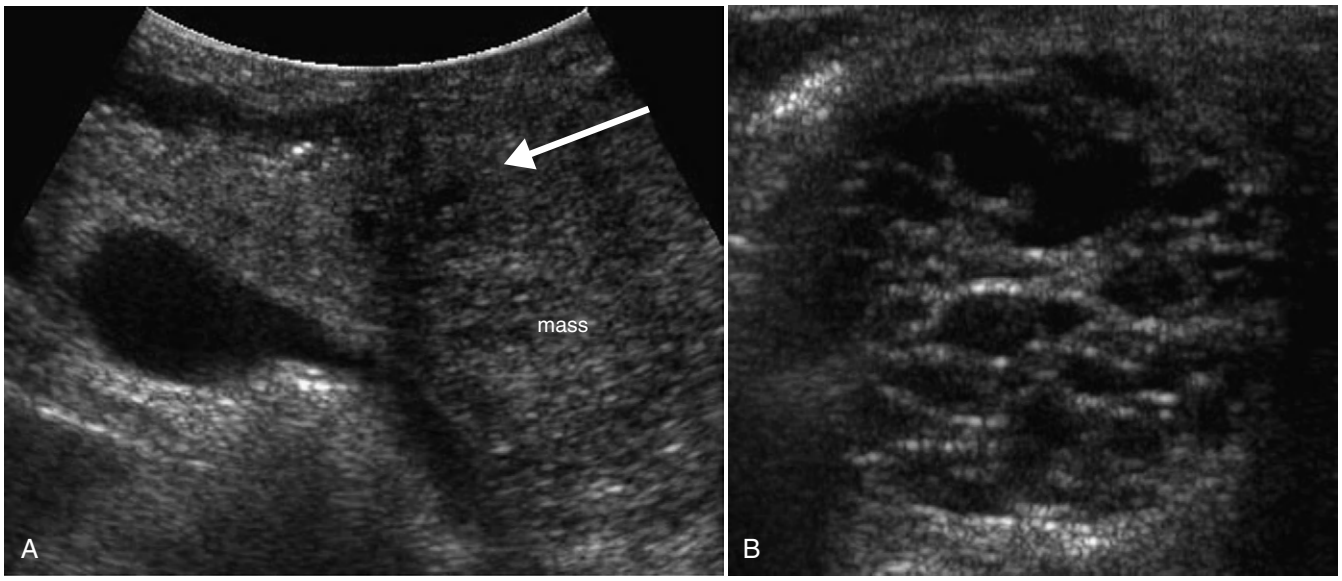


FIGURE 13.33. Serous (microcystic adenoma) of the pancreas. Transverse intraoperative ultrasound images of the pancreas. **A,** Mass in the pancreatic tail has a small cyst (*arrow*). **B,** On magnified higher frequency images, the mass has honeycomb architecture.

visualize the peripancreatic vasculature, such as the celiac axis and superior mesenteric vessels, which are often encased in locally advanced disease (Atri & Finnegan, 2005).

In contrast to adenocarcinomas, neuroendocrine tumors of the pancreas are commonly hypervascular masses (see Chapter 61). They are typically more hypoechoic than adenocarcinomas and may be well defined and smoothly marginated. Intraoperative ultrasound is often a useful adjunct to surgery for pancreatic neuroendocrine tumors, because many are localized and can be safely enucleated. In patients with multiple endocrine neoplasia type I (MEN-I), real-time intraoperative scanning can also help identify additional subcentimeter neuroendocrine tumors that may escape CT detection (Shin et al, 2009).

Cystic Neoplasms of the Pancreas

Cystic pancreatic neoplasms (see Chapter 57) fall into two major categories: *serous* (microcystic) neoplasms and *mucinous* (macrocystic) neoplasms. The two should be distinguished on imaging, because serous tumors are always benign, but mucinous tumors have malignant potential. Differentiation can be made on imaging studies based on the internal architecture and size of the cysts. Serous tumors have cysts ranging in size from less than 1 mm to 2 cm in size, and the internal architecture is often described as having a honeycomb appearance (Fig. 13.33). However, these tumors can vary considerably in sonographic appearance based on the sizes of the internal cysts they comprise. Serous tumors composed of relatively larger cysts will appear as partially solid cystic masses on sonography. As the cysts in a serous tumor get smaller, the less likely it is that the individual cyst cavities and walls will be resolvable on ultrasound; instead, the numerous interfaces created by the walls of the cysts will confer an overall echogenic appearance to the mass. A central stellate scar is a characteristic feature of many serous cystadenomas and may be visible as an echogenic or frankly calcified focus with shadowing (Atri & Finnegan, 2005; Hutchins et al, 2009).

Mucinous neoplasms, by contrast, are typically unilocular or multilocular cystic masses. The cysts within these tumors are larger than 2 cm, and a solid mural nodule within any of the cyst cavities is suspicious for malignancy in these lesions. Intraductal papillary mucinous tumors (IPMTs) arise from the epithelium of the main pancreatic duct or side branches. Side-branch type IPMTs commonly appear as small unilocular cysts or multilocular cystic masses within the pancreatic parenchyma. Main-duct type IPMTs show up as focal or diffuse dilation of the main pancreatic duct. Again, any internal mural nodularity is concerning for malignancy in these tumors.

Endoscopic ultrasound is very useful in evaluation of cystic pancreatic neoplasms, because the internal architecture of the lesions is much better demonstrated. The lesions can also be aspirated under endoscopic ultrasound, and the fluid can be evaluated for the presence of glycogen (serous tumors), mucin (mucinous tumors), and tumor markers such as carcinoembryonic antigen (Hutchins et al, 2009).

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CHAPTER 14

Endoscopic ultrasound of the biliary tract and pancreas

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IMAGING AND DIAGNOSIS

The diagnosis of benign and malignant diseases of the pancreas and biliary tree has traditionally relied on a detailed history and complete physical examination, with correlation of the results of clinical chemistries. Imaging of the hepatic and pancreatic parenchyma and ductal anatomy has, however, evolved as critical for accurate diagnosis and for guiding therapy. Routine radiography does not provide the soft-tissue resolution required, but ultrasonography (US; see Chapter 13), computed tomography (CT; see Chapter 16), and magnetic resonance imaging (MRI; see Chapter 17) have become important noninvasive modalities in the routine investigation of almost any symptom, physical sign, or laboratory abnormality potentially relating to pathologic conditions of the liver or pancreas.

Invasive procedures for imaging the biliary and pancreatic ductal systems, primarily percutaneous cholangiography (PTC) or endoscopic retrograde cholangiopancreatography (ERCP) remain important therapeutically, but with respect to diagnosis, these have been almost entirely replaced by noninvasive modalities. Endoscopic ultrasonography (EUS) has also become an important tool for diagnosis and treatment. Its high-resolution images complement the more general findings of cross-sectional imaging and result in a higher sensitivity for diagnosis of early-stage disease. The new-generation EUS instruments (Figs. 14.1 and 14.2) permit guided passage of needles and devices through the endoscope, allowing biopsies to be obtained and permitting therapeutic interventions. This chapter discusses the techniques of radial and linear endosonography in the diagnosis, staging, and treatment of benign and malignant disease of the pancreas and biliary tree.

ENDOSCOPIC ULTRASOUND TECHNIQUE

Because the normal pancreas is located posterior to the stomach, the entire gland is readily seen by EUS imaging through the wall of the stomach and duodenum. With the transducer in the duodenum, the pancreatic head and uncinate process, ampulla of Vater, pancreatic ducts, common bile ducts (CBDs), and the surrounding vascular and nodal structures can be visualized. With the transducer in the stomach, the pancreatic body and tail and the celiac, splenic, hepatic, and superior mesenteric arteries and the splenic, superior mesenteric, and portal veins are all seen in detail.

The normal pancreatic parenchyma has a homogeneous echogenic appearance (Fig. 14.3), and tumors usually appear hypoechoic, often with irregular borders, in sharp distinction from normal tissue (Fig. 14.4). Large tumors of the pancreas may be difficult to evaluate completely because of limited penetration of the tumor by US. Conversely, small tumors of the pancreas that are often missed by CT or MRI are readily imaged by EUS. For example, islet cell tumors, which are often encapsulated and small, are frequently detected on EUS and appear as well-demarcated hypoechoic lesions (Fig. 14.5). Other neuroendocrine tumors, such as gastrinomas, may be isoechoic within the pancreatic parenchyma and difficult to identify without careful, tedious, real-time imaging. Ampullary tumors are also often seen and staged on EUS because of their relation to the duodenal wall, CBD, and pancreatic duct (Fig. 14.6). Extrahepatic bile duct tumors can also be detected and described in detail with EUS imaging (Fig. 14.7).

Cysts of the pancreas are generally anechoic and well demarcated and thus easily identified even when small. Some cysts may have internal echoes or solid areas, which raise concern for a mucinous lesion or associated tumor (Fig. 14.8). If the cysts are complex with septa (Fig. 14.9), they are best distinguished from vascular structures using the Doppler flow feature of the linear array echoendoscopes. Serous cystadenomas may also appear isoechoic with the pancreas and require careful imaging for proper identification (Fig. 14.10). Pseudocysts can vary in size and sonographic features but usually lack a discrete wall and septa, particularly if acute. However, internal echoes often are seen as a result of necrotic debris (Fig. 14.11).

Endoscopic Ultrasound-Guided Fine Needle Aspiration

The development of linear array echoendoscopes, which scan an area orthogonally in line with the endoscope (thus in line with the biopsy channel), has allowed the development of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA). The indications for EUS-FNA include pathologic confirmation of a suspected pancreatic or periampullary cancer prior to nonoperative therapy, evaluation of pancreatic masses or lymph nodes of unclear etiology, and aspiration of pancreatic cysts to help distinguish mucinous from inflammatory or serous lesions. EUS-FNA has also provided the framework for investigations into novel therapies (see EUS-Guided Therapy and Novel Therapeutics below).

Endoscopic Ultrasound Fine Needle Aspiration Technique

Within the duodenum or stomach, the US probe is positioned in close proximity to the target lesion, typically less than 3 cm away. The area is then interrogated with Doppler flow US to ensure the absence of significant vascular structures in the needle path. A 25-, 22-, or 19-gauge needle can then be directed into the target lesion. The tip and shaft of the needles used for FNA are manufactured to produce a bright, hyperechoic image.



FIGURE 14.1. Radial echoendoscope.

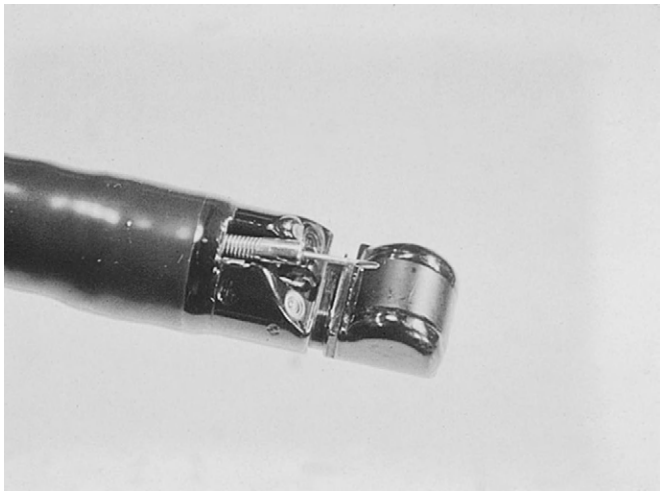


FIGURE 14.2. Linear array echoendocope.

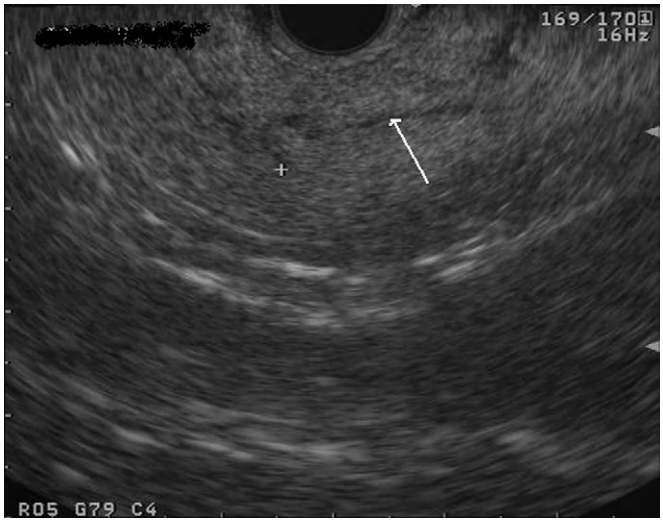


FIGURE 14.3. Normal endoscopic ultrasound image of the body of the pancreas with thin main pancreatic duct (*arrow*).

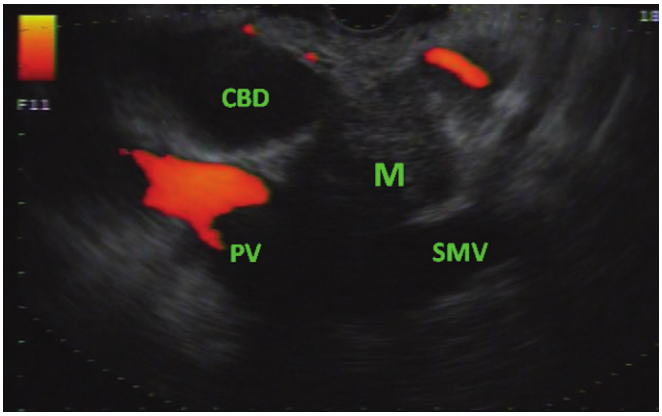


FIGURE 14.4. Solid, irregular, hypoechoic mass (*M*) in the pancreatic head seen with abrupt termination of a dilated common bile duct (*CBD*) and contact with the portal confluence (portal vein [*PV*] and superior mesenteric vein [*SMV*]). Cytology obtained by endoscopic ultrasound–guided fine needle aspiration proved to be adenocarcinoma.

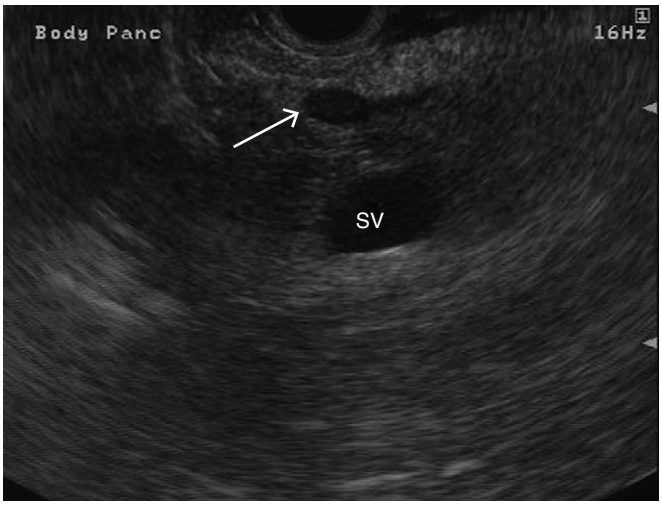


FIGURE 14.5. Small, well-circumscribed, hypoechoic appearance of an insulinoma (*arrow*) in the body of the pancreas with splenic vein below (*SV*).

This allows the needle to be followed in real time to ensure precise positioning within the target lesion (Fig. 14.12). Ideally, a cytopathologist or cytotechnologist should be present at the time of the FNA to determine the cellular adequacy of the specimen. Alternatively, multiple punctures (up to seven) should be performed to ensure an adequate cytologic specimen (LeBlanc et al, 2004). Cyst fluid can also be aspirated and sent for cytology, tumor markers, and chemical analysis (Fig. 14.13).

DIAGNOSIS OF PANCREATIC CANCER

Endoscopic Ultrasound Fine Needle Aspiration of Solid Pancreatic Lesions

Solid masses of the pancreas may represent a primary pancreatic cancer, neuroendocrine tumor, metastatic lesion, or focal pancreatitis. These masses may be difficult to visualize and are often indistinguishable on noninvasive imaging. Percutaneous CT-guided biopsy has a pooled sensitivity of 87% and negative

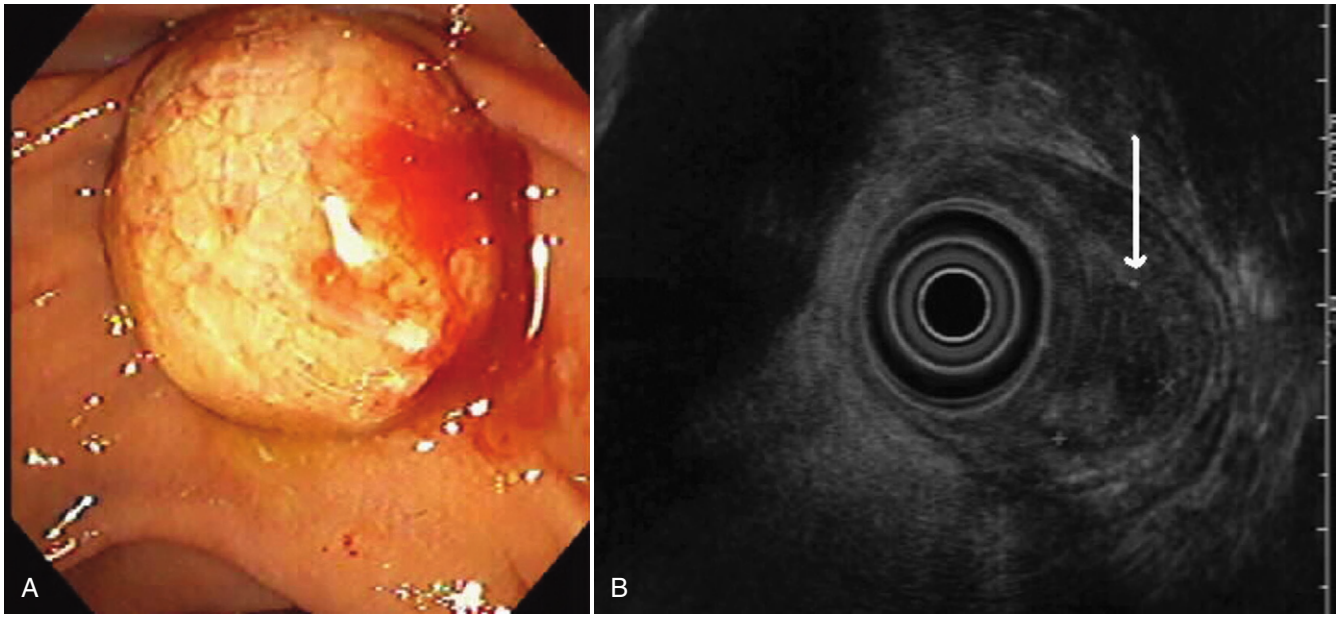


FIGURE 14.6. Endoscopic (**A**) and endoscopic ultrasound (**B**) imaging of an ampullary tumor (*arrow*).

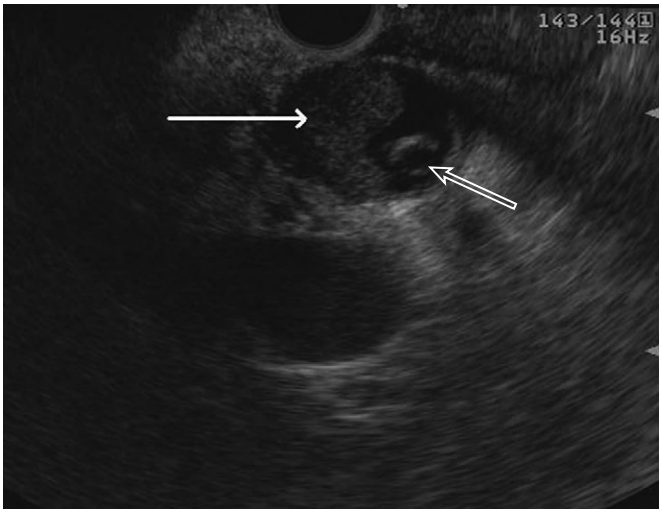


FIGURE 14.7. Hypoechoic mass appearance of cholangiocarcinoma of the common bile duct (*solid arrow*) with biliary stent visible (*open arrow*).

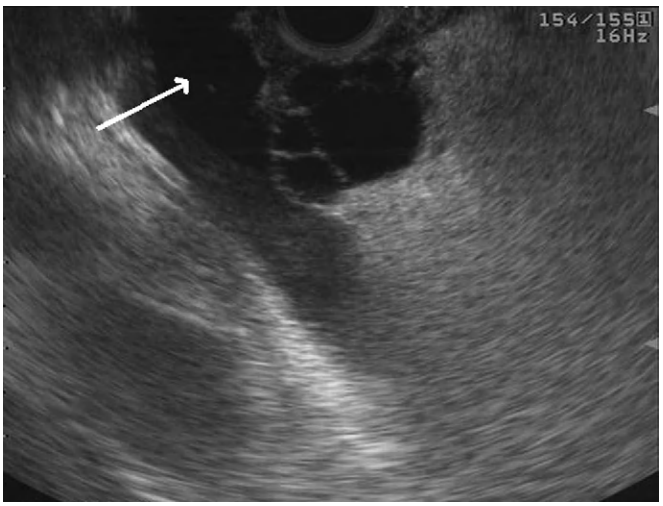


FIGURE 14.9. Multiseptated mucinous cystic lesion in the head of the pancreas (*arrow*).

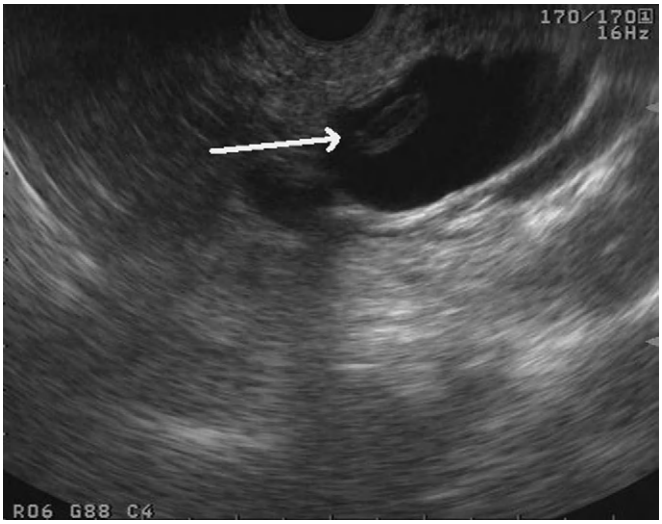


FIGURE 14.8. Mucinous cystic lesion in the head of the pancreas with mural nodule (*arrow*).

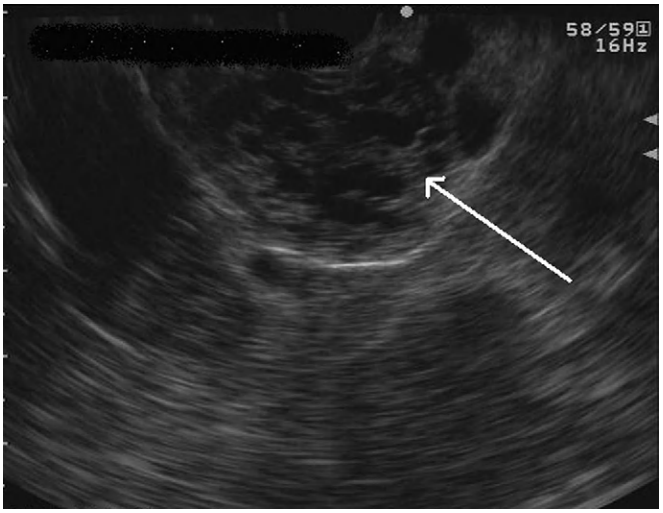


FIGURE 14.10. Typical microcystic appearance of a serous cystadenoma in the head of the pancreas (*arrow*).

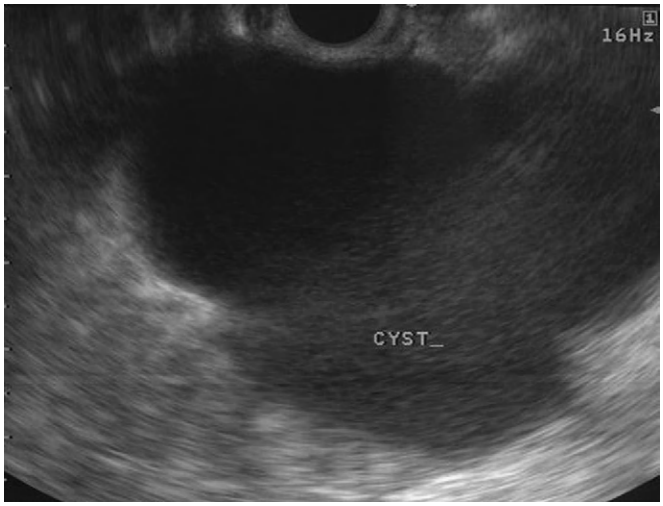


FIGURE 14.11. Large debris-filled pseudocyst adjacent to the tail of the pancreas.



FIGURE 14.12. Bright appearance of fine needle aspiration of a solid mass in the head of the pancreas.

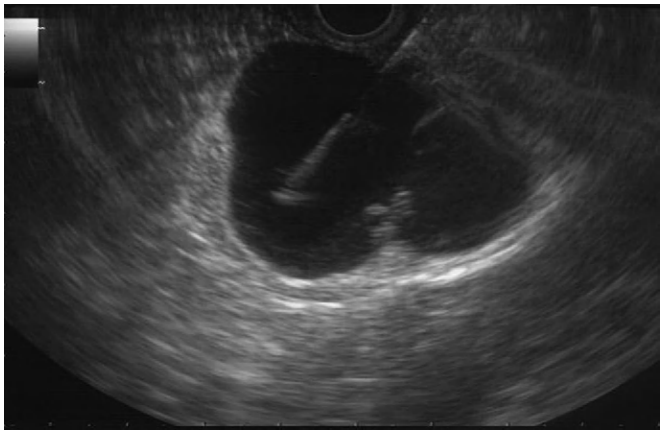


FIGURE 14.13. Fine needle aspiratin of cyst fluid.

predictive value of only 58% (Hartwig et al, 2009), and it carries the risk of cutaneous or peritoneal tumor seeding. Therefore a percutaneous biopsy is best indicated in patients with unresectable disease to help establish a diagnosis and plan palliative care. Similarly, the sensitivity of cytology obtained from brushings during cholangiography is poor (approximately 40%) and cannot adequately exclude cancer (Wakatsuki et al, 2005).

EUS-FNA is highly accurate in diagnosing patients with suspected pancreatic cancer with a sensitivity of 77% to 95%, specificity of 94% to 99%, positive predictive value (PPV) of 98% to 100%, and a negative predictive value (NPV) of 86% to 92% (Wiersema et al, 1997; Yusuf et al, 2009; Turner et al, 2010; Table 14.1). EUS-FNA should be considered as the initial approach to lesions in or adjacent to the pancreas. In a prospective study of 102 patients with suspected pancreatic cancer who had a negative CT-guided biopsy, EUS-FNA had a sensitivity of 95%, specificity of 100%, PPV of 100%, and a NPV of 92% (Gress et al, 2001). With EUS, the issue of needle-tract tumor seeding is minimized, as the FNA is generally performed through a segment of duodenal or stomach wall that will be removed as part of a resection, should the patient be an appropriate surgical candidate. The utility of preoperative EUS-FNA was further demonstrated in a prospective study of 44 patients with resectable pancreatic mass lesions by cross-sectional imaging. EUS with or without FNA precluded surgery in 27% of patients by determining vascular invasion and nodal involvement or by diagnosing lymphoma of the pancreas (Chang et al, 1997).

Endoscopic Ultrasound Fine Needle Aspiration of Pancreatic Cystic Lesions

Cystic lesions of the pancreas remain a diagnostic and therapeutic challenge. The differential diagnosis includes retention/simple cysts, pseudocysts, cystic neoplasms, and cystic degeneration of solid masses (Table 14.2). EUS provides detailed

Table 14.1

Performance Characteristics for EUS in the Diagnosis and Staging of Pancreatic, Ampullary, and Extrahepatic Biliary Tumors

	Sensitivity	Specificity	Accuracy
Pancreatic Tumors			
Diagnosis*			
Tumor >3 cm	86%-95%	94%-99%	86%-94%
Tumor <3 cm	85%-95%	87%-100%	93%-100%
Tumor staging	—	—	72%-98%
Nodal staging	—	—	44%-66%
Resectablity	33%-50%	78%-100%	79%-95%
Ampullary Tumors			
Diagnosis	—	—	93%-100%
Resectability	—	—	61%-88%
Bile Duct Tumors			
Diagnosis*	—	—	43%-86%
TN staging	—	—	60%-80%

*Includes the use of fine needle aspiration to obtain cytology.
EUS, endoscopic ultrasound; TN, tumor node.

Table 14.2

Imaging Characteristics and Fluid Analysis of Pancreatic Cystic Lesions

	EUS Morphology	Communication with Pancreatic Duct	Fluid Amylase	Fluid CEA	Fluid Cytology
Retention cysts	Unilocular, thin walled	No	Variable	Low	Normal duct or centroacinar cells
Pseudocyst	Unilocular, thick walled with debris	Yes	Very high	Low	Inflammatory cells, no epithelial cells
Serous cystadenoma	Microcystic with central calcification	No	Low	Low	Small cuboidal cells, positive glycogen stain
Mucinous cystadenoma	Macrocystic with thick septations	Occasionally	Low	High	Atypical ductal cells, positive mucin stain
IPMN	Dilated, tortuous pancreatic duct and/or side branches	Yes	High	High	Atypical ductal cells, positive mucin stain

EUS, endoscopic ultrasound; CEA, carcinoembryonic antigen; IPMN, intraductal papillary mucinous neoplasm.

information about the entire pancreas—location and number of cysts, size, ductal dilation or communication, signs of chronic pancreatitis, cyst wall thickness, mural nodules, papillary projections, and intracystic structures such as septations, debris, and mass component. Retention cysts are generally small, thin-walled, and unilocular; they carry no malignant potential and can be left untreated. Pseudocysts develop as a result of acute inflammation. On EUS, they are thick-walled as they become chronic and may have debris within the cyst cavity (see Fig. 14.11). They can be seen in or adjacent to the pancreas and often communicate with the pancreatic duct. FNA will yield thick fluid with inflammatory cells but no epithelial cells, and tumor marker levels (carcinoembryonic antigen [CEA], CA19-9) in the cyst fluid are low or undetectable; by contrast, fluid amylase is usually markedly elevated.

Regarding cystic neoplasms, it is important to distinguish mucinous and papillary tumors from serous lesions (see Chapter 57). Serous tumors have little or no malignant potential and do not require resection unless symptoms occur. Typically, serous cystadenomas are composed of a honeycomb of microcysts with no communication with the pancreatic duct (see Fig. 14.10). They can be large and exhibit central stellate calcification on imaging studies. Papillary lesions, solid and pseudopapillary tumors, carry the risk of malignant transformation and usually should be referred for resection. Mucinous lesions—mucinous cystic neoplasm (MCN) and intraductal papillary mucinous neoplasm (IPMN)—also harbor malignant potential that appears to correlate with size; however, universally accepted management criteria are lacking, and treatment recommendations often vary. Mucinous cysts are generally composed of one or more large cystic spaces with thickened walls or septa (see Fig. 14.9). In the case of IPMNs, distinguishing main-duct from side-branch types is important clinically, because the former are associated with a much higher risk of malignant change. Cross-sectional imaging may help in this regard by demonstrating a dilated pancreatic duct characteristic of main-duct IPMN. However, diagnostic uncertainty is not uncommon, and communication with the main pancreatic duct may be demonstrated on EUS.

Although these anatomic characteristics are helpful, EUS cyst morphology alone is insufficient to characterize the lesion (Ahmad et al, 2003; Brugge et al, 2004). Aspiration of cyst fluid via EUS-FNA can further aid in the diagnosis. Cyst fluid can be analyzed for tumor markers, amylase, and molecular markers, and it provides material for cytopathologic assessment. Because of the low cellularity of cyst fluid, the sensitivity and negative predictive value of cytology is low (Centeno et al, 1997; Sedlack et al, 2002). The presence of thick, viscous fluid and a positive mucin stain is suggestive of a mucinous lesion. The concentration of several tumor markers in pancreatic cyst fluid has been examined, and CEA has been found to be the most useful. A cyst-fluid CEA concentration of more than 192 ng/mL predicts a mucinous lesion with a sensitivity of 73%, specificity of 84%, and an accuracy of 79% (Brugge et al, 2004).

Although helpful for diagnosing mucinous lesions, cyst-fluid CEA levels do not correlate with the presence of malignancy. Another limitation of cyst-fluid CEA analysis is that it requires aspiration of at least 1 mL of fluid, which can be difficult if the cavity is small or the fluid is very viscous, making it difficult to pull through a fine needle. More recently, cyst-fluid DNA analysis has shown promise in differentiating mucinous from nonmucinous cysts. This analysis can be done on as little as 200 µL of fluid. The presence of a *KRAS* mutation, high DNA content, and loss of polymorphic alleles are indicators of mucinous cysts. In a large validation study, early *KRAS* mutation followed by allelic loss was 96% specific and 37% sensitive for a malignant cyst (Khalid et al, 2009); however, a reliable and sufficiently sensitive marker for malignancy is still lacking.

Complications of Endoscopic Ultrasound Fine Needle Aspiration

EUS-FNA of the pancreas is a safe procedure. The reported rate of pancreatitis is 0% to 2% (Eloubeidi et al, 2004b; Gress et al, 2002a; O'Toole et al, 2001; Williams et al, 1999). In a multicenter analysis of almost 5000 EUS-FNAs of solid pancreatic masses, the incidence of pancreatitis was 0.3%, and the majority of cases were clinically mild (Eloubeidi et al, 2004b). EUS-guided aspiration of pancreatic cysts is similarly safe, with a pancreatitis rate of less than 1% and an overall complication rate of about 2% (Lee et al, 2005). Bacteremia is uncommon following EUS-FNA of solid lesions, with a rate similar to that for diagnostic upper endoscopy; thus prophylactic antibiotic administration is unwarranted (Levy et al, 2003; Janssen

et al, 2004). However, early data evaluating EUS-guided cyst aspiration showed increased infectious complications, leading to the recommendation of routine antibiotic prophylaxis for all patients undergoing this procedure (Adler et al, 2005). Major extraluminal hemorrhage is a rare complication and occurs at a rate of less than 1% (Affi et al, 2001).

STAGING OF PANCREATIC CANCER (SEE CHAPTER 58B)

The method of staging generally practiced in the United States is that published by the American Joint Committee on Cancer (AJCC). It follows the tumor, node, and metastasis (TNM) staging system and is outlined in Table 14.3.

Endoscopic Ultrasound TNM Staging

Some of the first reports of EUS imaging of the pancreas described its ability to detect and diagnose pancreatic and periampullary tumors (Yasuda et al, 1988; Kaufman & Sivak, 1989). However, subsequent studies evaluated the ability of EUS to stage tumors and assess resectability (Tio & Tytgat, 1986; Rosch et al, 1992). Although the general approach to the preoperative evaluation of pancreatic cancer has focused on the TNM stage, the usefulness of such staging is questionable, particularly because T stage does not necessarily correlate with resectability. Initial studies favored EUS over CT in terms of staging accuracy. However, with the development of high-resolution, multidetector technology, CT has equaled if not surpassed the accuracy of EUS and is once again the preferred staging modality. The same can be said for determining vascular invasion and resectability of large pancreatic tumors (>3 cm).

The performance characteristics of EUS for the diagnosis and staging of pancreatic tumors is summarized in Table 14.1. For example, using the TNM system of cancer staging, Muller and colleagues (1994) showed that EUS has an accuracy of 75% for staging pancreatic cancer, as compared with 56% for CT and 57% for MRI. Recently, a prospective study comparing EUS with multidetector CT for diagnosis and staging of pancreatic cancer also found EUS to be more accurate for diagnosis and tumor staging (DeWitt et al, 2004). Of the 80 evaluated patients, the sensitivity for detecting a pancreatic mass was 98% for EUS and 86% for CT (P = .012). Both modalities were equivalent for nodal staging (44% vs. 47%) and for predicting resectability (88% vs. 92%). In contrast, another recent study favored CT, with an accuracy of 74% for tumor staging, 62% for node staging, and 83% for resectability compared with 62%, 65%, and 72%, respectively for EUS (Soriano et al, 2004).

Perhaps the most useful application of EUS is the diagnosis of small pancreatic tumors (<3 cm) in patients with equivocal radiologic imaging (see Table 14.1). Several studies have demonstrated that EUS is superior to CT scanning for evaluation of pancreatic lesions smaller than 3 cm. For example, Muller and colleagues (1994) reported sensitivities of 93% for EUS, 67% for MRI, and 53% for CT using surgical pathology as the gold standard. In addition, EUS far exceeds CT and MRI in the diagnosis and staging of tumors of the ampulla of Vater to determine whether local or radical resection may be appropriate (see Table 14.1). Other reports, as well as our own experience, have shown the usefulness of EUS in evaluating patients with dilated pancreatic and/or bile ducts but no demonstrable cause. EUS in this setting has been useful in the identification of small tumors of the ampulla, pancreas, or bile duct and nonneoplastic causes such as stone disease, chronic pancreatitis, or abnormal anatomy as may be found in patients with chronic narcotic use (Zylberberg et al, 2000). Therefore, when a pancreatic mass is suspected but cannot be identified by standard imaging modalities, EUS should be considered if further clarification is clinically warranted. A recent, large retrospective series reported a high specificity for EUS in the diagnosis of pancreatic cancer, with a negative predictive value of 100%, when the results of EUS showed a normal pancreas (Klapman et al, 2005).

Endoscopic Ultrasound Determination of Vascular Involvement

Some of the earlier descriptions of EUS in assessing pancreatic cancer focused on its accuracy in identifying vascular involvement. In this regard, Yasuda and colleagues (1993) reported an accuracy of 79% for EUS compared with 41% for CT and 72% for angiography. Rosch and colleagues (1992) showed that EUS

Table 14.3

AJCC Staging of Pancreatic Cancer

TNM Definitions	
Primary tumor (T)	
TX	Cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor confined to pancreas, ≤2 cm in diameter
T2	Tumor confined to pancreas, >2 cm in diameter
T3	Extrapancreatic extension, no celiac axis or SMA involvement
T4	Involvement of celiac axis or SMA
Regional lymph nodes (N)	
NX	Cannot be assessed
N0	Regional lymph node metastases absent
N1	Regional lymph node metastases present
Distant metastases (M)	
MX	Cannot be assessed
M0	Distant metastases absent
M1	Distant metastases present
AJCC TNM	
Stage 0	Tis, N0, M0
Stage I	
IA	T1, N0, M0
IB	T2, N0, M0
Stage II	
IIA	T3, N0, M0
IIB	T1-T3, N1, M0
Stage III	T4, N0-N1, M0
Stage IV	T1-T4, N0-N1, M1

TNM, tumor, node, metastasis; *AJCC*, American Joint Committee on Cancer; *SMA*, superior mesenteric artery.

From American Joint Commitee on Cancer, 2010: AJCC Cancer Staging Handbook, 7th ed. New York, Springer.

correctly identified portal vein invasion in 95% of 40 patients undergoing operation for ampullary and pancreatic cancer, compared to 85% for angiography, 73% for CT, and 55% for transcutaneous US. These authors also showed that arterial encasement was less reliably detected by EUS.

Some of these earlier studies were criticized, because the EUS findings were compared with the surgical findings based on manual assessment by the surgeon rather than by pathologic confirmation of vascular invasion. Aslanian and others (2005) carefully studied this issue by retrospectively comparing preoperative EUS findings with the surgical pathology of specimens, including tumors adherent to the vasculature. In this series, the reported sensitivity, specificity, PPV, and NPV of EUS for vascular invasion was 50%, 58%, 28%, and 82%, respectively, but the results were better when only the portal, superior mesenteric, and splenic veins were considered. Another recent report compared EUS and MRI staging of resectability based on arterial invasion or encasement. The sensitivity, specificity, NPV, PPV, and accuracy of MRI were 78%, 96%, 92%, 88%, and 91%, respectively, compared with 33%, 100%, 81%, 100%, and 82% for EUS, but these differences were not statistically significant ($P = .13$) (Borbath et al, 2005).

Preoperative Reassessment after Neoadjuvant Chemoradiotherapy

Studies on the treatment of pancreatic cancer have recently focused on neoadjuvant treatment with chemotherapy and radiation therapy, followed by attempted radical resection. Several studies have investigated the ability of EUS to reassess patients who have completed neoadjuvant therapy, with most suggesting that EUS is no better than CT for determining resectability. In one report, EUS correctly assessed residual tumor stage in 40% and node status in 90%, but it incorrectly suggested venous invasion in 43% (Bettini et al, 2005). These results suggest that inflammatory changes in the tumor bed, pancreas, and lymph nodes alter the anatomy and blur the distinction between normal tissue planes and between tumor and normal tissue.

DIAGNOSIS AND STAGING OF CHOLANGIOCARCINOMA

Primary bile duct cancers (see Chapters 50A through 50D) usually present with painless jaundice. Although transcutaneous US and CT scanning reliably show biliary dilation, they are less accurate for delineating tumors, especially if tumors are less than 2 cm. ERCP is the dominant invasive modality employed to evaluate extrahepatic bile duct strictures. Diagnostic specimens can be obtained by rubbing a cytology brush against the stricture, but the sensitivity is low, with a yield of only 40% to 50% (Wakatsuki et al, 2005; Ponchon et al, 1995). EUS has now emerged as a useful diagnostic and staging technique in this regard through the use of linear and radial echoendoscopes, as well as high-frequency radial miniprobes (passed into the bile duct over a guidewire through the working channel of an ERCP scope), to perform intraductal US.

For detecting benign causes of biliary obstruction, such as common bile duct stones, EUS, with a sensitivity of 89% to 94% and specificity of 94% to 100%, is more accurate than transcutaneous US, CT, MRCP, ERCP, or intraoperative cholangiography (Garrow et al, 2007; Tse et al, 2008). If a biliary stricture is visualized, malignancy is suggested by the presence of an irregular, thickened (>3 mm) bile duct wall (see Fig. 14.7). Hypoechoic infiltration invading through the biliary wall layers or an adjacent pancreatic mass can also be seen. Limited studies have reported on the accuracy of EUS-FNA in the diagnosis of bile duct strictures, but the reported sensitivity is 43% to 86% (DeWitt et al, 2006; Eloubeidi et al, 2004a; Rosch et al, 2004; see Table 14.1). For example, in a study of 24 patients with negative cytology brushings, EUS-FNA of the biliary stricture yielded a diagnosis in 19 patients, or 80% (DeWitt et al, 2006).

Intraductal US can also provide staging information with respect to depth of invasion, the maximal longitudinal extent of the lesion, and the presence of invasion into other organs and major blood vessels, particularly portal vein invasion, with a reported accuracy of 60% to 80% (Tamada et al, 1995, 1998; Inui & Miyoshi, 2005). Standard echoendoscopes are less accurate for tumor staging but can detect regional lymphadenopathy and allow for tissue acquisition via FNA.

ENDOSCOPIC ULTRASOUND–GUIDED THERAPY

Celiac Plexus Neurolysis

In patients with pain as a result of pancreatic cancer, EUS-guided celiac plexus neurolysis has been shown to be a safe and effective alternative to surgical or percutaneous approaches. The celiac axis is easily identified using a linear-array echoendoscope positioned in the stomach (Fig. 14.14), and it provides a quick method of palliating cancer-related pain in patients undergoing staging and diagnosis of pancreas cancer. A recent meta-analysis demonstrated pain relief in 80% of patients at a follow-up range of 1 to 6 months (Puli et al, 2009). In addition, decreased analgesic requirements and fewer opioid-induced side effects can be expected after EUS-guided neurolysis. Recent studies have suggested that bilateral ethanol injection to the right and left of the celiac axis is more effective than

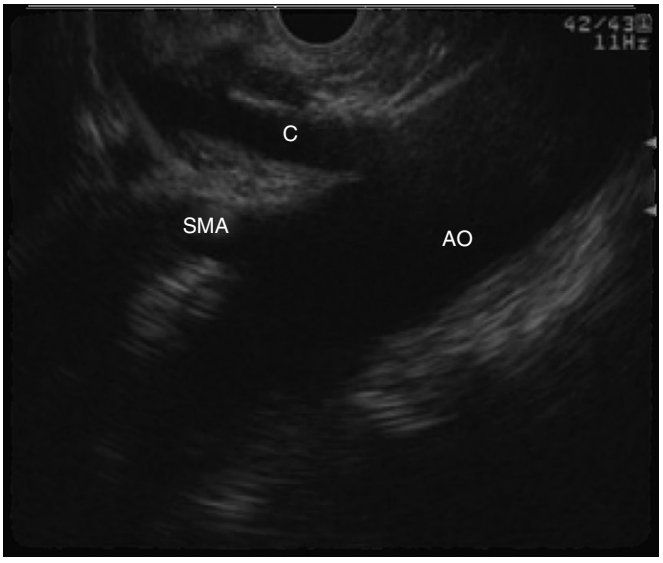


FIGURE 14.14. Endoscopic ultrasound appearance of the longitudinal course of the aorta (*AO*) with celiac (*C*) and superior mesenteric artery (*SMA*) origins.

unilateral or central injection (Puli et al, 2009; Sahai et al, 2009), and no reports of neurologic complications or pancreatitis have been reported with this technique (Puli et al 2009; O'Toole & Schmulewitz, 2009).

Drainage of Pseudocysts and Peripancreatic Collections

The role for EUS as a minimally invasive and effective technique for guiding drainage of peripancreatic fluid collections after acute pancreatitis (see Chapter 54; Varadarajulu et al, 2007; Lopes et al, 2007) or after pancreatic resection has been established. A fine needle is used to puncture the fluid collection, and one or more plastic catheters are inserted over a guidewire to establish transluminal drainage. Using real-time imaging and Doppler flow, intervening organs and vascular structures can be avoided. Thus there are fewer complications, such as bleeding and perforation, compared with the traditional percutaneous approach. True pseudocysts often contain a large amount of necrotic debris that typically requires debridement and is not effectively drained simply by placing drains. This technique has also been applied to the drainage of peripancreatic fluid collections after distal pancreatectomy (Varadarajulu et al, 2009).

Tumor Localization

Preoperative localization of small pancreatic tumors by fine needle tattooing can be performed safely using EUS (Gress et al, 2002b; Farrell et al, 2009). This precludes the need for intraoperative US and may allow the surgeon to perform a more limited pancreatic resection. A role for EUS-guided intratumoral placement of gold fiducials in localizing pancreatic tumors for targeted radiation therapy has also been demonstrated (Pishvaian et al, 2006; Yan & Van Dam, 2008). This modality of radiotherapy minimizes toxicity to the surrounding tissue by allowing delivery of highly conformal radiation treatments.

NOVEL THERAPEUTICS

EUS-guided ethanol ablation of cysts has been recently reported (Gan et al, 2005; DeWitt et al, 2009). Patients with asymptomatic, unilocular pancreatic cysts were treated by injection and lavage of the cyst with ethanol through an FNA needle. Compared to saline lavage, a significant decrease in mean cyst size was seen on follow-up imaging. Those that underwent resection showed histologic evidence of epithelial ablation, and 30% to 35% of patients had complete cyst resolution. Acute pancreatitis was observed at a rate of 0% to 4% with no instances of intracystic hemorrhage.

In patients with advanced abdominal malignancies, simultaneous duodenal and biliary obstruction can occur. Traditionally, these patients have required percutaneous or surgical biliary drainage, because transpapillary decompression via ERCP is often not possible. EUS-guided transduodenal or transgastric biliary drainage is a technique in development that may offer an alternate mode of internal decompression. Similar to pseudocyst drainage, the target—in this case, a dilated CBD or left hepatic duct—is localized with EUS and punctured with an FNA needle. A cholangiogram is performed (Fig. 14.15A) followed by guidewire insertion, dilation of the tract, and deployment of a plastic or self-expanding metal stent across the choledochoduodenostomy or hepaticogastrostomy tract (Fig. 14.15B). High technical and clinical success has been reported, with prompt relief of pruritus and jaundice and no major procedural complications (Park et al, 2009; Yamao et al, 2008; Will et al, 2007).

EUS-guided intratumoral therapy of solid masses is being actively investigated. Several therapeutic agents have been evaluated, including activated lymphocyte cultures, viral vectors,

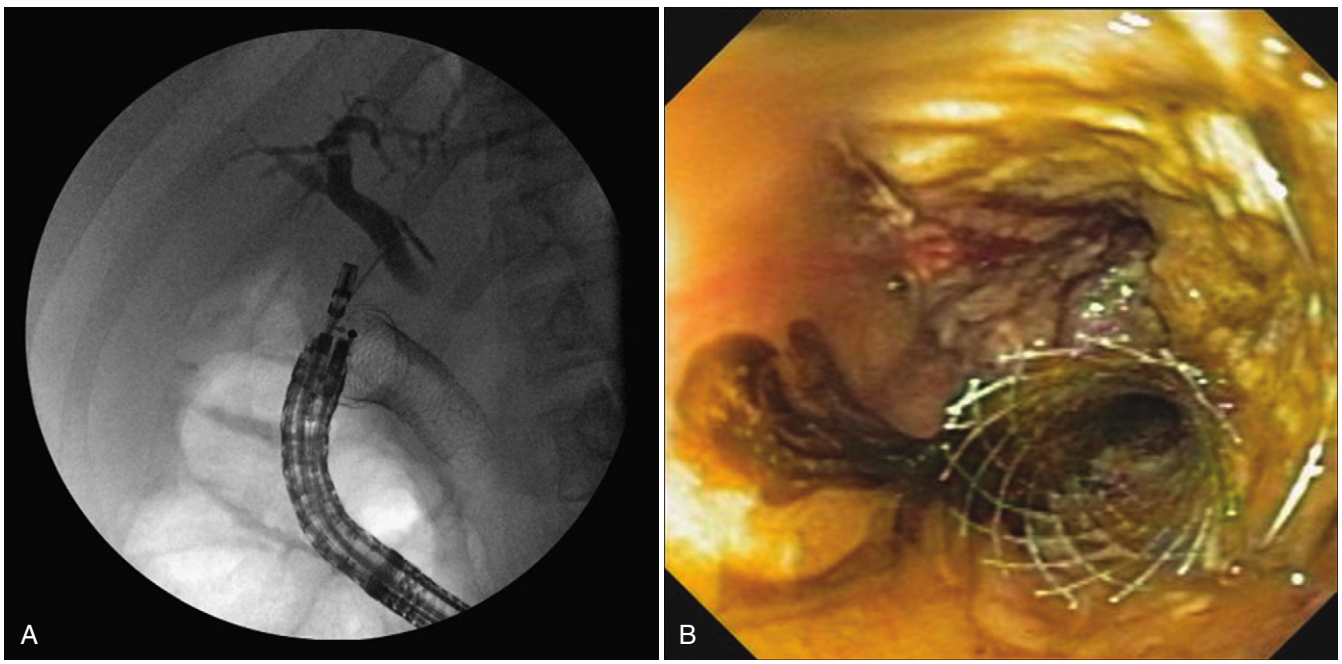


FIGURE 14.15. A, Cholangiogram obtained by endoscopic ultrasound (EUS)-guided puncture of the common bile duct by fine needle aspiration in preparation for EUS-guided biliary drainage. **B,** EUS image after deployment of self-expanding metal stent.

oncolytic viruses, and radioactive seeds (Chang et al, 2000; Senzer et al, 2004; Hecht et al, 2003; Jin et al, 2008). Early studies have established safety and demonstrated partial response or disease stabilization in most patients. The feasibility and safety of performing radiofrequency ablation and cryotherapy of the pancreas using an EUS platform has been established in animal models (Goldberg et al, 1999; Carrara et al, 2008).

SUMMARY

EUS is an important tool in the preoperative evaluation of patients with abnormalities that involve the pancreas and the biliary tree. It provides detailed images of the pancreas and bile ducts and complements the findings of noninvasive radiographic imaging. For patients seen initially with suspected pancreatic or bile duct cancer, multidetector CT scanning assists in identifying those with obvious masses, metastatic disease, and vascular involvement. The usefulness of EUS in this setting is limited, except to provide tissue diagnosis through the use of EUS-guided fine needle aspiration. For patients with small tumors, ampullary lesions, or equivocal findings detected by CT or MRI, the high sensitivity of EUS helps provide a diagnosis, with a high accuracy for tumor staging and determining resectability. Because EUS has poor sensitivity for identifying distant metastatic disease, CT scanning and laparoscopy will remain important tools in the evaluation of patients with pancreatic and bile duct cancer who are being considered for surgery. EUS-FNA is a safe and valuable tool in the evaluation of patients with a suspected solid or cystic mass of the pancreas or extrahepatic bile ducts. It has a higher diagnostic sensitivity and specificity than noninvasive imaging and allows tissue sampling as part of the same procedure. As molecular testing improves, the utility of EUS-FNA as a diagnostic modality is likely to grow. Similarly, the evolution of EUS-FNA from a diagnostic to a therapeutic procedure for pancreatic tumors is in its earliest stages but seems promising.

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CHAPTER 15

Nuclear medicine techniques in hepatobiliary and pancreatic disease

Timothy Akhurst

OVERVIEW

The care of patients with hepatobiliary disease has been improving continually. Although much of this improvement is due to innovative surgical techniques and improved anesthesia, diagnostic imaging also has made major contributions to better care. Advances in cross-sectional imaging have led to improved presurgical planning so that there are fewer "surprises" found at operation. Modern nuclear medicine contributes to presurgical diagnosis with a vital role in the differential diagnosis of right upper quadrant pain and presurgical staging of malignant neoplasms involving liver.

Nuclear medicine should be regarded as the study of human pathophysiology, because the uptake of radiotracers used for nuclear imaging depends on the function or molecular composition of normal or neoplastic tissues. Computed tomography (CT), ultrasound (US), magnetic resonance imaging (MRI), and plain radiography excel at showing anatomy. The addition of pathophysiologic information to high-quality cross-sectional imaging improves patient care by characterizing the processes that led to a structural change. The power of nuclear medicine lies in its ability to perform dynamic studies to document physiologic processes quantitatively and to show the presence or absence of malignancy in normal-sized structures.

The workhorse of nuclear medicine has been the γ-camera, which is capable of planar, tomographic, and dynamic acquisitions. The increasing availability of machines capable of acquiring positron emission data of the whole body has revolutionized the practice of nuclear medicine, particularly in the field of nuclear oncology; this is due to the improved physics of imaging positron-emitting radionuclides and to the fact that positron emitters are available for the most important biologic elements (i.e., carbon-11 [^{11}C], fluorine-18 [^{18}F], and oxygen-15 [^{15}O]). The development of positron emission tomography (PET) CT has removed the anatomic uncertainty from PET imaging, improving the specificity of interpretation. In addition, new radiopharmaceuticals have been developed that offer more selective targeting to alterations in molecular structure of tissues. One example is indium 111 (^{111}In) octreotide, which targets tumors that express somatostatin receptor; this particular agent has a variety of PET analogues that permit exquisite anatomic and biologic resolution.

Fluorodeoxyglucose (FDG) PET is now an established area of nuclear medicine practice that is changing the management of patients with colorectal cancer metastatic to the liver. FDG PET also is being investigated in the management of other hepatobiliary malignancies. Hepatobiliary scintigraphy remains a powerful tool in the assessment of the functional status of the biliary tract and is the gold standard noninvasive test for the exclusion of cystic duct obstruction and, by inference, acute cholecystitis. Using planar γ-camera imaging and single-photon emission computed tomography (SPECT) with a variety of technetium-99m (^{99m}Tc)-labeled and ^{111}In-labeled compounds, general nuclear medicine imaging continues to play an important role in preoperative assessment and postoperative care of patients with hepatobiliary disease.

NEW DEVELOPMENTS IN SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY

Hybrid SPECT imaging systems enable the same coregistration techniques that have been embraced by clinicians with regard to PET CT. In part, the difficulties in developing and commercializing new radiopharmaceuticals from a regulatory perspective have left a market niche for SPECT systems capable of showing the anatomic localization of SPECT tracers already in the marketplace. There has been an evolution in these machines, with initial models that used low-dose, low-resolution CT being gradually replaced in the marketplace by SPECT systems coupled to high-resolution spiral CT devices.

POSITRON EMISSION TOMOGRAPHY

Physics

Some elements undergo radioactive decay by ejecting a positron from their nucleus (Table 15.1). A positron is a nuclear particle that has the same mass as an electron, but it has a positive charge. When ejected, the positron moves through surrounding tissues for 1 mm or so, until it eventually combines with a nearby electron, and the mass of both particles is converted to two photons of energy (γ-rays) of 511 keV, which are emitted 180 degrees apart. The PET camera detects these two photons.

Camera Issues

Dedicated Positron Emission Tomography Systems

PET machines are constructed using multiple rings of circularly arranged detectors comprising scintillator crystals, such as bismuth germanium oxide crystals, lutetium oxyorthosilicate, or gadolinium orthosilicate, usually without associated collimators. These cameras all work in coincidence, meaning that a true count is generated only when the two 511 keV γ-rays emitted during positron decay simultaneously strike a set of paired

Table 15.1

Positron Emission Tomography Isotopes in Clinical Use

Isotope	Maximal Range (mm)	FWHM (mm)	Half-life (min)	Products/Use
Fluorine-18	2.6	0.22	110	FDG, F-MISO, FLT, fluorocholine
Carbon-11	4.2	0.28	20	Methionine and other amino acids; colchicine
Nitrogen-13	5.4	0.35	10	Ammonia
Oxygen-15	8.4	1.22	2	Water
Rubidium-82	17.1	2.6	1.3	Myocardial perfusion
Gallium-86	9	1.35	68.3	Antibodies, peptides
Iodine-124	10	8	6048 (4.2 days)	Antibodies, peptides

FWHM, full width at half maximum; FDG, fluorodeoxyglucose; F-MISO, fluoromisonidazole; FLT, fluorothimidine.

From Cho ZH, et al, 1975: Positron ranges obtained from biomedically important positron-emitting radionuclides. J Nucl Med 16:1174-1176.

detectors (Fig. 15.1). These types of PET imaging devices have high sensitivity. A large amount of usable data is obtained from a given amount of material injected into a patient so that the camera is able to detect small accumulations of injected tracer. The resolution of these machines is defined as the smallest distance between two sources of radiation, whereby the imaging instrument is able to show two sources of radiation rather than one. This distance is currently around 5 mm for most clinical systems; animal imaging devices are now available that have 1-mm resolution (for ^{18}F).

Computed Tomography/Positron Emission Tomography Hybrid Systems

γ-Rays originating in the center of the body have to pass through tissue for a considerable distance to reach the detector, and if one or more of the paired annihilation photons are absorbed, that decay is not recorded as a true count. An anatomically central source would be underrepresented if no attempt were made to correct for differing body tissue density and the depth of the origin of the γ-rays. One of the major advantages of PET imaging is that an accurate correction can be made for this process of attenuation, or loss of counts. Combination machines have been developed (Beyer, 2000) that contain a CT and a PET device in the same imaging gantry. Attenuation correction maps extrapolated from the CT acquisition overcome the attenuation of activity originating in the center of the body. In this way, the PET image becomes quantitative so that the process of computerized data reconstruction ultimately generates a map of the three-dimensional distribution of radioactivity. It is essential that attenuation be performed to obtain quality information from areas such as the porta hepatis, particularly if quantification of radioactivity content in the lesion is to be attempted.

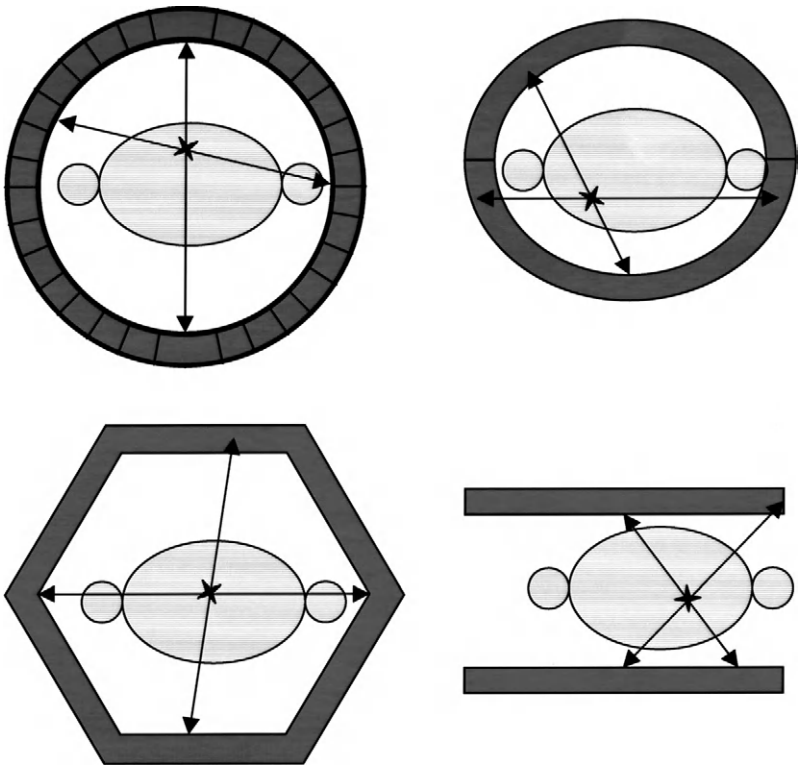


FIGURE 15.1. Stylized representation of the end-on geometry of types of cameras used for positron emission tomography in medicine, arranged in decreasing detector performance. The *top left image* is of a dedicated bismuth germanium oxide–based system, showing one detector ring of many with a single crystal represented by one of the gray segments. The *star* represents the site of positron decay in the patient. *Arrows* represent two photon pairs emitted as a result of positron decay. The *top right image* represents a dedicated curved sodium iodide (NaI) detector system. These systems usually have six large, curved NaI crystals. The *bottom left image* is of a hexagonally arranged system with six large, flat NaI crystals. The *bottom right image* is of a hybrid γ-camera system.

Using PET CT enables coregistration of structural and functional information; this promises near-perfect anatomic localization of areas of functional changes. Some drawbacks with these machines are related to misregistration of the CT data used for attenuation correction in the region of the diaphragm and around the heart, related to cardiorespiratory motion (Beyer et al, 2003). At present there are multiple approaches to this issue but no universally accepted methodology of addressing it.

Biochemistry

The most common radiopharmaceutical used in PET imaging is FDG, a glucose analogue that crosses cell membranes, sharing the glucose transporter molecules used by glucose. Similar to glucose, it undergoes phosphorylation by the enzyme hexokinase. The resulting molecule, FDG-6-phosphate, is polar; it cannot cross cell membranes and is not a substrate for glucose-6-phosphate isomerase, which converts glucose-6-phosphate to fructose-6-phosphate. FDG-6-phosphate is not a substrate for glucose-6-phosphatase in any tissue except the normal hepatocyte. The net effect is a continuous accumulation and retention of FDG in cells (Fig. 15.2).

Warburg (1930) reported that cancer cells show increased rates of glycolysis compared with normal cells. This discovery has stood the test of time and now underpins the utility of FDG PET imaging in cancer. Glucose metabolism is the most efficient form of energy transfer, and all normal tissues have characteristic glucose metabolic rates. The brain has a high rate of glucose metabolism, and the lung and white fat have low rates. A clump of tumor cells is easier to detect in the lung or in fat than in the brain, because the target-to-background ratio is high in these tissues. The liver has an intermediate glucose metabolic rate. Active inflammatory cells exhibit an increased rate of glycolysis, and sites of active inflammation exhibit increased FDG uptake, although in general the rate of glucose metabolism is lower in inflammatory sites than in most tumors. Sarcoidosis in particular can be quite FDG avid and may have similar patterns and degrees of uptake as some malignancies, such as lymphoma and small cell lung cancer. In such cases, clinical judgment is called into play just as it is in the interpretation of opaque masses in the lung on CT scan.

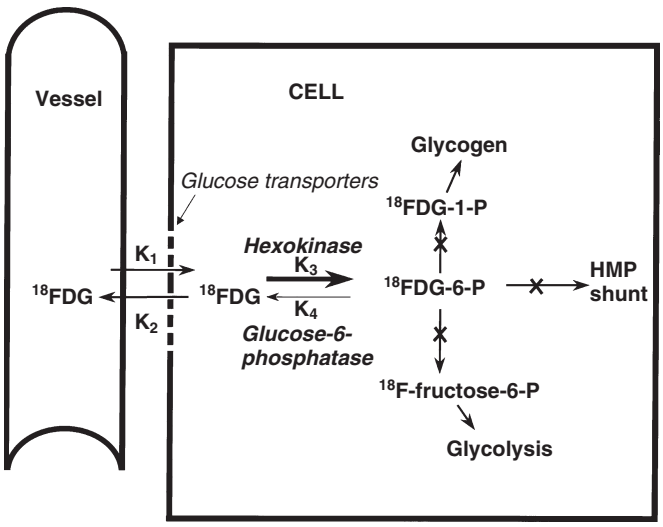


FIGURE 15.2. The metabolic fate of ^{18}F fluorodeoxyglucose (*FDG*) after injection. The curved diagram at *left* represents the blood vessel; the gap represents the extracellular space, and the cell is on the right. ^{18}F-FDG is phosphorylated by hexokinase and thereafter is not effectively metabolized further. HMP, hexose monophosphate.

The process of ^{18}F and ^{18}F-FDG production and distribution is now routine, and most major cities have intracity distribution of unit doses, as they do for many other radiopharmaceuticals. Most tertiary hospitals are likely to have some form of positron imaging–capable camera in the near future, and many will install dedicated high-end systems, as clinicians realize the advantage of high-resolution PET CT in their practices.

FDG PET Imaging in Patients with Colorectal Cancer Metastatic to Liver (See Chapter 81A)

Historical Review

The earliest human study of FDG PET in colorectal cancer was performed by Yonekura and colleagues in 1982; this study of large hepatic metastases in three patients with colorectal cancer was successful and showed that these tumors were highly glucose avid. Numerous publications from multiple centers have established that colorectal cancer is readily detected on FDG PET, and colorectal cancer is a common reason for referral of patients for a scan. The value of FDG PET in colorectal cancer patients is based on the consistently accelerated levels of glycolysis seen in colorectal cancer, which results in high FDG uptakes on PET scanning.

Technique

FDG PET studies (Figs. 15.3 to 15.13) are typically performed as a screening procedure that obtains a whole-body image in an attempt to find as many sites of disease as possible. The usual FDG PET CT study of the whole body takes between 7 and 20 minutes, depending on the machine used. The amount of time spent imaging the liver alone is 2 to 4 minutes. If an acquisition of the liver were performed for 1 hour, the accuracy of PET would improve over the values reported in the literature. Nevertheless, FDG PET imaging performs remarkably well with an extraordinary safety profile, with no adverse effects reported in more than 81,000 doses administered over a 4-year period in 22 centers (Silberstein, 1998).

Staging

Preoperative imaging identifies sites of disease in relation to the vascular anatomy of the liver and excludes disease that renders the patient inoperable. Cross-sectional imaging with CT, MRI, and US are the methods of choice to elucidate the vascular anatomy of the liver (see Chapters 13, 16, and 17); nuclear medicine plays no direct role. A secondary role of preoperative imaging is in the demonstration of disease that renders the patient nonresectable. In the best of centers, many patients who are scheduled for hepatic resection are found intraoperatively to have disease that if shown initially would have led to a nonoperative treatment plan (Jarnagin et al, 1999). In a series reported by Scheele and colleagues in 1995, the rates of resection with curative intent steadily increased from 1960 to 1992. Among the many reasons for this increase are improved treatment options and better preoperative imaging that allows more accurate selection of patients with potentially resectable disease.

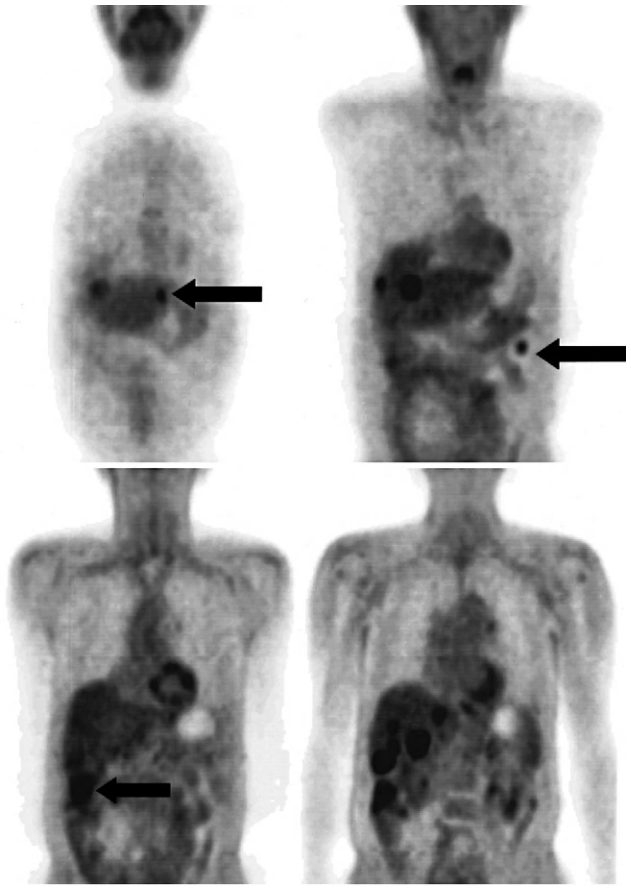


FIGURE 15.3. A 74-year-old man with colorectal cancer synchronously metastatic to the liver was referred for fluorodeoxyglucose (FDG) positron emission tomography to assess for possible localized treatment to the liver. Increased FDG metabolism was seen in at least eight sites within both lobes of the liver, consistent with multiple liver metastases (*arrow, upper left panel*). A further focus of abnormal FDG metabolism is seen in the left upper quadrant (*arrow, upper right panel*), consistent with an omental deposit, and at the hepatic flexure (*arrow, lower left panel*), consistent with a probable anastomotic recurrence. A prior computed tomographic scan revealed liver disease only. As a result of this scan, the patient underwent systemic chemotherapy.

Conventional cross-sectional imaging with helical CT in arterial and portal phases is the standard study for detection of colorectal metastases, and MRI may also be used in conjunction for preoperative evaluation. The previous standard, CT arterial portography, has been supplanted by helical CT, which has equivalent sensitivity for detection of hepatic metastases and results in fewer false positives (Valls et al, 1998).

Fluorodeoxyglucose Positron Emission Tomography for Detection of Hepatic Metastases

A head-to-head retrospective comparison of CT versus FDG PET clinical readings showed an advantage of FDG PET over CT (Table 15.2). The values reported were 23 with disease (n = 58) and FDG PET sensitivity of 95% and specificity of 100% compared with CT sensitivity of 74% and specificity of 85% (Ogunbiyi et al, 1997). The limitations of this study are its retrospective nature and the lack of information regarding the use of intravenous contrast material; in addition, the FDG PET scans were read with knowledge of the CT, whereas the converse may not have been true.

Another report of 34 patients with colorectal cancer that was potentially resectable, comparing CT with contrast and FDG PET, revealed FDG PET had a sensitivity of 89% and specificity of 67% compared with CT, with a sensitivity of 100% and specificity of 14%, giving an overall accuracy of 85% for FDG PET versus 82% for CT (Lai et al, 1996). A further series of 24 patients, 19 of whom had liver metastases, compared CT, computed tomography in arterial portography (CTAP), and FDG PET on a lesion-by-lesion basis. In terms of accuracy, FDG PET performed better than the radiologic methods: 93% compared with 76% for CT and CTAP. The reason the more sensitive CTAP performed worse than FDG PET is because the specificity of CTAP was only 9%. A separate group reported similar findings; FDG PET accuracy was 92% compared with CT arterial portography (CTAP) and CT accuracy of 80% and 78%, respectively. The low specificity of CTAP (5%) worked to its detriment (Delbeke et al, 1997). Many centers now combine a dedicated CT of the liver as part of the PET CT examination.

Fluorodeoxyglucose Positron Emission Tomography for Detection of Extrahepatic Disease

There has been a remarkable consistency in the rate that FDG PET alters the preoperative stage of a patient after standard-of-care preoperative diagnostic imaging (Table 15.3). In a wide variety of tumors, including colorectal cancers, about 30% of patients conventionally staged have their treatment plans altered as a result of FDG PET. The National Oncology PET Registry (NOPR) study of nearly 23,000 patients revealed a management rate of change of 36% (Hillner et al, 2008). A report of 34 patients with potentially resectable hepatic disease (Lai et al, 1996) found retroperitoneal nodal metastases in six patients, pulmonary metastases in three patients, and locoregional recurrences in two patients. One patient had unexpected disease in two sites, and FDG PET had an influence on clinical management in 10 of 34 patients (29%). The experience at Memorial Sloan-Kettering Cancer Center in the preoperative assessment of patients at high risk of recurrence after hepatic resection of colorectal cancer is similar. We found nine (23%) of 40 patients had their management radically altered owing to FDG PET findings of extensive unresectable disease, with management in another seven patients being influenced by the FDG PET findings confirming isolated, resectable extrahepatic disease, giving a total of 40% of patients in whom management was influenced.

A real strength of FDG PET is its ability to detect extrahepatic disease and alter the surgical plan for the patient. Most if not all lesions detected with FDG PET are within the resolution of conventional imaging modalities and theoretically should be detectable, but lesions either are not recognized as being abnormal ("missed"), or they appear normal. One reason why FDG PET performs so well is that the accelerated glucose metabolism of the tumors makes the tumor stand out against the background of normal tissue, just as the light of a match is easily discerned, even at a distance, on a dark night. The effectiveness of FDG PET is due to its ability to show lesions that mimic a normal structure, particularly intraperitoneal disease (see Figs. 15.4, 15.7, and 15.10), which mimics unopacified loops of bowel and normal-sized lymph nodes replaced by tumor. The influence of a finding of extrahepatic disease depends on the aggressiveness of the approach to disease the treating clinician and the patient wish to undertake. Local pelvic recurrence, if completely resectable, should not prevent a

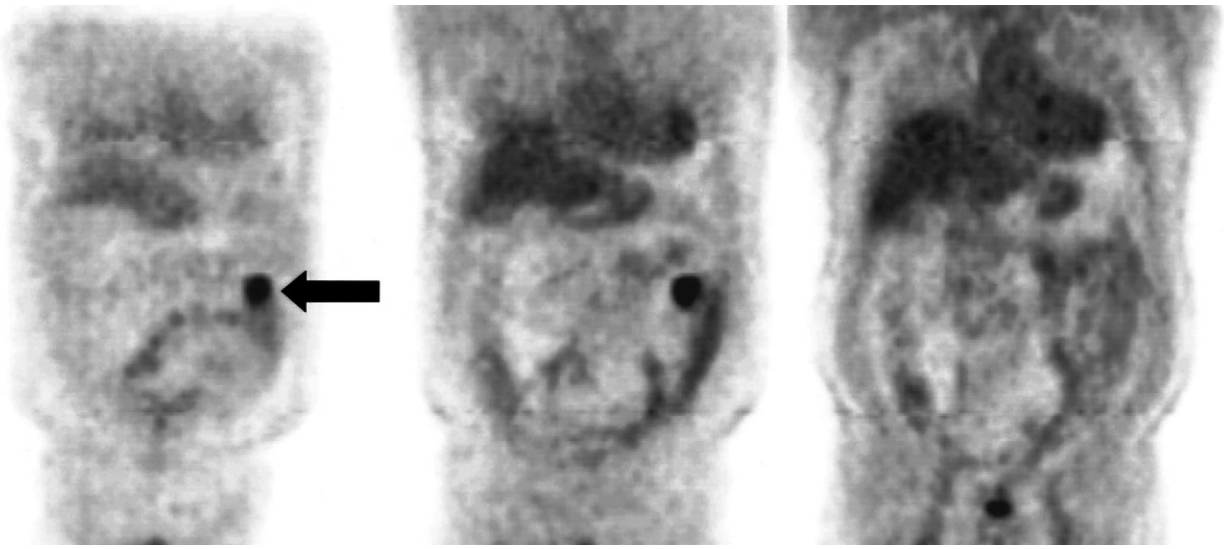


FIGURE 15.4. A 49-year-old man with colon carcinoma was sent for evaluation of rising carcinoembryonic antigen after resection of his primary tumor. Two coronal views of the fluorodeoxyglucose positron emission tomography scan are shown. Workup, including computed tomography of the abdomen and pelvis, was negative. At operation performed 6 weeks later, a solitary metastasis was found in the jejunal mesentery, 4.5 × 4 × 2 cm in size. The arrow shows the jejunal mesenteric metastasis.

patient from undergoing hepatic resection. FDG PET is not a panacea, however, because an imaging study does not change the biology of a disease, and the fact that disease cannot be detected with FDG PET does not rule out micrometastatic disease. It is important in terms of informed consent that patients appreciate that a workup including FDG PET does not rule out the later appearance of a distant metastasis.

Evaluation of Patients After Treatment

There is a dearth of literature on the relative sensitivities of FDG PET and conventional imaging in the detection of recurrent intrahepatic disease after liver surgery (see Figs. 15.11 to 15.13). Some patients develop subphrenic abscesses after resection, which are difficult to differentiate from recurrent tumor; however, even in this situation, FDG PET seems to perform well. In an initial report of seven patients who had undergone resection previously, PET correctly differentiated recurrent disease from postsurgical change in all; CT misdiagnosed two of six, with one false-positive result and one false-negative result; CTAP misdiagnosed three of five patients, all false-positive results (Vitola et al, 1996b). In the assessment of the effectiveness of chemoembolization (see Chapter 83), FDG PET has been shown to be useful (Vitola et al, 1996a), although an increment over CT and tumor markers has yet to be shown.

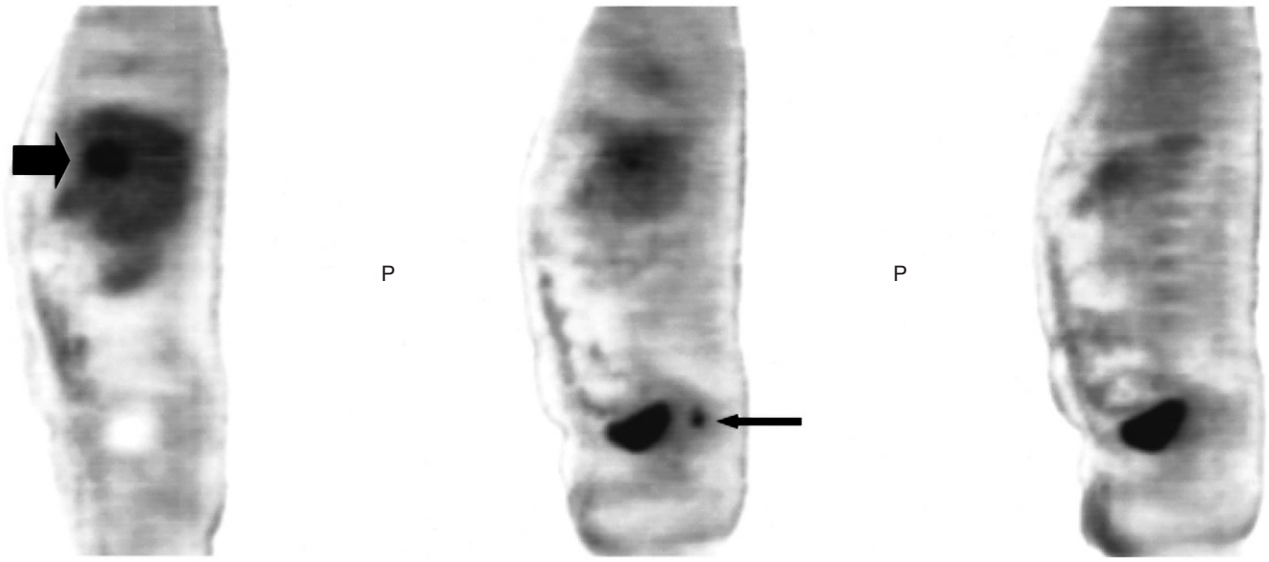


FIGURE 15.5. A 66-year-old man underwent a low anterior resection and at the time of surgery was found to have synchronous liver metastases. He underwent 5-fluorouracil and leucovorin chemotherapy for 1 year and pelvic radiotherapy. His carcinoembryonic antigen level had been progressively rising, and he was found to have liver metastasis. He was referred with a view to hepatic cryotherapy. The fluorodeoxyglucose positron emission tomography scan reveals a presacral pelvic recurrence (biopsy proven; *arrow, middle panel*) and the known liver metastasis (*arrow, left panel*).

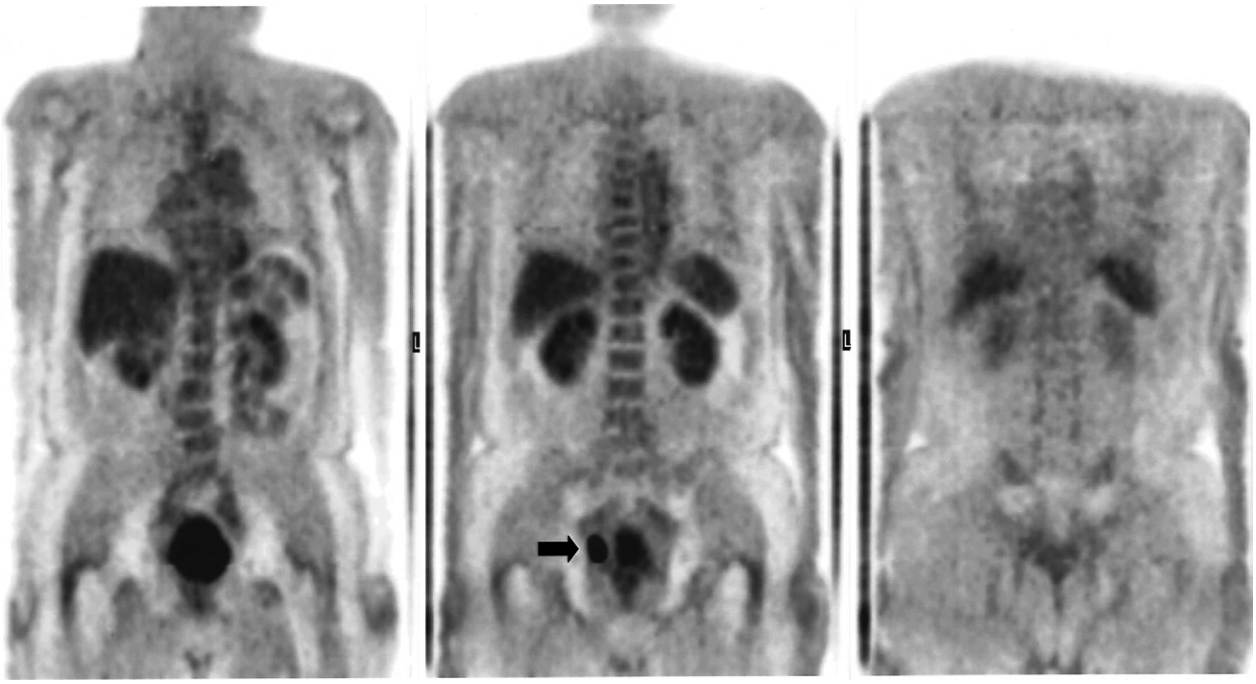


FIGURE 15.6. A 57-year-old man was referred with a rising carcinoembryonic antigen level. The patient underwent anteroposterior resection and treatment with 5-fluorouracil and leucovorin. An exploratory laparotomy 1 year later was negative, but a positron emission tomography scan performed 2 months after the negative exploratory procedure showed an abnormal area in the posterior pelvis, beside the bladder (*arrow*).

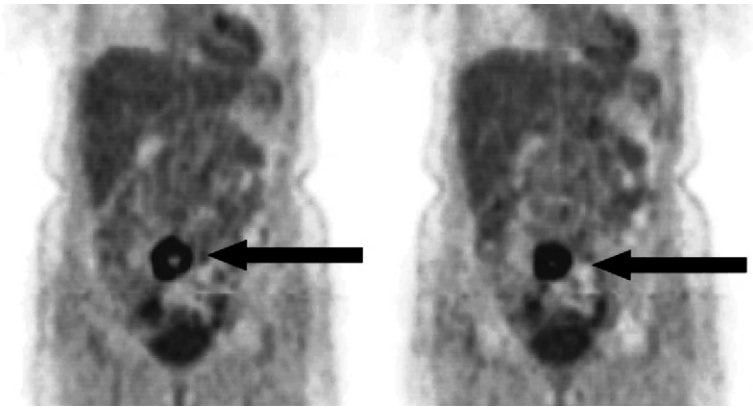


FIGURE 15.7. A 59-year-old woman was referred for assessment of fluorodeoxyglucose metabolism in the setting of recurrent rectal cancer after surgery, radiation, and chemotherapy. The scan reveals a large mass with partial necrosis within the peritoneum (*arrows*).

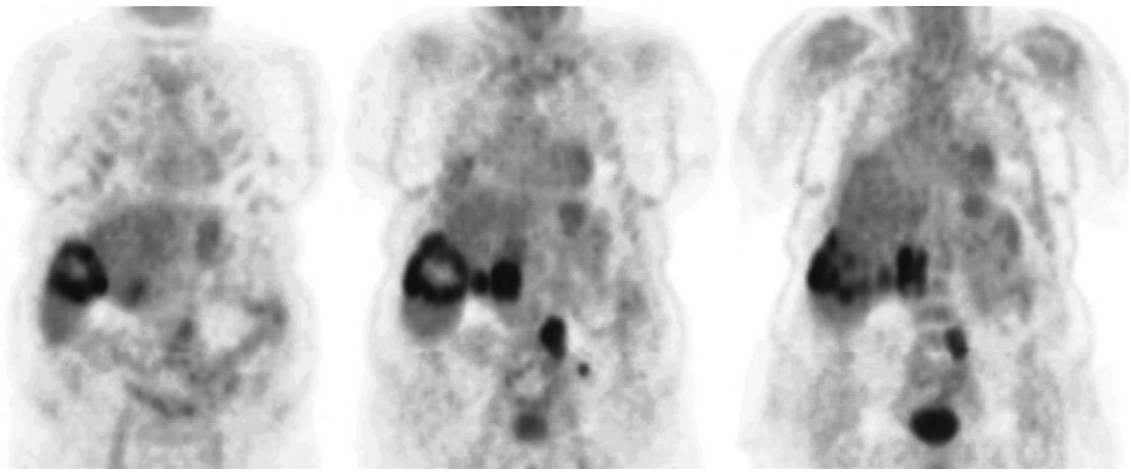


FIGURE 15.8. A 74-year-old man presented with a T3N1 right colon cancer invading the psoas muscle; he was treated with 5-fluorouracil and leucovorin. Computed tomography showed a caudate lesion, one lesion in segment IV, and questionable lesions elsewhere within the liver. Fluorodeoxyglucose positron emission tomography images show liver metastases with associated omental metastases.

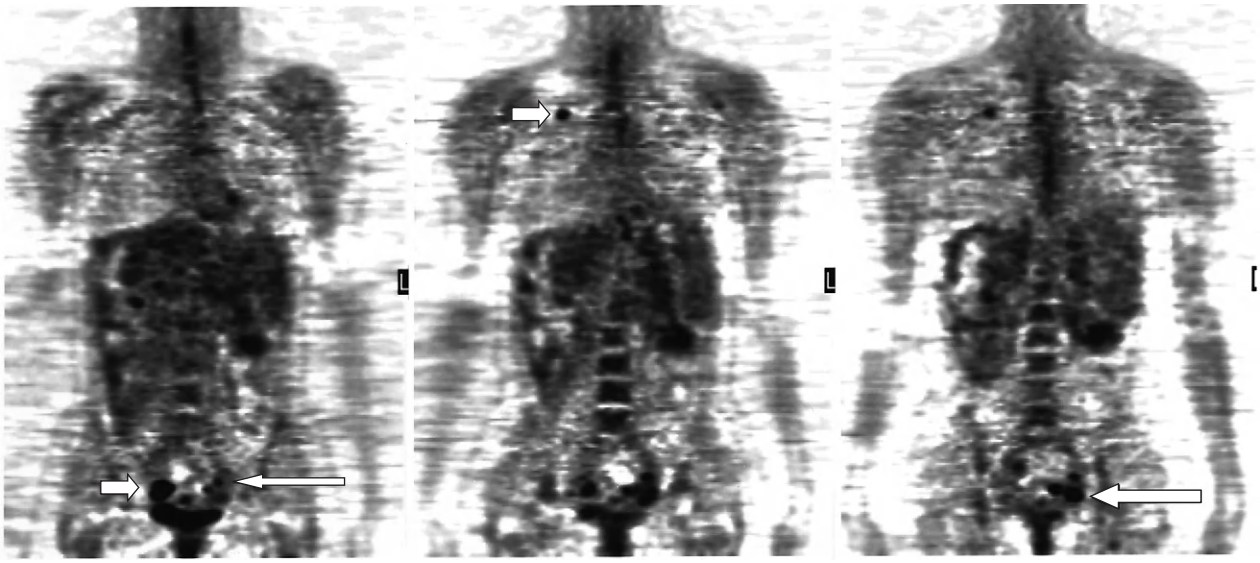


FIGURE 15.9. A 31-year-old woman with colon cancer after colon resection and right hepatectomy, recently treated with systemic and intraarterial pump chemotherapy with a known pulmonary nodule, was referred for evaluation for possible resection of the right pulmonary nodule. The images show the right pulmonary nodule (*arrow, middle panel*) and pelvic recurrence of disease (*arrows, right and left panels*) that subsequently was surgically confirmed. The liver reveals right lobe hypertrophy; the activity to the left of the liver is due to large bowel ptosed into the potential space left by the liver resection.

Preliminary investigations suggest FDG PET performed within 24 hours after hepatic cryotherapy (see Chapter 85B) can predict sites of recurrent disease based on the pattern of FDG uptake (Akhurst et al, 1999). This is an exciting development, because it helps clinicians identify patients in whom cryotherapy has been unsuccessful (see Fig. 15.13). The early demonstration of potential treatment failure can assist in further treatment planning. We also have been using FDG PET to follow patients who are being treated with hepatic artery pump therapy (see Chapter 6). In two cases, the information derived from FDG PET would not have been obtainable from conventional imaging, because the effects of cryotherapy persist on CT and US, leading to an inability to differentiate posttreatment change from residual tumor.

Management of Patients with Hepatocellular Carcinoma (See Chapter 80)

Diagnosis

In general, the ease of lesion detection on imaging depends on the target/background ratio. The higher the target-to-background ratio, the easier it is to detect a lesion. A low-grade lesion is likely to have a metabolic profile similar to the surrounding normal tissues. From an imaging standpoint, the liver is a relatively homogeneous solid structure. Because hepatomas are derived from liver tissue, they share many imaging characteristics with a normal liver and are therefore difficult to detect (Schroder et al, 1998). A study aiming to evaluate FDG PET in the diagnosis of liver masses found all primary sarcomas and adenocarcinoma metastases and all cholangiocarcinomas had increased

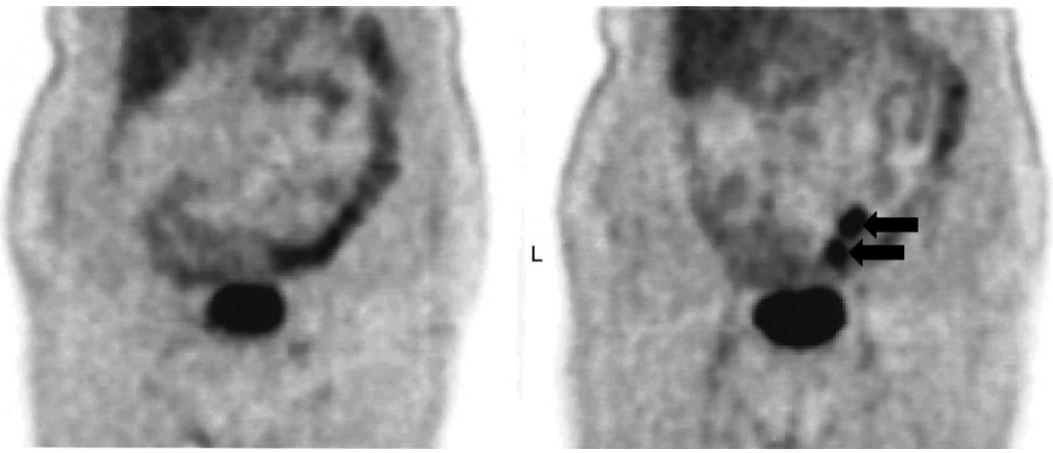


FIGURE 15.10. A 68-year-old woman with colon cancer, rising carcinoembryonic antigen level, and an equivocal CT scan for hepatic metastasis but no other disease. She had no postoperative chemotherapy and felt well. Fluorodeoxyglucose positron emission tomography scan reveals two intraperitoneal lesions (*arrows*) that were confirmed at operation.

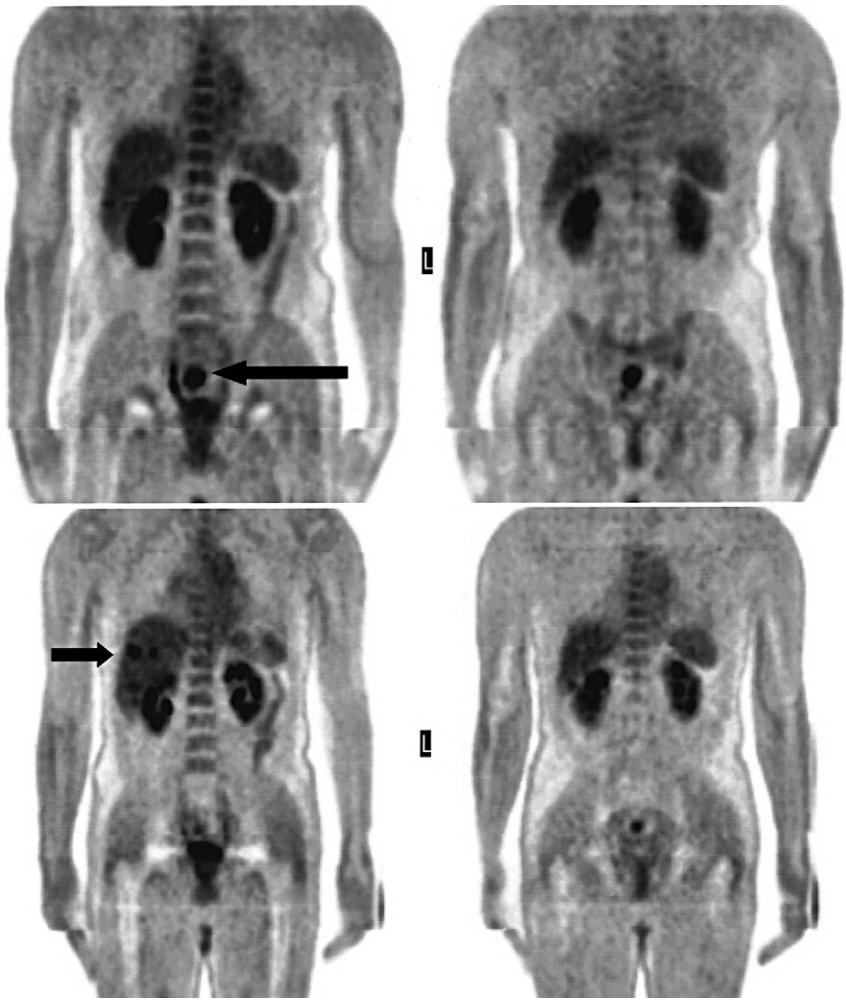


FIGURE 15.11. A 59-year-old man with primary rectal cancer underwent two fluorodeoxyglucose positron emission tomography scans separated by chemotherapy with 5-fluorouracil and leucovorin and pelvic radiotherapy. The top panels are the pretreatment images and show the primary tumor (*arrow, top left panel*) with a local nodal metastasis (*top right panel*) and a liver metastasis seen lateral to the right kidney. The bottom panels show involution of the primary lesion but progression of the liver metastases (*arrow, bottom left panel*).

Table 15.2

Fluorodeoxyglucose and the Detection of Hepatic Disease*

Reference	Patients with Disease	PET			CT			CTAP		
		Sens.	Spec.	Acc.	Sens.	Spec.	Acc.	Sens.	Spec.	Acc.
Ogunbiyi et al, 1997	23/58	95	100	—	74	85	—	—	—	—
Flamen et al, 1999†	45/103	99	100	99	93	95	94	—	—	—
Lai et al, 1996	27/34	89	67	85	100	14	82	—	—	—
Vitola et al, 1996b‡	19/24	90	100	93	86	58	76	97	9	76
Delbeke et al, 1997‡	?/61	91	96	92	81	60	78	97	5	80
Schiepers et al, 1995§	34/80	94	100	98	85	98	93	—	—	—
Valk et al, 1998	57/118	95	100	97	84	95	90	—	—	—

*All studies used surgical findings, pathology, or clinical follow-up of at least 1 year as the gold standard.
†Equivocal lesions were treated as negative.
‡Lesion-by-lesion analysis was used.
§A combination of ultrasound and computed tomography was used as the comparative conventional test.
Acc., accuracy; CTAP, computed tomography in arterial portography; PET, positron emission tomography; Sens., sensitivity; Spec., specificity.

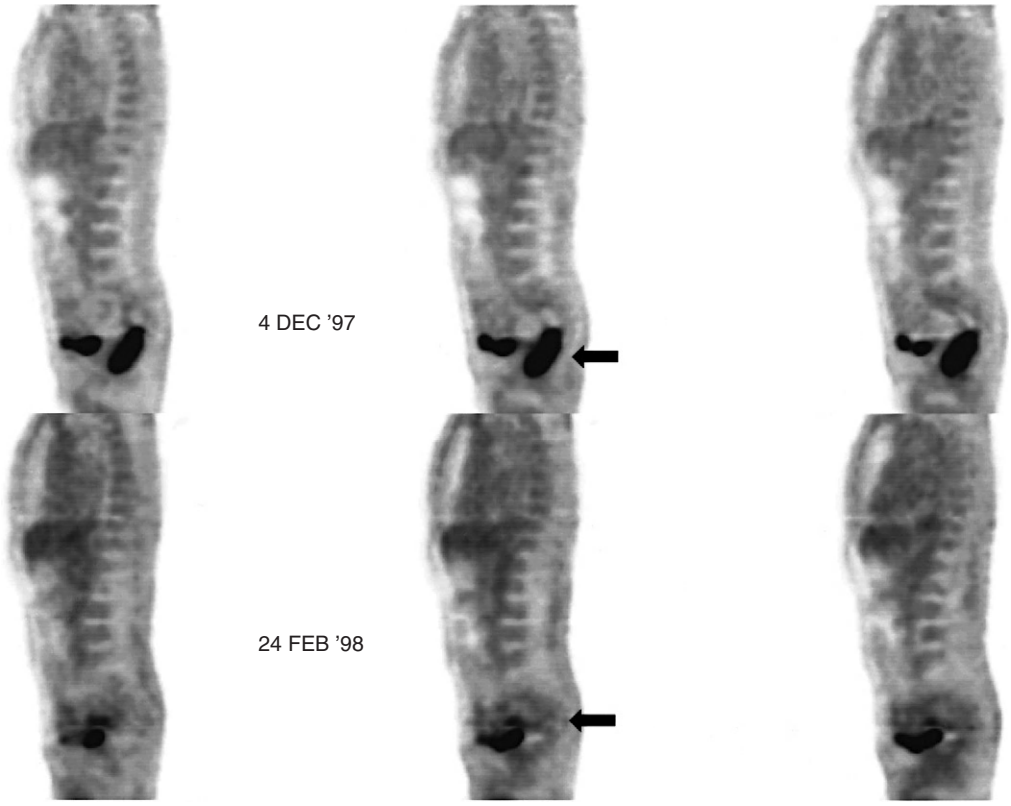


FIGURE 15.12. Note the metabolic response of the primary rectal cancer (*arrows, upper and lower middle panels*) to the combination of chemotherapy with 5-fluorouracil and leucovorin and radiotherapy as a preoperative treatment.

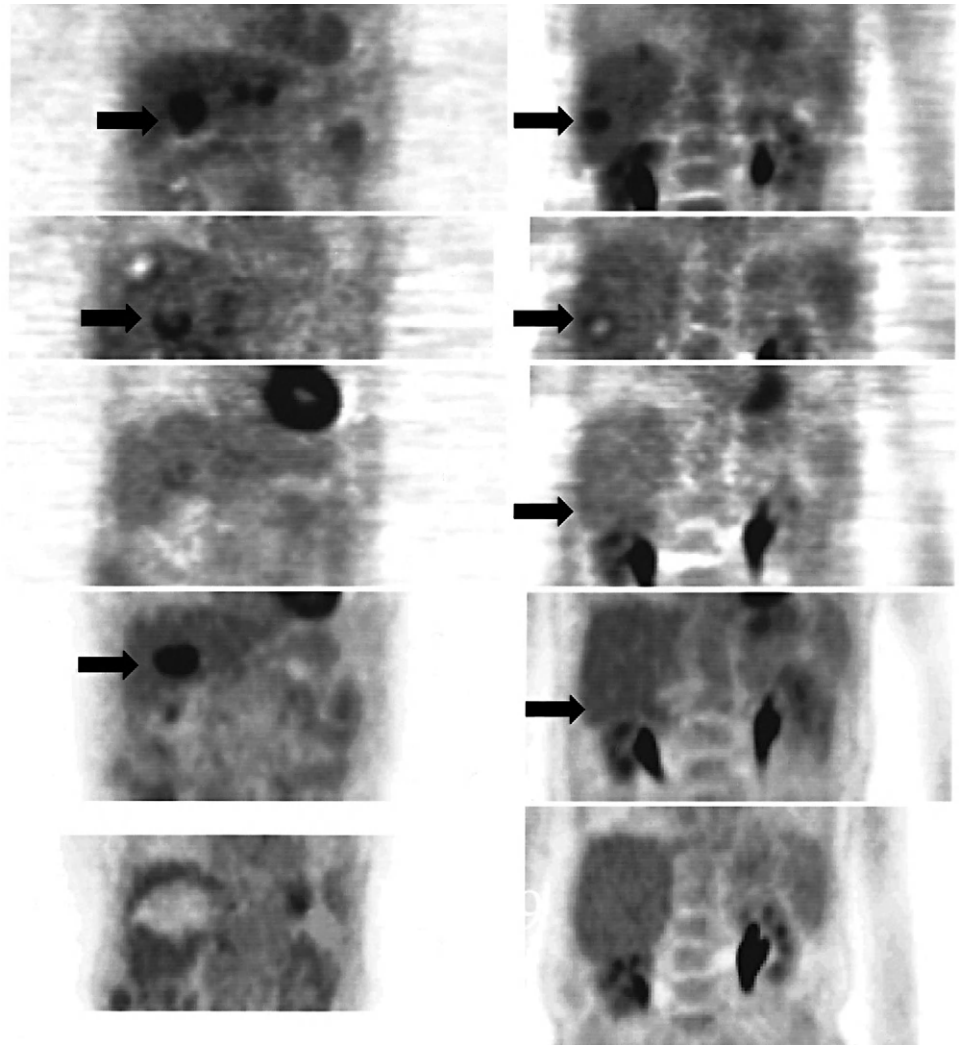


FIGURE 15.13. Series of images performed on a 70-year-old patient with colorectal cancer metastatic to liver who underwent fluorodeoxyglucose positron emission tomography study before intervention (*upper panels*), immediately after cryotherapy (*second row*), while on hepatic artery pump therapy at 5 months (*third row*), and at 10 months after cryotherapy (*fourth row images*). The images show a lesion after incomplete cryotherapy (*arrows in the left panels*), which recurred, compared with a lesion after effective cryotherapy (*arrows in the right panels*), which did not recur. The bottom panel reveals the resection cavity after resection of recurrence.

Table 15.3

Influence of FDG PET on Patient Management

Reference	No. Considered for Surgical Resection	Management Changed as a Result of FDG PET (%)
Ogunbiyi et al, 1997	23	43
Flamen et al, 1999	37	11
Lai et al, 1996	34	29
Vitola et al, 1996b	24	25
Delbeke et al, 1997*	61	28
Schiepers et al, 1995†	76	26
Valk et al, 1998	38	32

FDG PET; fluorodeoxyglucose positron emission tomography.
*All patients in the study group included as potentially hepatic resection patients were not reported as a separate group.
†25 unexpected lesions found in 20 patients.

FDG uptake values, but that seven of 23 patients with hepatocellular carcinoma (HCC) had poor FDG uptake (Delbeke et al, 1998). A sound pathophysiologic basis underlies this reduced efficacy, as shown by Torizuka and colleagues (1995) in a study of HCC greater than 3 cm in size. They showed that undifferentiated HCC had a pattern of continual FDG uptake shared by most solid tumors, whereas a moderately differentiated HCC showed a pattern of uptake similar to the normal liver, with an initial rise and then a slow fall. The difference in pattern was due to marked differences in the activity of transporters carrying glucose into the cell and in hexokinase activity, but it may also be due to a similarity between normal liver and HCC in terms of the rate of dephosphorylation of FDG-6-phosphate.

Treatment Planning and Assessment of Prognosis

The survival rate of HCC patients seems to correlate with the degree of FDG uptake into the tumor, with patients with low FDG uptake showing a longer survival than patients with high FDG uptake (Enomoto et al, 1991). FDG uptake may correlate with the degree of expression of p53 (Schroder et al, 1998; Yoon et al, 1998), a known factor in hepatocellular carcinogenesis (Hui et al, 1998). In a similar fashion to other tumors, FDG PET has been shown to be effective in monitoring lipiodol chemoembolization in HCC (Torizuka et al, 1994).

FDG PET is valuable in the management of patients with HCC. Its greatest utility is likely in cases in which the tumor is technically unresectable. In these cases, a pretreatment scan determines whether FDG PET can detect the tumor, and then FDG PET can be used in therapeutic monitoring. If the primary is known to be FDG avid, or tissue specimens show high levels of hexokinase activity, a follow-up FDG scan may be useful in determining a site of recurrence or metastatic disease.

Cholangiocarcinoma (See Chapter 50)

The detection of cholangiocarcinoma in patients with primary sclerosing cholangitis can be difficult, because imaging findings of the underlying disease may mimic those of tumor. Preliminary reports indicate a potential role of FDG PET, because cholangiocarcinoma seems to be FDG avid (Delbeke et al, 1998; Keiding et al, 1998), although this may be limited to follow-up assessment (Berr et al, 1999). If active cholangitis is present, the mucosal inflammation may obscure small sites of carcinoma in situ. If strictures are stented, the resultant mucosal irritation also may make the diagnosis of malignancy more difficult. Screening for cholangiocarcinoma may require interrogation of a different metabolic pathway, such as that of protein synthesis or proliferation.

In an analysis of data at Memorial Sloan-Kettering Cancer Center, 82 patients with cholangiocarcinoma were studied; 24% of the 62 newly diagnosed patients had their management changed as a result of the detection of occult metastases. FDG PET detected 95% of the intrahepatic tumors and 69% of the extrahepatic tumors; this is not surprising, because central cholangiocarcinomas are more often clinically silent and present later in terms of size than extrahepatic tumors. In terms of the detection of metastases, 100% of metastases from intrahepatic tumors and 93% from the extrahepatic group were detected (Corvera et al, 2004). An example of a cholangiocarcinoma detected with FDG PET is shown in Figure 15.14.

Focal Liver Lesions

A focal liver lesion in a patient with a recent history of colorectal cancer and increasing carcinoembryonic antigen (CEA) is likely due to a metastasis; this partly explains the high success rates in detecting malignant disease reported by some groups (Delbeke et al, 1998). In a separate group, FDG PET was not found to be useful in the characterization of liver masses in patients with chronic hepatitis C infection (Schroder et al, 1998).

Diagnosis and Follow-up of Pancreatic Diseases

Pancreatic Cancer (See Chapter 58)

The clinical presentation of painless jaundice in a middle-aged individual should immediately raise the clinical suspicion of the presence of a cancer obstructing the common bile duct; this is most commonly due to a cancer of the head of the pancreas. Classic approaches to imaging of masses of the head of the pancreas still have validity, with US being the least invasive test available. If surgical resection is to be considered, MRI is likely to give the best possible local soft-tissue discrimination, allowing for planning of a surgical approach and the best assessment of the pancreatic and biliary ducts. Most solid pancreatic adenocarcinomas are FDG avid (Fig. 15.15), allowing for the screening of patients for unexpected distant disease and for the possibility of assessment of the response of the pancreatic mass to induction therapy, if that is considered appropriate. The implementation of PET CT allows much greater confidence in the localization of focal epigastric FDG uptake to a particular anatomic structure; previously epigastric FDG uptake was described as a regional, rather than an organ-specific, phenomenon.

The mechanism of FDG uptake into cells is exactly the same as for unlabeled glucose, so according to the laws of mass action, a high serum concentration of unlabeled glucose (as seen in diabetics with insulin resistance) reduces the amount of FDG uptake into cancer cells, leading to a reduction in sensitivity. In a study of 106 patients with pancreatic masses, of which 32 were benign, PET showed an overall sensitivity of 85%, a specificity of 84%, a negative predictive value of 71%, and a positive predictive value of 93%. In a subgroup of patients with normal serum glucose levels (n = 72), the results were 98%, 84%, 96%, and 93%, respectively (Zimny et al, 1997). Insulin-sensitive

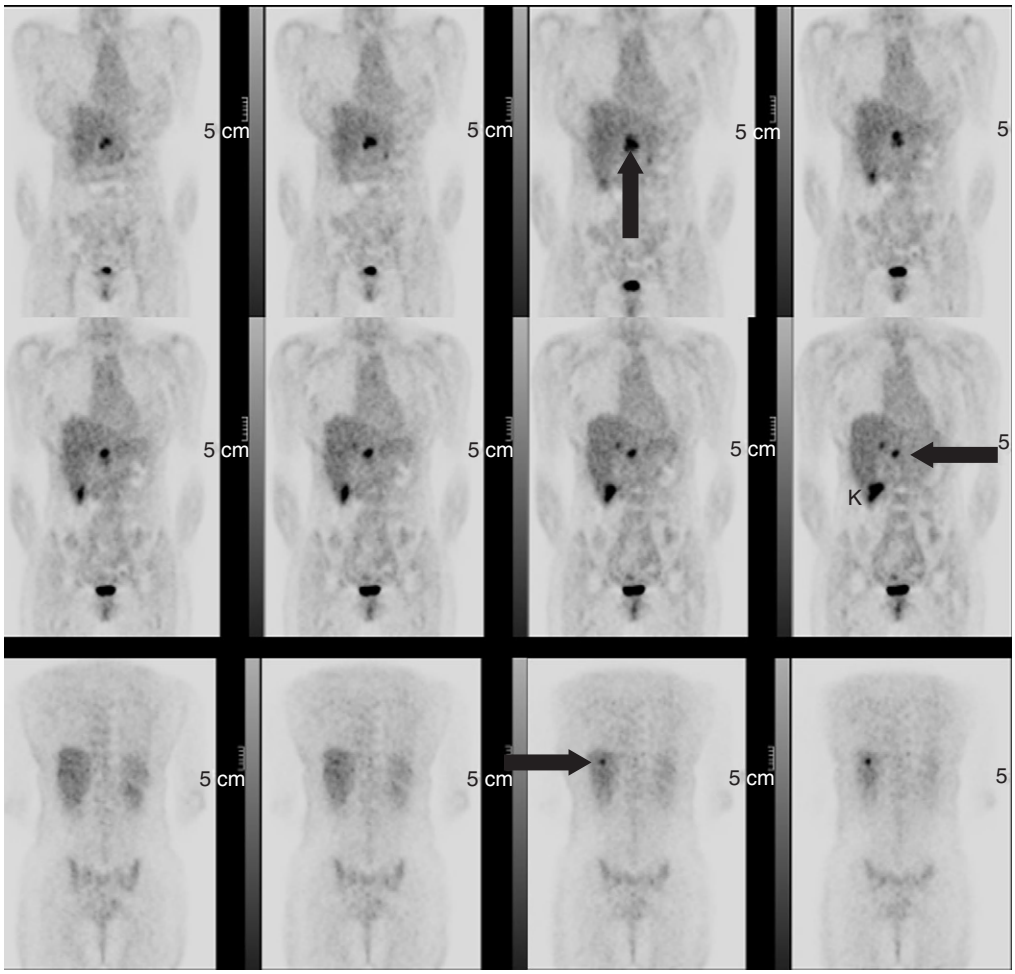


FIGURE 15.14. A 38-year-old woman with bile duct cancer referred for staging. Computed tomography and magnetic resonance imaging failed to show the segment VII lesion seen on fluorodeoxyglucose positron emission tomography. The patient had an exploratory laparotomy, at which time a bile duct cancer (*up arrow*) and metastases in the common hepatic artery lymph node chain (*right arrow*) and segment VII of the liver (*left arrow*) were confirmed.

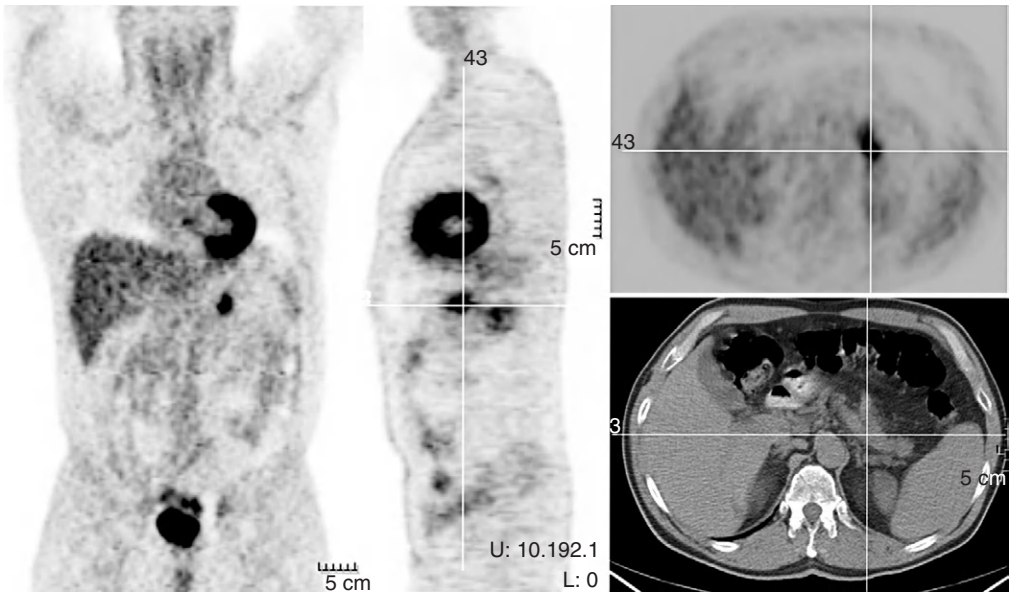


FIGURE 15.15. Axial and coronal slices of a pancreatic adenocarcinoma with corresponding transaxial positron emission computed tomography (PET CT) images shown without intravenous contrast material. Notice how the integrated PET CT device allows exact localization of the metabolic activity to the pancreas, rather than "the epigastrium."

patients also present an interesting problem because incorrect timing of the FDG injection in relation to the insulin injection may lead to much of the injected FDG being driven into muscle, reducing tumor sensitivity.

Cystic pancreatic masses (see Chapter 57) present a difficult imaging problem, because they consist of a thin layer of cells surrounding a large void (Fig. 15.16). A large report of 599 patients with cystic masses of the pancreas found 280 (46.8%) were pseudocysts, 102 (17%) were intraductal papillary mucinous tumors, 100 (16.7%) were serous tumors, 62 (10.4%) were mucinous tumors, 39 (6.5%) were mucinous cystadenocarcinoma, and 16 (2.7%) were solid papillary cystic tumors (Bassi et al, 2003). Clues that a cystic mass of the pancreas may be neoplastic, rather than due to a pseudocyst, include the absence of symptoms (Fernandez-del Castillo et al, 2003) and the presence of calcification in the wall of the cyst, rather than the entire pancreas, as is seen in chronic pancreatitis. Multiloculated cystic lesions favor a neoplastic origin, rather than the single cyst seen in a pseudocyst.

In lung and esophageal cancers, the standardized uptake value (SUV) predicts prognosis in surgically resected patients. The underlying assumption is that the rate of glycolysis reflects the degree of differentiation of the tumor. The use of the SUV is proposed by some authors to differentiate benign and malignant lesions of the pancreas.

Because of the relatively low resolution of all nuclear medicine techniques and partial volume averaging, it is extremely problematic to attempt to characterize a cystic pancreatic mass. Two tumors with the same metabolic rate may have different standardized uptake value measures related solely to the thickness of the cyst wall (Fig. 15.17). If a portion of the mass is thick, characterization can be attempted, but most often this portion of a lesion is adjacent to normal tissues, making accurate characterization difficult. In addition, if inflammation or infection of the pancreatic mass is suspected, the specificity of focal FDG uptake as a predictor of malignancy is reduced dramatically. For this reason, a single FDG PET scan is unlikely to be completely successful in characterizing cystic pancreatic masses.

Follow-up of patients after resection typically is performed with CT or MRI, because these two modalities are very sensitive in the detection of small liver lesions. FDG PET usually is reserved as a modality to document unexplained increases in CEA or other tumor markers or to characterize indeterminate masses seen on other cross-sectional imaging. Novel tracers targeting the pancreas include radioiodinated phenylalanine derivatives, which seem to have preclinical promise in that they show higher affinity for pancreatic tumor xenografts in murine models than FDG with less uptake in inflammatory lesions. These compounds may lead to improved specificity in the diagnosis of pancreatic malignancy in patients with coexistent chronic pancreatitis (Hellwig et al, 2005).

Assessment of Pancreatic Reserve

EXOCRINE PANCREATIC FUNCTION. An experimental approach to the assessment of pancreatic exocrine function illustrates the wide-ranging potential of PET. ^{11}C-methionine is a PET radiopharmaceutical that is taken up into normal pancreas and liver. Initial studies of pancreas involved the use of selenium 75-methionine in the 1960s; the production of ^{11}C-methionine was described in 1976 (Comar et al, 1976). Good correlations of secretin-induced duodenal amylase and

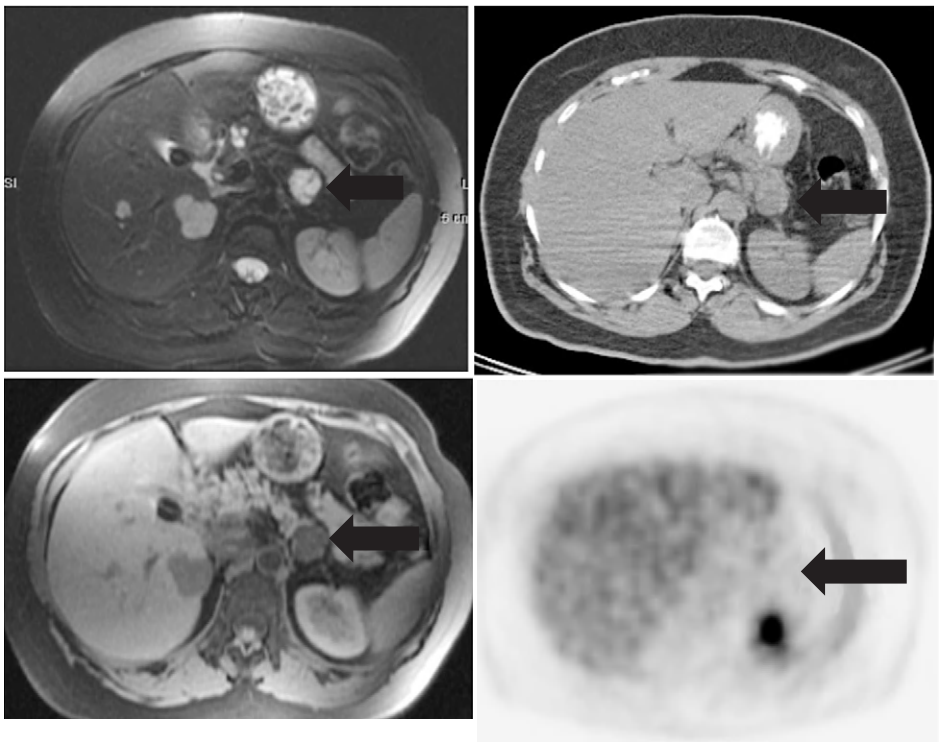


FIGURE 15.16. A 56-year-old woman presented with a multicystic pancreatic mass (*arrows in all images*) for evaluation. The positron emission computed tomography (PET CT) images are in the right panels. The CT shows the lesion, and the corresponding FDG PET slices reveal no evidence of accelerated metabolism in the same anatomic position. Left panels are corresponding magnetic resonance images.

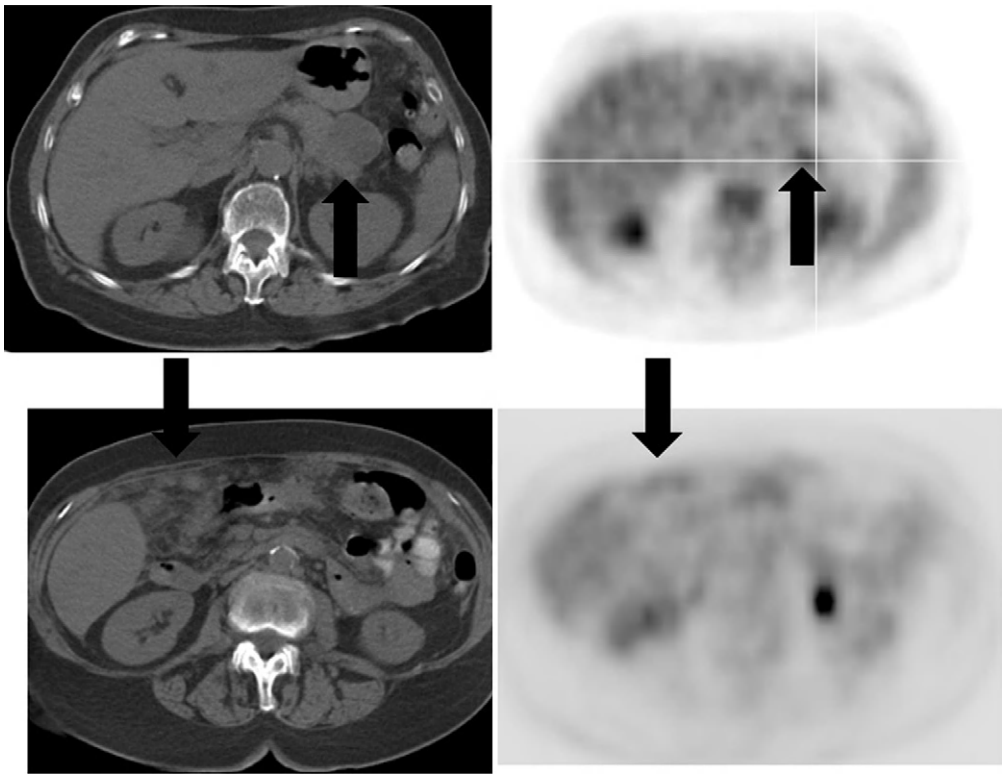


FIGURE 15.17. Cystic pancreatic mass with fluorodeoxyglucose (FDG) uptake only in the thickest portion of the cyst wall. Note the relatively low-grade FDG activity in the mass within the primary lesion (*arrows in top panels*) and the peritoneal metastases (*arrows in lower panels*).

bicarbonate concentrations with the pancreas-to-liver ^{11}C-methionine ratios 4.5 minutes after injection of the methionine have been reported (Takasu et al, 2001). The investigators found that a pancreas-to-liver ^{11}C-methionine ratio at 4.5 minutes after injection of greater than 1.25 had 100% sensitivity and 86% specificity for the detection of chronic pancreatic impairment.

ENDOCRINE PANCREATIC IMAGING. Because of the 100-fold fewer β cells compared with exocrine cells, β cell imaging poses additional problems over and above imaging of exocrine pancreatic cells. It has been suggested that a successful β-cell imaging agent must have a β/exocrine cell affinity ratio of greater than 1000:1 (Sweet et al, 2004). Realization of this problem has focused efforts on specific β-cell surface markers. The use of the monoclonal antibody to image β cells successfully in mice has been described (Moore et al, 2001). Such approaches represent a proof of principle of one method of following up patients in experimental programs aimed at preserving β-cell function in the setting of diabetes and pancreatic transplantation.

GASTROENTEROPANCREATIC NEUROENDOCRINE TUMORS (SEE CHAPTER 81B)

Gastroenteropancreatic neuroendocrine tumor imaging and therapy is a developing field. The standard bearer of somatostatin imaging, ^{111}In octreotide, which will be discussed later in this chapter, is increasingly being substituted with gallium 68 (^{68}Ga) somatostatin receptor imaging. ^{68}Ga, a generator-derived, 68-minute half-life positron emitter, has been coupled to a variety of somatostatin analogues; the only difference between the somatostatin analogue [DTPA^0,Tyr^3] *octreotate* and [DTPA^0,Tyr^3] *octreotide* is that the C-terminal threoninol is replaced with threonine. Octreotate binds with greater affinity to somatostatin receptor subtype II than octreotide, making this tracer particularly suitable for tumors of pancreatic origin. The advantages of using a PET camera over a SPECT camera are significant because of improved quantification and resolution. A parallel development in radiopeptide therapy has occurred, whereby the same somatostatin analogues have been bound using the same chelators to lutetium-177, a 6.71-day half-life radioisotope that has both a 208 keV γ-emission suitable for imaging and a β-emission with an average energy of 0.13 MeV, which provides therapeutic efficacy. Lutetium radiopeptide therapy has proved to be less nephrotoxic than yttrium-90 (^{90}Y) radiopeptide therapy, particularly when administered under the cover of renoprotective amino acid infusions using lysine and arginine. Administration of 5-fluorouracil (5-FU) at a starting dose of 200mg/m^2 for a 3-week period around the time of the lutetium-177 (^{177}Lu) is well tolerated and has the radiosensitizing potential to increase the tumoricidal effects of the ^{177}Lu (Hubble et al, 2010).

^{68}Ga octreotate imaging is complementary to the use of FDG PET and cross-sectional imaging. Growing neuroendocrine tumors that are moderately to intensely FDG avid but ^{68}Ga octreotate negative will not respond to radiopeptide therapy, and either local ablative or other systemic approaches should be evaluated. Growing neuroendocrine tumors that are concordantly ^{68}Ga octreotate and FDG avid are quite likely

to respond to radiopeptide therapy, and following radiopeptide therapy reassessment with imaging at 6 to 12 months after treatment, such tumors will often demonstrate an FDG-avid component of the tumor that has diminished with preservation of the ^{68}Ga octreotate–avid component, reflecting the relative sensitivity of the clones of cells to the radiation treatment (Figs. 15.18 and 15.19). Retreatment leads to long-term tumor control (Kwekkeboom et al, 2008), but caution must be exercised, as cumulative doses greater than 100 GBq have been associated with preleukemic states.

HEPATOBILIARY SCINTIGRAPHY

Scintigraphic imaging of the hepatobiliary system aims to mimic the extraction of the precursor of bile from the blood, the formation of bile, and the excretion of bile into the bile ducts and gut. Iminodiacetic acid derivatives can be labeled with ^{99m}Tc. These compounds are extracted rapidly from the circulation by hepatocytes and are excreted into the biliary system without undergoing conjugation. The hepatic half-clearance time varies with the agent used (Table 15.4), and some renal excretion of iminodiacetic acid derivatives occurs with proportionally increased renal excretion in hepatocellular dysfunction (Fig. 15.20).

Patient preparation is important in the performance and interpretation of hepatobiliary scintigraphy. Detailed clinical information is required for the proper interpretation of the studies. To image the gallbladder, the patient should be fasted for 2 to 24 hours. If a study is performed immediately postprandially, the gallbladder is contracted, leading to nonvisualization (Klingensmith et al, 1981). An overdistended gallbladder leads to nonvisualization in patients fasted for more than 24 hours (Larsen et al, 1982).

Normal Scan

A hepatobiliary study usually is acquired in many dynamic acquisitions; the immediate postinjection sequence is performed with rapid frame times (2 to 5 seconds) to assess perfusion (Fig. 15.21). The later images are acquired for a longer duration (2 to 5 min/frame) to assess the uptake and excretory phases (Fig. 15.22). Right lateral or oblique images often are needed to distinguish gallbladder activity from underlying renal pelvis or duodenal activity (Fig. 15.23).

After injection of the radiopharmaceutical tracer, a biphasic influx of the tracer to the liver is seen (see Fig. 15.21) that reflects delivery of tracer from the hepatic arterial and then the portal circulation. The hepatocytes are efficient at extracting the tracer, so uptake is rapid and leads to hepatic uptake quickly

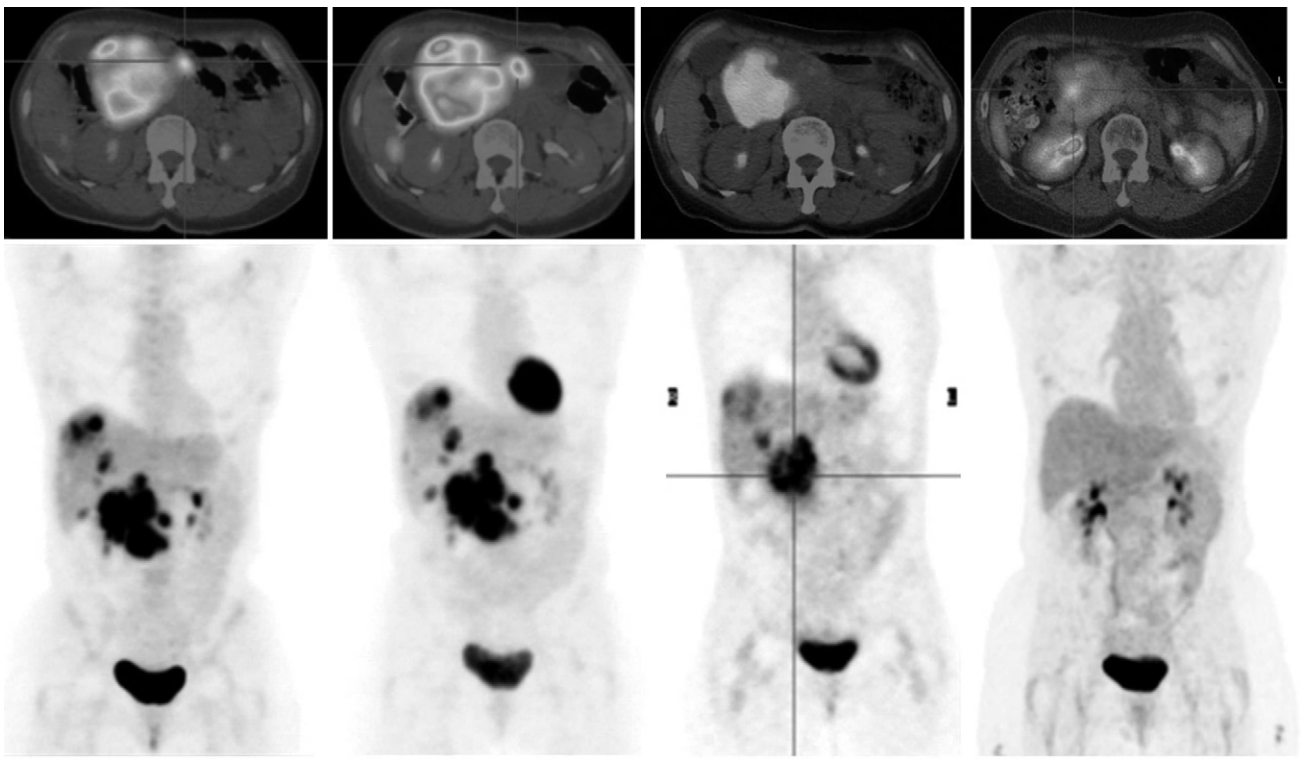


FIGURE 15.18. This 60-year-old female with a pancreatic neuroendocrine tumor underwent a series of fluorodeoxyglucose positron emission computed tomography (FDG PET CT) scans prior to and following her radiopeptide therapy with and 5-fluorouracil as a radiosensitizer. The figure comprised the fused PET CT images in the top row with FDG images in the lower row. The leftmost column of images is the baseline study, and the second column is after 3 cycles of conventional chemotherapy with carboplatin and etoposide; it demonstrates an increase in the degree of FDG uptake, best seen in the top row. One month after the images in the second column were taken, the patient commenced radiopeptide therapy, which was repeated three times over a 12-week period. The third column is a scan performed 25 weeks after the first radiopeptide therapy and demonstrates a significant reduction in the amount of FDG uptake into the tumors. The final column reveals an almost complete metabolic response 24 months later, after two additional radiopeptide treatments.

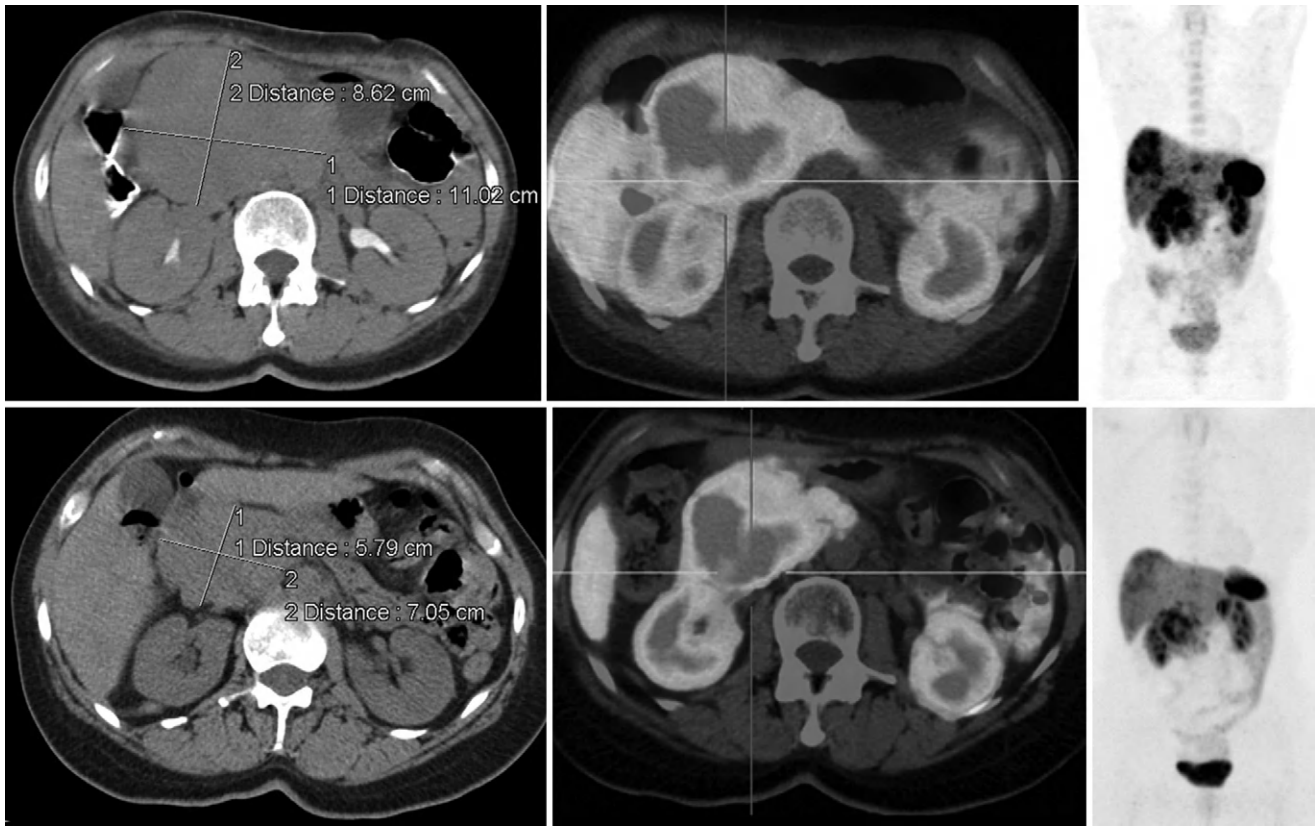


FIGURE 15.19. The same patient as in Figure 15.18, comprising in the top row a pretreatment computed tomography (CT) through the pancreatic mass, a fused ^{68}Ga octreotate positron emission tomography (PET) CT image, and the whole-body ^{68}Ga octreotate PET image performed at baseline. The same sequence is seen in the bottom row after nearly 3 years and five treatments of a total of 41 GBq of ^{177}Lu octreotate therapy with concomitant 5-fluorouracil chemotherapy (200 mg/m^2 given as a radiosensitizer). Note the reduction in size of the pancreatic mass that retains somatostatin receptor 2 expression, in spite of the near-complete resolution of FDG activity in the pancreatic mass shown in Figure 15.18.

exceeding that of the cardiac blood pool. The hepatic activity reaches a peak at about 10 minutes after injection. The hepatocytes clear the tracer into the biliary canaliculi, and within 30 minutes, the right and left hepatic ducts and the common hepatic duct can be seen, although such detail may not be seen in very small infants. The gallbladder is seen in 90% of normal individuals within 30 minutes after injection, and 100% are seen within 1 hour. The bowel is seen in 80% of normal individuals within 60 minutes, and the remaining 20% eventually drain to the gut, with delayed drainage as a result of mild dehydration or mildly increased sphincter of Oddi dysfunction.

Table 15.4

Iminodiacetic Acid Derivatives

Name	Liver Half-Clearance Time (min)	Hepatic Uptake (%)
Mebrofenin	17	98
Disofenin	19	88
o-Diethyl	37	82
o-Dimethyl	42	84
p-Isopropyl	59	85
p-n-Butyl	107	94

In patients who have had a cholecystectomy, the gut usually can be seen by 20 minutes (Fig. 15.24; Sostre et al, 1992b), and bile reflux into the stomach often can be seen (Fig. 15.25; also see Fig. 15.22). If a patient has a contracted gallbladder, as is often seen in chronic cholecystitis, gallbladder filling may be delayed (Fig. 15.26).

Augmented Hepatobiliary Scintigraphy

Numerous drugs affect the function of the hepatobiliary tree and are used to improve the diagnostic efficacy of hepatobiliary scintigraphy. Phenobarbital is used to increase the production of bile in infants to improve the diagnostic accuracy of the test in cases of neonatal jaundice. Cholecystokinin infusion leads to increased bile flow, contraction of the gallbladder, and relaxation of the sphincter of Oddi. Nitroglycerin relaxes the sphincter of Oddi (Staritz, 1988), and morphine contracts it; this effect is promptly relieved by cholecystokinin or naloxone (Helm et al, 1988; Patch et al, 1991). The duration of increase of pancreatic cholecystokinin levels secreted in response to a fatty meal is much longer than the effects of infusion. A repeat dose of cholecystokinin given after a cholecystokinin infusion as premedication leads to an equivalent gallbladder ejection of bile. Patients who have had a prolonged fast can have one injection to empty the gallbladder to enable subsequent filling and a later injection to assess gallbladder ejection fraction in

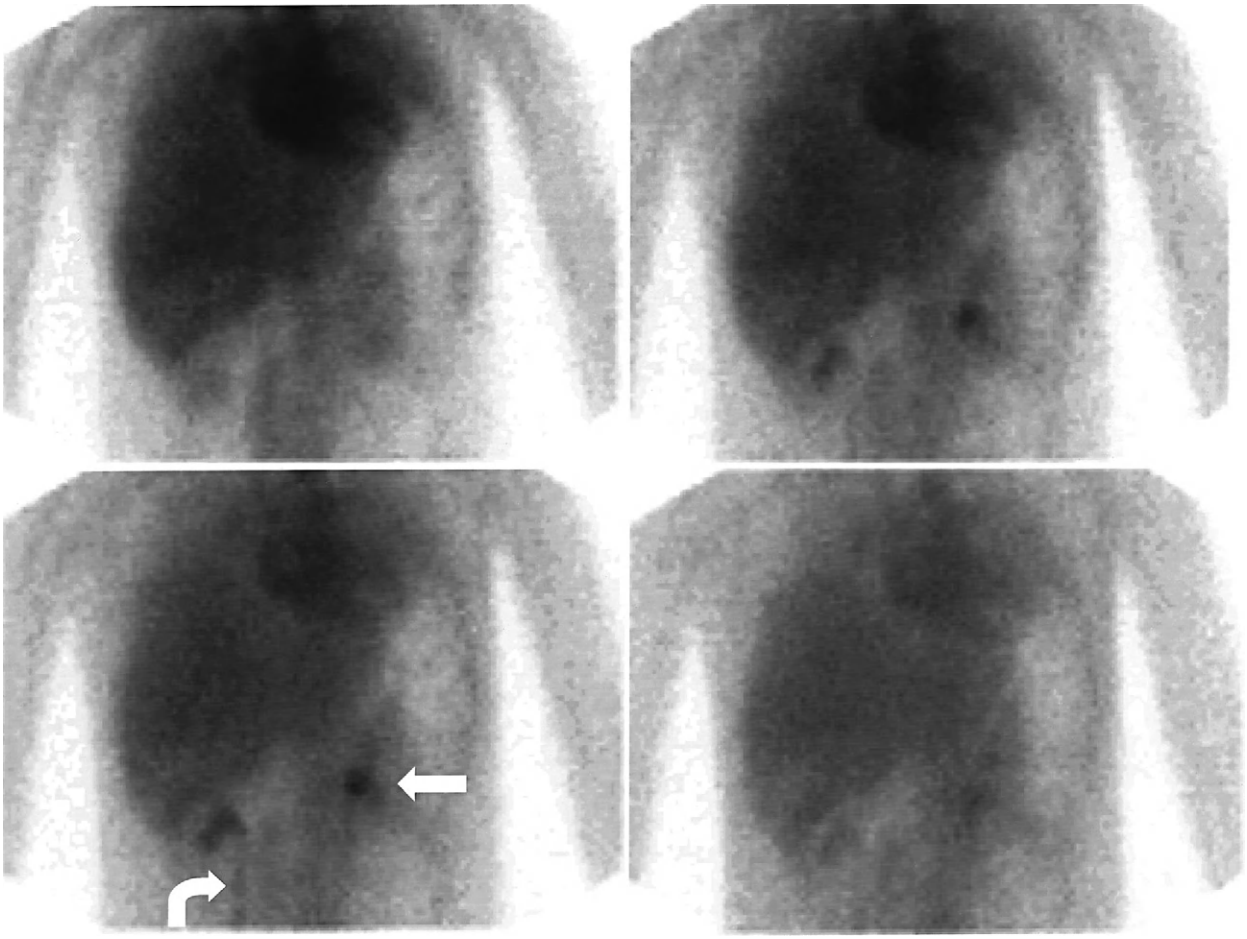


FIGURE 15.20. This study shows severe hepatocellular dysfunction, with the kidneys exhibiting increased clearance of the tracer. Note the parallel reduction in activity in the cardiac blood pool and the liver. The two bright foci beneath the liver are due to activity in the pelvis of the right and left kidneys. The straight arrow points to the left renal pelvis; the curved arrow points to the right ureter. Images were acquired at 2, 15, 25, and 60 minutes after injection.

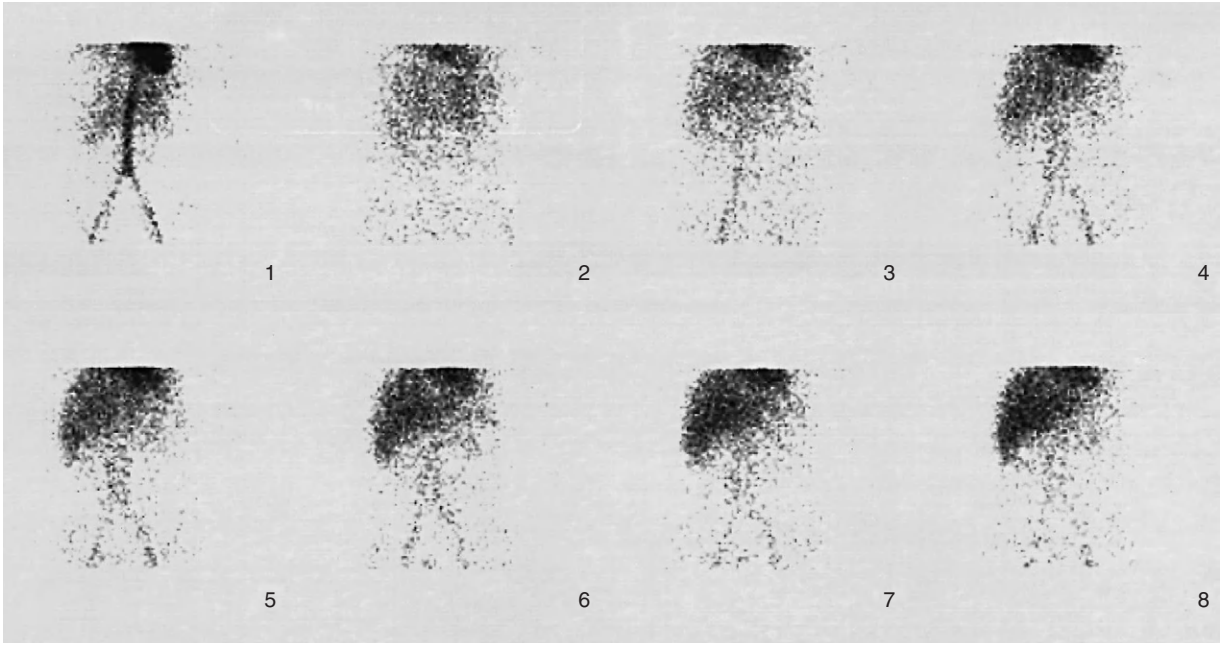


FIGURE 15.21. Normal hepatobiliary iminodiacetic acid perfusion study shows the biphasic influx of tracer into the liver, reflecting the dual blood supply. The relatively reduced uptake coincides with aortic activity.

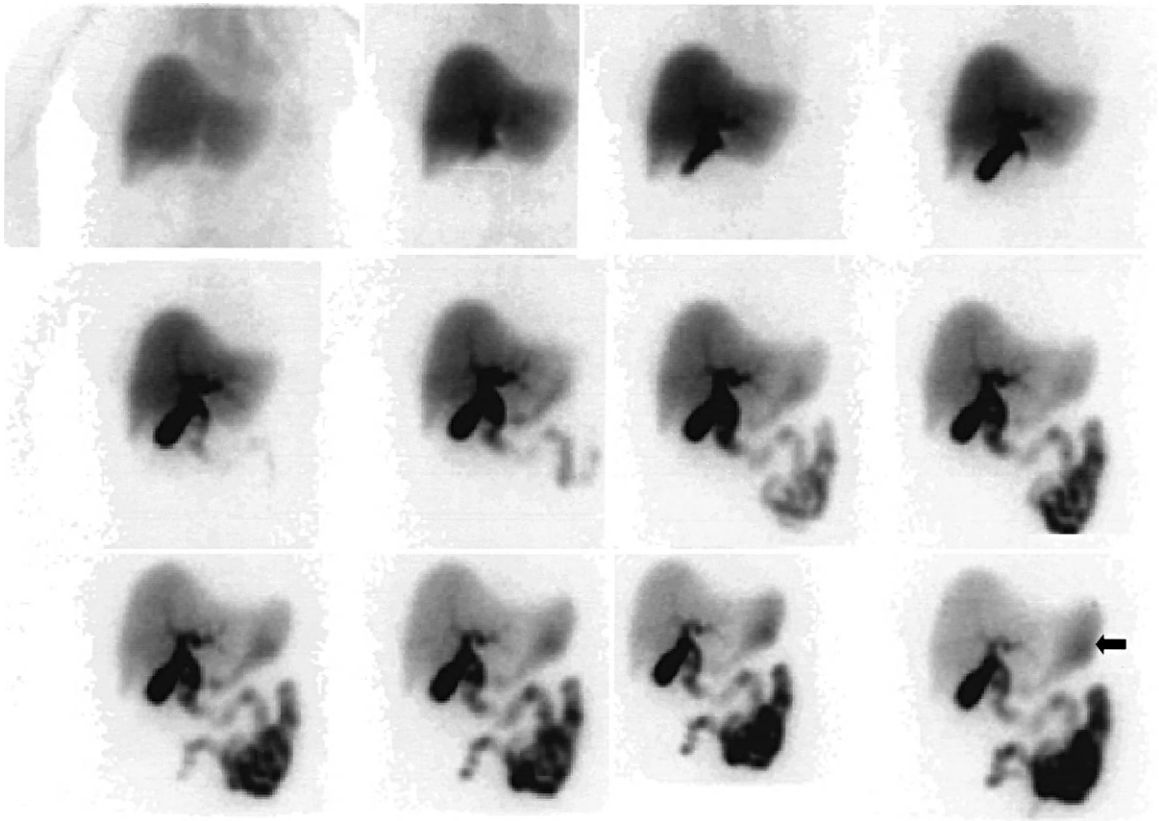


FIGURE 15.22. Normal hepatobiliary iminodiacetic acid study shows free passage of the tracer into the proximal bile ducts and gallbladder with subsequent free drainage into the gut. The images were acquired in the anterior projection 5 minutes apart for 1 hour. Note the reflux of bile into the stomach (*arrow*) seen after 30 minutes, reaching a peak at 55 minutes.

the same sitting, with no loss of diagnostic accuracy (Sostre et al, 1992a).

Right Upper Quadrant Pain

The differential diagnosis of right upper quadrant pain is beyond the scope of this chapter, but hepatobiliary scintigraphy has a role in the assessment of acute and chronic right upper quadrant pain (see Chapter 31). A 30% increase has been seen in the number of cholecystectomies performed since the 1990s. Another phenomenon is the change in the indications, with rates of operations for biliary dyskinesia, acute acalculous cholecystitis, and chronic acalculous cholecystitis increasing 348%, 139%, and 138%, respectively, in the same time frame (Johanning & Gruenberg, 1998). This study was a review of the *International Classification of Diseases* (9th revision) discharge codes,

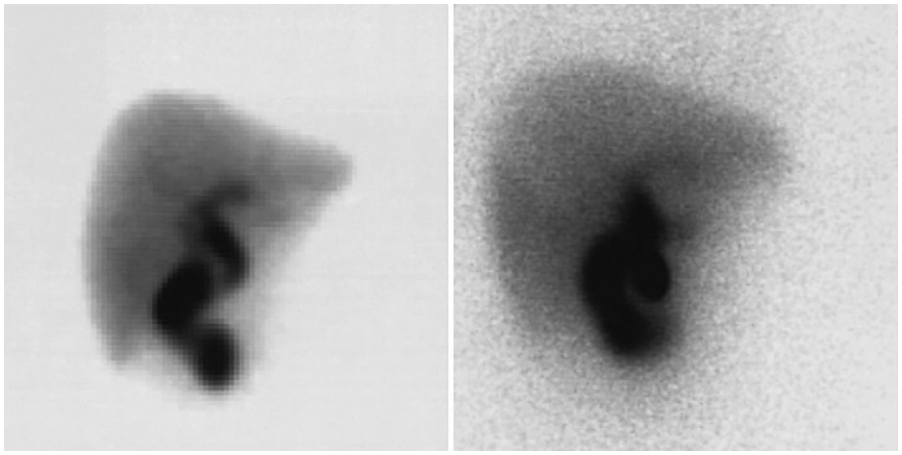


FIGURE 15.23. This study shows the benefit of a right anterior oblique view in separating the gallbladder and renal pelvis. Images were acquired 60 minutes after injection.

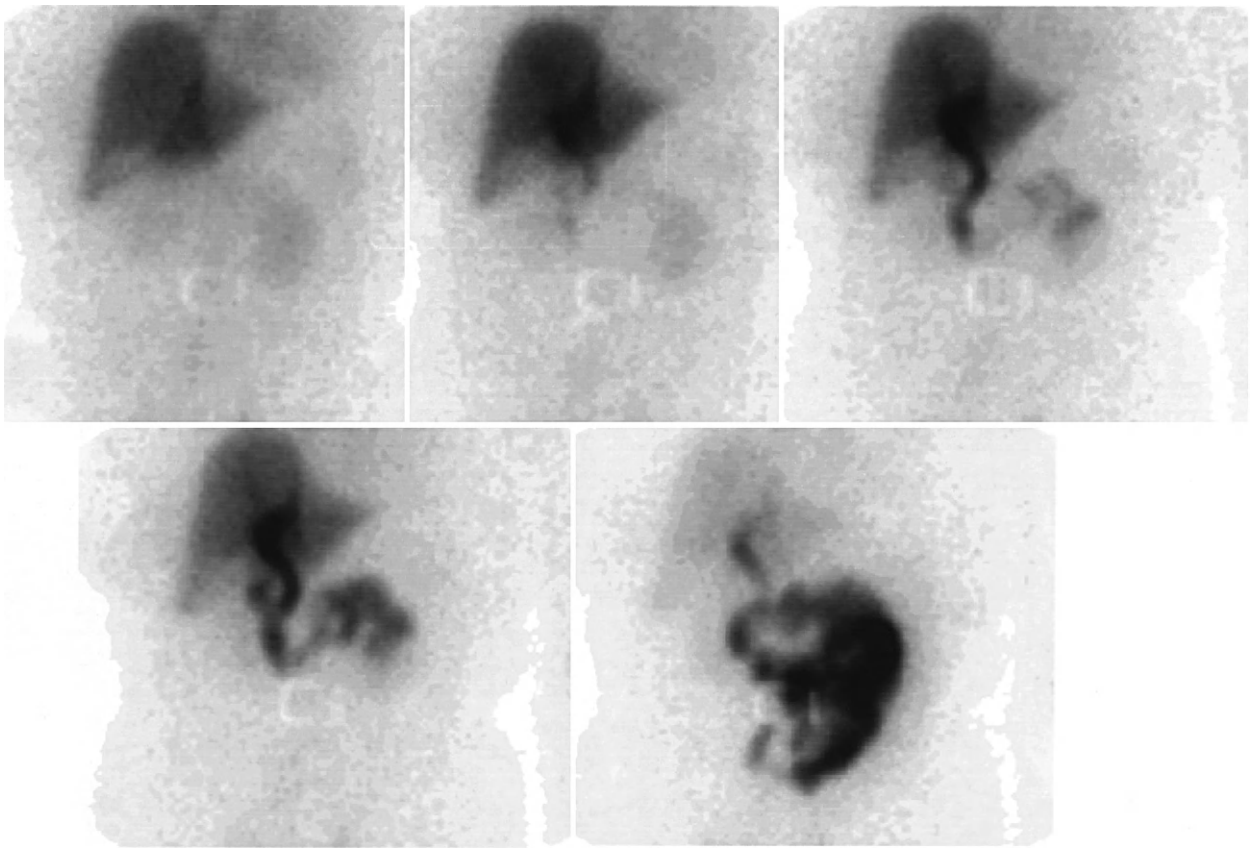


FIGURE 15.24. This study shows rapid transit into the gut after cholecystectomy; the intestines are seen 10 minutes after injection. Images were acquired 2, 5, 10, 15, and 60 minutes after injection.

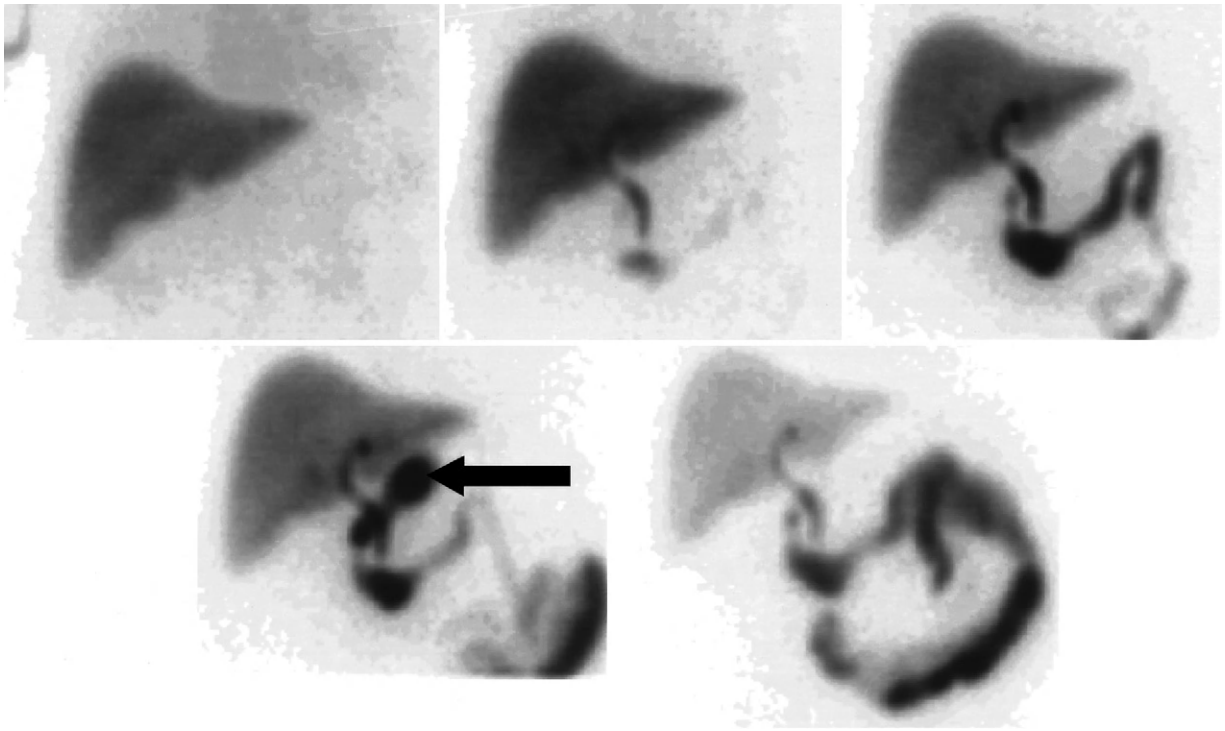


FIGURE 15.25. This study reveals nonvisualization of the gallbladder even after administration of morphine. Pathology revealed acute cholecystitis. Images were acquired 10, 30, 40, and 60 minutes after injection of tracer and 20 minutes after morphine injection. The 60-minute image reveals refluxed activity in the stomach (*arrow*).

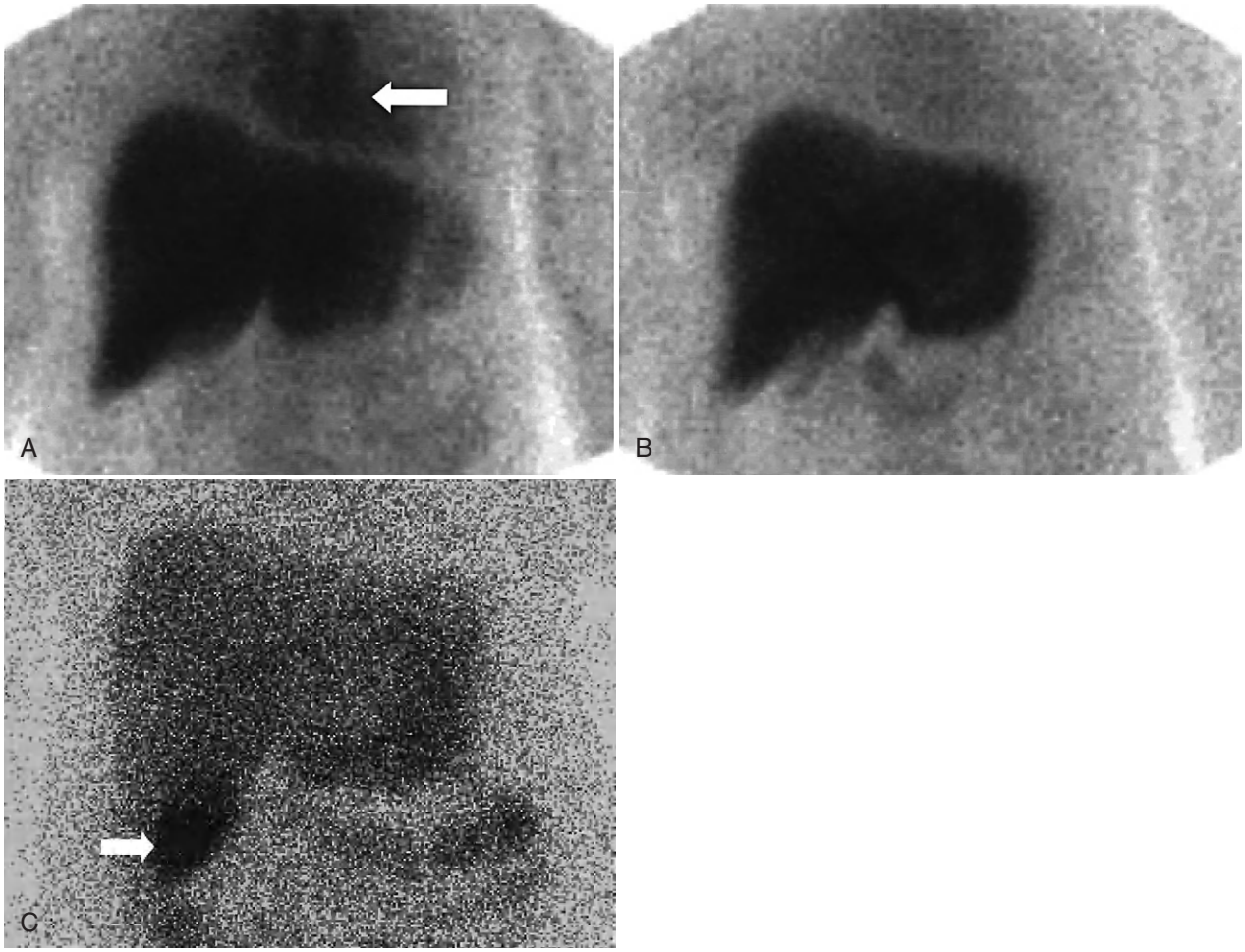


FIGURE 15.26. Delayed gallbladder demonstration. **A,** The *left arrow* outlines blood pool activity at 10 minutes after injection. **B,** Nonvisualization of the gallbladder at 60 minutes after injection. **C,** The 4-hour image shows the gallbladder (*right arrow*). The 6-hour half-life of ^{99m}Tc and biologic clearance of the tracer lead to a reduction in counts acquired in time, producing a grainy image at 4 hours.

and the results may be due in part to a reporting bias, as these disease states become more widely appreciated; but they are more likely due to the reduced morbidity of the laparoscopic operative procedure. Preoperative testing with biliary scintigraphy predicts patients with acalculous biliary pain who are likely to benefit from cholecystectomy (Goncalves et al, 1998; Reed et al, 1993), and it should be performed in this patient group (Barron & Rubio, 1995).

Cholecystitis (See Chapter 30)

The diagnosis of acute cholecystitis is largely clinical, although ancillary tests are often performed to increase clinical confidence before surgery. The two competing imaging tests are US and hepatobiliary scintigraphy. The key finding on hepatobiliary imaging is nonvisualization of the gallbladder (see Fig. 15.25). Sensitivity rates of greater than 96% have been reported consistently by many groups (Freitas et al, 1982; Suarez et al, 1980; Szlabick et al, 1980; Velasco et al, 1982). An additional finding of a hot rim around the gallbladder fossa is strongly associated with a diagnosis of acute cholecystitis (Cawthon et al, 1984), but it is not 100% specific, as had previously been thought (Oates et al, 1996). The specificity of unaugmented hepatobiliary scintigraphy is lower, however, because prolonged fasting may lead to nonvisualization of the gallbladder. This finding has led to many investigators routinely using morphine augmentation (Choy et al, 1984) or cholecystokinin pretreatment (Eikman et al, 1975) to increase biliary tree pressure and show cystic duct patency. The addition of this step increases the specificity of hepatobiliary scintigraphy (Cabana et al, 1995; Chen et al, 1997; Choy et al, 1984; Fink-Bennett et al, 1991a) over and above delayed imaging (Kim et al, 1993). Morphine-augmented hepatobiliary scintigraphy in the detection of acute cholecystitis has sensitivity, specificity, positive predictive value, and negative predictive value of 95%, 99%, 97%, and 98%, respectively (Fink-Bennett et al, 1991a). These figures compare favorably with US, and hepatobiliary scintigraphy seems to be the diagnostic test of choice in the diagnosis of acute cholecystitis (Shea et al, 1994). US relies on a combination of sonographic findings, including the presence of stones, gallbladder wall thickening, perigallbladder fluid, and a positive Murphy sign over the gallbladder fossa rather than demonstration of cystic duct obstruction itself (Dykes et al, 1986; Lauritsen et al, 1988; Samuels et al, 1983; Soiva et al, 1986; van Weelde et al, 1986).

Chronic Cholecystitis

In patients with chronic cholecystitis, the crucial imaging finding is the presence of cholelithiasis, and this is best shown with US (Shea et al, 1994). Most patients with chronic cholecystitis show cystic duct patency. Delayed filling of the gallbladder is associated with chronic cholecystitis, but this is a nonspecific finding, because fasting may give the same appearance (see Fig. 15.26). US remains the diagnostic test of choice in the detection of chronic cholecystitis.

Chronic Acalculous Right Upper Quadrant Pain

Chronic acalculous disorders of the biliary tree comprise acalculous cholecystitis, cystic duct syndrome, sphincter of Oddi dysfunction, and gallbladder dyskinesia.

ACALCULOUS CHOLECYSTITIS AND THE CYSTIC DUCT SYNDROME. *Cystic duct syndrome* is defined as fibrotic narrowing of the cystic duct lumen by 60%, kinking or adhesions of the duct seen at surgery, or both. *Chronic cholecystitis* is defined pathologically as hypertrophy of the gallbladder wall (>1.5 to 2 mm thick) and the presence of Rokitansky-Aschoff sinuses, a mononuclear infiltrate, foamy macrophages, diffuse muscularis hypertrophy, and yellow papillary nodules (Fink-Bennett et al, 1991b). Using a standardized protocol of cholecystokinin infusion (0.2 μg/kg administered over 3 minutes), a normal range for the ejection of bile from the gallbladder has been established. Fink-Bennett and colleagues (1991b) studied this group in detail. Patients with reduced gallbladder ejection fraction (<35% ejected in the first 20 minutes after cholecystokinin infusion) were considered abnormal. Of patients with an abnormal gallbladder ejection fraction, 108 (94%) of 115 had either cystic duct narrowing or chronic cholecystitis on pathology, with only 1 of 106 who had follow-up reporting no amelioration of symptoms; 69 of 78 (89%) who were medically managed had continued symptoms suggesting biliary colic. This study suggests the finding of reduced gallbladder ejection fraction in response to cholecystokinin is a strong indicator of the need for surgical intervention. Only seven (6%) of the 115 patients with histopathologic confirmation of disease had a gallbladder ejection fraction greater than 35%, a false-negative result. The negative predictive value of a normal gallbladder ejection fraction is 91%, with 130 of 143 patients with improvement after treatment for nongallbladder pathology having a gallbladder ejection fraction greater than 35% (Fink-Bennett et al, 1991b).

POSTCHOLECYSTECTOMY SYNDROME AND SPHINCTER OF ODDI DYSFUNCTION (SEE CHAPTER 38). A significant proportion of patients subjected to cholecystectomy have continued pain postoperatively. Many are diagnosed as having irritable bowel syndrome, pancreatitis, gastritis, and esophagitis, but about 6% have unexplained pain. Sphincter manometry is considered one of the main objective tests for the presence of sphincter of Oddi dysfunction (SOD).

The overall incidence of pancreatitis in patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) manometry alone has been reported as 9.3%, with a 26% incidence if sphincterotomy is combined with manometry (Maldonado et al, 1999). The high rate of this side effect serves as a continued stimulus to investigate noninvasive methods for diagnosing SOD. Augmented hepatobiliary scintigraphy is a promising method in the noninvasive diagnosis of SOD. The most common abnormal finding with hepatobiliary scintigraphy is an obstructive pattern of biliary drainage, but some patients who have no symptoms at the time of the examination have a normal study. A variety of criteria for analysis have been developed using quantitative hepatobiliary scintigraphy (Roberts-Thomson et al, 1986). Augmentation techniques include an improvement in biliary drainage after amyl nitrate therapy (Madacsy et al, 1994) to exclude a fixed stenosis that would not respond to drug therapy and the development of an obstructive pattern with prostigmine-morphine administration observed by Madacsy and colleagues (1995), who suggested that only patients with prostigmine-morphine–induced obstruction should undergo manometry.

Biliary Tract Complications after Surgery (See Chapter 42)

The complication rates of laparoscopic cholecystectomy decrease as the number of cases performed by a particular surgical group increases (Walker et al, 1993). Hepatobiliary scintigraphy is a powerful, noninvasive tool to detect bile leak and iatrogenic biliary obstruction (Reichelt, 1978). When there is clinical suspicion of bile duct injury after surgery, hepatobiliary imaging should be one of the first tests considered (Figs. 15.27 to 15.32). The degree of leak can be assessed, and this can assist in the triaging of patients with bile leak to conservative or operative repair. After bile drainage has been achieved, a follow-up scan can assist in the triaging of patients who require further intervention (Walker et al, 1992). Improved disease-free survival after hepatic resection of metastases has led to an increase in the complexity and aggressiveness of hepatic resection, including complex operations involving the biliary tree. Hepatobiliary scintigraphy can assess the efficacy of biliary drainage after these complex procedures.

Liver Transplantation (See Chapter 97)

The major role of hepatobiliary imaging in liver transplant patients is in the postoperative assessment of the presence or absence of bile duct injury (Mochizuki et al, 1991; see Chapter 100). The noninvasive assessment of the integrity of a bile duct anastomosis is best done by hepatobiliary scintigraphy, because conventional imaging cannot characterize the nature of ascitic fluid. Bile duct stenoses do occur, and these are well shown with scintigraphy. Acute vascular rejection is an uncommon event in liver transplantation, and scintigraphy allows the assessment of perfusion noninvasively (Williams et al, 1985). Preservation injury or peritransplantation infarction is demonstrable on scintigraphy and may give the clinician a clue for the level of function expected from the graft (Karademir et al, 1994), but such information is unlikely to change posttransplant treatment. Cholestasis and rejection are two common posttransplantation problems, and the two overlap in terms of their scintigraphic appearance (Engeler et al, 1992). This problem had led to many units not including scintigraphy in the postoperative assessment. Attempts to further analyze the information within the hepatobiliary scan to assess transplant viability more accurately have been promoted by some authors but have not become widely used (Brown et al, 1988; Shah et al, 1995; Tagge et al, 1987). A normal study effectively excludes rejection or severe cholestasis, but this information is unlikely to be additive to other simpler tests. Nuclear medicine studies are useful in the assessment of immunosuppressed patients with pyrexia of unknown origin.

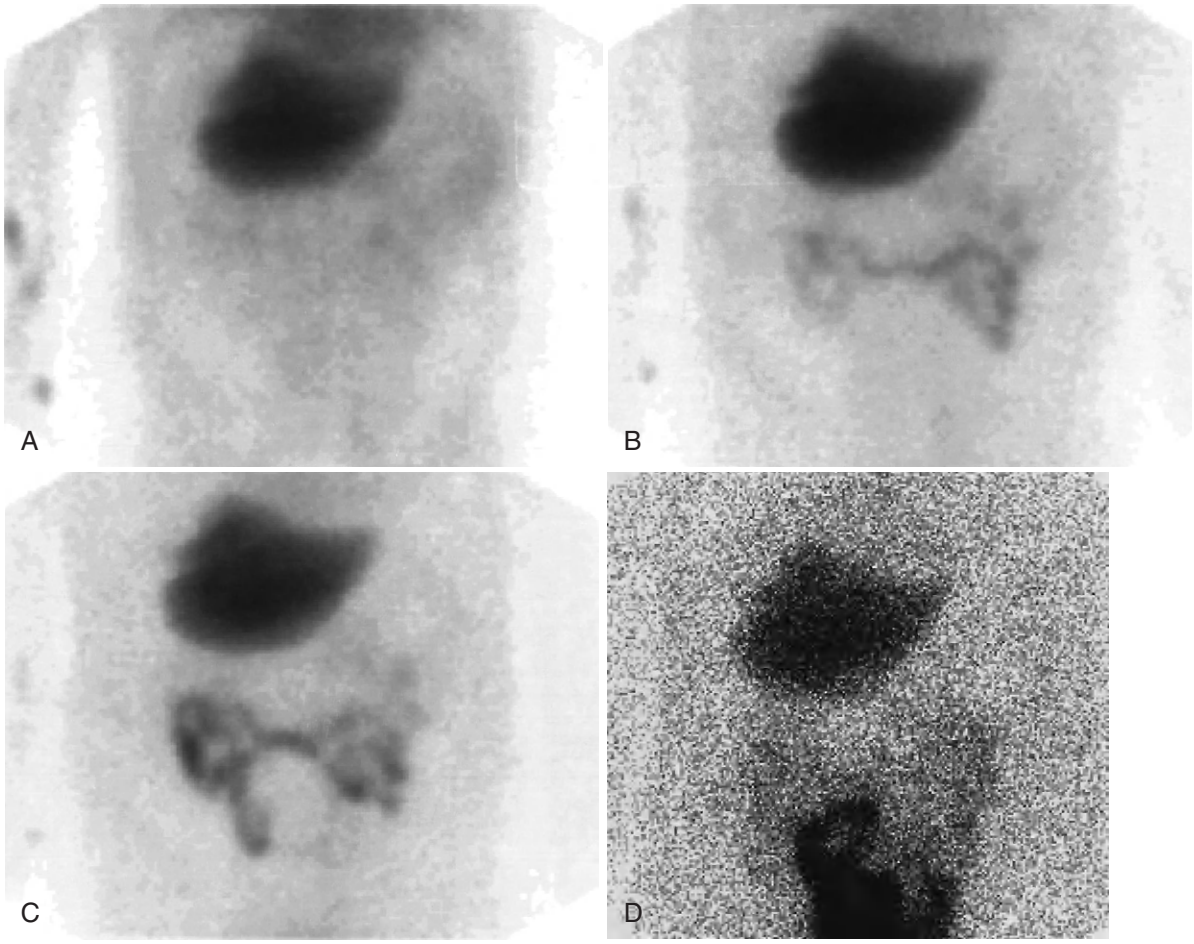


FIGURE 15.27. Normal scan 12 days after right trisegmentectomy. Images were acquired at 0, 30, and 60 minutes and at 3.5 hours after injection.

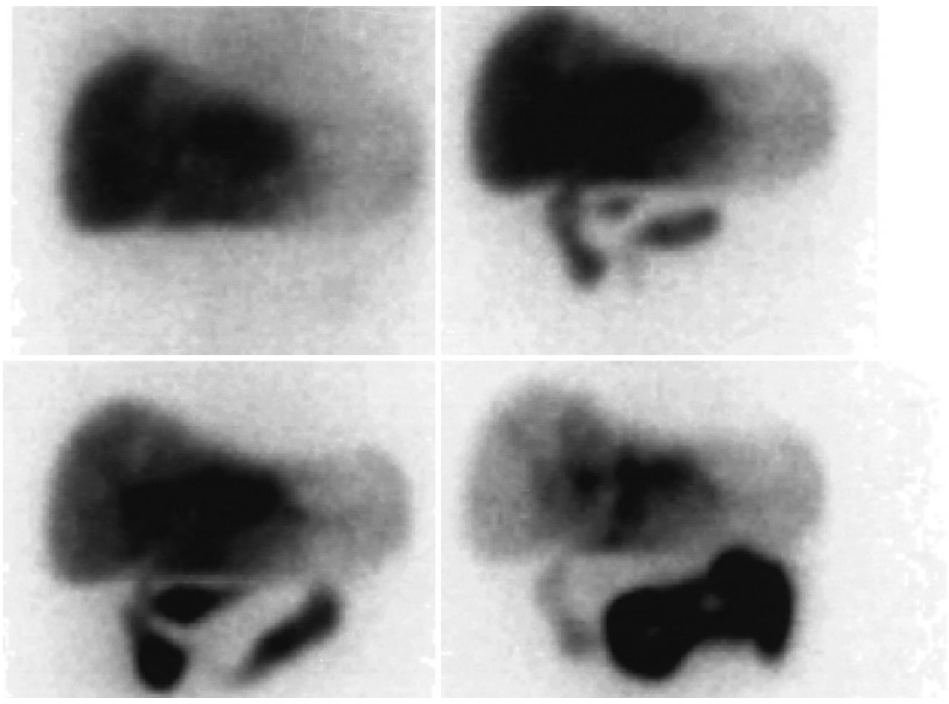


FIGURE 15.28. A 47-year-old man with hypereosinophilic syndrome after right liver lobectomy for liver abscess was referred to rule out biliary obstruction and to evaluate the segmental drainage 0, 10, 20, and 60 minutes after injection. The images show impaired drainage of the left ductal system with bile duct retention. Ultrasound showed bile duct stones, and the patient required percutaneous drainage.

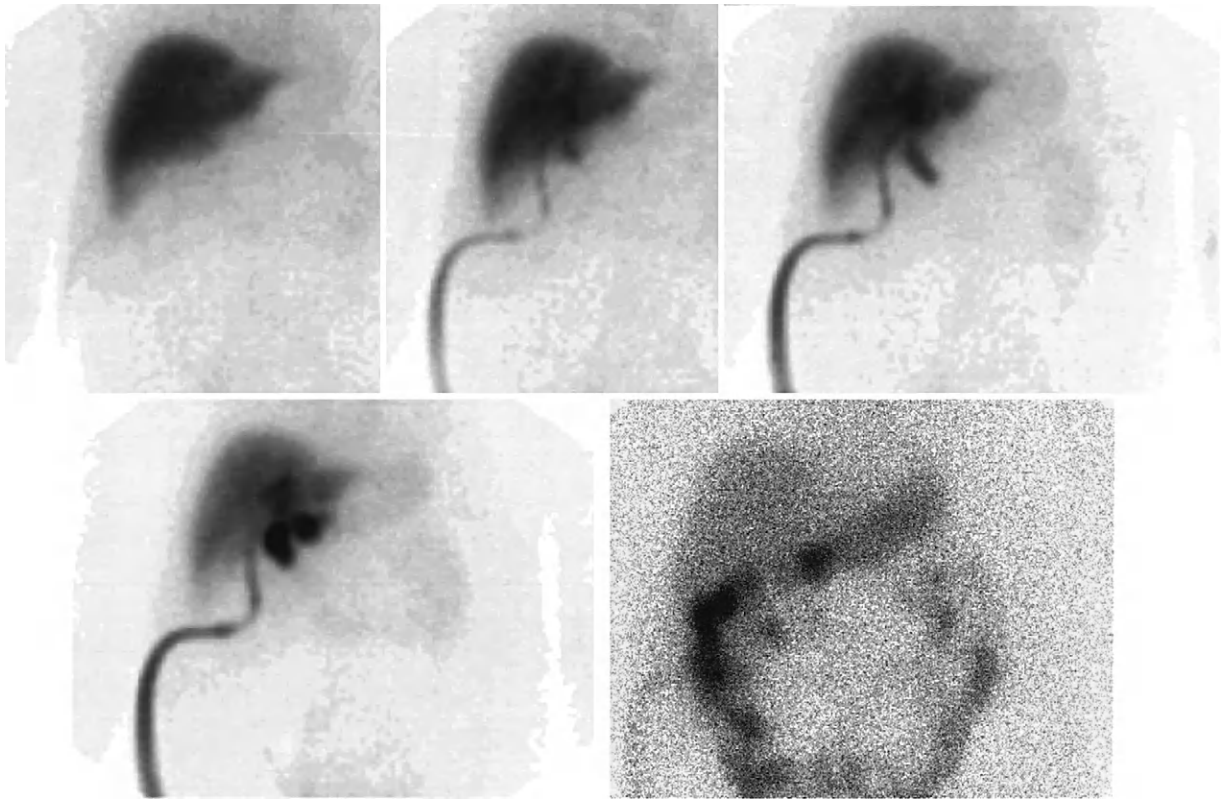


FIGURE 15.29. A 70-year-old man with inoperable duodenal carcinoma had persistent bile drainage into the intraperitoneal drain tube inserted intraoperatively. The study revealed free passage of bile from the drain tube with some drainage into the bowel. Images were acquired 20, 30, 40, and 60 minutes and at 3.5 hours after injection.

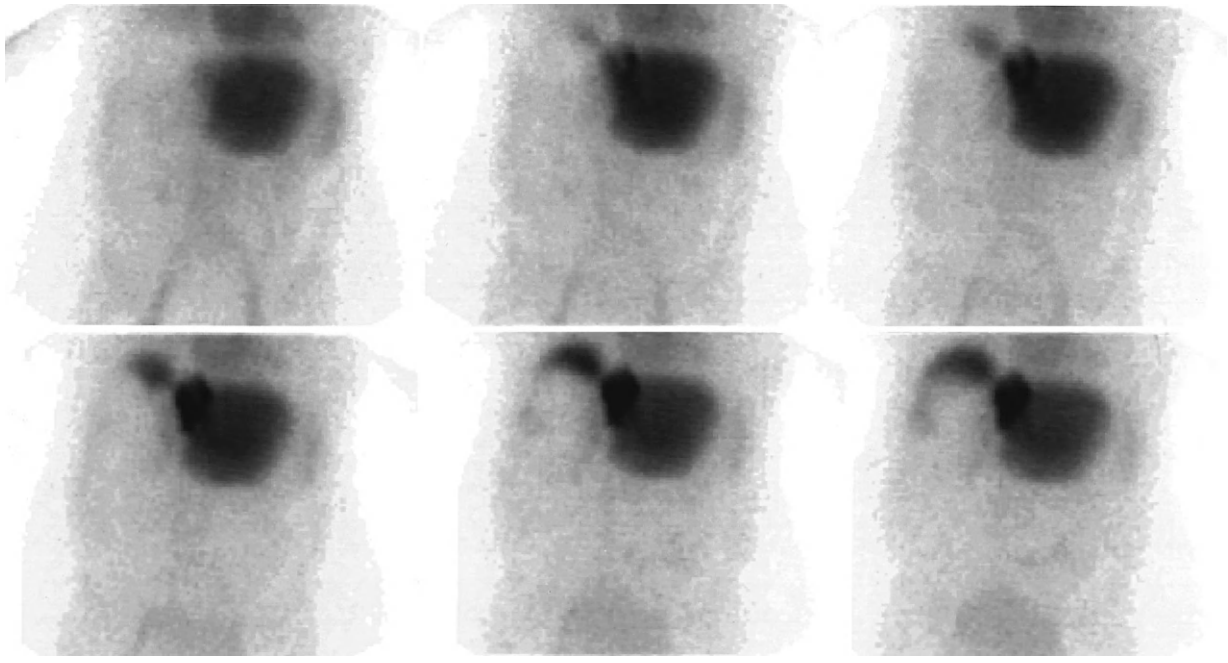


FIGURE 15.30. A 63-year-old woman with a history of colon carcinoma metastatic to the liver was referred after right trisegmentectomy for assessment of bile leak. The images show leakage from the anastomosis with tracking of the isotope into the right subphrenic space. The images shown are 10 minutes apart, acquired over 1 hour.

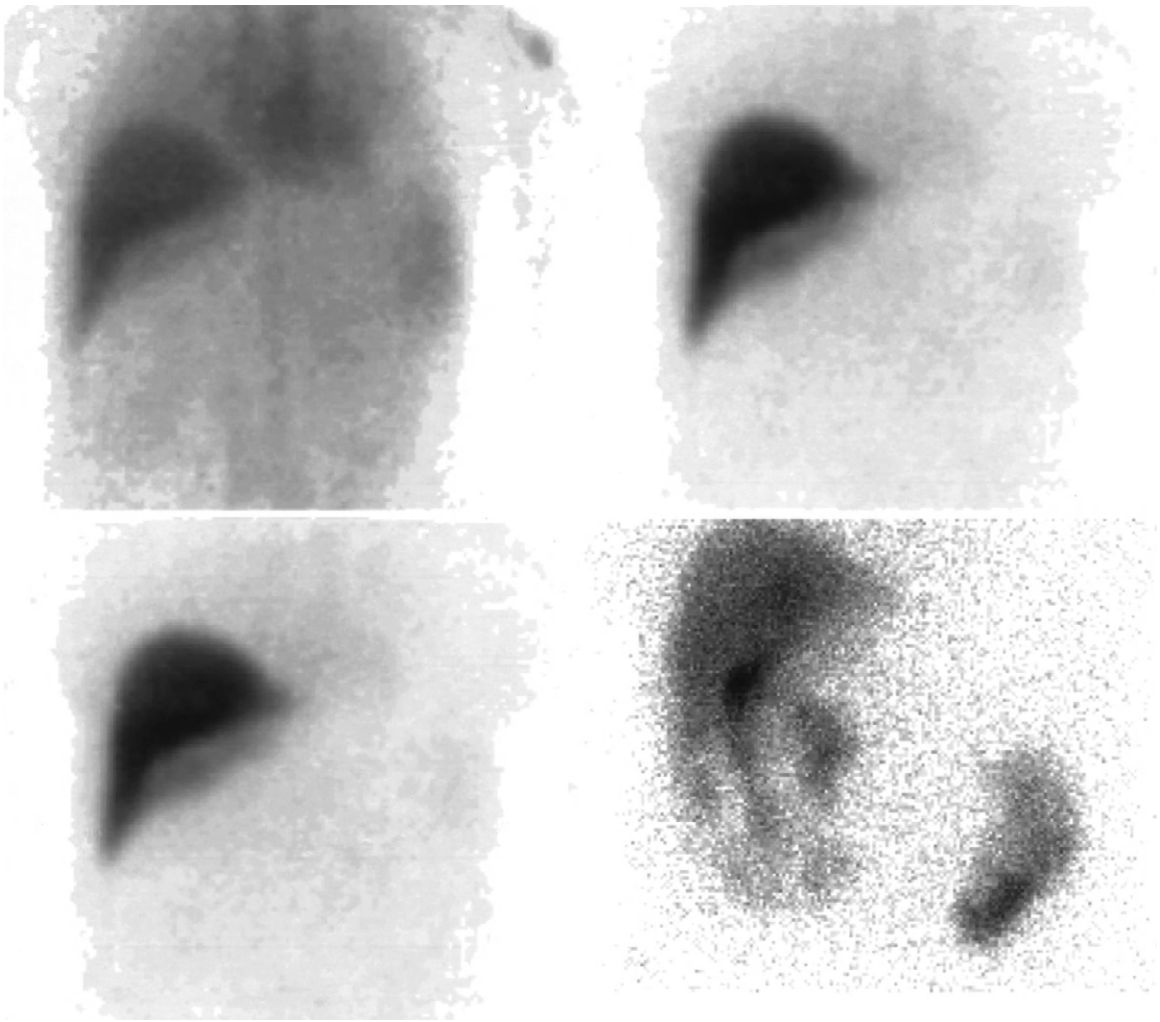


FIGURE 15.31. A 40-year-old woman with repeated cholangitis after a Whipple procedure is referred for assessment of possible biliary obstruction. After this study, an 8.5-Fr biliary drainage catheter was placed across a 1.5-cm high-grade biliary-enteric obstruction. Images were acquired at 0, 30, and 60 minutes and at 3 hours after injection.

Hepatocellular Carcinoma

HCC has a variable pattern of uptake, seen with hepatobiliary tracers. Poorly differentiated HCC appears as a cold lesion; well-differentiated HCC typically exhibits retention of the tracer on delayed images, performed 2 to 3 hours after injection, that a normal liver would have cleared. Sequential studies can be used to follow well-differentiated HCC, if the clinician and patient wish to undertake such a course. Focal nodular hyperplasia (FNH) is the differential diagnosis of focal retention of tracer, but an image at 5 to 10 minutes after injection should differentiate between FNH (isointense with normal liver) and HCC (usually hypointense).

Pediatric Imaging

Neonatal Jaundice

The task of the physician faced with a newborn who is jaundiced is to determine the cause to decide whether intervention is required. Most cases of neonatal jaundice are due to physiologic causes, breast milk jaundice, and, less commonly, erythroblastosis fetalis. Idiopathic neonatal hepatitis is rare, as is biliary atresia (see Chapter 40). Both of these conditions result in either mixed or conjugated prolonged hyperbilirubinemia (direct bilirubin of >15%). Early diagnosis of biliary atresia is important, because it leads to the development of cirrhosis and liver failure with an average survival of 12 months if untreated (Emblem et al, 1994). The differentiation of neonatal hepatitis and biliary atresia is difficult on clinical grounds and occasionally at liver biopsy (Manolaki et al, 1983).

Biliary Atresia (See Chapter 40)

Differentiation of biliary atresia and neonatal hepatitis on histopathology depends on the presence of ductal proliferation and portal fibrosis, both of which may take some time to develop; this may reduce the accuracy of a biopsy performed too soon after birth. The diagnosis of biliary atresia using hepatobiliary scintigraphy is based primarily on nonvisualization of the gut at

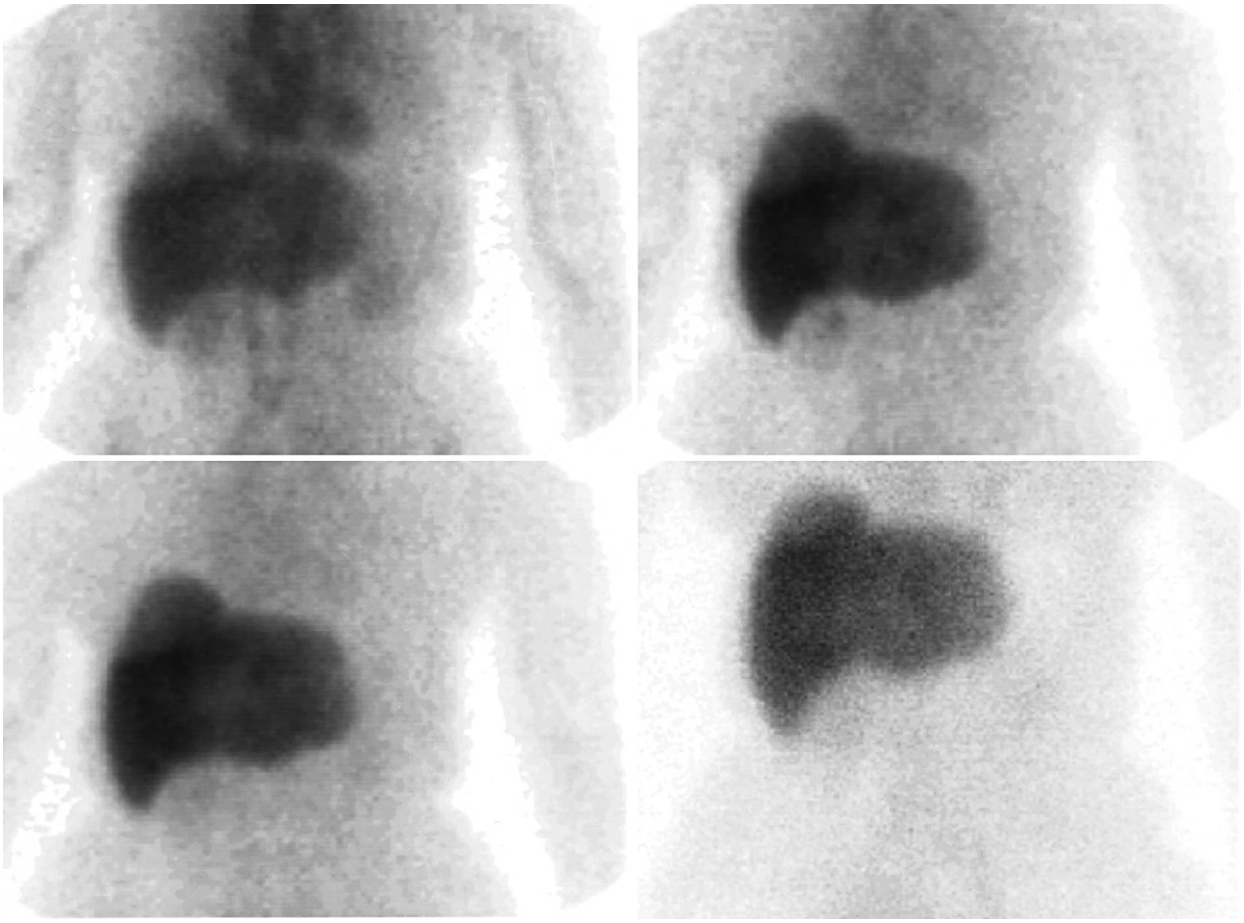


FIGURE 15.32. Complete biliary obstruction. Images are immediately postinjection, and at 30 minutes, 60 minutes, and 3 hours. Note the lack of biliary excretion and the breast shadow over the right lobe of the liver.

24 hours, but a secondary criterion of rapid uptake of the tracer into the liver without biliary excretion also suggests the presence of biliary atresia. Idiopathic neonatal hepatitis is characterized by impaired uptake of the tracer by the liver with slow hepatic clearance of the tracer, which occurs in parallel to cardiac blood pool, owing to renal excretion (this finding is mimicked by biliary atresia as cirrhosis develops, leading to impaired hepatocyte extraction of the tracer). It is advisable to perform hepatobiliary imaging before 3 months of age to reduce the likelihood of the development of cirrhosis. Premedication with phenobarbital (5 mg/kg/day for 5 days) leads to increased bile flow and improved specificity of the test, as it reduces the number of cases in which the gut is not visualized. The differential diagnosis of nonvisualization of the gut at 24 hours includes biliary atresia, bile plug syndrome, cystic fibrosis, or severe hepatocellular dysfunction secondary to idiopathic neonatal hepatitis, total parenteral nutrition (Cooper et al, 1985), infectious hepatitis, and septooptic dysplasia (Kumura et al, 1987). Bile plug syndrome is seen in dehydrated, septic infants. The characteristic scintigraphic features of this syndrome are excretion of the tracer into a dilated proximal biliary tract without gut excretion.

The diagnosis of biliary atresia on US is based on numerous features, including inability to see a gallbladder, a hypoplastic gallbladder, no change in gallbladder size with food, and a new feature known as the *triangular cord sign.* Recently reported in many publications by a single group of researchers, the triangular cord sign appears to have high sensitivity, specificity, and accuracy (85%, 100%, and 95%, respectively) (Choi et al, 1996, 1998; Park et al, 1997). The reported efficacy of diisopropylacetanilido-iminodiacetic acid scanning (sensitivity 96%, specificity 35%, accuracy 56%) by this group is less than reported in most other literature; however, using these criteria alone, US sensitivity of 85% translates into 15% of infants with biliary atresia having a delayed surgical procedure; a combined approach would therefore seem appropriate as the authors suggest. US is a good initial test, and it is useful in ruling out the presence of a choledochal cyst, which also may manifest with neonatal jaundice. Hepatobiliary scintigraphy in such a case is useful, if it shows filling of the cyst with bile (Fig. 15.33).

Lin and colleagues (1997) directly compared US with hepatobiliary scintigraphy using premedication with phenobarbital and cholestyramine premedication in a group of 66 patients with neonatal jaundice. The diagnostic sensitivity, specificity, and accuracy of scintigraphy in differentiating biliary atresia from other forms of neonatal jaundice were 100%, 87.5%, and 90.5%, respectively, compared with US results of 86.7%, 77.1%, and 79.4%, respectively (Lin et al, 1997). Premedication with oral phenobarbital increases test accuracy by accelerating biliary excretion (Majd et al, 1981a, 1981b). Reduced specificity of

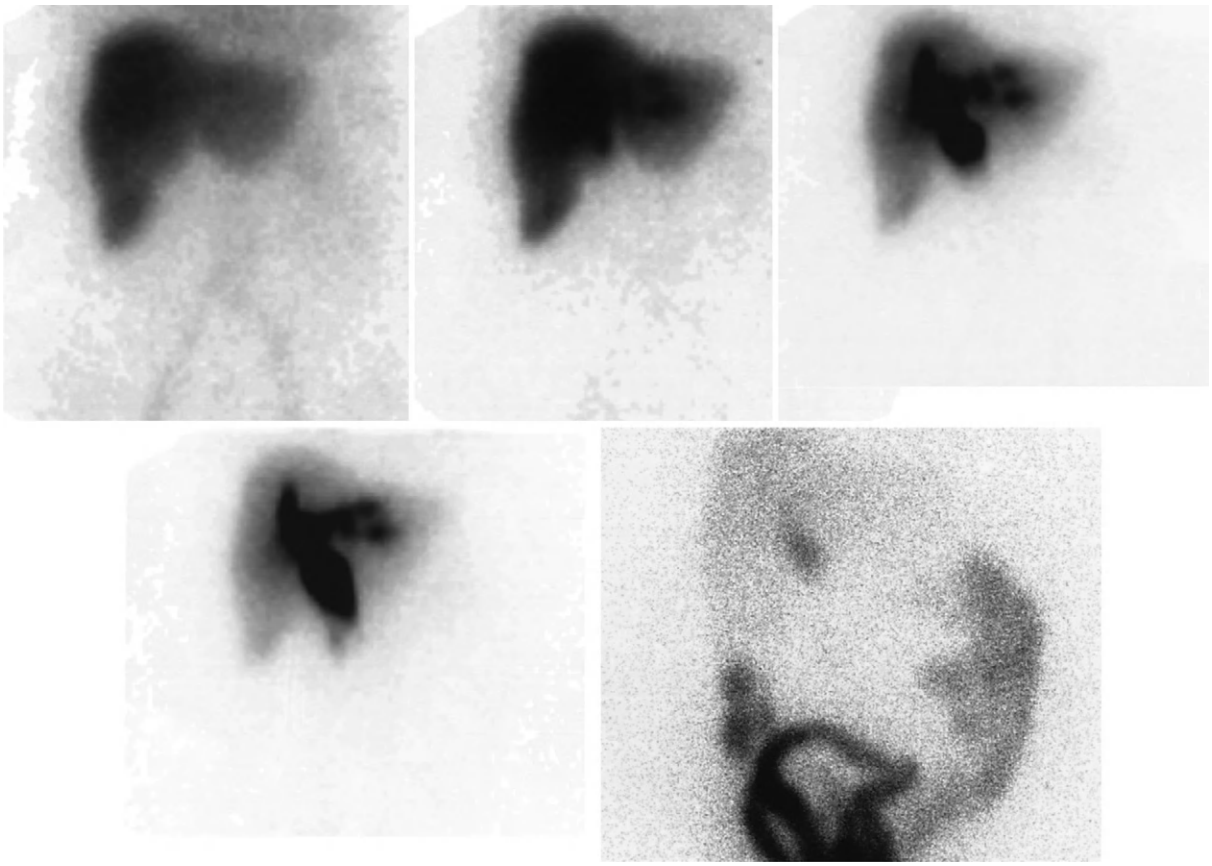


FIGURE 15.33. A 70-year-old woman who previously had undergone a cholecystectomy was referred for assessment of a possible choledochal cyst. The study reveals a large bile-filled structure beneath the hepatic hilum consistent with a choledochal cyst. Images were acquired at 0, 20, 40, and 60 minutes and at 4 hours after injection.

hepatobiliary scintigraphy is seen if the infant's birth weight is less than 2,200 g (Spivak et al, 1987). Hepatobiliary scintigraphy is the diagnostic test of choice in the diagnosis of cystic duct obstruction; it predicts response to cholecystectomy in patients with acalculous biliary pain and plays a vital role in the assessment of patients with biliary tract injury and neonatal jaundice.

ROLE OF GENERAL NUCLEAR MEDICINE IN ASSESSMENT OF ADULTS WITH MALIGNANT INVOLVEMENT OF THE LIVER AND HEPATOBILIARY TREE

Cardiac Preoperative Risk Assessment (See Chapter 22)

It is prudent to perform preoperative testing to attempt to risk-stratify patients before major surgery when risk of coronary disease is significant. Patients who have been recommended to undergo preoperative testing include those with two or more of the following: diabetes, prior congestive cardiac failure, prior myocardial infarction, Canadian class 1 or 2 angina, poor functional capacity (<4 metabolic equivalents on a treadmill exercise test), or a planned prolonged surgical procedure with large fluid shifts, blood loss, or both (Leppo & Dahlberg, 1998). Preoperative testing with myocardial perfusion scintigraphy with either thallium-201 (^{201}Tl)- or ^{99m}Tc-based perfusion agents is a powerful predictor of perioperative events. The initial reports of thallium scintigraphy showed a high positive predictive value of the test on the order of 20%, but the positive predictive value has declined slowly over time (Leppo & Dahlberg, 1998). In part, this decline may be due to changes in scanning protocols (SPECT versus planar acquisition) or to physicians overreading the scans to avoid possible litigation, as the biology of the disease is unlikely to have changed significantly. A negative test remains highly predictive (>99%) of a cardiac event–free perioperative period.

Sulfur Colloid Imaging

Historical Background

Before high-resolution CT, US, and MRI were developed, the initial imaging investigation to evaluate potential hepatic involvement with tumor was colloidal scintigraphy. The initial work was done with radiolabeled gold, but this was supplanted by ^{99m}Tc-labeled colloids. Injected colloids undergo phagocytosis by reticuloendothelial cells found in liver, spleen, and bone marrow.

In a normal patient, approximately 90% of the injected dose of ^{99m}Tc–sulfur colloid is taken up by the liver, with the spleen and bone marrow each accounting for 5% (Fig. 15.34). Sulfur colloid imaging has been used in the assessment of diffuse

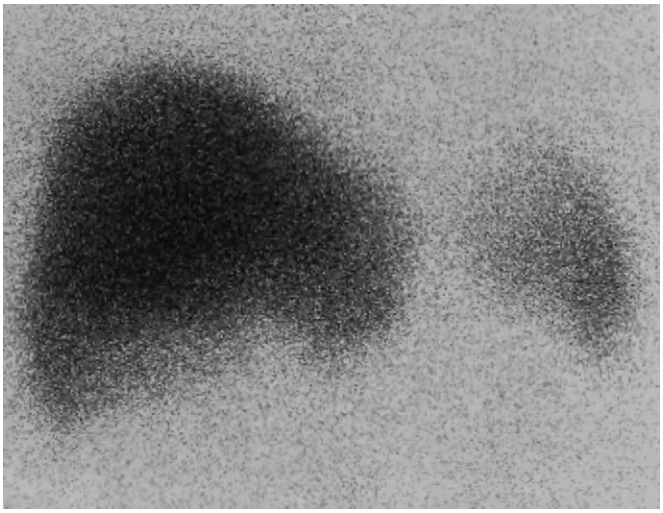


FIGURE 15.34. Anterior delayed view of a normal liver and spleen scan after injection of ^{99m}Tc–sulfur colloid.

parenchymal disease of the liver, with ratios of liver to spleen and bone marrow, the *colloid shift,* being used to assess the degree of hepatocellular dysfunction. The finding of a hypertrophied caudate lobe raises strong suspicions of the presence of Budd-Chiari syndrome. The advent of high-speed CT and color Doppler US has reduced the demand for liver and spleen imaging for the establishment of this diagnosis.

Diagnosis of Malignancy

The typical appearance of a malignant deposit is a focal cold defect on ^{99m}Tc–sulfur colloid imaging, because metastases do not contain the phagocytic cells necessary for uptake of the radiopharmaceutical. "Cold spots" on colloid imaging are nonspecific findings; hepatic cysts, hemangioma, and hepatic adenoma all may appear cold, because they do not contain Kupffer cells (Table 15.5). A solid lesion identified on cross-sectional imaging that is not accompanied by a photopenic defect on sulfur colloid imaging is likely to be FNH (Sandler et al, 1980) or the rare hepatoblastoma, usually only seen in children (Tanasescu et al, 1991). Hepatic adenomas that take up sulfur colloid are quite rare (Low & Khangure, 1990) and usually are gallium avid.

Table 15.5

Cold Defects and Hot Lesions on Technetium 99m–Sulfur Colloid Imaging

Lesion	Explanation
Cold Defects	
Hepatic pseudotumor	Hepatic regeneration or scar in cirrhotic patients, may or may not be hot
Acute radiation injury	Radiosensitive reticuloendothelial cells
Extrahepatic masses	Deformation of normal liver
Simple cysts	No target cells in lesion
Polycystic liver disease	No target cells in lesion
Hemangioma	No target cells in lesion
Adenoma	Usually cold; rare cases with uptake present have been reported
Hamartoma	No target cells in lesion
Hydatid cyst	No target cells in lesion
FNH	Variably hot or cold because it may contain reticuloendothelial cells
Hot Lesions	
Budd-Chiari syndrome	Typically caudate lobe hypertrophy
Cirrhosis	
Hepatoma	
Hemangioma	
Hamartoma	
Abscess	
FNH	

FNH, focal nodular hyperplasia

Dual-Tracer Studies

The relatively low specificity of sulfur colloid imaging led to the development of a variety of dual-tracer studies involving gallium 67 (^{67}Ga) citrate (Beihn et al, 1974; Rovekamp et al, 1983), ^{99m}Tc-labeled red blood cells, ^{111}In-labeled white blood cells (Fawcett et al, 1985), and more recently ^{201}Tl (Mochizuki et al, 1994). The principle of the dual-tracer studies was to use tracers of known physiologic processes to add specificity to the colloid findings. ^{201}Tl acts as a potassium analogue when injected intravenously, and it accumulates in viable cells. It has been used for many years for myocardial scintigraphy, and after serendipitous uptake in a tumor, it was investigated as a tumor-seeking agent. Subtraction imaging with ^{201}Tl-labeled and ^{99m}Tc-labeled colloids has been used in the assessment of HCC (Mochizuki et al, 1994). ^{67}Ga citrate is a nonspecific tumor-seeking agent whose efficacy probably is related to shared metabolic pathways with iron. A lesion negative on colloidal imaging but positive on labeled white blood cell scan suggests abscess; a lesion positive on ^{67}Ga and negative with colloid imaging is more likely to be a hepatoma (given the absence of fever and other signs of infection). Serial ^{67}Ga studies can be a useful follow-up tool in patients after resection of HCC (Serafini et al, 1988). The improvements in the image achievable with US, CT, and MRI and the limits of resolution (1.5 to 2 cm) of the tracer techniques have led to the gradual replacement of colloid imaging with conventional radiologic investigations. If there are contraindications to biopsy or equivocal lesions, combined tracer studies remain a useful noninvasive technique.

Hemangioma Studies (See Chapter 79A)

A hepatic hemangioma is almost always negative on sulfur colloid imaging (Fig. 15.35). If a lesion suspicious for a hemangioma can be identified as a cold spot with sulfur colloid, a red blood cell study can add weight to the diagnosis of hemangioma. A red blood cell study involves the labeling of the patient's red blood cells with ^{99m}Tc using a stannous chloride chelate, which bonds the ^{99m}Tc to the red blood cells (Royal et al, 1981). Because hemangiomas have an increased blood volume compared with normal tissues, they appear as a hot spot on a blood pool scan and may be visualized when other imaging modalities are negative (Krausz et al, 1997). Lesions 1.5 to 2 cm can be reliably detected with sensitivities of 89%

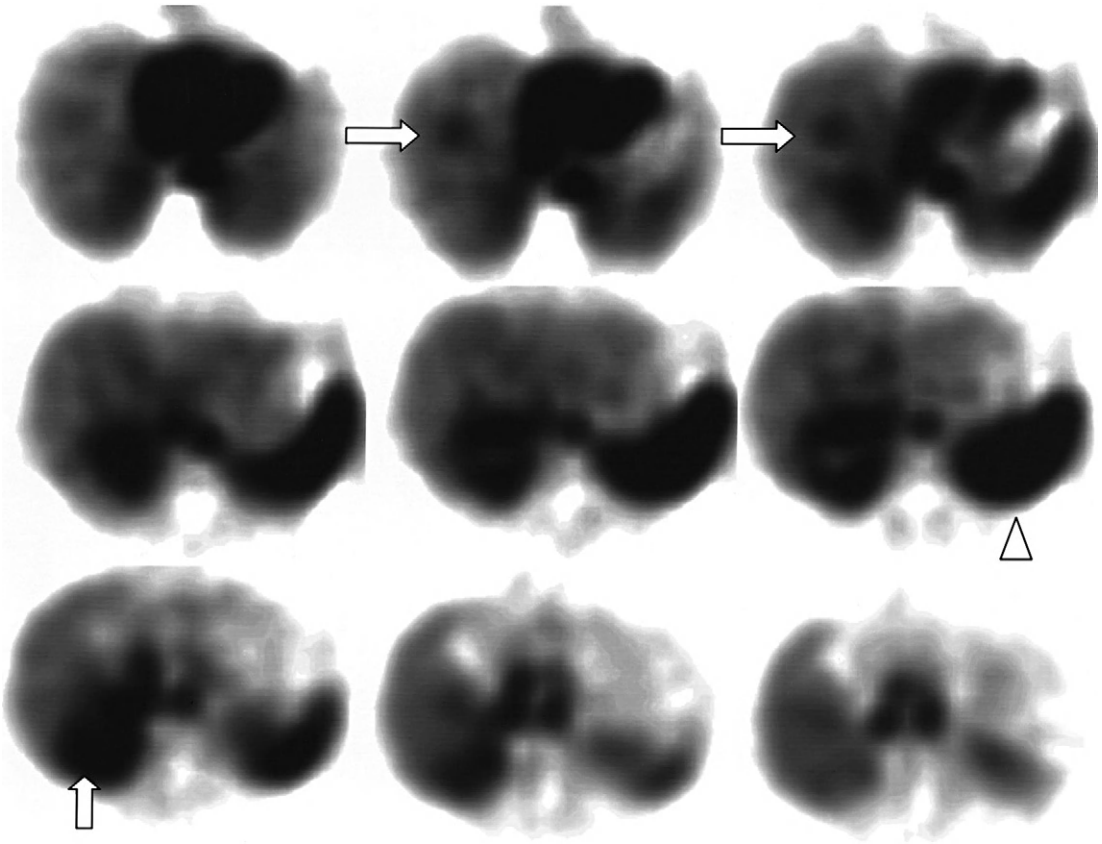


FIGURE 15.35. A 52-year-old woman with breast cancer was found to have lesions suggesting hemangioma in her liver and was referred for assessment. The images are sequential transaxial sections through the lower chest and upper abdomen. The study shows the right and left ventricles in the top right image; the right arrows point to a small hemangioma in the upper liver. The *arrowhead* points to the spleen; the up arrow points to the larger hemangioma in the posterior right lobe of the liver.

(Guze & Hawkins, 1989; Siegel & Mazurek, 1997; Ziessman et al, 1991). Hypervascular metastases do occur but are rare (Farlow et al, 1993; Ginsberg et al, 1986; Shih et al, 1996; Swayne et al, 1991).

Neuroendocrine Receptor Imaging (See Chapters 61 and 81B)

Many neuroendorine tumors can be imaged using ^{111}In-labeled octreotide, a somatostatin analogue, including carcinoids, gastrinomas, insulinomas, glucagonomas, medullary carcinoma of the thyroid, meningiomas, small cell lung cancer, and other tumors such as Hodgkin and non-Hodgkin lymphomas (Krenning et al, 1992). These agents can be used to characterize liver lesions in patients with the aforementioned underlying conditions. Uptake in the normal liver may obscure small lesions, so unless a lesion can be seen as a cold spot or a hot spot, there is limited diagnostic information in a scan showing homogeneous liver uptake of octreotide. The real advantage of somatostatin receptor imaging is in the demonstration of extrahepatic metastases that may not have been shown with the conventional imaging modalities, altering the stage of the patient. Most patients with neuroendocrine tumors should have an octreotide scan before an attempted curative resection for metastatic disease (Fig. 15.36). If available, ^{68}Ga somatostatin receptor imaging should be performed in place of ^{111}In octreotide because of the time savings to the patient and the improved imaging characteristics of the PET agent over the γ-camera agent (Fig. 15.37).

Hepatic Arterial Perfusion Studies (See Chapter 86)

Technetium-99m Macroaggregated Albumin

The radiopharmaceutical ^{99m}Tc–macroaggregated albumin (MAA) is available in kit form and is commonly used for pulmonary perfusion scintigraphy. A heating process makes an aggregate of the albumin, resulting in MAA particles, 90% of which are between 10 and 90 μm in diameter. The net effect is that this pharmaceutical embolizes into the first capillary bed it meets and does not pass on through the remainder of the circulation when injected. This preparation has been used to assess the perfusion of the liver by direct injection into the hepatic artery (Yang et al, 1982). The addition of ^{99m}Tc–sulfur colloid imaging provides information regarding the relative perfusion of the liver via the hepatic artery as assessed by ^{99m}Tc–MAA and the intrahepatic distribution of the hepatic metastases as shown by ^{99m}Tc–sulfur colloid imaging (Figs. 15.38 to 15.41; Ridge et al, 1987). Direct injection of chemotherapeutic agents into the hepatic artery has been shown to deliver 10 times the

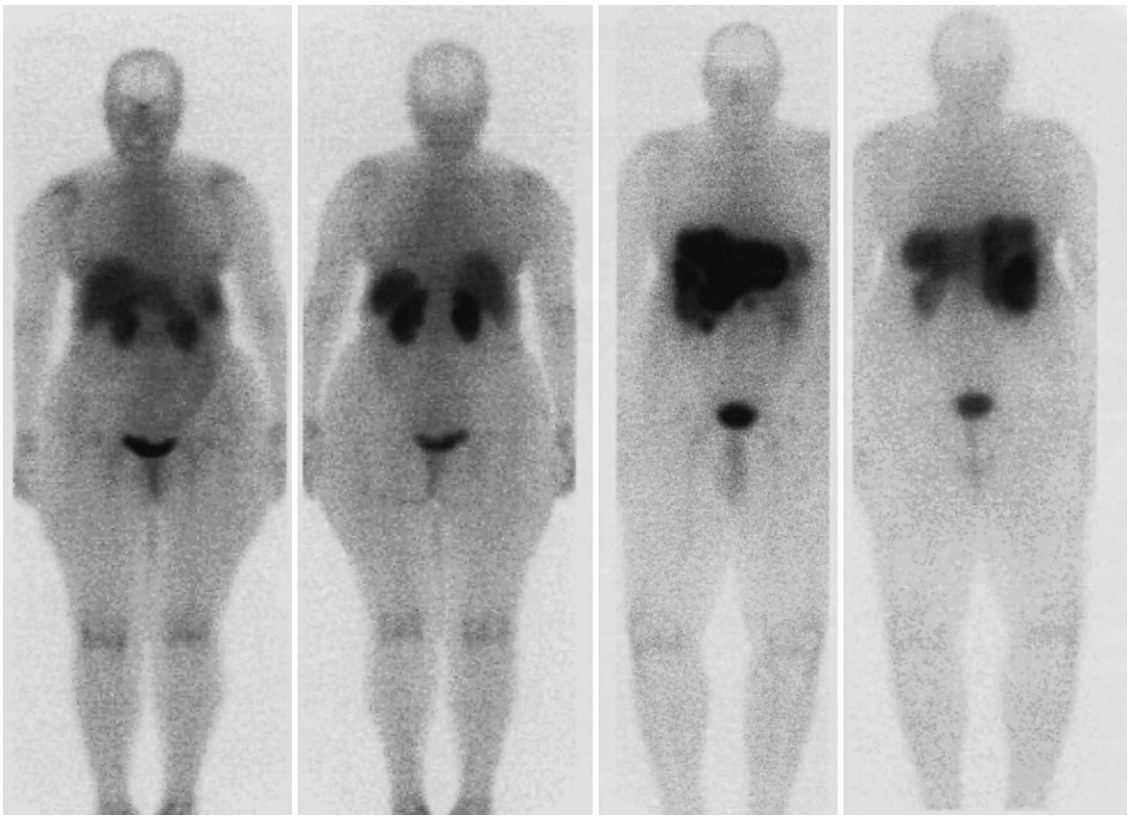


FIGURE 15.36. A normal octreotide study in a woman is shown on the left. On the right are images of a 53-year-old man who presented with confusion and was found to be hypoglycemic. Abdominal examination revealed hepatomegaly, and computed tomography revealed metastases. Fine needle aspiration revealed small round cells, suggesting a neuroendocrine origin. There is normally low-grade uptake of the tracer in the liver, spleen, and kidneys. The images on the right reveal extensive hepatic metastases and an epigastric mass.

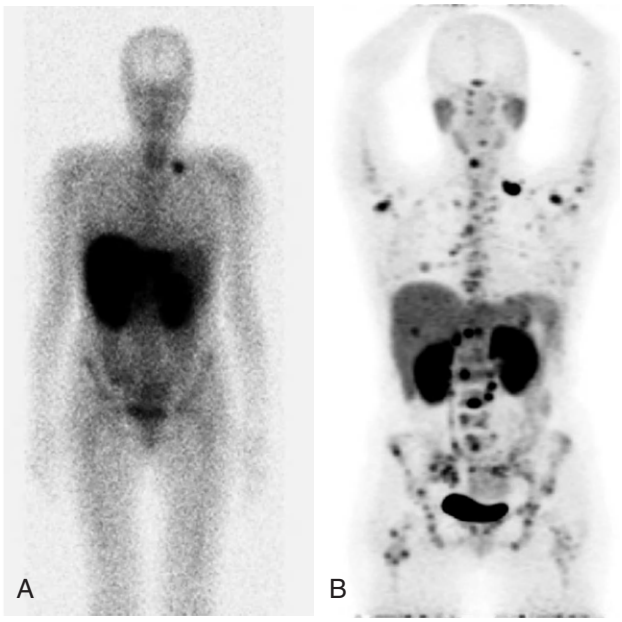


FIGURE 15.37. An abnormal indium 111 octreotide scan. **A,** A left supraclavicular node in a woman with a known neuroendocrine tumor. **B,** The gallium 68 (^{68}Ga) octreotate positron emission tomography scan was performed less than 1 week later and revealed abormalites in multiple bones and intraabdominal nodes in addition to the same supraclavicular node that was seen on the octreotide study. The greater sensitivity of the ^{68}Ga octreotate scan is well demonstrated. *(Images courtesy Dr. Michael Hofman.)*

concentration of 5-fluorouracil (5-FU) into liver metastases than delivery via the intravenous route (Hohenberger et al, 1993).

The advent of intrahepatic arterial drug therapy has led to increasing use of combined ^{99m}Tc–MAA and ^{99m}Tc–sulfur colloid imaging to exclude extrahepatic delivery of the radiopharmaceutical, which may necessitate catheter revision (Habbe et al, 1998). Inadvertent direct perfusion of the stomach, small intestine, or pancreas can cause local chemotoxicity, leading to localized inflammation that is often symptomatic (Figs. 15.42 and 15.43; Choplin et al, 1983; Chuang et al, 1981; Ku et al, 1998; Ottery et al, 1986). In some cases, the distribution of the tracer on scintigraphy has predicted the pattern of response of the metastases to the therapy (Borzutzky & Turbiner, 1985) and is a useful adjunct in the assessment of response to therapy (Savolaine et al, 1989). Hepatic artery scintigraphy also has been used to show the presence of arteriovenous shunting in hepatic tumors, which can modify therapy in an attempt to limit pulmonary toxicity (see Fig. 15.41; Leung et al, 1994).

Hepatic Arterial Therapy using Radiopharmaceuticals (See Chapter 84A)

An adaptation of the chemotherapy approach has been made by many groups, using therapeutic doses of unsealed radiotherapy. MAA imaging is also integral to the workup of a patient being considered for hepatic arterial embolization with radioactive microspheres, another approach to the palliation of liver tumors that share similar toxicity profiles when administered

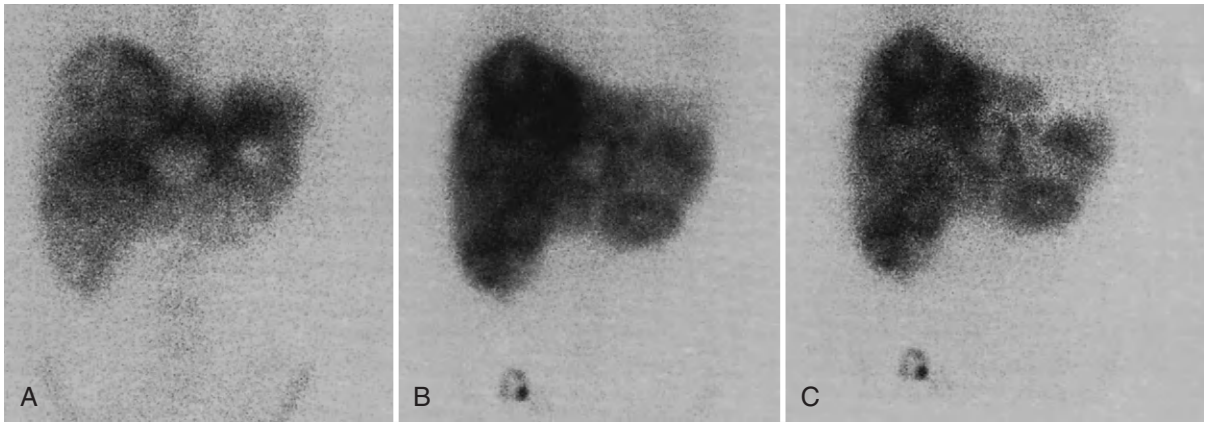


FIGURE 15.38. The methodology of subtraction scintigraphy with ^{99m}Tc–sulfur colloid and ^{99m}Tc macroaggregated albumin (MAA). The tracer requiring in vivo processing is injected first in a dose of 1 mCi (37 MBq). The second tracer, MAA, is injected through the hepatic catheter in a dose of 5 mCi (185 MBq). **A,** Sulfur colloid image. **B,** MAA image. **C,** MAA minus the sulfur colloid image. Multiple hepatic metastases are seen showing a hot rim of the MAA in the hypervascular rim of tumor. The activity in the right lower portion of the image is retained activity in the catheter.

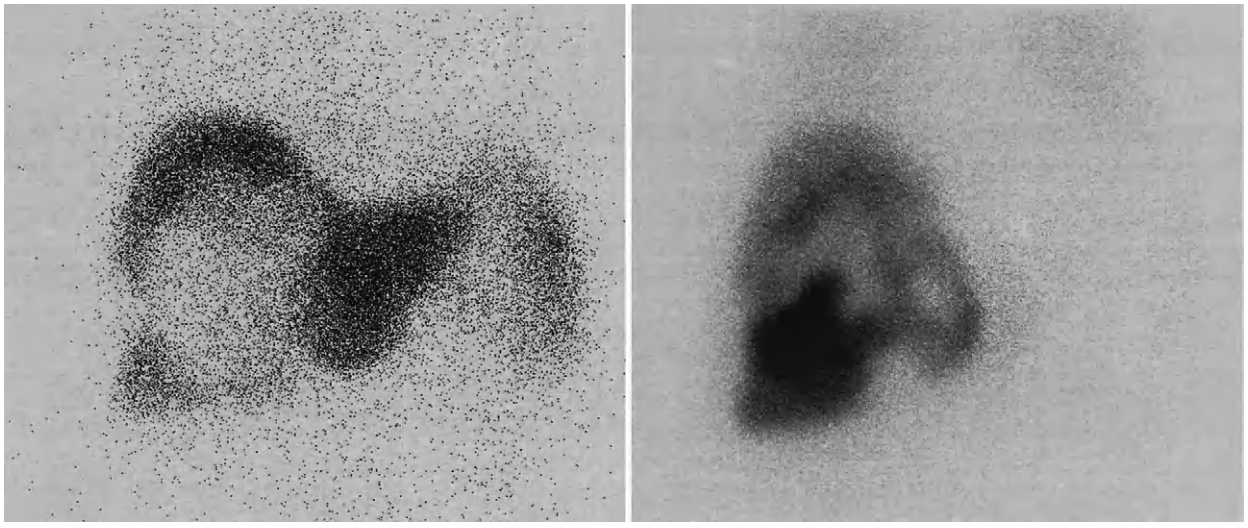


FIGURE 15.39. Image of a patient with a lesion in the lower right liver shows reduced uptake of sulfur colloid (*left*) but relative hyperperfusion (*right)* taken after injection of macroaggregated albumin intraarterially. This case shows the principle of metastases being supplied by the hepatic artery rather than by the portal vein.

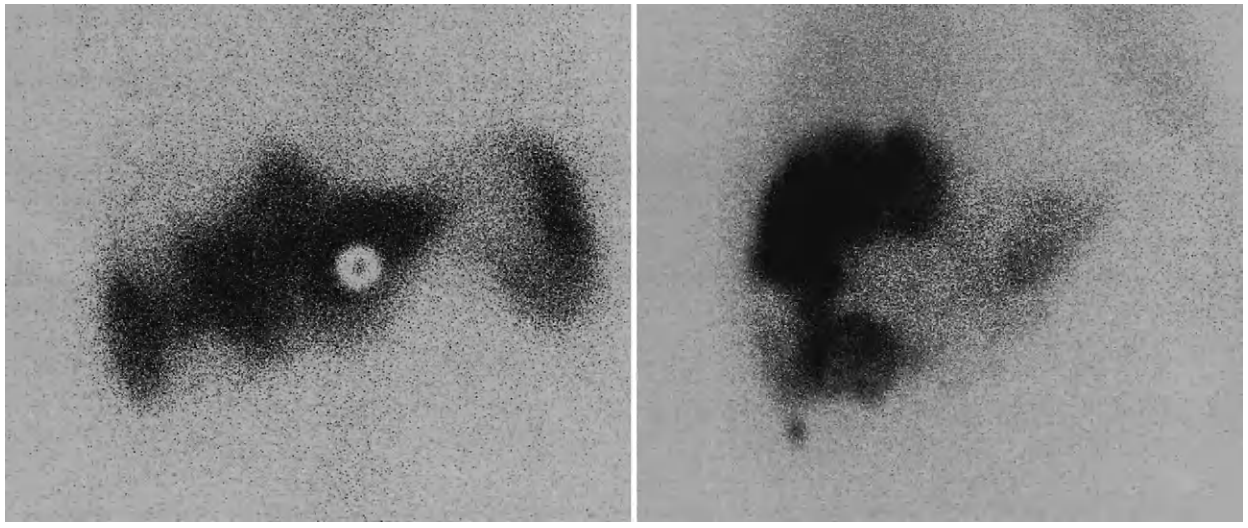


FIGURE 15.40. Image of a patient with a lesion in the upper right liver shows reduced uptake of sulfur colloid (*left*) but relative hyperperfusion (*right*) taken after injection of macroaggregated intraarterially. This case shows the principle of metastases being supplied by the hepatic artery rather than by the portal vein. The *inferior black dot* is an umbilical marker; the upper "cold" dot is an epigastric marker.

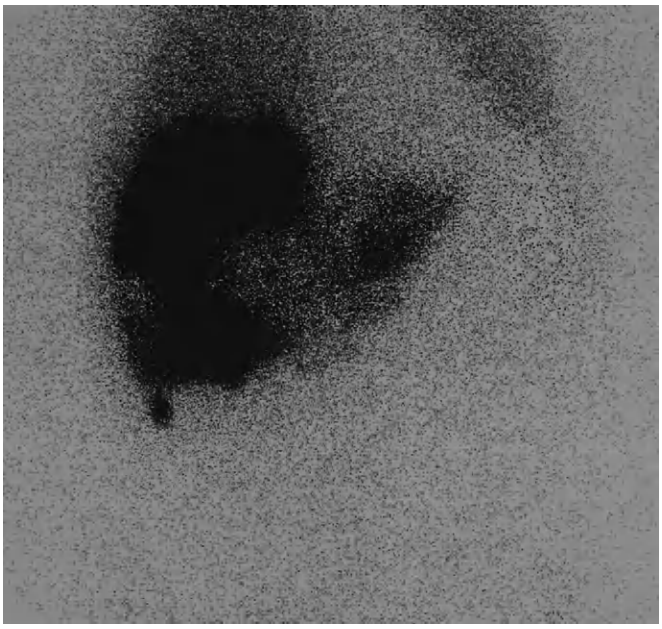


FIGURE 15.41. Same patient as in Figure 15.40. The window and level of display are "wound up," showing hepatopulmonary shunting.

inaccurately. Hepatic delivery of β-particle–emitting radiopharmaceuticals, such as ^{90}Yt- or ^{131}In-labeled microspheres, has been associated with improved median survival and reductions in tumor markers (Lau et al, 1994).

SUMMARY

Nuclear medicine is a diverse specialty. The tracer principle has been adapted to provide diagnostic information in the preoperative and postoperative setting and toward the therapeutic administration of radiopharmaceuticals. Hepatobiliary scintigraphy plays a vital role in the noninvasive assessment of patients with acute and chronic right upper quadrant pain and in the assessment of biliary dynamics in patients after biliary tract intervention. FDG PET-CT has become a mainstream tool in the diagnosis of metastatic disease in patients with cancer, and it shows great promise in the assessment of response to treatment. The integration of FDG PET-CT information into treatment assessment is currently occurring and should lead to more appropriate management, as treatment algorithms become more refined over time. Other nuclear medicine techniques, such as receptor imaging and therapy, have a niche in the planning and follow-up of patients with gastroenteropancreatic neuroendocrine tumors.

References are available at expertconsult.com.

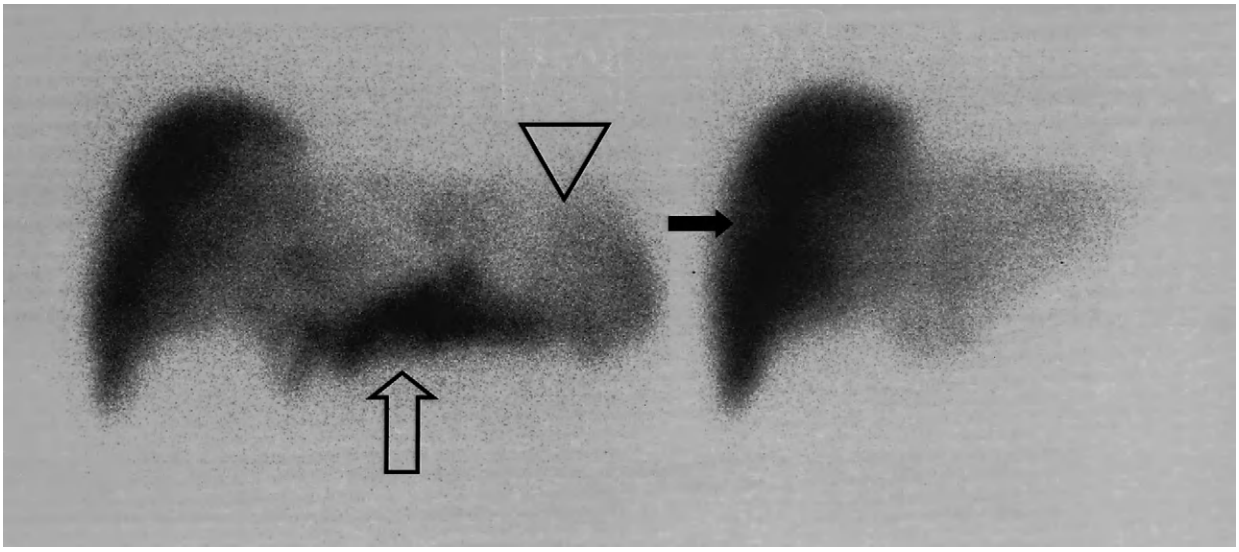


FIGURE 15.42. This study shows perfusion of the pancreas and spleen that was corrected with repositioning of the hepatic arterial catheter. The images to the right were acquired after the injection of ^{99m}Tc–macroaggregated albumin into the hepatic artery catheter, and they show aberrant perfusion of the pancreas (*open arrow*) and the spleen (*arrowhead*). After repositioning of the catheter, the metastasis can be seen in the right lobe of the liver (*solid arrow*) with no extrahepatic perfusion.

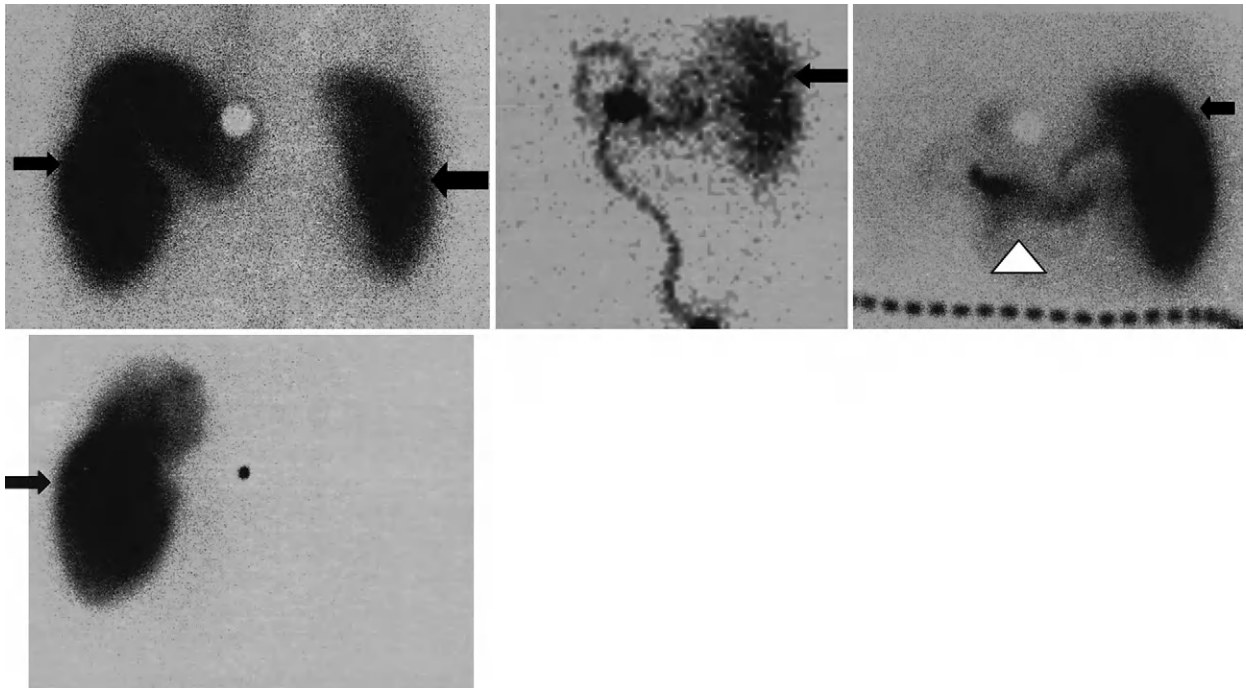


FIGURE 15.43. Composite anterior projection images. ^{99m}Tc–sulfur colloid images (*top left panel*) and perfusion phase of hepatic pump study with ^{99m}Tc–macroaggregated albumin (*top center panel*) are shown. Top right panel shows delayed pump study showing perfusion of pancreas and spleen, and the bottom left panel shows perfusion of the liver after repositioning of the arterial catheter.

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CHAPTER 16

Computed tomography of the liver, biliary tract, and pancreas

Corinne Winston and Jerrold Teitcher

IMAGING OVERVIEW

Technologic advances have dramatically expanded the role of computed tomography (CT) in hepatobiliary and pancreatic imaging. New developments in CT technology, image display, and three-dimensional postprocessing have broadened the role of CT in patients with hepatobiliary and pancreatic disease. The role of imaging has extended beyond lesion detection to vascular mapping, assessment of tumor vascularity, and surgical planning (see Chapter 90). As technology continues to be refined, CT remains the main imaging modality for evaluating the liver and pancreas.

TECHNICAL ADVANCES

Major innovations have occurred in image acquisition (CT scanning), image viewing (picture archiving and communication system [PACS]), and three-dimensional post processing. Helical (spiral) CT, developed in the late 1980s, uses continuous tube rotation to acquire volumetric imaging data, while the patient moves through the gantry in a single breath hold. The data can be reconstructed into standard axial images or manipulated further to display two-dimensional or three-dimensional reconstructions of the area of interest. An important advantage of helical CT is the ability to reconstruct the data acquired on the initial scan at small intervals; this improves diagnostic accuracy by reducing partial volume artifact. Another important advantage of helical CT is reduced scan time, which reduces respiratory misregistration and allows imaging to be performed during the different phases of parenchymal enhancement after intravenous administration of a contrast agent. Helical CT makes it possible to image the liver in the hepatic arterial, portal venous, and delayed phases of enhancement, improving the detection and characterization of focal hepatic lesions.

Helical CT has undergone another major advance with the development of a new class of multidetector array scanners (MDCTs), which use a substantially greater percentage of the x-rays emitted from the tube cathode. This improves tube efficiency and permits even faster scanning. Multiple acquisitions through the liver may be obtained in a single breath hold to obtain images in the early and late arterial phases. Early arterial phase images are useful to identify variant vascular anatomy before hepatic arterial embolization, prior to placement of a hepatic arterial chemoinfusion pump, or before hepatic resection. Late arterial phase images are useful in the detection of hypervascular hepatic lesions. MDCT also allows thinner collimation (submillimeter), which improves resolution and increases detection of small hepatic lesions by 46% (Weg et al, 1998).

High-resolution images are particularly useful for CT angiography, which is used not only to determine the arterial supply to a tumor but also to assess tumor involvement along the major arteries and to delineate variant arterial anatomy. Another major advantage of MDCT is the ability to change the slice thickness of an image after it is taken. As long as the raw data are stored, the technician can retrospectively create a thinner slice and improve resolution in the craniocaudad plane.

Since the initial introduction of MDCT, technologic advances have been made to increase the number of detectors. Early MDCT scanners had four detectors accruing information per tube rotation, but more recent MDCT scanners have 64 detectors, and images now can be acquired with unprecedented speed. The increase in the number of detectors also results in a decrease in the minimum slice thickness and improved resolution in the craniocaudad plane, referred to as the *z-axis*. The improved resolution in the *z*-axis allows for the creation of isotropic *voxels*, volumes of imaging data that are equal in all dimensions, for more accurate three-dimensional images.

The introduction of PACS technology also has revolutionized CT image display. PACS permits storage, rapid retrieval, and display of CT data and provides a convenient venue for electronic distribution and review of images. PACS workstations have improved markedly the radiologist's ability to interpret the multiple images acquired for each examination. It is now possible to view images by scrolling rapidly through areas of interest. Interactive image viewing in the cine mode facilitates tracing tubular structures that course through different planes, such as the dilated biliary tree and hepatic arteries. The ability to magnify images and alter image contrast also greatly facilitates image interpretation. Ready access to recent and prior CT images is provided when PACS workstations are placed throughout the hospital, in clinical offices, and in the operating room.

CT data are acquired in volumetric data sets that can be postprocessed on a three-dimensional workstation. The generation of 16-slice MDCT scanners acquires isotropic voxels that are essentially perfect cubes of information, resulting in three-dimensional models without image distortion. Several different types of postprocessing techniques are available (Salgado et al, 2003). Maximum intensity projection (MIP) images depict only the brightest structures within the volume of data (Johnson et al, 1996, 2003; Magnusson et al, 1991; Rubin, 2003; Salgado et al, 2003; Zeman et al, 1994). When focusing on the liver in the portal venous phase of contrast enhancement, MIP images produce a concise depiction of portal venous and hepatic venous anatomy (Fig. 16.1). Volume-rendered reconstructions provide a lifelike three-dimensional model of complex anatomy that can be rotated in any direction (Fig. 16.2; Johnson et al, 1996, 2003; Rubin, 2003; Zeman et al, 1994). This type of

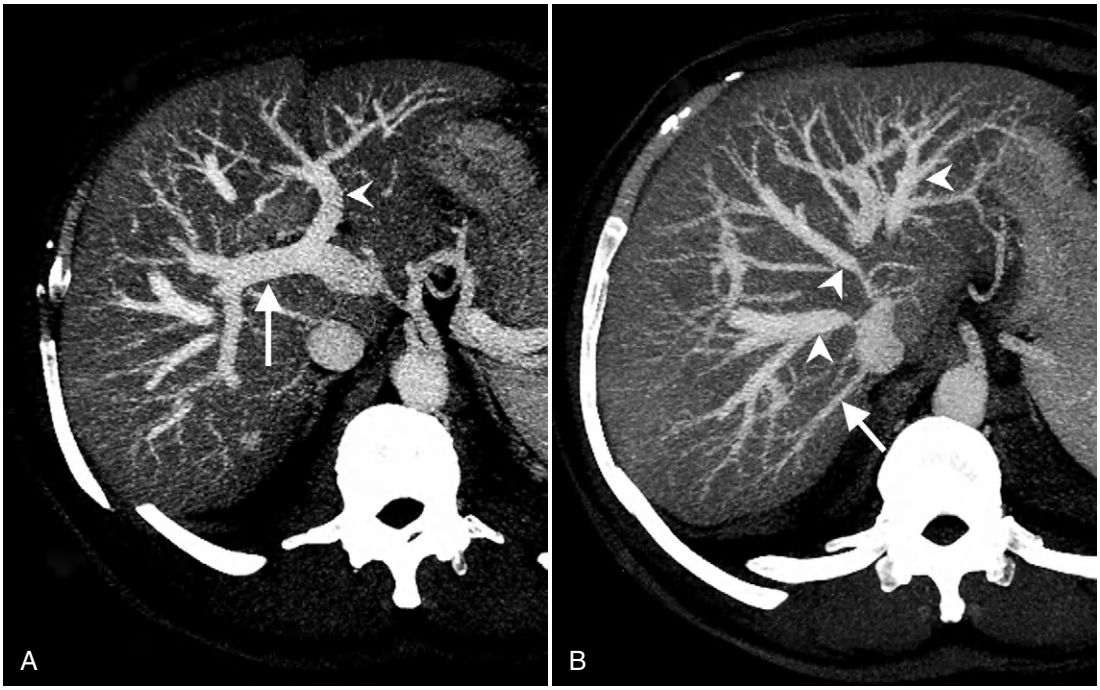


FIGURE 16.1. **A,** Thick-slab maximum intensity projection (MIP) through the portal veins reveals standard bifurcation of the main portal vein into the right (*arrow*) and left (*arrowhead*) portal veins. The anterior and posterior sectoral branches of the right portal vein are evident, as are the medial and lateral sectoral branches of the left portal vein. **B,** Thick-slab MIP image through the hepatic veins reveals the three major hepatic veins (*arrowheads*) and an accessory hepatic vein (*arrow*) draining into the inferior vena cava.

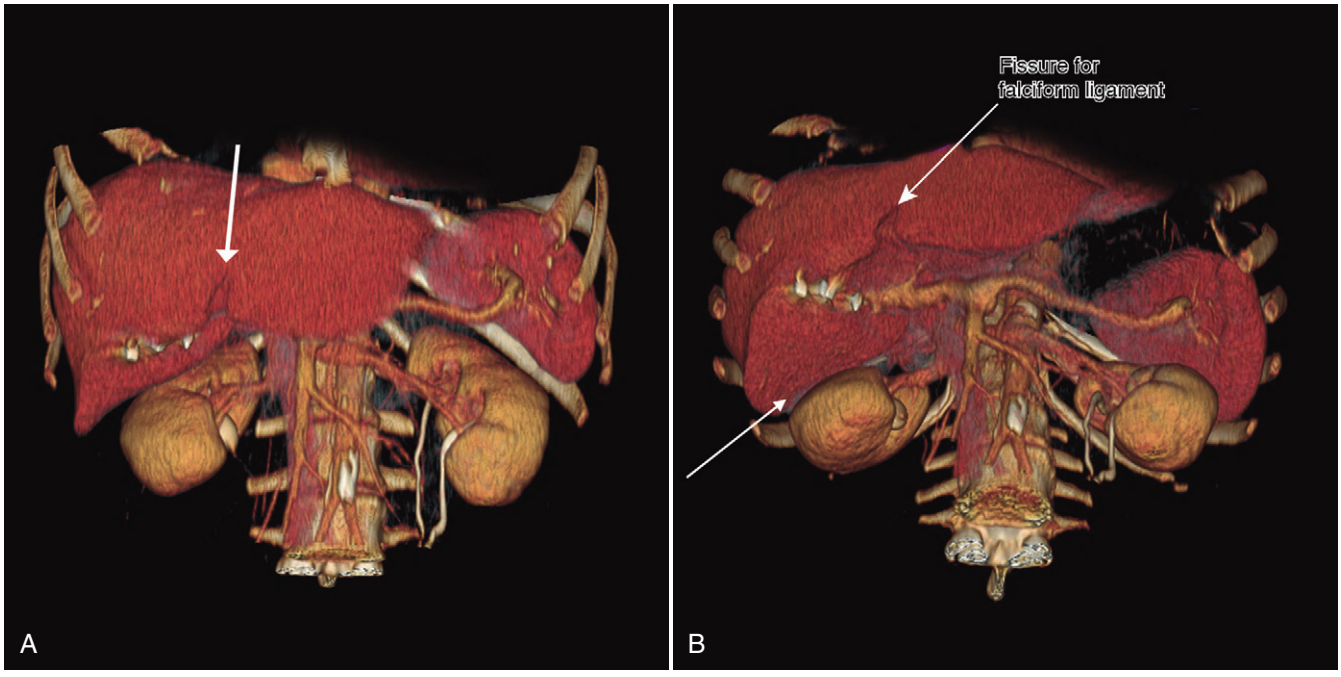


FIGURE 16.2. **A,** Volume-rendered three-dimensional (3D) image of the external contour of the liver created from contrast-enhanced axial computed tomographic data. Note the fissure for the falciform ligament seen en face (*arrow*). **B,** Volume-rendered 3D image of the same patient rotated upward reveals the undersurface of the liver. Note the surgical clips in the gallbladder fossa and the bare area of the liver (*short arrow*).

reformatting transforms the numerous axial images into an interactive three-dimensional model. Hepatic arterial anatomy can be displayed with a three-dimensional model composed of reconstructed axial images (Fig. 16.3). The relationship of tortuous vessels to the hepatic parenchyma and lobar anatomy can be depicted clearly (Fig. 16.4). It is also possible to view a rotating model that depicts the relationship of a mass to the adjacent vessels from any angle to help the surgeon conceptualize preoperatively what would be encountered at surgery (Fig. 16.5; see Chapters 90 and 92).

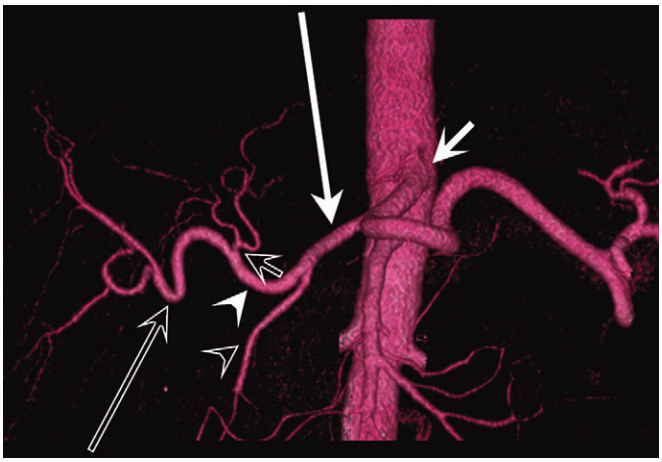


FIGURE 16.3. Classic arterial anatomy. Volume-rendered three-dimensional image created from axial contrast-enhanced computed tomographic data reveals classic branching arterial anatomy. The celiac axis (*small solid arrow*) trifurcates into the splenic artery, common hepatic artery (CHA; *long solid arrow*), and left gastric artery. The CHA gives rise to the gastroduodenal artery (*open arrowhead*) and the proper hepatic artery (*solid arrowhead*). The right hepatic artery (*long open arrow*) and the left hepatic artery (*small open arrow*) originate from the proper hepatic artery.



FIGURE 16.4. Three-dimensional reformatted image reveals the course of the left portal vein, which ascends in the umbilical fissure before looping anteriorly and inferiorly (*short arrow*) to branch into the medial (*arrowhead*) and lateral (*long arrow*) sectoral branches.

ROLE OF COMPUTED TOMOGRAPHY IN LIVER AND BILIARY IMAGING

Detailed knowledge of anatomy, patterns of disease spread, and an understanding of the surgical relevance of imaging findings are essential to the interpretation of hepatobiliary imaging studies. Although the primary goal of CT imaging is lesion detection and characterization, CT also plays a vital role in the triage of patients with malignant disease to different treatment options. Determination of the local extent of tumor, lymphadenopathy, carcinomatosis, and extraabdominal disease is crucial in staging malignant disease.

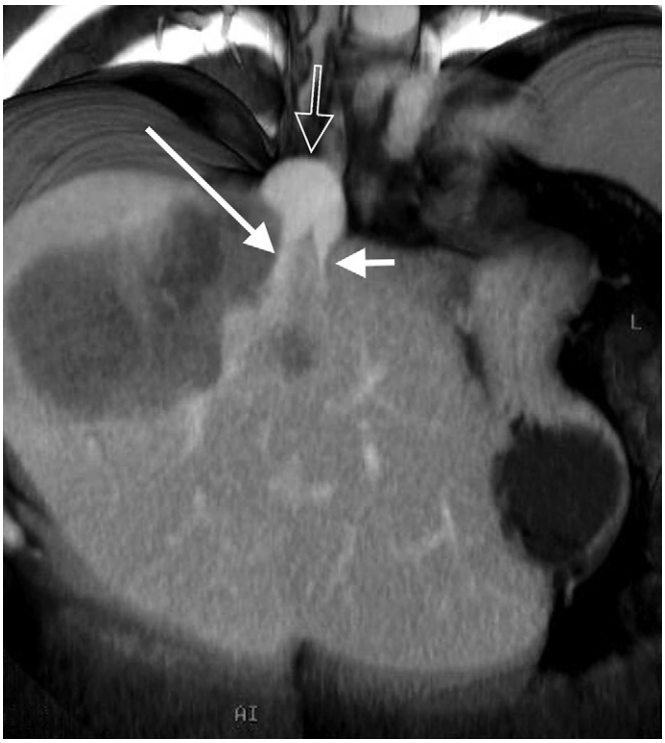


FIGURE 16.5. Volume-rendered three-dimensional image of the liver from above reveals a large colorectal metastasis involving the right lobe with extension into the medial sector of the left lobe. The mass is in continuity with the middle hepatic vein (*long arrow*) at its confluence with the inferior vena cava (IVC; *open arrow*). The middle hepatic vein and left hepatic vein (*short arrow*) drain separately into the IVC.

CT is particularly valuable in planning for hepatic resection. Using the contrast-enhanced portal and hepatic veins as anatomic landmarks, the radiologist can localize tumors into the specific hepatic segments (Fig. 16.6). The proximity of tumor to the major portal pedicles, hepatic veins, and inferior vena cava (IVC) is evident, and this information determines the extent of hepatic resection required to achieve clear surgical margins (Figs 16.7 and 16.8). CT can also help predict whether sufficient hepatic reserve will exist after hepatic resection (see Chapters 90 and 92). Hepatic atrophy (Fig. 16.9), resulting from biliary obstruction with or without portal venous occlusion, and compensatory hypertrophy can be identified on CT. Fatty infiltration and hepatic cirrhosis, processes that affect the remnant liver's ability to regenerate, are apparent. CT angiography can identify the arterial supply to tumor and can delineate the extent of tumor involvement along the arteries.

An important additional role of CT angiography for evaluating patients with hepatobiliary malignancy is the delineation of variant arterial anatomy, which occurs in more than half of the population (Michels, 1955). Visualization of the surgical field often can be limited in patients with hepatobiliary malignancy, especially with prior surgery, if the patient is obese, or when local inflammation is present, such as that accompanying a biliary stent. Preoperative knowledge of variant anatomy can assist in surgical planning (see Chapter 90 and 92), facilitate surgical dissection, and help avoid iatrogenic injury (Winston et al, 2007). CT angiography is a noninvasive alternative to direct catheter angiography for preoperative planning before

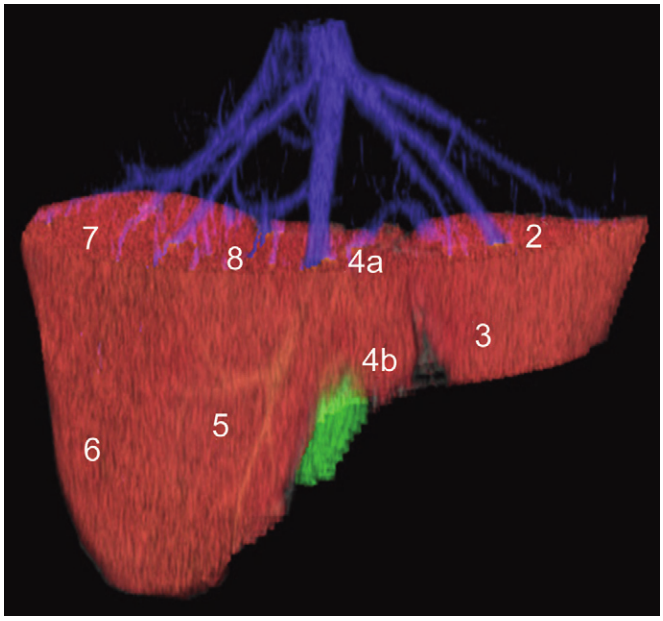


FIGURE 16.6. Volume-rendered three-dimensional model of the liver created from axially acquired computed tomographic data. The superior portion of the hepatic parenchyma has been removed to reveal the course of the hepatic veins through the liver substance as they drain into the inferior vena cava. The gallbladder is depicted in green, and hepatic segments are indicated.

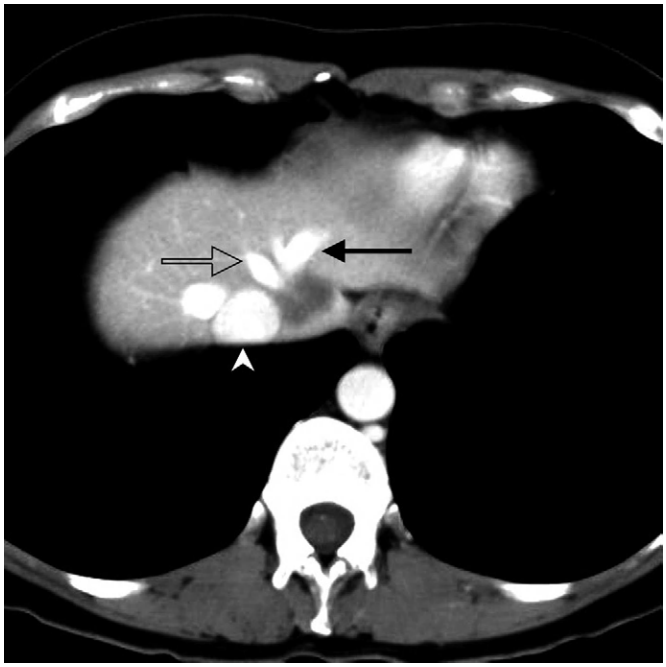


FIGURE 16.7. Contrast-enhanced computed tomography reveals a small malignant lesion in segment I abutting the middle hepatic vein (*open arrow*) and left hepatic vein (*solid arrow*) at their confluence with the inferior vena cava (*arrowhead*). The location of this small mass mandates a large hepatic resection to achieve clear surgical margins.

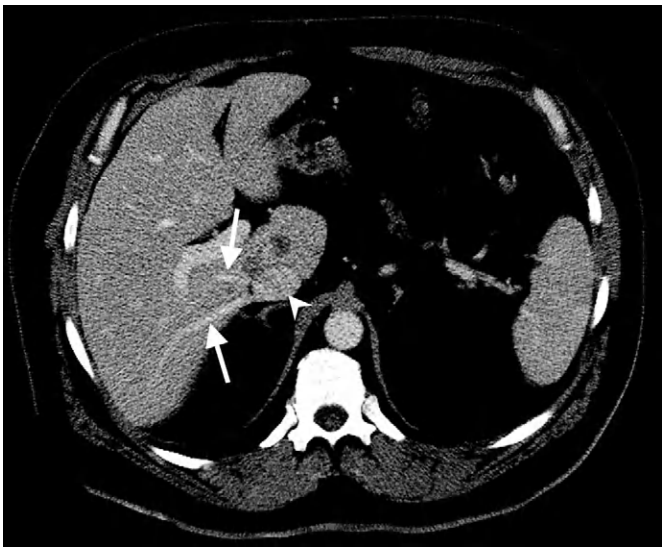


FIGURE 16.8. Contrast-enhanced computed tomography reveals a segment I mass that abuts the inferior vena cava (IVC; *arrowhead*). Two accessory hepatic veins (*arrows*) are draining into the IVC.

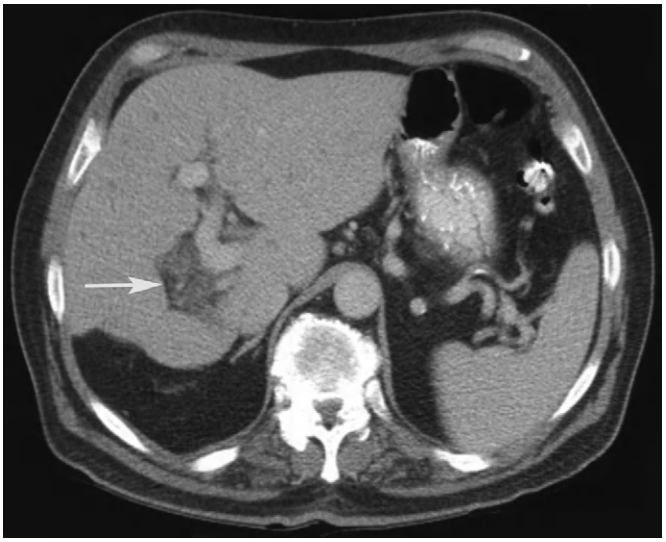


FIGURE 16.9. Right lobe atrophy as a result of an infiltrative tumor involving the right portal pedicle (*arrow*). Note the counterclockwise rotation of the porta hepatis.

placement of an intraarterial chemoinfusion pump (Kapoor et al, 2003; see Chapter 86).

The trend in surgery is toward minimally invasive procedures, and diagnostic radiology has evolved accordingly. Vascular mapping, now performed with CT, was previously possible only using invasive procedures. Continued advances in imaging and three-dimensional postprocessing undoubtedly will broaden the role of radiology in the diagnosis and treatment of patients with hepatobiliary disease.

Technique

State-of-the-art CT evaluation of the liver for hepatic resection includes contrast-enhanced CT and CT angiography. The

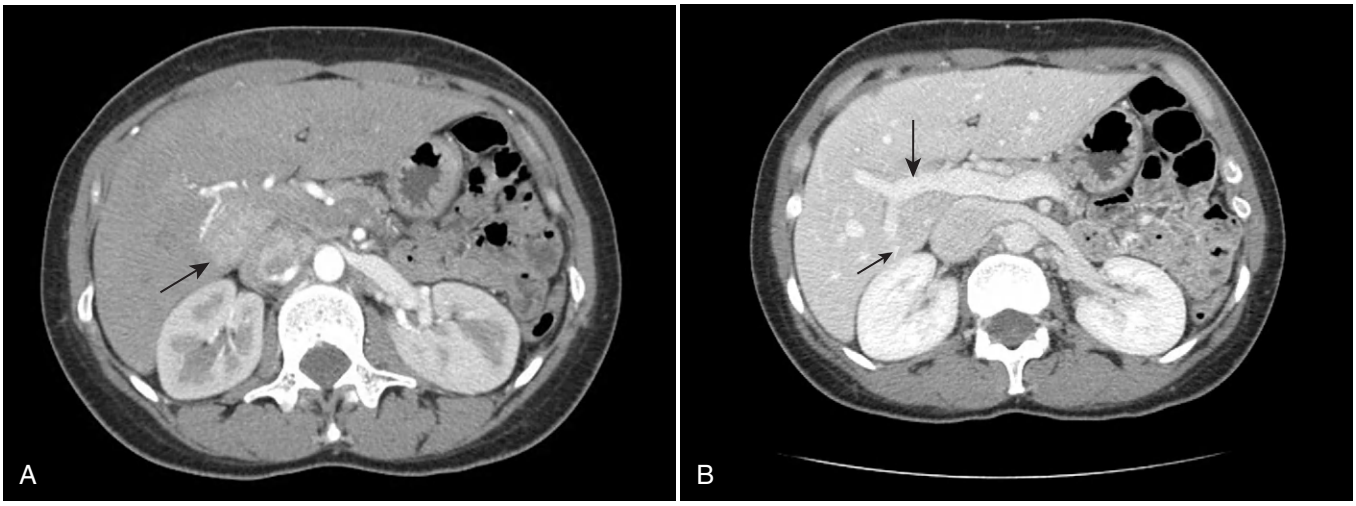


FIGURE 16.10. A, Arterial phase image through the inferior right hepatic lobe reveals branches of the right hepatic artery. Faint enhancement of a hypervascular mass is seen in segment VI, which proved to be focal nodular hyperplasia (*arrow*). **B,** Portal venous phase image through the same level reveals enhancement of the right portal vein (*long arrow*) and the sectoral branches. The mass (*short arrow*) is nearly hypointense to the liver.

specific protocols vary with the specific tumor type being evaluated, but most hepatic neoplasms are low attenuation on contrast-enhanced CT and are evaluated best during the portal venous phase of imaging. Hypervascular neoplasms, such as hepatocellular carcinoma (HCC) and metastatic neuroendocrine tumors, are evaluated using a triphasic protocol including non–contrast-enhanced CT, hepatic arterial phase images, and portal venous phase images (Fig. 16.10). Oral contrast medium is administered routinely for CT, but water is substituted when CT angiography is performed. Routine hepatic parenchymal imaging generally is performed using 5-mm slices.

Non–Contrast-Enhanced Computed Tomography of the Liver

The attenuation value of the normal liver typically varies between 54 and 60 Hounsfield units (HU), which is approximately 8 HU greater than that of the spleen, owing to glycogen and iron stores in the liver. Increased density may be seen in hemochromatosis, glycogen storage disease, Wilson disease, β-thalassemia, sickle cell disease, and with certain drugs (amiodarone, cisplatin). A false appearance of increased hepatic density may occur in anemia, in which the decreased attenuation of the blood pool gives the impression of increased hepatic density relative to the intrahepatic vessels. Decreased hepatic density most frequently is related to fatty infiltration of the liver or occasionally secondary to hepatic edema. Noncontrast CT is useful for detecting diffuse abnormalities, such as hemochromatosis or fatty infiltration (Figs. 16.11 and 16.12), in which the attenuation of the liver is increased (hemochromatosis) or decreased (fatty infiltration). Both of these processes may be obscured by the administration of intravascular contrast

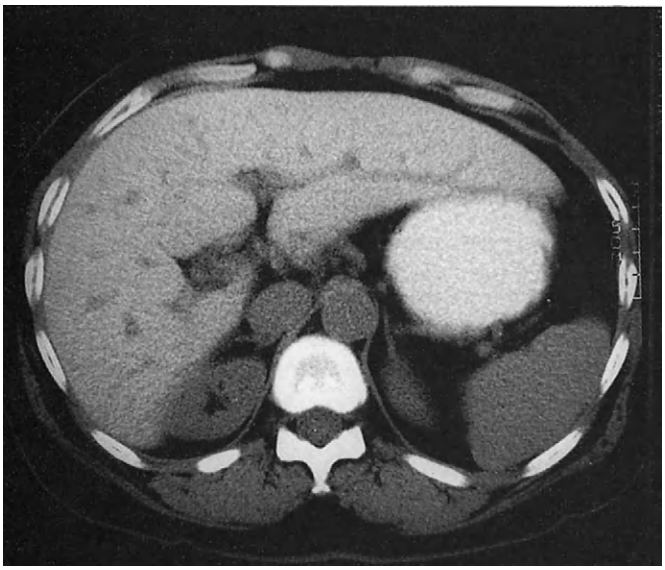


FIGURE 16.11. Nonenhanced computed tomography through the liver of a patient with hemochromatosis shows diffuse increased attenuation of the liver compared with the spleen.



FIGURE 16.12. Nonenhanced computed tomography through the liver of a patient with fatty infiltration shows low attenuation of the hepatic parenchyma compared with the hepatic blood vessels and liver capsule.

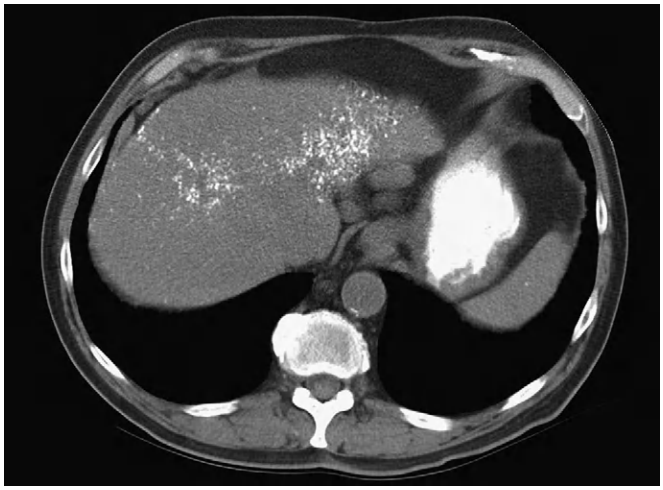


FIGURE 16.13. Unenhanced computed tomography reveals numerous calcifications in a patient with amyloid.

medium. Hemorrhage or faint calcifications also are better visualized on unenhanced CT (Fig. 16.13).

Hepatic neoplasms usually have a high water content, resulting in relative hypoattenuation compared with liver parenchyma. The portal veins and bile ducts also are of lower attenuation than liver parenchyma, and a vessel running vertically through a section may mimic a small tumor, leading to errors in diagnosis. On unenhanced studies, the attenuation difference between liver and tumor may be subtle and may require viewing at very narrow window widths to allow focal lesion detection, but much higher lesion-to-liver attenuation difference can be achieved by the administration of intravenous contrast medium (Tidebrant et al, 1990).

Contrast-Enhanced Computed Tomography of the Liver

The administration of an iodinated contrast agent serves many purposes in hepatic CT imaging, including improved lesion detection and characterization and better vascular mapping. Because a precise rate of injection is essential to image quality, a dedicated power injector is required. Different methods are commercially available to determine the time of maximal arterial enhancement for each patient, depending on factors such as cardiac function and state of hydration (Sica et al, 2000).

Lesion conspicuity is enhanced when there is maximal contrast between a lesion and the surrounding parenchyma. The liver receives 75% to 80% of its blood supply from the portal venous system and only 20% to 25% from the hepatic artery; however, the majority of liver tumors receive most of their blood supply from the hepatic arterial system (Honda et al, 1992). The noncirrhotic liver displays maximal contrast enhancement at approximately 70 seconds from the start of the intravenous administration of contrast medium. At this time, referred to as the *portal venous phase* of enhancement, maximal contrast between a liver lesion and the surrounding parenchyma is seen with clear delineation of the portal and hepatic veins. Routine evaluation of the liver should be performed using portal venous phase imaging.

The pattern of contrast enhancement also is important for lesion characterization. Certain lesions, such as focal nodular hyperplasia (FNH) and hemangiomata (discussed in greater detail later in this chapter), have specific patterns of enhancement on arterial phase and portal venous phase images. Hypervascular malignant neoplasms, such as HCC and metastatic neuroendocrine carcinoma, display prominent contrast enhancement and increased lesion conspicuity on the arterial phase images, but these lesions may become isodense to the remaining liver and and may be invisible on the portal venous phase images (Fig. 16.14). When HCC or neuroendocrine mestastases are suspected, arterial phase images should be acquired in addition to the routine portal venous phase images.

Computed Tomographic Angiographic of the Liver

MDCT scanners can acquire high-resolution images (<1-mm slice thickness) of the aorta and hepatic arterial anatomy, referred to as *early arterial phase images*. The intravenous administration of contrast material is performed using a high injection rate of 4 to 5 mL/s to provide maximal contrast enhancement of the arteries, before opacification of the veins or abdominal organs. The same volume of intravenous contrast material is

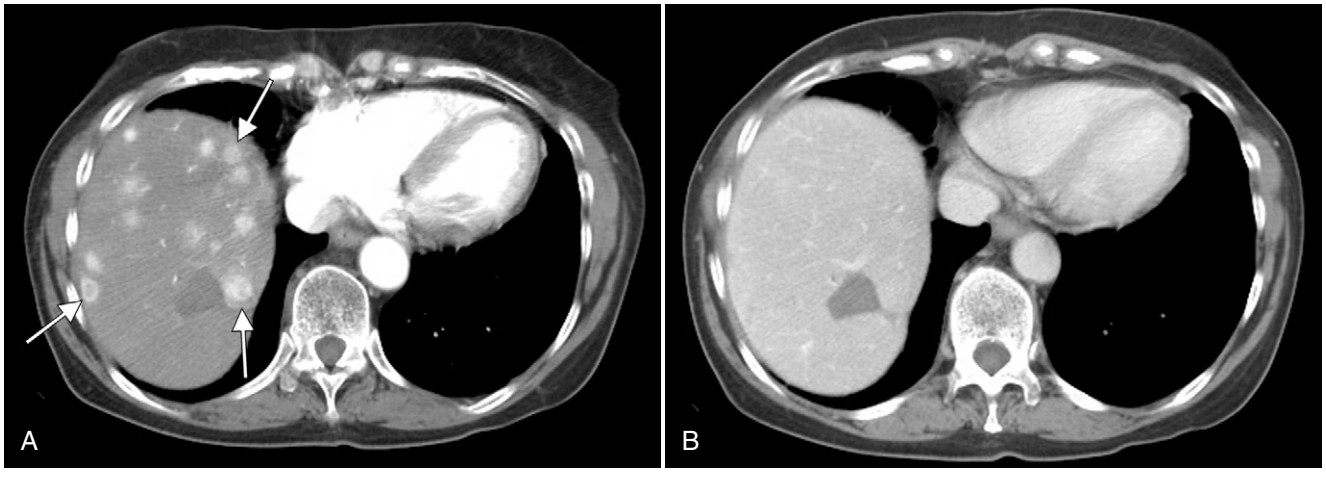


FIGURE 16.14. Arterial and portal venous phase images as part of a triphasic examination in a patient with metastatic renal cell carcinoma. **A,** Late arterial phase image reveals multiple hypervascular enhancing foci of metastatic renal cell carcinoma (*arrows*). **B,** Portal venous phase image at the same level does not reveal the numerous masses. The low-attenuation lesion represents a partially treated hypoattenuating metastasis.

administered as that for routine abdominal CT. Water is administered as a negative contrast agent to facilitate three-dimensional postprocessing. Additional late arterial phase images can be obtained through the hepatic parenchyma in the same breath hold in patients with suspected hypervascular lesions. A major attribute of CT angiography is that it is performed as an adjunct to a routine CT scan. CT of the chest, abdomen, and pelvis can be performed during the same examination to allow for a staging examination in addition to vascular mapping.

Lesion Evaluation

In a patient with multiple hepatic lesions, each lesion should be evaluated independently, because benign and malignant lesions may coexist (Fig. 16.15). Mistaking an incidental benign lesion for a malignant mass has clear and potentially important implications in patient management, perhaps leading to unnecessary invasive procedures or resulting in a diagnosis of metastatic disease that alters treatment recommendations. When assessing lesion size for treatment response on serial CT scans, it is important to compare serial, unenhanced CT scans with unenhanced CT scans and to also compare contrast-enhanced scans with contrast-enhanced scans. Nazarian and colleagues (1999) showed that colorectal metastases appeared different in size on pre–contrast-enhanced and post–contrast-enhanced CT scans obtained as part of the same examination. On average, hepatic metastases from colorectal carcinoma appeared significantly smaller after contrast media administration (Nazarian et al, 1999).

Anatomy

Gross Morphology

Three scissurae interrupt the surface of the liver and help define its segmentation (see Chapter 1B). The interlobar fissure is an incomplete structure that defines the inferior separation between the right and the left liver; the scissura here is generally difficult to identify on axial CT, but its position may be estimated, because it is orientated in a vertical plane defined by the gallbladder fossa inferiorly (Fig. 16.16) and the middle hepatic vein superiorly. The gallbladder lies in the main interlobar scissura on the inferior surface of the liver. Three-dimensional reformatting of axial CT data provides a clear depiction of the interlobar scissura and its relationship to the hepatic segments (see Fig. 16.6).

Slightly to the right of midline, toward the patient's left side, the anteroinferior portion of the diaphragmatic surface of the liver is notched by the fissure for the ligamentum teres, or *umbilical fissure,* which defines the inferior border between the medial and lateral segments of the left liver. The ligamentum teres passes through this fissure and usually is surrounded by a small amount of fat. When the ligamentum teres passes out of the liver ventrally, it is located in the free edge of the falciform ligament. The third fissure is present at the point of contact between the lateral segments of the left hepatic lobe and the caudate lobe. This is the fissure for the ligamentum venosum, which is in continuity with the umbilical fissure.

Segmental Anatomy

The segmental anatomy of the liver is based on both the hepatic venous outflow and the inflow pedicles. A functional scheme that corresponds to the liver anatomy and is useful surgically has been described (Bismuth, 1982). The three main hepatic veins divide the liver into four sectors, each of which is independent in that it receives a separate portal venous and hepatic arterial supply and is drained by a separate bile duct. The middle hepatic vein divides the liver into a right and left liver. The right liver is divided into two sectors by the right hepatic vein, and the left liver is divided similarly by the left hepatic vein. Because axial CT readily shows the course of all three major hepatic veins on contrast-enhanced scans obtained near the diaphragm, the major hepatic sectors are easy to identify at this level. The inferior boundary between the anterior and posterior sectors of the right lobe has to be estimated by extrapolating the line of the right hepatic vein onto lower sections. An imaginary line drawn between the IVC and the gallbladder divides the right and left liver on caudal sections and corresponds to the line of the middle hepatic vein. Three-dimensional reformatting can assist in localization of the hepatic segments (see Fig. 16.6). The fissure for the ligamentum teres divides the medial and lateral segments of the left liver and corresponds to the line of the left hepatic vein. The anterior and posterior sectors of the right lobe are subdivided into inferior (V and VI) and superior (VIII and VII) segments. The right portal vein runs horizontally as it enters the right liver, and this level demarcates the anterior and posterior sectors.

Vascular Anatomy

In classic arterial anatomy (see Chapter 1B), the celiac axis gives rise to the common hepatic artery, which bifurcates into the proper hepatic artery and the gastroduodenal artery (see Fig. 16.3). The proper hepatic artery divides into the right and left branches before entering the liver, but the point at which the proper hepatic artery gives rise to the left and right hepatic arteries varies. Although classic arterial anatomy is the most common pattern seen, variant hepatic and celiac arterial anatomy has been reported in 55% of patients based on initial cadaveric dissections by Michels (1955). Many of these variants have significance for preoperative planning and surgical management. Preoperative knowledge of variant anatomy can assist in selection of treatment options and in surgical planning, and

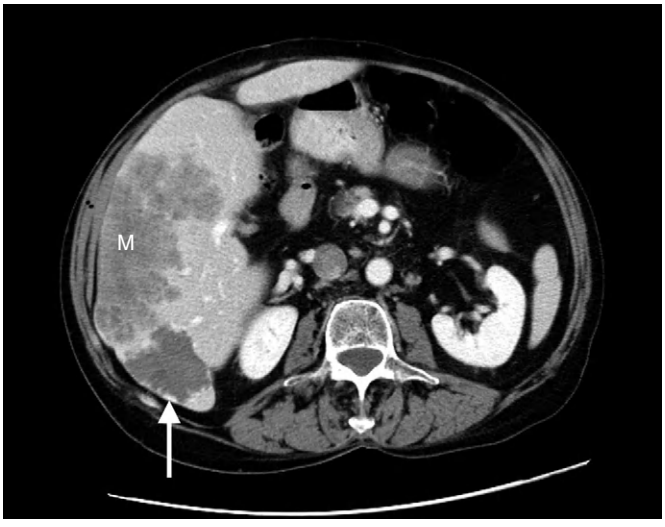


FIGURE 16.15. Metastatic disease (*M*) adjacent to a hemangioma. Note the peripheral nodular, clumplike enhancement (*arrow*) within the hemangioma.

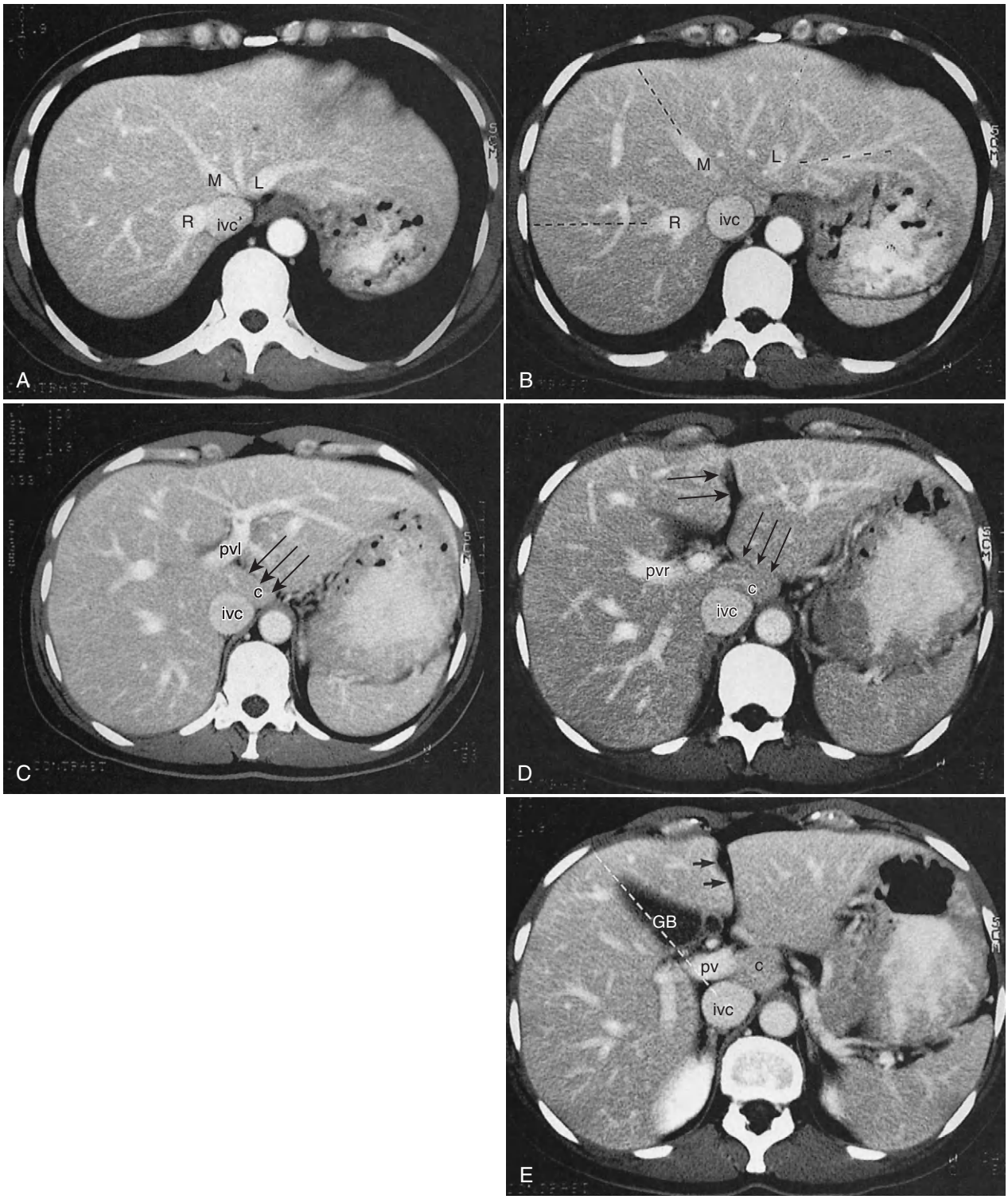


FIGURE 16.16. Normal hepatic segmental and vascular anatomy on computed tomography. **A,** On cephalad sections, the three hepatic veins are seen to enter the inferior vena cava (*ivc*). **B,** The lines of the hepatic veins divide the liver into sectors. The right hepatic vein divides the right liver into anterior and posterior sectors; the middle hepatic vein separates the right from the left liver and represents the line of the interlobar scissura; the left hepatic vein separates segments II and III of the left lobe. **C,** Approaching the midpoint of the liver, the left portal vein (*pvl*) is seen. The fissure for the ligamentum venosum (*arrows*) divides the caudate lobe (*c*) from the left lateral segments. **D,** The next section shows the horizontal portion of the right portal vein (*pvr*). The fissure for the ligamentum teres is now seen (*large arrows*); this structure divides the lateral segments of the left liver from the caudate lobe (*c*), segment IV. **E,** On the last section, the gallbladder (*GB*) has come into view; a line drawn along the axis of the gallbladder to the IVC represents the inferior extent of the interlobar scissura. *R,* right hepatic vein; *M,* middle hepatic vein; *L,* left hepatic vein.

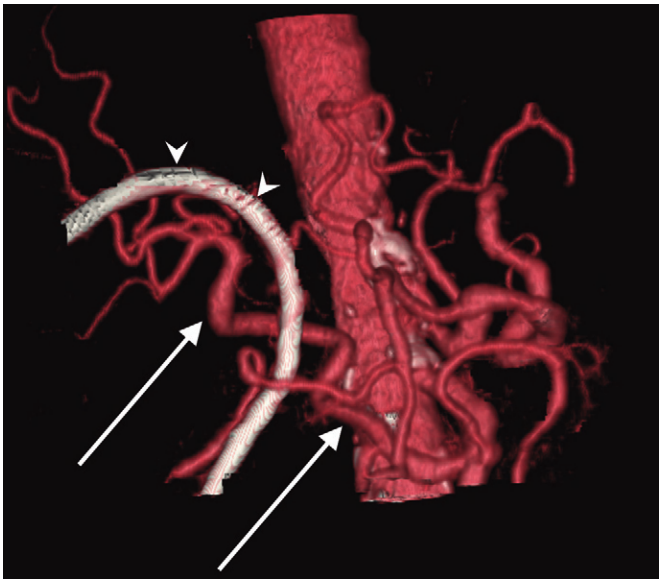


FIGURE 16.17. Three-dimensional volume-rendered computed tomographic angiogram reveals a replaced right hepatic artery (*arrows*) originating from the superior mesenteric artery. The right hepatic artery courses posterior to a stent in the common bile duct (*arrowheads*).

it facilitates surgical dissection and may help avoid iatrogenic injury (Figs. 16.17 and 16.18).

The portal vein originates at the junction of the splenic vein (SV) and superior mesenteric vein (SMV), immediately posterior to the neck of the pancreas. It courses toward the right and cephalad, as it enters the hepatoduodenal ligament. Within this ligament, the portal vein courses parallel to the proper hepatic artery, which lies on its anteromedial surface, and the common bile duct, which lies on its anterolateral surface. After entering the hepatic parenchyma, the portal vein branches to supply each portal sector (see Fig. 16.1A) and subsequently each segment. A spectrum of portal venous variants has been described, many of which have major implications for safe and efficacious hepatic resection and percutaneous hepatobiliary intervention. Covey and colleagues (2004) reported the presence of variant portal venous anatomy in 35% of a group of 200 patients studied. CT is ideally suited to display these variants, an awareness of which may help avoid iatrogenic injury (Fig. 16.19).

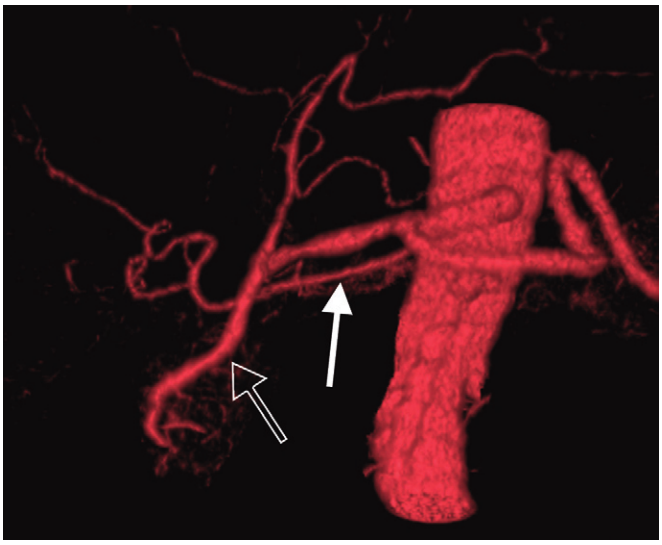


FIGURE 16.18. Three-dimensional volume-rendered computed tomographic angiogram reveals the right hepatic artery (*solid arrow*) originates from the celiac axis and courses posterior to the gastroduodenal artery (*open arrow*).

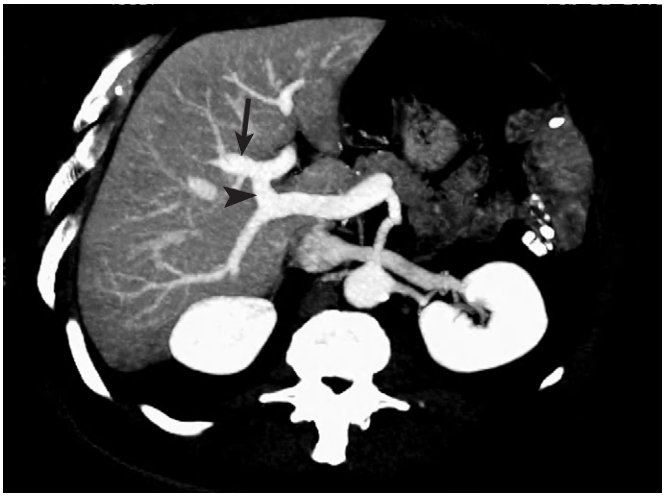


FIGURE 16.19. Variant portal venous anatomy. Thick-slab maximum intensity projection reveals that the portal venous branch perfusing the anterior sector of the right hepatic lobe (*arrow*) shares a common trunk with the left portal vein (*arrowhead*).

The hepatic veins course between the hepatic sectors and have a short extrahepatic course before joining the IVC (Blumgart et al, 2001). The right hepatic vein drains directly into the IVC, and the middle hepatic vein and left hepatic vein usually join before draining into the IVC. A variable number of retrohepatic veins drain from the posterior aspect of the liver into the IVC, and a large inferior right hepatic vein, referred to as an *accessory right hepatic vein,* may be present in some patients (see Fig. 16.1B).

Biliary Anatomy

The intrahepatic biliary tree branches in a fashion nearly identical to the portal system (Fig. 16.20; see Chapter 1B). The left and right hepatic ducts form the common hepatic duct, near the lateral margin of the main portal vein, near its junction with the right portal vein. The common hepatic duct continues inferiorly toward the left and posteriorly, and it maintains its anterolateral position with respect to the portal vein throughout its course within the hepatoduodenal ligament. It becomes retroperitoneal at the level of the head of the pancreas and occupies a position on the posterolateral surface of the pancreas, until it joins the pancreatic duct immediately before entering the ampulla of Vater. The confluence of the right and left hepatic ducts is often seen lying anterior to the portal venous confluence.

Visualization of the intrahepatic bile ducts with CT originally was considered to be evidence of biliary obstruction; but with newer scanners and thin collimation, peripheral bile ducts measuring 1 to 3 mm may be seen in normal subjects (Liddell et al, 1990). The common duct, which measures 3 to 6 mm in cross-sectional diameter, is seen as a circular structure of near-water density posterolateral to the head of the pancreas on a

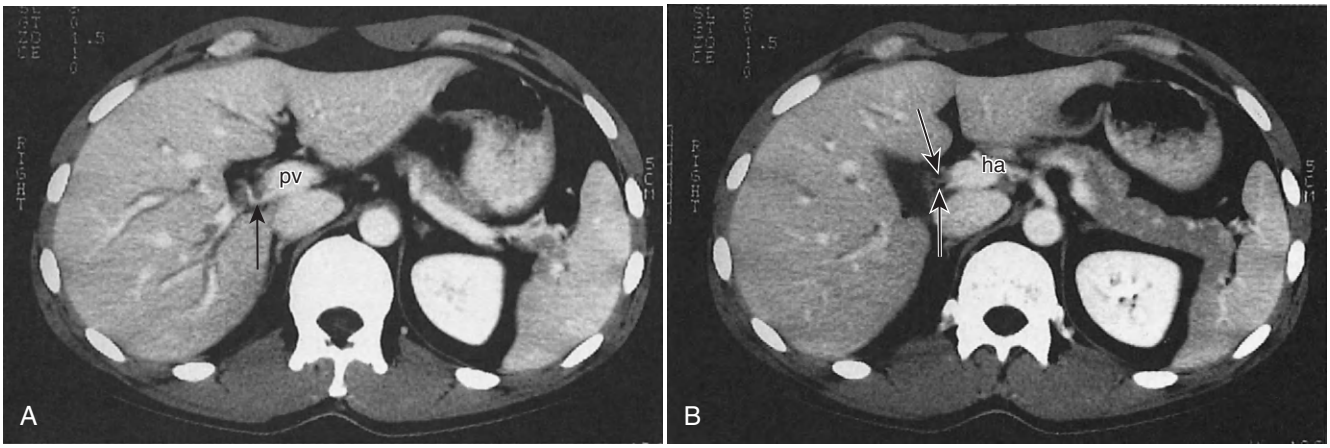


FIGURE 16.20. Contrast-enhanced computed tomography in a patient with a minimally dilated biliary system. **A,** The intrahepatic bile ducts are seen as branching, low-attenuation structures adjacent to the portal veins. At the porta hepatis, the hepatic artery (*arrow*) is seen to pass between the main portal vein (*pv*) and the common hepatic duct. **B,** A scan caudal to the porta hepatis shows the common hepatic duct and the cystic duct running adjacent to each other in the hepatoduodenal ligament (*arrows*). The hepatic artery (*ha*) is in a more medial position.

postcontrast scan. The CT diagnosis of biliary obstruction is based on the demonstration of dilated intrahepatic or extrahepatic bile ducts. Dilated intrahepatic ducts appear on CT as linear branching or circular structures of near-water density that enlarge as they approach the junction of the left and right hepatic ducts in the porta hepatis. The extrahepatic bile duct is considered unequivocally dilated if it is 9 mm or more in diameter; less than 7 mm is considered normal. High-resolution images and reformatting techniques allow for depiction of the biliary tree on CT that was once impossible (Fig. 16.21).

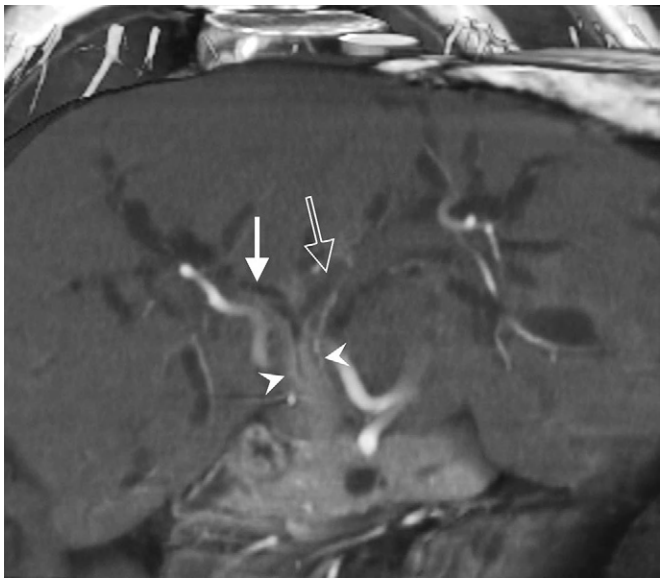


FIGURE 16.21. Coronal reformatted image of the confluence of the right (*solid arrow*) and left (*open arrow*) hepatic ducts reveals soft tissue thickening and enhancement along the common bile duct (*arrowheads*), reflecting recurrent gallbladder carcinoma in a patient after cholecystectomy. Note the bilobar intrahepatic biliary ductal dilation.

Although CT has proved to be accurate in establishing a diagnosis of biliary obstruction, a direct correlation between the caliber of the biliary tree and the presence of clinically significant obstruction has not been found. In patients with significant dilation of the biliary tree, in whom the obstruction is later relieved surgically or by spontaneous passage of a calculus, the bile duct may remain more dilated than normal for the remainder of the patient's life. In such patients, the CT findings may falsely suggest the presence of biliary obstruction. Likewise, a normal-caliber bile duct can be observed in the presence of a surgically correctable cause of jaundice. Intermittently obstructing calculi and subtle strictures of the extrahepatic duct may be present when the overall duct caliber is normal. When a discrepancy exists between clinical or biochemical evidence and the CT findings, magnetic resonance cholangiopancreatography (MRCP) or direct cholangiography by the percutaneous or endoscopic route should be performed to resolve the problem.

CT can also help ascertain the cause of obstruction in many cases. Although abrupt termination of the extrahepatic duct suggests a malignant process, smooth and gradual tapering of bile ducts favors benign disease. The use of water as a negative oral contrast agent aids in identification of small distal bile duct calculi.

Benign Tumors and Tumorlike Conditions of the Liver

Cyst (See Chapters 69 and 79)

Hepatic cysts are common and occurr in 2% to 7% of the population (Horton et al, 1999). Hepatic cysts may be either *congenital* or *acquired.* Congenital cysts are more common and are thought to be caused by a malformation of a bile duct that has lost its communication with the remainder of the biliary tree. Lined by a single layer of cuboidal or columnar epithelium that secretes fluid, the cyst fills with serous fluid (Blumgart et al, 2001). The acquired type of hepatic cyst is usually secondary to inflammation, trauma, or parasitic disease. Hepatic cysts typically are discovered incidentally and have no malignant potential.



FIGURE 16.22. Multiple simple hepatic cysts in a patient with polycystic kidneys.

At CT, a hepatic cyst is round or ovoid and sharply defined with an imperceptible wall; it shows water attenuation and does not enhance after administration of an intravenous contrast agent. Although small cysts do not affect the adjacent hepatic parenchyma, very large cysts may result in lobar atrophy with contralateral compensatory hypertrophy (Blumgart et al, 2001).

Multiple hepatic cysts may be associated with polycystic renal disease (Fig. 16.22) but may occur in the absence of renal cysts. Occasionally, patients may present with discomfort or biliary obstruction secondary to a large cyst (Fig. 16.23). In such cases, therapeutic intervention may be indicated.



FIGURE 16.23. Giant simple cyst arising in right lobe of liver. It is well circumscribed and has homogeneous, near-water attenuation.

Hemangioma

Hemangiomas (see Chapter 79) are the most benign solid tumors of the liver (Blumgart et al, 2001). The incidence of cavernous hemangiomata has been reported as 7% in an autopsy series (Karhunen, 1986). Cavernous hemangiomata may range in size from less than 1 cm to greater than 40 cm, referred to as *giant hemangiomata* (Blumgart et al, 2001). Hemangiomata usually are incidentally detected lesions seen in women (Horton et al, 1999).

Hemangiomata are composed of endothelium-lined vascular spaces separated by fibrous septa, and they derive their blood supply from the hepatic artery (Horton et al, 1999). On unenhanced CT, a hemangioma has low attenuation compared with the adjacent hepatic parenchyma. After the intravenous administration of contrast material, peripheral globular enhancement is seen on the arterial phase images. The attenuation of the peripheral nodules equals that of the aorta (Quinn & Benjamin, 1992), and venous phase images reveal centripetal enhancement to the center of the lesion (Leslie et al, 1995; Nelson & Chezmar, 1990). Because the peripheral, nodular, clumplike enhancement is seen best on arterial phase images, it is important to acquire images during this phase (Fig. 16.24).

Giant hemangiomata (>6 to 10 cm; Bouras et al, 1996; Mitsudo et al, 1995; Ros et al, 1987) have a heterogeneous appearance with a low-attenuation central scar on unenhanced CT. The low attenuation is attributed to thrombosis, hyalinization, and fibrosis (Ros et al, 1987). The typical early, peripheral, nodular, clumplike enhancement is observed on the arterial phase images, but giant hemangiomata often do not completely fill in with contrast material on delayed images (Fig. 16.25; Vilgrain et al, 2000).

Most hemangiomata do not cause clinical symptoms. However, larger tumors are more likely to cause symptoms such as abdominal pain, increasing abdominal girth, early satiety, and nausea and vomiting (Blumgart et al, 2001). These symptoms are attributed to the rapid expansion of the tumor or thrombosis and infarction resulting in stretching or inflammation of the Glisson capsule (Blumgart et al, 2001). Large hemangiomata can lead to complications such as an inflammatory process manifested by low-grade fever, weight loss, abdominal pain, and elevated erythrocyte sedimentation rate (Takayasu et al, 1990). Other complications include Kasabach-Merritt syndrome, a coagulopathy with systemic fibrinolysis and thrombocytopenia (Maceyko & Camisa, 1991), intratumoral hemorrhage, spontaneous rupture resulting in hemoperitoneum (Vilgrain et al, 2000), and volvulus of a pedunculated hemangioma (Tran-Minh et al, 1991). Pain or secondary complications may necessitate surgical intervention. CT angiography can play an important role in delineating the arterial supply to these tumors, facilitating surgical enucleation or hepatic resection.

Focal Nodular Hyperplasia

FNH (see Chapter 79) is the second most common benign liver tumor, with a reported prevalence ranging from 0.9% (Nguyen et al, 1999) to 3% (Karhunen, 1986). FNH usually is incidentally detected when patients are scanned for other reasons (Carlson et al, 2000). With the increased use of CT and faster scan protocols, FNH is being detected more frequently (Carlson et al, 2000). FNH is more commonly seen in women, and it occurs in relatively young patients (Nguyen et al, 1999). At histopathologic analysis, classic FNH contains nodular

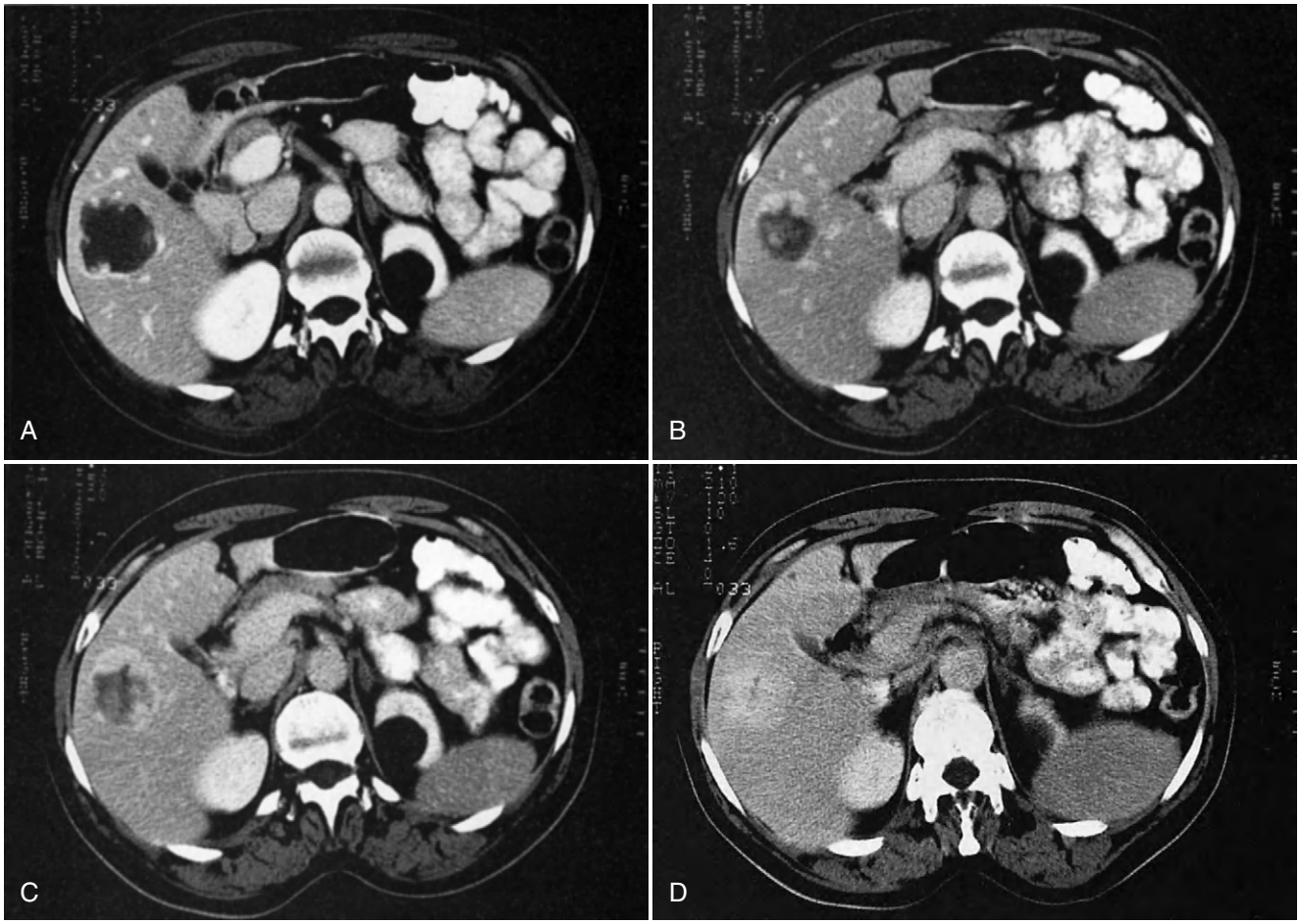


FIGURE 16.24. Cavernous hemangioma of the right liver showing typical enhancement starting at the periphery of the lesion (**A** to **C**) and finally showing complete opacification (**D**).

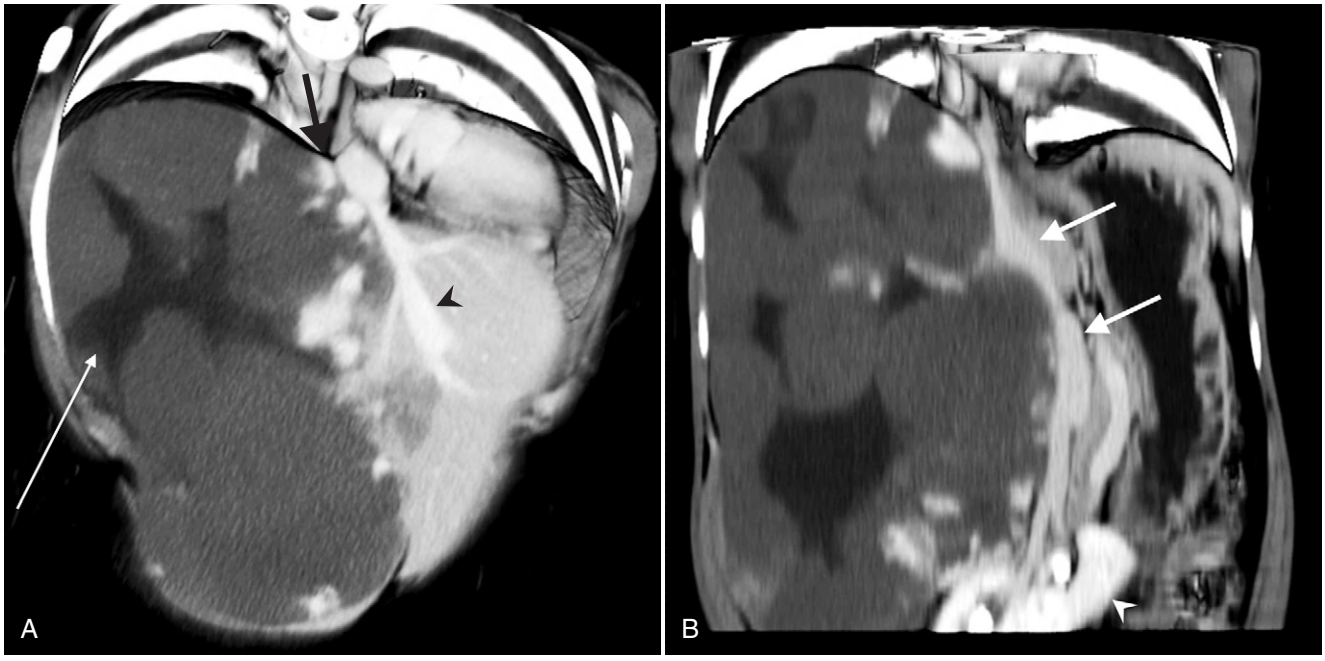


FIGURE 16.25. A, Volume-rendered three-dimensional image of a giant hemangioma. The image is oriented such that the patient is facing forward, with the observer looking down from above. Note the peripheral nodular, clumplike enhancement (*black arrow*) and the central low-attenuation scar (*white arrow*). The hemangioma is in contact with the left hepatic vein (*arrowhead*) and with the inferior vena cava (IVC). **B,** Volume-rendered coronal image of the same patient. The giant hemangioma exerts mass effect on a long segment of the IVC (*arrows*), which is displaced to the left of midline. The right kidney (*arrowhead*) is displaced inferomedially by the mass. Resection was performed with a good result. *(Courtesy L.H. Blumgart, MD.)*

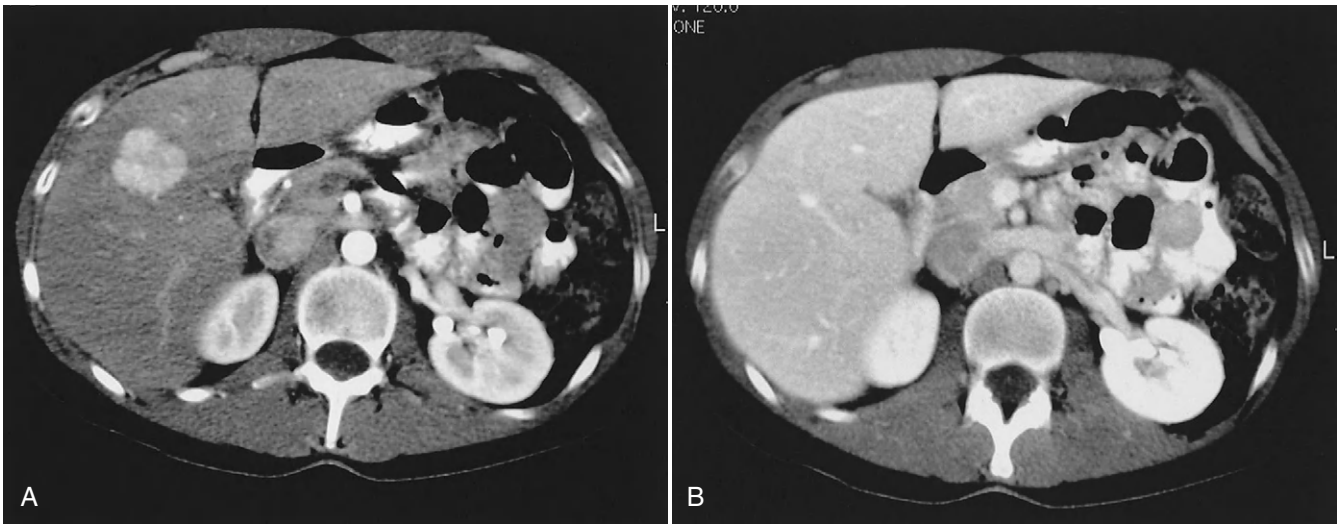


FIGURE 16.26. Focal nodular hyperplasia. **A,** Arterial phase image shows a well-circumscribed, brightly enhancing lesion in segment IV/V. **B,** During the portal phase, the lesion is isodense with liver parenchyma and cannot be identified.

hyperplastic parenchyma that is at least partially surrounded by fibrous septa and a central scar. The central scar contains fibrous connective tissue, cholangiolar proliferation with surrounding inflammatory infiltrates, and malformed vessels (Nguyen et al, 1999; Wanless et al, 1985).

On unenhanced CT, FNH has the same or slightly lower attenuation than the liver. When FNH has the same attenuation as the liver, the lesion may be invisible or may be detectable only because of the central, low-attenuation scar or mass effect on the adjacent structures (Carlson et al, 2000). The value of unenhanced images is to ensure the absence of intralesional hemorrhage, intratumoral fat, and calcifications, findings atypical of FNH (Carlson et al, 2000). During the early phases (arterial, early portal venous), the typical pattern of FNH is diffuse, immediate, homogeneous, hyperdense contrast enhancement. The prompt, diffuse arterial enhancement is due to the rich arterial supply. Rapid washout of contrast material is seen in the late portal venous phase and on delayed images, as lesions tend to become isodense to the liver on these views (Figs. 16.26 and 16.27; Carlson et al, 2000).

A central scar is thought to be present at histopathology in almost all cases of FNH, but on CT, scars are less frequently

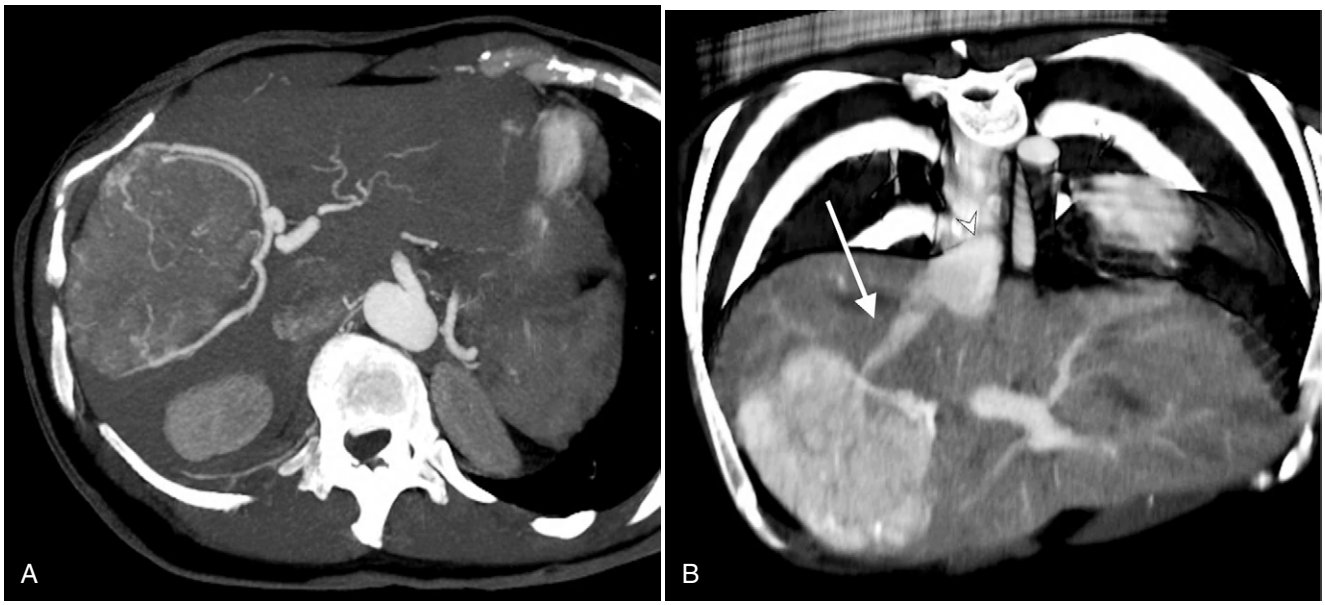


FIGURE 16.27. Focal nodular hyperplasia. **A,** Contrast-enhanced computed tomographic image acquired in the late arterial phase reveals the arterial supply to a well-circumscribed hypervascular mass in the right hepatic lobe. **B,** Oblique coronal, volume-rendered three-dimensional reformatted image of the same patient reveals early venous drainage from the mass via a large vein (*arrow*) into the inferior vena cava (*arrowhead*). The major hepatic veins have not yet opacified with contrast material.

visualized, seen in approximately one third of patients (Shamsi et al, 1993; Welch et al, 1985). The central scar is usually hypodense to the liver on unenhanced and early contrast-enhanced images, and it displays gradual fill-in on the portal venous phase and delayed images owing to diffusion of contrast material into the myxomatous stroma.

Adenoma

Hepatic adenoma (see Chapter 79) is an uncommon benign neoplasm usually discovered in women. A causative link has been described between the use of oral contraceptives and the development of hepatic adenomas (Blumgart et al, 2001). Other risk factors for the development of this neoplasm are androgen-containing steroids (Soe et al, 1992) and type I glycogen storage disease (Labrune et al, 1997). Adenomas are usually solitary but may be multiple in 30% of patients (Foster & Berman, 1977). A distinct entity referred to as *liver adenomatosis*, a term coined in 1985, refers to multiple (>10) adenomas in a patient without other known risk factors (Flejou et al, 1985).

Adenomas contain large plates of hepatocytes separated by dilated sinusoids perfused solely by peripheral arterial feeding vessels (adenomas lack a portal venous supply) under arterial pressure. Adenomas have poor connective tissue support, and the combination of poor connective tissue support and arterial pressure predisposes to hemorrhage. Multiple and large adenomas are more prone to spontaneous hemorrhage (Leese et al, 1988). Intracellular and intercellular lipids manifest as macroscopic fat within the tumor (Ichikawa et al, 2000).

The imaging appearance of adenomas parallels the histopathologic appearance. Unenhanced CT may be valuable in detecting the presence of intralesional hemorrhage or fat. Calcifications have been reported in 10% of lesions (Grazioli et al, 2000, 2001). Adenomas tend to be isoattenuating relative to normal liver on unenhanced CT and on portal venous phase images. Small adenomas usually enhance homogeneously in the arterial phase and are hyperattenuating to the liver (Grazioli et al, 2001). Larger adenomas are more heterogeneous in appearance than smaller lesions (Grazioli et al, 2001), presumably because of the presence of acute or prior hemorrhage. Peripheral enhancement reflects the presence of large subcapsular feeding vessels, with a resultant centripetal pattern of enhancement.

Biliary Hamartoma

Bile duct hamartoma (see Chapter 79), also known as *von Meyenburg complex,* is a common benign tumor composed of disorganized bile ducts and ductules with a fibrocollagenous stroma (Horton et al, 1999). The tumors usually range from 1 to 15 mm, do not communicate with the biliary tree, and are scattered throughout the liver (Wei et al, 1997). Bile duct hamartomas may be single, although they are often multiple (Blumgart et al, 2001), and they have a nonspecific imaging appearance such that they may be mistaken for metastases or microabscesses (Eisenberg et al, 1986; Lev-Toaff et al, 1995; Sada & Ramakrishna, 1994).

Bile Duct Adenoma

Bile duct adenomas are usually incidentally detected, benign, asymptomatic lesions (Welch et al, 1985). Bile duct adenomas are usually solitary and subcapsular, ranging in size from 1 mm to 1 cm. On unenhanced CT, a bile duct adenoma appears as a well-defined hypoattenuating or isoattenuating mass. Usually, little or no enhancement is seen after contrast administration. There is no specific imaging finding, however, and definitive diagnosis can be made only at histologic analysis (Horton et al, 1999).

Inflammatory Conditions

Pyogenic Abscess

Recent surgery, biliary disease, diverticulitis, Crohn disease, and alcoholism all predispose to pyogenic hepatic abscess (see Chapter 66), commonly caused by *Clostridium* species and gram-negative bacteria such as *Escherichia coli* and *Bacteroides*, which enter the liver via the biliary tree or portal venous system (Mergo & Ros, 1997). Ascending cholangitis and portal phlebitis are the most common causes of pyogenic hepatic abscesses (Murphy et al, 1989).

As a result of the widespread use of broad-spectrum antibiotics, the clinical presentation and CT appearance vary widely (Halvorsen et al, 1984). Pyogenic hepatic abscesses may be classified as either *microabscesses* (<2 cm) or *macroabscesses*, larger confluent lesions. Microabscesses appear as small, well-defined, hypodense lesions on contrast-enhanced CT. They may be widely scattered or clustered with a tendency to coalesce (Jeffrey et al, 1988). Larger pyogenic abscesses range in appearance from unilocular cavities with smooth outer margins to highly complex and septated structures with internal debris and irregular contours. Most large pyogenic abscesses appear as a well-defined mass of low attenuation on unenhanced CT. The attenuation value of the abscess cavity depends on the age of the abscess; it becomes lower as the abscess matures. Gas bubbles may be seen if anaerobic bacteria are present, and the periphery and internal septa may enhance after contrast agent administration. Abscesses often have a thick wall, which enhances with contrast administration (Fig. 16.28). In addition, there may be hepatic enhancement peripheral to the enhancing wall, secondary to increased capillary permeability. This is referred to as the *double-target sign* (Mendez et al, 1994; Murphy et al, 1989).

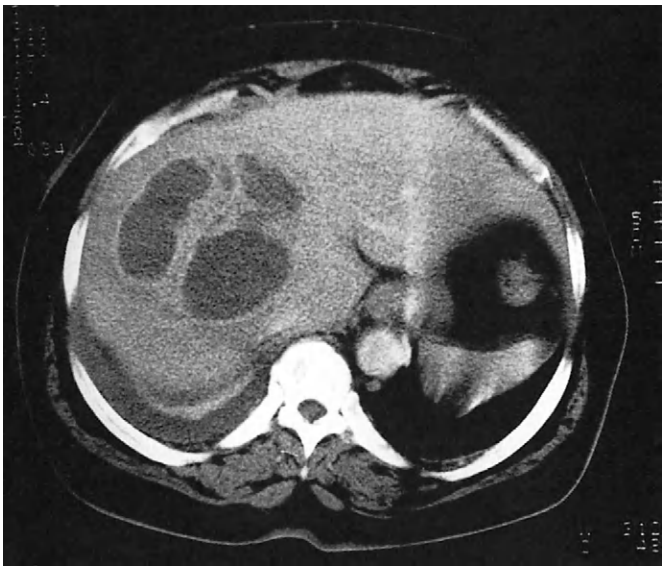


FIGURE 16.28. Contrast-enhanced computed tomography of a pyogenic liver abscess shows enhancement of the walls and internal septa. A sympathetic right-sided pleural effusion is seen.

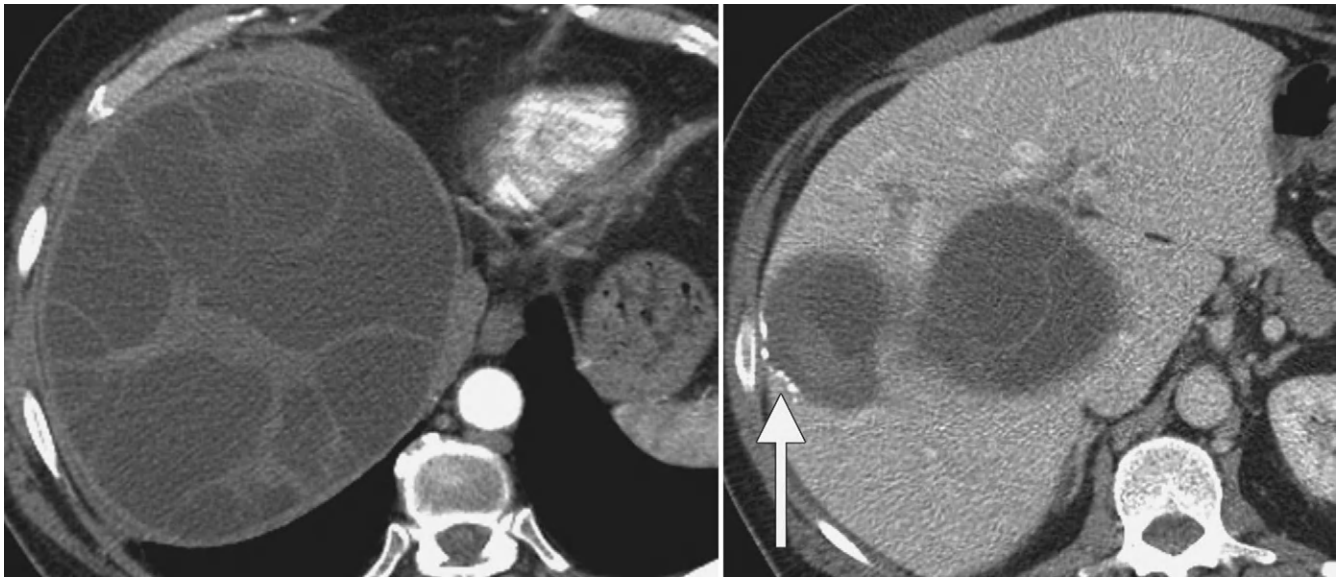


FIGURE 16.29. Contrast-enhanced axial computed tomography reveals a multiseptated echinococcal cyst in the right hepatic lobe. Note eccentric calcifications along the wall of one of the cysts (*arrow*).

Fungal Abscesses

Fungal hepatic abscesses generally are disseminated microabscesses that occur in immunosuppressed patients. The most common fungal organism implicated is *Candida albicans*. Other fungal infections that cause microabscesses include cryptococcus, histoplasmosis, and mucormycosis. With contrast-enhanced CT, hepatic microabscesses appear as small, hypodense lesions ranging from several millimeters to 1.5 cm in size. A bull's-eye appearance may be identified, with a small, high-attenuation focus centrally surrounded by a low-attenuation zone. Authors have reported significant increase in the sensitivity and lesion conspicuity using arterial phase CT, compared with portal venous phase CT, when evaluating liver lesions in immunocompromised patients suspected to have hepatosplenic fungal infections (Metser et al, 2005).

Echinococcus

In endemic areas, involvement of the liver by hydatid disease is a common finding. *Echinococcus granulosus* (see Chapter 68) presents with a large solitary mass or multiple well-defined cystic lesions, which often contain internal "daughter" cysts (Fig. 16.29). Coarse calcifications of the wall are present in 50% of patients (Fig. 16.30), and daughter cysts are identified in approximately 75% (de Diego Choliz et al, 1982; Murphy et al, 1989). Communication between the cysts and the biliary tree is found in approximately 25% of patients (de Diego Choliz et al, 1982), and frank rupture of cyst contents into the bile ducts occurs in 5% to 10%, accompanied by clinical features of cholangitis. In contrast, *Echinococcus alveolaris* infection resembles an infiltrating hepatic tumor clinically and radiographically with its irregular margins and heterogeneous density (Didier et al, 1985).

Amebic Abscess (See Chapter 67)

The protozoan *Entamoeba histolytica* infects 10% of the world's population. Hepatic abscess is the most common extraintestinal complication of amebiasis and occurs in approximately 8.5% of all patients with amebic infection (Ralls, 1998). On CT, amebic abscesses appear as well-defined masses of near-water attenuation with a thick enhancing rim. One or more internal septations may be present. A feature of amebic liver abscess that may aid in distinguishing it from other focal hepatic lesions is its tendency to extend beyond the surface of the liver (Radin et al, 1988). The CT findings are not specific, however, and serologic tests are necessary to confirm the diagnosis.

Diffuse Hepatocellular Diseases

Fatty Infiltration

Fatty infiltration (see Chapter 65), as seen in patients on chemotherapy or in patients with systemic disorders, such as diabetes mellitus, cystic fibrosis, or malnourishment, results in



FIGURE 16.30. Unenhanced computed tomography reveals a calcified rim of echinococcal cyst (*arrow*). Air within the cyst was from recent instrumentation.



FIGURE 16.31. Numerous foci of fatty infiltration. Contrast-enhanced computed tomography reveals numerous low-attenuation lesions in a patient with breast cancer. Note lack of mass effect or distortion of the hepatic vessels. Lesions were stable over time and were shown to represent focal fatty deposition on magnetic resonance imaging.

a decrease in hepatic density. Mild degrees of fatty change may be subtle, unless liver density is compared carefully with the density of the spleen. The liver is normally 6 to 12 HU higher in attenuation than the spleen, and reversal of this relationship is the earliest CT indication of fatty infiltration. With more advanced changes, the hepatic parenchyma becomes less dense than the intrahepatic vessels. In most instances, fatty infiltration is diffuse and uniform (see Fig. 16.12), but a nonuniform, focal distribution also can occur and occasionally may mimic a mass (Fig. 16.31). Fatty infiltration should be suspected if blood vessels can be seen passing through the focal area in a normal pattern (Fig. 16.32).

An awareness of the common locations of focal fatty infiltration and focal fatty sparing is important, so as not to mistake these for tumor. Common locations for focal fatty infiltration include segment IV adjacent to the falciform ligament (Ohashi et al, 1995; Paulson et al, 1993) and around the gallbladder (Yoshimitsu et al, 1997). A common location for focal fatty sparing is in the posterior aspect of segment IV (Matsui et al, 1995; White et al, 1987) or along the gallbladder fossa. It has been suggested that areas of focal fatty sparing are due to aberrant venous drainage to the liver, because these areas do not receive portal venous flow from the main portal trunk (Gabata et al, 1997; Marchal et al, 1986; Matsui et al, 1995).

It has been shown that focal fatty sparing in a fatty infiltrated liver may occur secondary to a mass. This occurrence is presumably due to regionally decreased portal blood flow caused by compression of the adjacent portal venous branch distal to a mass. This fatty sparing can appear as wedge shaped, peripheral, segmental, or lobar, depending on the site of the portal venous compression (Grossholz et al, 1998).

Assessment for fatty infiltration is better performed with unenhanced CT than with contrast-enhanced CT, because factors such as the rate of contrast injection and timing of measurements significantly influence the optimal liver-to-spleen ratio threshold for diagnosing fatty liver. The required ratios are



FIGURE 16.32. Focal fatty infiltration. A wedge-shaped area of low attenuation is visible in the right liver. The hepatic vessels pass through the area normally with no deviation.

protocol specific, which limits the clinical usefulness of such measurements (Jacobs et al, 1998; Johnston et al, 1998). If it is unclear based on the CT findings whether an area of focal low attenuation represents a mass, magnetic resonance imaging (MRI) using opposed-phase gradient echo images may make a definitive diagnosis.

Cirrhosis (See Chapter 70)

CT is capable of showing morphologic changes associated with advanced hepatic cirrhosis. Typical CT features are a nodular hepatic outline (in macronodular cirrhosis) caused by regenerative nodules of variable size, bands or regions of confluent fibrosis, relative atrophy of the right hepatic and quadrate lobes, and hypertrophy of the left lateral segment and caudate lobe (Fig. 16.33; Torres et al, 1986). Measurement of the transverse dimension of the caudate lobe compared with the adjacent right lobe provides an index of right hepatic lobe shrinkage and a relatively specific morphologic measurement of hepatic cirrhosis (Harbin et al, 1980). A caudate/right lobe ratio greater than 0.65, using the bifurcation of the main portal vein to divide the lobes provides 96% confidence in the diagnosis of cirrhosis. An MRI study suggested that using the right portal vein to set the lateral boundary of the caudate lobe when assessing the caudate/right lobe ratio was more accurate for diagnosing cirrhosis than using the main portal vein (Awaya et al, 2002). Evidence of coexistent portal hypertension is found with ascites, splenomegaly, and portal-systemic varices. MDCT combined with three-dimensional reformatting can help determine the extent of portosystemic collateral vessels, such as the left gastric vein, short gastric vein, esophageal and paraesophageal varices, splenorenal and gastrorenal shunts, and paraumbilical and abdominal wall veins (Kang et al, 2002).

Budd-Chiari Syndrome

Budd-Chiari syndrome (see Chapter 77) is caused by chronic hepatic venous congestion secondary to obstruction to hepatic venous outflow. The CT appearance is characterized by hepatomegaly and ascites; the hepatic veins are either obliterated and not seen, or they contain thrombus (Fig. 16.34). Precontrast scans show decreased attenuation of hepatic parenchyma because of congestion; postcontrast scans show normal enhancement of the caudate lobe, which is hypertrophied in chronic cases, and patchy enhancement of the remainder of the liver (Vogelzang et al, 1987). Concomitant portal vein thrombosis is present in 20% of patients with Budd-Chiari syndrome. A similar CT appearance of the liver, with patchy enhancement, is seen in patients with congestive heart failure; in contrast to patients with true Budd-Chiari syndrome, these patients have patent and enlarged hepatic veins (Moulton et al, 1988).

Hepatic Infarction

Hepatic infarction is rare and implies compromise to the arterial and portal venous supply to a segment or lobe of the liver. CT findings include a well-defined, wedge-shaped area of low attenuation in segmental or subsegmental distribution, extending to the liver surface. After contrast administration, the affected zone is enhanced minimally; a peripheral, thin, subcapsular rim often contains enhancing hepatic tissue. Gas formation within sterile infarcts is a recognized finding and does not imply superimposed infection. A late complication of hepatic infarction is formation of bile lakes in the affected segments as a result of disruption of biliary radicles.

Malignant Lesions of the Liver

Hepatocellular Carcinoma

HCC (see Chapter 80) is the most common primary hepatic malignancy worldwide, with the highest incidence in Asia, Southeast Asia, and sub-Saharan Africa. Although less common in the West, the incidence of HCC in the United States has been increasing (Arakawa et al, 1986). The most significant risk factors include cirrhosis and hepatitis B and C viruses. Approximately 70% of HCCs develop in cirrhotic livers (Blumgart et al, 2001), and detection of HCC in the cirrhotic liver poses a great diagnostic challenge, because the hepatic parenchyma is distorted by nodular regeneration and fibrosis. In addition, there are alterations in arterial and portal venous blood flow. These

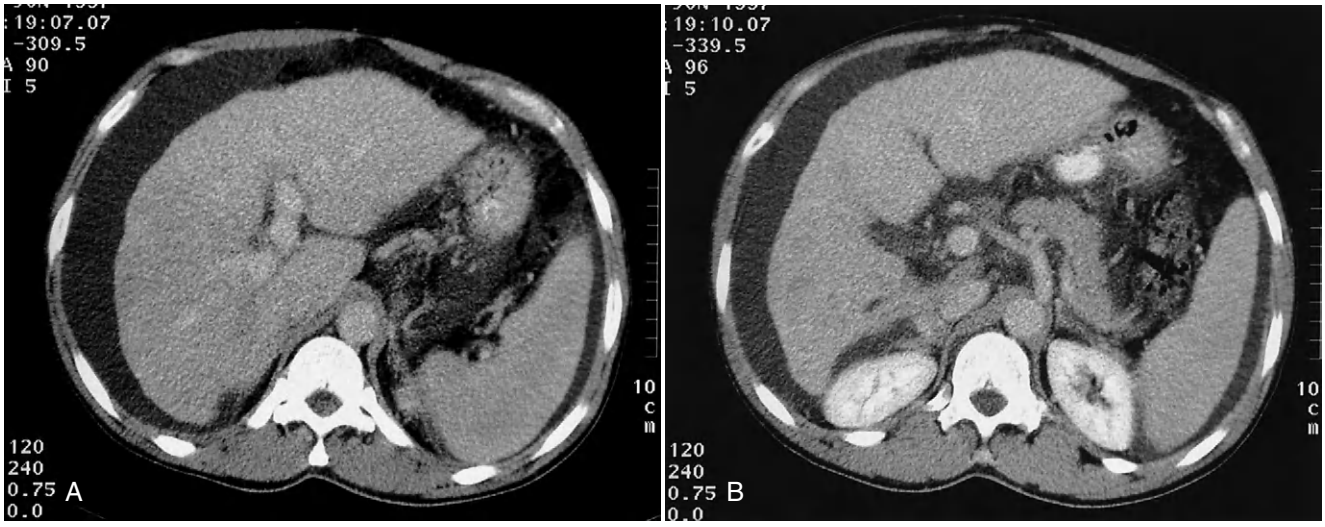


FIGURE 16.33. Cirrhosis. **A,** The liver has an irregular outline. **B,** The interlobar fissure, delineated by the gallbladder, is deviated toward the right as a result of atrophy of the right liver with hypertrophy of the left liver and the caudate lobe.

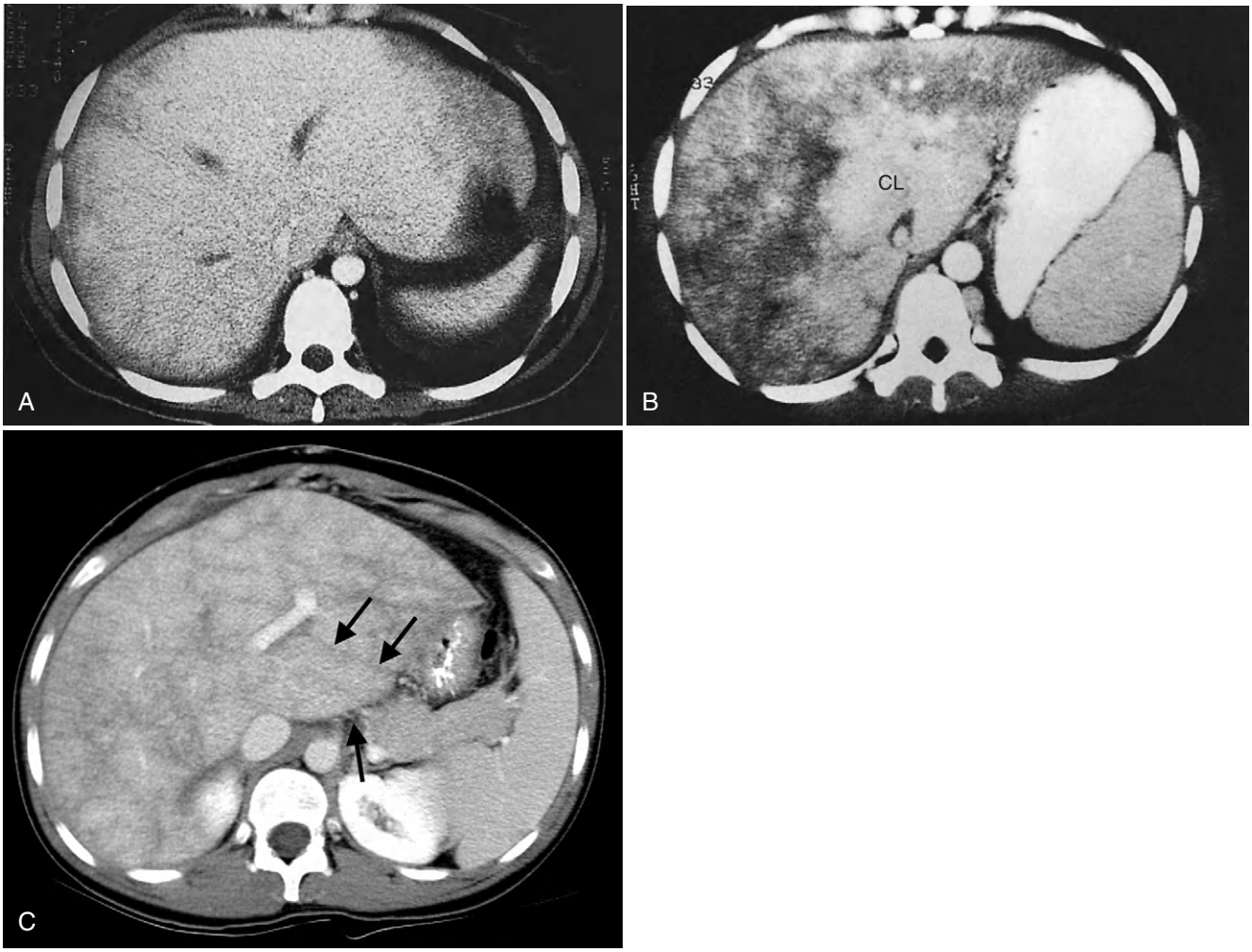


FIGURE 16.34. **A,** Contrast-enhanced computed tomography (CT) in a patient with acute hepatic venous thrombosis leading to Budd-Chiari syndrome shows nonenhancement of the thrombosed hepatic veins. There also is patchy peripheral parenchymal enhancement. **B,** In a patient with chronic Budd-Chiari syndrome resulting from a congenital stricture of the intrahepatic inferior vena cava, enlargement of the caudate lobe (*CL*) and marked homogeneity of parenchymal enhancement are seen. Splenomegaly also is seen. **C,** Contrast-enhanced CT reveals mottled parenchymal enhancement and enlargement of the caudate lobe (*arrows*) in a patient with occlusion of the hepatic veins secondary to paroxysmal nocturnal hemoglobinuria.

changes can obscure malignant lesions and conversely can simulate disease (Baron & Peterson, 2001).

Regenerative nodules within the cirrhotic liver, especially large nodules (8 to 10 mm), are readily identifiable at CT, because they distort the hepatic contour. When these nodules contain iron, referred to as *siderotic nodules,* they have high attenuation on unenhanced CT. These nodules typically do not enhance during the arterial phase, and this is an important characteristic that differentiates regenerating nodules from dysplastic nodules and HCC. Regenerative nodules enhance homogeneously during the portal venous phase to the same degree that surrounding fibrotic tissue does and thus are not visible as distinct from the adjacent parenchyma (Baron & Peterson, 2001).

Dysplastic nodules contain cellular atypia and are precursors to frank HCC in some cases. Dysplastic nodules may contain nontriadal arterial flow pathologically, which distinguishes them from regenerative nodules. Dysplastic nodules typically do not display vivid arterial enhancement on CT but occasionally do enhance in this phase and may mimic HCC (Baron & Peterson, 2001).

The appearance of HCC on CT varies. Most small HCC nodules enhance on arterial phase images and display a washout of contrast material during the portal venous phase (Fig. 16.35). A few are hypovascular and are best seen in portal venous phase or equilibrium phase imaging. Larger lesions (>5 cm) tend to be heterogeneous with a mosaic pattern of enhancement (Stevens et al, 1996); they may be surrounded by a tumor capsule and may contain necrosis and fatty metamorphosis. Tumor can invade the portal or hepatic veins directly (Freeny et al, 1992), with enhancing tumor thrombus evident on CT (Figs. 16.36 and 16.37). Tumor extension into the bile duct, resulting in biliary obstruction, also can be seen on CT.

Distortion of the liver related to the underlying cirrhosis can lead to abnormalities at CT that may be misinterpreted as HCC. A false-positive diagnosis of HCC was made on CT in 8% of 1329 patients with cirrhosis who were referred for hepatic transplantation in an experienced liver transplant center

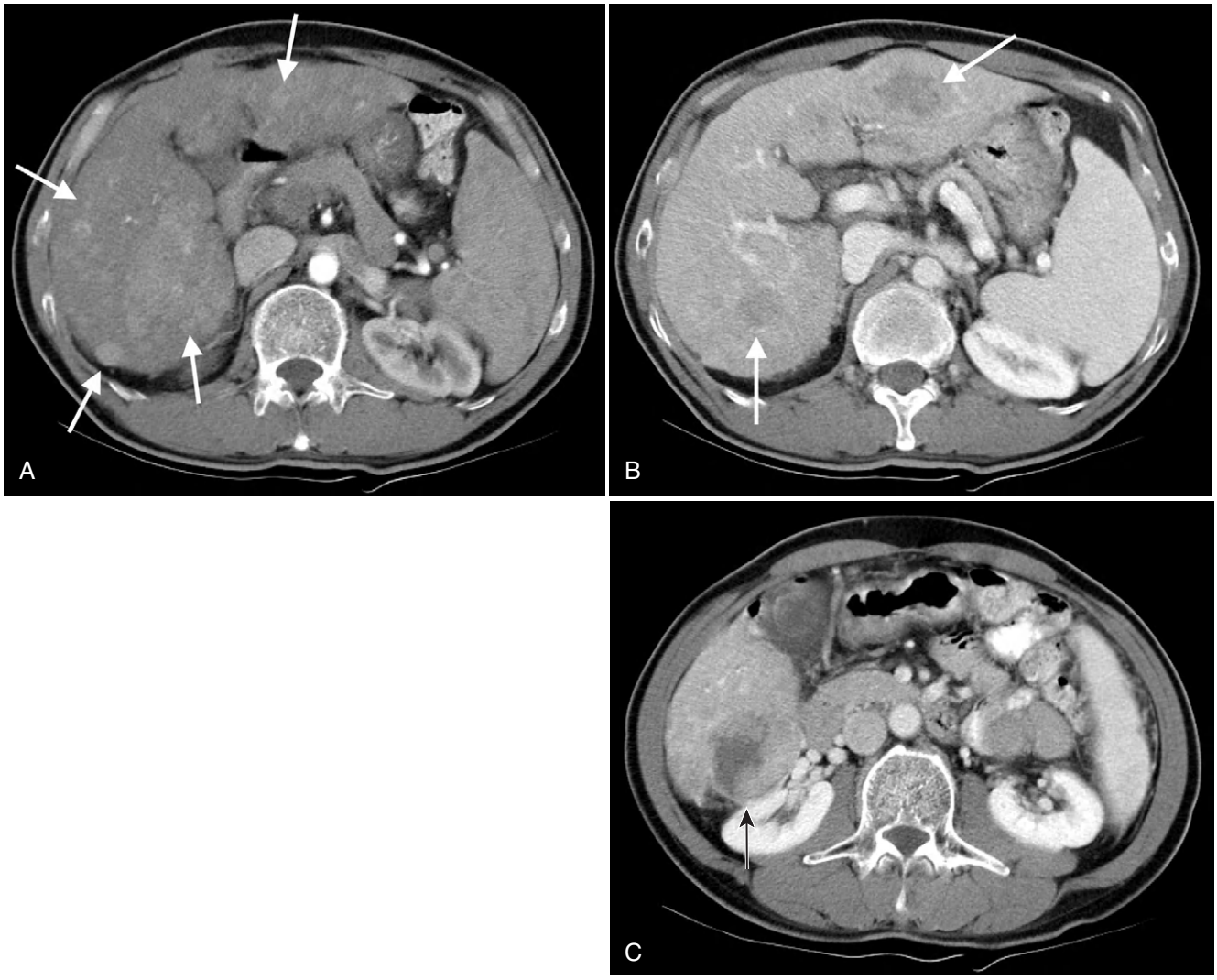


FIGURE 16.35. Arterial phase and portal venous phase images in a patient with multifocal hepatocellular carcinoma (HCC). **A,** Arterial phase images reveal numerous hypervascular masses (*arrows*) in a patient with multifocal HCC. **B,** Portal venous phase image reveals low-attenuation masses (*arrows*). **C,** Portal venous phase image reveals an exophytic heterogeneous mass reflecting an additional focus of HCC (*arrow*).

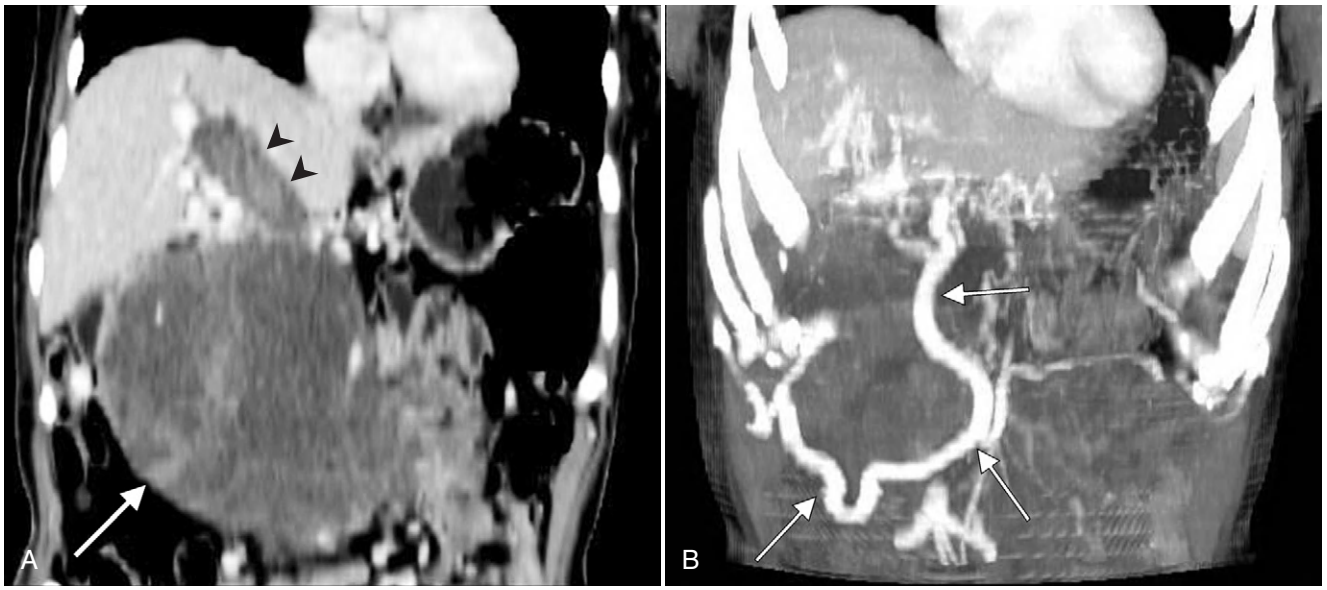


FIGURE 16.36. **A,** Contrast-enhanced computed tomography reveals an exophytic hepatocellular carcinoma (*arrow*) with tumor thrombus extending up the main portal vein (*arrowheads*). **B,** Coronal maximum intensity projection image in the same patient reveals extensive collateral venous flow (*arrows*) about the mass.

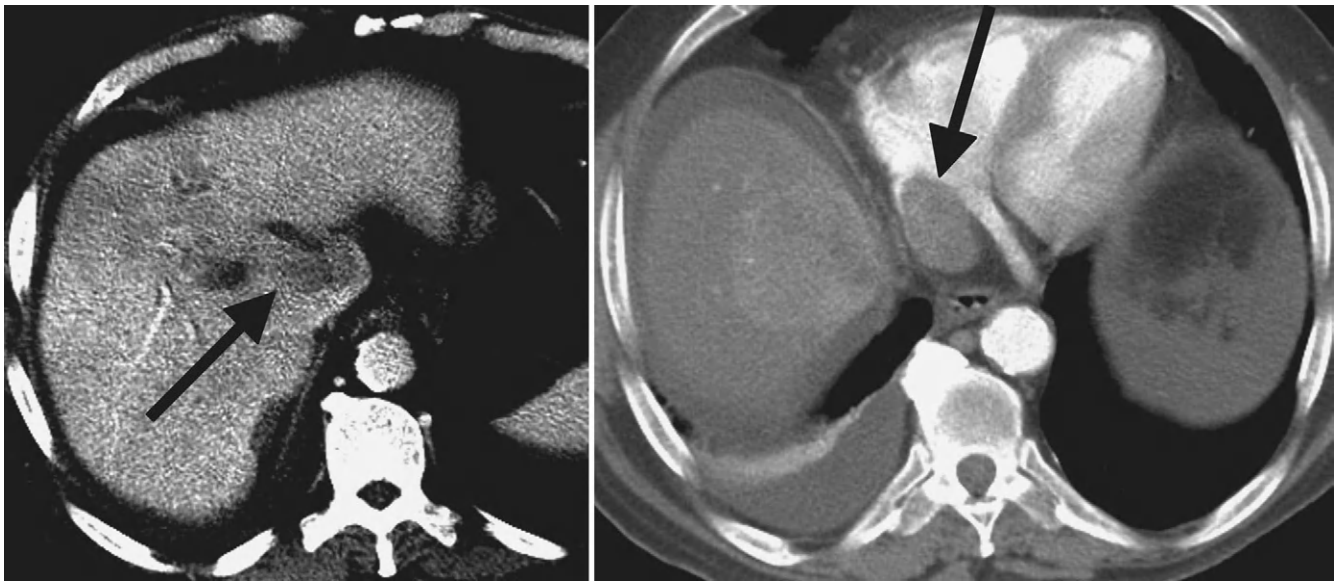


FIGURE 16.37. Hepatocellular carcinoma (HCC). Contrast-enhanced computed tomography reveals HCC involving segment I of the liver (*arrow*). Tumor thrombus extends into the inferior vena cava and right atrium (*arrow*).

(Brancatelli et al, 2003). Benign lesions mistaken for HCC include focal confluent fibrosis, transient hepatic attenuation difference, flash-filling hemangiomata, peliosis, and benign regenerative nodules showing dysplastic change.

HCC may be predominantly intrahepatic or pedunculated, with a large exophytic component "hanging" off the liver (see Fig. 16.36A). This finding is evident on cross-sectional imaging and has implications for surgical resectability (Vauthey et al, 1995). Approximately 5% of HCCs are seen with spontaneous rupture and hemoperitoneum (Blumgart et al, 2001).

The appearance of HCC differs in cirrhotic and noncirrhotic livers. HCC in a cirrhotic liver commonly appears as multifocal small lesions, whereas HCC in a noncirrhotic liver is more typically a large, hypervascular solitary or dominant mass with small satellite nodules and central necrosis (Fig. 16.38; Brancatelli et al, 2002; Winston et al, 1999b). The pathogenesis of HCC differs in these two patient groups. HCC may arise de novo in an otherwise normal liver, whereas a multistep sequence of carcinogenesis has been described in patients with cirrhosis (Okuda et al, 1982). It has been shown that venous invasion by tumor is more common in cirrhotic patients than in patients without underlying liver disease (Smalley et al, 1988). Patients with minimal or no cirrhosis have a better prognosis after resection than patients with cirrhosis (Fong et al, 1999).

Fibrolamellar Hepatocellular Carcinoma

Fibrolamellar HCC is a malignant hepatocellular tumor with distinct clinical, pathologic, and radiologic differences from HCC. Fibrolamellar carcinoma typically manifests as a large hepatic mass in adolescents or young adults with no evidence of cirrhosis, and it accounts for 1% to 9% of all HCCs (Berman et al, 1980; Craig et al, 1980; Goodman et al, 1985; Pinna et al, 1985). There are no known risk factors for the development of this lesion. The main diagnostic challenge is to distinguish it from FNH, a benign lesion occurring in the same age group.

On unenhanced CT scans, fibrolamellar carcinoma usually appears as a hypoattenuating, solitary mass with well-defined lobular margins (McLarney et al, 1999) and a central scar. Calcification, a finding used to help differentiate this lesion from FNH, has been reported in 35% to 55% of tumors (Brandt et al, 1988; Friedman et al, 1985; Soyer et al, 1991). During the arterial and portal phases of enhancement, the nonscar portion of the tumor enhances heterogeneously (McLarney et al, 1999). This heterogeneous enhancement is also an important imaging finding used to differentiate fibrolamellar HCC from FNH, which should display homogeneous arterial enhancement around a central scar. On delayed images, increasing homogeneity of the mass and occasional scar enhancement may simulate the appearance of FNH, underscoring the need to

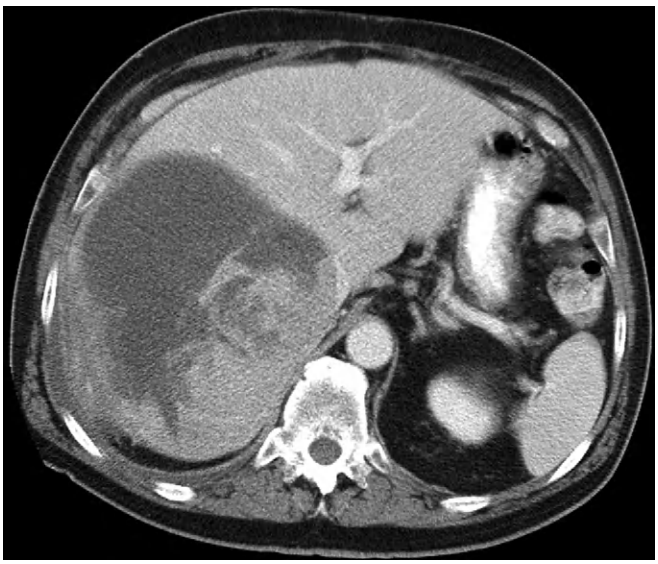


FIGURE 16.38. Hepatocellular carcinoma in a noncirrhotic liver.

scan the liver during the arterial and portal venous phases. Although fibrolamellar HCC does not typically have a true capsule, the liver surrounding the mass may be compressed and may form a pseudocapsule (McLarney et al, 1999). Associated findings of vascular invasion, lymphadenopathy, or peritoneal implants strongly suggest fibrolamellar HCC.

Angiosarcoma

Risk factors for angiosarcoma of the liver include hemochromatosis, radiotherapy, and exposure to compounds such as polyvinyl chloride (PVC), arsenic, or Thorotrast. Angiosarcoma is a vascular hepatic neoplasm that appears as an infiltrating, brightly enhancing mass on CT (Silverman et al, 1983). High-attenuation thorium deposition may be seen in a patchy distribution in the liver, perihepatic lymph nodes, and spleen. Histologic "cavernous" angiosarcoma may enhance in a way similar to that of hemangioma, with the tumor becoming wholly or partly isodense with liver on delayed scanning (Itai & Teraoka, 1989; White et al, 1993).

Hepatic Lymphoma

Primary lymphoma of the liver is rare, but the liver is a common secondary site of lymphomatous involvement in patients with Hodgkin disease and non-Hodgkin lymphoma. At autopsy, hepatic involvement is seen in 50% of patients with non-Hodgkin lymphoma and in 60% of patients with Hodgkin disease. Approximately 6% to 20% of patients with Hodgkin disease have hepatic involvement at presentation (Castellino, 1982; Fishman et al, 1991; Sandrasegaran et al, 1994). Liver involvement usually is associated with lymph node disease and almost invariably is associated with splenic disease. The more extensive the splenic involvement, the greater the likelihood of hepatic involvement (Figs. 16.39 and 16.40).

On CT, hepatic involvement usually appears diffuse; discrete nodular lesions are seen in only 10% of cases. The sensitivity of CT in the detection of hepatic disease is low, presumably because liver involvement is diffuse. It is thought that extensive disease must be present before becoming apparent at imaging, and CT may reveal only hepatomegaly with no focal lesion. Diffuse or infiltrative forms of the disease result in irregular infiltration in the portal areas.

Hepatic Metastases (See Chapter 81)

The liver provides a fertile soil for metastases, not only because of its dual blood supply from systemic and portal systems, but also because of humoral factors that promote cell growth. The liver is second only to regional lymph nodes as a site of metastatic disease. The CT appearance of metastases varies and depends on the size and vascularity of the tumor, the degree of necrosis, and the CT technique used (see Technique section). Borders may be sharp, poorly defined, or nodular; the shape may be round, ovoid, or irregular. Attenuation is usually lower than that of surrounding hepatic parenchyma on unenhanced CT. Intravenous contrast enhancement increases the sensitivity of lesion detection.

Scanning during the appropriate phase of enhancement (arterial, portal, delayed) increases detection even further (see Technique section). Peripheral ring enhancement occurs in metastases, but this is usually not appreciated in hypovascular metastases, which have low attenuation compared with surrounding, intensely enhancing hepatic parenchyma during portal phase scanning. Hypervascular metastases may be obscured during the portal phase and are most clearly visualized during the arterial phase (see Fig. 16.14). Metastases from mucinous carcinomas tend to contain punctate or amorphous calcification. Cystic metastases can be distinguished from benign simple cysts, because the former often contain mural nodules, fluid-fluid levels, or septations. Differentiation of multiple hepatic metastases from multifocal HCC may be difficult, but metastases rarely protrude prominently from the liver surface, a feature that is commonly seen with HCC.

The appearance of metastases may change in response to treatment. Lesions may appear of lower attenuation as they undergo necrosis (Figs. 16.41 and 16.42). Hepatic metastases from gastrointestinal stromal tumors (GISTs) that respond to

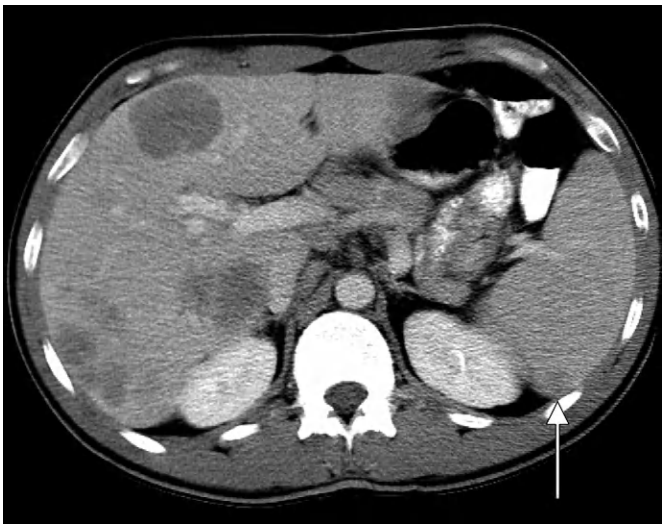


FIGURE 16.39. Contrast-enhanced computed tomography reveals multiple hepatic masses in a patient with lymphomatous involvement of the liver and spleen. Note the low-attenuation mass in the spleen (*arrow*).

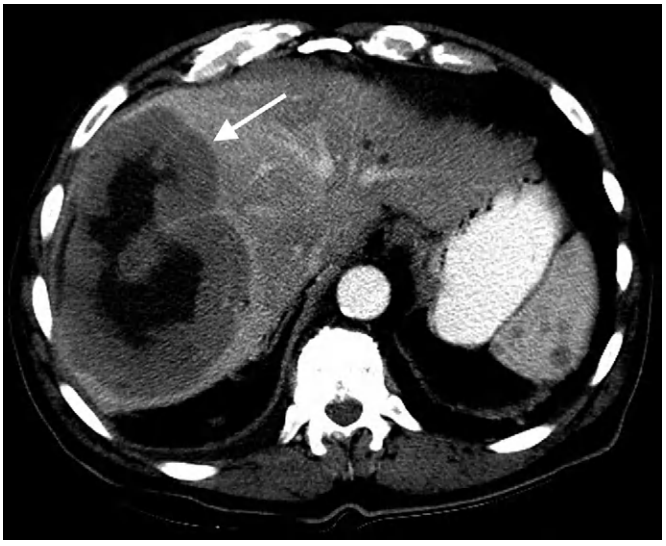


FIGURE 16.40. Large unifocal lymphomatous mass in the right hepatic lobe (*arrow*). Small splenic lesions are also seen.

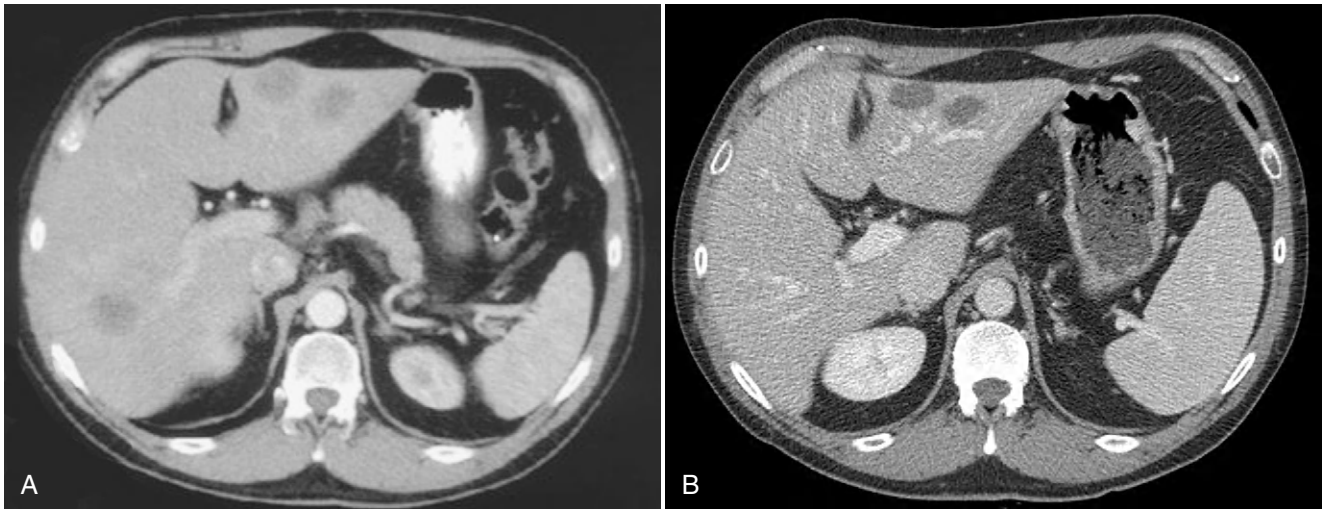


FIGURE 16.41. Metastatic colon cancer. **A,** Before treatment. **B,** After treatment.

imatinib mesylate become near cystic on contrast-enhanced CT. These metastases may resemble cyts, but they display a slightly higher HU (Chen et al, 2002). Therefore when evaluating the liver at CT in a patient with a history of GIST, it is very important to know whether the patient has undergone treatment; comparison with pretreatment images becomes essential. Metastases may result in focal biliary ductal dilation secondary to compression or invasion of the adjacent bile duct (Fig. 16.43).

Biliary System

Advances in technology have expanded the role of CT in evaluating the biliary tree. The ability to obtain high-resolution, thin-slice images in a single breath hold and the ability to view these images in cine mode are ideal for tracing the dilated bile ducts to the point of obstruction. Delineation of variant biliary anatomy is possible if the biliary tree is dilated (Fig. 16.44). Additionally, the relationship of arteries to the bile ducts can be identified, which is valuable information for surgical planning (Fig. 16.45; see Chapter 90).

Gallstones

CT is inferior to ultrasound for detection of gallstones, but it may reveal unsuspected gallstones during studies performed for other reasons. Visualized gallstones are calcified or of lower attenuation than the surrounding bile because of a high cholesterol content. Stones that are missed on CT are mixed cholesterol stones that are isodense with bile.

Cholecystitis (See Chapter 31)

CT should not be used as a screening technique for the detection of acute cholecystitis, but occasionally, patients with cholecystitis who display a confusing clinical picture may undergo

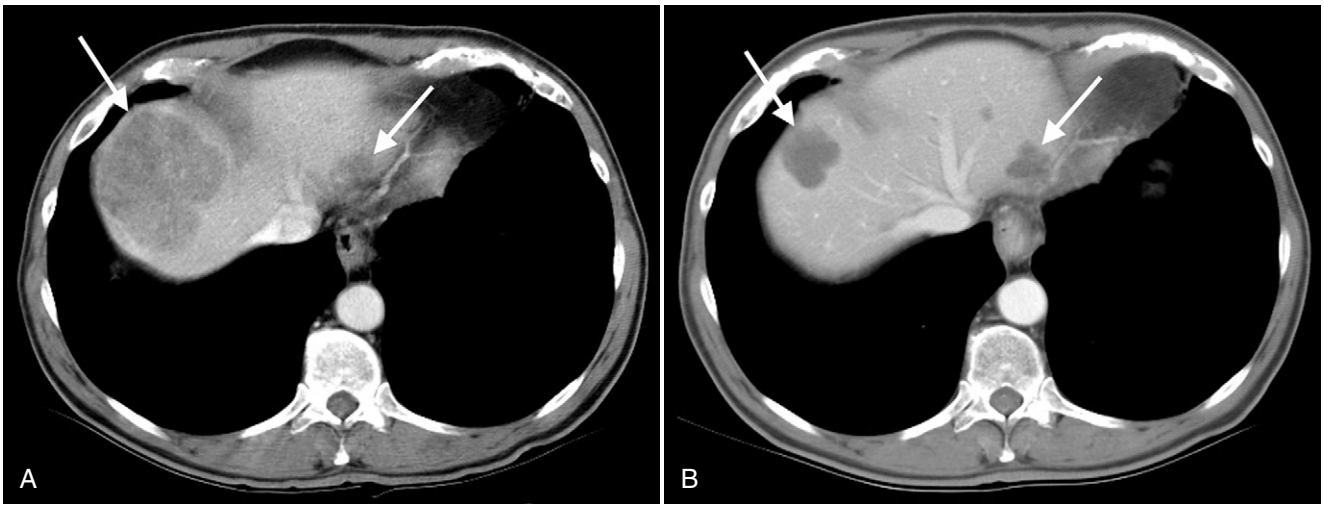


FIGURE 16.42. Contrast-enhanced computed tomography in a patient with metastatic gastrointestinal stromal tumor. **A,** Before treatment, heterogeneous solid enhancing masses are seen in the right and left hepatic lobes (*arrows*). **B,** After treatment, lesions have lower attenuation and appear more cystic (*arrows*).

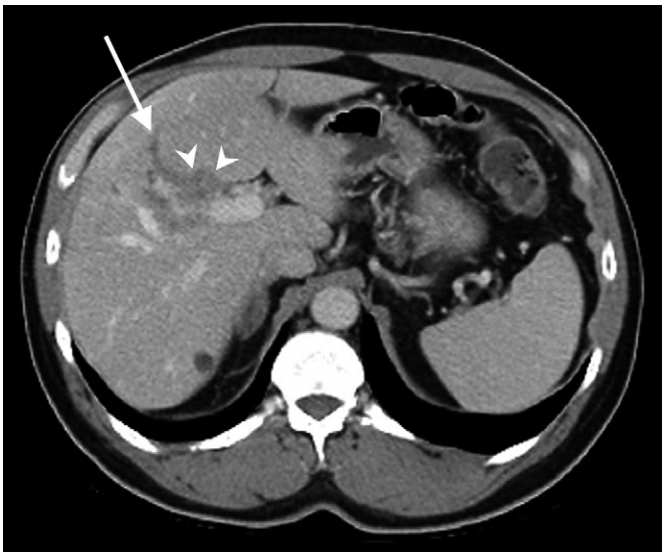


FIGURE 16.43. Contrast-enhanced computed tomography in a patient with metastatic colorectal cancer reveals infiltrative tumor invading the bile duct (*arrowheads*). Note the resultant biliary dilation (*long arrow*).

CT examination before the precise nature of the disease is clear. Gallbladder distension, wall thickening, and gallstones are often present in acute cholecystitis, but these are nonspecific signs that occur in most patients with chronic cholecystitis. The presence of ill-defined pericholecystic lucency within the hepatic parenchyma adjacent to the gallbladder suggests gallbladder inflammation (Fig. 16.46). Intramural edema within the gallbladder wall may be seen in acute cholecystitis and is a useful sign in an appropriate clinical setting, but it also can be seen in patients with ascites or hypoalbuminemia. The attenuation of the gallbladder bile is usually increased, and extremely high attenuation is seen in patients with hemorrhagic cholecystitis, a rare complication.

Although many of the CT findings in uncomplicated acute cholecystitis are nonspecific, CT is valuable when



FIGURE 16.44. Coronal reformatted image created from axial computed tomographic data acquired after intravenous administration of contrast medium. Bile is displayed as *bright areas* with marked dilation of the intrahepatic bile ducts and the common bile duct (*CBD*). Note the distended gallbladder (*asterisk*) and the aberrant biliary drainage of segment VI (*arrowheads*) directly into the common bile duct.

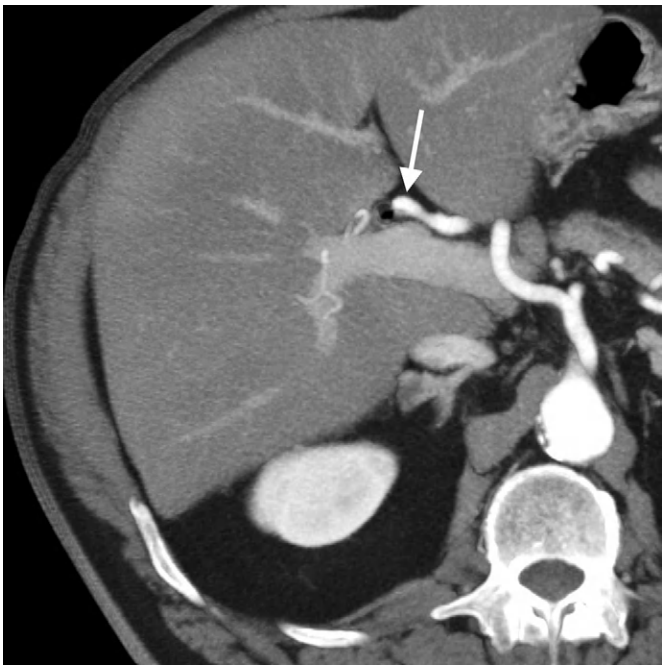


FIGURE 16.45. Arterial phase image reveals the right hepatic artery (*arrow*) coursing anterior to the common hepatic duct, which contains air from a papillotomy.

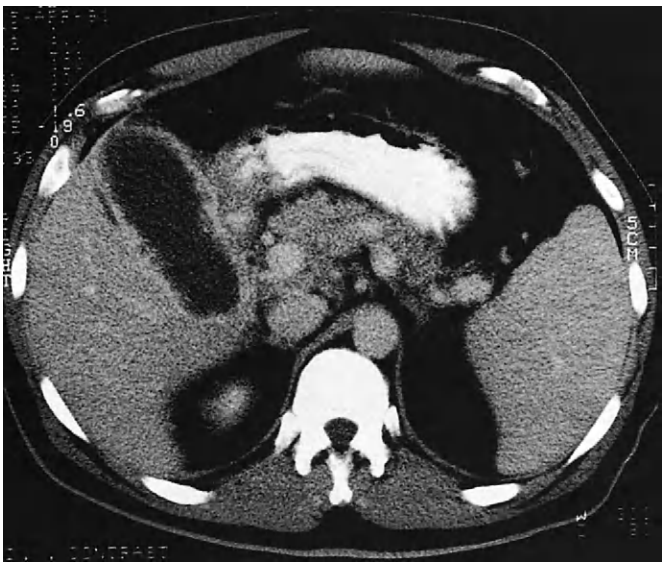


FIGURE 16.46. Acute cholecystitis. computed tomography shows a distended, thick-walled gallbladder with pericholecystic fluid. No gallstones are seen.

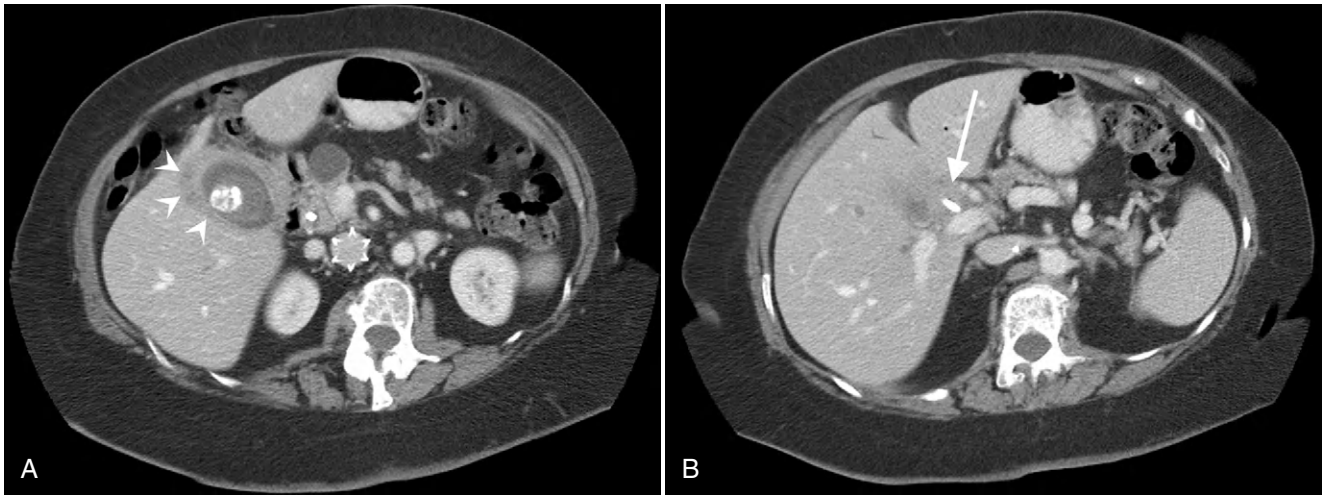


FIGURE 16.47. Mirrizi syndrome. **A,** Contrast-enhanced computed tomography reveals a large calcified gallstone associated with gallbladder wall thickening and extensive pericholecystic inflammatory change (*arrowheads*). **B,** Extensive inflammatory change surrounds the internal biliary stent (*arrow*).

complications such as pericholecystic abscess, emphysematous cholecystitis, or gallbladder perforation are present, and CT can identify patients in need of emergency surgery. CT findings most specific for acute gangrenous cholecystitis are gas in the gallbladder wall or lumen, intraluminal membranes, irregular gallbladder wall enhancement, and pericholecystic abscess (Bennett et al, 2002).

Mirizzi Syndrome

Mirizzi syndrome is an uncommon condition in which the common hepatic duct is obstructed because of stones impacted in or extruded from a Hartmann pouch or cystic duct. Cholecystobiliary and cholecystoenteric fistulae are common complications. It is clinically important to recognize the diagnosis before surgery, because failure to appreciate the extraluminal obstructing process results in unrewarding exploration of the common duct and persistent obstruction. The typical CT features of Mirizzi syndrome are dilation of the biliary system above the level of the neck of the gallbladder with a normal system below. CT reveals a gallstone impacted in a cystic duct or gallbladder neck, and the stone usually appears eccentrically located relative to the bile duct. An irregular cavity with surrounding edema and inflammation may be seen adjacent to the gallbladder neck (Fig. 16.47). Because not all of the findings may be present on CT, direct cholangiography or MRI cholangiopancreatography can be obtained to document the nature of the obstruction and the presence or absence of a biliary fistula.

Choledocholithiasis (See Chapters 35 to 37)

The insensitivity of sonography in detecting choledocholithiasis has been well documented, with a reported detection rate of 18% to 22%, whereas CT has a detection rate of 76% (Baron, 1987). Meticulous attention must be paid to technique, and when a change in duct caliber is detected, thin collimation scans should be performed through the transition area to detect the calculus. The only reliable indicator of choledocholithiasis is the presence of dense intraluminal calcification, or a *target sign*, which is due to a halo of bile surrounding the higher density stone. Calcified stones lying within an obstructed duct present no challenge to the radiologist. Most errors in diagnosis are due to cholesterol stones, which may blend imperceptibly with the surrounding bile. Errors of diagnosis also occur when choledocholithiasis occurs without ductal dilation, which occurs in about one third of patients with choledocholithiasis.

Intrahepatic calculi (see Chapter 39) are rare in Western countries but most frequently occur in association with iatrogenic bile duct strictures (Fig. 16.48). CT is of little value when stones are small and noncalcified and bile duct dilation is minimal or absent. Intrahepatic choledocholithiasis may give a bizarre appearance, owing to segmental or subsegmental biliary radicles filled with calculi. In Asian patients with recurrent pyogenic cholangitis, who subsequently form bile pigment stones,



FIGURE 16.48. Intrahepatic cholelithiasis. Intrahepatic duct dilation is seen after recurrent anastomotic stricture formation at a hepaticojejunostomy. Several laminated, noncalcified calculi can be seen within the dilated ductal system.

the debris filling the biliary system generally has higher attenuation than normal bile. Marked bile duct dilation is present, and often the larger intrahepatic ducts are dilated without side-branch dilation. Eccentric and diffuse extrahepatic bile duct wall thickening is usually seen (Schulte et al, 1990).

Gallbladder Carcinoma

Gallbladder carcinoma (see Chapter 49) is the sixth most common gastrointestinal malignancy in the United States. Risk factors include female gender, age, postmenopausal status, and cigarette smoking (Khan et al, 1999). Gallstones are present in 74% to 92% of patients with gallbladder carcinoma and represent another well-established risk factor (Lowenfels et al, 1985; Nagorney & McPherson, 1988). *Porcelain gallbladder,* a term used to describe calcification within the gallbladder wall, places a patient at increased risk for gallbladder carcinoma. Older studies suggested that 10% to 25% of patients with a porcelain gallbladder develop gallbladder carcinoma (Berk et al, 1973), but more recent reports indicate that the risk may be lower and related to the type of calcification (lower risk with complete calcification of the entire wall compared with selective calcification; Stephen & Berger, 2001; Kim et al, 2009). Most patients with gallbladder carcinoma are diagnosed with advanced disease. Early-stage gallbladder carcinoma typically is detected incidentally because of inflammation related to coexistent cholelithiasis or cholecystitis. In 1% of patients undergoing cholecystectomy for cholelithiasis, gallbladder carcinoma is discovered incidentally (Wanebo & Vezeridis, 1993).

The CT imaging appearances of gallbladder carcinoma include a mass replacing the gallbladder (seen in 40% to 65% of patients), focal or diffuse gallbladder wall thickening (seen in 20% to 30%; Fig. 16.49), and an intraluminal polypoid mass (seen in 15% to 25%; Fig. 16.50) (Franquet et al, 1991; Lane et al, 1989; Yeh, 1979; Yum & Fink, 1980). Additional imaging findings associated with gallbladder carcinoma reflect the pattern of disease spread. The most common mode by which gallbladder carcinoma spreads is direct invasion into the adjacent organs. Direct tumor invasion is enhanced by the thin gallbladder wall, which contains only a single muscle layer. The perimuscular connective tissue of the gallbladder is continuous with the interlobular connective tissue of the liver, facilitating the direct spread of tumor into the hepatic parenchyma (Henson et al, 1992). The liver is the organ most frequently invaded, followed by the colon, duodenum, and pancreas (Sons et al, 1985).

The gallbladder lies in the intersegmental plane between segments IVb and V (see Fig. 16.6), and tumors of the gallbladder fundus may invade directly into these segments at an early stage (Blumgart et al, 2001). Air may be seen within the gallbladder lumen if tumor results in a fistula to the transverse colon or duodenum. Tumors involving the infundibulum or cystic duct may invade directly and obstruct the common bile duct or portal vein, precluding surgical resection (Blumgart et al, 2001). Associated biliary dilation resuting from infiltrative tumor along the cystic duct to the extrahepatic bile duct, lymphadenopathy compressing the bile duct, or intraductal spread of tumor is apparent on CT (Levy et al, 2001). Tumor growth through the gallbladder wall away from the liver results in peritoneal carcinomatosis.

Laparoscopic cholecystectomy has become increasingly accepted as a treatment for symptomatic uncomplicated cholelithiasis (Southern Surgeon's Club, 1991), and approximately 15% to 30% of gallbladder carcinomas are detected incidentally at microscopic review of cholecystectomy specimens (Clair et al, 1993). A serious potential complication of laparoscopic cholecystectomy is the inadvertent dissemination of unsuspected gallbladder carcinoma (Winston et al, 1999a). Wibbenmeyer and colleagues (1995) reported that gallbladder carcinoma recurs more rapidly after laparoscopic cholecystectomy than after open cholecystectomy. Tumor can recur in the laparoscopic port tracks, even if surgical resection of the port sites is performed at subsequent hepatic resection for attempted cure. Recurrent tumor may appear as a mass along the anterior abdominal wall with extension into the subjacent omental fat (Fig. 16.51; Winston et al, 1999a). These observations underscore the need to correctly identify findings suggestive of

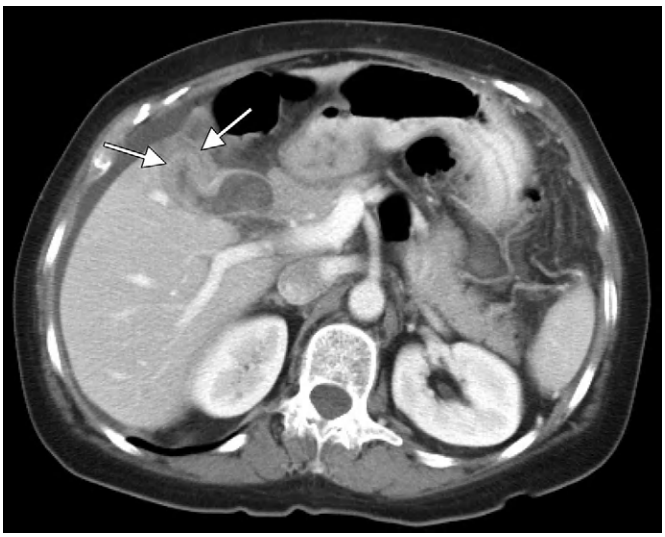


FIGURE 16.49. Contrast-enhanced computed tomography reveals focal gallbladder wall thickening (*arrows*) in a patient with gallbladder cancer.

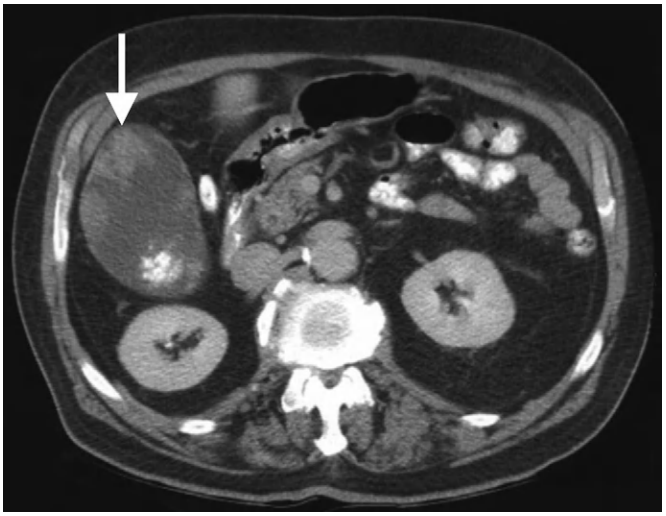


FIGURE 16.50. Gallbladder carcinoma. The gallbladder is distended and contains calcified stones. Nodular soft tissue emanates from the gallbladder wall into the lumen (*arrow*).

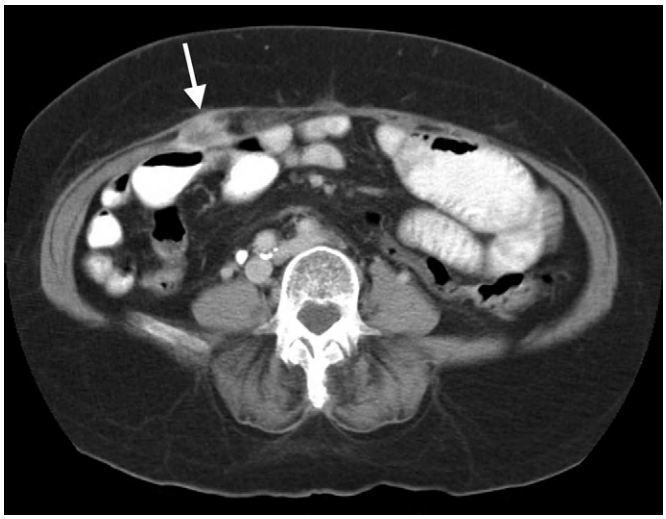


FIGURE 16.51. Contrast-enhanced computed tomography in a patient who had previously undergone laparoscopic cholecystectomy. The enhancing mass (*arrow*) within the anterior abdominal wall reflects recurrent gallbladder carcinoma within a laparoscopic port tract.

gallbladder carcinoma on preoperative imaging when elective laparoscopic cholecystectomy is planned.

Cholangiocarcinoma

Cholangiocarcinoma (see Chapter 50) is an adenocarcinoma that arises from bile duct epithelium. Conditions that place patients at increased risk for developing cholangiocarcinoma include clonorchiasis, hepatolithiasis, choledochal cyst, Caroli disease, hepatitis C viral infection, and primary sclerosing cholangitis (Sherlock & Dooley, 1997). Cholangiocarcinoma usually is classified as either intrahepatic or extrahepatic, and intrahepatic cholangiocarcinoma is classified further as either hilar or peripheral in location; these three types of cholangiocarcinoma—*peripheral*, *hilar*, and *extrahepatic*—are often regarded as distinct clinical and radiologic entities (Han et al, 2002), although this classification scheme is controversial. The Liver Cancer Study Group of Japan (1997) categorized intrahepatic cholangiocarcinoma into three types based on the macroscopic appearance: *mass forming*, *periductal infiltrating*, and *intraductal*.

The hepatic hilus is the most common location of cholangiocarcinoma, occurring in 40% to 60% of patients (Burke et al, 1998; Nagorney et al, 1993; Nakeeb et al, 1996). Tumors involving the distal bile duct account for 20% to 30% of all cholangiocarcinomas, and approximately 10% of cholangiocarcinomas arise peripherally within the intrahepatic biliary tree (Berdah et al, 1996; Chu et al, 1997; Harrison et al, 1998).

HILAR CHOLANGIOCARCINOMA. Cholangiocarcinoma can arise anywhere in the biliary tree, but tumors involving the biliary confluence, termed *hilar cholangiocarcinoma*, are the most common; these are further broken down into *infiltrating*, *exophytic*, and *polypoid* types. Infiltrating hilar cholangiocarcinoma is the most common type, accounting for more than 70% of cases (Fig. 16.52); such tumors usually are seen as focal thickening of the duct wall with obliteration of the lumen (Han et al, 2002). Exophytic cholangiocarcinoma appears as a mass showing peripheral rim enhancement; its appearance is similar to peripheral cholangiocarcinoma. The polypoid type of hilar cholangiocarcinoma appears as an intraductal soft-tissue mass that expands the duct lumen; this type of tumor may be mulifocal within the biliary tree, and it involves the intrahepatic and extrahepatic bile ducts (Han et al, 2002).

Generally, long-term survival is possible only with an en bloc resection of the liver and the extrahepatic biliary ducts (Jarnagin & Winston, 2005). Jarnagin and colleagues (2001) proposed a staging system for hilar cholangiocarcinoma that predicts resectability, likelihood of metastatic disease, and survival. Preoperative imaging should focus on addressing factors that determine resectability. Four crucial components of resectability are 1) level and extent of tumor within the biliary tree, 2) vascular invasion, 3) hepatic lobar atrophy, and 4) distant metastatic disease.

High-resolution MDCT in combination with interactive image viewing in cine mode using PACS has enhanced the radiologist's ability to address these issues (see Fig. 16.52). It is possible to trace the individual dilated bile ducts to determine the point or points of obstruction (Fig. 16.53). Zandrino and colleagues (2002) reported that multislice CT performed without a cholangiographic contrast agent correctly identified the cause of biliary obstruction in 31 (86%) of 36 patients.

One feature of cholangiocarcinoma is subepithelial spread of tumor along the duct wall and periductal tissues, and significant tumor may extend beneath an intact epithelial lining. For this reason, radiologic studies may underestimate the full extent of tumor. This possibility emphasizes the need for frozen section analysis of duct margins (see Fig. 16.52; Jarnagin & Winston, 2005).

Tumor extent along the hepatic arteries can be identified with CT angiography. Lobar atrophy, also apparent on CT, is an important finding in patients with cholangiocarcinoma. Atrophy is a major factor in the proposed clinical T-stage criteria, and it affects resectability. Although long-standing obstruction of the ipsilateral bile duct may cause moderate atrophy, associated portal venous obstruction causes rapid and severe atrophy of the affected lobe (Fig. 16.54; Jarnagin & Winston, 2005). Atrophy also is important to recognize at imaging when biliary decompression is planned. Drainage of an atrophic lobe does not relieve jaundice and is not indicated, unless it is done as treatment for biliary sepsis (Jarnagin & Winston, 2005).

PERIPHERAL CHOLANGIOCARCINOMA. The most common type of intrahepatic cholangiocarcinoma is mass-forming peripheral cholangiocarcinoma. On contrast-enhanced CT, peripheral cholangiocarcinoma appears as a low-attenuation mass with peripheral rim enhancement (Fig. 16.55), and it is associated with focal dilation of the intrahepatic bile ducts around the mass. Contrast enhancement of the mass is often seen on the delayed images (Keogan et al, 1997; Lacomis et al, 1997; Valls et al, 2000). This delayed enhancement is likely due to the increased stromal fibrosis seen within these tumors (Valls et al, 2000).

EXTRAHEPATIC CHOLANGIOCARCINOMA. Infiltrating cholangiocarcinoma is the most common type of cholangiocarcinoma involving the extrahepatic bile duct. It usually appears as a mass or thickening of the bile duct wall at the site of biliary obstruction. The radiologic and pathologic features are identical to those of hilar cholangiocarcinoma, and the assessment and treatment of distal bile duct cancers is similar to that of pancreatic head carcinoma (Blumgart et al, 2001).



FIGURE 16.52. Hilar cholangiocarcinoma. **A,** Axial contrast-enhanced computed tomography (CT) reveals an infiltrative, low-attenuation tumor (*arrow*) surrounding an internal biliary stent (*arrowhead*), resulting in bilobar intrahepatic biliary duct dilation. **B,** Axial contrast-enhanced CT reveals confluent tumor (*large arrows*) encasing a replaced right hepatic artery (*small arrow*), which originates from the superior mesenteric artery. Despite the biliary stent, intrahepatic biliary duct dilation is evident. **C,** Oblique axial maximum intensity projection image reveals narrowing of the right portal vein (*large arrow*) secondary to infiltrative tumor. Bilobar intrahepatic biliary ductal dilation is evident (*smaller arrows*).

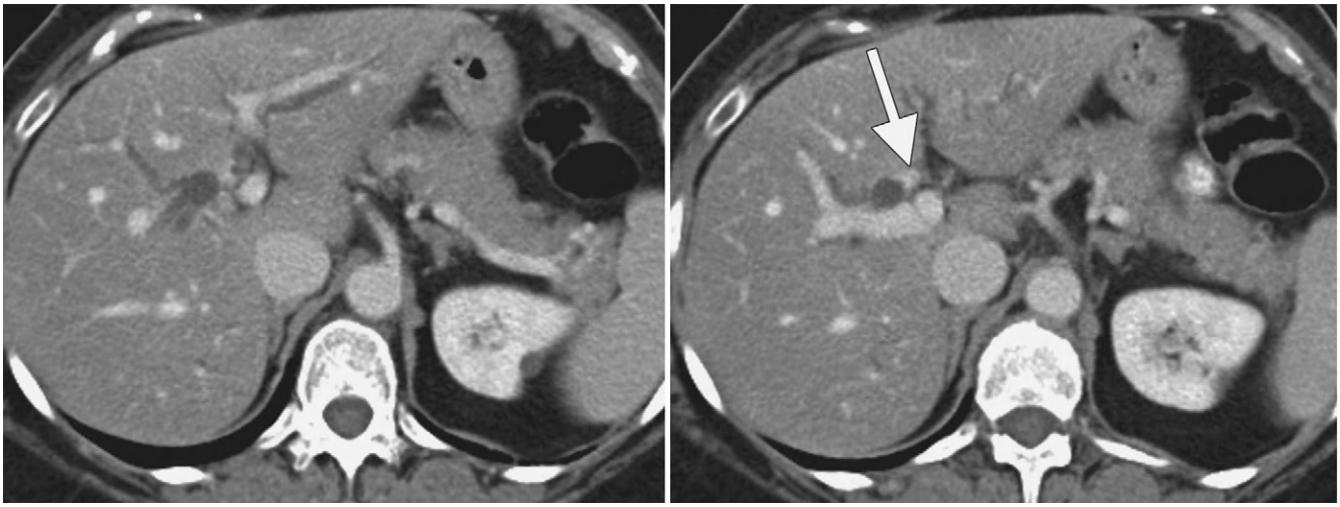


FIGURE 16.53. Cholangiocarcinoma. Contrast-enhanced computed tomography reveals bilobar central intrahepatic biliary duct dilation as a result of an obstructing enhancing mass at the hepatic hilus (*arrow*).



FIGURE 16.54. Infiltrative hilar cholangiocarcinoma. Reformatted oblique axial image with dilated bile ducts appearing bright. The infiltrative mass (*long arrow*) in the left hepatic lobe resulted in left-sided intrahepatic biliary ductal dilation (*short arrows*). Tumor extends along the central portion of the right portal vein with mild atrophy of the left lobe.

The intraductal polypoid or papillary variant of cholangiocarcinoma accounts for approximately 10% of all cholangiocarcinomas. The most common location for this type is the distal bile duct (Baer et al, 1990). As opposed to the infiltrative cholangiocarcinoma that narrows the duct lumen, papillary tumors are intraductal masses that expand the bile duct lumen. Papillary tumors have minute, frondlike projections that may be fixed to or detached from the bile duct wall. On CT, enhancement of the mass depends on whether or not the tumor is fixed or detached to the duct wall, and there may be segmental asymmetric thickening of the bile duct wall with enhancement. Tumors are friable and slough easily, which may result in intermittent or partial biliary obstruction (Lim et al, 2003). Some papillary tumors produce a profuse amount of mucus, resulting in severe biliary dilation (Lim et al, 2004). Recognition of a papillary cholangiocarcinoma is important, because these tumors are more likely resectable and carry a more favorable prognosis than other types (Pitt et al, 1995).

Biliary Cystadenoma and Cystadenocarcinoma

Biliary cystadenomas (see Chapter 48) are uncommon benign cystic lesions that occur predominantly in middle-aged women between 42 and 55 years (Ishak et al, 1977). Although benign, these lesions may recur after excision and have the potential to develop into biliary cystadenocarcinomas. Cystadenomas are most often intrahepatic (83%), but they may also occur within the extrahepatic bile ducts (13%) or gallbladder (0.02%) (Devaney et al, 1994).

CT shows cystadenomas to be multiloculated cystic lesions with internal septations; only rarely are they unilocular (Fig. 16.56). Calcifications may be present within the wall of the cyst or within the septa, and septa may enhance with intravenous contrast media (Fig. 16.57). The attenuation of the cyst fluid depends on the content of the fluid, which may be hemorrhagic, mucinous, proteinaceous, or bilious (Buetow et al, 1995). Tumor nodules and papillary projections extending into the cyst typically enhance with intravenous contrast medium. No specific imaging feature permits reliable differentiation of biliary cystadenoma from biliary cystadenocarcinoma (Buetow et al, 1995a).

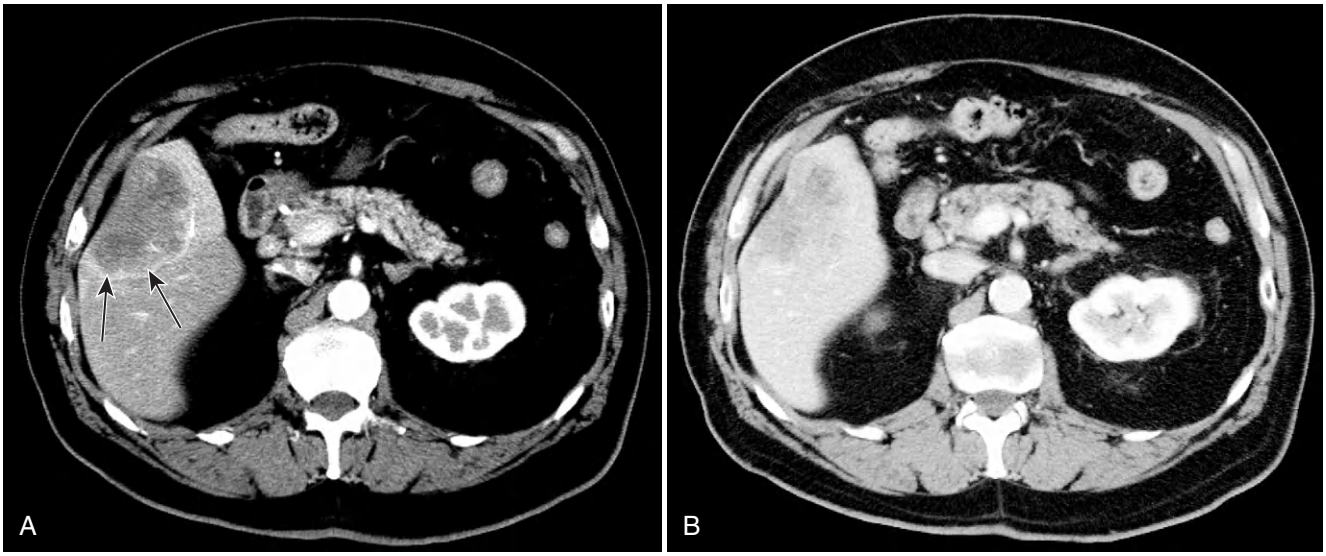


FIGURE 16.55. Late arterial phase and portal venous phase images of a patient with a peripheral cholangiocarcinoma. **A,** Late arterial phase image reveals peripheral enhancement of a heterogeneous mass in the right hepatic lobe (*arrows*). **B,** Portal venous phase image reveals heterogeneous enhancement of the central portion of the mass.

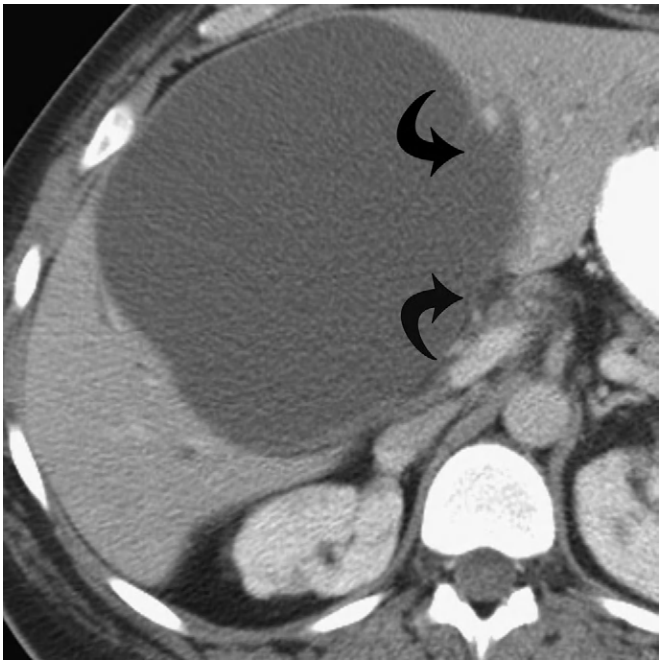


FIGURE 16.56. Biliary cystadenoma. Contrast-enhanced computed tomography reveals a large cystic mass with a very subtle internal septation (*curved arrows*).

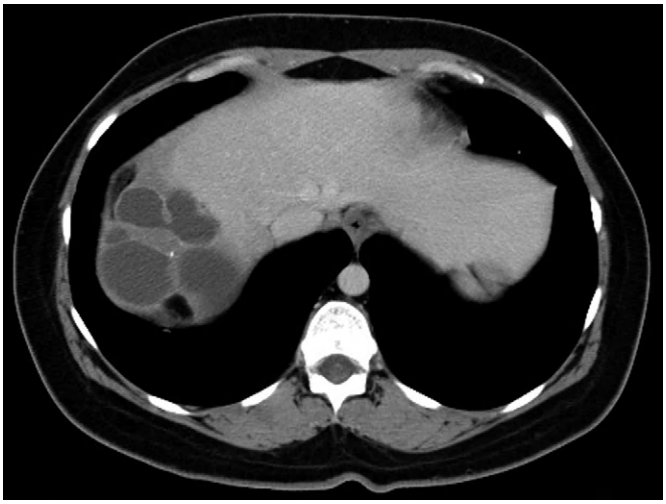


FIGURE 16.57. Recurrent biliary cystadenoma after resection. A multiloculated cystic lesion is seen at the resection margin containing enhancing septa and calcification.

COMPUTED TOMOGRAPHY OF THE PANCREAS

Historical Review

Evaluation of the pancreas was revolutionized by the advent of helical CT scanning, which enabled rapid evaluation of the pancreas during different phases of contrast injection (Ferrucci, 1999; Ishiguchi et al, 2001; Mertz et al, 2000; Van Hoe & Baert, 1997). Newer MDCT scanners have improved pancreatic imaging further by allowing extremely rapid data acquisition, retrospective change in slice thickness and location, and three-dimensional image review in multiple projections (Ferrucci, 1999; Horton & Fishman, 2000; Ishiguchi et al, 2001; Johnson et al, 2003; Mertz et al, 2000; Rubin, 2003; Van Hoe & Baert, 1997).

Technique

The imaging of the pancreas relies on the differential intravenous contrast enhancement between tumor tissue and normal pancreatic parenchyma. The use of intravenous contrast injection is mandatory for accurate diagnosis, and timing of the contrast injection and accurate delivery of the appropriate volume requires use of a dedicated CT power injector. Dedicated pancreatic protocols employ thin-section imaging (slice thicknesses ≤5 mm), but protocol slice thicknesses vary according to the clinical indications. Preoperative planning for surgical pancreatic resection demands a much more detailed evaluation of the pancreas and surrounding vascular structures than does a follow-up scan performed to evaluate response to chemotherapy. Such preoperative protocols often employ scan thicknesses of 2.5 mm or less.

Preoperative imaging to determine resectability of pancreatic carcinoma requires a study directed toward clinically relevant findings and accurate detailed evaluation of peripancreatic arteries and veins. CT angiography has emerged as the technique of choice because of the high-quality imaging, speed of the examination, ease of performance, and ready availability. CT angiography was initially limited by the breath-hold time required for a single-detector helical scanner, but with multidetector scanning, the time for image acquisition has been shortened to less than 15 seconds; with 64-slice scanners, scan time can be shortened to 5 seconds or less, a reasonable breath hold for most patients.

Computed Tomography Scan Protocols for the Pancreas

Initial scan protocols for evaluation of the pancreas recommended four phases for the preoperative evaluation of the pancreas: The *noncontrast phase* permits evaluation of pancreatic calcifications and allows localization of the precise levels for imaging on the postcontrast study. The next two phases are combined early and late arterial phases, obtained within a single breath hold; the *early arterial phase* permits evaluation of pancreatic vasculature without interference from venous opacification. The *late arterial phase* is of greatest benefit to distinguish pancreatic neoplasms from adjacent normal pancreatic tissue by maximizing differences in contrast enhancement. It also is useful to evaluate hypervascular liver metastases as seen in patients with neuroendocrine tumors of the pancreas. The fourth phase is the *routine portal venous phase*, which is best to evaluate for hypovascular liver metastases (Cantisani et al, 2003; Takeshita et al, 2002) in patients with adenocarcinoma. More recent reports (Fletcher et al, 2003) have shown no need for the early angiographic phase of imaging of the pancreas, because the pancreatic and hepatic arterial anatomy and pancreatic parenchyma are well evaluated on the late arterial phase of imaging. This practice further shortens the scan time and reduces the radiation dose to the patient.

An exciting new development in multidetector CT is the promise of dual-energy CT, a technique that scans the patient at

both 80 kvp and 140 kvp simultaneously. Because of the different interactions of soft tissue, bone, and intravenous contrast material, it is possible to eliminate the noncontrast images and obtain a "virtual" noncontrast image. This is done by scanning the patient by injecting contrast and using the differential interactions with the two different scanning energies to digitally subtract the intravenous contrast. It is also possible to eliminate bone with this technique. This technology is still in early development, but it holds great promise for imaging multiple anatomic areas of the body, including hypervascular tumors of the liver and pancreas (Graser et al, 2009; Marin et al, 2009), with the expectation of reducing radiation dose.

For CT angiography of the pancreas, the patient should be fasting to ensure that the stomach and proximal bowel are empty; before the examination, the patient should drink approximately 750 to 1000 mL of water. CT angiography requires the substitution of water for dilute radiopaque oral contrast medium (Lawler & Fishman, 2002; Soriano et al, 2004; Takeshita et al, 2002) to isolate the enhanced vessels from the gastrointestinal tract. Enhanced vessels have CT densities similar to contrast-filled bowel. Water within the lumen of the bowel facilitates identification of vascular anatomy, allows evaluation for possible invasion into adjacent bowel, and facilitates analysis on the three-dimensional workstation.

Noncontrast images are acquired initially to localize the pancreas accurately before intravenous contrast administration and to evaluate for the presence of calcifications. Injection of intravenous contrast medium is done at a high flow rate of 4 to 5 mL/s, with scanning beginning during the late arterial phase; this permits evaluation of the peripancreatic vasculature and maximizes contrast differences between tumor and normal pancreatic tissue. Different methods exist to initiate scanning at the time of maximal arterial enhancement, which may vary from patient to patient. A small timing bolus (Kalra et al, 2004) may be used to determine the appropriate time delay, or CT scanning may be triggered automatically when a vascular structure reaches a predefined density. Other authors use a standard delay for imaging all patients, a potential pitfall in patients with cardiac disease.

Routine scanning for the follow-up of pancreatic cancer in a postoperative patient or for evaluation of response to therapy is done with oral and intravenous contrast material. These patients drink 750 mL of a 2% barium sulfate suspension or equivalent water-soluble iodine solution 45 minutes before scanning, which is performed approximately 70 seconds from the start of intravenous contrast injection using a dedicated power injector for CT, but this will vary with the speed of the scanner. Routine injection is via a 20-gauge catheter placed in an antecubital vein and injected at a rate of 2.5 mL/s with contiguous 5 mm or thinner scans.

Anatomy of the Pancreas

The normal pancreas (see Chapter 1) is well imaged on routine CT of the abdomen. It is a retroperitoneal structure bounded anteriorly by the stomach and posteriorly and inferiorly by the third portion of the duodenum, and it lies medial to the C-loop of the duodenum and medial to the spleen. Crucial to the evaluation of the pancreas and possible tumor resection is its relationship to vessels. The body and tail of the pancreas lie immediately anterior to the splenic vein, and the neck, head, and uncinate process of the pancreas are in close relationship to the superior mesenteric artery (SMA) and vein and lie just caudal to the celiac axis. The normal pancreas has a fat plane completely surrounding the SMA, whereas no fat plane lies between the SMV and the pancreatic head (Fig. 16.58).

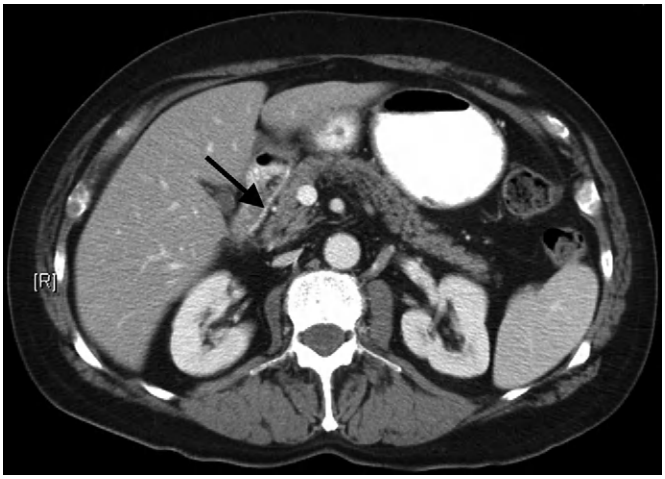


FIGURE 16.58. Normal pancreas. Note the gastroduodenal artery along the anterior margin of the pancreas (*arrow*).

Patients may sometimes be seen with fatty infiltration of a portion of the pancreas or involving the gland diffusely (Fig. 16.59). In such instances, the gland is best identified by identification of surrounding vascular structures and bowel. Severe fatty infiltration permits visualization of fine vascular detail within the pancreas, but a potential pitfall is that a small island of residual normal pancreatic parenchyma may be confused with an intrapancreatic mass.

Vascular anatomy is depicted in exquisite detail on CT angiography (Ibukuro, 2001; Ibukuro et al, 1995; Yamada et al, 2000; Ferrari et al, 2007; Horiguchi et al, 2008). In addition to assessment of the celiac and superior mesenteric arteries and vein and their major branches, smaller vessels are routinely visualized and assessed, including the gastroduodenal artery,

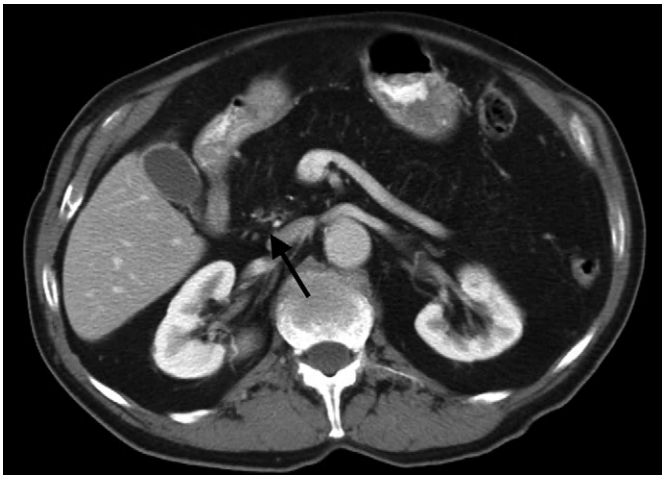


FIGURE 16.59. Extensive fatty replacement of the pancreas. Minimal pancreatic acinar tissue is visible in the posterior aspect of the pancreatic head (*arrow*).

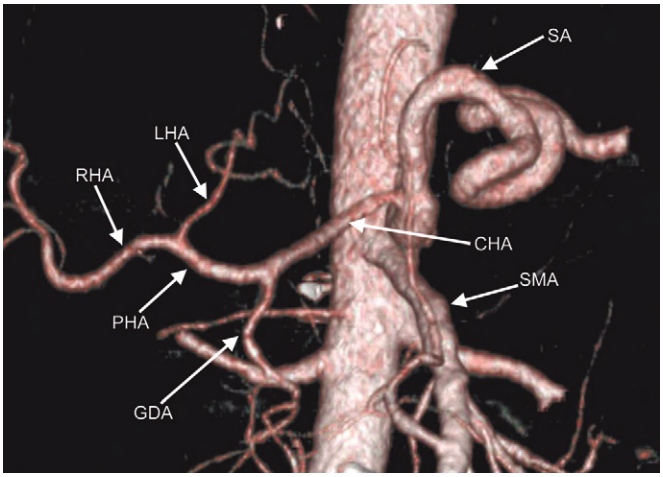


FIGURE 16.60. Volume-rendered computed tomographic angiogram of the hepatic vasculature. *RHA,* right hepatic artery; *LHA,* left hepatic artery; *PHA,* proper hepatic artery; *GDA,* gastroduodenal artery; *SA,* splenic artery; *CHA,* common hepatic artery; *SMA,* superior mesenteric artery.



FIGURE 16.61. Low-attenuation mass (*arrow*) in the head of the pancreas.

pancreaticoduodenal vessels, and pancreatic branches (Fig. 16.60). MDCT permits even more exquisite evaluation of these small vessels and better three-dimensional evaluation of the data (Fishman & Horton, 2001; Fishman et al, 2000; House et al, 2004; Johnson et al, 2003; Takeshita et al, 2002).

Tumors of the Pancreas

Pancreatic Adenocarcinoma

Pancreatic adenocarcinoma (see Chapter 58A) is the fourth most common cause of death from malignancy (Kim et al, 2004a) and is often discovered at an advanced and inoperable stage. Operative mortality and morbidity rates of 2.8% and 40%, respectively (Wagner et al, 2004), underscore the need for preoperative evaluation to select the subgroup of patients who may be candidates for curative resection.

A recent report describes a new scoring system for tumor invasion that looks at both the length and degree of circumferential encasement of the peripancreatic arteries and veins to determine resectability, using data obtained from 16-slice scanners (Klauss et al, 2008). This score evaluates the length of tumor contact and circumferential extent of tumor involving the SMV, splenic vein, portal vein, aorta, celiac trunk, hepatic artery, splenic artery, and SMA. Veins were also assessed for contour deformations. The authors of this study reported sensitivity and specificity of 89% and 99% for vascular invasion and a sensitivity of 94% and specificity of 89% for the evaluation of resectability.

Pancreatic ducts represent only 4% of the pancreatic tissue but are the source of 90% of pancreatic malignancies (Cubilla & Fitzgerald, 1975; Morohoshi et al, 1983). Adenocarcinoma is the most common form of pancreatic cancer, and it occurs in later life. The clinical presentation depends on the location within the gland; cancers within the pancreatic tail are clinically silent and may not show up until metastasis is widespread, but cancers within the pancreatic head or periampullary region tend to show up earlier, with biliary obstruction a common sign in 50% of patients.

Pancreatic adenocarcinoma appears as a low-attenuation mass, often deforming the contour of the pancreas with secondary signs depending on the tumor location (Figs. 16.61 and 16.62). A mass in the pancreatic head is more commonly associated with biliary or pancreatic ductal dilation. The pancreas proximal to the obstruction is often atrophic, a secondary and often early indication of the tumor site.

Knowledge of vascular involvement or encasement is crucial to preoperative evaluation of the pancreas, because involvement of the superior mesenteric artery or vein, common hepatic artery, or celiac axis generally precludes operative resection for cure. Involvement of the main portal vein is not a contraindication to surgery, because a portion of the main portal vein may be resected and reanastomosed proximal to the jejunal branches (Chae et al, 2003; Lygidakis et al, 2004; Nakao et al, 2004; Yoshimi et al, 2003). Kitagawa and colleagues (2008) reviewed patterns of spread of adenocarcinoma of the pancreatic head



FIGURE 16.62. Dilated pancreatic duct (*arrow*) secondary to carcinoma in the head of the pancreas.

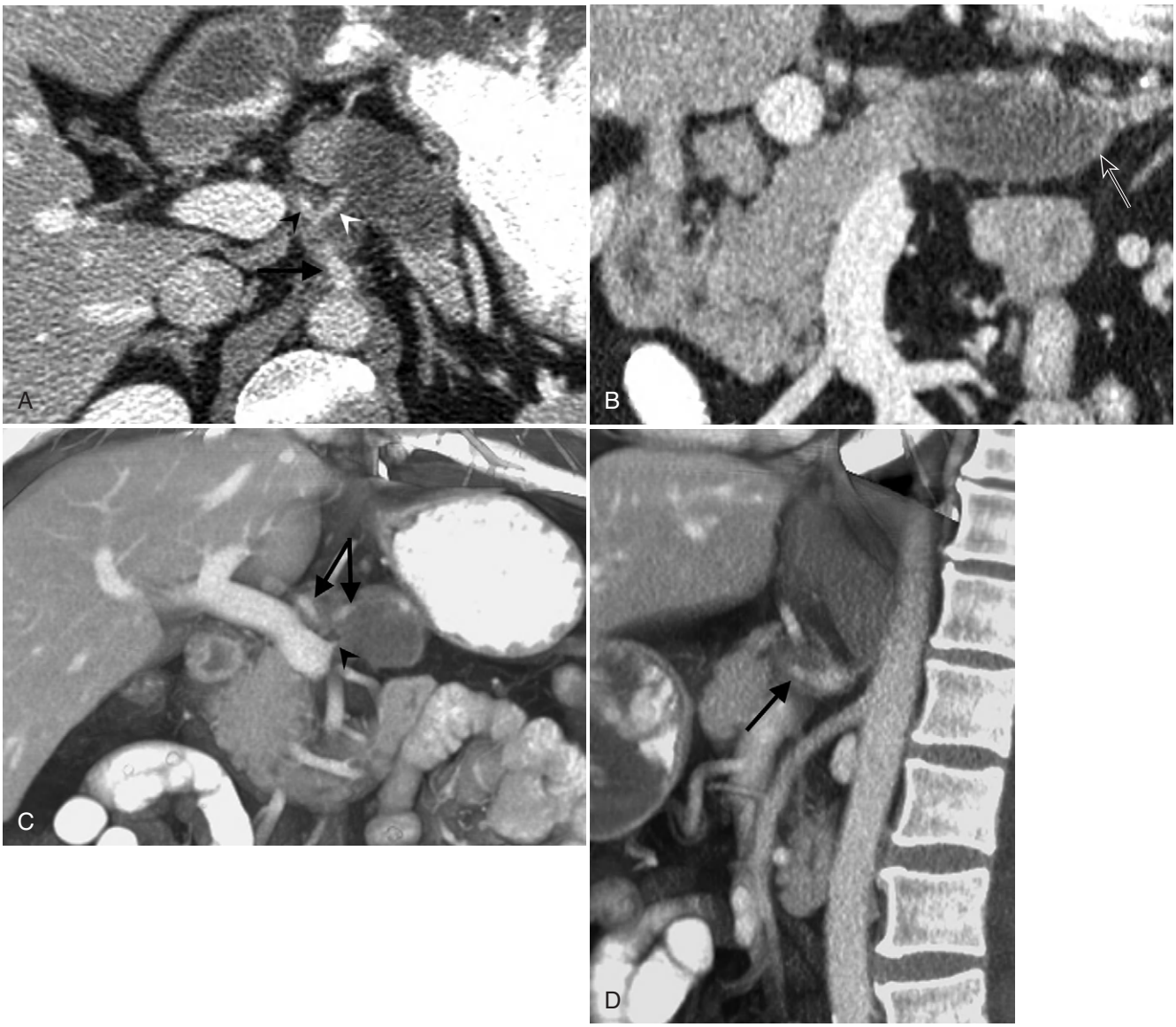


FIGURE 16.63. Pancreatic cancer with vascular encasement. **A,** Cancer in the body of the pancreas tracks posteriorly to encase the celiac axis, proximal hepatic artery (*black arrowhead*), and splenic artery (*white arrowhead*). **B,** Curved multiplanar reconstruction showing the mass (*arrow*) in the body of the pancreas. **C,** Coronal volume-rendered image shows a mass in the body of the pancreas occluding the splenic vein (*arrowhead*) and encasing celiac axis branches (*arrows*). **D,** Sagittal volume-rendered image shows mass encasing the celiac axis (*arrow*).

and found specific patterns, depending upon the origin of the cancer from the dorsal or ventral pancreatic anlagen on an embryologic basis. Tumors confined to the ventral pancreas had metastases along the SMA and peripancreatic nodes, whereas tumors that arose from the dorsal pancreas domain metastasized to the common hepatic artery, hepatoduodenal ligament, and the peripancreatic nodes. Tumors that extended into both domains metastasized widely.

Early findings of pancreatic cancer may be extremely subtle and difficult to detect. In a study at the Mayo Clinic in Rochester, Minnesota, 62 scans obtained before the histologic diagnosis of pancreatic cancer in 28 patients were retrospectively reviewed by two radiologists. Half of the scans obtained before diagnosis showed findings that were interpreted as definite or suspicious for pancreatic carcinoma 2 to 6 months and 6 to 18 months before diagnosis (Gangi et al, 2004). Pancreatic duct dilation and cutoff were early findings. A limitation of this study is that it was a retrospective review of scans obtained between August 1994 and June 2001. Current techniques of thin-section, high-resolution scanning during optimal pancreatic enhancement should improve detection of small lesions. More commonly, pancreatic cancer is detected at an advanced stage, associated with arterial vascular encasement or invasion, venous involvement, peripancreatic adenopathy, hepatic metastases, or ascites (Figs. 16.63 and 16.64). Local arterial encasement or venous occlusion or both preclude resection for attempted cure. Centers with a high volume of pancreatic surgery do a partial resection of the portal vein and primary reanastomosis, but this mandates a cuff of remaining normal portal vein proximal to the first jejunal branch (Chae et al, 2003; Yoshimi et al, 2003). Three-dimensional workstations permit visualization of vascular involvement in coronal and

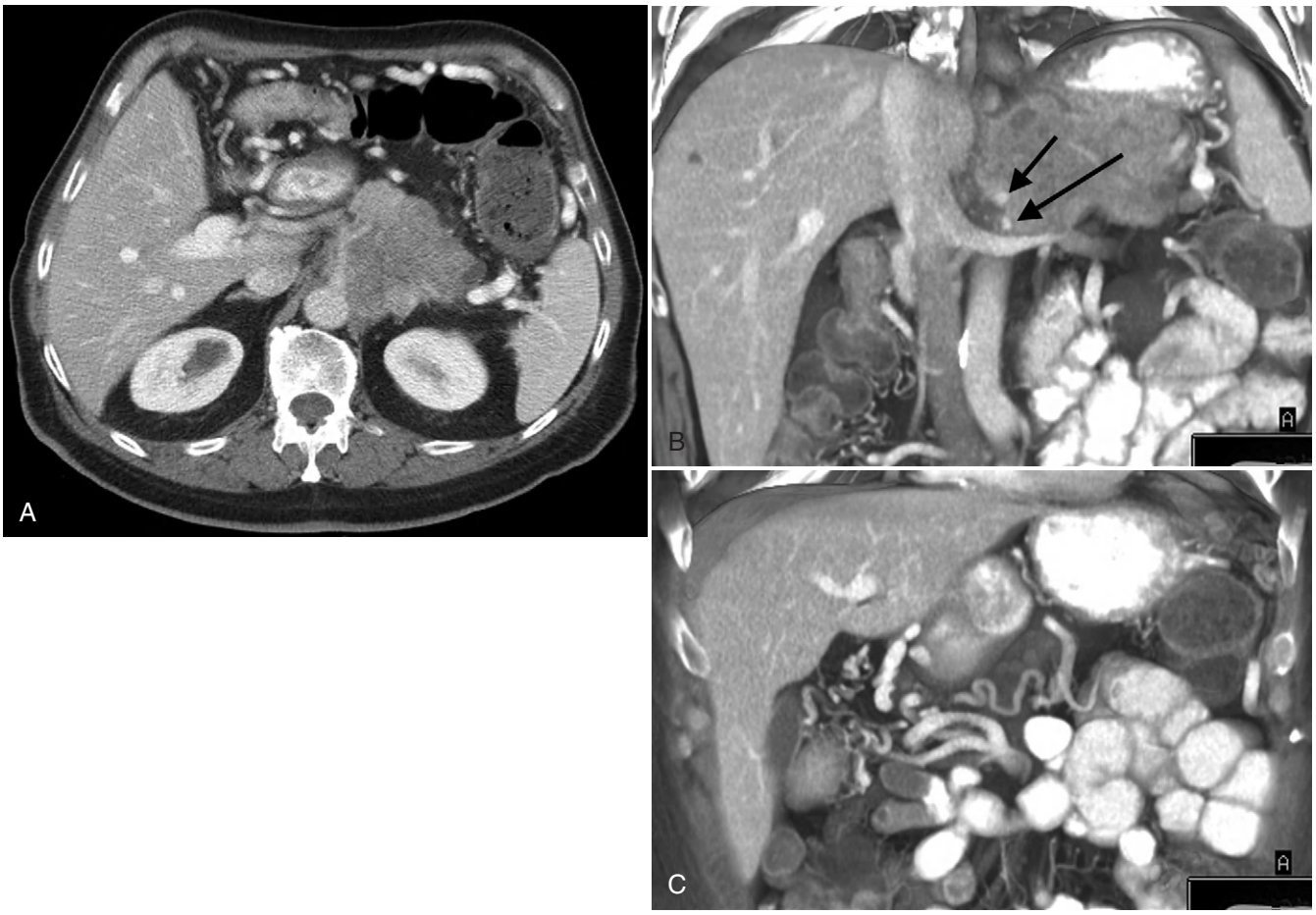


FIGURE 16.64. Large pancreatic mass with vascular encasement and collateral vessels. **A,** Mass in the body and tail of the pancreas encases the celiac artery and its branches. **B,** Coronal volume-rendered image shows the pancreatic mass and encasement of the celiac and superior mesenteric arteries (*arrows*) by tumor. **C,** Coronal volume-rendered image shows extensive collateral vessels in the abdomen from encasement of the splenic vein by pancreatic cancer.

sagittal planes and permit three-dimensional reconstructions using maximum intensity projections or volume rendering (Prokesch, 2003; Tamm & Charnsangavej, 2001; Tamm et al, 2001). Curved multiplanar reformatted images can offer a superb display of pancreatic anatomy and demonstration of adjacent vascular encasement (Vargas et al, 2004, Gong et al, 2004).

Neuroendocrine Cancer of the Pancreas

Neuroendocrine cancer of the pancreas arises predominantly from the islets of Langerhans and may arise in a sporadic fashion or in patients with multiple endocrine neoplasia type I (MEN-I). Pancreatic neuroendocrine tumors generally have a much more favorable prognosis than pancreatic adenocarcinoma. Presentation is diverse and often depends on the presence of hormonal activity and its associated symptoms (Kulke, 2003). Hormonally active tumors may present earlier and are generally smaller than non–hormonally active tumors.

The CT and MR appearances of endocrine tumors of the pancreas according to the World Health Organization (WHO) classification was reviewed recently (Rha et al, 2007). Masses are often hypervascular on imaging and may be associated with liver or nodal metastases or both (Fig. 16.65). Careful attention to detail is required, particularly for imaging of the hormonally

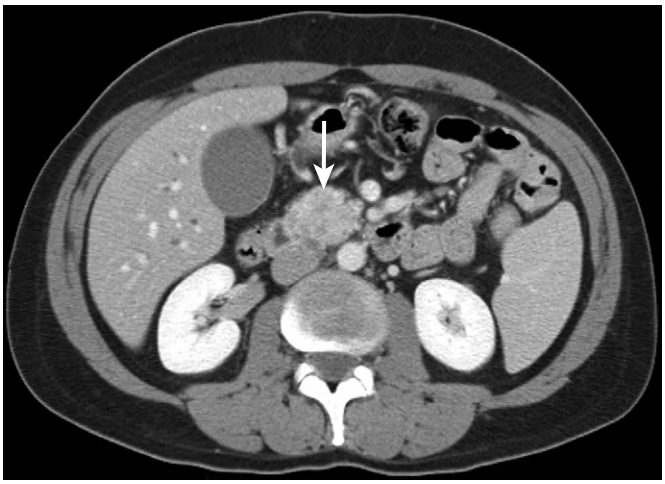


FIGURE 16.65. Pancreatic neuroendocrine cancer/hypervascular mass (*arrow*) on the portal venous phase.

active tumors, which may be small hypervascular masses that often require dedicated thin-section pancreatic protocols for initial detection (Gouya et al, 2003). Arterial phase imaging is necessary to detect masses that otherwise may be isodense on the portal venous phase of imaging (Fig. 16.66). Insulinomas are the most common type of functioning islet cell tumor of the pancreas and are generally extremely hypervascular. Routine follow-up of these patients is best assessed with triphasic scans of the liver to detect masses that may become isodense on portal phase imaging.

In a retrospective review of 50 patients with neuroendocrine cancer (Chu et al, 2002), median survival was 40 months, with overall 1-, 2-, and 5-year survival rates of 84%, 69%, and 36%, respectively. Long-term survival of these patients was related to surgical resection of the primary tumor, absence of liver metastases, metachronous liver metastases, and aggressive treatment of liver metastases using surgery, intrahepatic chemotherapy, or chemoembolization. A German review of 254 patients with neuroendocrine tumors showed 29% to be of pancreatic origin. The 5-year survival from the time of initial diagnosis for this subgroup of patients with pancreatic tumors was 43%. A smaller sized primary tumor (<2 cm) and histologic grading as low-grade malignant were associated with a longer survival (Pape et al, 2004).

Cystic Pancreatic Neoplasms

Cystic pancreatic neoplasms (see Chapter 57) represent a spectrum of disease that includes both benign and malignant entities. Distinguishing benign neoplasms from pancreatic pseudocysts can be difficult, and serial imaging may be necessary to evaluate for stability (Allen et al, 2003; Visser et al, 2004). Included in this group of neoplasms are serous cystadenomas, lymphoepithelial cysts and cystic neuroendocrine tumors, and pseudocysts. Mucinous cystic neoplasms have malignant potential and may present a challenge to distinguish from other benign pancreatic cysts.

INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM. Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a spectrum of disease, ranging from benign to malignant and characterized overall by improved survival compared with pancreatic adenocarcinoma. There is a greater male/female predominance, with a reported 57% of patients male in the Johns Hopkins experience (Sohn et al, 2004) and a 2.2:1 male/female predominance in a reported Japanese experience (Kimura et al, 1996). The tumor is classified into that of main pancreatic duct, branch duct, or mixed involvement (Bassi et al, 2000; Nagasaka & Nakashima, 2001; Nakamura et al, 2002; Tanaka, 2004; Tan

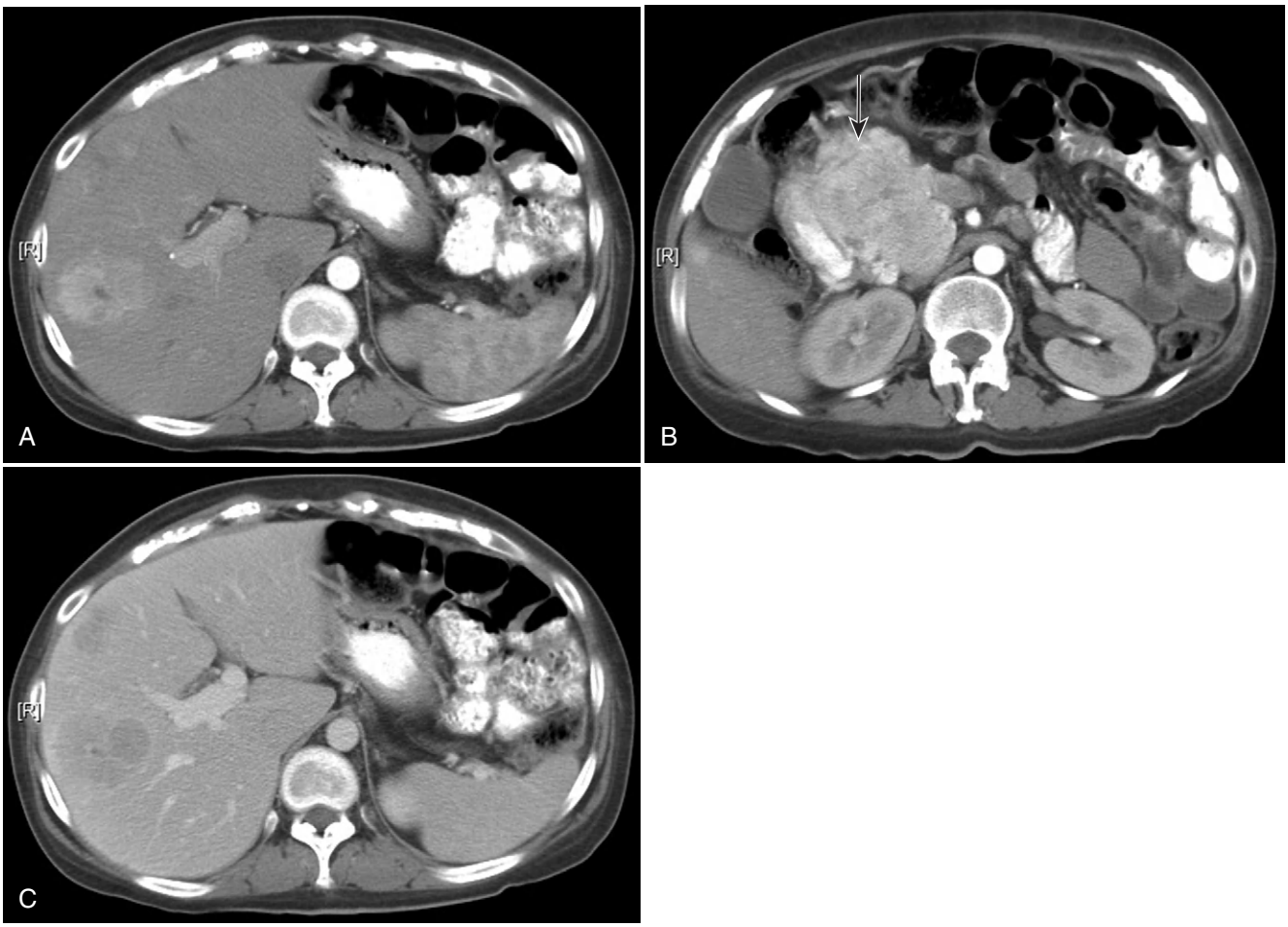


FIGURE 16.66. Islet cell tumor. **A,** Arterial phase scan shows hypervascular liver metastasis from islet cell cancer of the pancreas. **B,** Arterial phase scan shows hypervascular islet cell cancer of the pancreas (*arrow*). **C,** Liver metastasis from islet cell cancer of the pancreas is a lower attenuation than hepatic parenchyma on portal venous phase.



FIGURE 16.67. Intraductal papillary mucinous tumor of the pancreatic head (*arrow*).

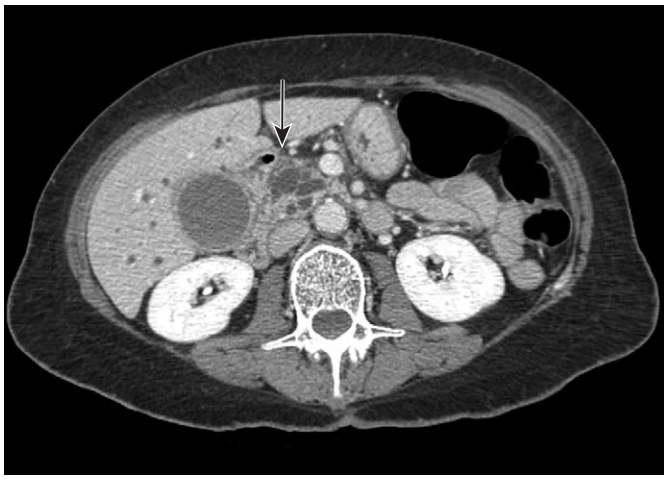


FIGURE 16.68. Intraductal papillary mucinous tumor (*arrow*) of the pancreatic head with invasive adenocarcinoma at pathologic examination; note associated biliary ductal dilation.

et al, 2009; Ogawa et al, 2008; Freeman, 2008). A review of surgical experience of 136 IPMNs from Johns Hopkins (Sohn et al, 2004) found 62% to be benign, and the remaining 38% had IPMNs with associated invasive cancers. The most common presenting symptoms are abdominal pain, weight loss, and nausea and vomiting; patients with invasive IPMNs also may be seen with jaundice.

IPMNs may occur in any portion of the gland. Branch-type neoplasms are most commonly benign, whereas the main duct and mixed types are frequently malignant (Tanaka, 2004; Tan et al, 2009). Multiplanar reformatted images may prove invaluable in the discrimination of branch-type IPMN from main-duct type (Takada et al, 2005). They are cystically dilated ducts that connect to the remainder of the ductal system, lined by flat or papillary mucinous or oncocytic epithelium with or without a component of invasive adenocarcinoma, and they are recognized as identifiable cystic structures of at least 1 cm radiographically or at surgery (Fig. 16.67). Careful attention to radiographic technique, including thin-section imaging with rapid injection of intravenous contrast medium, is crucial to detect these often small masses. Appropriate timing of scanning with the administration of contrast medium is designed to scan the pancreas during the *pancreatogram phase*, when pancreatic parenchyma is maximally enhanced, which maximizes contrast differences between the cystic mass and the enhanced pancreas. Location of the mass within the pancreatic head (Fig. 16.68) may compress the common bile duct with resulting dilation of the intrahepatic bile ducts. Invasive adenocarcinoma may be found at pathologic examination and has been reported to correlate most closely with the presence of mural nodules and pancreatic duct dilation of 7 mm or greater (Sugiyama et al, 2003; Kawamoto et al, 2005; Fig. 16.69). D'Onofrio and colleagues (2009) reported a case of an 8-mm undifferentiated pancreatic adenocarcinoma that had a

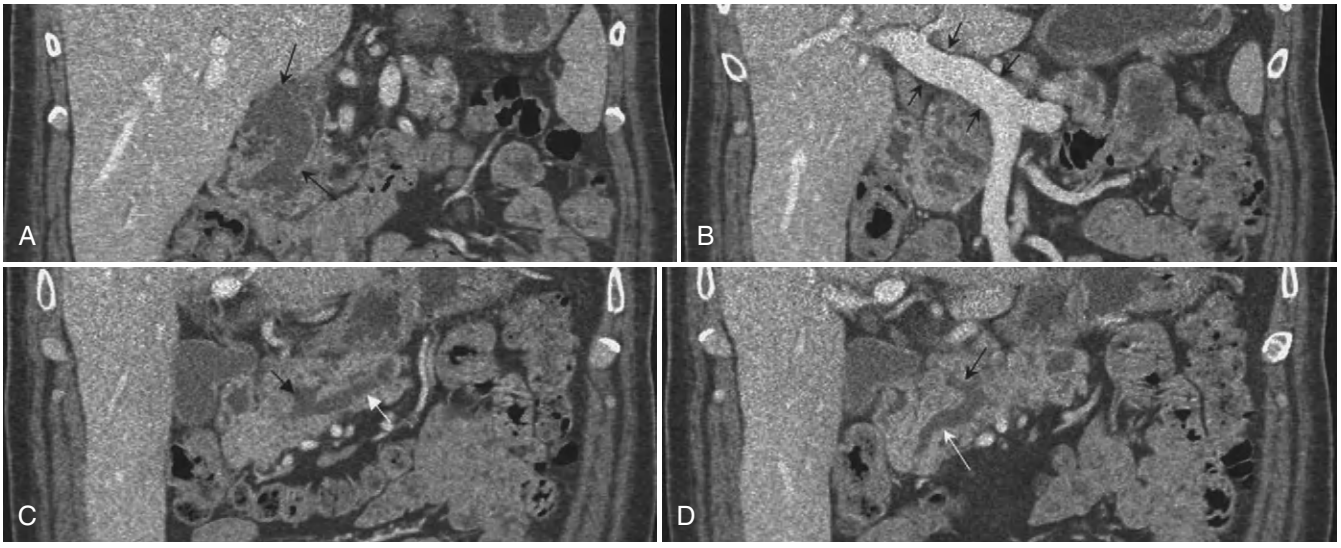


FIGURE 16.69. Intraductal papillary mucinous neoplasm. **A** to **D,** Diffuse involvement of the main (*white arrows*) and branch (*black arrows*) pancreatic ducts with invasive adenocarcinoma. **B,** No evidence of vascular encasement is found, as shown on the normal-appearing portal vein (*arrows*), and none was found at surgery or at pathologic examination.

desmoplastic reaction on an adjacent pancreatic duct, which was dilated and mimicked an IPMN. Intraductal papillary mucinous tumors have a high reported incidence of associated extrapancreatic synchronous and metachronous malignancies of 23.6% to 32%, especially colorectal carcinoma (Sugiyama & Atomi, 1999), and a high incidence of associated pancreatic malignancies (Yamaguchi et al, 2002).

SEROUS CYSTADENOMAS. Often discovered incidentally on abdominal CT scans performed for other indications, pancreatic serous cystadenomas are slow-growing tumors with a 2:1 female/male predominance. These tumors present at a mean age of 63 years versus 54 years for mucinous cystadenomas/carcinomas. Symptoms include vague abdominal pain or back pain. Other symptoms—including nausea, weight loss, and vomiting—are less common. Initially, these tumors were called *microcystic adenomas,* a term that has fallen into disfavor because of reported *macrocystic* tumors (Anderson & Scheiman, 2002).

Serous cystadenomas generally are surrounded by a fibrous capsule and contain numerous tiny cysts, which are sometimes so small that the cystic nature is difficult to appreciate, because it is below the limits of CT resolution. In these instances, ultrasound or MRI may reveal the cystic nature more clearly. Cyst sizes may vary from 1 mm to 2 cm, but occasionally cysts several centimeters in size may be encountered; differentiation from mucinous cystic neoplasms may therefore be difficult (Warshaw et al, 1990; Visser et al, 2008; Chaudhari et al, 2007; Kim et al, 2006). A central stellate scar, when present, is helpful to make the diagnosis. MRI may be useful to visualize the cystic nature when CT findings are equivocal (Allen et al, 2003; Sahani et al, 2002; Visser et al, 2004). Because of their slow-growing nature and vague symptoms in only 50% of patients, these masses may be quite large at the time of discovery (Figs. 16.70 and 16.71).

MUCINOUS CYSTIC NEOPLASMS. Mucinous cystic adenomas of the pancreas often present a mixed picture pathologically, including benign mucin-producing epithelium, dysplasia, carcinoma in situ, and tissue invasion. No imaging criteria permit differentiation of benign from malignant tumors, and all mucinous cystic tumors should be considered malignant or premalignant and should be excised completely (Sarr et al, 2000; Visser et al, 2004; Wilentz et al, 2000).

Mucinous cystic adenomas are found more frequently in women (9:1 predominance) and are frequently within the body and tail of the pancreas. In a series of 52 female patients with pathologically proven mucinous cystic tumors (Procacci et al, 2001), the most highly associated features of malignancy were a thick wall (>2 mm), septations, and calcification in the wall or within septations (Fig. 16.72).

OTHER CYSTIC PANCREATIC MASSES. Cystic masses may also be secondary to degeneration of previously solid masses. Neuroendocrine cancers may become necrotic and present with cystic degeneration (Fig. 16.73). Mucinous tumors may invade adjacent structures and present as cystic masses (Fig. 16.74).

Metastatic Disease to the Pancreas (See Chapter 60)

A pathology review (Adsay et al, 2004) of surgical and autopsy cases showed the most common primary malignancies metastatic to the pancreas were lung carcinomas, gastrointestinal carcinomas, and lymphomas. These are usually found in patients with widely disseminated disease. As at other sites in the body, pancreatic lymphoma tends not to occlude vessels but to encase them. This is a major distinguishing feature useful for diagnosis (Fig. 16.75). Detection of metastatic disease to the pancreas requires a high index of suspicion, because primary pancreatic carcinomas of ductal origin are far more common. When clinical suspicion is present, the study can be tailored to optimize the likelihood of detection. In a patient with renal carcinoma, hypervascular metastases to the pancreas may be detected on routine scanning or triphasic examination (Fig. 16.76).



FIGURE 16.70. Computed tomography showing low-attenuation pancreatic serous cystadenoma in the pancreatic tail (*arrow*) and hepatic hemangioma.

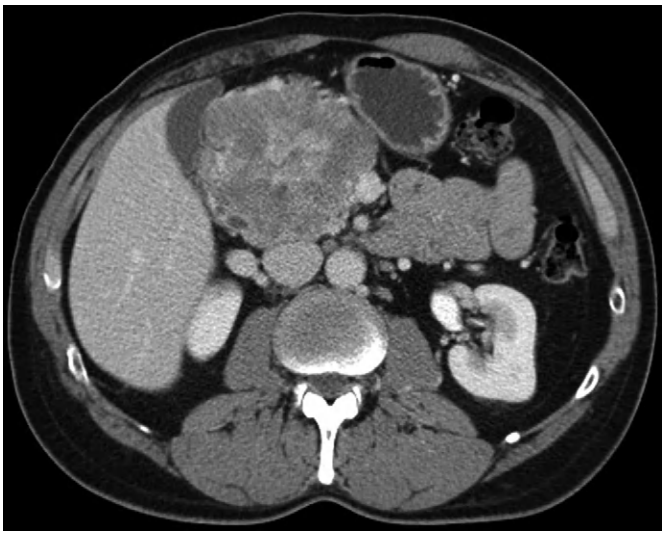


FIGURE 16.71. Serous cystadenoma of the pancreatic head shown in the portal phase.

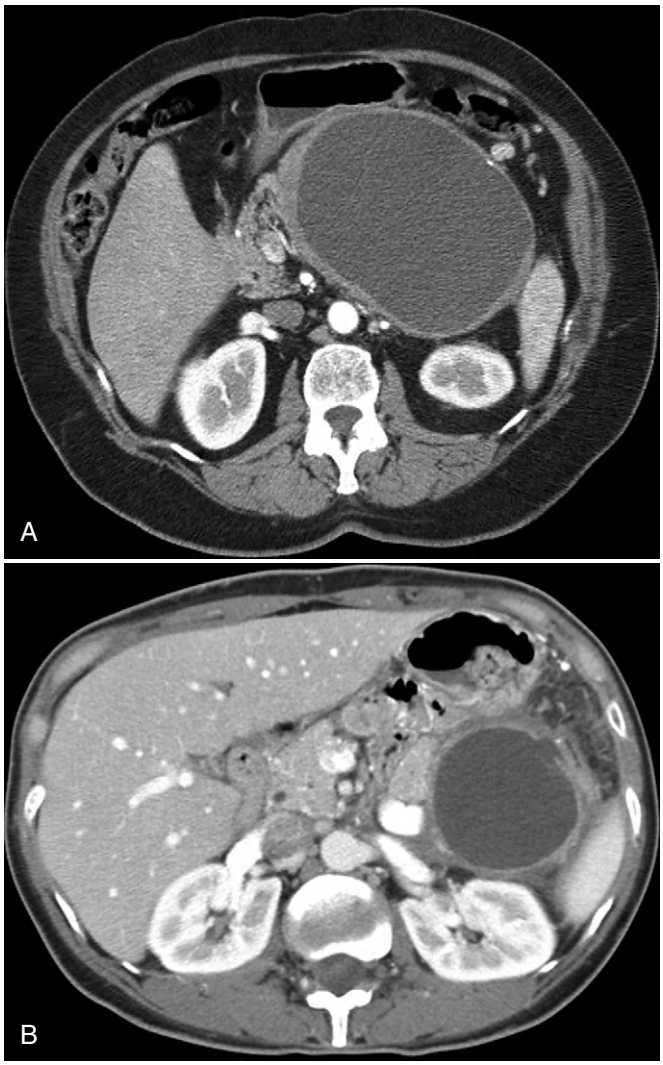


FIGURE 16.72. Mucinous cystadenocarcinoma. **A,** Contrast-enhanced computed tomography (CT) shows thick-walled cystic mass with punctate mural calcification. **B,** Contrast-enhanced CT shows thick-walled cystic mass with mural ulceration.



FIGURE 16.73. Pancreatic neuroendocrine neoplasm with cystic degeneration in the portal venous phase.

Solid and Papillary Epithelial Neoplasm of the Pancreas

Solid and papillary epithelial neoplasm (SPEN) of the pancreas is a rare tumor with a low malignant potential (Madan et al, 2004). SPEN has a reported incidence of 0.13% to 2.7% of all pancreatic malignancies and is most commonly encountered in the first three decades of life (Crawford, 1998; Cubilla & Fitzgerald, 1980; Lam et al, 1999), although the reported age range is 8 to 72 years with a mean age of 27 years. Female/male predominance is 9.5:1 (Mao et al, 1995), and these tumors are more common in nonwhites. Patients with malignant SPEN are often older and more often male (Lam et al, 1999). In a review of patients with pathologically proven SPENs, presenting complaints included abdominal pain, palpable mass, dyspepsia with bloating, and early satiety (Buetow et al, 1996; Yoon et al, 2001). Typically, laboratory findings are normal, with no elevation of tumor markers or serum amylase.

On CT, these tumors may have varied findings. They are often large and may have internal hemorrhage or cystic degeneration. Calcification is common (Fig. 16.77), but internal septations are not characteristic for this tumor (Buetow et al, 1996; West & Brady-West, 2000). Although this tumor is of low malignant potential, patients should be followed, because late metastases can occur.

Acinar Cell Carcinoma of the Pancreas

Acinar cell carcinoma is predominantly a tumor of the elderly man, with peak incidence in the 60s and many more men affected than women. Accounting for approximately 1% of all pancreatic tumors, acinar cell carcinoma of the pancreas is defined as a carcinoma of the exocrine pancreas exhibiting pancreatic enzyme production by the neoplastic cells (Cubilla & Fitzgerald, 1975; Morohoshi et al, 1983). They have a characteristic microscopic appearance of a relatively circumscribed periphery and minimal desmoplastic stroma within the tumor, with cells arranged in nests and cords. The tumor is most common in the head, neck, and uncinate process of the pancreas but may arise in any portion of the gland (Holen et al, 2002; Klimstra et al, 1992). Initial symptoms include abdominal pain or fullness, postprandial vomiting, and jaundice. Some patients may be asymptomatic, and the mass may be detected incidentally. Serum tumor markers may be normal, or there may be mild elevation of serum α-fetoprotein, carcinoembryonic antigen (CEA), and CA19-9.

CT features include a well-defined tumor with a thin, enhancing capsule and central necrosis, which may contain areas of internal calcification (Fig. 16.78). Such calcification may be a useful feature in distinguishing this entity, because only 2% of ductal adenocarcinomas and 22% of nonfunctioning islet cell tumors contain calcification (Buetow et al, 1995b; Eelkema et al, 1984). In a more recent series (Chiou et al, 2004), tumor diameters ranged from 3.3 to 18 cm, with an overall mean size of 7.2 cm. Most of these tumors were hypodense with respect to normal pancreatic parenchyma, although some showed hypervascular enhancement on the early arterial phase, some of which persisted into the portal venous phase.

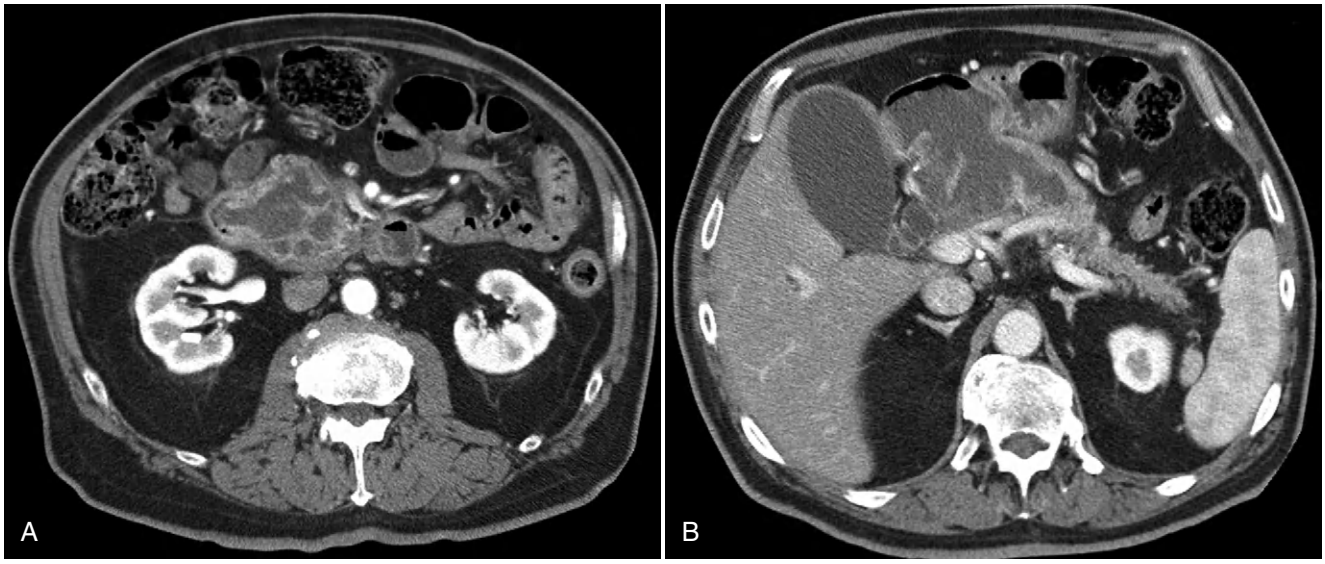


FIGURE 16.74. Intraductal papillary mucinous tumor with invasive mucinous adenocarcinoma. **A,** Large multicystic tumor extends into the papilla. **B,** Computed tomography shows that the mass also invades into the duodenum and stomach.

Inflammatory Diseases of the Pancreas

Pancreatitis (See Chapters 54 and 55)

The most common cystic mass of the pancreas is not a malignancy but rather a complication of acute or chronic pancreatitis. Fluid collections occur in approximately 50% of patients with moderate to severe pancreatitis. Of these, approximately 50% resolve spontaneously within 6 weeks (Baron & Morgan, 1997; Byrne et al, 2002), and 10% to 15% may progress to pseudocyst formation after developing a capsule. Pseudocyst formation is more common in patients with chronic pancreatitis and may occur in 20% to 40% of these patients.

Common causes of pancreatitis include alcohol, gallstones, idiopathic hypertriglyceridemia, drugs, pancreas divisum, trauma, and endoscopic retrograde cholangiopancreatography (Baron & Morgan, 1997). Clinical presentation includes nausea, vomiting, and epigastric pain. Serum amylase, frequently used to monitor pancreatitis, may be normal in acute pancreatitis and elevated in nonpancreatitic conditions. Elevation of the serum lipase may support the diagnosis of acute pancreatitis.

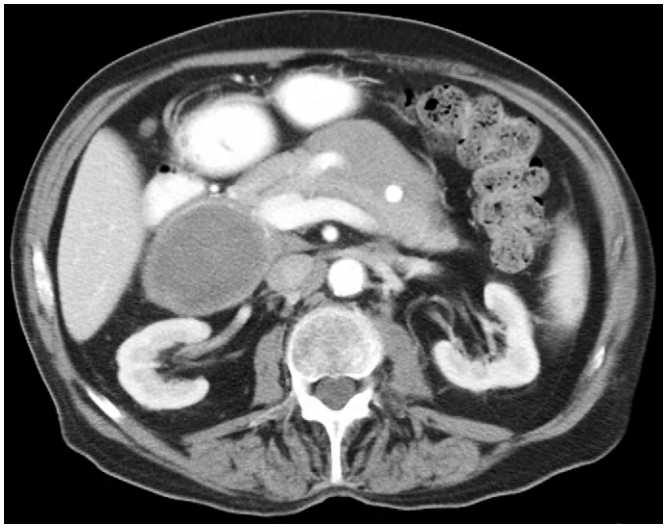


FIGURE 16.75. Lymphoma of the pancreas. Note absence of vascular narrowing.

Mild acute pancreatitis may appear on CT scan as enlargement of the pancreas with loss of definition of the borders of the pancreas. Depending on the part of the pancreas involved, there may be thickening of the right or left anterior pararenal fascia or diffuse thickening of adjacent fascial planes (Figs. 16.79 and 16.80). Acute fluid collections associated with pancreatitis are enzyme-rich collections, which lack a defined wall.

Pancreatic fluid collections may present as an acute fluid collection interspersed with pancreatic parenchyma without a defined wall. The fluid collection may be well circumscribed, or it may infiltrate throughout the pancreas and retroperitoneum; this may dissect retroperitoneal planes and resolve spontaneously 50% of the time. An *acute pseudocyst* is defined as a collection of pancreatic juice confined by a nonepithelialized wall of granulation tissue that occurs as a result of acute pancreatitis (Baron & Morgan, 1997) and requires at least 4 weeks to form (Fig. 16.81). It is characterized by the presence of a well-defined wall and may contain internal septations.

Lymphoplasmacytic Pancreatitis

Lymphoplasmacytic pancreatitis, also known as *autoimmune pancreatitis* (Kawaguchi et al, 1991; Kim KP et al, 2004; Yoshida et al, 1995), was first described as a "primary inflammatory sclerosis of the pancreas" (Sarles et al, 1961). It is characterized by a mixed inflammatory infiltrate centered around pancreatic ducts and ductules, combined with obliterative phlebitis (Hardacre et al, 2003). The clinical presentation can be identical to that of pancreatic adenocarcinoma, with abdominal pain, jaundice, weight loss, and elevated levels of CEA or CA19-9. Elevation of pancreatic enzymes is not a prominent feature of this entity, with mild elevation in serum amylase or lipase levels most commonly reported. Elevated levels of IgG and

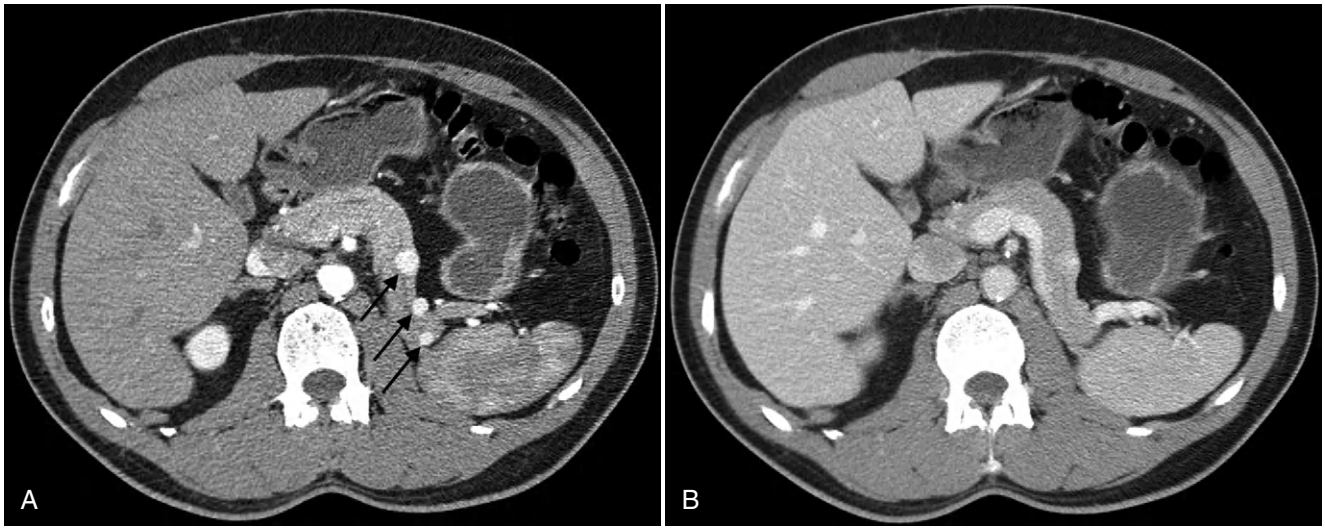


FIGURE 16.76. Renal cell carcinoma metastatic to pancreas. **A,** Computed tomographic angiogram of the pancreas shows hypervascular pancreatic metastases (*arrows*) from renal carcinoma. **B,** Portal venous phase imaging shows far fewer masses.



FIGURE 16.77. Papillary epithelial neoplasm of the pancreas with calcification: portal venous phase.



FIGURE 16.79. Pancreatitis involving the body and tail of the pancreas. Note the loss of fat planes to the spleen and in the left anterior pararenal space.



FIGURE 16.78. Acinar pancreatic cancer (*arrow*).

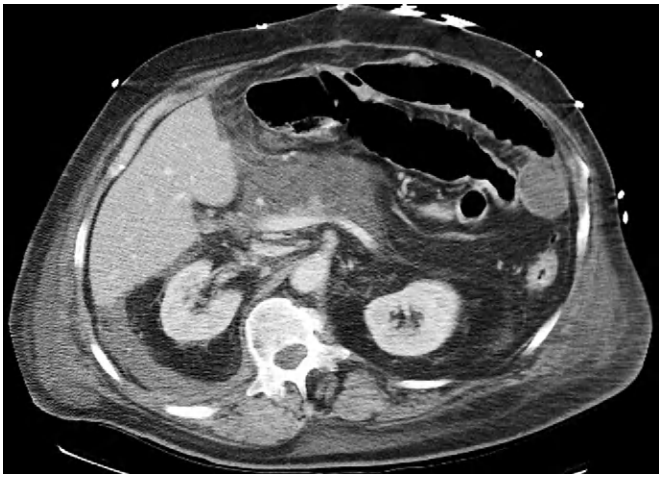


FIGURE 16.80. Severe pancreatitis obliterates tissue planes in a patient after gastrectomy.

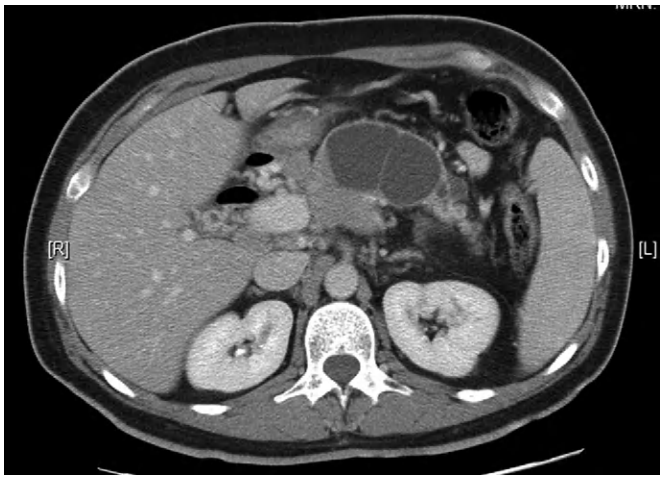


FIGURE 16.81. Pancreatic pseudocyst in portal venous phase. The patient also has adenopathy from an islet cell tumor.



FIGURE 16.82. Lymphoplasmacytic pancreatitis causing diffuse pancreatic enlargement.

hypergammaglobulinemia are reported in 37% to 76% of patients with autoimmune pancreatitis (Kim et al, 2004b). Patients may also present with fluctuating obstructive jaundice without pain (Kamisawa et al, 2007).

Imaging features of this disease include diffuse or focal enlargement of the pancreas without pancreatic calcification or peripancreatic inflammation, often with nonvisualization of the pancreatic duct and associated with a low-attenuation rim around the pancreas (Fig. 16.82). Imaging also may show thickening of the wall of the common bile duct and gallbladder wall (Kawamoto et al, 2004; Takahashi et al, 2008), which pathologically is due to diffuse lymphoplasmacytic infiltration and fibrosis (Kloppel et al, 2003). Distinguishing lymphoplasmacytic pancreatitis from adenocarcinoma is important, because

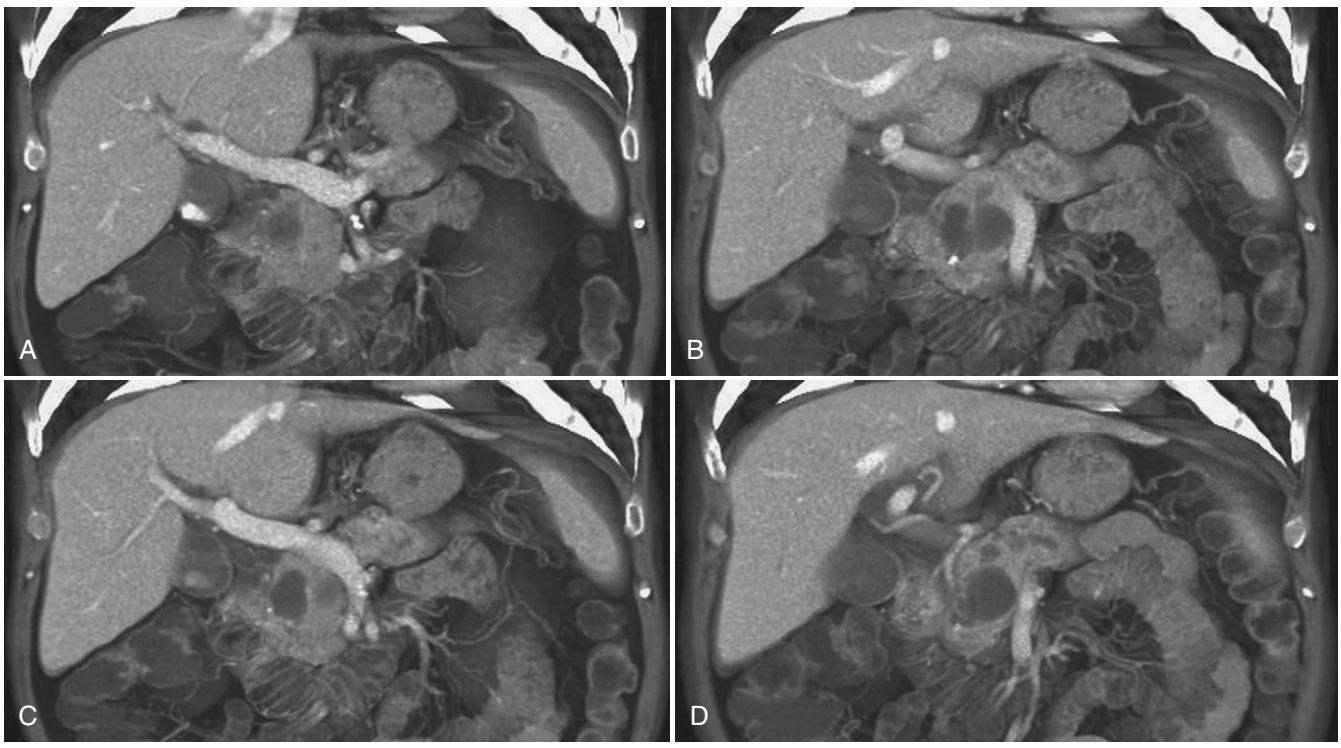


FIGURE 16.83. Groove pancreatitis. Images **A** to **D** show paraampullary duodenal wall cysts with extension to the pancreas along with cystic dilation of the pancreatic duct. At pathologic examination, no malignancy was found. The duodenal wall showed fibrosis and chronic inflammation, and the adjacent pancreas showed focal chronic pancreatitis. The gallbladder showed changes of chronic cholecystitis.

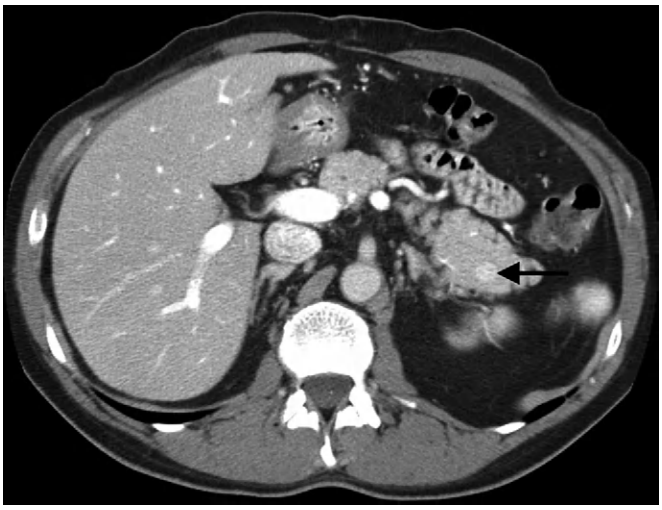


FIGURE 16.84. Hypervascular mass in the pancreatic tail (*arrow*) from ectopic splenic tissue.

lymphoplasmacytic pancreatitis responds to oral steroid administration. Distinguishing focal lymphoplasmacytic pancreatitis with localized stenosis of the main pancreatic duct and associated pancreatic duct dilation from pancreatic carcinoma is often not possible, however, and the diagnosis is made only at laparotomy. A multifocal form of autoimmune pancreatitis has also been reported (Kajiwara et al, 2008).

Groove Pancreatitis

Groove pancreatitis affects the groove between the pancreatic head, duodenum, and the common bile duct and was first described by Becker and named by Stolte and colleagues (Becker, 1973; Stolte et al, 1982). This can be extremely difficult to distinguish from groove pancreatic carcinoma, as patients are seen initially with abdominal pain and vomiting secondary to duodenal stenosis. This represents chronic pancreatitis that occurs with a platelike mass between the head of the pancreas and the duodenum, and it may cause intrahepatic and extrahepatic biliary duct dilation. Duodenal stenosis may be associated with wall thickening and cystlike lesions in the duodenal wall or in the groove area (Gabata et al, 2003; Lauffer et al, 1999; Triantopoulou et al, 2009; Fig. 16.83). Pancreatic duct dilation is much less common than bile duct dilation, and distinguishing groove pancreatitis from groove pancreatic carcinoma is done from a biopsy.

Other Nonneoplastic Pancreatic Masses: Ectopic Splenic Tissue

An unusual masslike entity that may be encountered in the pancreas is ectopic splenic tissue (Fig. 16.84). Autopsy studies have shown that 10% of patients have accessory spleens, and of these, nearly 20% are found in or near the tail of the pancreas (Halpert & Alden, 1964; Halpert & Gyorkey, 1959; Lauffer et al, 1999). This accessory spleen enhances in tandem with the spleen, but prospective diagnosis of this entity is difficult. A Japanese report described identical enhancement of the intrapancreatic splenic tissue and the major spleen, although this was a study using CT angiography and not peripheral venous access (Miyayama et al, 2003). Differentiating ectopic splenic tissue from other hypervascular masses, particularly neuroendocrine cancer, is difficult.

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CHAPTER 17

Magnetic resonance imaging of the liver, biliary tract, and pancreas

Lawrence H. Schwartz

Magnetic resonance imaging (MRI) is a cross-sectional scanning technique that allows images to be taken in any plane (Fig. 17.1). MRI uses magnetic fields and radiofrequency pulses to generate images with outstanding tissue contrast and excellent spatial resolution. MR techniques are not new and were first described in the 1940s by Bloch and colleagues (1946) and Purcell and colleagues (1946) as a method for in vitro chemical analysis. Several decades later, Damadian (1972) and Lauterbur (1973) applied some of these basic principles to design an MRI technique capable of in vivo imaging. Today, MRI is used extensively as an imaging tool throughout the body to visualize and distinguish normal and pathologic tissue.

PRINCIPLES OF MAGNETIC RESONANCE IMAGING

MRI is based on the principles of nuclear magnetic resonance. Certain nuclei have a magnetic movement or spin. These nuclei react to placement in a strong magnetic field by aligning themselves in the direction of the field. A proton aligns itself in one of two directions, either up or down. In addition, when placed in a magnetic field, the nuclei rotate or spin parallel to the magnetic field. The precise frequency of the nuclear spin is termed the *Larmor frequency,* which depends on the specific type of nuclei imaged within the magnetic field and the strength of the magnetic field. The most commonly imaged nucleus in clinical practice is hydrogen (^{1}H) because of its great abundance in the human body. Other nuclei that may be imaged by MRI include phosphorus (^{31}P), sodium (^{23}Na), and carbon (^{13}C).

When nuclei are within the stable magnetic field, they are considered to be in equilibrium: an almost an equal number of nuclei are in an "up" or "down" alignment, and an equal number of transitions exist between the two states. Adding a momentary radiofrequency pulse at the precise frequency of the nuclear spin (the Larmor frequency) produces resonance, hence the term magnetic *resonance* imaging. This radiofrequency pulse causes a change in the energy and a change in the transition state. The radiofrequency pulse is then turned off, and the nuclei in the body return to the equilibrium state, emitting a radiofrequency signal. The strength of this emitted signal and the amount of time for the nucleus to return to the equilibrium state determine the signal intensity of a tissue. The precise tissue signal intensity depends on several factors, including longitudinal relaxation (T1), transverse relaxation (T2), proton density (nuclear spin), and flow.

The T1 value, longitudinal or *spin-lattice* relaxation, is the time required for the rotating nuclei to return to the equilibrium state after the radiofrequency pulse. The initial energy absorbed by the nuclei is released and dissipated into the surrounding molecular environment or lattice. The precise T1 value is the time it takes the MRI signal to return to 63% of its maximum value. Most tissue T1 values vary between 200 and 800 ms. Tissue with a short T1 value appears bright (hyperintense) on T1-weighted images by convention.

The T2 relaxation time, transverse or *spin-spin* relaxation, is a measure of the loss of signal in a plane perpendicular to the long axis of the magnetic field. This loss of signal is due to subtle inhomogeneities in the magnetic field because of the presence of spinning protons. The T2 value for a tissue is the time it takes for the signal to decrease to 63% of its equilibrium value. Most tissue T2 values vary between 50 and 200 ms, and the T2 value can never be longer than the T1 value. By convention, tissues with a long T2 value appear bright on T2-weighted images.

The motion of fluid, such as from blood, plays a major role in the appearance of every MRI image. In general, blood flow tends to produce spin dephasing, which results in a loss of signal in an MRI image. Certain pulse sequences are sensitive to flow, and flow produces a higher signal intensity. MRI angiography techniques use this principle to produce images in which flowing blood is bright and background tissue is relatively dark. This technique takes advantage of the fact that blood flow produces moving protons that have a different signal from the static protons within the slice being imaged.

Improvements in MRI equipment and software used to control this machinery have resulted in a decrease in the time needed to create an image. State-of-the-art scanning equipment may create an image in less than 1 second. Also, specialized surface coils, local antennas used to receive the magnetic resonance signal, are now used to obtain images with higher spatial resolution. Fast techniques can produce images with either T1 weighting or T2 weighting. Gradient-recalled echo techniques can be applied to produce high-quality T1-weighted images covering the entire liver in a total scan time of less than 20 seconds. This fast scanning permits breath-hold imaging and allows for the dynamic administration of certain contrast material with hepatic MRI. New techniques using a half-Fourier technique—acquisition of slightly more than 50% of the data and the computer reconstruction of the remaining data set—create subsecond T2-weighted images. Although rapid T2 weighting has been accomplished previously with techniques such as echo-planer imaging, the half-Fourier techniques have significantly fewer artifacts. These new subsecond T2 sequences have several vendor-specific trade names, such as Single Shot Fast Spin Echo (SSFSE) or Half-Fourier Acquisition Turbo Spin Echo (HASTE). Despite different nomenclature, these techniques produce similar, highly effective results.

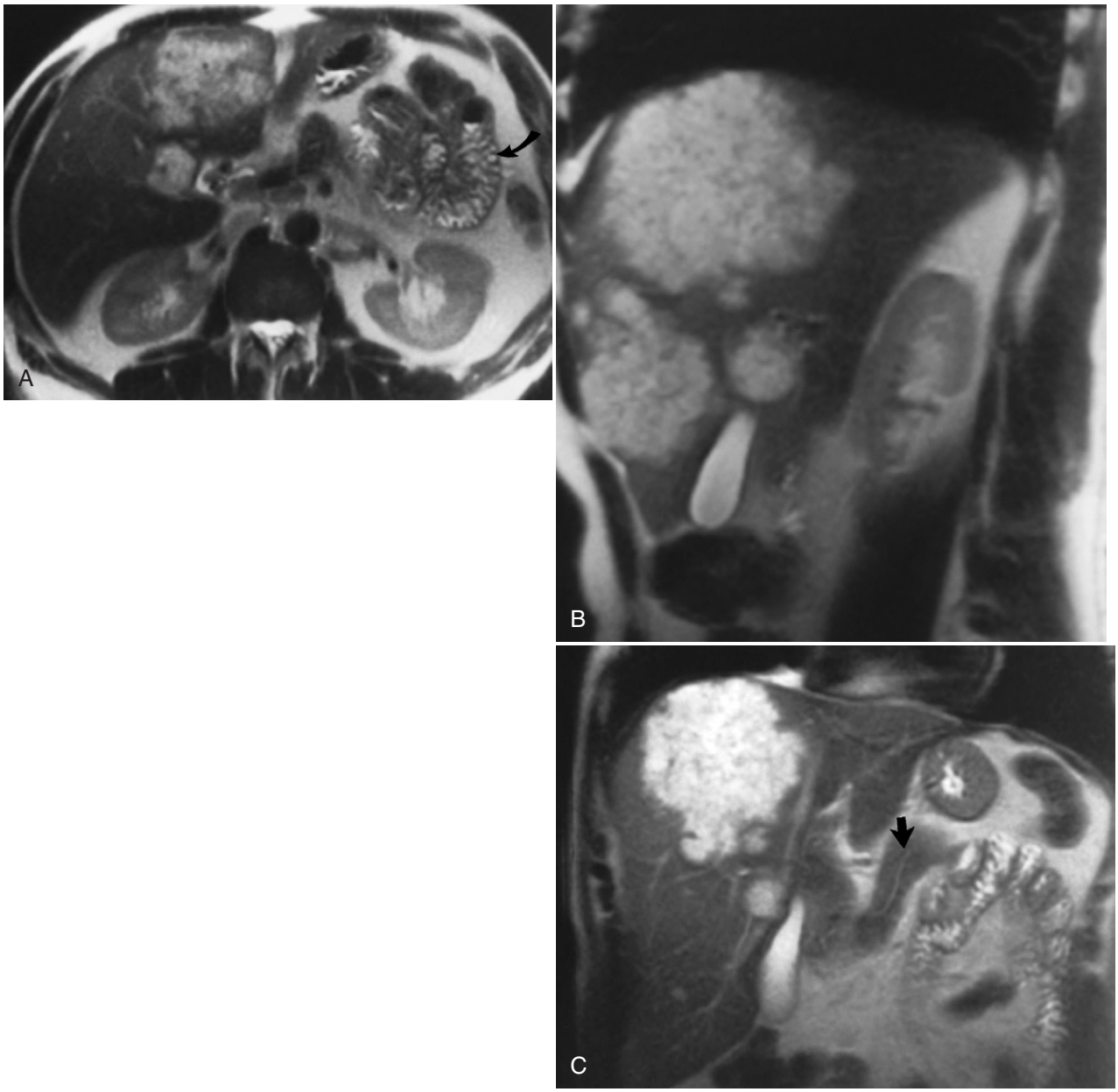


FIGURE 17.1. Multiplanar T2-weighted images through the liver in a patient with multiple hepatic metastases. **A,** Axial image. **B,** Sagittal image. **C,** Coronal image. A variety of techniques can be used to obtain these images. Note that fluid-containing structures, including small bowel (*curved arrow,* **A**), gallbladder, biliary tree, and pancreatic duct (*arrow,* **C**) are bright.

Diffusion MRI is also a new MRI method that produces images of tissues weighted with the local structural properties of water diffusion. Diffusion-weighted imaging (DWI) of the liver may be used to characterize focal hepatic masses and may also be used, for instance, to assess liver fibrosis. In DWI, each image *voxel*, a three-dimensional pixel, has an image intensity that reflects a single best measurement of the rate of water diffusion at that location. This measurement is more sensitive to early changes after a stroke than more traditional MRI measurements such as T1 or T2 relaxation rates. DWI is most applicable when the tissue of interest is dominated by isotropic water movement, for example, gray matter in the cerebral cortex and major brain nuclei, in which the diffusion rate appears to be the same when measured along any axis.

MAGNETIC RESONANCE IMAGING SAFETY

MRI is safe for most patients. However, physicians and patients should be aware of some important considerations, as several contraindications to MRI examination exist. Absolute contraindications include a cardiac pacing device, implanted neurostimulator, intracranial aneurysm clip of unknown composition, and a metallic fragment in the globe of the eye. Relative contraindications for MRI include recent intravascular stent or filter and pregnancy. Depending on the location and composition of a particular stent or filter, a variable time frame exists before an MRI examination is obtainable. Pregnancy is a relative contraindication, because there are no known long-term effects of MRI on the human fetus. It is prudent, however, to

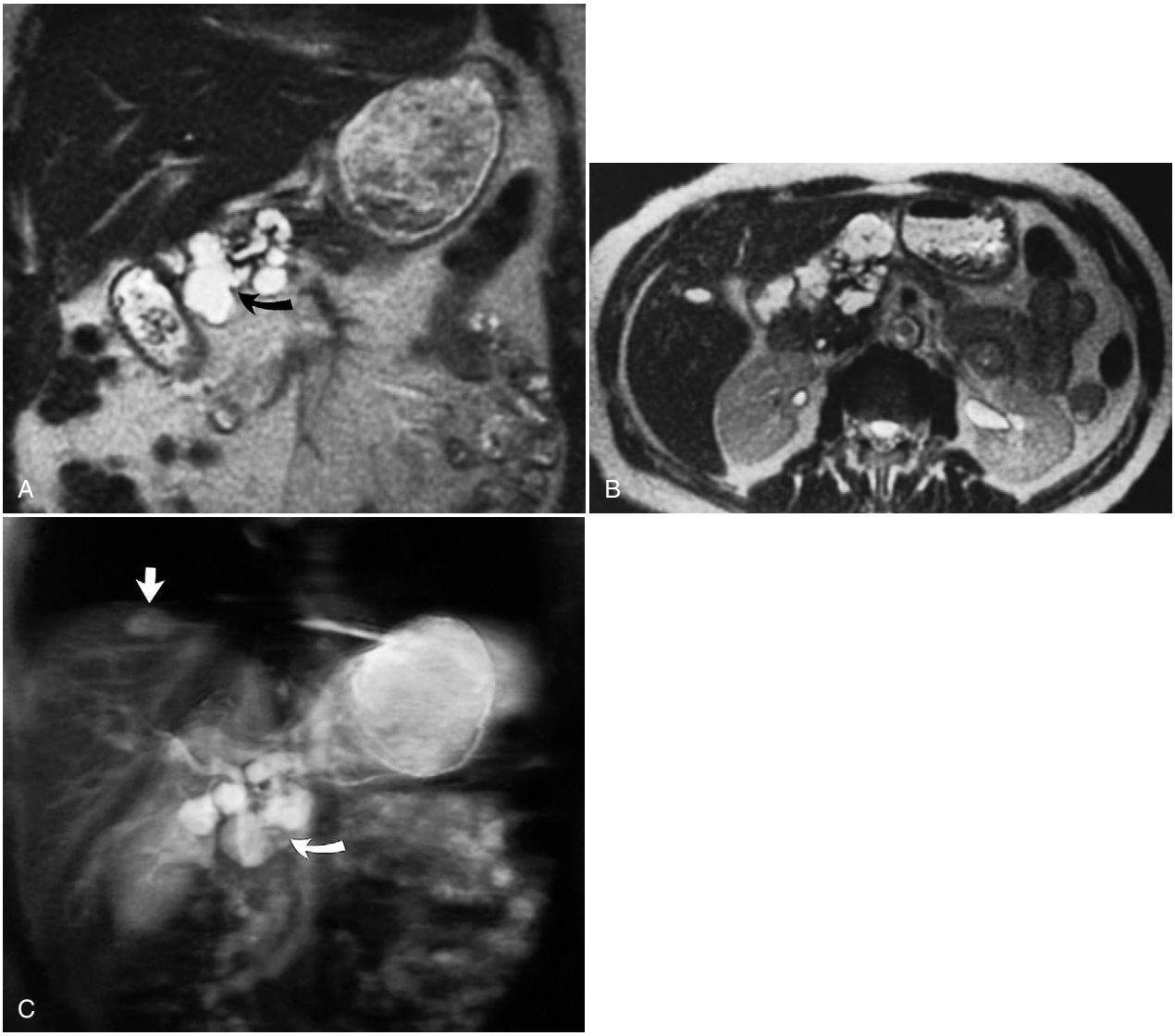


FIGURE 17.2. Cross-sectional images and projection image of the same patient as in Figure 17-1. **A,** Cross-sectional coronal image obtained at a slice thickness of 4 mm. A focal mass (*arrow*) in the pancreas is hyperintense and composed of multiple cysts. **B,** Axial image through the pancreas also shows the mass. **C,** Projection of the abdomen obtained at a slice thickness of 40 mm. The cystic mass within the pancreas (*curved arrow*) is easily identified. Fluid-containing structures and lesions that act like fluid are easily seen with this technique. Note a small hemangioma at the hepatic dome (*straight arrow*).

avoid scanning a pregnant patient before completion of organogenesis. These contraindications are not all-inclusive, and if questions arise about the safety of the patient, it is best to consult with the MRI specialist performing the examination.

MAGNETIC RESONANCE IMAGING CHOLANGIOGRAPHY

MRI cholangiography and MRI cholangiopancreatography (MRCP) are imaging techniques used to evaluate the biliary system. Heavily T2-weighted images are used to provide an overview of the biliary system and pancreatic duct. Excellent diagnostic-quality images are obtainable, with high sensitivity and specificity for evaluation of biliary duct dilation, strictures, and intraductal abnormalities (Sandrasegaran et al, 2010; Palmucci et al, 2010a; Palmucci et al, 2010b; Hekimoglu et al, 2008). Cross-sectional images and projection images (Fig. 17.2) may be produced easily with current MRCP techniques, and the projection images are similar to direct contrast-enhanced cholangiograms obtained with either endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC; see Chapter 18).

The basic principle of MRCP is to use T2-weighted images, in which stationary or slowly moving fluid, including bile, is high in signal intensity; all the surrounding tissues, including retroperitoneal fat and the solid visceral organs, are lower in signal. MR-specific techniques for obtaining cholangiographic images include two-dimensional and three-dimensional sequences, breath-hold or non–breath-hold techniques, and respiratory gated techniques. MRCP plays an important role in imaging benign disorders of the biliary and pancreatic system, and it is part of a comprehensive imaging evaluation of

malignancies of the biliary system (Kim et al, 2002b; Lee et al, 2003; Vaishali et al, 2004). MRCP is noninvasive, eliminating the morbidity associated with ERCP or PTC (Zhong et al, 2004). An additional advantage of MRCP includes visualization of the extrabiliary anatomy, allowing for exclusion or inclusion of alternative diagnoses. Surgical clips may create an artifact known as *susceptibility*, which may obscure the region of interest by producing areas of signal void. This artifact may mimic a stone, so caution must be used in evaluating MRCP images in postoperative patients to avoid a false-positive diagnosis.

MAGNETIC RESONANCE IMAGING CONTRAST AGENTS

MRI contrast agents work by altering the T1 and T2 relaxation times of various tissue types. In the hepatobiliary system, MRI contrast agents can potentially improve the detection of liver lesions and improve the characterization of focal liver abnormalities. MRI contrast agents for hepatobiliary imaging are divided into two basic categories: *intracellular* and *extracellular* agents. The most commonly used contrast agents are the extracellular agents, such as gadopentetate dimeglumine (gadolinium diethylenetriaminepentaacetic acid [Gd-DTPA]), which is distributed within the intravascular compartment initially and rapidly diffuses through the extravascular space, similar to the action of iodinated contrast agents in computed tomography (CT; see Chapter 16). Agents such as gadolinium require fast MRI pulse sequences to preferentially enhance either tumor or normal tissue, so that the difference between the two tissues is great. Metastatic liver lesions enhance irregularly, predominantly in the periphery of the lesion, and slowly; the central portion may or may not accumulate contrast material. Using extracellular contrast agents such as gadolinium and dynamic fast scanning, hepatic hemangiomas can be differentiated from other tumors by their characteristic enhancement patterns. Hepatic hemangiomas fill in slowly (5 to 20 minutes) from the periphery with a nodular appearance (see Chapter 79). An advantage of gadolinium over iodinated CT contrast agents is the lack of renal toxicity even at high doses (Prince et al, 1996). This fact has clinical implications in patients with decreased renal function or in those at risk for potential nephrotoxic effects of iodinated contrast agents.

Several new hepatobiliary-specific contrast agents have been developed to overcome some of the limitations associated with the general extracellular contrast agents. These hepatobiliary-specific contrast agents are taken up to varying degrees by functioning hepatocellular tissue and are excreted at least partially in the bile. They function because of their paramagnetic properties, which cause T1 shortening both of the liver and biliary tree. Hepatobiliary-specific agents include mangafodipir trisodium, gadopentetate dimeglumine, and gadoxetic acid, and both gadobentate dimeglumine (Gd-BOPTA) and gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DPTA) have been approved in the United States. These contrast agents are all administered intravenously, although the dose and duration of the administration are different. These two agents are sometimes referred to as *combination agents* because of their dual capacity for imaging both in the dynamic phase and in the delayed, hepatocyte-specific phase. These agents have the potential to provide extensive and comprehensive information about the lobes of the liver, bile ducts, and liver vasculature. (Giovagnoni & Paci, 1996; Iman & Bluemke, 2000; Stern et al, 2000).

NORMAL HEPATIC APPEARANCE ON MAGNETIC RESONANCE IMAGING

Hepatic MRI is a sensitive technique to evaluate diffuse and focal abnormalities. In normal hepatic parenchyma on T1-weighted images, the liver is brighter (hyperintense) than the spleen. Depending on the specific technique chosen, the vessels may appear dark (flow voids on spin-echo technique), or they may be bright (gradient-echo technique). On T2-weighted images, the spleen is relatively brighter than the liver (Fig. 17.3). Fluid is dark on T1-weighted images and bright on T2-weighted images as a result of long T1 and T2 values. Although many hepatic lesions are low in signal intensity on T1-weighted images, they may be of variable intensity on T2-weighted images, depending on their water content.

DIFFUSE HEPATIC DISEASE

Fatty Infiltration of the Liver

Fat may accumulate within hepatocytes for many reasons, including alcohol abuse, diabetes, drugs, and obesity (see Chapter 65). Fatty change may be diffuse, patchy, or focal. The pattern of fatty infiltration is related to regional differences in perfusion. It is often difficult to distinguish fatty infiltration from focal hepatic lesions on CT, because both appear low in attenuation. Additionally, focal fatty sparing may appear similar to a vascular neoplasm on contrast-enhanced CT. It is easy, however, to distinguish these entities on MRI because of different signal characteristics. On T1-weighted images, areas of fatty infiltration appear bright because of the low T1 value of fat. The appearance on T2-weighted images depends on the specific type of T2-weighted sequence acquired. Conventional spin-echo T2-weighted sequences are relatively insensitive to the presence of fat (Wenker et al, 1984). Areas of focal fatty infiltration may appear hyperintense to normal hepatic parenchyma on fast T2-weighted images because of the high signal intensity of fat in these sequences. Using chemically selective fat suppression techniques, these areas of focal fatty infiltration appear dark.

Chemical shift imaging is another technique that allows differentiation of the signals from fat and water protons. These chemical shift techniques are the most sensitive techniques for distinguishing fatty infiltration (Fig. 17.4; Mitchell et al, 1991; Siegelman, 1997; Springer et al, 2010). Chemical shift imaging techniques rely on the different resonant frequencies present in fat and water protons. Using fast imaging techniques, the signal emanating from fat and water protons may be equal but opposite. Tissues that have relatively equal quantities of fat and water appear dark, because the signals from fat and water cancel each other out. Areas of fatty sparing remain relatively hyperintense to the fatty infiltrated regions. Focal fatty infiltration should not enhance after gadolinium administration. A lesion with characteristic signal intensity findings on T1, T2, and gradient-echo opposed-phase imaging is diagnostic of fatty infiltration (Kreft et al, 1992; Mitchell et al, 1991). Any one of these sequences alone is not characteristic, because other lesions, including hepatocellular carcinoma (HCC) and adenoma, may contain small quantities of fat within them (see Chapters 78, 79, and 80).

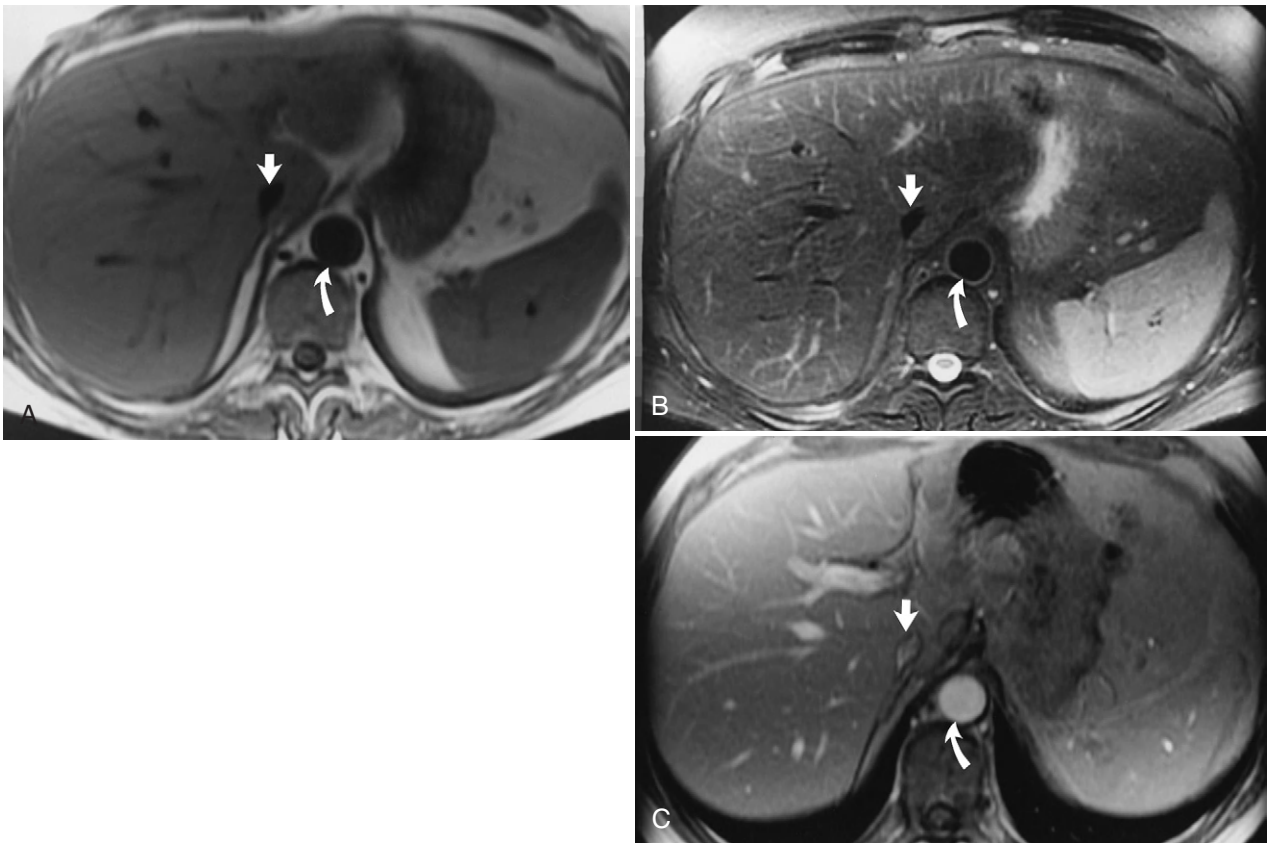


FIGURE 17.3. Normal hepatic magnetic resonance image. **A,** T1-weighted spin-echo image. The liver is brighter (hyperintense) relative to the signal of the spleen. There are normal flow voids that appear as dark areas in the visualized vessels. *Straight arrow,* intrahepatic portion of the inferior vena cava; *curved arrow,* aorta. **B,** T2-weighted fast spin-echo image. Because of reversal of the liver/spleen contrast, the normal spleen is brighter than the liver. Note the flow voids within the vessels. *Straight arrow,* intrahepatic portion of the inferior vena cava; *curved arrow,* aorta. **C,** Postcontrast T1-weighted gradient-echo image. Normal enhancement in the liver and spleen is evident, and the parenchyma of both is about equal in this phase of the injection. All the vessels (*straight arrow,* intrahepatic portion of the inferior vena cava; *curved arrow,* aorta) are bright as a result of the T1 shortening effect of gadolinium.

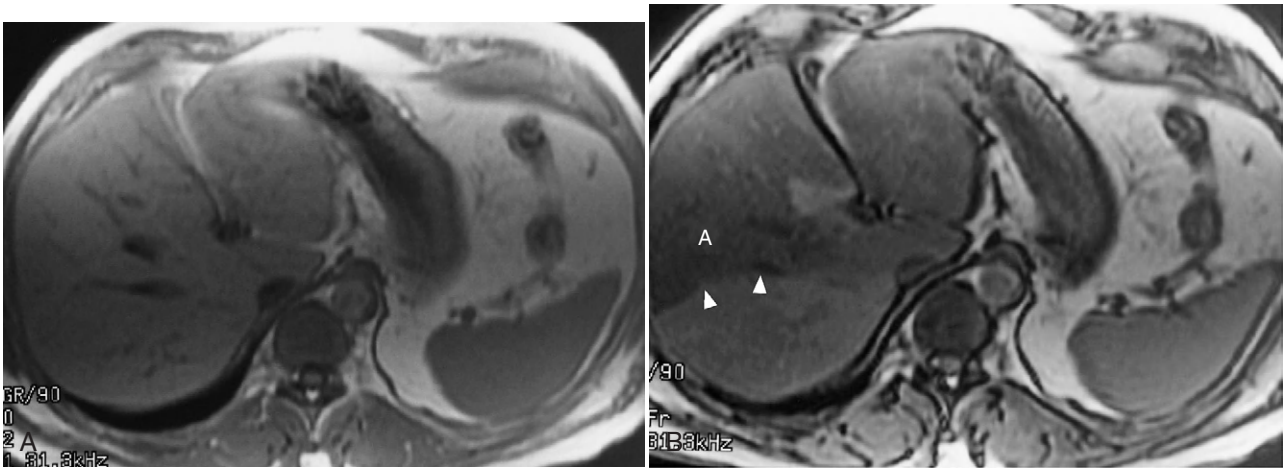


FIGURE 17.4. Fatty infiltration of the liver. **A,** T1-weighted in-phase gradient-echo image (TE 4.2) shows normal liver/spleen contrast. **B,** T1-weighted out-of-phase image (TE 1.8) at the same level shows a geographic area (*A*) that has lost signal (approached signal of the spleen); the transition to normal hepatic parenchyma is shown (*arrowheads*). This area has normal vascularity coursing through it; no mass was present—the typical appearance of fatty infiltration on chemical shift imaging. On the out-of-phase images, a black line "India ink effect" surrounds tissue interfaces.

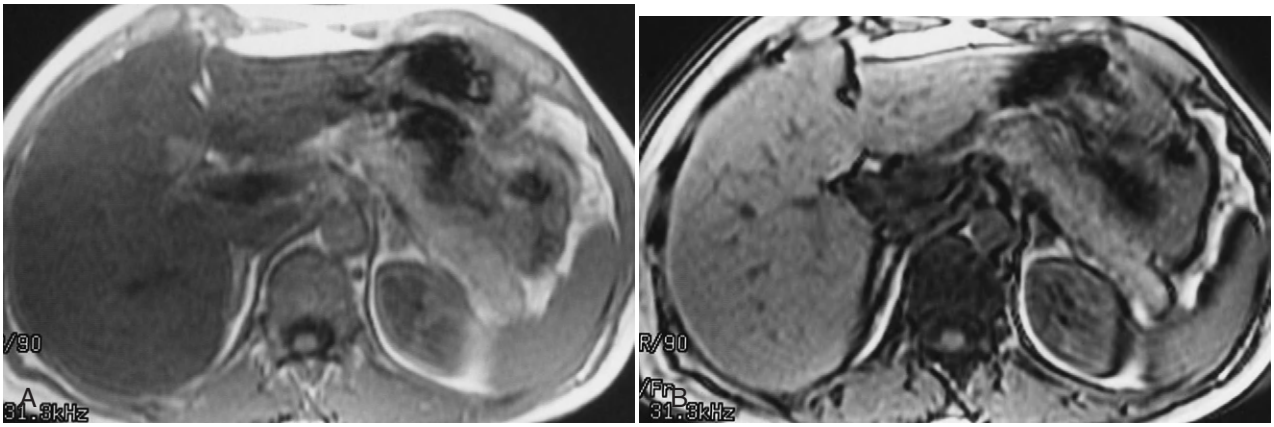


FIGURE 17.5. Hemochromatosis. **A,** T1-weighted in-phase gradient-echo image (TE 4.2) shows abnormal liver/spleen contrast. The liver is homogeneously darker than the spleen from preferential deposition of iron within the hepatic parenchyma. Note the difference from Figure 17.4. **B,** T1-weighted out-of-phase gradient-echo image (TE 1.8) shows the liver/spleen contrast returns to normal, with the liver being brighter than spleen. This is opposite from Figure 17.4 and shows early iron deposition disease within the liver.

Iron Deposition Disease

Iron accumulation within the liver has two main causes: *hemochromatosis* and *hemosiderosis*. Hemochromatosis is characterized by abnormal intestinal absorption of iron, the accumulation of which is predominantly in hepatocytes until late in the disease, when there is "spillover" into the pancreatic parenchyma. The liver shows abnormally low signal intensity compared with spleen on T1-weighted sequences. Gradient-echo sequences are the most sensitive sequence for detecting the presence of iron within the hepatic parenchyma. Primary, or genetic, hemochromatosis is important to diagnosis, because this entity may be unnoticed until late in the disease process, and its long-term sequelae include fibrosis, cirrhosis, and HCC, which also may be imaged with MRI. In addition, screening of family members is important in primary hemochromatosis, because it is an autosomal recessive trait.

Hemochromatosis must be distinguished from hemosiderosis, which is not genetically linked but is associated with multiple blood transfusions; conversely, it has a benign course, with accumulation of hepatic iron in the reticuloendothelial system. MRI is excellent for identifying these entities, because iron changes the expected signal intensities of abdominal organs (Pomerantz & Siegelman, 2002; Queiroz-Andrade et al, 2009). In patients with hemochromatosis, the normal liver–spleen pattern is reversed on T1-weighted images. In more advanced stages, iron also is deposited in the pancreatic parenchyma. Hemosiderosis affects the spleen and bone marrow early on in the disease process, with the liver being affected later. These distinguishing characteristics, and the patient's history, allow for correct differentiation; gradient-echo imaging is sensitive for the detection and characterization of these two processes (Fig. 17.5; Kim et al, 2002a; Rofsky & Fleishaker, 1995).

FOCAL HEPATIC LESIONS

Cysts

Cysts are common hepatic lesions that may be simple (see Chapter 69) or associated with polycystic disease of the kidney (Fig. 17.6). Small cysts (<1 cm) may be difficult to characterize on CT because of volume averaging. The MRI criteria for a simple cyst is a lesion that is homogeneously low in signal intensity on T1-weighted images and homogeneously bright on T2-weighted images. Lengthening the TE value on T2-weighted images allows for "heavier" T2 weighting. Cysts maintain their high signal on these heavy T2 images, and a cyst should not enhance after Gd-DTPA administration. Hepatic cysts may also be associated with infectious causes, such as echinococcal disease. Echinococcal cysts (see Chapter 68) have a different MRI appearance, are usually multiloculated and complex, and may have components that enhance (Mortele et al, 2009).

Hemangioma

Hepatic hemangiomas (see Chapter 79) are benign tumors of the liver found in 7.3% of autopsy specimens (Birnbaum et al, 1990; Ishak & Rabin, 1986). Most hemangiomas are found incidentally on other imaging studies, such as CT or ultrasound. MRI is ideal for characterizing hemangiomas and is the preferred modality for imaging. On T1-weighted images, hemangiomas are hypointense compared with the surrounding hepatic parenchyma; have smooth, well-marginated borders; and are frequently lobulated. Hemangiomas are hyperintense compared with normal liver on T2-weighted images and have a lobulated, well-demarcated border. Hemangiomas tend to retain their high signal on more heavily T2-weighted sequences. The presence of hyperintense peripheral nodular enhancement, especially when large, with either partial or complete filling in after gadolinium administration has been shown to be 100% specific, 84% sensitive, and 95% accurate for the diagnosis of hemangioma (Fig. 17.7; Silva et al, 2009; Mathieu et al, 1997; Semelka & Sofka, 1997).

Dynamic fast MRI after administration of intravenous gadolinium is useful for increasing the specificity of diagnosis of hepatic hemangioma and for differentiating this lesion from others, including metastases and HCCs (Yoon et al, 2003). Larger hemangiomas tend to follow these criteria more

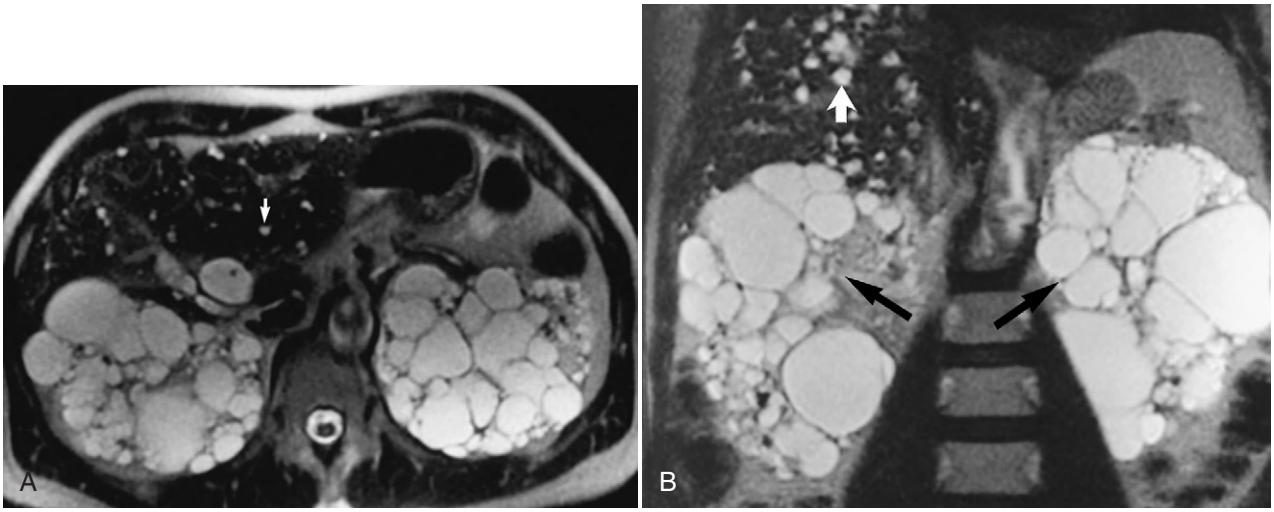


FIGURE 17.6. Hepatic cysts associated with polycystic kidney disease. **A,** Axial T2-weighted image at the level of kidneys shows bilaterally enlarged kidneys with multiple hyperintense cysts. Little normal renal parenchyma is present at this level, and multiple small hepatic cysts (*arrow*) are seen. **B,** Coronal T2-weighted images through the kidneys show similar findings of enlarged kidneys containing multiple cysts (*black arrows*), and small hepatic cysts are identified (*white arrow*).

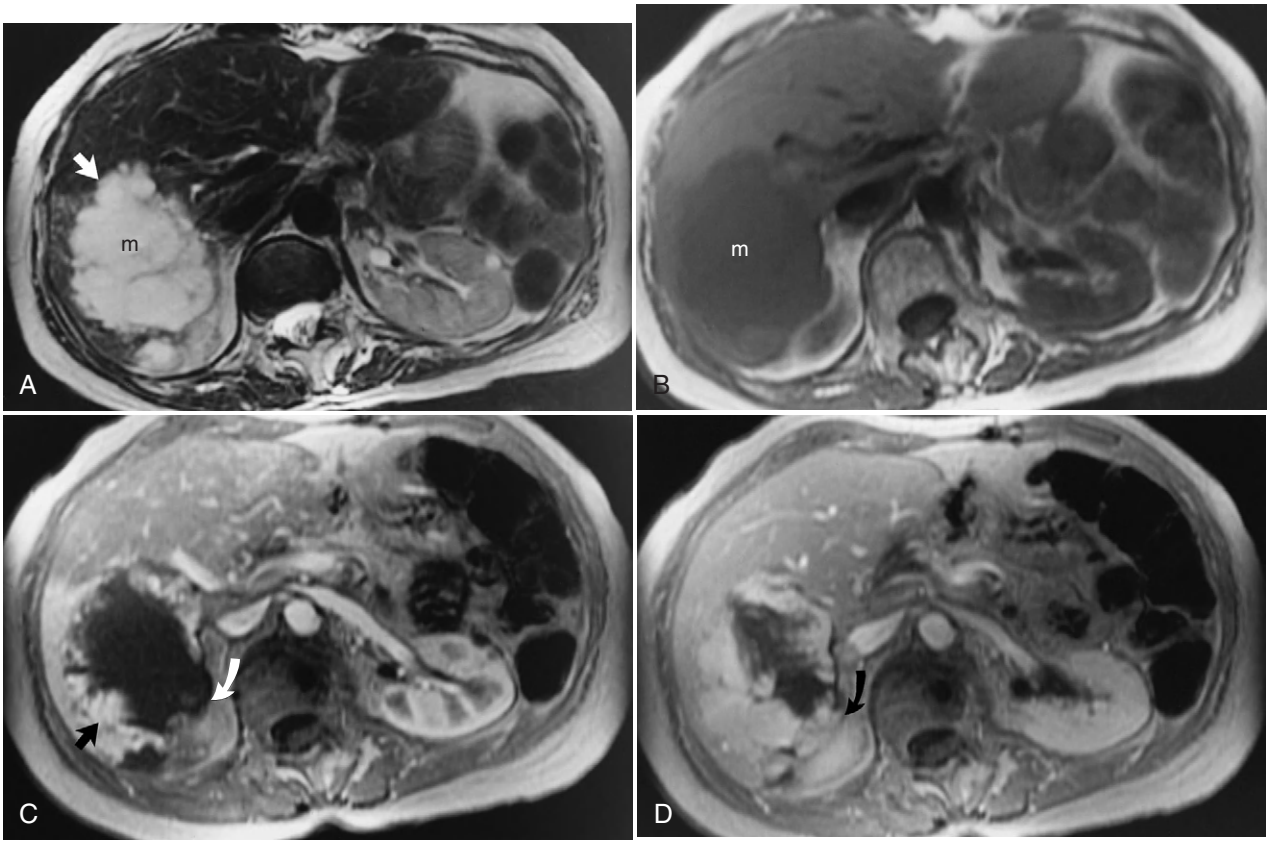


FIGURE 17.7. Hepatic hemangioma. **A,** Heavily T2-weighted image (TE 150) shows a mass (*m*), which is hyperintense to hepatic parenchyma and contains some internal architecture. Note the lobulated, well-defined margins of this lesion (*arrow*). **B,** Precontrast T1-weighted gradient-echo image at the same level shows the mass (*m*) to be dark compared with background parenchyma. **C,** T1-weighted gradient recalled-echo image during contrast administration shows peripheral nodular or broken ring enhancement within this mass (*arrow*). The posterior medial aspect of this lesion fails to show enhancement during this phase of the contrast injection (*curved arrow*). **D,** A delayed T1-weighted gradient-echo sequence postcontrast image shows the lesion has partially filled in toward the central portion. The region identified in *C* has filled in on delayed images (*curved arrow*). This constellation of findings is typical for hepatic hemangioma.

frequently, although giant hemangiomas also may have variable signal intensity (Danet et al, 2003; Yang et al, 2001). Problems arise with smaller hemangiomas, however, which may "flash fill" and appear as hypervascular lesions. These smaller lesions (usually <1 cm) may be distinguished by their T2 characteristics (Outwater et al, 1997). Hemangiomas also may be diagnosed after the administration of iron-based contrast agents (Harisinghani et al, 1997).

Focal Nodular Hyperplasia

Focal nodular hyperplasia (FNH; see Chapter 79A) is another common benign tumor of the liver, although it occurs less frequently than hemangioma. Pathologically, FNH contains all the elements of normal liver and may have a central fibrous scar surrounded by hepatocytes and small bile ducts. FNH is the second most common benign tumor of the liver, and it has been associated with oral contraceptive use (Christopherson et al, 1977). Most FNH lesions are isointense or slightly hypointense compared with the normal liver parenchyma on T1-weighted images, and they are either isointense or minimally hyperintense on T2-weighted images (Fig. 17.8A and B). Frequently, FNH is visualized by displacement of the normal hepatic vasculature, and classic FNH has an early arterial peak enhancement with dynamic administration of an intravenous contrast agent.

A common feature of FNH is the presence of a central scar. Generally, this scar is hypointense on T1-weighted images and hyperintense on T2-weighted images. The central scar shows contrast enhancement as well, but in a delayed fashion and with prolonged enhancement (Fig. 17.8C; Mortele et al, 2002). Superparamagnetic iron oxide contrast agents are taken up by FNH, because the FNH contains Kupffer cells. Many reports indicate that FNH takes up a significant percentage of superparamagnetic iron oxide particles after administration, showing signal loss (Grazioli et al, 2005). This finding is consistent with the experience of nuclear scanning with technetium 99m–sulfur colloid. Lesions of FNH can be characterized with a high degree of specificity using a variety of MRI techniques (Silva et al, 2009; see Chapter 79A).

Hepatic Adenoma

Hepatic adenomas (see Chapter 79A) also are benign lesions associated with the use of oral contraceptives. They are commonly large, may cause upper abdominal pain, and may rupture and bleed. Hepatocytes are present within adenomas; however, these lesions lack hepatic veins and bile ducts. In addition, there are only a few if any reticuloendothelial cells present, and iron oxide scans show less uptake than with scans of FNH. Hemorrhage, which is one of the most common causes of pain, may be life threatening if it extends into the peritoneum. MRI tissue characterization of hepatic adenomas varies, but they are generally hyperintense on T1-weighted images because of the presence of hemorrhage or fat. Infrequently, the T1-weighted

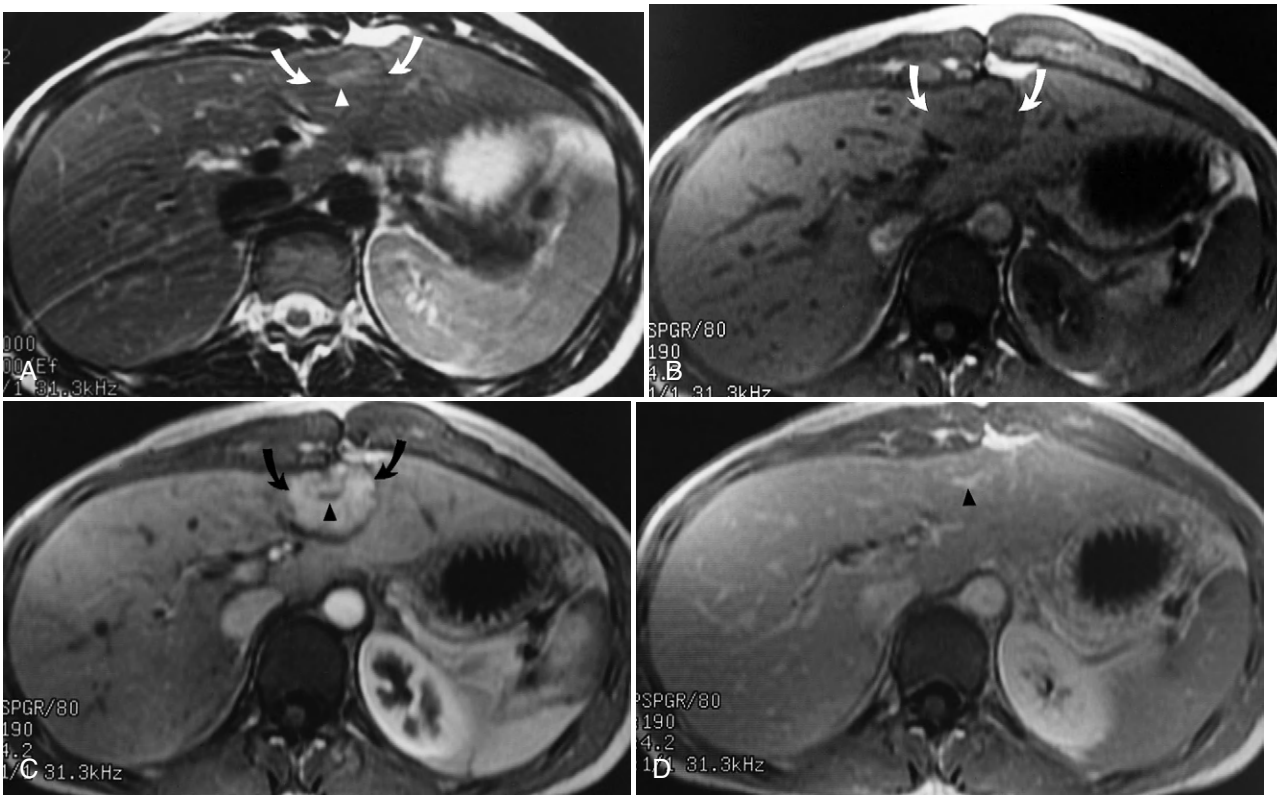


FIGURE 17.8. Focal nodular hyperplasia (FNH). **A,** T2-weighted image shows a mass that is isointense to hepatic parenchyma (*arrows*). Centrally within this mass is a linear, hyperintense focus (*arrowhead*). **B,** A precontrast, T1-weighted gradient-echo image shows the mass (*arrows*) to be mildly hypointense to liver. **C,** Arterial dominant phase T1-weighted gradient-echo sequence shows that the mass enhances intensely with respect to hepatic parenchyma (*arrows*). The central focus, which was bright on the T2-weighted images, does not show enhancement on this phase of the injection (*arrowhead*). **D,** Postcontrast equilibrium phase images show the mass to be isointense to background hepatic parenchyma. The central portion of scar shows delayed enhancement (*arrowhead*) characteristic of FNH.

images may show a low signal intensity pseudocapsule surrounding the adenoma, similar in appearance to HCC (Gabata et al, 1990). A central scar also may be seen within certain adenomas (Rummeny et al, 1989). Adenomas are hypervascular lesions that show enhancement during the arterial dominant phase of the contrast injection. Small adenomas without hemorrhage may be difficult to differentiate from FNH without a central scar and from well-differentiated HCC.

Hepatic Abscesses

CT is generally the modality of choice in recent postoperative patients in whom there is a clinical suspicion of a hepatic abscess (see Chapter 66). Patients with more atypical symptoms may present a diagnostic dilemma. Although some patients show symptoms suggesting abscesses, others do not, but patients suspicious for abscesses may be imaged with MRI. Abscesses are usually hyperintense on T2-weighted images with an irregular rim of intermediate signal intensity surrounding a hyperintense outer rim. Abscesses are generally hypointense on T1-weighted images, unless they have hemorrhage or proteinaceous debris within them. After administration of contrast material, the rim enhances, whereas the central portion does not enhance. The imaging findings may overlap with malignancies, including gallbladder cancer.

Hepatic Metastases

The liver is the most common site for the hematogenous spread of malignant neoplasms (see Chapter 81). Other hepatic lesions, including hemangiomas or fatty infiltration, may appear similar to metastases when imaged with CT or ultrasound. In addition, several types of lesions may coexist in the same patient, which may be challenging for the diagnostic radiologist. These lesions may be distinguished using MRI. In general, metastases are of low signal intensity on T1-weighted images and are hyperintense on T2-weighted images. Metastases tend not to be as bright on T2-weighted images as hemangiomas or cysts. Metastases also tend to have less well-defined borders than other benign lesions and may have peripheral high signal intensity, which has been shown to represent viable tumor (Fig. 17.9). During contrast administration, metastases may show early peripheral rim enhancement. This peripheral rim washes out and appears hypointense on delayed images (Fig. 17.10).

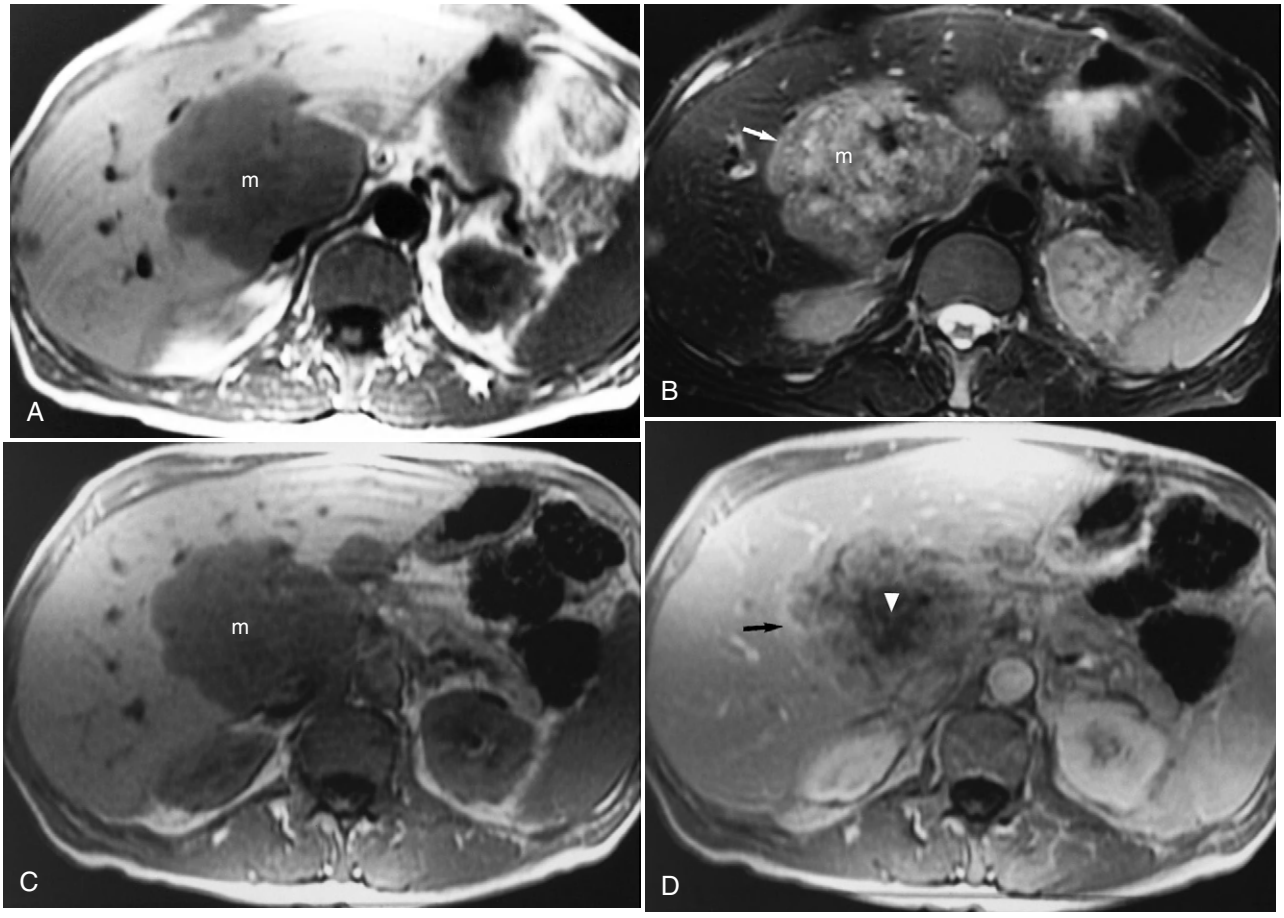


FIGURE 17.9. Hepatic metastasis from colorectal carcinoma. **A,** T1-weighted image shows a large, central, low signal intensity metastasis (*m*) with several smaller lesions within the liver. **B,** T2-weighted image shows the mass (*m*) is brighter than background hepatic parenchyma. The borders are ill defined, and there appear to be internal septations within this lesion. The periphery of the lesion is a rind of tissue (*arrow*) that is mildly hyperintense to liver but darker than the central portion of the mass. **C,** Pre–contrast-enhanced, T1-weighted gradient-echo image shows the large hepatic metastasis (*m*) in contrast to the normal hepatic parenchyma. **D,** Pre–contrast-enhanced, T1-weighted gradient-echo images fail to show the peripheral portion (*arrow*), and internal septations have enhanced, representing viable tumor, whereas the central necrotic portion (*arrowhead*) fails to enhance. Note the distinct difference in appearance from hemangioma (see Fig. 17.7).

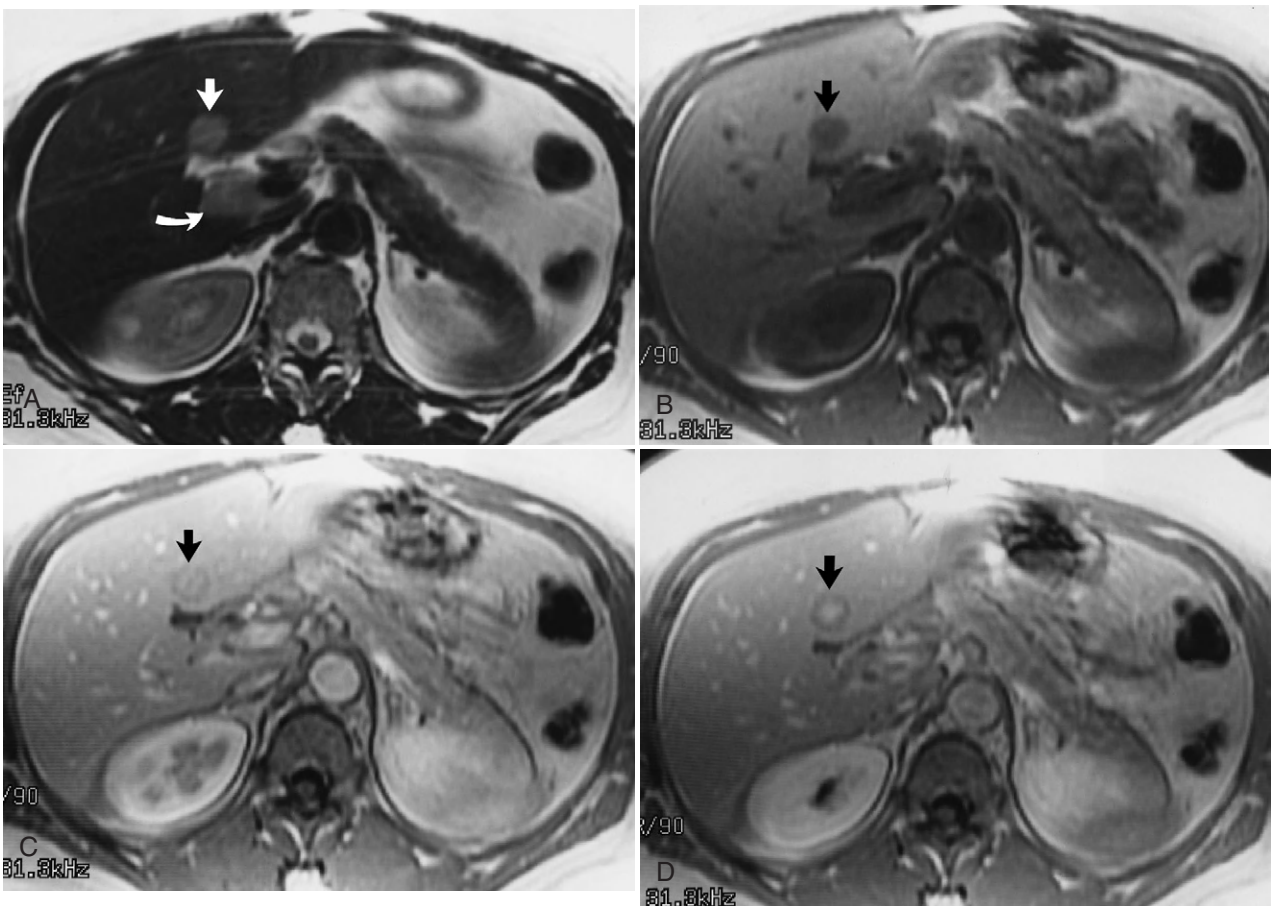


FIGURE 17.10. Hepatic metastasis from breast carcinoma. **A,** T2-weighted image shows a small lesion within the liver (*straight arrow*) that is mildly hyperintense. Portal lymphadenopathy also is present (*curved arrow*). **B,** Pre–contrast-enhanced, T1-weighted gradient-echo image shows a well-defined mass (*arrow*) that is hypointense to liver. **C,** T1-weighted gradient-echo image after the administration of contrast shows the peripheral portion that enhanced irregularly during the arterial dominant phase (not shown) beginning to wash out, suggesting an early target appearance (*arrow*). **D,** Delayed postcontrast gradient-echo image shows continued filling of the central portion of this lesion; the periphery has washed out (*arrow*).

Although this delayed hypointense rim is seen in only a few cases, it is 100% specific for the diagnosis of hepatic malignancy (Mahfouz et al, 1994). Larger metastases tend to have a thick irregular rim of enhancement representing viable tumor with areas of central necrosis. MRI is less invasive and more cost effective than CT arterial portography and is an excellent screening tool for staging hepatic metastases for surgical resection (Iman & Bluemke, 2000). In addition, MRI can easily map out hepatic vasculature and image in multiple planes—coronal, sagittal, and oblique—to allow for complete surgical planning.

Hepatocellular Carcinoma

The diagnosis of HCC (see Chapter 80) on CT and ultrasound is difficult because of its association with chronic liver disease, which appears heterogeneous on CT and MRI (Fig. 17.11), making it difficult to distinguish focal hepatic lesions in these patients. The heterogeneity is created by the presence of a nodular configuration. These nodules may represent regenerative nodules, dysplastic nodules, or HCC. The advantage of MRI in the evaluation of HCC is that areas of carcinoma show signal intensity changes relative to areas of cirrhotic hepatic parenchyma. HCC generally is hypointense on T1-weighted images and hyperintense on T2-weighted images, although the signal intensity can be variable in these sequences (Silva et al, 2009). Well-differentiated HCC is hyperintense on T1-weighted images because of the presence of intracellular lipid (Fig. 17.12; Basaran et al, 2005). On T2-weighted images, large HCCs may have a "mosaic" appearance produced by multiple centers of growth interspersed with areas of necrosis and regenerating liver tissue (Fig. 17.13; Choi et al, 1990; Fujita et al, 1997; Lalonde et al, 1992). The fibrolamellar type of HCC may have a central scar. These fibrous scars tend to be low in signal intensity on T1-weighted and T2-weighted images. The presence of this fibrous scar cannot reliably distinguish between benign and malignant hepatic lesions, however, because FNH also may have a central scar (Kim et al, 2009).

Gradient echo (bright blood technique), MRI, and other flow-sensitive techniques are excellent for evaluating vascular hepatic tumor invasion. MRI is more sensitive than CT, sonography, or angiography for detecting vascular intrahepatic invasion (Itoh et al, 1987). Contrast-enhanced MRI with Gd-DTPA shows irregular and variable patterns of enhancement owing to the vascular nature of the tumor. Most HCCs are hypervascular in nature and show enhancement during the arterial dominant phase of the injection, in contrast to other nodules seen

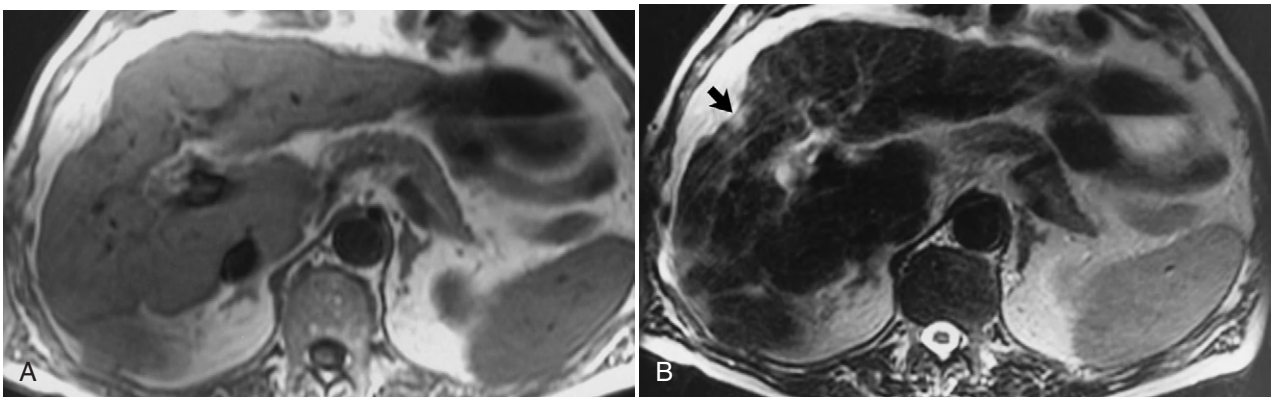


FIGURE 17.11. Liver with cirrhotic configuration. **A,** T1-weighted spin-echo image at the level of the portal vein shows hypertrophy of the left lobe and caudate with atrophy of the right lobe of the liver. **B,** T2-weighted image of the liver at the same level shows mildly heterogeneous signal in the atrophied right lobe, making exclusion of an underlying mass difficult. Note also the focal hepatic scarring (*arrow*).

in cirrhotic livers. Those lesions tend to be isointense to the background liver parenchyma during the equilibrium phase of the examination. Although HCCs are typically hypervascular lesions, multiple dysplastic nodules appearing as hypervascular masses on CT and MRI has been reported (Krinsky et al, 1998; Taouli et al, 2004). MRI also is excellent for identifying additional characteristics that may aid in the diagnosis of HCC, including a capsule surrounding the lesion, which is low in signal intensity on the arterial dominant phase and enhances on delayed images (Fig. 17.14).

LESS COMMON HEPATIC TUMORS

Lymphoma

Non-Hodgkin lymphoma accounts for most hepatic lymphomas. MRI shows masses of varying size, which are generally low in signal intensity on T1-weighted images and hyperintense on T2-weighted images (Rizzi et al, 2001). The degree of hyperintensity is not as great as with other focal benign hepatic lesions, such as hemangiomas or cysts. This difference in signal intensity makes it relatively easy to determine the malignant nature of the lesion but not the specific cause. The imaging characteristics of lymphoma overlap with other malignant hepatic lesions.



FIGURE 17.12. Hepatocellular carcinoma containing intracellular lipids. T1-weighted in-phase gradient-echo image shows a mass (*m*) in the liver that is brighter than normal parenchyma. Siderotic nodules are diffusely present within the liver and present in the spleen (gamma Gandy bodies; *arrow*).

Mesenchymal Tumors

Rarely, tumors of mesenchymal origin—including angiosarcoma, leiomyosarcoma, and fibrous histiocytoma—may be present within the liver (Anderson et al, 2009). The MRI appearance of these tumors is nonspecific; they are generally of low intensity on T1-weighted images and hyperintense on T2-weighted images.

Epithelioid Hemangioendothelioma

Epithelioid hemangioendothelioma (EH) is a rare tumor of adults that should be distinguished from infantile hemangioendothelioma, which occurs in infants and children. The prognosis is better for EH than for other parenchymal tumors, such as sarcoma, although extrahepatic metastases do occur. EH is generally low in signal intensity on T1-weighted images and hyperintense on T2-weighted images, but not as hyperintense as hemangiomas. After Gd-DTPA administration, an irregular nodular and concentric enhancement may be seen. Capsular retraction also may be seen with EH, helping to elucidate the diagnosis (Lin et al, 2010).

Biliary Cystadenoma and Biliary Cystadenocarcinomas

Biliary cystadenomas and biliary cystadenocarcinomas are rare tumors of the liver that present as a predominantly cystic mass containing septations (Fig. 17.15; see Chapter 79B). These lesions may be of low, intermediate, or increased signal on T1-weighted images, depending on the protein content within the mass, and they are usually hyperintense on T2-weighted sequences. The malignant variety may show nodular or irregular internal soft tissue; however, distinction between the two is not always possible.

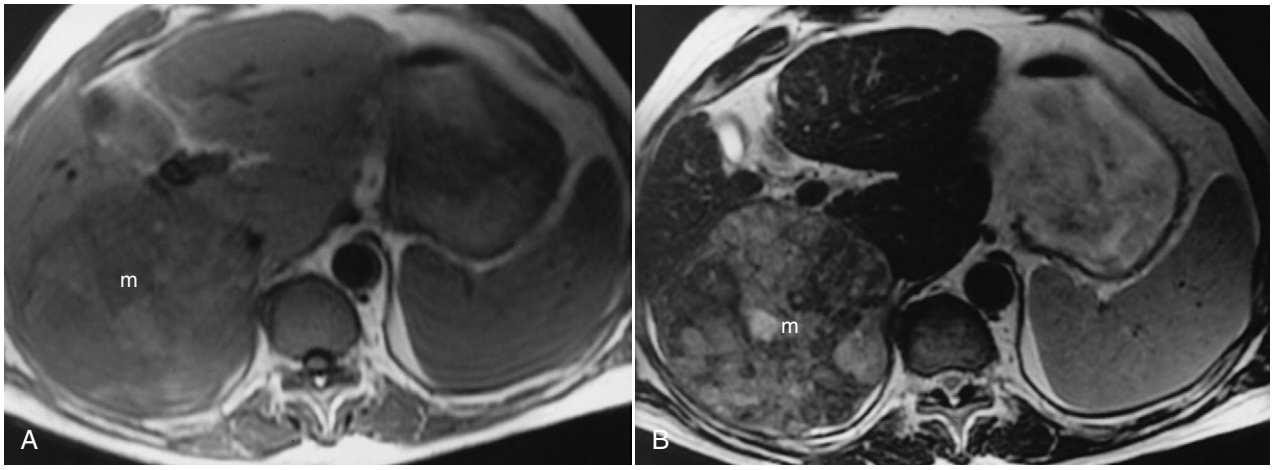


FIGURE 17.13. Large hepatocellular carcinoma showing the mosaic pattern. **A,** T1-weighted image shows a large heterogeneous mass (*m*) in the liver. Note the hypertrophied left hepatic lobe and caudate. **B,** T2-weighted image also shows the mass (*m*) to be heterogeneous, with islands of tissue that are hyperintense with respect to other portions of the same mass. This pattern is known as the *mosaic pattern*, and it can be seen in hepatocellular carcinoma, especially when the lesion is large.

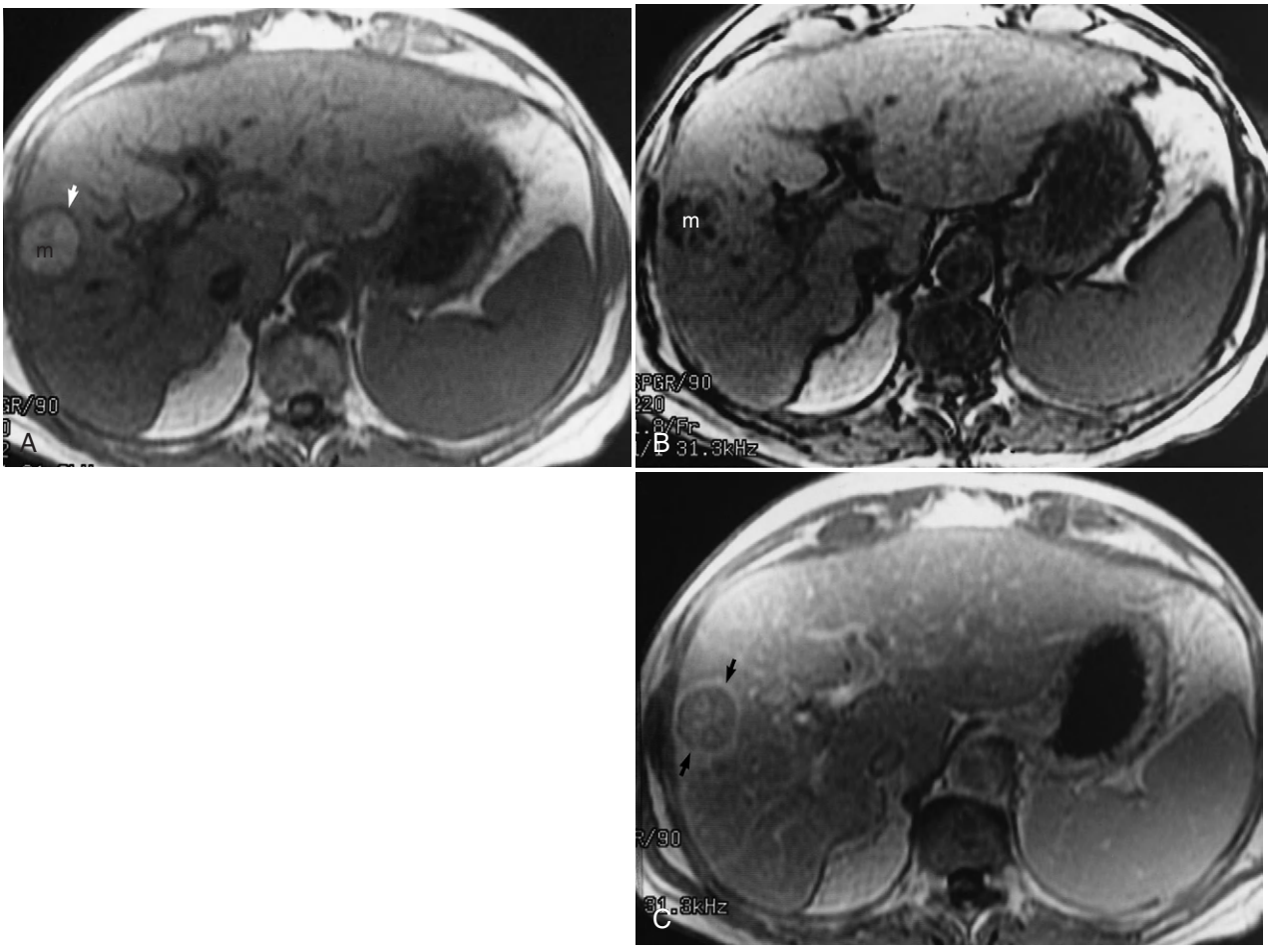


FIGURE 17.14. Hepatocellular carcinoma with intracellular lipid and capsular enhancement. **A,** T1-weighted in-phase gradient-echo image shows a focal hyperintense mass (*m*). A dark rim around this mass makes it appear encapsulated (*arrow*). **B,** A T1-weighted out-of-phase image shows signal loss in this mass (*m*), representing intracellular lipid and water of approximately equal distribution. **C,** Delayed postcontrast image through the lesion shows the "capsule" around the lesion to be enhanced (*arrows*); the capsule did not enhance on the immediate postcontrast images (not shown).

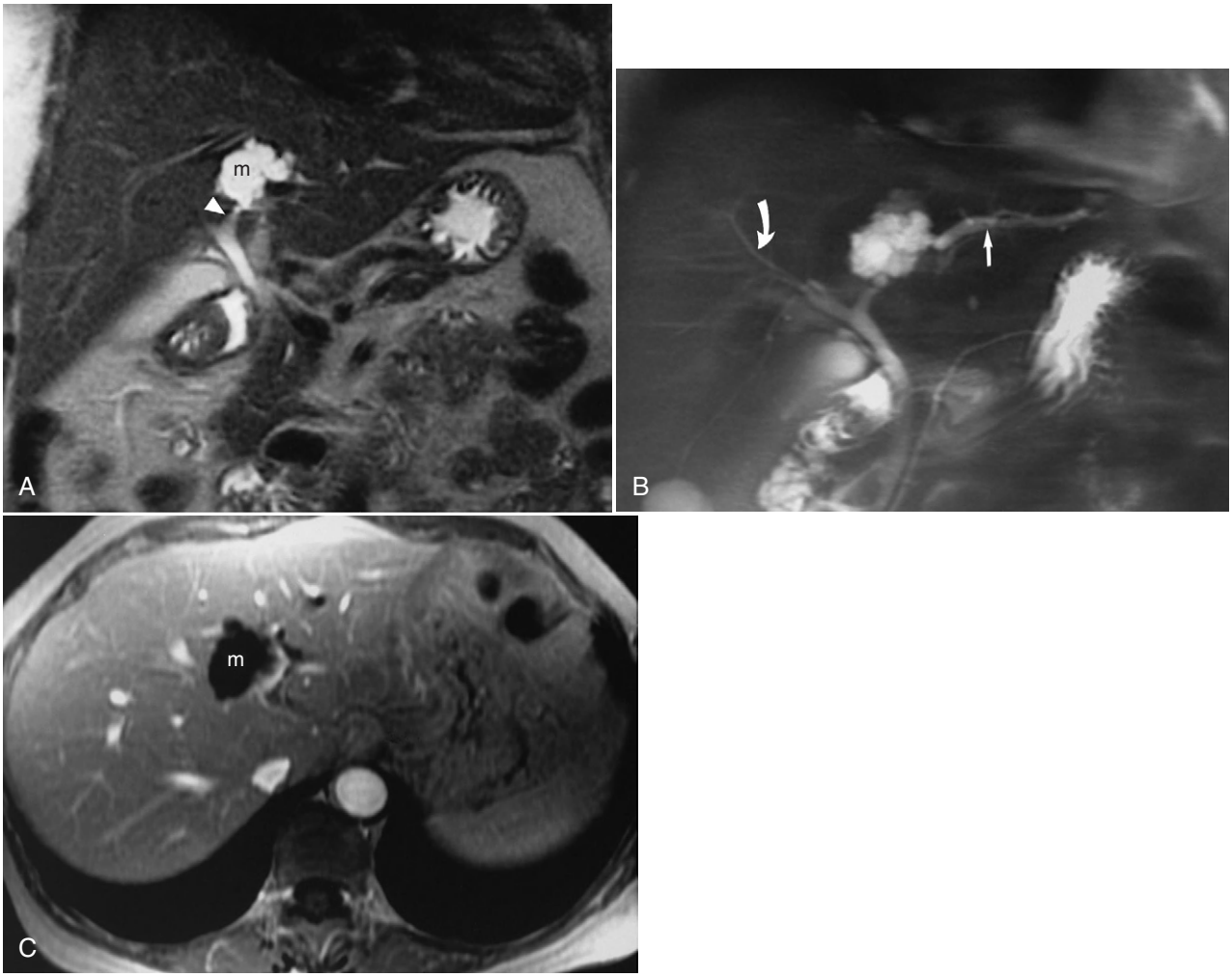


FIGURE 17.15. Biliary cystadenoma. **A,** Coronal T2-weighted image shows a lobulated mass (*m*) in close proximity to the left hepatic duct (*arrowhead*). **B,** Projection image in the coronal oblique plane shows the well-defined hyperintense mass to be in continuity with a mildly dilated left-sided biliary radicle (*straight arrow*). The normal right-sided biliary radicle (*curved arrow*) is easily seen with this technique. **C,** Postcontrast, T1-weighted gradient-echo image shows no enhancement within this mass (*m*).

BILIARY TUMORS

Gallbladder Carcinoma

Gallbladder carcinoma (see Chapter 49) is well evaluated with MRI. This entity is best seen on T2-weighted images as thickening of the gallbladder wall, generally adjacent to multiple gallstones. Cholelithiasis is a predisposing condition. Evidence of liver invasion and spread to regional lymph nodes also may be identified with MRI, which is optimal for evaluation of these lesions because of its outstanding tissue contrast and ability to image directly in multiple planes (Dai et al, 2009; Schwartz et al, 2002; Sikora et al, 2006).

Bile Duct Cancer

Bile duct tumors (see Chapters 50A and 50B) are easily seen on MRI. Central lesions (hilar cholangiocarcinomas) are generally associated with biliary dilation, which is bright on T2-weighted images. The central tumors may be seen as areas of mildly hyperintense signal on T2-weighted images (Fig. 17.16), less so than the surrounding biliary dilation. The level of obstruction and continuity of the tumor with the vasculature are well evaluated with MRI (Lee et al, 2003; Schwartz et al, 2003). Peripheral or intrahepatic cholangiocarcinomas generally present as high signal intensity masses on T2-weighted images. They may appear similar to other malignant neoplasms of the liver, but they generally do not have capsules or areas of high signal intensity on T1-weighted images as may be seen in HCCs. Distinction of peripheral cholangiocarcinoma and confluent hepatic fibrosis is sometimes difficult; however, late enhancement is seen in the malignant lesion.

BENIGN DISEASES OF THE BILIARY TRACT

Cholelithiasis

Gallstones are easily identifiable on T2-weighted images and on MRCP sequences (Fig. 17.17; see Chapter 30). They usually appear as low signal intensity structures in a fluid-filled gallbladder. MRI is usually not the modality of choice in the

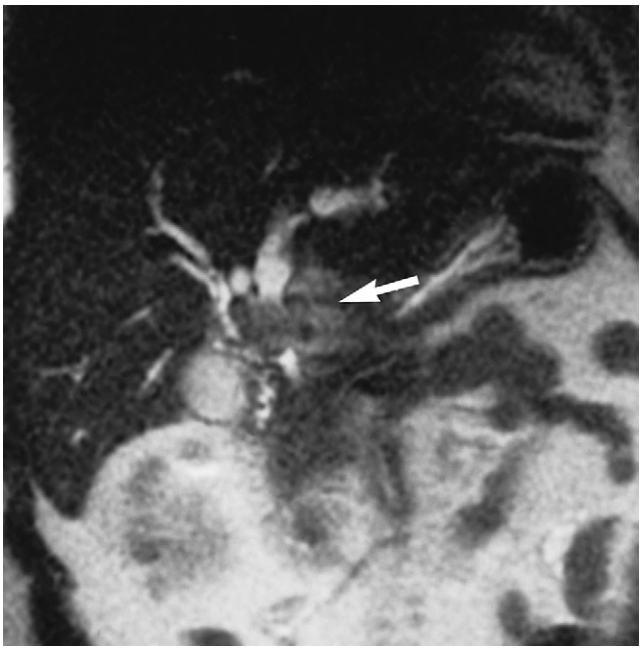


FIGURE 17.16. Hilar cholangiocarcinoma. Oblique coronal T2-weighted image shows dilation of the intrahepatic biliary tree. A soft tissue mass (*arrow*) is present at the bifurcation of the common hepatic duct, causing the duct dilation.

evaluation of cholelithiasis, because ultrasound is highly sensitive and less expensive in uncomplicated cases, but choledocholithiasis can be imaged effectively by MRI (Johnson et al, 2010; Samaraee et al, 2009). Common duct stones are relatively uncommon in children (Rescorla, 1997) but are more common in elderly patients (Catheline et al, 1998; Gonzalez et al, 1997). Direct coronal T2-weighted imaging, readily available with MRI, easily identifies common duct stones. In addition, if multiple stones are present in the common duct, they too should be identifiable by MRI (see Fig. 17.17). MRCP can also be obtained to evaluate whether retained stones are present after cholecystectomy. If no stones are present on MRCP, this may obviate the need for ERCP.

Choledochal Cysts

Choledochal cysts (see Chapter 46) represent dilation of the extrahepatic bile ducts with possible associated intrahepatic biliary duct dilation. This entity is a relatively uncommon congenital anomaly that usually presents before 10 years of age. The classic triad includes a palpable mass, abdominal pain, and jaundice. Five types of cysts have been described (Todani et al, 1977): type I has been subdivided into A, B, and C, in addition to types II, III, IVa and IVb, and V. MRI is well suited not only to diagnose these cysts but also to classify the type of cyst. Not only can MRI cholangiograms be generated to depict the normal and abnormal anatomy, but also direct coronal imaging can be obtained for clearer evaluation.

Postoperative Biliary Complications

Complications from surgical procedures include bile leaks, abscess formation, and biliary strictures (see Chapters 25 and 42). Although using other imaging modalities in the immediate postoperative setting to assess for bile leaks and abscesses may be prudent, MRI is uniquely suited for the assessment of the postoperative biliary tract. Bile duct injuries after surgery can be caused by a number of things, but these may all lead to the same result—a stricture at the anastomotic site. MRI using long-echo train-length imaging (MRCP technique) is uniquely suited for addressing this problem. Surgical clips near the anastomosis may create streak artifacts during CT scanning. MRI has multiplanar capabilities and superior tissue contrast, and MRCP sequences can minimize susceptibility to artifacts, owing to multiple 180-degree refocusing pulses; this can allow for improved visualization of the region of the anastomosis and improved diagnostic confidence (Fig. 17.18; Coakley et al, 1998).

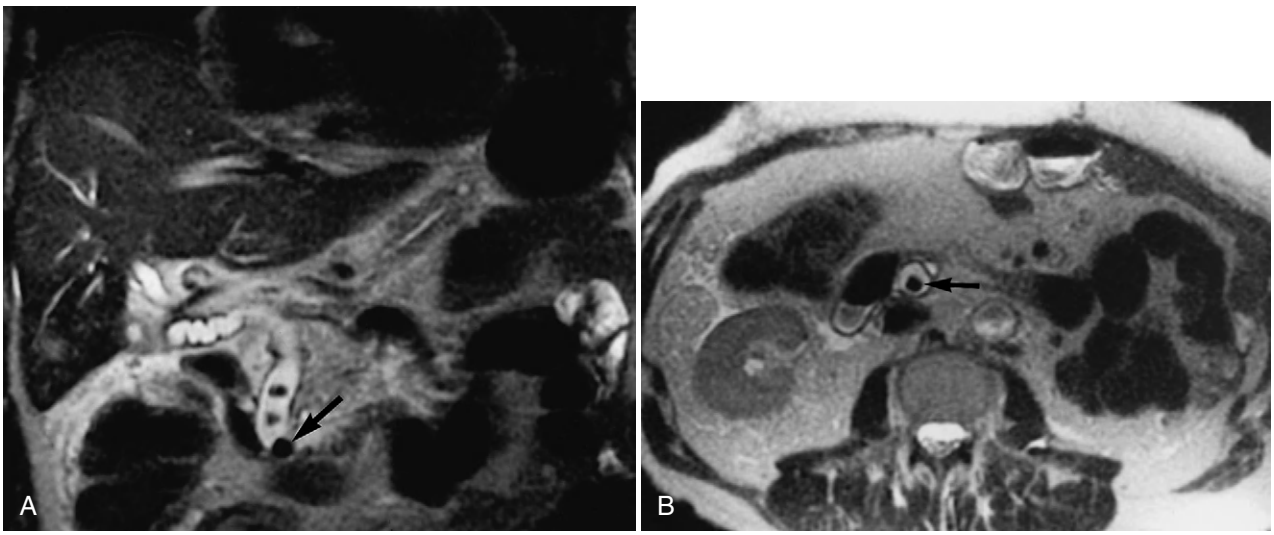


FIGURE 17.17. Choledocholithiasis. **A,** Coronal T2-weighted Single Shot Fast Spin Echo image through the common duct in a patient after cholecystectomy shows multiple stones within the common bile duct. Note the distal stone impacted at the level of the ampulla (*arrow*). **B,** Axial T2-weighted image with the same technique also shows a stone, surrounded by bile, in the distal common bile duct (*arrow*).

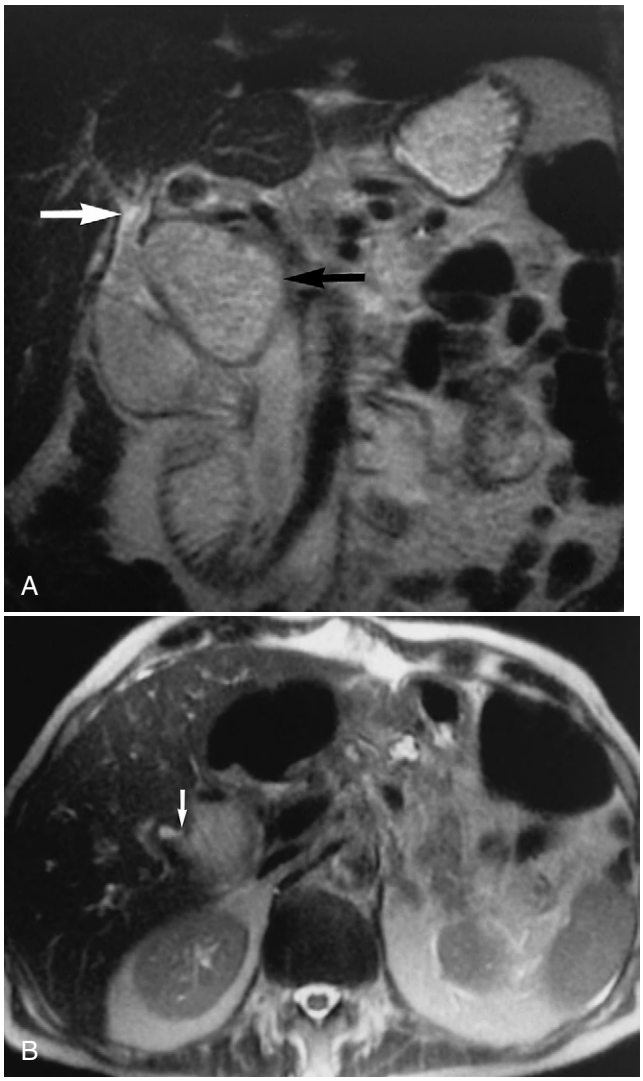


FIGURE 17.18. Afferent loop syndrome. **A,** Coronal T2-weighted sequence in a patient after pancreaticoduodenectomy for pancreatic carcinoma. The patient has a hepatojejunostomy with a patent anastomosis (*white arrow*). The afferent loop is markedly dilated (*black arrow*) compared with other loops of bowel. No mechanical obstruction was noted. **B,** Axial T2-weighted image through the level of the anastomosis (*arrow*) shows the site to be patent without evidence of a stricture. The afferent loop is dilated.

PANCREAS

Pancreatic Cancer

Pancreatic carcinoma (see Chapter 58) is well evaluated on MRI and MRCP. The faster MRI sequences help stage patients with pancreatic cancer and help to characterize lesions of the pancreas. MRI is generally thought to be highly accurate in assessing for vascular invasion, local-regional tumor extension, and liver metastases (Hanninen et al, 2002). Similar to other modalities, accuracy is limited for assessment of lymph node metastases with conventional and fast MRI techniques. Newer lymph node–specific contrast agents may play a role in improving the specificity of MRI for detection of lymph node metastases.

Cystic Lesions of the Pancreas

Pancreatic cystic lesions (see Chapter 57) are relatively common imaging findings and are usually secondary to benign processes, but they may be malignant. Multiple imaging modalities may be used to identify and visualize pancreatic cystic lesions including ultrasound, CT, and MRI. Soft-tissue contrast is optimal with MRI imaging, which permits optimal depiction of the internal features of pancreatic cysts, such as septations, nodularity, and soft-tissue masses. One particularly useful sequence is the single-shot fast spin-echo sequence. Cystic lesions are high in T2 and are bright on these sequences (Zhang et al, 2002; Acar et al, 2010). Evaluation after contrast (Gd-DTPA) administration helps assess cyst wall irregularity or enhancement. Intraductal papillary mucinous tumors may be distinguished from other lesions on MRI by combining ductal visualization with postcontrast images (Lim et al, 2001).

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CHAPTER 18

Direct cholangiography: approaches, techniques, and current role

George Getrajdman and Robert C. Kurtz

DIRECT CHOLANGIOGRAPHY OVERVIEW

Direct cholangiography, the introduction of contrast medium into the biliary system, can be achieved radiologically, endoscopically, or intraoperatively via surgically placed tubes. The nonoperative techniques are percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiopancreatography (ERCP). Currently, noninvasive magnetic resonance imaging (MRI) and computed tomographic (CT) cholangiography have virtually eliminated the indications and need for direct cholangiography (Stroszczynski & Hünerbein, 2005; Miller et al, 2007; Bakhal et al, 2009; see Chapters 16 and 17). Today ERCP and PTC are almost exclusively performed only as part of a planned interventional procedure, such as drainage, stenting, stone extraction, or stricture dilation (see Chapters 27 and 28).

The most obvious benefits of noninvasive cholangiography are that it is painless, does not require sedation, and has few complications. Thin-section scanning techniques with multiplanar reconstruction allow for a large field of view that enables visualization of the entire biliary tree (Fig. 18.1). Reconstructed three-dimensional data sets can be displayed as a cholangiogram and manipulated in space. By contrast, direct dye injection only allows visualization of the structures in continuity with the opacified, nonisolated segments of the biliary system (Fig. 18.2). In PTC, even with multiple puncture sites and injections, simultaneous cross-sectional imaging may be required to ensure that the entire biliary tree has been opacified. In addition, noninvasive cholangiography has overall superior diagnostic accuracy compared with invasive techniques, allowing for visualization of structures contiguous to the biliary system and the bile duct wall.

PERCUTANEOUS TRANSHEPATIC CHOLANGIOGRAPHY (SEE CHAPTER 28)

History

The first report of radiologic visualization of the biliary tree was presented by Burckhardt and Müller in 1921, and cholecystocholangiography was achieved by percutaneous puncture of the gallbladder. The first report of PTC was by Huard and Do-Xuan-Hop in 1937, and cholangiography was performed with the suboptimal contrast agent Lipiodol. The use of transhepatic cholangiography as a diagnostic tool gained popularity 15 years later, after Carter and Saypol's (1952) discussion of PTC with the use of a water-soluble contrast agent. In the ensuing years, many investigators (Flemma & Shingleton, 1966; Glenn et al, 1962; Mujahed & Evans, 1966; Seldinger, 1966; Shaldon et al, 1962; Weicher, 1964) described a variety of different methodologic details, including the use of sheathed or unsheathed needles of various sizes, different sites and directions of puncture, and various numbers of puncture trials to maximize success. The procedure remained associated with a significant risk of bile peritonitis, especially in obstructed systems, and the less frequent complication of hemorrhage. The last essential refinement in transhepatic cholangiography, the use of fine needle technique, was developed at Chiba University and was first presented by Ohto and Tsuchiya (1969) and later by Tsuchiya (1969). The value and decreased complication rate of the fine needle technique was verified by numerous authors (Benjamin et al, 1978; Ferrucci et al, 1976; Fraser et al, 1978; Gold & Price, 1980; Harbin et al, 1980; Hinde et al, 1977; Jain et al, 1977; Pereiras et al, 1977), and the fine needle technique has been generally accepted as the standard.

At present, diagnostic transhepatic cholangiography has been completely supplanted by noninvasive imaging techniques for the evaluation of the biliary tree. In 1985, Kadir reported that less than 5% of patients referred for evaluation of biliary disease required concomitant drainage procedures. With continued advancement of cross-sectional imaging techniques, including the development of MRI cholangiography (Park et al, 2004; Romagnuolo et al, 2003; Simone et al, 2004; Vaishali et al, 2004; Zhong et al, 2003) and CT cholangiography, diagnostic PTC should be performed only as part of a planned radiologic interventional procedure.

The most obvious benefits of noninvasive cholangiography are the elimination of complications and pain, but several other advantages are also important. Puncture and contrast injection techniques in high bile duct obstruction with isolated systems visualize only the portions of the biliary tree that are in continuity with the puncture site, and multiple interventions may be required to visualize the entire biliary tree if there are areas of duct isolation (see Fig. 18.2). Even with multiple punctures and contrast injections, cross-sectional imaging may be necessary sometimes to ensure that the biliary tree has been completely assessed. MRI cholangiography has the advantage of showing the entire biliary system even in the presence of isolation (see Fig. 18.1). Finally, there is the diagnostic advantage gained with cross-sectional imaging. By allowing visualization of many more organs than just the biliary system, diagnostic accuracy of cholangiography is significantly increased.

Preprocedural Preparation

All patients require cross-sectional imaging consisting of CT, ultrasound, or MRCP before the procedure. This imaging is especially important in patients who have undergone hepatic

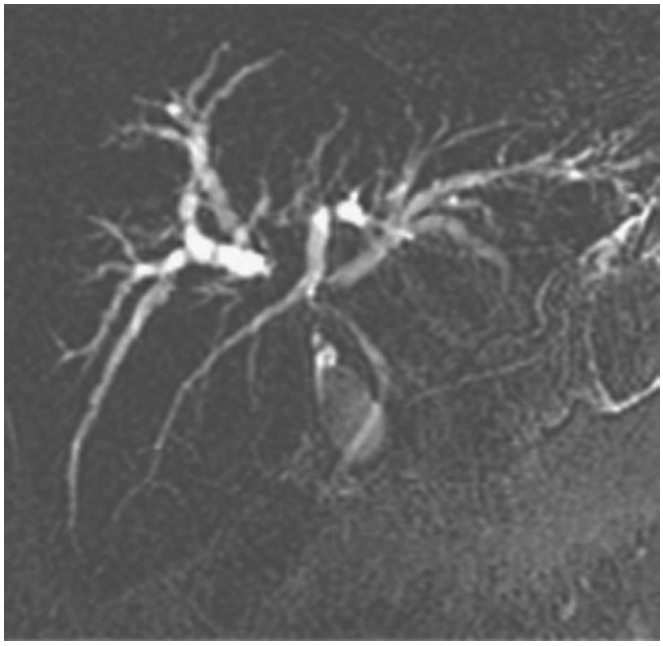


FIGURE 18.1. Magnetic resonance cholangiography showing complete isolation of left-sided and right-sided bile ducts. This clinical scenario would require multiple punctures for percutaneous transhepatic cholangiography delineation of the entire biliary tree.



FIGURE 18.2. Hilar cholangiocarcinoma involving first-order right and left hepatic ducts. Separate needle punctures were required to fill the right and left ducts.

resection. In the authors' institution, intravenous contrast-enhanced CT is the procedure of choice because of its ready availability and its ability to show the level of obstruction, position of the liver, presence of lobar atrophy, status of the portal veins, and relationship of bile ducts to other structures, which could greatly facilitate successful puncture.

Coagulation parameters and platelet count should be corrected when necessary. Patients generally require conscious sedation consisting of midazolam and a pain medication, such as meperidine (Demerol), fentanyl, or morphine, and they should receive only clear liquids after midnight the night before the procedure. All patients must receive broad-spectrum intravenous antibiotic coverage, and antibiotics should be administered 1 hour before the procedure to ensure maximal blood levels at the time of PTC.

Procedure

The procedure is ideally performed on a tilting fluoroscopic table. Because the specific gravity of contrast material is greater than that of bile, when the fluoroscopic table can be tilted, less contrast agent is required to fully delineate the biliary tree.

Right-Sided Puncture

After the patient has been prepared and draped in a sterile fashion, a puncture site is selected in the right midaxillary line one or two interspaces below the costophrenic angle. Puncture sites are generally kept below the ninth intercostal space to avoid inadvertent entry into the pleural space. A 21- or 22-gauge, 15- to 20-cm styletted needle is advanced under fluoroscopic guidance over the rib, rather than under, to avoid laceration of an intercostal vessel. The puncture is performed neither from a particular intercostal space nor aiming at a particular vertebra, rather the site and direction of puncture are chosen based on evaluation of the patient's cross-sectional imaging studies.

Care should be taken to avoid puncture of the gallbladder or extrahepatic biliary tree. A small amount of water-soluble contrast agent is injected while slowly withdrawing the needle until a bile duct is identified. Injection of contrast agent into a bile duct has the appearance of oil being dropped in water. Inadvertent opacification of a vascular structure is recognized by the rapid clearance of the contrast agent. If a bile duct is not entered during withdrawal of the needle, the needle is reintroduced in a slightly different direction. It is generally recommended, however, that the needle not be withdrawn completely from the liver to minimize damage to the liver capsule. When opacification of the biliary tree is difficult, particularly when the ducts are not dilated, the same puncture site may be used up to 12 times before a new intercostal space is selected for needle placement. In patients with biliary obstruction, 10 to 20 mL of contrast agent injected slowly is usually sufficient to opacify the bile ducts. The use of a tilting table is valuable to avoid biliary tree overdistension, which could lead to bacteremia or sepsis. A larger volume of contrast material is often required in nonobstructed systems. When the bile ducts are visualized, radiographs should be obtained in multiple projections to identify specific portions of the biliary tree and to completely delineate abnormal findings.

Left-Sided Puncture

Because the left lateral segment of the liver has variable size and anatomic position, careful review of preprocedural cross-sectional imaging is required to select a proper puncture site. Although left-sided punctures could be performed from the right side, via an anterior axillary line approach into the segment IV bile ducts, the more accepted method is a subxiphoid approach into segment II or III. Ultrasound guidance is more

useful for left-sided subxiphoid punctures than for any transcostal right-sided procedure.

Success Rate and Accuracy

Opacification of the bile ducts is successful in 95% to 100% of patients with biliary obstruction (Mueller et al, 1981; Harbin et al, 1980; Jain et al, 1977). A success rate of 60% to 95% is reported for nondilated biliary systems. The chance of success in the nondilated system is increased by the number of needle passes performed (Jaques et al, 1980). Usually, the level of obstruction is accurately determined by careful attention to detail and liberal use of a tilt table, but the technique is less definitive for determining the cause of obstruction. No radiologic descriptions of obstructed bile ducts are pathognomonic for differentiation of benign and malignant disease (Hadjis et al, 1985; Wetter et al, 1991). Many malignant masquerades are well described, and it is not always possible to differentiate between calculous disease and papillary bile duct cancer. Other radiologic findings and cytology or histology are often required for accurate diagnosis.

Pitfalls in Interpretation

Lack of Opacification

Failure to inject adequate volume of contrast agent can lead to false localization of the level of obstruction. This can occur with complete obstruction and may be recognized by the presence of a hazy margin at the level of the apparent obstruction (Fig. 18.3; Kittredge and Baer, 1975). In high bile duct obstruction, especially when associated with variant anatomy, isolated segments of the biliary tree can be visualized only by direct puncture. If direct cholangiography is incomplete, there also may be difficulty diagnosing duct injuries and bile leaks, both of which can be missed unless the proper duct is punctured and opacified.

Ductal Dilation

Absence of ductal dilation does not exclude obstruction. Disorders such as sclerosing cholangitis, AIDS, and chemotherapy-induced biliary scleroses (CIBS) have associated fibrosis that may impede normal duct dilation. Conversely, dilated bile ducts do not always mean obstruction. An example is the nonobstructive dilation that may be seen in patients with Caroli disease or choledochal cysts.

Complications

Serious complications of PTC are rare and occur in approximately 3% of patients (Harbin et al, 1980). The most common major complications are bile leakage (1% to 2%), sepsis (2% to 3%), and hemorrhage (0.2% to 0.4%); much rarer complications include pneumothorax, biliothorax, colon puncture, and abscess formation. Many of these complications can be decreased and avoided. Ultrasound guidance and puncture below the ninth intercostal space will clearly decrease the incidence of pulmonary complications, and septic complications can be avoided by appropriate antibiotic coverage and by not overdistending the biliary tree. At times, aspiration and decompression of the biliary tree will be valuable in allowing injection of larger volumes of contrast agent without leading to sepsis.

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY (SEE CHAPTER 27)

History

ERCP was first reported in 1968 by McCune and colleagues and has remained an important diagnostic modality frequently used in the management of patients with hepatobiliary and

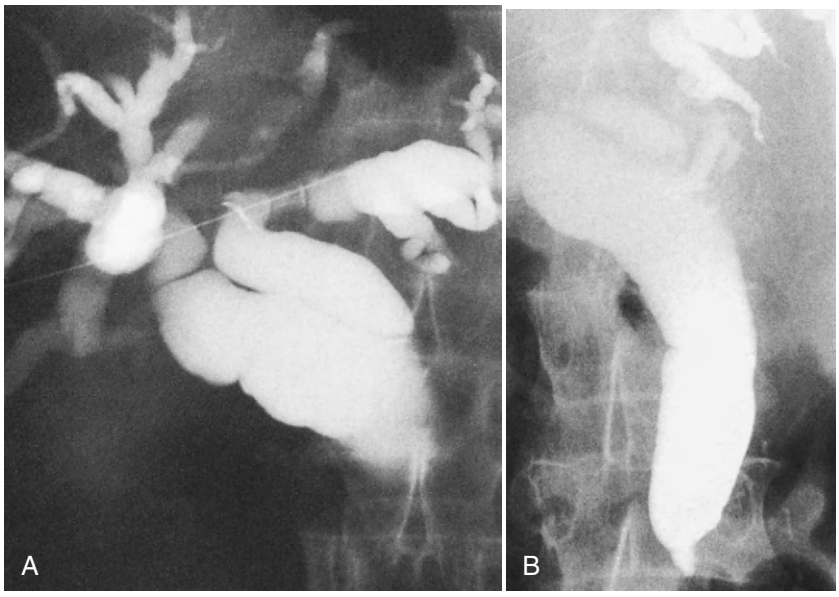


FIGURE 18.3. Ampullary carcinoma. **A,** With the patient supine, contrast pools proximally, giving a false impression of a high bile duct obstruction. The spurious nature of the level is suggested by the hazy inferior margin to the contrast column. **B,** With the patient sitting semierect, the contrast pools at the true point of obstruction, which is sharply defined.

pancreatic diseases (Cotton, 1977; Cotton et al, 1972; Freeney, 1988; Oi et al, 1970). Since the 1970s, there has been continued progress in ERCP instrumentation. One major innovation was the development in the late 1980s of video, or electronic, endoscopy. Video endoscopy enables high-quality photographic and videotape documentation of important endoscopic findings and has made the training of physicians in the technique of ERCP much easier. The endoscopic skills needed to perform ERCP are more difficult to learn than the standard procedures of upper endoscopy and colonoscopy, but now many endoscopists throughout the world can perform diagnostic ERCP easily, rapidly, and safely. Working with a cooperative patient and a well-trained team, this procedure often can be completed in less than 15 minutes. Diagnostic ERCP is rapidly being replaced, however, by noninvasive imaging techniques, such as MRCP.

A 2002 National Institutes of Health consensus conference on ERCP concluded that although MRCP and ERCP had similar sensitivity and specificity in diagnosing common bile duct stones, ERCP, as an invasive procedure, is more operator dependent and has risks associated with it because of the required sedation, and it carries the risk of injection pancreatitis. As a result, stand-alone diagnostic ERCP is being used much less frequently. It is most commonly combined with a therapeutic endoscopic procedure, such as endoscopic sphincterotomy and stone extraction for choledocholithiasis, or the insertion of an endobiliary stent for malignant biliary obstruction.

Technique

Patient selection is important, because ERCP is commonly done in an outpatient setting. Patients should be alert and oriented and must be able to give informed consent. In the rare situation in which this is not possible, such as with an intubated patient on mechanical ventilation, consent is obtained from the next of kin. Patients with uncorrected shock, cardiac arrhythmias, profound neutropenia, or significant coagulopathy should not have an elective diagnostic test such as ERCP performed.

Age is not a contraindication to ERCP, because the procedure is safe even for selected patients in their 90s. Although children less commonly have pancreatic and biliary disease, the standard technique is often all that is necessary for children, and instrumentation is the same except in children younger than 6 months old. General anesthesia is rarely needed for children older than 11 or 12 years (Buckley & Connon, 1990). ERCP has been shown to be a valuable adjunct in the evaluation of infantile cholestasis (Wilkinson et al, 1991). In a case-control study comparing children undergoing ERCP with adults, there were no differences in the success rate or the rate of complications (Varadarajulu et al, 2004). Elderly patients can safely undergo ERCP, and they have the same risks of bleeding and perforation as younger patients do but have a lower risk of pancreatitis.

Patient comfort is maintained by the use of intravenous sedation under monitored control. Drug combinations include narcotics such as meperidine and droperidol and the benzodiazepines midazolam or diazepam. Dosages are titrated for each patient with a total dose of meperidine generally ranging from 50 and 100 mg and midazolam between 2 and 10 mg. More recently, propofol, at 190 μg/kg/min, administered by anesthesia personnel, has been replacing meperidine and a benzodiazepine. Studies have shown that propofol is more effective than sedation with midazolam, it is safe, and it is associated with a faster postprocedure recovery (Wehrman et al, 1999). In some centers, if the endoscopic procedure is expected to be difficult, or if the patient has significant comorbid medical conditions, general anesthesia is used. Excess duodenal motility is controlled by bolus injections of 0.2 to 1 mg of intravenous glucagon. Oxygen is administered by nasal cannula to avoid the hypoxemia that has been described in 40% of patients undergoing ERCP (Woods et al, 1989). The patient's electrocardiogram, blood pressure, oxygen saturation, and overall condition are continually monitored throughout the procedure by a dedicated nurse. Antibiotics are not given routinely for diagnostic procedures except when biliary obstruction is expected. All endoscopic equipment used for this procedure, including the endoscopes, is either chemically disinfected or gas sterilized.

A side-viewing duodenoscope is used to afford excellent visualization of the ampulla of Vater. In patients with a Billroth II type gastrojejunostomy, a standard forward-viewing upper endoscope or pediatric colonoscope may be needed to successfully approach the ampulla. An initial endoscopic evaluation of the stomach and duodenum is performed before cannulation of the ampulla. The pancreatic and biliary ducts are selectively cannulated and identified, and a contrast agent, such as diluted Renografin-60, is injected into the desired duct under fluoroscopic control, with subsequent radiographic images obtained of the duct anatomy. The use of a guidewire to cannulate the ampulla without using contrast is becoming common. In one recent series, 795 (99%) of 801 ERCPs were performed without contrast to initially identify access to the common bile duct (CBD). The pancreatitis rate in this series was 1.3%, as was guidewire perforation of the bile duct, which also occurred infrequently (Adler et al, 2010). An additional way of gaining access to the difficult-to-cannulate CBD is to selectively place a pancreatic duct stent first and then attempt wire-guided cannulation of the bile duct.

Material for pathologic and cytologic evaluation can be obtained from either the biliary or pancreatic duct system with a variety of dedicated endoscopic biopsy forceps and cytology brushes. Pathologic and cytologic material also may be obtained from the ampulla of Vater, duodenum, and stomach.

A skilled endoscopist can be expected to identify the ampulla of Vater in almost all patients with normal anatomy. If the ampulla is inside a duodenal diverticulum, or if the second portion of the duodenum is stenotic, compressed, or invaded by a pancreatic mass, identification of the ampulla may be difficult. When the ampulla is found, success rates for selectively cannulating the CBD and pancreatic duct are greater than 90% (Rosch, 1985). When difficulty occurs in cannulation of the CBD, invasive maneuvers, such as precut papillotomy, can improve the success rate but with an associated increase in the complication rate (Shakoor & Geenen, 1992). In a patient with a Billroth II gastrojejunostomy, success rates for bile duct cannulation are much lower (Katon et al, 1975; Osnes & Myren, 1975).

Endoscopy and Pancreatography during Endoscopic Retrograde Cholangiopancreatography

The ability to perform endoscopy and pancreatography in addition to cholangiography during ERCP affords a major advantage to this procedure. It is common for endoscopic examination

of the stomach and duodenum to provide important diagnostic information that is helpful in management planning. Displacement of the antrum or pylorus or a stricture or narrowing of the second portion of the duodenum may indicate the presence of a pancreatic mass responsible for obstructive jaundice. The diagnosis can be confirmed by biopsy and cytologic specimens taken during the procedure from the infiltrated or ulcerated duodenal wall.

Duodenal diverticula almost always are located near the papilla in the descending duodenum. Large juxtapapillary diverticula are clinically significant, because they are often associated with choledocholithiasis. Although it was thought that periampullary diverticula may make cannulation of the ampulla more difficult, more recent work has shown that this may not be true (Tham & Kelly, 2004). On inspection of the ampulla, anatomic variants should be looked for before attempting cannulation (Phillip et al, 1974). Occasionally, two orifices are found, and this indicates separate biliary and pancreatic duct systems. The minor ampulla is located about 1 to 2 cm above the major papilla. Impacted gallstones give rise to a characteristic distension or bulge of the papilla, and previous spontaneous passage of bile duct stones can be recognized by a fissured splitting of the papillary orifice. Previous surgical dilation of the papilla or spontaneous gallstone perforation above the papilla also produces a characteristic appearance. Occasionally, a fistulous perforation in the roof of the papilla is found as a result of a false passage produced at surgical dilation (Tanaka & Ikeda, 1983). Biliary–enteric anastomoses appear as circular or slitlike openings.

The endoscopic diagnosis of ampullary carcinoma is not difficult, especially if the tumor is exophytic. The diagnosis becomes more challenging, however, when the tumor is predominantly intramural. In such instances, the diagnosis is frequently confirmed by biopsy and cytologic specimens, after endoscopic papillotomy allows the tumor to be exposed. In a series from the Medical College of Wisconsin, the correct diagnosis was made by endoscopic biopsy in 42 of 44 patients with ampullary neoplasia and in 16 of 18 patients with invasive ampullary cancer (Komoroski et al, 1991).

Imaging the pancreatic duct can be an important adjunct to cholangiography during ERCP. Strictures, stones, and other obstructing lesions can be identified. With increasing age comes progressive atrophy and fibrosis of the pancreas. The diameter of the main pancreatic duct also increases with age, although one study found no difference in pancreatic duct length among patients younger than 40 years compared with older patients. Duct diameter throughout the pancreas was significantly greater, however, in patients over 40 (Anand et al, 1989).

Anatomic variations, such as pancreas divisum (Fig. 18.4), also may be identified on a pancreatogram. This abnormality has been described in 7.5% of ERCP procedures and can be confirmed by cannulation of the main pancreatic duct through the orifice in the minor papilla (Bernard et al, 1990).

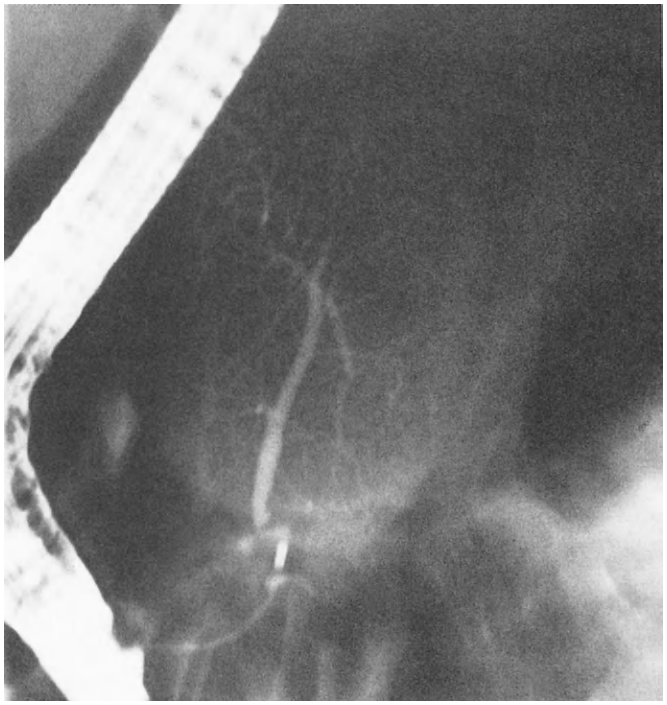


FIGURE 18.4. Pancreas divisum. The cannula is in the major papillary orifice, and contrast injection opacifies the proximal portion of the major pancreatic duct (Wirsung). Injection through the minor papillae allows opacification of the duct of Santorini and the distal duct of Wirsung.

Complications

The experience of the endoscopist is one of the most significant factors related to the development of ERCP complications (Bilbao et al, 1976). Statistics on complication rates vary accordingly. High case volume also has an impact on the complication rate. In a study conducted in Austria, endoscopists performing more that 50 ERCP procedures per year were compared with on those performing fewer than 50 per year. Those in the higher case volume group had a significantly higher success rate (86.9% vs. 80.3%; $P < .001$) and a lower overall complication rate (10.2% vs. 13.6%, $P = .007$; Kapral et al, 2008).

Acute pancreatitis after ERCP occurs in less than 7% of patients (Christensen et al, 2004; Rosch et al, 1981) and should be distinguished from transient asymptomatic hyperamylasemia, which occurs in 40% to 75% of cases (Classen & Demling, 1975). Asymptomatic hyperamylasemia disappears within 1 to 2 days, as do hypertrypsinemia (Phillip & Hagenmuller, 1983) and elevations of serum lipase and elastase 1 levels (Okuno et al, 1985). Radiographic documentation of renal excretion of the contrast agent injected into the pancreatic duct does not predict the development of acute pancreatitis (Hopper et al, 1989), and necrotizing pancreatitis, a serious complication, is observed in about 0.1% of pancreatograms. The prevalence of post-ERCP pancreatitis in children is quite low, about 2.5% in one study (Iqbal et al, 2008).

The use of nonionic contrast medium of low osmolarity has shown no advantage over the less expensive ionic contrast medium in preventing ERCP-related pancreatitis (Hannigan et al, 1985). The risk of pancreatitis is reduced by careful and gentle injection of the contrast medium into the pancreatic duct, by avoiding overdistension or "acinarization" of the pancreatic duct, and by minimizing repeated injection of the pancreatic duct when encountering difficulty in filling the CBD. Prophylactic administration of somatostatin or its analog octreotide has not been shown to prevent pancreatitis during diagnostic or therapeutic ERCP (Borsch et al, 1984; Sternlieb et al, 1992). A large, prospective, randomized,

placebo-controlled study from Italy looked at the efficacy of somatostatin and gabexate in preventing post-ERCP pancreatitis; 966 patients were studied, and no difference in the rate of pancreatitis was observed between the groups (Andriulli et al, 2004). A randomized control study demonstrated that 24 hours of octreotide prophylaxis before ERCP significantly decreased the incidence of post-ERCP pancreatitis compared with a placebo group (2/100 [2%] vs. 9/101 [8.9%]; $P = .03$) (Thomopoulos et al, 2006). Other investigators have suggested that when injection pancreatitis is a possibility, the use of a temporary pancreatic duct stent may serve to prevent its occurrence (Singh et al, 2004). In addition, when pancreatitis has developed, the use of somatostatin does not improve its clinical course (Phillip et al, 1985).

A serious complication of ERCP is the development of postprocedure cholangitis. This condition occurs most commonly when there is a significant and high-grade bile duct obstruction. When an obstructed bile duct is identified on ERCP, it is important to treat the obstruction rapidly by nonsurgical or surgical means (Classen & Phillip, 1982). Although no studies confirm the benefit of prophylactic antibiotics, it is reasonable to administer intravenous antibiotics that are preferentially excreted from the liver into the bile until adequate biliary drainage is achieved.

One study looked at the prophylactic use of antibiotics in routine ERCPs (Sauter et al, 1990). The authors found no difference in cholangitis rates when antibiotics were used, although the frequency of procedure-related bacteremia was significantly reduced. Antibiotics added to the injected radiographic contrast medium are of no benefit (Jendrzejewski et al, 1980). In addition, it was found that endoscopic instruments used in ERCP can be the source of serious infections (Earnshaw et al, 1985). *Salmonella* species are the most common organisms transmitted by contaminated endoscopes (Axon, 1991), and for this reason, it is imperative to ensure that the endoscopic equipment used for ERCP is adequately disinfected or sterilized.

DIRECT CHOLANGIOGRAPHY AND PANCREATOGRAPHY BY PERCUTANEOUS TRANSHEPATIC CHOLANGIOGRAPHY OR ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

Biliary Anatomy

The anatomy of the bile ducts is discussed in Chapter 1. Knowledge of the common variations of ductal branching is essential for accurate interpretations of cholangiograms, and these are shown in Figures 18.5 and 18.6; segmental nomenclature is summarized in Table 18.1. In the right lobe, the posterior segments lie more laterally than the anterior segments, so that the most lateral ducts on a cholangiogram are usually segments VI inferiorly and VII superiorly. The posterior sectoral duct is often recognizable by an arched course near the confluence (Figs. 18.7 and 18.8B). A right sectoral duct crosses to the left to join the left hepatic duct in 28% of cases according to Healey and Schroy (1953); in 22%, this is the posterior sectoral duct (see Figs. 18.6B and 18.8B), and in 6%, this is the anterior duct (see Figs. 18.6C and 18.8D). Occasionally, a right sectoral or segmental duct, posterior more often than anterior, courses inferiorly and enters the common hepatic duct directly (Fig. 18.9).

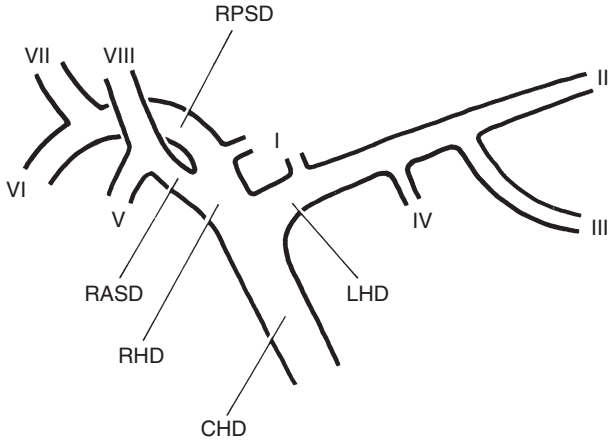


FIGURE 18.5. Standard intrahepatic ductal anatomy. The segments are numbered according to Couinaud's description (see Table 18.1). CHD, common hepatic duct; LHD, left hepatic duct; RASD, right anterior sectoral duct; RHD, right hepatic duct; RPSD, right posterior sectoral duct.

The confluence of the right and left ducts takes the form of a trifurcation rather than a bifurcation in 12% of cases according to Couinaud (1957; see Fig. 18.6A).

In the left lobe, the superior and inferior lateral segment ducts, segments II and III, unite in the line of, or to the right of, the umbilical fissure in 92% of cases. In the latter instance, the

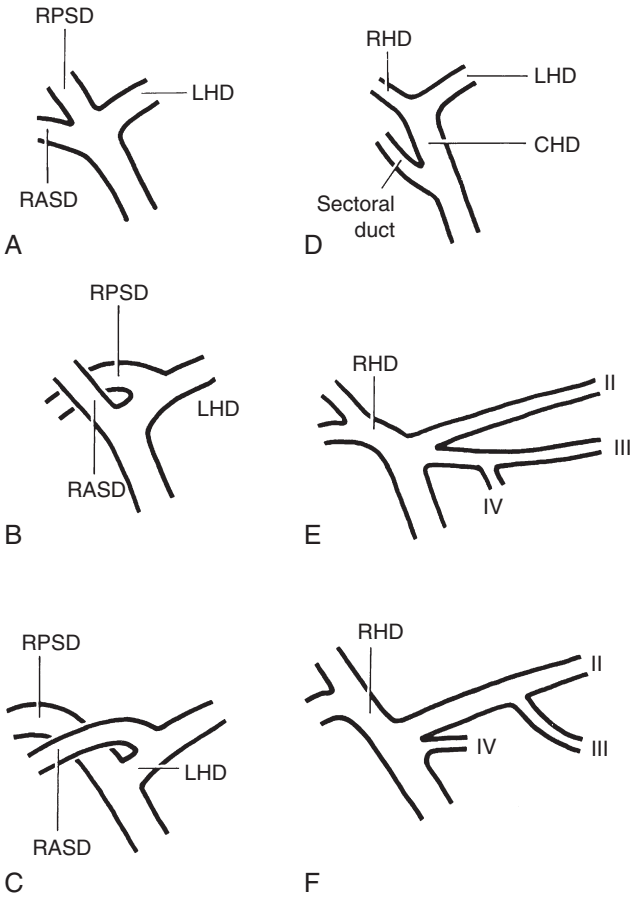


FIGURE 18.6. Variations of perihilar ductal anatomy. CHD, common hepatic duct; LHD, left hepatic duct; RASD, right anterior sectoral duct; RHD, right hepatic duct; RPSD, right posterior sectoral duct.

Table 18.1

Segmental Nomenclature

I	Caudate lobe
II	Left lateral superior segment
III	Left lateral inferior segment
IV	Left medial segment or quadrate lobe
V	Right anterior inferior segment
VI	Right posterior inferior segment
VII	Right posterior superior segment
VIII	Right anterior superior segment

Table 18.2

Average Duct Diameters Measured Directly from 50 Normal Percutaneous Transhepatic Cholangiography Examinations

Duct Diameter (mm)
Right hepatic = 4.7
Left hepatic = 5.2
Common hepatic = 6.5
Common bile = 7.6

From Okuda K, et al, 1978: Frequency of intrahepatic arteriovenous fistula as a sequela to percutaneous needle puncture of the liver. Gastroenterology 74:1204-1207.

quadrate lobe, segment IV, may drain wholly or partially into the segment II duct. Rarely, segment II and III ducts join at or close to the confluence (see Figs. 18.6E and 18.8C), and segment IV drains directly into the common hepatic duct in 1% of cases (see Fig. 18.6F; Healey & Schroy, 1953).

The caudate ducts are often difficult to identify. Usually two or three ducts drain most commonly into the right posterior sectoral duct, right hepatic duct, or left hepatic duct (Healey & Schroy, 1953). The recognizable caudate ducts are usually a few centimeters long and drain downward or to the right.

The left hepatic duct (average length, 17 mm) is considerably longer than the right hepatic duct (average length, 9 mm) and has a longer extrahepatic course. The normal diameters of the main bile ducts as measured at PTC are shown in Table 18.2. These figures are greater than the true duct dimensions because of some distension produced by direct cholangiography together with considerable magnification occurring on any fluoroscopic "spot film." The magnification is of the order of 40% (Nichols & Burhenne, 1984) and affects all structures in the image, including calculi, tubes, and strictures.

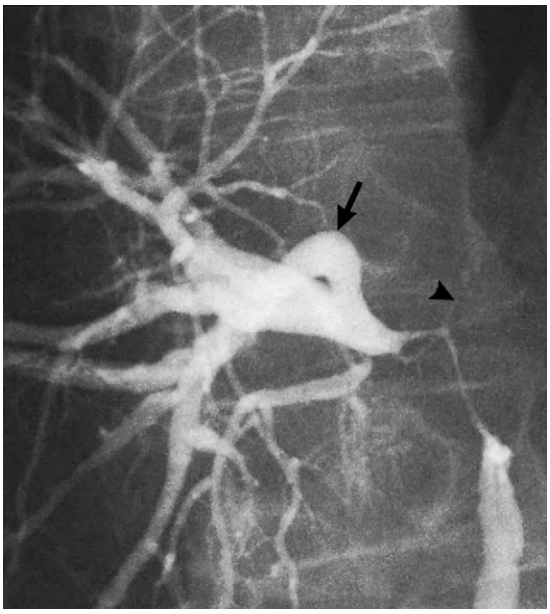


FIGURE 18.7. Hilar cholangiocarcinoma involving first-order right hepatic duct, proximal common hepatic duct, and faintly opacified left hepatic duct (*arrowhead*). Note the characteristic arched course of the right posterior sectoral duct (*arrow*).

The upper limits of normal for the diameter of the extrahepatic bile ducts as measured by ERCP vary between 9 mm and 14 mm (Niederau et al, 1984). Combined radiologic and manometric studies (Poralla et al, 1985) have shown that even in the absence of extrahepatic cholestasis, the diameter of the bile ducts and the pressure difference therein increases with advancing age. The diameter of the bile ducts as measured by ultrasonography is less than those measurements obtained during ERCP (Niederau et al, 1984). Anatomic abnormalities of the hepatobiliary system include cystic dilations (Fig. 18.10) of the bile duct or of the intrahepatic bile ducts (Caroli disease; see Chapter 46). There is a wide variation in where the cystic duct joins the common hepatic duct. A low junction with a correspondingly long cystic duct (Fig. 18.11) may result in difficulties if not recognized,. This is especially true when a cholecystojejunostomy is performed as a palliative biliary bypass for carcinoma of the head of the pancreas, and the jaundice either is not relieved or recurs rapidly in the postoperative period.

Interpretations

Because of its inherent weakness of only allowing visualization of the bile duct lumen, the main problem with the use of direct cholangiography is its lack of specificity. There are few, if any, pathognomonic radiologic findings. Many disease entities, from benign to malignant, overlap greatly in their cholangiographic appearances. The combination of history, blood markers, associated radiologic findings, and clinical scenario can often significantly narrow the differential diagnosis. However, it must be stressed strongly that because the cholangiographic appearance of many biliary diseases may be indistinguishable, biopsy is often required to rule out malignancy or to confirm suspected diagnosis.

Bile Leaks

Bile leaks are seen as sites of free extravasation of contrast agent at a site of bile duct injury. Injury may be secondary to trauma, but most commonly it is iatrogenic in nature. Associated bilomas may be seen at the point of bile leak. Although puncture or opacification of the correct duct is necessary for diagnosis, this is perhaps the remaining diagnostic scenario in which invasive direct cholangiography has a distinct advantage over noninvasive techniques. Because leaking intrahepatic bile ducts are usually not dilated, nonvisualization and inability to localize this finding on MR and CT cholangiography is common. Cystic

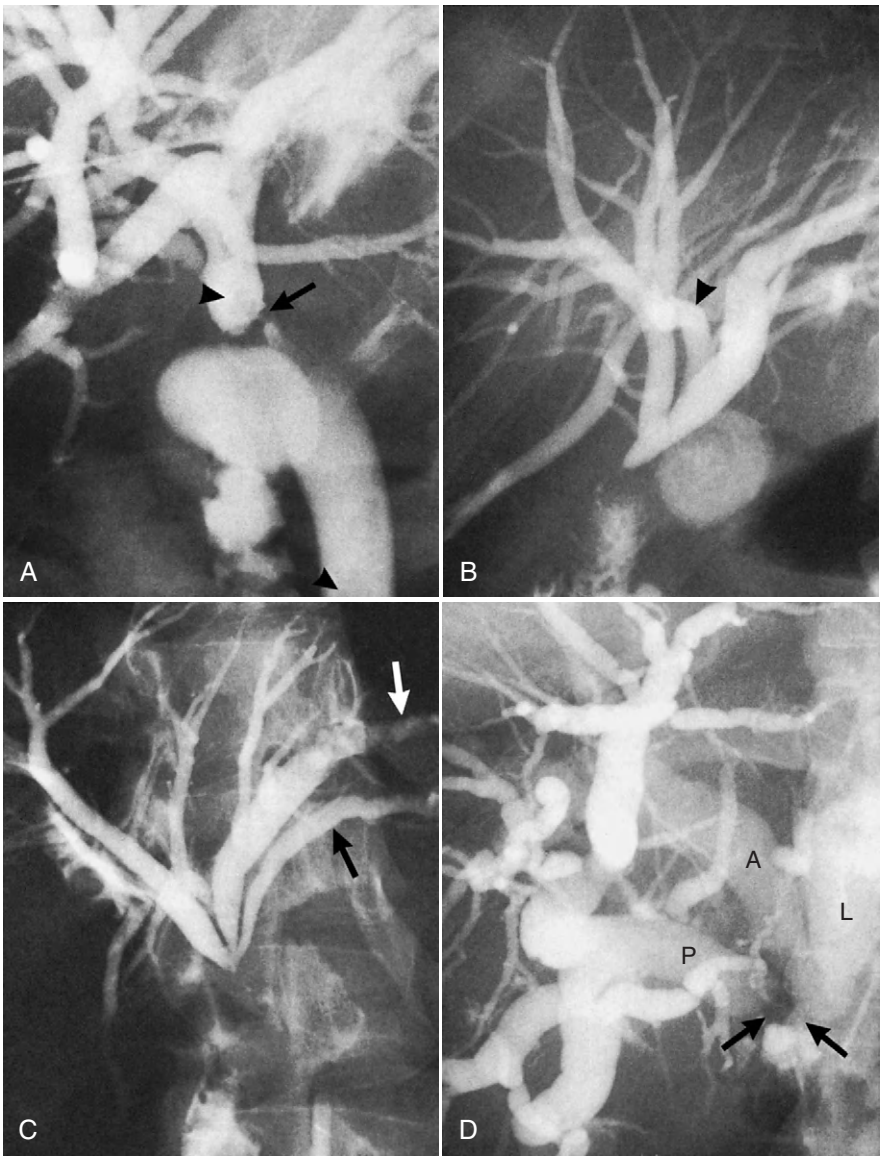


FIGURE 18.8. Postcholecystectomy strictures graded according to Bismuth. **A,** Grade I (>2 cm from the confluence of the right and left hepatic ducts; *arrowheads*): calculi lie above and below the stricture (*arrow*). **B,** Grade II (<2 cm from the confluence): there has been a previous hepatojejunostomy; the right posterior sectoral duct (*arrowhead*) has an exaggerated arched course and enters the left hepatic duct as a normal variant. **C,** Grade III (the confluence is involved by stricture, but the right and left hepatic ducts are not completely separated): ducts of segment II (*white arrow*) and segment III (*black arrow*) join the confluence independently as a normal variant. **D,** Grade IV (the right and left ducts are separated by the stricture): the right anterior sectoral duct (*A*) is draining into the left hepatic duct (*L*), which is separated from the right posterior sectoral duct (*P*) by the stricture (*arrows*).

duct leaks, minor injuries to extrahepatic bile ducts, and leaking anastomoses may also be unidentifiable and nonlocalizable with indirect techniques. Diagnosis and localization of bile duct leaks is therefore perhaps the only remaining indication for direct cholangiography.

Filling Defects

Air Bubbles, Blood Clots, Calculi, Primary and Secondary Bile Duct Cancers, and Parasitic Diseases

Air bubbles, though confusing, most commonly declare themselves by their perfectly circular shape and their distribution to nondependent structures. Blood clots in the bile duct are seen more frequently with PTC than with ERCP. Hemobilia can sometimes take more than 48 hours to resolve, and when it is more severe; it can be castlike and may mask other filling defects.

Calculous disease (see Chapters 36, 37, and 39) remains the most common filling defect in the biliary system. Distinguishing characteristics of gallstones and primary bile duct calculi include a faceted radiologic appearance and disposition to move to gravity-dependent positions. Calculi may be seen as discrete filling defects (Figs. 18.12 and 18.13) or castlike structures filling entire ducts, as occurs in oriental cholangiohepatitis, cystic diseases of the bile ducts, or even proximal to strictures of any etiology. Impacted calculi may be difficult to differentiate from strictures or tumors.



FIGURE 18.9. Pancreatitis producing a typical, incomplete long stricture of the common bile duct. The right posterior sectoral duct has a low entrance into the common hepatic duct, an uncommon but important normal variant.

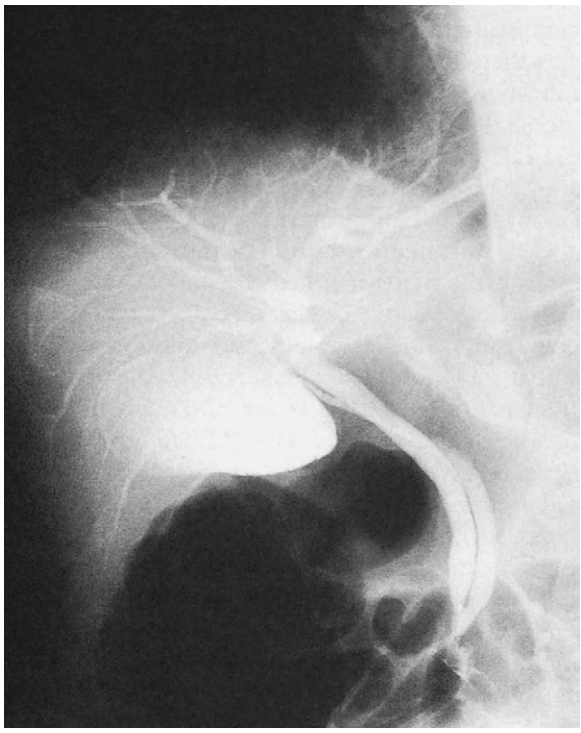


FIGURE 18.11. Long cystic duct.

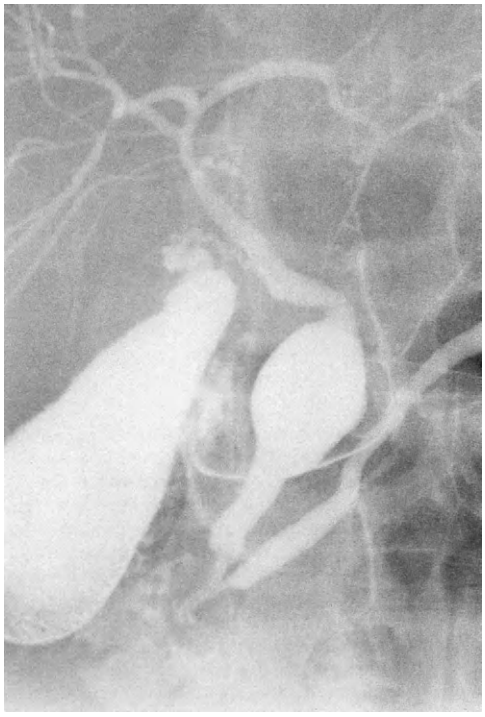


FIGURE 18.10. Choledochal cyst.



FIGURE 18.12. Choloedocholithiasis.



FIGURE 18.13. Benign stricture of the right hepatic duct (*arrow*) with multiple ductal calculi proximal to it. The hepatojejunostomy is partially strictured.

Primary bile duct cancer (see Chapter 50), specifically papillary cholangiocarcinomas, can also present as cholangiographic filling defects (Fig. 18.14). T-shaped filling defects may also be detected (Torok & Gores, 2001; Fig. 18.15), and papillary bile duct cancers may cause filling defects as a result of mucin production (Fig. 18.16). Other malignancies, including melanoma and intraductal metastases, such as colon cancer, are also more unusual causes of cholangiographic filling defects (Riopel, 1997).

Parasitic infections (see Chapter 45), such as with hydatid disease or with *Ascaris lumbricoides* or *Clonorchis sinensis,* are



FIGURE 18.14. Papillary hilar cholangiocarcinoma (*arrowheads*). Only the right ducts are opacified.

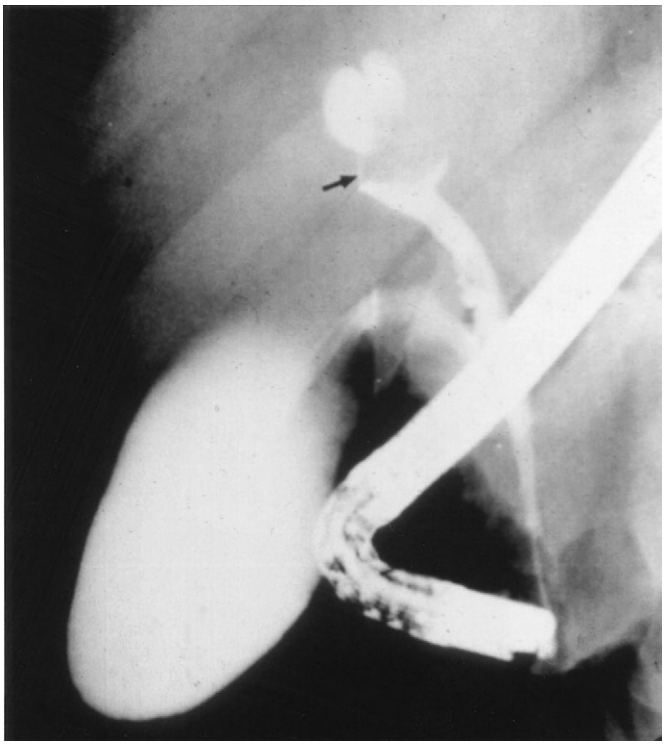


FIGURE 18.15. "Golf tee" appearance of a papillary bile duct cancer (*arrow*) involving the common hepatic duct.



FIGURE 18.16. Nasobiliary cholangiogram opacifying left hepatic ducts. Main left hepatic duct contains a small mucin-secreting papillary cholangiocarcinoma (*arrow*). The mucin results in expansion of the common bile duct below the tumor and appears as strandlike filling defects. *(Courtesy Dr. A. Speer.)*

diseases with worldwide distribution that can also present cholangiographically as intraductal filling defects. A proportion of hepatic hydatid cysts (5% to 10%) rupture into the bile ducts and may simulate choledocholithiasis (see Chapter 68). Calcified cysts are easy to recognize on radiographs, and daughter cysts can cause biliary obstruction. When the calcified cyst is not obvious, biliary strictures with obstruction may be noted on cholangiogram. The biliary ducts can show considerable irregularities in caliber and extensive displacement of the intrahepatic branches secondary to the mass effect of a large hydatid cyst (Cottone et al, 1978; Dyrszka & Sanghavi, 1983; Ibrahim & Kawanishi, 1981).

Ascaris lumbricoides is a commonly seen helminth that has worldwide distribution. Its prevalence is 90% in some parts of Africa and Asia. If the worm passes through the sphincter of Oddi, it may cause acute pancreatitis or a cholestasis syndrome (Winters et al, 1984). In the acute stage, the worm occasionally may be found and extracted from the ampulla, and it can be detected in the biliary tract by cholangiography.

Eating raw meat has been associated with *Clonorchis sinensis* infestation. The prevalence of this disease has been estimated to be 60% of the general population of Hong Kong based on stool ova examinations. This worm can penetrate through the papilla into the bile ducts. In an ERCP study of 31 consecutive patients, the typical filamentous, wavy, or elliptical appearance of the worm in the bile ducts was believed to be pathognomonic. Other common cholangiographic findings include widely dilated extrahepatic bile ducts, which are filled with biliary sludge and stones, and intrahepatic duct strictures, which are predominantly found in the branches of the left hepatic duct (Yellin & Donovan, 1981). The eggs of *C. sinensis* act as a nucleus for the development of the bile duct stones (Lam et al, 1978). Naval and colleagues (1984) reported successful endoscopic biliary lavage to eliminate the eggs.

Invasion of *Fasciola hepatica* into the biliary tract also may cause serious lesions. In the chronic stage, *F. hepatica* infection can resemble sclerosing cholangitis (Hauser & Bynum, 1984). The appearance on ERCP is that of dilated bile ducts with unexplained sludge in the distal bile duct (Figs. 18.17 and 18.18).



FIGURE 18.17. Liver flukes in the distal bile duct presenting as "biliary sludge."

Cystic Diseases

Typing of choledochal cysts (see Chapter 46) is according to the Todani et al (1977) classification. Type 1 cysts, the most common kind (80% to 90%), manifest as a fusiform dilation of the CBD, common hepatic duct (CHD), or both (see Figs. 18.10 and 18.19). A type 2 cyst (2% to 3%) is seen as a diverticular outpouching of the CBD or CHD. A type 3 cyst, also referred to as *choledochocele*, is a dilation of the intraduodenal (mural) portion of the distal CBD. Type 4 cysts (10% to 15%) have intrahepatic and extrahepatic cystic components in any combination, and type 5 cysts, also known as *Caroli disease*, is a rare form in which cysts are only seen in the intrahepatic bile ducts. Although most patients with choledochal cysts are diagnosed in infancy or childhood, 20% to 30% are diagnosed as adults. Associated calculous diseases secondary to bile stasis or stricture are frequently seen with cystic diseases. However, these must be differentiated from other more significant entities, such as bile duct cancers, because of the marked predisposition of biliary malignancies in patients with choledochal cysts (Fig. 18.20).

Bilomas, saccular intrahepatic contrast collections, may be secondary to occlusive disease or trauma, including iatrogenic trauma and trauma from transarterial chemoembolization (TACE) (Sakamito et al, 2003; Kim et al, 2001). Particularly in occlusive disease, bilomas can become infected and may appear as abscesses. Microabscesses seen with suppurative cholangitis typically appear as grapelike clusters in terminal bile ducts (Fig. 18.21).

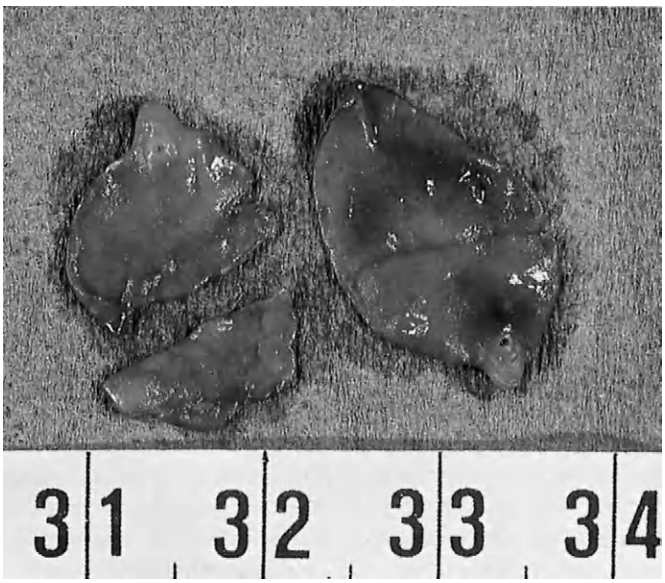


FIGURE 18.18. Extracted liver flukes (same patient as in Figure 18.34).

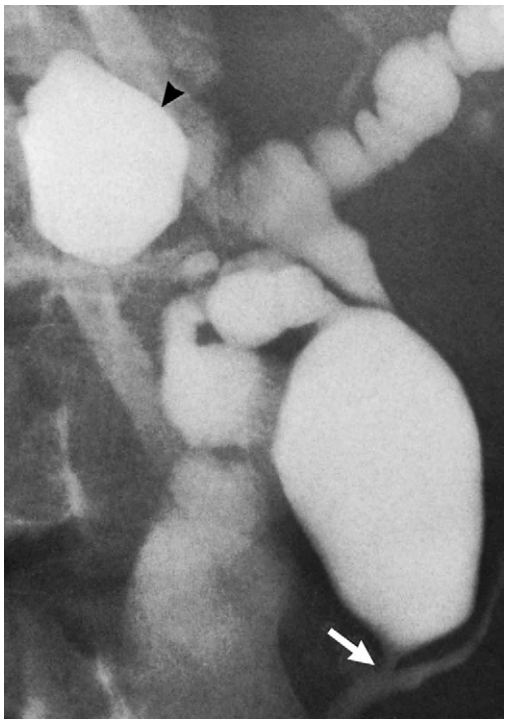


FIGURE 18.19. Choledochal cyst with intrahepatic cyst formation (*arrowhead*). The common bile duct has an abnormally proximal junction with the pancreatic duct (*arrow*).

Strictures

Bile duct strictures may be classified by their morphologic appearance or level of obstruction. Level of obstruction classification, as described by Bismuth and colleagues (1992), has significant surgical implications. When used strictly for etiologic diagnosis, however, neither level of obstruction nor morphologic appearance description is as clinically rewarding. Cholangiographic strictures are present in a diverse group of diseases.



FIGURE 18.20. Cholangiocarcinoma within a choledochal cyst.



FIGURE 18.21. Multiple hepatic abscesses associated with suppurative cholangitis in a patient with hilar duct obstuction.

Many benign and malignant conditions can have strictures that encompass the entire gamut of cholangiographic appearances. Any combination of intrahepatic or extrahepatic distribution, shouldered or smooth, beaded or nonbeaded, long or short, and with or without associated proximal dilation has been described in most of these diseases. Diagnostic limitations of direct cholangiography are due to this great overlap in findings. Visualization of only the bile duct lumen, as achieved with direct cholangiography, offers no advantages over noninvasive imaging techniques when evaluating bile duct strictures. Direct cholangiography is generally reserved for when concomitant biliary intervention is anticipated. In much of the diagnostic spectrum of stricture disease, biopsy is frequently required to rule out malignancy.

Sclerosing cholangitis (see Chapter 41) can produce cholangiographic changes in the intrahepatic and extrahepatic biliary trees, and it is commonly seen in both (La Russo, 1984). The bile ducts in primary sclerosing cholangitis (PSC) are characterized by an annular concentric stenosis, usually multifocal, with areas of normal or mildly dilated ducts between strictures (Fig. 18.22; Rogers et al, 1972). Larger bile ducts can appear beaded (Fig. 18.23), and other radiologic findings include a "prune tree" appearance, from reduction of peripheral bile duct radicles, and diverticular outpouchings of the extrahepatic bile ducts (Gulliver et al, 1991; La Russo et al, 1984; Fig. 18.24). Ulcerative colitis is identified in as many as 70% of patients with PSC, and coexisting cholangiocarcinoma can occur in 15% of these patients (MacCarty et al, 1985; Crippin & Lindor, 1992). Detecting a cholangiocarcinoma in a background of sclerosing cholangitis is difficult. Cholangiographic features suggesting cholangiocarcinoma include progressive focal stricturing, the presence of uniform proximal duct dilation, and nodular filling defects (Li-Yeng & Goldberg, 1984). It has been suggested that evaluating these features together with cross-sectional imaging can detect many tumors (Campbell et al,

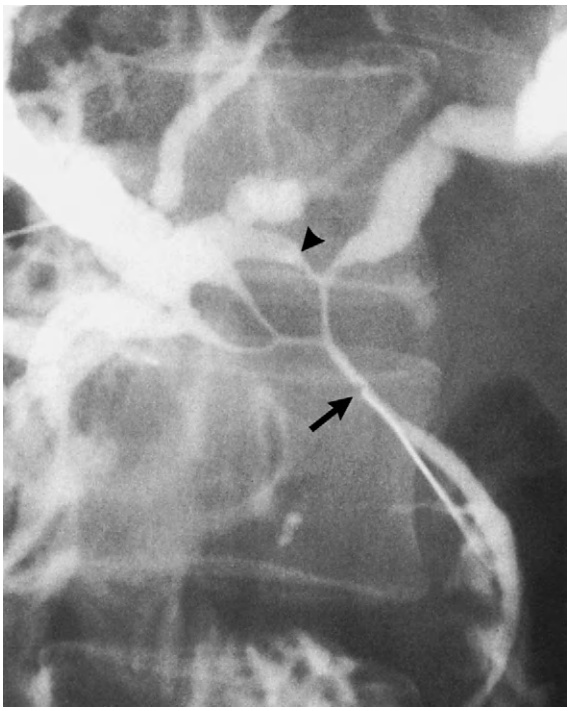


FIGURE 18.22. Sclerosing cholangitis producing a stricture of the common hepatic duct extending into second-order ducts bilaterally. Differentiation from cholangiocarcinoma is aided by fine-needle aspiration cytology (*arrow*). Note the right posterior sectoral duct (*arrowhead*) entering the left hepatic duct.



FIGURE 18.24. Sclerosing cholangitis with multiple intrahepatic and extrahepatic segments of stricturing. A characteristic "diverticulum" (*arrow*) overlies the confluence of the right and left hepatic ducts.



FIGURE 18.23. Primary biliary sclerosis with typical irregularity and beading of large ducts.

1998). Again, biopsy is generally required for definitive diagnosis.

Cholangiocarcinoma (see Chapter 50) is commonly seen as the classic sclerosing Klatskin type with a high-grade Y-shaped obstruction involving the right and left main bile ducts and the proximal common hepatic duct (see Fig. 18.7). Extension of stenoses to subsegmental bile ducts is frequently seen, and biliary dilation proximal to the obstruction is expected, as is a decompressed gallbladder. Klatskin tumors may cause obstruction of adjacent portal veins, resulting in hepatic atrophy that manifests itself cholangiographically as dilated, tortuous, or even beaded, crowded bile ducts (Fig. 18.25).

Like central lesions, the more common (60%) peripheral bile duct cancers are demonstrated in direct cholangiography



FIGURE 18.25. Hilar cholangiocarcinoma with crowded left ducts indicating left lobe atrophy. The right ducts are opacified by a percutaneous transhepatic drainage catheter.

as nonspecific stenoses or obstructions (Longmire et al, 1973; Ohto et al, 1980; Tompkins et al, 1981; Warren et al, 1972). They may also present with bilevel obstruction as a result of central lymphadenopathy. The additional diagnostic benefits of CT and MR cholangiography make these noninvasive techniques preferable for preprocedural planning and in differential diagnosis (Tompkins et al, 1990; Stroszczynski & Hünerbein, 2005).

Direct cholangiography for the diagnosis of gallbladder cancer (see Chapter 49) is rarely required. Gallbladder cancer is best diagnosed with CT, ultrasound, or MRI. Cross-sectional imaging reveals the common radiologic findings of associated calculous disease and direct extension of tumor into the adjacent hepatic parenchyma. Findings in direct cholangiography consist of high-grade stricture or occlusion of the biliary tree at any level (Fig. 18.26), typically with no visualization of the cystic duct or gallbladder.

Approximately two thirds of pancreatic cancers occur in the region of the papilla of Vater and the head of the pancreas, and the bile duct is usually involved (see Chapter 58). Characteristic cholangiographic findings include occlusion of the distal CBD with proximal dilation. The CBD above the occlusion may have a more horizontal course (Freeney, 1988; Fig. 18.27). Cystic duct patency is often preserved, and dilation of the gallbladder may be marked. ERCP, CT, and MRI may show occlusion or stenosis of the main pancreatic duct with proximal pancreatic duct dilation. The more classic double-duct sign of simultaneous obstruction of the pancreatic duct and CBD at proximate levels is also best determined with these techniques (Fig. 18.28).

Periampullary cancer (see Chapter 59) also causes obstruction of the CBD at the level of the papilla of Vater. The site of origin may be the duodenum or distal bile duct, which is indeterminate cholangiographically. A short-segment obstruction with proximal dilation most often identified though more central biliary abnormalities could also be seen (Fig. 18.29). A polypoid filling defect may also occasionally be seen with periampullary cancers. The filling defect, however, is not pathognomonic and must be differentiated from other possible malignancies or filling defects.

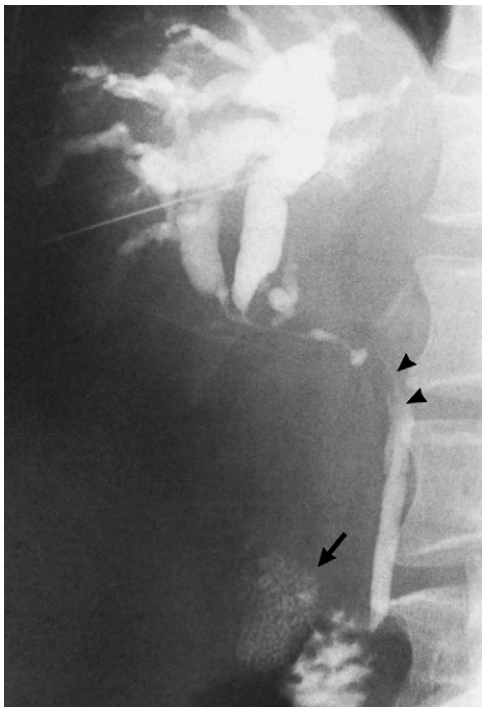


FIGURE 18.26. Gallbladder carcinoma involving right third-order ducts and deviating upper common hepatic duct medially (*arrowheads*). Multiple small calculi appear in the gallbladder fundus (*arrow*), which is separated from the strictured ducts by the tumor.

Malignant bile duct obstruction has also been described with metastatic colon, breast, lung, and gastric cancers (Fig. 18.30). Obstructions can be intrahepatic and/or extrahepatic and may be due to lymph node involvement or direct extension (Lokich et al, 1987). Bile duct obstruction from lymphoma is more commonly extrahepatic, and extrahepatic bile duct strictures can also be seen with benign lymph node enlargements such as in Castleman disease (Przkora et al, 2003).

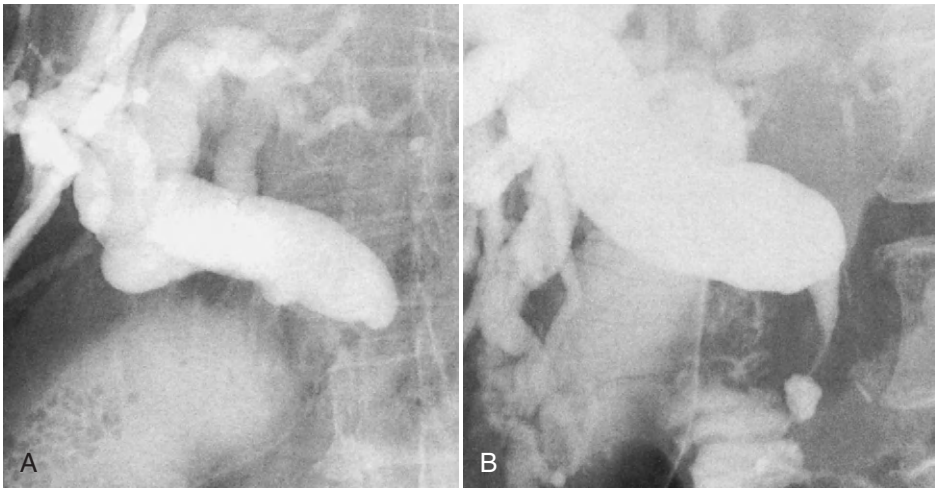


FIGURE 18.27. Two of the common appearances of carcinoma of the pancreas. **A,** Rounded obstruction with characteristic horizontal common bile duct. Note the coincidental stones in the distended gallbladder. **B,** Tapered obstruction with slight shouldering. Compare this with pancreatitis (see Figure 18.9), in which shouldering tends to be absent.

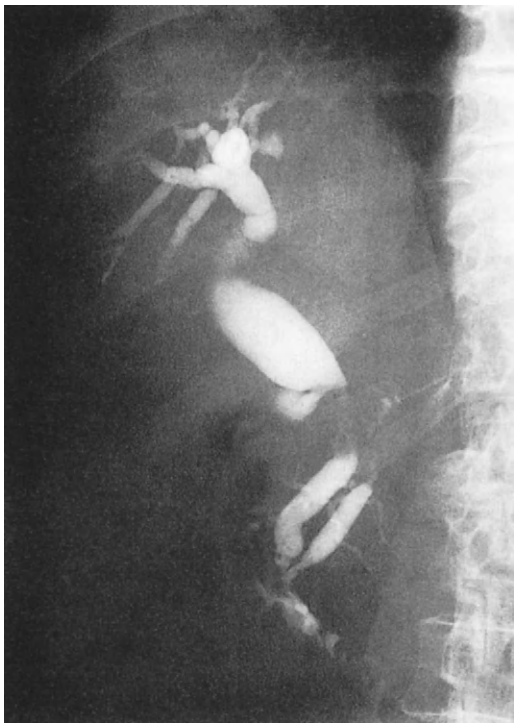


FIGURE 18.28. Double-duct sign, stenosis of the bile duct and pancreatic duct, in a case of pancreatic carcinoma.

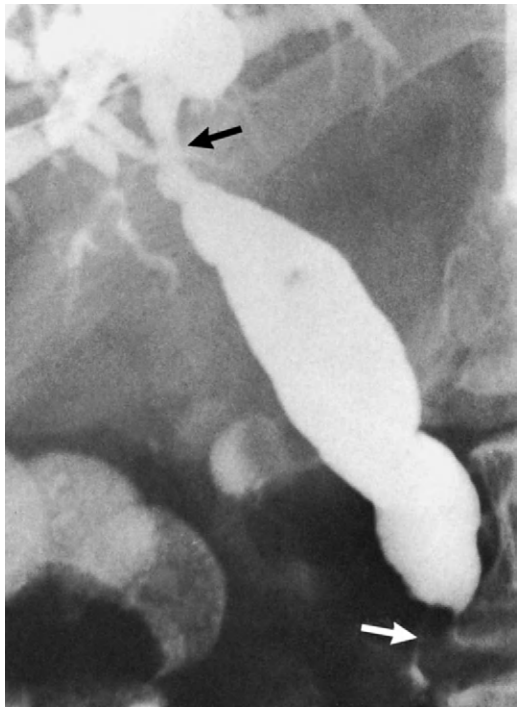


FIGURE 18.29. Periampullary carcinoma producing localized stricture of distal common bile duct (*white arrow*) indistinguishable from pancreatic cancer. Stricturing of the upper common hepatic duct (*black arrow*) is due to porta hepatis lymphadenopathy.

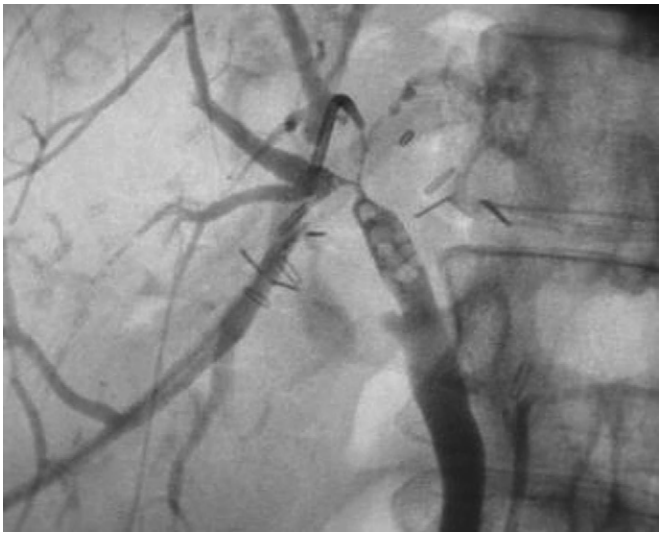


FIGURE 18.30. Hilar obstruction from metastatic breast cancer.

The conundrum of "malignant masquerade" (see Chapter 42) present with direct cholangiography is perhaps most classically demonstrated by Mirizzi syndrome (Hadjis et al, 1985; Clemett & Lowmann, 1965; Becker et al, 1994), which occurs when a gallstone is impacted in the cystic duct or gallbladder neck, causing inflammatory obstruction of the common hepatic duct. The obstruction may be limited and focal or may extend into the intrahepatic bile ducts. On cholangiogram the syndrome is indistinguishable from cholangiocarcinoma, gallbladder cancer, or other malignant strictures (Figs. 18.31 and 18.32).

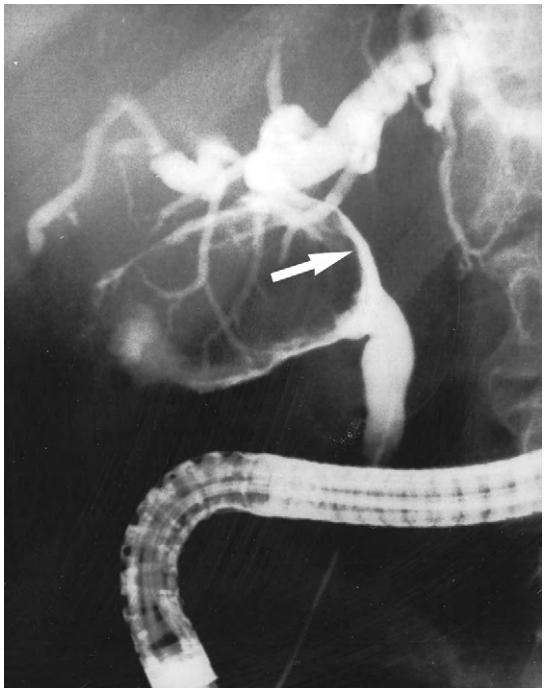


FIGURE 18.31. Mirizzi syndrome. A large gallbladder calculus has eroded into the common hepatic duct (*arrow*), which is narrowed and deviated medially.

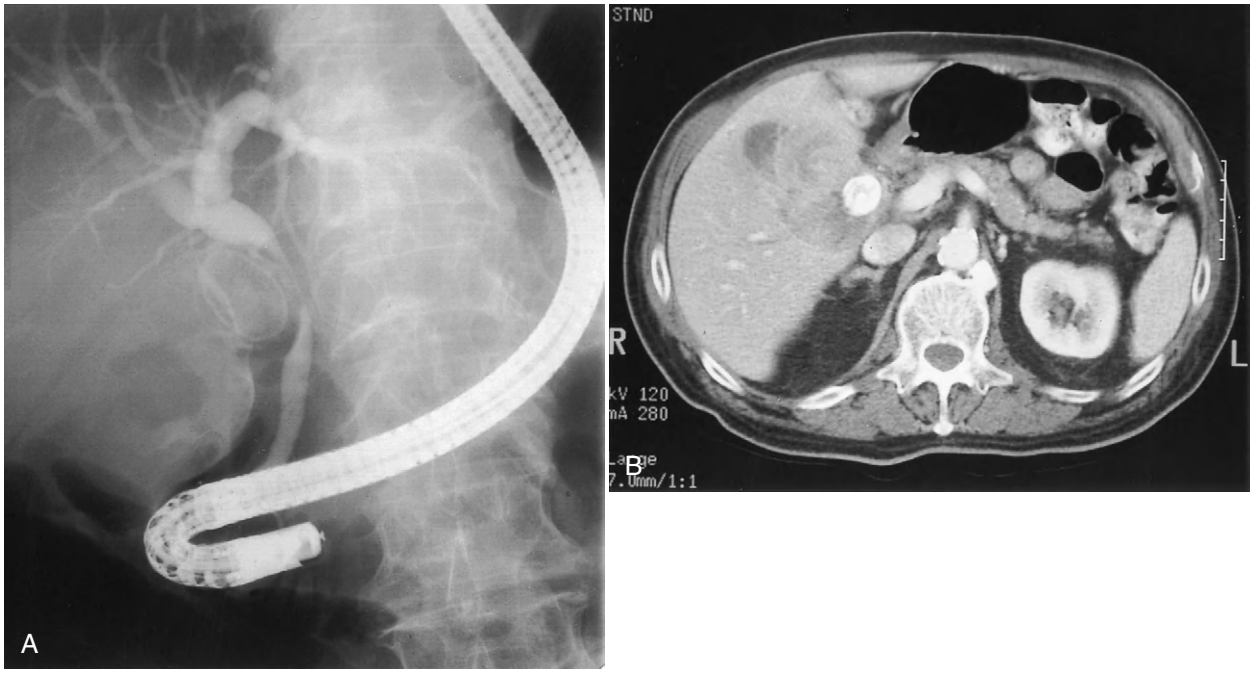


FIGURE 18.32. Mirizzi syndrome. **A,** Endoscopic retrograde cholangiopancreatography shows common hepatic duct stricture resulting from gallstone in a Hartmann pouch of the gallbladder. **B,** CT scan shows the impacted stone. An associated gallbladder cancer is also shown.

Oriental cholangiohepatitis (see Chapter 44) is generally seen in Asian populations. Cholangiography demonstrates strictured intrahepatic or extrahepatic bile ducts with markedly dilated proximal bile ducts. The dilated proximal bile ducts are packed with filling defects, which represent pigmented stones. Although all segments of the biliary tree can be involved, disease in the lateral segment of the left lobe is most common (Lim, 1991). Oriental cholangiohepatitis is characterized by recurrent episodes of cholangitis and is therefore commonly referred to as *recurrent pyogenic cholangitis.*

Acute pancreatitis (see Chapter 54) is usually diagnosed by combination of history, serum chemistry (amylase and lipase elevation), and cross-sectional imaging. Direct cholangiography, especially ERCP, is rarely performed during an acute episode because of the possibility of exacerbation of disease or introduction of infection. Once the episode has subsided, ERCP can be performed and may demonstrate a distal stricture and possible choledocholithiasis (Fig. 18.33). Care must be taken, however, as pancreatic cancer and periampullary cancer can not only have similar cholangiographic appearances but may coexist or even present clinically as acute pancreatitis (Mujica et al, 2000; Murakami et al, 2006; Akatsu et al, 2008).

In chronic pancreatitis as in acute pancreatitis, distal bile duct stricture is the most common cholangiographic abnormality, seen in approximately 25% of patients with chronic pancreatitis (Fig. 18.34; see Chapters 42 and 55). Stricture length and morphology are variable, and the frequently described long, smoothly tapered stenosis occurs in only 27% to 56% of patients (Stolte et al, 1984). MRI and ERCP have greater sensitivity than PTC in chronic pancreatitis because of their ability to demonstrate pancreatic duct abnormalities such as enlargement, ectasia, beading, and the presence of chronic pseudocysts. The development of a pseudocyst can also cause pressure obstruction of more central segments of the bilinear tree.

Hepatic artery infusional chemotherapy via hepatic artery infusion pump (HAIP) and with transarterial chemoembolization have both been implicated as causes of biliary sclerosis (Kim et al, 2001; Brown et al, 1997). Stricture formation is due to either direct action of the chemotherapeutic agent or from ischemia secondary to damage of the arterial vasculature

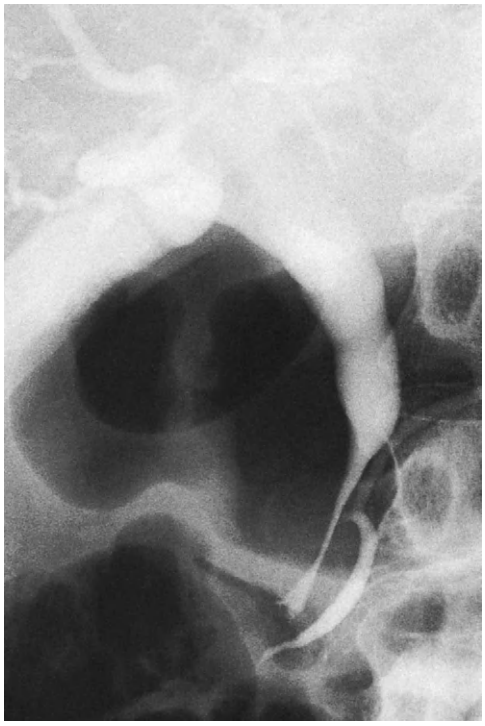


FIGURE 18.33. Acute pancreatitis with pseudocyst in the head of the pancreas (verified on operation), leading to cholestasis.



FIGURE 18.34. Filiform stenosis caused by chronic pancreatitis.

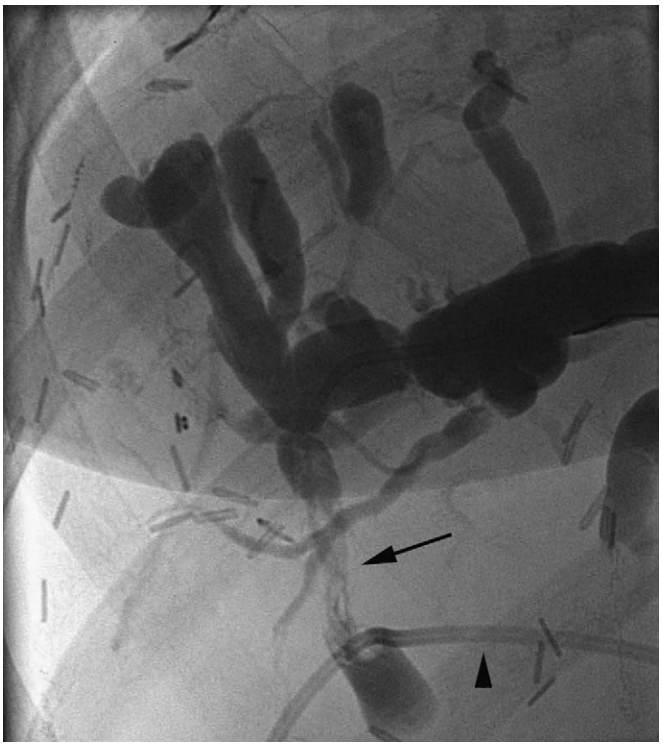


FIGURE 18.35. Chemotherapy-induced biliary sclerosis (CIBS) from hepatic artery infision pump (HAIP) therapy. Note catheter portion of pump (*arrowhead*) and fuzzy, striated appearance of commom hepatic duct stenosis.

supplying the bile ducts. Chemotherapy-induced biliary sclerosis (CIBS) secondary to HAIP most commonly presents cholangiographically as high-grade obstruction of the common hepatic duct (50%) indistinguishable from a Klatskin tumor. Frequently, the area of CHD obstruction takes on a fuzzy, striated, ill-defined appearance (Fig. 18.35); peripheral stenoses may also be seen but are not always present. Biloma formation with or without associated infection (abscess) is not uncommon and may be due to peripheral bile duct necrosis.

Patients with AIDS may have bile duct inflammation from opportunistic infections such as cytomegalovirus and *Cryptosporidium*. The most common radiologic findings are gallbladder and bile duct wall thickening that are not demonstrated with direct cholangiography. Direct cholangiographic findings in AIDS-related cholangitis are very similar to those seen in sclerosing cholangitis: multiple strictures with intervening areas of dilation, beading, and even prune-tree appearances have been described (Farman et al, 1994; Schneiderman et al, 1987; Texidor et al, 1991; Miller et al, 1996).

CONCLUSION

The role of direct cholangiography in the diagnosis of biliary disease has for the most part been supplanted by less invasive CT and MR cholangiography. The ability to visualize the entire biliary tree, the bile duct wall, and other structures besides the bile duct lumen greatly increases the accuracy of the noninvasive techniques and renders them diagnostically superior to direct cholangiography. Coupled with the lack of need for sedation and their minimal complication rate, CT and MR cholangiography have become the gold standard for cholangiography. Other than its use for localization and documentation of bile leaks, direct cholangiography is generally reserved for situations involving concomitant planned therapeutic intervention. The choice of PTC versus ERCP is therefore mostly dependent on the available expertise and likelihood of successful therapeutic intervention of one or the other.

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CHAPTER 19

Diagnostic angiography in hepatobiliary and pancreatic disease: indications

Robert K. Kerlan Jr.

IMAGING OVERVIEW

The role of catheter angiography has changed substantially with the development of multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI). These developments have allowed computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) to demonstrate the visceral arterial and venous structures with clarity in many patients. Although catheter angiography remains a critical test in highly selected patients with hepatobiliary and pancreatic disease, the indications for this procedure are quite different than a decade ago.

In the 1980s and 1990s, selective angiography was commonly used as a diagnostic and staging technique. Indications would include ascertaining the organ of origin of an abdominal mass, assessing for vascular invasion by pancreatic or cholangiocarcinoma, and preoperative planning prior to hepatic resection. CT (see Chapter 16) and MRI (see Chapter 17) have completely replaced catheter angiography for these indications. In a prior edition of this book published in 2000, it was suggested that catheter angiography was a dying specialty and that angiographers should accept their fate with grace. However, a new age has dawned, and the volume of selective visceral angiography has increased considerably. The majority of these arteriograms are performed for the purpose of a diagnostic assessment prior to performing catheter-based interventions including radioembolizations (see Chapter 84A), chemoembolizations (see Chapter 83), chemoperfusions (see Chapters 86 and 89), and embolizations of bleeding arteries (see Chapter 25). In addition, endovascular therapies have replaced open surgical arterial interventions in patients with primary vascular pathology using angioplasties, stents, and the placement of stent grafts.

Another technologic advance that involves catheter angiography is the development of hybrid imaging. Hybrid imaging couples two imaging modalities to create unique images that can provide information that would not be available with either technique alone. Catheter angiography can be coupled with a cross-sectional imaging modality, usually MDCT but occasionally MRI. The images can be postprocessed and rendered in a three-dimensional format to provide an anatomic depiction that would not be available by either technique alone. This hybrid imaging is particularly useful in delineating complex splanchnic venous anatomy in patients with portal vein occlusive disease being evaluated for potential portal systemic shunting procedures.

This chapter will be divided into two sections: one will cover arteries, the other will discuss veins. Regarding arteriography relevant to hepatobiliary and pancreatic surgery, we will discuss arteriographic anatomy and technique, arteriography prior to arterial interventions and surgery, localization of occult neuroendocrine tumors of the pancreas, arterial diseases, and hemorrhage. Our discussion on splanchnic veins will include venographic anatomy, venous sampling, techniques of catheter-based venous imaging, and venous imaging prior to surgical or percutaneous venous interventions.

ARTERIES

Arteriographic Technique

Over the past two decades, technologic advances have improved the safety and efficiency of catheter angiography. The historical technique of cut-film angiography is no longer available and has been replaced by highly sensitive flat-panel digital detectors. These detectors are capable of generating a volumetric data set that allows an image to be displayed in multiple formats. Rotational angiography with three-dimensional postprocessing and C-arm computed tomography (CCT) using the angiographic imaging unit are replacing digital subtraction image-intensified designs.

Unless serious comorbidities are present, catheter angiography is routinely performed as an outpatient procedure. The purpose of the examination should be evaluated by the angiographer to confirm that the examination is indicated and can be conducted with a high level of safety. The patient should be interviewed, and consent should be obtained prior to the procedure. A limited physical examination should be completed that includes a detailed pulse examination and assessment of the airway, heart, and lungs to ensure the safety of conscious sedation.

The relevant laboratory parameters include serum creatinine or estimated glomerular filtration rate, hematocrit level, platelet count, and international normalized ratio (INR), and these should be reviewed. The necessity of obtaining laboratory values in otherwise healthy patients without a clinical risk of renal impairment or abnormal bleeding is controversial.

If the patient has impairment of renal function, a number of prophylactic measures have been recommended to diminish the risk of contrast-induced renal failure. These measures include intravenous hydration with a sodium bicarbonate solution as well as the administration of N-acetyl cysteine. The effectiveness of these prophylactic measures is controversial; however, they carry a minimal risk to the patient and have been adopted by the majority of practitioners.

The risk of bleeding from the puncture site is low, and hematomas complicate 1% of femoral punctures and 3% of upper extremity punctures. An abnormal bleeding profile related to

thrombocytopenia or prolongation of the INR increases the risk of hemorrhage. The necessity to correct an underlying coagulopathy is dependent upon the specific procedure to be performed and the preference of the angiographer. Most centers desire a platelet count in excess of $50{,}000 \times 10^6$ per liter and an INR of 1.5 or less. For 6 hours prior to the examination, the patient should be given nothing by mouth, as mild to moderate conscious sedation improves the patient's experience, although the procedure itself is not painful and can be performed solely with local anesthetic agent. Intravenous hydration is recommended before, during, and after the arteriogram to diminish adverse effects of contrast media on renal function. The patient should also be encouraged to drink plenty of fluids following the procedure.

The favored puncture site is the right common femoral artery, although the left common femoral artery, axillary artery, brachial artery, or radial artery may be used as alternatives when clinically appropriate. The desired puncture area is cleansed and the patient is draped in sterile fashion. In most centers, arterial entry is performed under real-time ultrasound guidance using a 21-gauge micropuncture set. The use of ultrasonography allows assessment of the quality of the common femoral artery, depicts the position of the profunda femoris, and detects the presence of aberrant veins extending ventral to the puncture site. Following entry into the vessel, the appropriate catheter is inserted for catheterization of the desired vessel. After diagnostically adequate images are obtained, the catheter is removed, and one of a variety of closure devices is deployed to seal the arteriotomy. Patients are observed in a postprocedural area until they have recovered from sedation, and most can be discharged home 2 to 4 hours later.

Arteriographic Anatomy

Arterial anatomy has been discussed elsewhere (see Chapter 1) and will only be briefly reviewed here. The most frequently encountered anatomy (Fig. 19.1) is the left gastric artery, splenic artery (SA), and common hepatic artery (HA) taking origin from the celiac axis. The common HA divides into the gastroduodenal artery (GDA) and proper HA, with the latter dividing into the right and left hepatic arteries. The right gastric artery most often originates from the base of the left HA, and the cystic artery most often originates from the right HA, but considerable variations in the origins of these arteries exist. Moreover, accessory duodenal arteries, either representing a supraduodenal or a retroduodenal artery, are frequently encountered; this is critical to recognize when planning chemoembolization and radioembolization.

The normal arterial supply to the liver is shown in Figure 19.2 (see the Extrahepatic Vasculature section in Chapter 1B), which shows the commonly recognized variations of the left hepatice artery (LHA), taking origin from the left gastric artery, and the right hepatic artery (RHA), taking origin from the superior mesenteric artery (SMA). It is important to recognize that either a part or the entirety of the right and left hepatic arteries may have these variant origins. When the entire vessel has a variant origin, it is termed *replaced.* If the entire trunk does not take a variant origin, the vessel is termed *accessory.* For example, if the right lobe is supplied by a right HA originating from the common HA, as well as a right HA taking origin from the SMA, the latter would be termed an *accessory right HA*. If the entire right lobe was supplied by an artery taking origin from the SMA, it would be called a *replaced right HA*.

In most patients, the arteries to Couinaud segments I, II, III, and IV are branches of the left HA, and arteries to segments V, VI, VII, and VIII are branches of the right HA. The most variable segmental branch is to segment IV. Although most frequently the artery to segment IV takes origin from the LHA, it may also take origin from the RHA, assuming the misnomer of a "middle hepatic" artery in older works. Separate origins of segment IVa, usually from the LHA, and segment IVb from the RHA are frequently identified. Also, a branch from the segment IV artery is often seen extending outside of the liver, supplying the falciform ligament. Recognition of this vessel is important

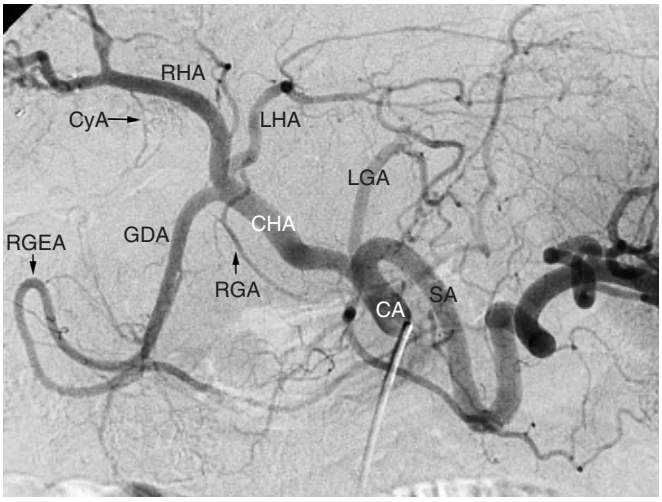


FIGURE 19.1. Conventional celiac artery anatomy. CA, celiac axis; LGA, left gastric artery; SA, splenic artery; CHA, common hepatic artery; GDA, gastroduodenal artery; RGA, right gastric artery; RHA, right hepatic artery; LHA, left hepatic artery; CyA, cystic artery; RGEA, right gastroepiploic artery.

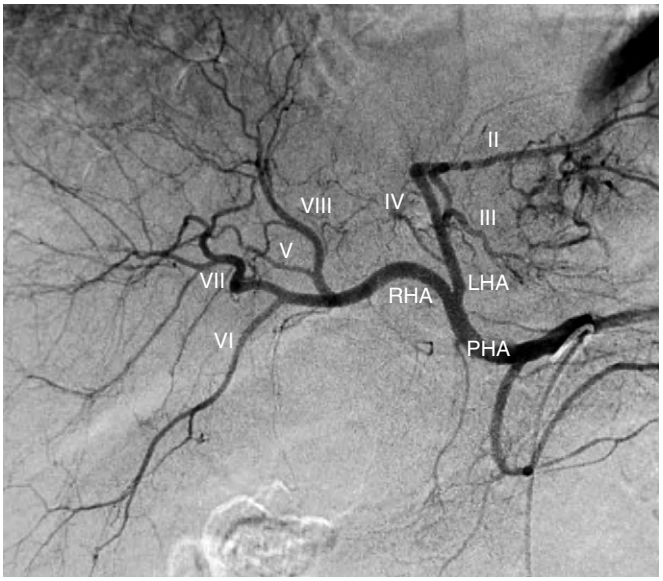


FIGURE 19.2. Arterial anatomy of the liver. PHA, proper hepatic artery; RHA, right hepatic artery; LHA, left hepatic artery. Additional vessels are labeled in accordance to the Couinaud segment they supply.

when conducting chemoembolization or radioembolization to avoid nontarget embolization.

The RHA conventionally divides into an anterior (ventral) and posterior (dorsal) branch. The anterior branch usually is more vertically oriented and supplies segments V and VIII. The posterior branch is usually more horizontally oriented and supplies segments VI and VII. More than one projection is usually required to ascertain with certainty which is the anterior branch and which is the posterior branch. In the right anterior oblique projection, the anterior branch moves medially and the posterior branch moves laterally when compared with the postero-anterior (PA) projection. The entire segmental arterial supply to the liver should be accounted for prior to hepatic arterial therapy, major hepatic resection, partial hepatectomy, or living-donor liver transplantation (LDLT, see Chapter 98B).

The arterial supply to the pancreas is somewhat variable. The most consistent supply is to the pancreatic head, afforded by an arcade formed by the inferior pancreaticoduodenal (IPD) branch of the SMA to the anterior superior and posterior superior pancreaticoduodenal branches of the GDA (Fig. 19.3). The transverse pancreatic artery runs along the middle portion of the long axis of the pancreas and may take origin from the arterial arcade in the head of the pancreas, directly from the GDA, or as a branch of the dorsal pancreatic artery, which variably originates from the common HA or SA (Fig. 19.4). A number of small branches from the SA supply the pancreatic body and tail, but the number and location of these arteries vary and must be identified in each individual patient when clinically relevant.

Preoperative Angiography: Historical Perspective

Prior to the advent of multidetector computed tomography angiography (MDCTA), visceral angiography was performed to assess the resectability of pancreatic and biliary tract tumors by demonstrating the presence or absence of vascular invasion. The sensitivity of catheter angiography for this purpose was low, and MDCTA has replaced catheter angiography for this indication. Using angiography for diagnosis of a hepatic mass, such as differentiating a cavernous hemangioma from a hepatocellular carcinoma, is no longer performed, as no improvement in diagnostic accuracy can be achieved over conventional cross-sectional imaging techniques (see Chapters 16 and 17).

Preoperative arterial mapping of the arterial anatomy of the liver also was routinely performed in some centers prior to major hepatic resections. This procedure has also been replaced by MDCTA and is no longer performed routinely. On rare occasion, there is a specific piece of critical anatomic information that cannot be ascertained with certainty by MDCTA, such as the origin and course of the artery to segment IV prior to a living-donor partial hepatectomy. In this circumstance, catheter angiography can be useful to answer the question.

On extremely rare occasions, large tumors are identified on cross-sectional imaging, but the organ of origin cannot be determined. The majority of these are large sarcomas of the retroperitoneum, but excluding a pancreatic source may be difficult. A similar situation can occur with large right adrenal or renal tumors blending with the hepatic parenchyma. In these highly selected cases, catheter angiography can be useful in delineating the organ of origin by demonstrating the primary arterial supply.

Arteriography in Conjunction with Arterial Interventions

By far the most common use of arteriography is planning an arterial-based intervention such as chemoembolization, radioembolization, or chemoperfusion to treat a primary or metastatic hepatic malignancy. These specific interventions will be discussed elsewhere in this book, and a detailed description will not be repeated here. However, some points deserve emphasis.

Accurate delineation of arterial anatomy has increased in importance remarkably as radioembolization (see Chapter 84A) and chemoembolization (see Chapter 83) have gained widespread application. The inadvertent administration of radiation or chemotherapeutic agents into arteries supplying the stomach or duodenum can lead to significant adverse outcomes. When performing procedures designed to necrose tumor, it is imperative that normal structures be spared. To accomplish

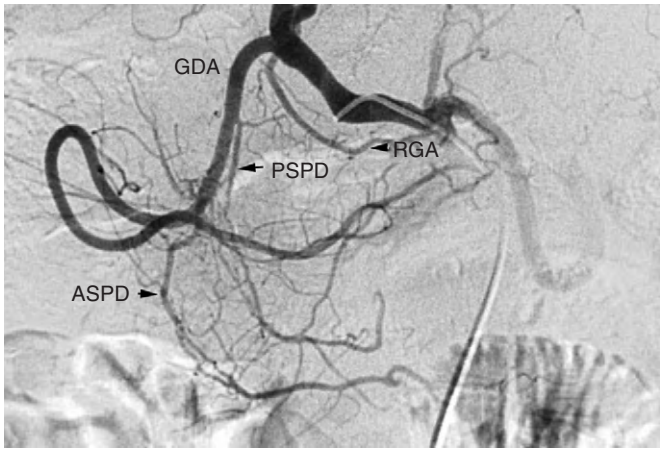


FIGURE 19.3. Arterial anatomy of the pancreas. GDA, gastroduodenal artery; PSPD, posterior-superior pancreaticoduodenal artery; ASPD, anterior-superior pancreaticoduodenal artery; RGA, right gastric artery.

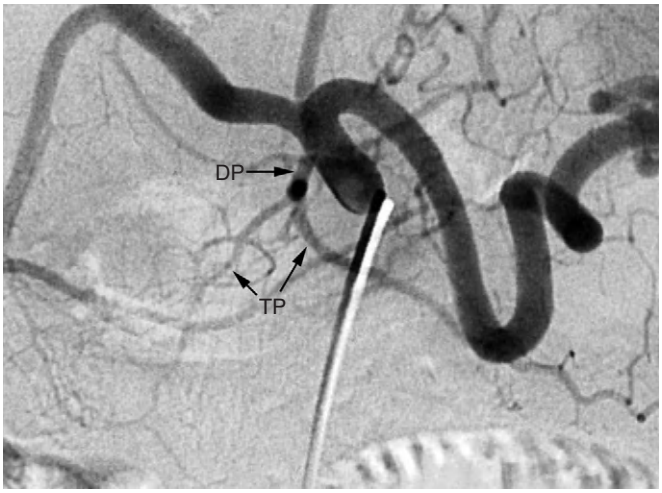


FIGURE 19.4. Arterial anatomy of the pancreas. DP, dorsal pancreatic artery; TP, transverse pancreatic artery.

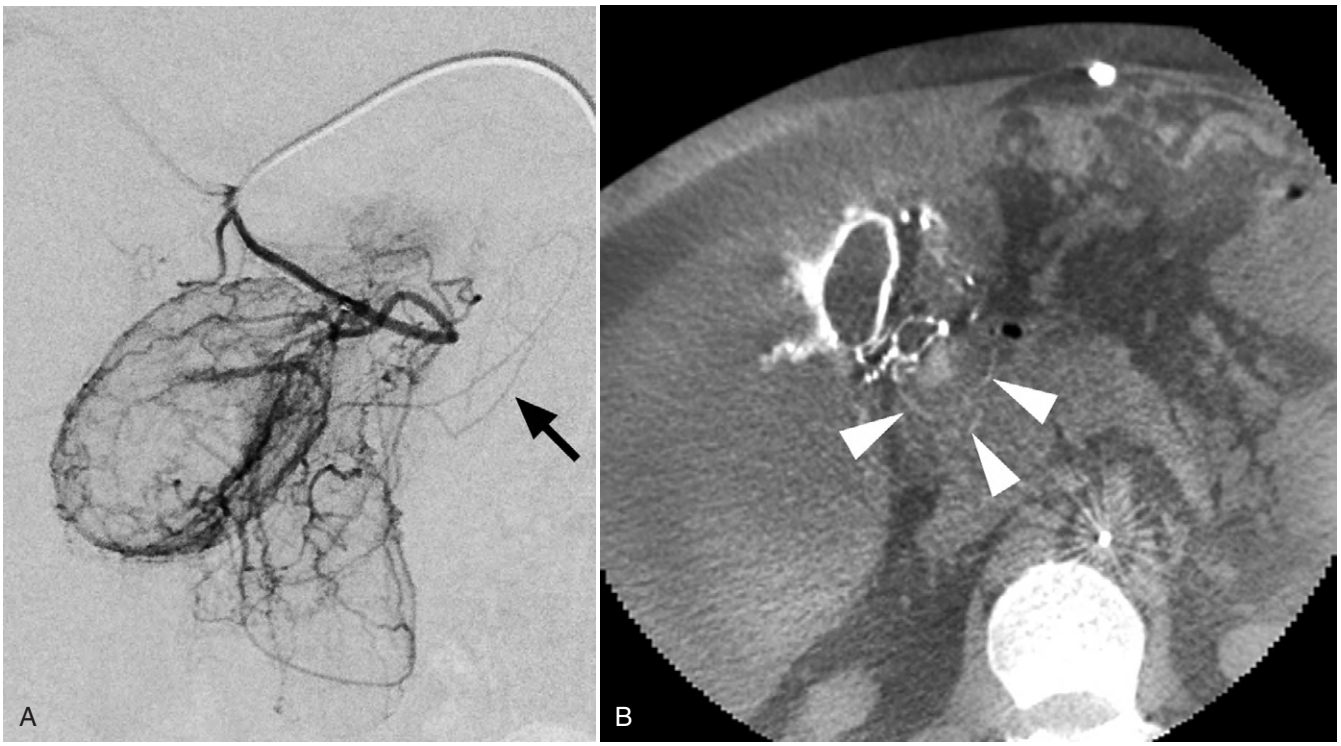


FIGURE 19.5. Extrahepatic perfusion detected with C-arm computed tomography (CCT). **A,** Selective cystic arteriogram shows the gallbladder and several branches extending medially (*arrow*). **B,** CCT performed during contrast injection of the cystic artery confirms aberrant perfusion of the duodenum (*arrowheads*). *(Courtesy Daniel Sze, Stanford University.)*

this, variant anatomy must be recognized. The importance of accessory branches to the duodenum, including the supraduodenal and retroduodenal arteries, is now well known. Communications from intrahepatic branches to the lower esophagus, stomach, and diaphragm are of equal importance (Miyayama et al, 2009; Liu et al, 2005).

With current angiographic technology, it is possible to obtain a volumetric digital image during the arterial injection of contrast media and to display the images in a computerized tomographic format (i.e., C-arm CT) (Wallace et al, 2008). Using this technique it is possible to identify extrahepatic perfusion from aberrant hepatic arterial branches that may be unrecognized on the basis of the angiogram alone (Fig. 19.5).

Hemorrhage

Bleeding from the liver, pancreas, or spleen is most often secondary to iatrogenic or noniatrogenic trauma, but it may occur spontaneously in patients with mycotic aneurysms or pancreatitis. Angiography is usually not used to ascertain whether arterial hemorrhage is present but rather to precisely localize and treat the offending vessel. Embolization of arterial bleeding will be discussed elsewhere in this book, but salient features will be reviewed in this chapter.

Splenic Bleeding

The most common cause of bleeding from the spleen is blunt trauma, and nonoperative management is currently the standard of practice. SA embolization has been established as a method to increase the success rate of nonoperative management of traumatic splenic injuries (Dent et al, 2004). A comparative study between two cohorts consisting of 625 patients over a 15-year period revealed an improved success rate of nonoperative management from 77% to 96% with the advent of splenic embolization (Rajani et al, 2006). The indications for splenic arteriography and splenic arterial embolization are based upon CT findings and include active contrast extravasation, splenic vascular injuries, and significant hemoperitoneum. Moreover, the American Association for the Surgery of Trauma recommends angiography for grade III, IV, and V splenic injuries (Raikhlin et al, 2008).

Two techniques are used to perform splenic embolization: the first is occlusion of the proximal splenic artery with coils or Amplatzer plugs (AGA Medical, Plymouth, MN), and the second is selective small intrasplenic arterial embolization with a gelatin sponge or coils. Collaterals through the short gastric arteries and the gastroepiploic arcade usually maintain splenic viability following occlusion of the proximal splenic artery. Intrasplenic embolization generally results in a variable degree of splenic infarction, depending upon the size of the artery occluded, as intrasplenic arteries have no significant collateral routes. Both techniques are associated with a risk of complications. Minor complications including fever, pleural effusion, and partial splenic infarction have been reported in up to 62% of patients. Major complications including total splenic infarction, splenic atrophy, and postprocedure bleeding have been observed in 28.5% of patients (Wu et al, 2008).

Hepatic Bleeding

Hemorrhage from the liver may be encountered from blunt or penetrating trauma (see Chapter 102) but is most commonly due to an iatrogenic injury related to a biopsy (see Chapter 20)

or percutaneous transhepatic biliary drainage (PTBD; see Chapters 18 and 28). Arteriographic findings indicating a source of hemorrhage include extravasation, pseudoaneurysm formation, and/or arteriovenous fistula (see Chapter 104). Superselective catheterization using coaxial microcatheters to deposit coil-spring emboli both distal and proximal to the area of injury is the preferred technique for embolization when a discrete bleeding site can be identified. In contrast to the spleen, a rich collateral network exists in the hepatic arterial bed, making proximal occlusion of the offending artery ineffective in many cases. For more diffuse injuries with multiple bleeding sites secondary to blunt trauma, using particulate embolization with a gelatin sponge may be a useful adjunct.

As with blunt splenic injuries, nonoperative management has become the preferred method of management in hemodynamically stable patients, with a success rate exceeding 90% (Christmas et al, 2005). In the setting of blunt trauma, hepatic arteriography may also be indicated following surgical exploration and packing of a hepatic parenchymal injury with evidence of continued bleeding or hemodynamic instability. Even patients who present with hemodynamic instability who can be successfully resuscitated can be treated effectively with transcatheter embolization (Misselbeck et al, 2009). The yield of arteriography in identifying an arterial injury amenable to embolization is higher when the CT scan suggests a vascular injury.

Complications following embolization of a hepatic arterial injury secondary to blunt trauma are relatively frequent. These complications include hepatic ischemia, infarction, decompensation of hepatic function, gallbladder ischemia, bile leak, and abscess formation. Obviously, the contribution of the embolization to these complications may be difficult to distinguish from sequelae of the underlying traumatic injury.

Iatrogenic injury to the HA is suspected when a biliary drainage tube puts out blood following placement, or the patient develops melena secondary to hemobilia following an intervention through the hepatic parenchyma. CT in these patients may or may not reveal an abnormality, and patients should undergo hepatic arteriography when a clinical suspicion of a hepatic arterial injury exists. Patients with iatrogenic injuries usually have a single, discrete bleeding source that can be addressed with superselective embolization techniques. Complications related to the embolization procedure tend to be lower when compared with patients who have had blunt trauma, as the traumatic injury to the liver is less extensive.

Pancreas

Bleeding from the pancreas is not common following trauma (see Chapter 103). Bleeding is more commonly encountered in patients with pancreatitis (see Chapter 54) or pancreatic surgery (see Chapter 62). Hemorrhage can occur in the retroperitoneum, or it may extend from the retroperitoneum into the peritoneal cavity or into the gastrointestinal tract via communication with the pancreatic duct (hemosuccus pancreaticus). Hemorrhage complicating acute or chronic pancreatitis is usually arterial in origin. Although this complication is encountered in only 2% to 5% of cases, it may be life threatening. Proteolytic enzymes coupled with intense inflammation can erode small arterial branches and create foci of extravasation or create small pseudoaneurysms. Pseudocysts may erode small arterial branches, leading to hemorrhage within the pseudocyst, or it may erode into larger arterial branches and create a large pseudoaneurysm (Fig. 19.6). These pseudoaneurysms are most frequently identified in the splenic artery or its branches (60% to 65%), followed by the GDA (20% to 25%), pancreaticoduodenal arteries (10% to 15%), HA (5% to 10%), and left gastric artery (2% to 5%) (Kirby et al, 2008).

MDCT has been reported to have 90% sensitivity in detecting pseudoaneurysms in patients with acute pancreatitis, however, tiny aneurysms in the intrapancreatic arteries may not be visible (Hyare et al, 2006). When a patient has clinical evidence of significant hemorrhage, or a CT scan reveals a pseudoaneurysm, arteriography followed by embolization is indicated. When the bleeding site is identified angiographically, it can be controlled with embolotherapy in up to 88% of patients (Mansueto et al, 2007).

In the patient who has bleeding following pancreatic surgery, angiography and embolization may also be useful. Significant hemorrhage was noted in 5.7% of 1669 consecutive patients following partial or total pancreatectomy (Yekebas et al, 2007). Bleeding may manifest clinically as gastrointestinal hemorrhage, retroperitoneal or intraperitoneal bleeding, or bleeding through percutaneous or surgically placed drains. When a pancreaticojejunal anastomosis has been created, disruption of the anastomosis may lead to false localization of the bleeding site. Specifically, an extraluminal bleeding site may drain into the bowel through the dehisced anastomosis, or bleeding from the bowel at the anastomosis may extend outside the lumen to cause an intraperitoneal hematoma or hemorrhage through a drain.

Angiography can be extremely useful in the diagnosis and treatment of these patients. In 25 of 43 patients undergoing angiography to diagnose and treat postpancreatectomy hemorrhage, a bleeding site was located and embolized with an 80% success rate in controlling the hemorrhage (Yekebas et al, 2007). The relatively low rate of positive angiograms may be explained by the high incidence of venous bleeding encountered in the postpancreatectomy patient. Many of these patients develop regional portal hypertension as a result of splenic or superior mesenteric venous compression or occlusion secondary either to the underlying pathology or a surgical complication. Venous extravasation is rarely identified by arteriography but may be suggested by CT. If the underlying etiology is compression of the splenic vein (SV), percutaneous transhepatic stenting of the SV may be potentially useful.

Primary Arterial Disorders

Arterial Occlusive Disease

Many arterial disorders that involve the primary branches of the celiac trunk, as well as the SMA, can be assessed adequately with MDCT or MRA. However, delineation of pathology in smaller branches, such as with vasculitis, or subtle pathologic changes may require the increased morphologic detail afforded by catheter angiography.

Arterial occlusive disease as a result of atherosclerosis and compression of the celiac axis by a median arcuate ligament are common diseases that do not generally influence the conduct of hepatobiliary or pancreatic surgery. The principle exception is in the performance of orthotopic liver transplantation (OLT), when preservation of brisk hepatic arterial flow is essential. In that circumstance, the inflow must be corrected either by surgical or endovascular interventions. Another potential area of concern is pancreaticoduodenectomy, particularly in jaundiced patients. In this situation, sacrifice of the GDA is required, which interrupts the retrograde arterial flow from the SMA to

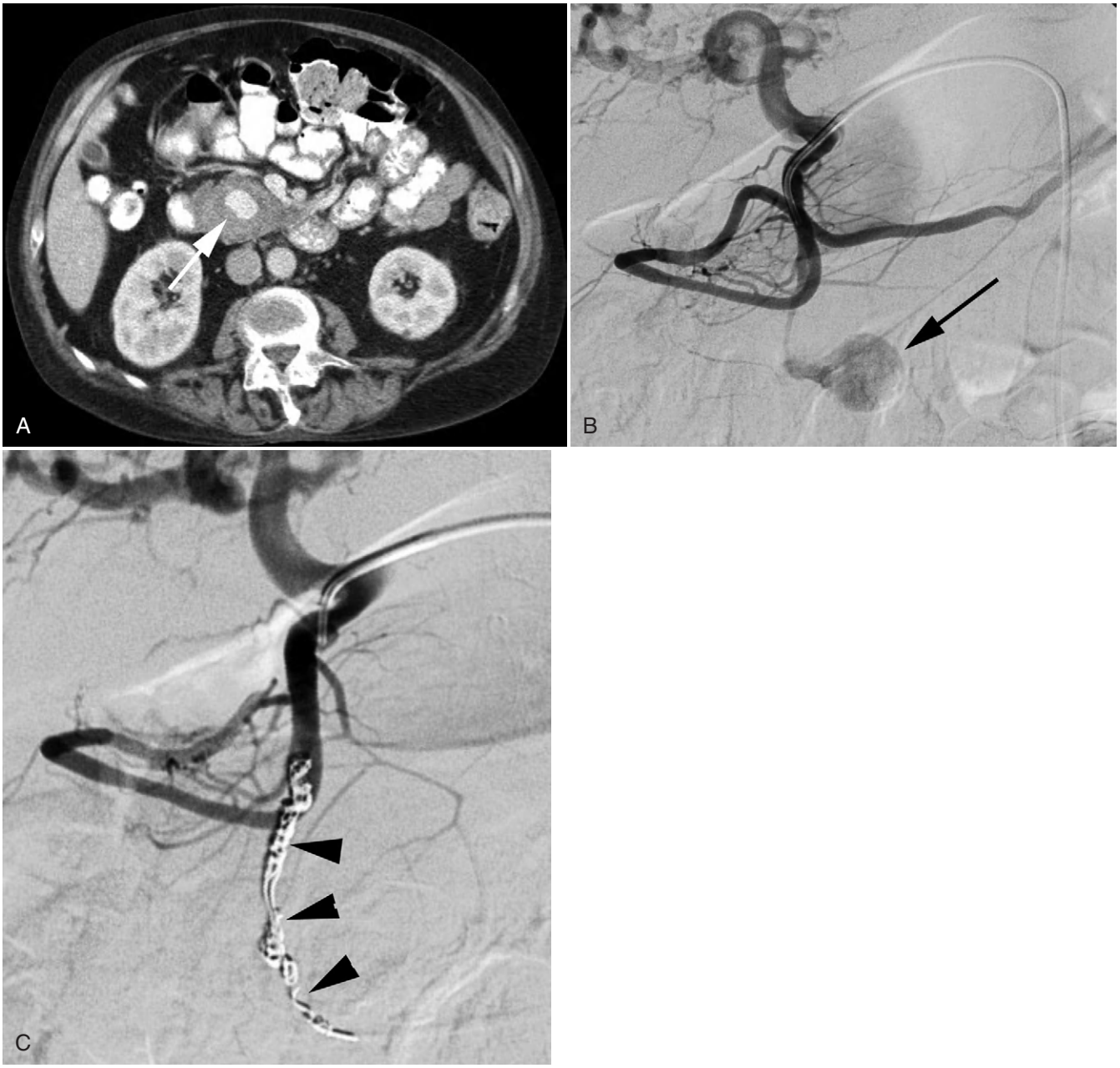


FIGURE 19.6. Pseudoaneurysm secondary to pancreatitis treated with coil embolization. **A,** Contrast-enhanced computed tomography reveals a pseudoaneurysm in the pancreatic head (*arrow*). **B,** Selective gastroduodenal arteriogram reveals the pseudoaneurysm (*arrow*) taking origin from a branch of the anterior superior pancreaticoduodenal artery. **C,** The pseudoaneurysm is occluded with coils (*arrowheads*).

the liver and could result in hepatic ischemia and necrosis. Likewise, fibromuscular dysplasia may rarely involve the SMA, but associated clinical sequelae are extremely uncommon. The SMA may also be compromised in very rare circumstances by a median arcuate ligament.

Visceral Artery Aneurysms

Aneurysms of the celiac, splenic, and hepatic arteries, and less commonly the SMA, have clinical relevance (see Chapter 104). True aneurysms are usually atherosclerotic or developmental in origin and differ from those encountered in pancreatic inflammatory disease, which are typically pseudoaneurysms. Splenic artery aneurysms in women of childbearing age are of particular concern because of their propensity to rupture during childbirth. This clinical circumstance is associated with a 75% mortality rate (Grotemeyer et al, 2009).

Aneurysms of the pancreaticoduodenal arcade are also associated with stenosis of the celiac axis, most commonly secondary to median arcuate ligament compression. In this situation, the increased flow and altered rheologic dynamics through the inferior pancreaticoduodenal arcade likely lead to aneurysm formation (Sugiyama et al, 2007).

Traditionally, visceral artery aneurysms have been managed with a variety of surgical options. More recently, endovascular

therapy using stent grafts has been successful (Rossi et al, 2008). For aneurysms located in nonessential vascular beds—such as the gastroduodenal, pancreaticoduodenal, and proximal splenic arteries—deployment of coil spring emboli in the artery proximal and distal to the aneurysm origin has been successful. Using this technique, a 72% success rate in managing 22 patients with visceral artery aneurysms was recently reported (Ikeda et al, 2008).

Segmental Arterial Mediolysis

A rare vascular disorder, segmental arterial mediolysis (SAM), may also require catheter angiography for definitive diagnosis. This disorder is characterized pathologically by noninflammatory destruction of smooth muscle cytoplasm, leading to arterial dissection and aneurysm formation. Multifocal lesions with skip areas involving the superior mesenteric, hepatic, renal, and middle colic arteries in patients in their fourth to sixth decades are typical (Fig. 19.7). Clinically these lesions are prone to both occlusion by dissection as well as rupture, leading to catastrophic abdominal hemorrhage. Treatment with coil embolization within noncritical arterial beds has been reported (Davran et al, 2009).

Vasculitis

Vasculitides involving the hepatic arterial system may require the spatial resolution provided by catheter angiography for definitive diagnosis, as the characteristic microaneurysms and areas of arterial narrowing may not be apparent by MDCT. The most common vasculitis with hepatic involvement is polyarteritis nodosa, which may not lead to symptoms despite involvement of the visceral arteries, although pancreatitis, cholecystitis, and hepatic dysfunction may be observed.

Arterial abnormalities in the liver have also been identified in patients with systemic lupus erythematosus and Wegener granulomatosus. In most patients, the underlying diagnosis is apparent, and the angiographic findings do not represent a diagnostic dilemma.

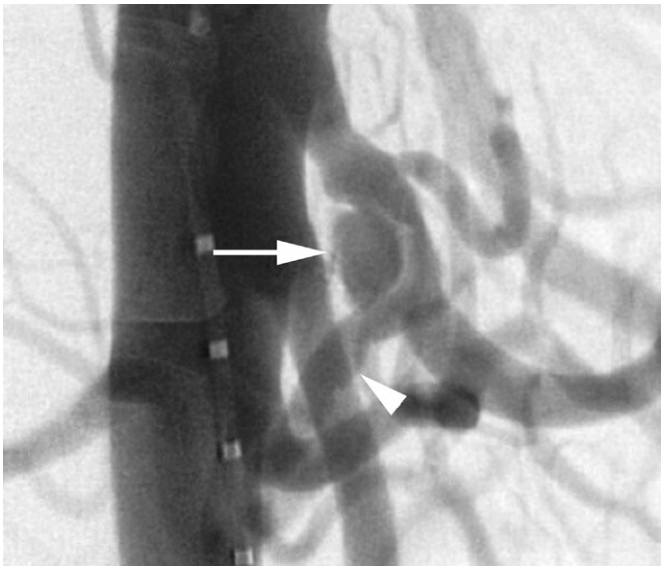


FIGURE 19.7. Segmental arterial mediolysis (SAM). Abdominal aortogram reveals a dissection with a small aneurysm in the celiac artery (*arrow*) as well as undulating irregularity of the common hepatic artery (*arrowhead*) typical of SAM.

Hereditary Hemorrhagic Telangiectasia

An additional condition in which diagnostic arteriography can be a useful adjunct to cross-sectional imaging is hereditary hemorrhagic telangiectasia (HHT). This disorder, also known as *Osler-Weber-Rendu syndrome,* is hereditary; it is transmitted as an autosomal dominant trait, characterized by telangiectasias of the skin and mucous membranes. HHT is also associated with arteriovenous malformations in the pulmonary and hepatic circulation that potentially pose a threat to life. The diagnosis can usually be established on the basis of the family history coupled with abnormalities visible on cross-sectional imaging. However, because of the variability in severity of clinical manifestations, individuals may be unaware that the condition exists in their family. The hepatic arterial malformations that shunt blood into the hepatic venous system may be initially noted on a cross-sectional imaging study, but the findings may be nonspecific. Catheter angiography can be diagnostic by depicting the malformations shunting hepatic arterial blood into the hepatic venous system (Fig. 19.8). Although this disorder has been treated with transcatheter techniques, embolotherapy has currently fallen out of vogue because of the risk of precipitating hepatic failure. OLT is curative if the patient develops high-output cardiac failure.

Peliosis Hepatis

Peliosis is an abnormality of the reticuloendothelia system that is most commonly encountered in the liver (peliosis hepatis). Pathologically it is characterized by blood-filled cystic spaces that range in size from a few millimeters to almost a centimeter. This abnormality has been associated with HIV infection as well as with the use of certain drugs including immunosuppressives, antimetabolites, and oral contraceptives. Although usually benign, it has been associated with spontaneous massive hemorrhage (Choi et al, 2009) and therefore may be encountered angiographically during the investigation of hepatic bleeding. Angiographically (Fig. 19.9) the lesions are easily visible as a disorganized collection of amorphous channels not dissimilar to those observed in HHT or hemangioma; however, the lack of shunting to the hepatic venous system distinguishes it from HHT, and the absence of sharp definition with persistence into the late venous phase distinguishes it from hemangioma.

Arterial Anastomotic Stenoses

Hepatic arterial anastomotic stenoses are observed in up to 12% of patients following OLT (Bechstein et al, 1987; see Chapter 98). Although these stenoses are usually detected by surveillance duplex ultrasound and confirmed with MDCTA, catheter angiography is often performed to improve morphologic delineation and assess the degree of stenosis in preparation for endovascular treatment. Stenosis of the HA anastomosis usually leads to allograft dysfunction, and stenoses of the HA may also be more diffuse (Fig. 19.10). Severe stenosis may lead to hepatic artery thrombosis (HAT). The HA supplies the bile duct, and the bile duct has been rendered devoid of collateral arterial supply during donor hepatectomy. Arterial insufficiency typically leads to biliary strictures and to potentially diffuse biliary ductal infarction. HA thrombosis may lead to irretrievable allograft damage and may necessitate retransplantation. When a hepatic arterial stenosis is identified prior to advanced biliary injury, endovascular therapy with either balloon angioplasty and/or stent placement is warranted.

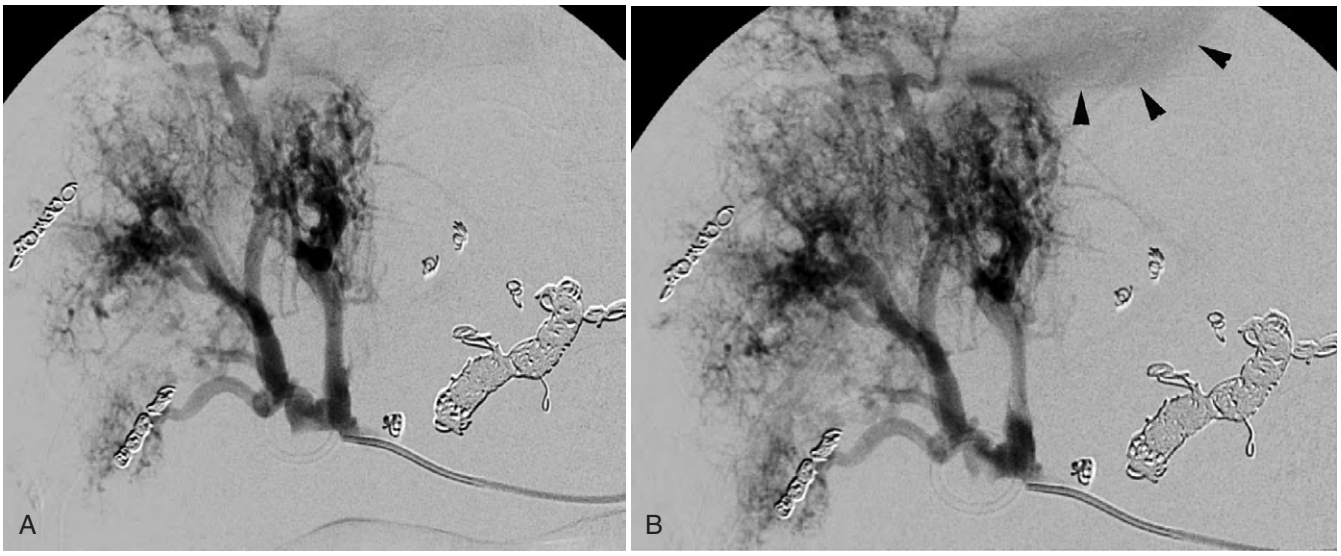


FIGURE 19.8. Hereditary hemorrhagic telangiectasia (HHT). **A,** Selective hepatic arteriogram shows disorganized and dilated intrahepatic vessels typical of HHT. Coils are being placed preoperatively for impending liver transplantation. **B,** Slightly later in the sequence, early opacification of the hepatic vein is visible (*arrowheads*).

Localization of Functioning Pancreatic Neuroendocrine Tumors

Insulinomas

Insulinomas are the most common tumors originating from the islets of Langerhans (see Chapter 61). Because these tumors are usually 2 cm in diameter or smaller, they may not be detected by noninvasive imaging techniques. In a series of 75 surgically proven insulinomas, the sensitivities of CT and MRI were 28% and 35%, respectively (Guettier et al, 2009). This series incorporated cross-sectional imaging dating back to the late 1980s that likely reduced the overall sensitivity. When cross-sectional imaging techniques were examined after 1994, the sensitivity of CT and MRI improved to 80% and 70%, respectively, owing to improved imaging technology (Nikfarjam et al, 2008). Moreover, endoscopic ultrasound (EUS; see Chapter 14) has been used to localize insulinomas with a reported sensitivity ranging from 82% to 94%, making this technique a valuable adjunct

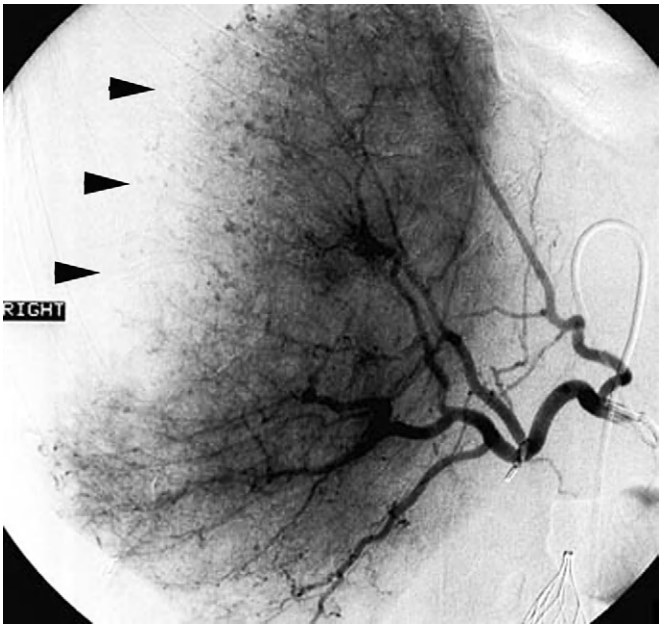


FIGURE 19.9. Peliosis hepatitis. Multiple small contrast collections can be seen within the hepatic parenchyma. This patient had spontaneous hemorrhage that created displacement of the hepatic parenchyma (*arrowheads*).



FIGURE 19.10. Hepatic artery stenosis following orthotopic liver transplantation. Celiac arteriogram shows mild diffuse narrowing of the hepatic artery with two areas of critical stenosis (*arrowheads*).

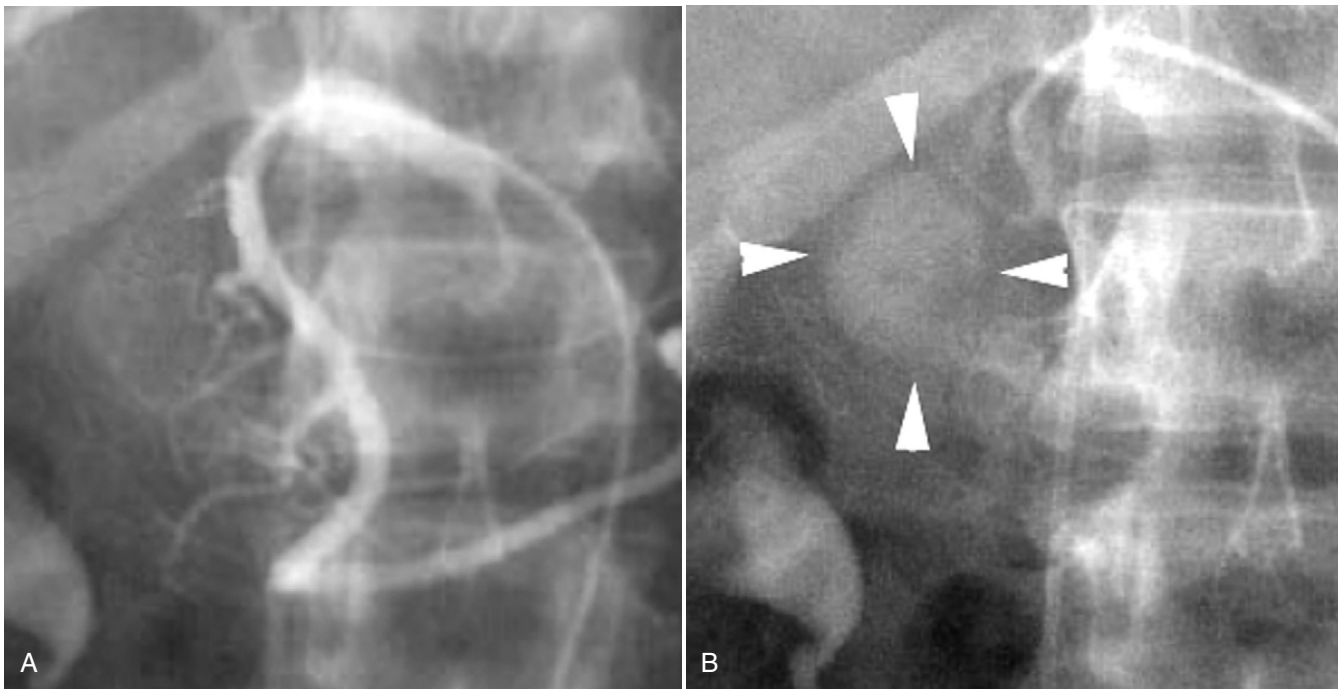


FIGURE 19.11. Insulinoma. **A,** Selective gastroduodenal arteriogram shows no definite abnormality during the arterial phase. **B,** A subtle area of hypervascularity is identified during the capillary phase, possibly representing an insulinoma (*arrowheads*). This was confirmed as the region of tumor by calcium stimulation with venous sampling.

in the management of these patients (McLean, 2004). EUS requires considerable expertise, is not available at all centers, and has reduced sensitivity for lesions in the tail of the pancreas, ranging from 50% to 60% (McLean, 2004).

Calcium stimulation arteriography was developed and described in 1991 (Doppman et al, 1991). Although unnecessary when imaging can confidently detect the offending pancreatic lesion, it is an extremely useful adjunct when the location of the lesion cannot be defined with confidence (Fig. 19.11). When 1 mL of 10% calcium gluconate is injected into an artery supplying the pancreas, tumor cells degranulate and release insulin into the portal venous circulation. Sequential blood samples obtained from the hepatic vein will demonstrate a significant rise in the concentration of insulin when the portion of the pancreas containing the tumor is injected. By sequentially injecting the arterial supplies to different regions of the pancreas, it is possible to ascertain the location of the tumor. The GDA supplies the head of the pancreas, the SMA supplies the head and uncinate process, and the SA supplies the body and tail. The origin of small branches supplying the pancreas from the SA and common HA are important to note in determining the approximate areas of pancreatic arterial supply. In the aforementioned article by Guettier and colleagues (2009), calcium stimulation arteriography was the most sensitive technique for localizing surgically proven insulinomas with an accuracy of 84%, a false-negative rate of 11%, and a false-positive rate of 4%.

Gastrinomas

Gastrin-secreting tumors are associated with Zollinger-Ellison syndrome. These tumors occur in association with multiple endocrine neoplasia (MEN) type 1 in about one third of cases, with the remainder being of the sporadic type. Fifty percent of gastrinomas occur in the pancreas, with the duodenum being the most common extrapancreatic location; about 60% to 90% of gastrinomas are malignant. When a sporadic gastrinoma is identified, surgical resection is indicated. The role of surgery in patients with MEN type 1 is more controversial because of multiplicity of tumors and lack of an established survival benefit.

The diagnosis and location of a gastrinoma can be established with a combination of somatostatin receptor scintigraphy and EUS in approximately 90% of patients. When an occult gastrinoma is encountered, angiography has been used for localization. The principles are identical to the localization of insulinomas; however, secretin has been used in addition to calcium gluconate as the stimulating agent. Sensitivities of arterial stimulation venous sampling (ASVS) in the detection of gastrinomas have ranged from 70% to 100% (Cohen et al, 1997; Turner et al, 2002).

Angiographically, gastrinomas are less hypervascular and more difficult to detect in comparison to insulinomas. Sensitivity of angiography alone without ASVS is less than 50%. Moreover, the 50% extrapancreatic location makes detection more difficult, often requiring superselective catheterization to evaluate the duodenum.

Glucagonoma

Glucagonomas may also occur sporadically, or they may be associated with MEN type 1. These tumors are usually larger than gastrinomas or insulinomas at presentation, therefore localization can generally be achieved with noninvasive imaging or EUS. A single case of successfully using ASVS with calcium gluconate as the stimulating agent to localize an occult glucagonoma has been reported (Okauchi et al, 2009).

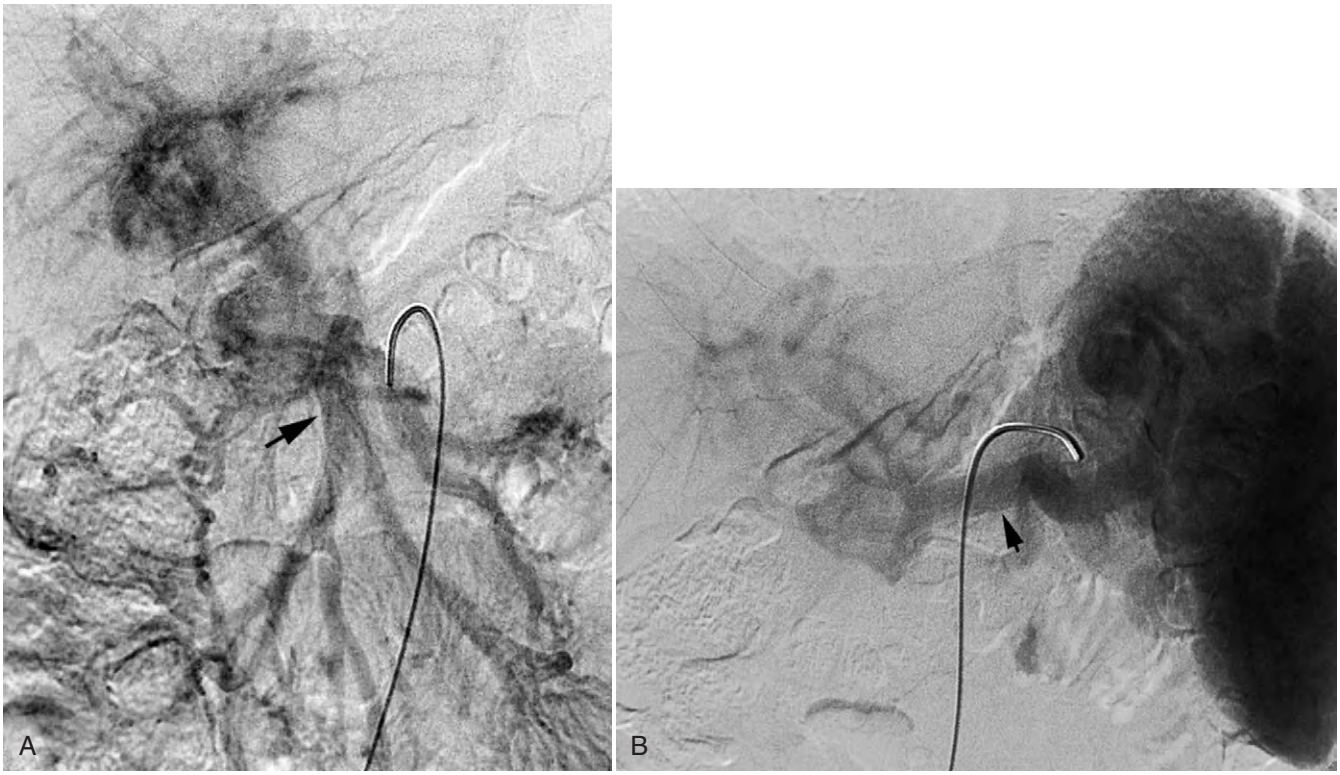


FIGURE 19.12. Arterial portography in a patient with cavernous transformation of the main portal vein. **A,** Venous phase of superior mesenteric arterial injection shows the superior mesenteric vein (*arrow*) and cavernous transformation of the main portal vein. **B,** Venous phase of splenic arterial injection from the same patient shows the splenic vein (*arrow*).

VEINS

Venographic Technique

MDCT, magnetic resonance venography, and ultrasound are usually sufficient for depiction of the major visceral venous trunks and their primary branches in the vast majority of patients. Cross-sectional imaging can accurately depict the relationship of a mass in the pancreas to both the splenic and superior mesenteric veins. It also has the advantage of simultaneous opacification of all of the venous structures. However, in certain clinical situations, it is desirable to visualize the venous structures with a higher level of clarity. These situations include planning of percutaneous venous intervention in situations where occlusions are suspected or occasionally to plan a surgical portosystemic shunt.

The most common technique to visualize the splanchnic vein is transarterial portography, in which selective splenic and superior mesenteric arteriograms are performed with delayed imaging into the venous phase, depicting the splenic and superior mesenteric veins, respectively (Fig. 19.12). When detailed visualization of the venous anatomy is required, a higher dose of contrast media can be used for the arterial injection, increasing the clarity of the venous opacification.

When an extremely detailed evaluation is required, a combination of transarterial portography during MDCT can be performed (Fig. 19.13). The increased contrast sensitivity of the MDCT coupled with multiplanar and three-dimensional reconstruction allows visualization of the veins



FIGURE 19.13. MDCT with three-dimensional reconstruction following superior mesenteric arterial injection. The superior mesenteric vein and cavernous transformation are easily visualized.

that cannot be achieved by any other single technique. This is particularly useful in the presence of portal vein (PV) occlusion, when a complex venous reconstruction or bypass is being considered.

Direct venography of the splanchnic veins can be achieved by three routes: *transjugular, transhepatic,* and *transsplenic*. In the transjugular approach, a catheter is placed into the jugular vein and manipulated into a hepatic vein. Obtaining pressure measurements through this catheter in both the free and wedged position will yield the corrected sinusoidal pressure in patients being assessed for portal hypertension. A biopsy of the hepatic parenchyma (transjugular liver biopsy) may be performed when desirable. Injection of carbon dioxide through a catheter wedged in a hepatic vein or through a balloon catheter will often yield an image of the PV. If direct portography is warranted, one of several specially designed needles can be inserted to puncture the PV through the intervening hepatic parenchyma and through catheters advanced into the portal, splenic, or superior mesenteric venous system. This procedure is performed almost exclusively in patients undergoing a transjugular intrahepatic portosystemic shunt (TIPS), but it is also used to manage selected patients with portal and superior mesenteric vein (SMV) thrombosis (Liu et al, 2009; see Chapter 76E).

The portal venous system may also be accessed by a percutaneous transhepatic approach (Semiz-Oysu et al, 2007). After sterile preparation of the right upper quadrant, an intrahepatic portal venous radicle is punctured under real-time ultrasonographic guidance, permitting a vascular access sheath to be placed using a Seldinger technique. Standard guidewire and catheter manipulations are then used through the sheath for selectively catheterizing the SV and the SMV or its branches. Once the diagnostic images have been taken or venous interventions have been performed, the catheter is removed. The transhepatic tract is then occluded by a variety of techniques including insertion of Gelfoam pledgets, deployment of coils, or injection of fibrin glue. The transhepatic venographic procedure is usually performed as part of a direct pancreatic venous sampling, lobar portal venous embolization to stimulate contralateral hypertrophy prior to major hepatic resection, assessment and management of an anastomotic portal venous stenosis following OLT, pharmacomechanical lysis of a splanchnic vein thrombosis, or rarely to control bleeding from a splanchnic vein.

Percutaneous injection of the splenic parenchyma can also be used to delineate the anatomy of the splenic and portal veins as well as the draining tributaries. This examination is somewhat antiquated and has been generally replaced by MDCT or magnetic resonance venography. In infants, cross-sectional imaging may be inconclusive, and transarterial portography is risky because of the diminutive size of the femoral arteries; however, it remains an alternative in planning a portosystemic shunt procedure.

Percutaneous catheterization of the splanchnic veins is also possible from a transsplenic approach using a technique identical to that described for transhepatic catheterization (Tuite et al, 2007). This procedure is usually done in conjunction with a percutaneous procedure to assess a PV stenosis or occlusion following OLT, but it may also be used in conjunction with the assessment and treatment of a splenorenal venous bypass, when access cannot be achieved from the systemic venous circulation.

Visceral Venographic Anatomy

The SV and SMV join to form the main PV (see Chapter 1B). The inferior mesenteric vein (IMV) usually enters the SV adjacent to the confluence, but it may also enter the SMV either at or just caudal to the confluence. The coronary vein most often drains into the cephalic aspect of the main PV just beyond the confluence of the SMV and SV. The number and location of veins draining the pancreas is variable. Multiple small, unnamed veins drain directly into the SV. Typically the anterior-superior pancreaticoduodenal vein drains directly into the PV, and the posterior-superior pancreaticoduodenal vein drains into the SMV. The inferior pancreaticoduodenal veins drain into the SMV at the caudal margin of the pancreas, and the PV courses obliquely cephalad from near the midline toward the liver, where it divides to supply the right and left lobes. This division, as well as the division into segmental branches, is variable and must be delineated when clinically relevant for each individual patient.

Selective Venous Sampling

Percutaneous transhepatic sampling of the splenic, superior, and portal venous system can be performed to diagnose occult neuroendocrine tumors of the pancreas. This may be done in conjunction with calcium stimulation as previously described, or it may be performed without stimulation because of the higher concentration of the hormone when obtained directly or adjacent to the venous tributary.

Preoperative Planning for Portal Decompression

The majority of portal decompression procedures, whether surgical or percutaneous, can be planned on the basis of venous



FIGURE 19.14. Transhepatic venogram evaluating a Rex shunt. Surgically placed autologous vein conduit (*arrowheads*) extends from superior mesenteric vein (*SMV*) to the left portal vein. A stenosis (*arrow*) is visible within the shunt that has led to portal hypertension with filling of the coronary vein (*CV*).

phase MDCT. The positions of the SMV, SV, PV, left renal vein, and inferior vena cava are well shown by either MDCT or MR. However, particularly in the case of extrahepatic portal venous obstruction, higher definition of the venous anatomy may be required by the surgeon or interventionalist. As previously discussed, transarterial portography coupled with MDCT during arterial injection can be invaluable in delineating the morphology of the splanchnic venous system.

An alternative procedure to portosystemic shunting in selected patients with symptomatic portal hypertension secondary to extrahepatic portal venous obstruction is the Rex shunt (Vanderlan et al, 2009). This procedure involves a venous bypass from the superior mesenteric vein to the umbilical segment of the left PV, the latter being accessed through the fossa of Rex (Fig. 19.14). When successful, this type of bypass avoids the complication of encephalopathy, as all of the splanchnic blood drains through the liver. Careful preoperative imaging is needed prior to this procedure to confirm the patency and demonstrate the size of the umbilical segment of the left PV. Arterial portography coupled with MDCT is ideal for this indication. When insufficient, direct transhepatic portography may be necessary.

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CHAPTER 20

Percutaneous biopsy

Anne M. Covey and Lynn A. Brody

BIOPSY OVERVIEW

Image-guided needle biopsy is the mainstay for diagnosis of nonpalpable masses almost anywhere in the body. The indications for biopsy continue to evolve, and although percutaneous biopsy of a given mass is possible, it may not be indicated (Thompson et al, 1985). As with any invasive procedure, percutaneous biopsy has associated risks that should be weighed prior to the procedure. Needle biopsy is warranted when the result of the biopsy would potentially affect patient management. These indications include confirmation of preoperative diagnosis, documentation of primary or metastatic disease in patients who are not surgical candidates, evaluation of organ dysfunction, and sampling for special studies such as receptor or gene mutation status.

Several methods are available to obtain tissue, including biopsy by percutaneous needle or by endoluminal and transvenous techniques. Needles ranging in size from 25- to 14-gauge are typically used, and outside the central nervous system, a biopsy can be obtained from almost any abnormality that can be imaged. Most needles contain an inner stylet, which is removed when the needle is appropriately positioned, immediately before obtaining the specimen; the stylet prevents the needle from coring interposed structures and accumulating nontarget material before optimal placement. Smaller "fine" needles (25 to 20 gauge) are used to obtain cytologic specimens or to obtain samples for culture or flow cytometry. Larger needles (19 to 14 gauge) are used to obtain tissue cores when histologic material is required for pathologic diagnosis or when special studies, such as immunohistochemical staining, are to be performed.

Common malignancies in which core specimens may be necessary for diagnosis include lymphoma, sarcoma, thymoma, and mesothelioma. Core material may also be required to diagnose well-differentiated hepatocellular carcinoma (HCC) or benign hepatic tumors. Tissue cores also may be required for mutational analysis in patients for whom targeted therapies are being considered. In most cases, fine needle aspirates are sufficient, and multiple immunohistochemical stains can be used on a single sample, allowing for accurate cell typing.

To increase the likelihood of a diagnostic biopsy and to minimize complications, a high-quality imaging study should be available for review both when the biopsy is being planned and when it is performed. In some cases, careful review of imaging studies may provide a definitive diagnosis, obviating the need for biopsy. Review of preprocedure imaging also influences selection of the most appropriate modality for guidance and patient positioning during the procedure, so that potential problems such as interposed lung, bowel, or blood vessels may be anticipated and avoided. In addition, knowledge of imaging findings allows for appropriate discussion of relevant risks in the informed consent. With proper preprocedure imaging, the biopsy can be planned to avoid unusual or unsustainable positions, complex needle angulation, and challenging breathing instructions.

Review of imaging studies before biopsy also facilitates targeting of the most viable area of a mass. As large masses outgrow their blood supply, they become necrotic, and diagnostic material cannot be reliably obtained in a background of necrosis. Preprocedure contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), and positron-emission tomography (PET) can allow for accurate targeting of areas most likely to yield a diagnostic specimen.

BIOPSY TECHNIQUE

Fine Needle Aspiration

A 25- to 20-gauge needle is advanced into the target lesion, and real-time (ultrasound, fluoroscopy, or CT fluoroscopy) or interrupted imaging (conventional CT or MRI) is performed to guide and assess needle position. Coaxial techniques are sometimes useful but are generally unnecessary, but some operators are partial to this technique. Although coaxial biopsy requires the introduction of a larger needle than is used for biopsy, it has the advantage that multiple samples may be obtained without creating a new tract for each pass, and the tract can be embolized or "plugged" to prevent hemorrhage in high-risk situtations (Billich et al, 2008).

Fine needles come in a variety of tip designs. Many physicians use a Chiba-style needle, in which the needle tip and inner stylet are beveled. Our preference is a Westcott-style needle: in addition to a beveled tip, it has a notch in the sidewall of the needle just proximal to the tip; this facilitates the operator's ability to choose more precisely the location from which the cells will be aspirated.

When needle position has been confirmed, the needle is attached to a disposable syringe. The plunger of the syringe is retracted to apply suction as the needle is moved back and forth within the lesion to obtain a sample. The needle is withdrawn after suction is released, and the specimen is deposited on a glass slide. Smears are made from the biopsy specimen, and these may be used for immediate analysis (e.g., Diff-Quik) or fixed in ethanol for immunohistochemical stains. In some cases, molecular studies may need to be performed on fine needle specimens, and charged slides may be used that electrostatically attract tissue and bind it to the slide. The residual material within the syringe and needle is rinsed in a

cell-preserving solution for preparation of a cell block. For cases in which non-Hodgkin lymphoma is suspected, a specimen for flow cytometry may be obtained by rinsing the needle and syringe in a nutrient-rich culture medium (e.g., Roswell Park Memorial Institute medium). When infection is suspected, material can be set aside for culture.

In the ideal situation, an on-site cytopathologist or cytotechnologist can provide an immediate interpretation of the sample; this has been shown to increase the sensitivity of the biopsy, shorten the procedure time, and minimize the number of passes required to obtain a diagnostic specimen (Nasuti et al, 2002; Silverman et al, 1989).

Core Biopsy

The technique for localizing a lesion is identical for fine needle and core biopsies. To obtain a good core sample, a target lesion should be at least 1 cm in maximum dimension, but preferably 2 cm. Because of the typically larger needle size (14 to 19 gauge) used to perform a core biopsy, care should be taken to minimize the possibility of traversing medium-sized arteries, which lack the muscular wall of larger arteries and have an increased tendency to bleed; traversing the colon can result in peritonitis or abscess. Core biopsy needles come in a variety of sizes and styles, including biopsy "guns" and cutting needles that obtain histologic samples manually as the needle is passed back and forth within the lesion.

To confirm adequacy of the specimen, a touch preparation may be prepared on a glass slide for immediate evaluation by a cytopathologist or cytotechnologist. Before being placed in formalin or saline, the core of tissue is placed on a glass slide and gently moved over the slide to allow some cells to collect on the surface. In addition to the tissue sample, material is often collected at the same time that is suitable for cytology, and this increases the diagnostic yield of the procedure. Core samples are commonly placed in formalin. Occasionally, specimens may be sent "fresh" to pathology in saline or on saline-soaked gauze for special studies. Because cells placed in saline eventually undergo cell lysis related to osmotic shifts of saline into the cell, a specimen in saline needs to be fixed or frozen within a few hours to avoid deterioration of the tissue sample. Tissue also may be snap frozen for future studies. The preferred method for processing tissue may vary from institution to institution, and the preference of the pathologists reviewing the material should be determined before initiating a biopsy.

Despite the fact that more tissue is usually obtained during a core needle biopsy than with a fine needle aspiration (FNA) biopsy, the diagnostic rates for most malignancies are not necessarily higher (Longchampt et al, 2000; Stewart et al, 2002). The incremental benefit of a core biopsy in the liver is most notable in the discrimination of a well-differentiated HCC from nodular regeneration in the setting of cirrhosis and in confirmation of benign diagnoses, including hemangioma, adenoma, and focal nodular hyperplasia (Kulesza et al, 2004; Kuo et al, 2004).

IMAGING GUIDANCE

Ultrasound

Ultrasound (US; see Chapter 13) is commonly used to guide percutaneous biopsies of the liver, because it is widely available, inexpensive, and portable. US may be used at the bedside or in patients in whom CT guidance is impractical. Lesions larger than 1 cm are often visible, and US allows for real-time visualization of the needle as it courses from the skin into the lesion. This is especially helpful in small lesions that move with respiration and are difficult to target with interrupted imaging modalities. Visualization of smaller caliber needles may be difficult, and many manufacturers make needles specially designed to enhance visibility with US.

Another advantage of US guidance is the capability of multiplanar imaging. This is particularly useful in finding a route to lesions at the hepatic dome that avoids aerated lung and eliminates the risk of causing pneumothorax. Because CT provides a two-dimensional image, complex triangulation often is required to accomplish the same result. Doppler imaging is occasionally helpful in performing a biopsy by enhancing the localization of small lesions. US contrast agents may help identify the most viable regions of a tumor, and it does not use ionizing radiation—a benefit to both the patient and the operator.

Limitations of US include interoperator variability and poor transmission through air and bone, which limits the visualization of some lesions. Additionally, patients who are sedated for biopsy may not be able to cooperate with breathing instructions necessary to facilitate visualization of some masses, including small lesions or those high in the hepatic dome.

Computed Tomography

CT (see Chapter 16) is a common modality for guiding percutaneous biopsies, because it provides superb anatomic detail that gives the operator the ability to plan a path from skin to lesion using the safest approach, clearly visualizing interposed structures. CT is the imaging modality of choice for biopsies of the pancreas, adrenal glands, abdominal and retroperitoneal lymph nodes, and bone and liver lesions that are not well visualized with US, or when biopsy is performed by operators who are not skilled with US. CT is also commonly used for lung lesions, although at our institution, fluoroscopy is preferred by some operators to capitalize on the real-time visualization of the target in the moving background of the lung.

Computed Tomographic Fluoroscopy

Many manufacturers now offer CT fluoroscopy as an option on diagnostic scanners. This produces CT images in near real time. It does expose the operator to ionizing radiation and requires that the operator wear lead, as with conventional fluoroscopy; but it is preferred by some physicians, owing to decreased time between needle manipulation and image availability.

Magnetic Resonance Imaging

Biopsies guided by MRI (see Chapter 17) have been made possible by the advent of open-bore MRI systems that provide access to patients during imaging and the availability of nonferrous biopsy needles and monitoring equipment. The superior contrast resolution of MR allows for targeting of lesions that are difficult to visualize with US and noncontrast CT, and the ability of MRI to image in any plane enhances the targeting of lesions that are not safe to approach or easy to access in the axial plane (Stattaus et al, 2008; Fig. 20.1). Owing to high cost and limited availability, MR-guided biopsies are generally reserved for patients whose lesion cannot be seen or targeted with US or

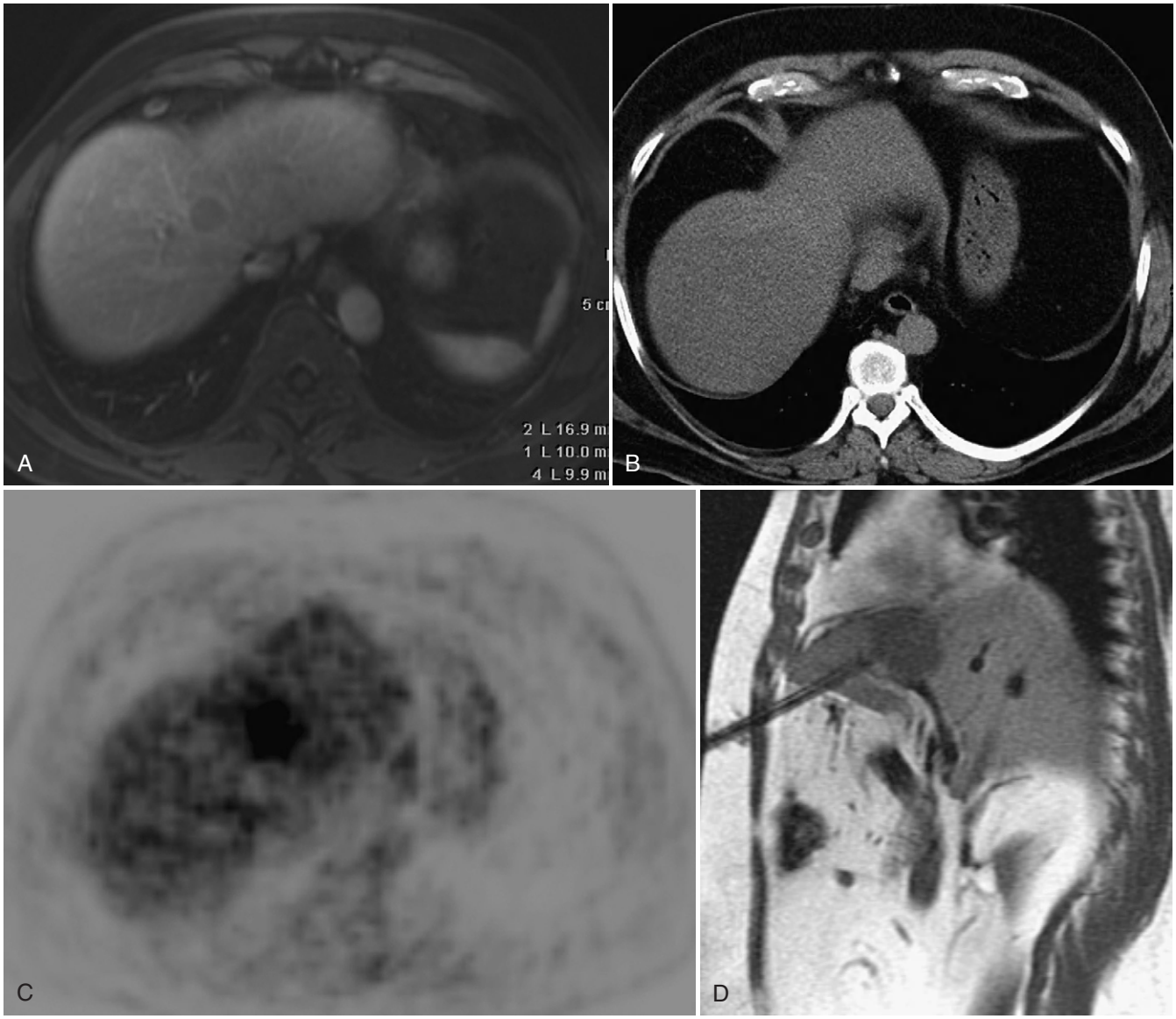


FIGURE 20.1. Magnetic resonance (MR)-guided percutaneous liver biopsy. **A,** Axial T1 MR after contrast administration shows a focal lesion in segment IV in a patient with hepatitis B. **B,** Noncontrast computed tomography in the same patient at the same level failed to show the lesion. **C,** Positron emission tomography scan was positive. **D,** The biopsy was successfully performed using MR guidance in the sagittal plane to avoid the risk of pneumothorax. The biopsy specimen confirmed the diagnosis of hepatocellular carcinoma.

CT. In addition, it is necessary to ensure that nonferromagnetic, MRI-compatible equipment is on hand and that the patient is able to undergo MRI.

Fluoroscopy

Fluoroscopy is useful for guiding bile duct biopsies. Benign and malignant biliary strictures (see Chapters 18, 42, and 50) often have similar cholangiographic appearances and rarely can be distinguished based on imaging alone (Hadjis et al, 1985; Corvera et al, 2005). Lesions originating within the duct may be sampled by either an endoluminal (see Chapter 14) or a direct percutaneous approach (see Chapter 18). Percutaneous transhepatic biliary drainage allows direct access to the biliary tract for endoluminal biopsy, when satisfactory decompression of the biliary tree has been achieved. Biopsy forceps or brush-biopsy catheters can be used through the existing tract to obtain tissue samples of suspicious areas (Fig. 20.2). The sensitivity of forceps biopsy is in the range of 40% to 80%, higher than that of brush biopsy, which is in the range of 30% to 60%. Specificity for each approaches 98% (Stewart et al, 2001; Govil et al, 2002; Weber et al, 2008), and sensitivity is highest for intraductal lesions and when biopsy is done in conjunction with choledochoscopy to provide direct visualization of the lesion (Ponchon et al, 1996).

Alternatively, after the biliary tree is opacified, a direct percutaneous biopsy of a bile duct lesion may be targeted with fluoroscopy using a transhepatic approach (see Chapter 18; Chawla et al, 1989). This technique is most useful for intrinsic bile duct lesions but may also be used to diagnose lesions

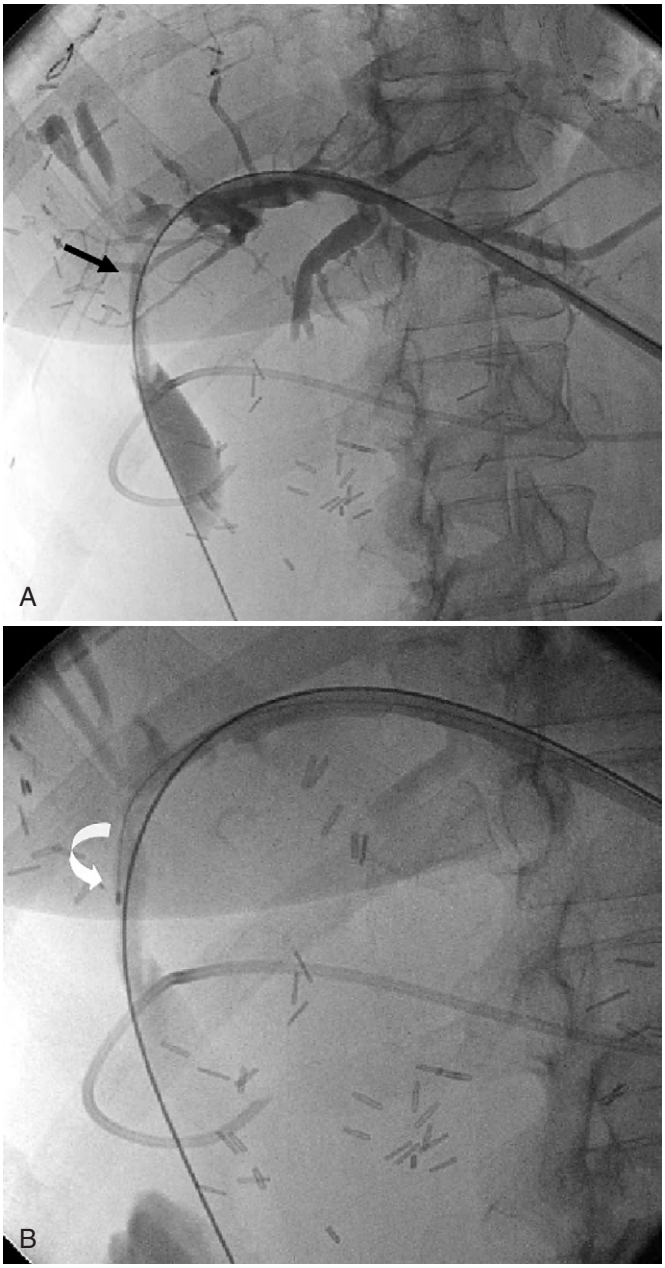


FIGURE 20.2. Biliary brush biopsy. **A,** Transhepatic cholangiogram shows a high bile duct stricture (*arrow*) in a patient with two indwelling endoscopic stents and a percutaneous biliary drainage catheter. Prior brush biopsy was nondiagnostic. **B,** A brush (*curved arrow*) was advanced to the stricture and used to obtain a specimen for cytology. The specimen was diagnostic of cholangiocarcinoma.

adjacent to the bile duct. With this technique, contrast is injected into an indwelling biliary drainage catheter to delineate the targeted bile duct abnormality. A needle is advanced through the anterior abdomen to the lesion, and a specimen is obtained. Confirmation of accurate needle position is made by obtaining oblique fluoroscopic images and by real-time fluoroscopy, when the needle is seen to move the duct or the indwelling catheter or both (Fig. 20.3). Fluoroscopy also is useful to guide percutaneous biopsy of lung nodules and for nontargeted transvenous biopsies of the liver or kidney.

New Guidance Equipment

New technology is being developed that allows fusion of multiple modalities. For example, CT and MRI scans can be overlaid with real-time US images to achieve the clarity of the one imaging modality and the real-time visualization capabilities of the other. PET images (see Chapter 15) also can be fused to demonstrate sites of highest metabolic activity. Additionally, robotic guidance systems have been piloted in an effort to optimize speed and accuracy of needle placement.

BIOPSY OF SPECIFIC SITES

Liver Biopsy

Percutaneous liver biopsy is performed to determine the nature of focal liver masses, the cause and extent of cirrhosis, or the cause of liver dysfunction (see Chapters 64, 65, and 70). Modern cross-sectional imaging techniques—including ultrasound, CT, and MRI—allow percutaneous biopsy of both subcentimeter and deep lesions to be performed on an outpatient basis with minimal morbidity. With current techniques, almost any liver lesion can be targeted percutaneously; most liver lesions larger than 5 mm are suitable for biopsy (Yu et al, 2001). Fine needle biopsy of liver lesions has a sensitivity of 69% to 97% (Ohlsson et al, 2002).

Focal Liver Lesions

Focal liver lesions may be solitary or multiple. For a solitary lesion, several benign conditions—cyst, hemangioma, focal nodular hyperplasia, and adenoma—often can be diagnosed confidently by high-quality cross-sectional imaging, obviating the need for biopsy (see Chapters 16, 17, and 79; Gibbs et al, 2004; Hussain et al, 2004; Kim et al, 2004). These diagnoses should be considered in all solitary liver lesions, unless they are known to be new in the setting of a known cancer or in patients at risk for primary HCC.

HCC may also be diagnosed based on imaging and clinical criteria. In patients with cirrhosis and an arterial enhancing liver mass greater than 2 cm, an α-fetoprotein value of greater than 400, or two concordant imaging studies diagnostic of HCC, biopsy is generally unnecessary (Bruix et al, 1981). When the diagnosis of HCC is considered, and these criteria are not met, the diagnosis often can be established based on cytology alone. Smaller, encapsulated tumors are more likely to be well differentiated, and tissue cores may be required to distinguish a well-differentiated tumor from normal or cirrhotic liver. Because of the risk of tumor seeding in the biopsy tract for a lesion highly suspicious for HCC (Chaudhry et al, 2004; Perkins, 2007; Durand et al, 2007), when a curative treatment is possible, biopsy should be performed only after consultation with a hepatobiliary surgeon and after referencing the most current imaging and clinical criteria.

Multifocal solid liver lesions most commonly represent metastatic disease. In such cases, biopsy may be requested to 1) confirm the presence of metastatic disease in a patient with a known primary; 2) establish tumor type and stage simultaneously at initial presentation; 3) acquire tissue for genetic analysis, such as *c-kit* mutation in a patient with metastatic gastrointestinal stromal tumor; or 4) obtain histologic samples for patients undergoing experimental therapies.

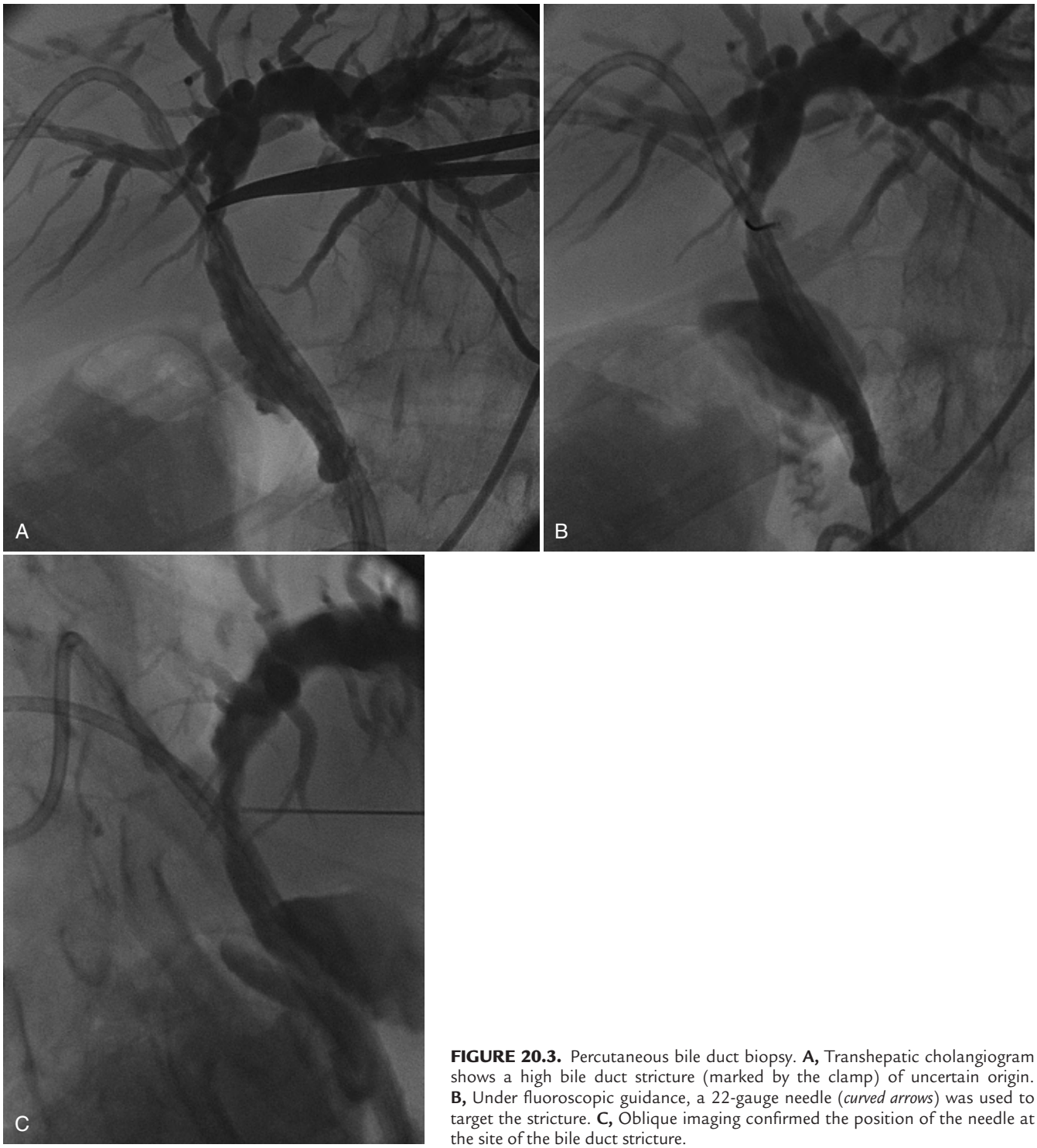


FIGURE 20.3. Percutaneous bile duct biopsy. **A,** Transhepatic cholangiogram shows a high bile duct stricture (marked by the clamp) of uncertain origin. **B,** Under fluoroscopic guidance, a 22-gauge needle (*curved arrows*) was used to target the stricture. **C,** Oblique imaging confirmed the position of the needle at the site of the bile duct stricture.

Liver Parenchyma Biopsy

Core liver biopsy is used to grade and stage liver disease in patients with abnormal liver function studies, chronic hepatitis, and known or suspected cirrhosis (see Chapters 64, 65, and 70). Gastroenterologists have historically performed most liver biopsies without imaging guidance; however, unusual anatomy occasionally makes imaging-guided biopsy advisable. Adequate tissue cores can be obtained with needles 20 gauge and larger, although needles 18 gauge and larger provide a more generous specimen for analysis (Guido & Ruggae, 2004; Maharaj et al, 1986).

Transvenous Biopsy

Transjugular liver biopsy is a useful alternative to percutaneous biopsy in patients with coagulopathy or when hepatic venous pressure measurements are required (Sawyerr et al, 1993;

Garcia-Compean & Cortes, 2004). Although transvenous biopsy is seemingly more invasive than percutaneous biopsy, the risk of significant bleeding in coagulopathic patients is minimized using a transvenous approach, because bleeding from the biopsy site tracks back into the venous circulation and not into the abdominal cavity, as can happen with percutaneous biopsies. Proper technique to avoid puncture of the liver capsule is crucial to optimize safety.

In this technique, a venous sheath is introduced into a hepatic vein, most commonly the right hepatic vein, from a right internal jugular approach. Pressure measurements may be obtained to evaluate the source (presinusoidal, sinusoidal, or postsinusoidal) and degree of portal hypertension. A core biopsy needle or biopsy forceps is introduced through the sheath into the liver parenchyma to obtain histologic samples (Fig. 20.4). Care must be taken to avoid performing the biopsy from a peripheral approach, because this increases the risk that the liver capsule will be punctured and that peritoneal hemorrhage will result.

Transvenous biopsy is only used for nontargeted parenchymal biopsy; it cannot be used for biopsy of a focal lesion. Transvenous biopsy of the kidney also has been reported and may be useful for evaluation of renal dysfunction in coagulopathic patients (Cluzel et al, 2000). This may be particularly convenient in coagulopathic patients who require both parenchymal hepatic and renal biopsies.

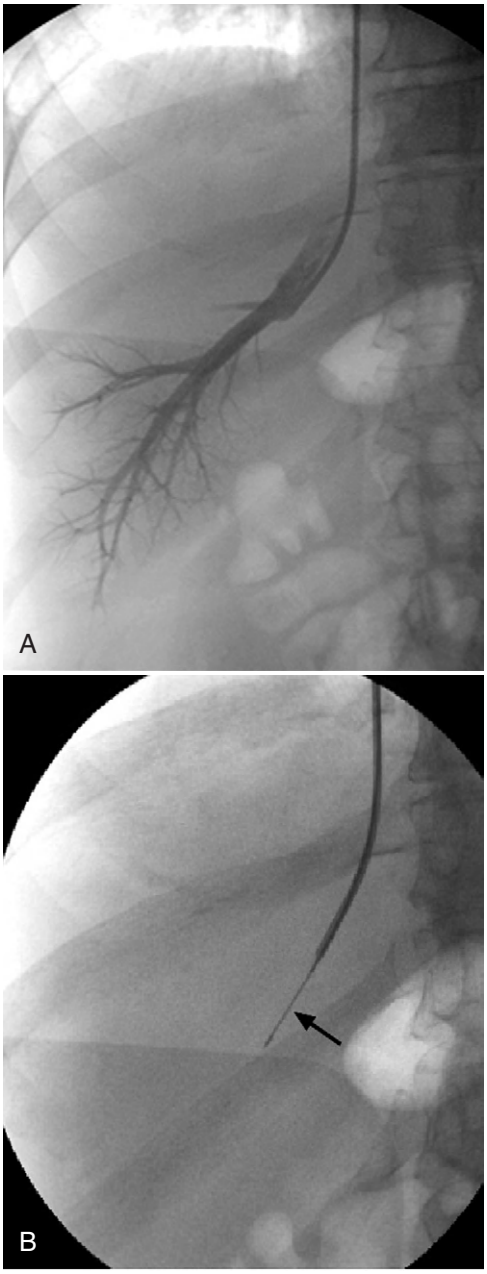


FIGURE 20.4. Transjugular liver biopsy. **A,** Right hepatic venogram through a sheath placed via the right internal jugular vein. **B,** A 19-gauge automated flexible biopsy needle with a 20-mm throw (*arrow*) is advanced through a metal cannula and directed anteriorly as the biopsy specimen is obtained.

Biopsy of Other Organs

Adrenal Biopsy

The adrenal gland is a common site of metastatic disease. This gland also is the site of many benign neoplasms, and adenomas occur in 5% of individuals (Abecassis et al, 1985; Libe et al, 2002). Adrenal biopsy can often be avoided, as MRI can sometimes distinguish between an adenoma and a metastasis (National Institutes of Health, 2002). In some cases, the mass remains indeterminate, and biopsy is indicated. Because of the posterior approach used for all left and some right adrenal biopsies, it is common to traverse the lung, introducing the possibility of a pneumothorax. The right adrenal gland can alternatively be targeted from a lateral, transhepatic approach to eliminate the risk of pneumothorax (Fig. 20.5).

Pancreas Biopsy

Despite the best efforts of clinicians and advances in imaging, most patients with pancreatic cancer still initially present with unresectable disease. Needle biopsy may be requested for tissue diagnosis so that treatment can be initiated, and it is essential to evaluate the preprocedure imaging carefully to determine the safest approach. An anterior approach to the pancreas may be difficult because of interposed colon, spleen, or mesenteric vessels, which we would prefer not to traverse. We often prefer a posterior, transcaval approach (Sofocleous et al, 2004) or a transhepatic approach, particularly for lesions in the head or uncinate process (Fig. 20.6).

Retroperitoneal and Pelvic Biopsy

Most retroperitoneal and pelvic biopsies are performed to determine the cause of lymphadenopathy. When the patient has a known malignancy with the proclivity to spread via retroperitoneal lymphatics, FNA biopsy is indicated, and this is easily and simply performed. When lymphoma is a consideration, biopsy specimens should be obtained either for flow cytometry or surgical pathology (cores), depending on local practice and expertise.

Occasionally, a biopsy is performed to diagnose a soft tissue mass suspected to be a sarcoma. In patients who are candidates for resection, the approach to the lesion should be discussed with the surgeon in case the surgeon plans to include the biopsy path in the resection specimen. For primary diagnosis of sarcoma, histologic material is useful for classifying the sarcoma, and core biopsy should be performed. If recurrence is the issue,

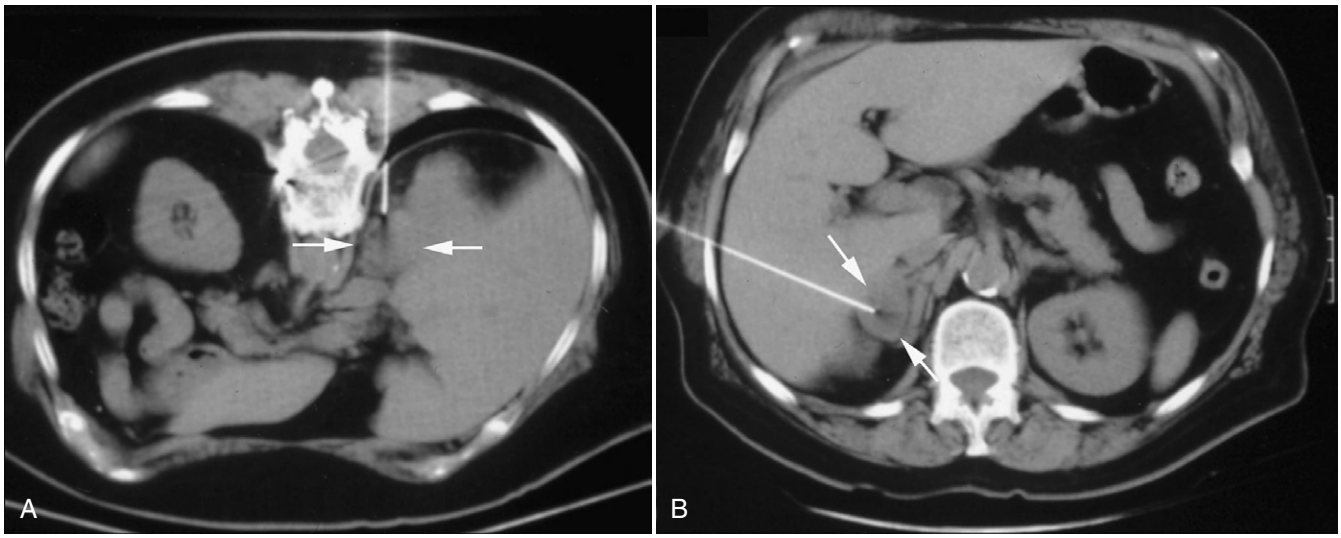


FIGURE 20.5. Adrenal biopsy. **A,** Transpeural biopsy of right adrenal mass (*arrows*). **B,** Transhepatic right adrenal mass (*arrows*) biopsy eliminates the risk of pneumothorax.

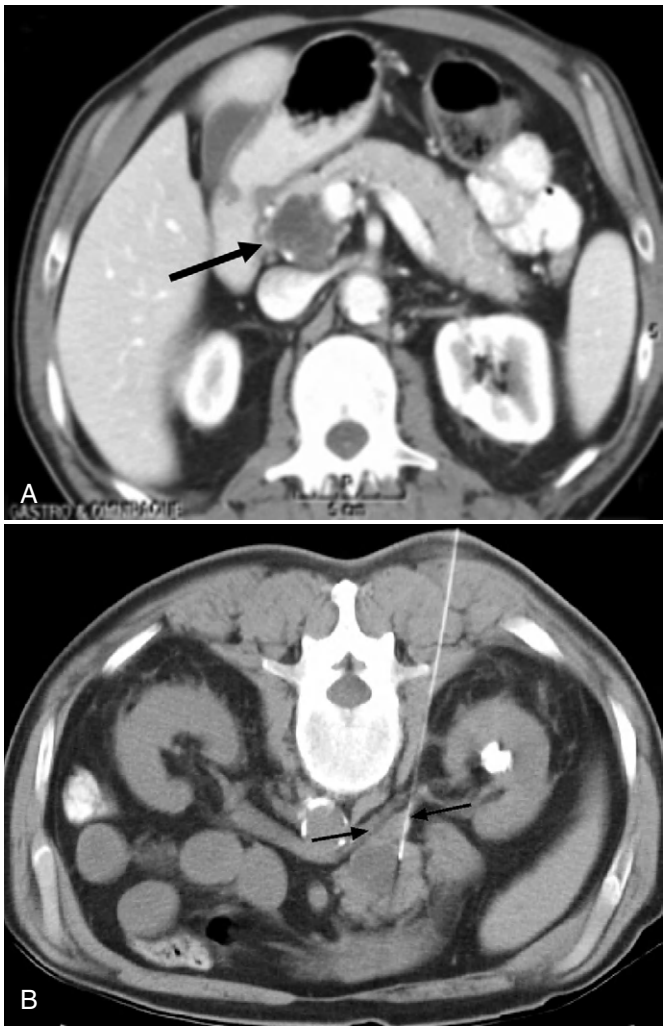


FIGURE 20.6. Transcaval pancreatic biopsy. **A,** Contrast-enhanced computed tomography scan shows a cystic mass (*arrow*) in the head of the pancreas in a patient with a history of non–small cell lung cancer. **B,** Transcaval biopsy performed in the prone position with a 22-gauge needle confirmed the diagnosis of metastasis. The inferior vena cava is indicated by the *arrows*.

the diagnosis usually can be established on the basis of cytology alone. In women with pelvic masses that might be adnexal, needle biopsy should be performed only after the diagnosis of ovarian cancer has been excluded, or after an oncologic gynecologist has been consulted. The biopsy procedure itself may result in peritoneal contamination, relegating the patient to intraperitoneal chemotherapy, when a simpler treatment regimen might have been possible. In addition to previously described guidance modalities, deep pelvic pathology is sometimes best approached using transrectal or transvaginal US guidance.

Lung and Mediastinum Biopsy

Lung biopsies can be performed with CT, CT fluoroscopy, or conventional fluoroscopy, but they are often easiest and fastest with conventional fluoroscopy. The size, location, and nature of the target lesion, as well as operator experience, determine which modality is used. Mediastinal biopsies are usually performed using CT guidance. The size of the needle used and type of specimen acquired vary depending on the clinical indication. Diagnostic rates for needle biopsy of malignant lung lesions have been reported as greater than 90% (Swischuk et al, 1998).

Bone Biopsy

Bone biopsies are typically performed using larger needles (11 to 15 gauge) than those used for organ or soft tissue. Purely lytic lesions are the exception, as small-caliber needles will often suffice to document metastases and are able to penetrate bone in the setting of cortical destruction. For surgical candidates, the biopsy path should be discussed with the surgeon to ensure that a planned procedure is not compromised by violating an uninvolved compartment.

COMPLICATIONS OF PERCUTANEOUS BIOPSY

Any invasive procedure has risks. Risks of biopsy include bleeding, pneumothorax, infection, bile leak, and needle-tract seeding of tumor. The risks vary depending on the organs involved. To

minimize the risk of bleeding, we advocate that all patients should have appropriate laboratory work before biopsy, including a complete blood count and coagulation profile. Although criteria differ from institution to institution and from physician to physician, a platelet count of greater than 50,000 μL and an international normalized ratio (INR) less than 1.5 are acceptable in most cases. Biopsy in thrombocytopenic patients can be performed with platelet coverage, although the decision to proceed with biopsy should be considered carefully. For patients with an elevated INR, transfusion of plasma or supplementation with vitamin K is required. Elevated partial thromboplastin time (PTT) in patients not on heparin usually is due to circulating antiphospholipid cardiolipins and is not typically clinically significant. A test of bleeding time may be performed to evaluate the significance of an elevated PTT in select patients. It is advisable to have patients stop antiplatelet medications, if possible, to minimize the risk of bleeding; however, the risk of stopping antiplatelet therapy must be weighed against the risk of bleeding from the biopsy; occasionally the balance favors performing the biopsy while the patient remains on the regular medication.

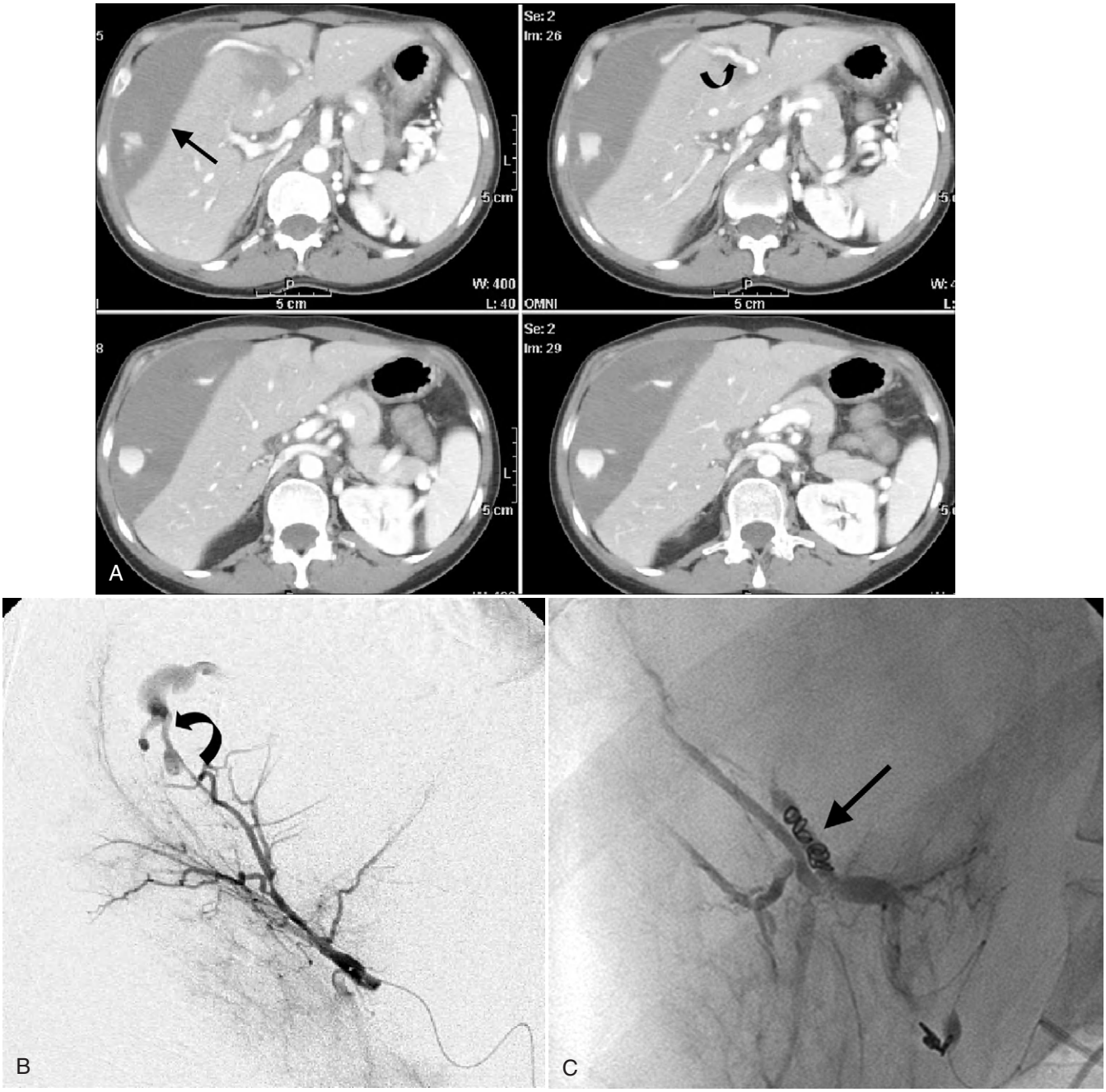


FIGURE 20.7. Hemorrhage complicating liver biopsy. **A,** Contrast-enhanced computed tomographic scan 5 days after liver biopsy shows a large subcapsular hematoma (*arrow*) with active extravasation of contrast from the liver mass (*curved arrow*). **B,** Angiography shows active extravasation (*curved arrow*) from peripheral segment VIII artery that was successfully embolized with stainless steel coils (**C;** *arrow*).

The risk of significant bleeding after liver biopsy is less than 1% (Piccinino et al, 1986; Riemann et al, 2000). In most cases, the bleeding is self-limited, and conservative management comprising observation and hydration is sufficient. In patients with more significant bleeding, hepatic angiography and potential embolization of an injured artery may be required (Fig. 20.7). Some authors advocate placing absorbable gelatin sponge (Gelfoam) pledgets in the biopsy tract through the needle after core biopsy, but this has not been shown definitively to decrease the risk of major bleeding (Hatfield, 2008).

Pain out of proportion to imaging findings after liver biopsy may be due to bile peritonitis (Ruben & Chopra, 1987). Care should be taken to minimize needle passes through the gallbladder, cystic duct, or dilated bile ducts. If the gallbladder is inadvertently punctured, it should be aspirated as completely as possible before removing the needle. Bile leaks resulting in discernible collections are rare after liver biopsy in the absence of downstream biliary obstruction.

Adrenal masses and lesions in the dome of the liver often require an approach for biopsy that crosses the lung base, putting patients at risk for pneumothorax. The two most common complications after lung biopsy include hemoptysis and pneumothorax (Westcott et al, 1997). Hemoptysis occurs in up to 30% of lung biopsies and is usually self-limited, but it can be frightening to the patient. Pneumothorax occurs in 20% to 30% of patients after biopsy and requires placement of a chest tube in approximately 6% of cases. The risk of pneumothorax is typically related more to patient than technical factors, although depth of the target lesion, number of pleural surfaces transgressed, and patient positioning (prone positioning decreases the risk of pneumothorax) have been shown to affect the likelihood. Elderly patients and patients with underlying chronic obstructive pulmonary disease are more prone to developing a pneumothorax requiring treatment (Covey et al, 2004). A symptomatic or enlarging pneumothorax is treated with a small-bore chest tube (generally 8 to 12 Fr) and occasionally necessitates hospital admission.

Hemorrhagic pericardial tamponade is a rare, potentially life-threatening complication after mediastinal biopsy (Kucharczyk et al, 1982). Although hypoxemia may be a feature, this complication can be distinguished from iatrogenic pneumothorax clinically by the development of hypotension with narrowing of the pulse pressure and diminished amplitude of the electrocardiogram complex on the monitor. The diagnosis can be confirmed immediately by scanning the heart and pericardium, and it can be treated by directly placing a drainage catheter into the pericardial space.

Needle-tract seeding after percutaneous biopsy is a worrisome complication. The interval between biopsy and appearance of a tract metastasis is 6 to 24 months (Kosugi et al, 2004; Schotman et al, 1999). The risk overall is likely greater than reported, but current understanding is that the risk in HCC is in the range of 2% to 3% (Perkins, 2007; Stigliano et al, 2007). Although the incidence is relatively small, the possibility of rendering a patient ultimately incurable because of tract or peritoneal seeding should be considered in the risk/benefit analysis for each patient. For this reason, some surgeons do not advocate percutaneous biopsy for patients with potentially resectable lesions highly suspicious for malignancy (Cha et al, 2002; Al-Leswas et al, 2008); this sentiment is particularly strong among transplant surgeons in regard to patients with HCC or other malignant disease undergoing evaluation for a new liver graft (see Chapters 97D and 97E).

CONCLUSION

Percutaneous needle biopsy is a well-established and safe diagnostic tool, and it is an important instrument in the diagnosis of tumors, for determining the cause of organ dysfunction staging, and for documenting recurrent or metastatic disease. Complications occur infrequently, and most are easily treated or self-limiting. Tract seeding has been reported but occurs infrequently. There is no such thing as a "negative" biopsy (Phillips et al, 1998). If a diagnosis of malignancy is not made, a specific benign diagnosis needs to be confirmed. If nonspecific findings are evident on cytology—including inflammatory or reactive changes, fibrous tissue, or normal site tissue—or if atypical cells are present, another biopsy should be performed, or the lesion should be closely followed up, depending on the pretest probability of disease.

The role of biopsy in patient management is evolving in tandem with the development of associated fields, including functional and molecular imaging. Until biopsies are no longer necessary, every effort should be made to keep morbidity low and diagnostic rates high.

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CHAPTER 21

Intraoperative diagnostic techniques

M.B. Majella Doyle and Wande B. Pratt

OVERVIEW

The management of hepatobiliary and pancreatic disease has evolved considerably since the 1990s. Today's operative surgeon has a number of valuable adjuncts to aid in accurate preoperative evaluation and planning for benign and malignant disease. Advances in contrast-enhanced computed tomography (CT), endoscopic ultrasound (EUS), magnetic resonance (MR) and endoscopic retrograde cholangiopancreatography (ERCP) have revolutionized the treatment of benign and malignant hepatobiliary and pancreatic disease. Despite these techniques, present-day management of these conditions relies on the appropriate use of intraoperative diagnostic modalities, particularly when confronted with challenging and unanticipated findings during surgical exploration.

Intraoperative ultrasonography (IOUS) continues to be an important component for assessing hepatic and biliary anatomy, for identifying and classifying malignant and cystic neoplasms, and for determining the resectability of malignant disease. Similarly, intraoperative cholangiography (IOC) assists the surgeon in assessing the biliary tree, its anatomy, and the occurrence of injury in both open and laparoscopic procedures. Diagnostic and staging laparoscopy (Table 21.1) have also emerged as important techniques for uncovering small-volume disease not revealed by even the most sophisticated imaging studies; however, controversy still exists regarding the true added value of the procedure (Table 21.2). This chapter will focus on these three intraoperative diagnostic modalities and their use in evaluating and managing hepatobiliary and pancreatic disease.

INTRAOPERATIVE ULTRASONOGRAPHY

IOUS is commonly used during both open and laparoscopic procedures. Particular attention must be given to port placement when IOUS will be performed laparoscopically. Ultrasonography (US) is most useful for evaluating the liver parenchyma or for assessing the extent of mesenteric vasculature involvement of pancreatic tumors (Jakimowicz, 1993). Other common applications include localization of pancreatic endocrine tumors, assessment of biliary calculi, and ablation of hepatic tumors.

Hepatic Disease

Technical Considerations

IOUS is now applied with increasing frequency during hepatic segmental or lobar resection, metastasectomy, and partial liver transplantation. It provides for more precise delineation of the spatial relationships of hepatic tumors to major vascular and biliary structures. Intraoperative transducers appropriate for liver surgery include high-frequency (6 to 10 MHz) T-shaped linear- or curvilinear-array transducers. These probes provide excellent high-resolution images and are capable of identifying lesions approximately 1 to 2 mm in size at depths of penetration of approximately 10 to 12 cm. Transducers with color-flow Doppler enable further discrimination of tumors and normal hepatic vasculature.

Techniques for IOUS continue to evolve. Typically, no coupling gel is required, because the natural surface moisture of the liver provides for adequate acoustic coupling. The transducer is initially held in a transverse position, and the survey of the liver begins by first identifying the confluence of the right and left portal pedicles. Next, all segmental pedicles on the right are visualized, then those on the left are identified. Each hepatic vein is visualized by scanning peripherally and then by traversing toward the vena cava. It is easiest to identify the hepatic veins by placing the transducer cranially, in a midline position and angled toward the heart. Only light pressure should be applied to the liver. The confluence of the left and middle vein has a characteristic appearance and should be observed in all sonographic exams. If the entire liver is to be scanned—for example, to search for metastases—sequential overlapping sagittal strokes are made, beginning at the most lateral margin of segment II and traveling toward the right. More focal scanning can be used to localize impalpable lesions situated deep within the liver parenchyma. Special care must be taken when imaging the high dome of the lateral right lobe, the posterior subdiaphragmatic bare area, and surface lesions, such as hamartomas; these areas are particularly challenging to visualize in the intraoperative setting.

Evaluation of the Liver

IOUS of the liver was first introduced into clinical practice in the early 1980s and rapidly became routine practice for management of malignant liver disease (Makuuchi et al, 1981; Nagasue et al, 1984; Gunven et al, 1985; Bismuth & Castaing, 1985; Belghiti et al, 1986; Gozzetti et al, 1986; Olsen, 1990; Gouillat et al, 1992; Solomon et al, 1992; Bloed et al, 2000). These early reports demonstrated that IOUS frequently altered the course of operative management of malignant hepatic tumors by more precisely delineating the relationship between tumors and major vascular and biliary structures and by detecting hepatic tumors not revealed on preoperative imaging studies (Fig. 21.1). In an analysis of 210 patients with primary and secondary hepatic malignancies, Bismuth and colleagues (1987) reported that IOUS provided additional information in 35% of cases and changed the operative plan in 20%. Parker and associates (1989) reported similar findings, with US influencing

Table 21.1

Benefits of Laparoscopic Staging

Shorter recovery
Shorter hospital stay
Decreased procedure-related morbidity
Improved quality of life
Shorter time to initiation of adjuvant therapy
Reduced hospital cost

Table 21.2

Potential Disadvantages of Staging Laparoscopy

Potential for morbidity
Risk of port site recurrence
Increased time of surgery and increased cost

49% of cases. A more recent analysis by Kruskal and Kane (2006) demonstrated that IOUS routinely identifies 25% to 35% more hepatic lesions than preoperative imaging studies.

It must be recognized that the yield of IOUS, particularly for identifying lesions not previously seen, depends critically on the quality of the preoperative imaging studies (see Chapters 13, 16, and 17). The results of these and other studies demonstrate the continued importance of IOUS in liver surgery for identifying and staging malignant disease.

IOUS is particularly useful for determining tumor resectability. Several reports from the 1990s have documented increased resectability rates in patients with hepatobiliary malignancy (Soyer et al, 1993; Lo et al, 1998; Jarnagin et al, 1999). More recent studies estimate that the use of IOUS will lead to changes in 15% to 25% of procedures. Regardless of these estimates, IOUS is a crucial component of the intraoperative assessment and is a useful tool in the armamentarium of liver surgeons (Zacherl et al, 2002).

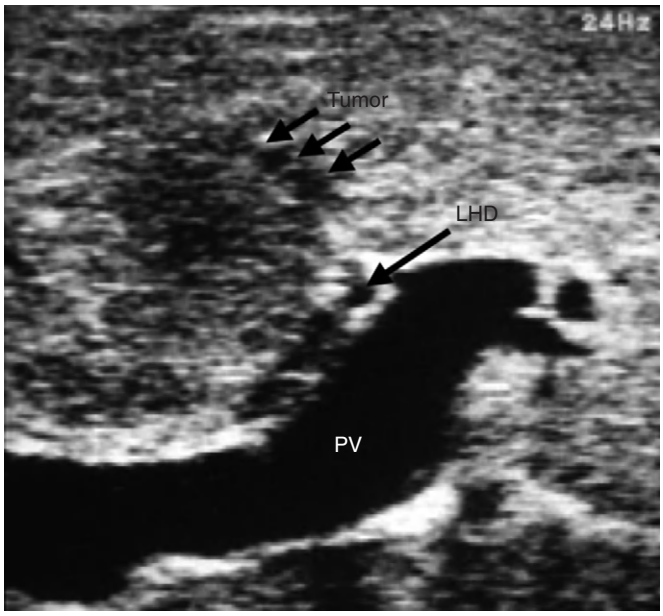


FIGURE 21.1. Intraoperative ultrasound view of a tumor (*arrows*) at the base of segment IV. The confluence of the right and left portal venous branches is shown (*PV*). Dilation of the left hepatic duct (*LHD*) is indicated and suggests possible involvement by tumor.

The sonographer must first evaluate the extent of intrahepatic disease and must then assess for vascular occlusion or invasion. Sonographic features of liver tumors vary and may be foreign to the novice sonographer. In our experience, it is prudent to communicate with radiologists preoperatively so that personnel and equipment are readily available when the surgeon is confronted with a suspicious or challenging lesion.

Recognition of malignant disease can be challenging without the assistance of trained radiologists. Hemangiomas are typically soft and usually lack any visible flow, or they demonstrate only minimal flow compared with adjacent liver parenchyma. Metastases from colon cancer are usually hyperechoic or isoechoic to adjacent liver parenchyma and are frequently surrounded by an ill-defined hypoechoic rim that may have a bull's-eye or target appearance. Mucinous colorectal cancer metastases may contain calcification that produces acoustic shadowing. Hepatocellular carcinoma (HCC) frequently invades major vascular structures and may be associated with porta hepatis lymphadenopathy (Jeffers et al, 1988). Documentation of lesions and their proximity to adjacent vessels will determine resectability. Resection margins of approximately 1 cm are generally sought and appear to be required for an oncologically adequate operation, although the optimal margin size is poorly defined. Keep in mind that an outline of the planned surgical margin with electrocautery of the liver capsule will produce acoustic shadowing and should be reserved until sonography is complete.

Biliary Disease

Technical Considerations

Evaluation of the biliary tree for the presence of common bile duct (CBD) stones is common during elective cholecystectomy. Although this is typically accomplished by cholangiogram, IOUS is a reasonable alternative that may provide comparable results. Laparoscopic US in particular has the added advantage of reducing the risk of biliary and vascular injury. The biliary tree and gallbladder are imaged best from a right subcostal port or from the periumbilical port. Sonographic exam of the gallbladder is approached through the liver using a 5- or 7-MHz transducer. The bile ducts can be visualized through a compressed duodenum or gastric antrum using a 7-MHz transducer, but placing the transducer directly on the ducts should be avoided, because reverberation artifact limits its sensitivity. Color flow images are helpful for distinguishing the CBD from the portal vein, for identifying the insertion of cystic duct into the CBD, and for identifying any aberrant biliary anatomy.

Evaluation of the Biliary Tree

As laparoscopic cholecystectomy has become the standard of care for gallbladder disease, the use of laparoscopic US during this procedure will emerge as an increasing possibility and a viable alternative to cholangiogram. Laparascopic US is now recommended as the primary screening modality for evaluating bile duct calculi because of its safety, efficiency, and overall cost effectiveness (Machi et al, 1999). IOUS is at least as good as cholangiogram, perhaps better, at detecting stones during laparoscopic cholecystectomy (Catheline et al, 1999; Siperstein

et al, 1999; Tranter & Thompson, 2003). Perry and associates recently published their results from a prospective study performed between 1995 and 2005. Laparoscopic US was performed in 236 (60%) of 396 laparoscopic cholecystectomies performed for cholelithiasis. US had a positive predictive value of 100%, a negative predictive value of 99.6%, a sensitivity of 92.3%, and a specificity of 100% for detecting CBD stones (Perry et al, 2008). Proficiency with IOUS requires some time to develop, which may explain why it is not employed more liberally for biliary disease.

Laparoscopic US is a useful adjunct for oncologic staging of gallbladder carcinoma and cholangiocarcinoma. Sonographic findings not only reveal subtle liver metastases but may help to further define the local extent of invasion of these tumors into the adjacent liver bed and also outline the involvement of the ductal system, and Doppler and color flow images may help distinguish biliary sludge from polyps and other intraluminal tumors. Other applications of laparoscopic US include evaluating biliary strictures and malignant biliary obstructions and planning of surgical reconstructions such as biliary bypass procedures. These approaches and others are summarized in a review by Berber and Siperstein (2004).

Pancreatic Disease

Technical Considerations

IOUS is commonly applied in conjunction with oncologic staging of pancreatic and periampullary tumors. When performed laparoscopically, a right upper or left upper quadrant port is used, so as to orient the probe transversely along the long axis of the pancreas. Frequently, a periumbilical port is required to image the head, neck, and uncinate process. A 7-MHz transducer is used that can be placed directly on the surface of the pancreas or through the overlying omentum.

Evaluation of the Pancreas

The principal application of IOUS for pancreatic disease is during staging laparoscopy. Its utility lies in demonstrating vascular invasion, liver metastases, and the degree of resectability. Approximately 20% to 35% of patients deemed resectable based on preoperative radiologic assessment harbor occult metastases or locally invasive disease, which preclude curative resection. These concepts will be discussed further for staging laparoscopy.

Other applications for US in pancreatic surgery include localizing islet cell tumors. These particularly small lesions may be difficult to visualize or palpate in the body or tail, and sonographic images may help delineate these and other malignant or premalignant tumors in the distal portions of the pancreas (Hayashibe et al, 2005). Finally, US can help identify pancreatic ductal abnormalities among patients with pancreatitis and may be useful during drainage procedures, such as cystogastrostomy.

INTRAOPERATIVE CHOLANGIOGRAPHY

Technical Considerations

Intraoperative cholangiography (IOC) is most commonly used during elective cholecystectomy to assess for retained stones and to provide clarification of the biliary anatomy; rarely is it necessary or helpful in assessing extent of biliary tumors or during hepatic resection (Sotiropoulos et al, 2004). Interestingly, Mirizzi first described the procedure in 1937, as a method to help delineate the anatomy of the biliary tree in advanced cases of biliary disease (Mirizzi, 1937).

IOC is typically performed by first identifying the cystic duct at its junction with the gallbladder neck (Yamakawa, 1976). The gallbladder is retracted laterally, and the cystic duct and artery are dissected free and cleared of the fat and overlying peritoneum in the area of the triangle of Calot. A small ductotomy (less than 50% of the duct circumference) is made in the cystic duct adjacent to the gallbladder neck. The cystic duct is best approached from a right subcostal port or from the periumbilical port; we prefer the former. A 60-cm, tapered 5-Fr cholangio catheter is then advanced directly into the cystic duct through the ductotomy. A specialized cholangiogram clamp, often termed an *Olsen cholangiogram clamp,* secures the catheter in place (Decker et al, 2003).

A second method of cholangiography is performed percutaneously. With this method, access to the cystic duct is achieved via a separate puncture in the abdominal wall using at least a 2-inch, 14-gauge needle. In a similar fashion, a 5-Fr cholangio catheter is guided through this needle and directly into the cystic duct. The catheter is first flushed with saline to confirm its patency, and then radiographic contrast is infused, and fluoroscopic images are obtained. A complete study demonstrates flow of contrast into the duodenum and shows opacification of both the right and left hepatic ducts.

Choledocholithiasis

Two factors must be considered when performing intraoperative cholangiography for the evaluation of retained bile duct stones (Hyser et al, 1999; Sigel et al, 1983; Tokumura et al, 2002). First, most stones in the biliary tree are suspected on clinical grounds or after serologic testing for liver enzyme elevation and are often visualized during preoperative US (see Chapter 13), ERCP (see Chapter 18), or MRCP (see Chapter 17). Common presentations include obstructive jaundice, cholangitis, biliary colic with abnormal liver function test results, and acute pancreatitis. The incidence of clinically silent choledocholithiasis is low, occurring in roughly one in 25 cases of biliary colic (Metcalfe et al, 2004; Nugent et al, 2005). Even when missed during cholecystectomy, these residual stones rarely if ever cause symptoms or become clinically relevant (Sarli et al, 2003a; see Chapters 30 and 35). Charfare and Cheslyn-Curtis (2003) investigated the incidence of retained biliary stones after 600 laparoscopic cholecystectomies. With a median follow-up of 3 years among 438 patients (73%), findings from this study indicate that residual bile duct stones occurred in only seven cases (1.2%).

The second factor to consider when performing IOC is that false-positive results are not uncommon, occurring up to 4% of the time (Metcalfe et al, 2004). As a result, routine application of IOC for the evaluation of unsuspected choledocholithiasis may subject patients to unnecessary bile duct explorations or ERCP studies, with considerable costs to both patients and providers (Cuschieri & Berci, 1984; Sarli et al, 2003b).

Biliary Injuries

In the late 1980s, IOC emerged as a method that could potentially help avoid major injury to the biliary system. Today laparoscopic cholecystectomy is the most commonly performed elective abdominal surgical procedure in the United States (see

Chapter 34), with more than 750,000 cases performed annually. Injury to the bile duct is rare but is a major contributor to patient morbidity (see Chapter 38). These injuries are typically due to either technical error or misidentification of the duct: the technical error is that the CBD is inadvertently transected, and a surgical clip is sometimes applied to a misidentified CBD.

Four mechanisms of injury have been described (Way et al, 2003). Class I injuries involve an incision (i.e., an incomplete transection) of the CBD and typically occur when the bile duct is mistaken for a cystic duct. Class II injuries represent lateral damage to the common hepatic duct. Class III injuries are the most common and represent a CBD mistaken for a cystic duct; these are not immediately recognized intraoperatively. Finally, class IV injuries occur when a right hepatic duct is mistaken for a cystic duct.

Flum and colleagues (2003) analyzed nationwide Medicare data from 1992 to 1999. Among 1.6 million cholecystectomies performed, roughly 8000 bile duct injuries occurred overall (0.5%); these occurred in 0.39% of patients undergoing cholecystectomy *with* intraoperative cholangiogram and in 0.58% of patients undergoing cholecystectomy *without* cholangiogram ($P < .001$). The adjusted relative risk of bile duct injury when cholangiogram was not employed was 1.71 (95%, confidence interval [CI], 1.38 to 2.28). Inexperienced surgeons were twice as likely to cause bile duct injuries when cholangiogram was not used, as compared with their more experienced colleagues. These estimates had been observed in an earlier study (Fletcher et al, 1999).

Another benefit of intraoperative cholangiogram, with respect to biliary injuries, is the earlier recognition and correction of biliary injury (see Chapters 42A and 42B). Ideally, IOC should be performed prior to dividing the presumed cystic duct. If cannulation of the CBD, rather than the cystic duct, occurs, the cholangiogram catheter can be removed, and the ductotomy can be addressed by placing a T-tube, without the need for formal biliary reconstruction. The T-tube enables the CBD to heal without stricture formation, and the tube can be removed nonoperatively several weeks after the cholecystectomy. The alternative scenario is complete transection of the CBD, a class III injury. In the absence of cholangiogram, this transection is seldom recognized intraoperatively, typically presents postoperatively, and results in significant patient morbidity. Management undoubtedly requires an open bilioenteric anastomosis for repair, thus intraoperative cholangiogram has the potential to not only prevent bile duct injury but also to mitigate its impact if injury does occur (Giurgiu et al, 1999).

Controversies

The routine application of IOC during elective cholecystectomy has been called into question in recent years and is still a matter of considerable debate (Mills et al, 1985; Soper & Brunt, 1994; Nickkholgh et al, 2006; Metcalfe et al, 2004; Massarweh & Flum, 2007). Critics of routine cholangiogram suggest that such an approach increases the risk of ductal complications (i.e., stricture) and pancreatitis, wastes time and money, and is seldom indicated if the critical view of safety is achieved. Proponents argue that routine cholangiogram is a safe, accurate, quick, and cost-effective method for evaluating the bile duct (Amott et al, 2005; Wenner et al, 2005). Although we favor a selective approach, we also recognize that the success of either approach is highly variable and likely to depend on each surgeon's familiarity with cholecystectomy and cholangiography. Whether a selective or routine cholangiogram policy is adopted, it is critical that surgeons become comfortable with interpreting cholangiogram results. Way and others (2003) reported that although 43 cholangiograms demonstrated a bile duct injury, only nine were correctly interpreted at the time of surgery.

STAGING LAPAROSCOPY

Management of hepatobiliary and pancreatic malignancies is contingent upon accurate oncologic staging to identify patients who might harbor curable disease. Despite refinements in several diagnostic modalities that include but are not limited to EUS, ERCP, high-resolution CT, and MRCP, few patients are appropriate candidates for curative resection. Oncologic staging seeks to determine tumor size and characteristics, the extent of regional spread to adjacent structures, and the magnitude of any distant spread.

The growth in popularity of laparoscopy in the early 1980s added a new modality to the field of hepatobiliary and pancreatic surgery. Specialty surgeons in these disciplines frequently confront occult, unresectable disease at the time of laparotomy (de Rooij et al, 1991; Espat et al, 1999; Lillemoe et al, 1999). Reports vary, but this scenario occurs roughly 20% to 25% of the time. Jarnagin and associates (2000) demonstrated that among a cohort of 186 patients with primary and secondary hepatic malignancies, 25% were noted to harbor unresectable disease at the time of laparoscopic staging, and 65% of this group were spared an unnecessary laparotomy. Callery and colleagues (1997) similarly revealed unresectable pancreatic and periampullary disease among 11 of 50 patients, and comparable outcomes have been described by others (D'Angelica et al, 2003; Vollmer et al, 2002). Overall, these findings demonstrate that staging laparoscopy can further clarify whether curative resection is possible, confirm unresectable disease, and help specialty surgeons tailor curative and palliative operations for patients with hepatobiliary and pancreatic malignancies (see Table 21.1). Controversy still exists, however, regarding the true added value of the procedure, particularly in an era of more effective preoperative imaging (see Table 21.2).

Surgical Technique

Technical Considerations

Staging laparoscopy is typically performed under general anesthesia. The patient is placed supine on the operating table and fully prepared as for laparotomy. The abdomen is marked for the intended open incision; at our institution, we favor a bilateral subcostal incision two to three fingerbreadths below the costal margin. In the case of pancreatic disease, access to the peritoneum is made through a 1-cm subumbilical incision; for hepatobiliary cases, a 1-cm incision is made along the midclavicular line. For both, the fascia and peritoneum are incised under direct vision, a blunt 5- or 10-mm port is placed, and insufflation is begun with the initial flow rate set at 2 L/min and gradually increased to 15 L/min to achieve an intraabdominal pressure of 10 to 14 mm Hg.

We use a 5- or 10-mm, 30-degree angled telescope to inspect the abdomen. Although we prefer a multiport technique to facilitate obtaining biopsy specimens and laparoscopic US, others may use a single-port approach. Two more ports are placed under direct vision, in the left and right upper quadrants. For pancreatic cases, another 5-mm port is inserted along the

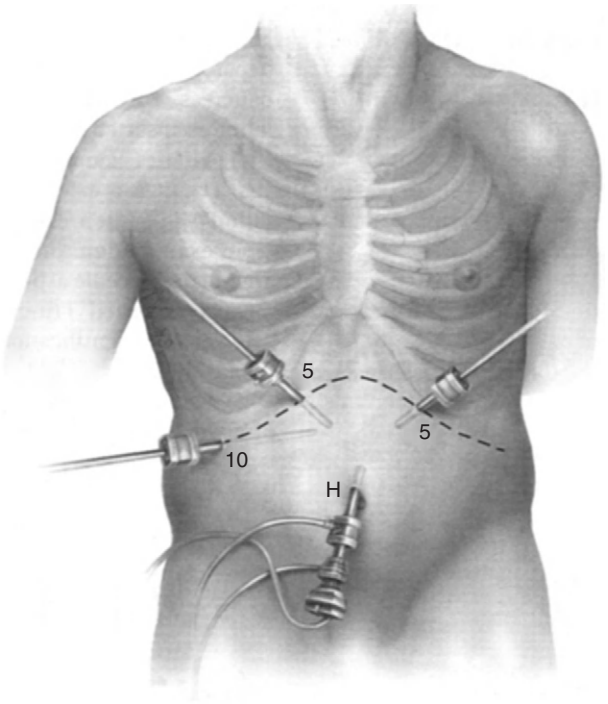


FIGURE 21.2. Port placement for laparoscopic staging. For patients undergoing staging for hepatobiliary diseases, the camera may be placed along the line of a subcostal incision.

incision line to the right of the midline (Fig. 21.2). Entry of these ports is followed by a systematic examination of the peritoneal cavity; adhesions may need to be divided to adequately inspect the abdominal viscera and peritoneum. All four quadrants are examined for evidence of peritoneal deposits; biopsies are taken of any suspicious lesions using standard biopsy forceps, and samples are sent for histologic examination (Fig. 21.3). If clinically indicated, peritoneal cytology can be sampled at this time. After instillation of 200 mL of warm normal saline

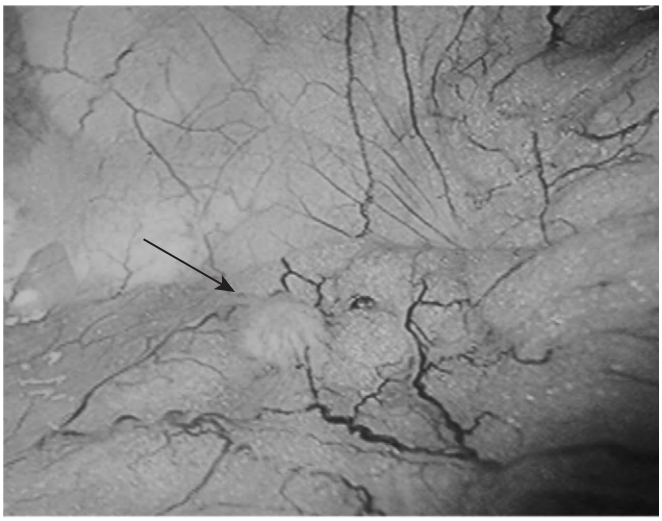


FIGURE 21.3. Peritoneal nodule. *Arrow* indicates a metastatic deposit, which can be sampled easily using a cup forceps to obtain a biopsy.

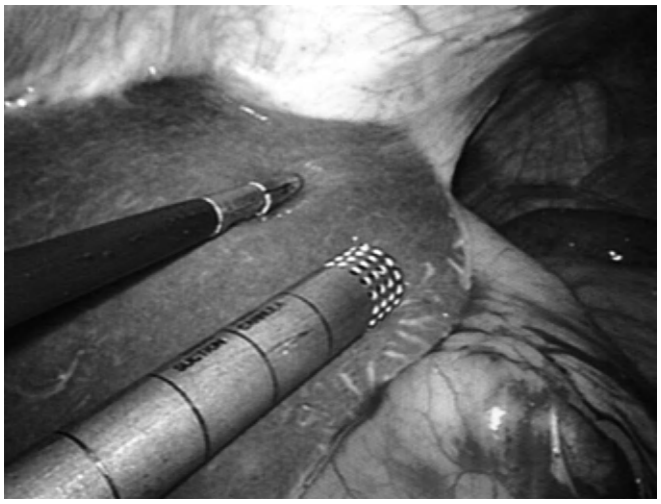


FIGURE 21.4. Examination of the liver. A blunt 10-mm instrument is used in conjunction with a 5-mm grasper.

and gentle agitation, the irrigant is aspirated from the right and left subhepatic spaces and from the pelvis, and a sample is sent for cytologic examination.

Following inspection of the peritoneum, attention is turned to the anterior and posterior surfaces of the left lateral segment of the liver and the anterior and inferior surfaces of the right lobe (Fig. 21.4). Next, the hepatoduodenal ligament, the foramen of Winslow, and hilum of the liver are examined for lymphadenopathy (Fig. 21.5). Any suspicious nodes are excised and sent for pathologic analysis. The patient is then placed in the 10-degree Trendelenburg position, and the omentum is retracted into the left upper quadrant. The ligament of Treitz and the inferior surface of the transverse mesocolon are inspected for metastatic deposits and for lymphadenopathy (Fig. 21.6).

The patient is repositioned in the supine position, and the left lateral segment of the liver is elevated superiorly with a

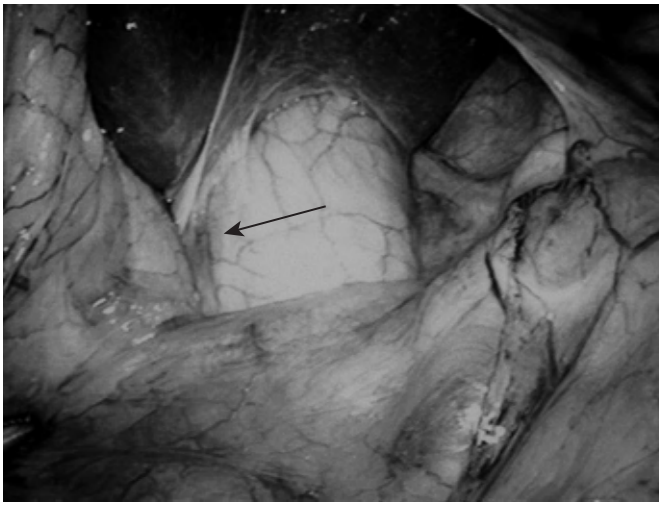


FIGURE 21.5. The hepatoduodenal ligament can be examined from the left (shown) or right side. Periportal adenopathy (*arrow*) is shown.



FIGURE 21.6. Examination of the ligament of Treitz. Proximal jejunum (*solid arrow*) and inferior mesenteric vein (*dashed arrow*) are shown.

retractor via the left upper quadrant port. The lesser omentum is opened to visualize the caudate lobe of the liver and the vena cava. From this vantage point, the anterior aspect of the head of the pancreas, posterior wall of the stomach, and "gastric pillar," which contains the left gastric artery and vein, can be seen (Fig. 21.7). The left gastric artery can be followed to its origin so as to allow inspection of the celiac axis (Table 21.3).

Laparoscopic Ultrasound

US can help the surgeon further assess the relationships of the primary tumor to adjacent structures (see Chapter 13). A systematic examination of the liver, biliary tree, and pancreas takes place as previously described. A 6- to 10-MHz T-shaped linear- or curvilinear-array transducer is placed over the left lateral segment to assess segments I, II, and III. The probe is moved to the right liver and placed on the dome of the liver. The vena cava is visualized posteriorly, and the hepatic and portal veins are seen as the probe is moved anteriorly.

Placement of the probe in the transverse direction over the hepatoduodenal ligament allows the common hepatic duct, CBD, hepatic arteries, and portal vein to be visualized (Fig. 21.8). Similarly, at the confluence of the portal vein, the splenic and superior mesenteric veins can be identified. Finally, the superior mesenteric artery is delineated, and its relationship to any pancreatic tumor is assessed. The probe is placed on the gastrocolic omentum and advanced first caudally and then through the window in the gastrohepatic omentum. Laparoscopic US can help facilitate pathologic biopsies and needle aspirations of any suspicious lesions (Fig. 21.9, Table 21.4).

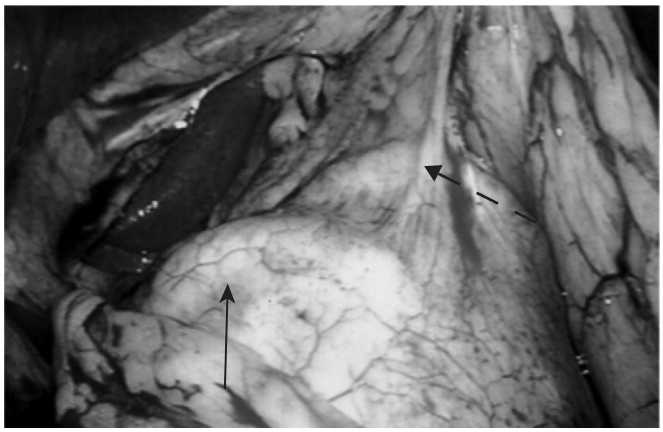


FIGURE 21.7. Lesser sac. The "gastric pillar" (*dashed arrow*) and hepatic artery (*solid arrow*) are shown.

Table 21.3

Steps for Staging Laparoscopy

Examination of peritoneal cavity
Placement of laparoscopic trocars
Instillation of 200 mL of normal saline and aspiration of cytologic specimens
Assessment of primary tumor
Examination of the liver and porta hepatis
Division of gastrohepatic omentum and examination of caudate lobe, vena cava, celiac axis, and lesser sac
Identification of the ligament of Treitz and inspection of the mesocolon, duodenum, and jejunum
Laparoscopic ultrasound

From Conlon KC, Brennan MF, 2000: Laparoscopy for Staging Abdominal Malignancies. St Louis, Mosby.

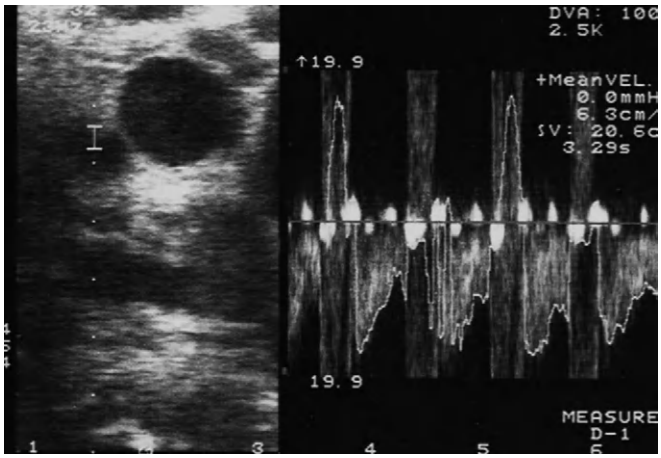


FIGURE 21.8. Laparoscopic ultrasound of the hepatoduodenal ligament. Doppler capability facilitates identification of the hepatic artery.

Complications

Morbidity associated with staging laparoscopy is uncommon, occurring in only 1% to 2% of cases. Major complications are similar to those for other laparoscopic procedures and consist of

Table 21.4

Steps for Laparoscopic Ultrasound

Insertion of laparoscopic ultrasound probe
Examination of liver: left lateral segment, right lobe
Transverse scan of hepatoduodenal ligament
Identification of superior mesenteric artery, portal vein, splenic vein
Examination of pancreas
Assessment of tumor

From Minnard EA, et al, 1998: Laparoscopic ultrasound enhances standard laparoscopy in the staging of pancreatic cancer. Ann Surg 228:182-187.

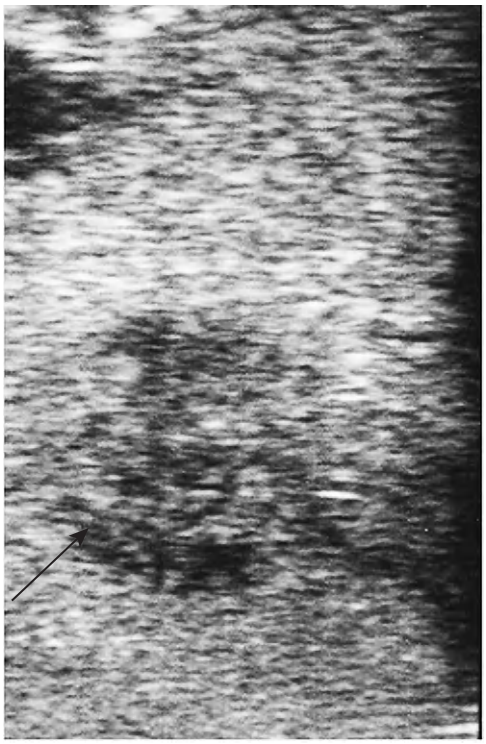


FIGURE 21.9. Hepatic metastasis (*arrow*) in a patient with pancreatic adenocarcinoma.

hemorrhage, visceral perforation, and intraabdominal infection. A common misconception is that suspected malignancy precludes staging laparoscopic examination. An early report raised concern about "port site" tumor implants 2 weeks after laparoscopy in a patient with malignant ascites (Dobronte et al, 1978); this concern was also expressed by later studies in the 1990s, which report rates of port-site recurrence ranging from 0.8% to 2% (Curet, 2004; Nieveen van Dijkum et al, 1999; Pearlstone et al, 1999). Shoup and colleagues (2002) examined this question in a series of 1650 diagnostic laparoscopic procedures, in which 4,299 trocars were inserted. The overall rate of port site recurrence was 0.8% (13 cases); five of those occurred in patients with local disease; the remaining eight occurred in patients with documented metastatic disease. The findings of this study suggest that recurrence is a marker of more advanced disease rather than being an isolated event directly attributable to laparoscopy. Overall, Shoup and associates concluded that staging laparoscopy can be performed safely in the setting of presumed malignancy. This concept has been confirmed by others, most recently by Velanovich (2004), who demonstrated that the incidence of port site recurrence (3%) is equivalent to that of wound recurrence in patients who had an exploratory laparotomy alone (3.9%).

Staging Laparoscopy for Potentially Resectable Disease

Hepatobiliary Malignancy

Determination of resectability of hepatobiliary malignancy begins with CT or MRI; however, laparoscopy plays an essential role in detecting occult disease (Jarnagin et al, 2001a; Jeffers et al, 1988; Lightdale, 1982; Torzilli et al, 2002). Roughly 20% to 25% of patients initially believed to have resectable disease will harbor occult disease detected by laparoscopy that precludes curative resection (Conlon et al, 2003; Weber et al, 2002). As a result, one in five patients is spared a laparotomy. When combined with laparoscopic US, these outcomes are more specific.

In addition to the quality of the preoperative imaging, the yield of laparoscopy will depend critically on the underlying disease. For example, hilar cholangiocarcinoma is frequently unresectable, based on local tumor extent, which is difficult to determine laparoscopically; it infrequently gives rise to peritoneal disease, which relatively easy to identify laparoscopically. The yield of laparoscopy is therefore lower than for other diagnoses, such as gallbladder cancer.

D'Angelica and others (2003) have provided a detailed analysis of staging laparoscopy for suspected hepatobiliary malignancy. Among 401 patients, a complete laparoscopic staging assessment was performed in 291 cases (73%), an incomplete assessment was done in 88 cases (22%), and 22 (6%) were failed examinations. Unresectable disease was discovered at the time of laparoscopy in 84 cases, for an overall incidence of 21%. Of the remaining 317 patients felt to have resectable disease during laparoscopic examinations, 69 had unresectable disease identified during open exploration, for an overall false-negative rate of 22%. This high false-negative rate was attributed primarily to failure to identify lymph node metastases or to detect vascular invasion. However, despite these outcomes, staging laparoscopy increased the resectability rate from 62% to 78%. Concomitant laparoscopic US has the potential to further increase resectability rates and to avoid unnecessary laparotomies, added benefits that have been described by several other studies (John et al, 1994; Callery et al, 1997).

Laparoscopy is most accurate for identifying peritoneal deposits (80% accuracy) and additional hepatic disease (63% accuracy), and it is least accurate for identifying nodal metastases (7% accuracy) and vascular invasion (18% accuracy). Factors that could improve the yield from laparoscopy include the surgeon's preoperative judgment regarding the likelihood of resectability, the completeness of laparoscopic staging examinations, and the primary diagnosis; the yield was highest with biliary malignancies and lowest with colorectal metastases (D'Angelica et al, 2003).

Laparoscopic staging can be used for management of colorectal metastases (Rahusen et al, 1999; see Chapter 81A). Approximately one half of all patients with new diagnoses of colorectal cancer will subsequently develop liver metastases, yet only 20% are suitable candidates for curative hepatic resection. Determination of resectability is less straightforward for these patients, and the controversy relates to the philosophy and expertise of the surgical team. In general, however, most authors agree that hepatic cirrhosis, extrahepatic tumor spread, and significant bilobar disease are relative contraindications for hepatic resection. A recent study explored the role of staging laparoscopy in 51 patients with colorectal liver metastases (de Castro et al, 2004). Occult disease at the time of laparoscopy was discovered in 12% of patients; however, 18% of cases were understaged, and unresectable disease was found at subsequent laparoscopy. The authors suggested that adhesions from prior colon resections contribute to this false-negative rate.

In an effort to improve the yield of staging laparoscopy for hepatic colorectal metastases, a study used a clinical risk score to try to determine which patients are more likely to have nonradiologically detectable disease. The clinical risk score uses five

Table 21.5

Criteria for Clinical Risk Score to Determine Risks for Extrahepatic Disease

Lymph node–positive tumor
Disease-free interval between primary and detection of metastasis: <12 mo
Number of hepatic tumors: >1 (based on preoperative imaging)
Carcinoembryonic antigen: >200 ng/mL within 1 mo of surgery
Size of the largest hepatic tumor: >5 cm

From Jarnagin WR, et al, 2001b: A clinical scoring system predicts the yield of diagnostic laparoscopy in patients with potentially resectable hepatic colorectal metastases. Cancer 91:1121-1128.

Table 21.6

Criteria for Unresectability in Pancreatic Cancer

Histologically confirmed hepatic, serosal, peritoneal, or omental metastases
Tumor extension outside pancreas
Celiac or high portal node involvement confirmed by frozen section
Extensive portal vein involvement by tumor or invasion/encasement of celiac axis, hepatic artery, or superior mesenteric artery

Data from Conlon KC, Brennan MF, 2000: Laparoscopy for Staging Abdominal Malignancies. St Louis, Mosby; and Conlon KC, Minnard EA, 1997: The value of laparoscopic staging in upper gastrointestinal malignancy. Oncologist 2:10-17.

clinical parameters: each is shown as an independent predictor of outcome after resection, and each criterion is assigned one point. Forty-two percent of patients with a clinical risk score greater than 2 had unresectable disease detected at laparoscopy versus 0% of patients with clinical risk score scores of 0 to 1 (Table 21.5; Grobmyer et al, 2004; Jarnagin et al, 2001b). Targeting laparoscopy to high-risk patients should avoid unnecessary laparoscopic staging in low-risk patients, whereas performing it in the high-risk group should prevent needless staging laparotomies and improve the yield overall from laparoscopy.

Pancreatic and Periampullary Malignancy

Our approach for the staging of pancreatic adenocarcinoma is illustrated in Figure 21.10. A minority of patients (20% to 35%) with pancreatic and periampullary malignancies (see Chapters 58 and 59) are suitable for curative resection (Conlon & Minnard, 1997; Conlon & Brennan, 2000; Jimenez et al, 2000). Similar to management of hepatobiliary malignancies, initial diagnostic evaluation begins with high-resolution CT. Today's studies can predict resectability in 57% to 88% of cases (Freeny, 2001; Pisters et al, 2001; Contreras et al, 2009; Mayo et al, 2009). Other useful investigative modalities that may augment CT evaluations include MRI, MRCP, ERCP, EUS, and positron emission tomography (PET).

Cuschieri and colleagues first described staging laparoscopy for pancreatic malignancy in 1978; they revisited it later, in 1988. In the earlier report, laparoscopic examinations demonstrated that 42 (57%) of 73 patients had unresectable disease, mainly peritoneal or omental metastases. Since these landmark papers, technologic advances have allowed laparoscopic staging to develop so as to allow it to be comparable to open exploration in defining resectability (Table 21.6). In 1993, Conlon and associates from Memorial Sloan-Kettering Cancer Center introduced laparoscopic staging for patients with suspected adenocarcinoma of the pancreas (Conlon et al, 1996). Prior to 1993, only about one third of patients considered to harbor resectable disease after preoperative assessment ultimately underwent curative resection procedures. Between 1993 and 1998, this rate increased considerably to roughly 63%.

Other groups have reported similar findings. Warshaw and colleagues (1990) compared CT, MRI, angiography, and laparoscopy in 88 patients and found that CT failed to show peritoneal disease in 22 cases discovered at laparoscopy. MRI conferred no further benefit, and laparoscopy had a sensitivity of 96%, having understaged 1 patient. This same group reported

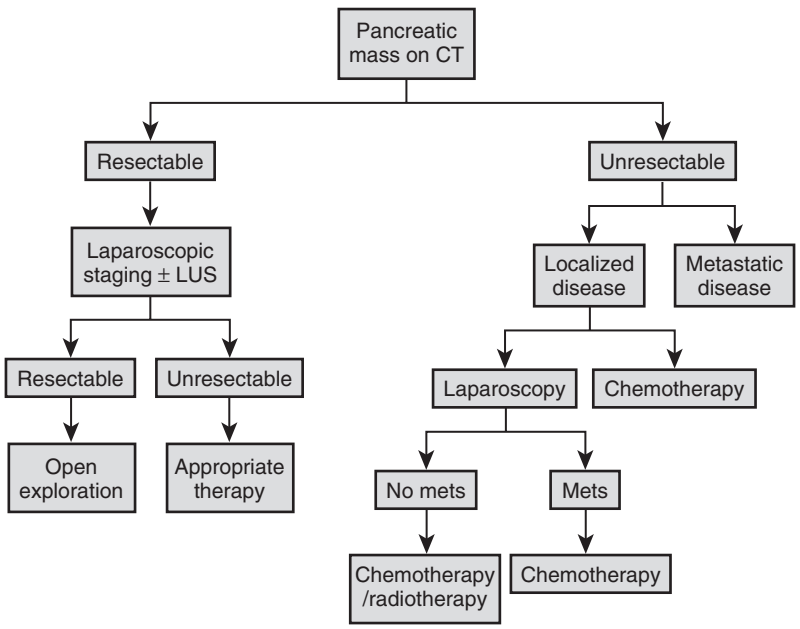


FIGURE 21.10. Use of laparoscopic staging in the management of adenocarcinoma of the pancreas. CT, computed tomography; Mets, metastases; LUS, laparoscopic ultrasound.

Table 21.7

Reviews on Staging Laparoscopy for Pancreatic Cancer

Reference	N	No. Resectable on CT	No. Resectable on CT but Unresectable at Laparoscopy	Laparoscopy Changed Operative Plan (%)
Reddy et al, 1999	109	99	29	29
Jimenez et al, 2000	125	70	39	31
Conlon & Brennan, 2000	577	577	211	36
Vollmer et al, 2002*	72	72	22	31
Doran et al, 2004	305	190	28	15
Contreras et al, 2009†	58	58	18	31
Mayo et al, 2009†	86	86	24	28

*Excluding ampullary malignancies
†Pancreatic adenocarcinoma only (including head and body/tail)

that 39 patients (44%) were spared a laparotomy because of metastases discovered at laparoscopy not seen on spiral CT. This group performed staging laparoscopy as a day-case procedure, further reducing inpatient hospital time. Reddy and associates (1999) confirmed these findings in a later report; 29% were spared further intervention. A more recent prospective study (Doran et al, 2004) reported outcomes of 239 patients with pancreatic cancer who were submitted to staging laparoscopy; of these, 190 were considered to have resectable disease based on CT findings. After staging laparoscopy, roughly 15% of patients were spared a laparotomy. This estimate likely reflects advancements in high-resolution imaging, but it also demonstrates that despite refinements in imaging techniques, peritoneal disease is not easily revealed on CT.

Beyond these estimates, staging laparoscopy enables the surgeon to more easily detect occult metastases (Shoup et al, 2004). Contreras et al (2009) discovered further that within a 4-year period, occult metastases among 52 patients with potentially resectable pancreatic tumors were more likely to be detected during staging laparoscopy when compared with open explorations (32% vs. 18%). Many other centers have reported similar results (Table 21.7).

Laparoscopic ultrasound is a useful adjunct during staging laparoscopy. John and colleagues (1995) demonstrated that the addition of US improved the sensitivity from 65% to 80%. Callery and associates (1997) similarly reported 96% specificity and 92% sensitivity when laparoscopic US was combined with staging laparoscopy. Vollmer and others (2002) studied 72 patients with pancreatic head cancers and found that 22 had metastatic disease that precluded resection; laparoscopy alone identified 14 of these 22 patients; the remaining 8 patients had major vessel encasement or liver metastases revealed by laparoscopic US. Minnard and colleagues (1998) similarly reported that laparoscopic US altered the planned surgical treatment in 14% of patients, whose staging laparoscopic procedures were equivocal. Sonography was particularly useful in identifying venous (42%) and arterial (38%) involvement, which precludes curative resection.

Controversies

Some critics of routine staging laparoscopy believe that unresectable disease due to vascular involvement or local extension can only be confirmed during open explorations (Friess et al, 1998). Others suggest that the role for laparoscopy is limited only to those patients who do not require some form of palliation, either biliary or gastric bypass (Holzman et al, 1997; Andren-Sandberg et al, 1998). Finally, some argue that staging laparoscopy is costly, time consuming, and of decreasing diagnostic yield because of improvements in radiologic imaging techniques (Spitz et al, 1997).

Two recent studies suggested that the utility of staging laparoscopy depends on the type of malignancy (Vollmer et al, 2002; Brooks et al, 2002). Staging laparoscopy has not been shown to be useful among patients with ampullary or duodenal tumors, because these cancers tend to present earlier and are less likely to have metastatic disease at the time of presentation. In contrast, staging laparoscopy may have a role in patients with nonfunctioning islet cell tumors (Hochwald et al, 2001), which manifest with a large tumor mass and often in the presence of metastatic disease.

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CHAPTER 22

Intraoperative and immediate postoperative management

Mary Fischer and Jose A. Melendez

OVERVIEW

Improvements in patient selection criteria and advances in hepatic surgical techniques and perioperative care have expanded the pool of patients who are candidates for hepatobiliary surgical procedures. Patients with known underlying hepatic parenchymal disease are at greater operative risk, particularly for liver-related and biliary tract–related procedures (see Chapters 2, 70B, and 90A). More recent studies have documented the progressive safety of liver resection in noncirrhotic patients (Belghiti et al, 2000; Jarnagin et al, 2002; Mullen et al, 2007). The anesthetic problems in connection with liver transplantation (Chapter 97B) and cirrhosis (Chapter 90A) are discussed elsewhere in this book. This chapter addresses the unique anesthetic considerations of noncirrhotic patients undergoing hepatobiliary operations, with an emphasis on problems related to joint anesthetic and surgical management.

PREOPERATIVE EVALUATION

With the advent of modern techniques, the anesthetic risk attributed to any surgical procedure depends heavily on the preoperative status of the patient. In hepatobiliary patients, the presence of preoperative pulmonary, cardiac, or hepatic disease significantly augments the incidence of postoperative morbidity and mortality. Although in the past, the presence of comorbidities favored elective intensive care unit (ICU) admission, currently they more appropriately designate a select group of patients who may potentially fail fast tracking. These patients need to be recognized at the preoperative visit and clinically optimized before surgery. Postoperative morbidity adversely affects long-term outcome after hepatic resection, therefore efforts aimed at reducing perioperative morbidity will likely further enhance the therapeutic benefit of resection (Ito et al, 2008).

Cardiac Evaluation

Patients undergoing liver surgery are at significant risk of cardiovascular morbidity and mortality. Although the perioperative event rate has declined as a consequence of better anesthetic and surgical techniques, perioperative cardiac complications remain a significant problem. The first step in preoperative care is to identify patients at risk for perioperative cardiac events. The risk of perioperative cardiac complications is the summation of an individual patient's risk and the cardiac stress related to the surgery. Clinical history, physical examination, and review of the electrocardiogram usually provide enough data to estimate cardiac risk. Active cardiac conditions may preclude all but emergent surgery.

For most stable patients, cardiac risk can be derived from the Revised Cardiac Risk Index (Lee et al, 1999b). This simple index identifies six independent risk factors: 1) high-risk type of surgery, 2) history of ischemic heart disease, 3) history of congestive heart failure, 4) history of cerebrovascular disease, 5) diabetes mellitus, and 6) renal insufficiency. The number of clinical risk factors, the risk level of the surgery, and the functional capacity of the patient will determine the need for further testing prior to surgery or pharmacologic intervention perioperatively (Poldermans et al, 2008). For those patients with clinical risk factors, the 2007 American College of Cardiology/American Heart Association guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery are an excellent framework for evaluating cardiac risk in the perioperative period for patients undergoing liver surgery (Fleischer et al, 2007).

Over the years, a shift in perioperative management has been seen, away from treating coronary obstruction with interventions such as surgery and stents and toward medical therapy aimed at stabilizing coronary plaque and preventing myocardial oxygen supply and demand mismatch. Today, preoperative cardiac testing, cardiac stenting, and coronary revascularization are performed for the same indications as those used in the nonoperative setting (Poldermans et al, 2008), but β-blockers, statins, and aspirin are now widely used in the perioperative setting. Compelling evidence supports perioperative β-blocker therapy, unless contraindicated, in patients with coronary artery disease. β-Blocker therapy has been shown to reduce the incidence of perioperative ischemic events and myocardial infarction (Goldman, 2001; Lee et al, 1999a). Recently the risk benefit of this therapy in patients without coronary artery disease has been challenged. The perioperative ischemic evaluation (POISE) study showed an increased incidence of ischemic stroke in combination with intraoperative bradycardia and hypotension (Devereaux et al, 2006). In a retrospective review of patients who underwent noncardiac surgery, perioperative β-blockers showed no benefit—and possible harm—in low-risk patients, but in high-risk patients, a benefit was seen (Lindenauer et al, 2005).

Communication among the patient's cardiologist, surgeon, and anesthesiologist is essential for the management of hepatobiliary surgical patients who have coronary artery stents. Clinical judgment is of the utmost importance to balance the risk–benefit ratio of antiplatelet therapy interruption versus continuation. Aspirin should never be interrupted, unless the risk of bleeding far outweighs the risk of stent thrombosis (Newsome et al, 2008).

In hepatobiliary patients with a history of alcohol abuse, cardiac assessment should include the evaluation of

myocontractile function. Cirrhotic cardiomyopathy classically occurs in men 30 to 55 years old who have been alcohol abusers for more than 10 years (Braunwald, 1997). Putative mechanisms of damage are direct toxic effects of 1) ethanol and its metabolite acetaldehyde; 2) nutritional deficiencies, particularly of thiamine (beriberi); and 3) additives in commercial products, such as cobalt in beer. Alcohol and acetaldehyde have been shown to decrease calcium binding and transport, myocardial lipid metabolism, myocardial synthesis, and myocardial adenosine triphosphatase (ATPase) activity. The two basic patterns of cardiac dysfunction are 1) left ventricular dilation with impaired systolic function and 2) left ventricular hypertrophy with diminished compliance and normal or increased contractile performance. Presenting manifestations range from insidious onset to catastrophic left-sided cardiac failure. Anginal chest pain does not occur, unless the patient has concomitant coronary artery disease or aortic stenosis.

Pulmonary Evaluation

Despite steady advances in care, patients with respiratory disease remain at increased risk for postoperative pulmonary complications (PPCs). Indeed postoperative pulmonary complications may rival cardiovascular complications in frequency and severity (Lawrence et al, 1995). Studies that examine risk factors for PPCs have limitations, but some consistent patterns are seen. The three most important risk factors for PPCs are 1) pulmonary disease, 2) cigarette smoking, and 3) the site of surgery, with abdominal surgery being one of the highest risk sites (Warner, 2000). Of note, pulmonary function testing per se is not useful in predicting risk (McAlister et al, 2003); thus routine pulmonary function testing is not justified unless it is part of an effort to optimize preoperative pulmonary status. The definition of "optimization" depends on the type of respiratory disease and the individual patient. Consultation with the surgeon and pulmonologist will help determine whether a course of systemic corticosteroids or antibiotics is warranted perioperatively. Despite the increased risk of PPCs in patients with preexisting pulmonary disease, no prohibitive level of pulmonary function has been established for which surgery is contraindicated (Nunn et al, 1988; Kroenke et al, 1993). A prospective study did not find an elevated $Paco_2$ level to be a risk factor among surgical candidates, hence clinicians should not use arterial blood gas analyses to identify patients for whom the risk of surgery is prohibitive (Kearney et al, 1994).

Obese patients are at risk of suffering from a number of respiratory derangements, including obstructive sleep apnea (OSA), obesity hypoventilation syndrome, and restrictive impairment. The increase in body mass also results in increased oxygen consumption and carbon dioxide production. With these isssues in mind, it is not surprising that acute PPCs are twice as likely in obese and OSA patients (Rose et al, 1994; Dindo et al, 2003). Many patients with OSA are undiagnosed, but a strong relationship exists between obesity and OSA (Strohl et al, 1996). The American Society of Anesthesiologists addressed this issue with practice guidelines to assess patients for possible OSA before surgery and to provide careful postoperative monitoring for those suspected to be at risk (Gross et al, 2006).

An association was also found between obesity and OSA and several medical conditions, such as increased risk of venous stasis, pulmonary embolism, hypertension, cerebral vascular acccidents, cardiomyopathy, arrythmias, and ischemic heart disease (Dominguez et al, 1993; Strohl et al, 1996; Gupta et al, 2001). With these issues in mind, the anesthesiologist should have an informed discussion with the patient about the increased risk of morbidity and mortality and should also work with other members of the patient care team to determine whether any interventions need to be initiated before surgery in an effort to minimize complication risk.

Polysomnography is the gold standard for diagnosis of OSA, but it is an expensive and limited resource. The most reasonable approach is to check room air pulse oximetry. If the patient has an oxygen saturation level less than 96%, further evaluation is warranted; a 2-week period of continuous positive airway pressure therapy has been shown to be effective in correcting abnormal ventilatory drive and improving cardiac function (Lin, 1994; Loadsman et al, 2001). In addition, deep venous thrombosis prophylaxis should be discussed with the surgeon.

Hepatic Evaluation

Risk factors and symptoms of liver disease are not as well defined as those in other organ systems. The diagnosis of liver disease requires a high degree of suspicion and careful probing of the clinical history to identify specific risk factors for liver disease, such as previous blood transfusions, jaundice, travel, tatoos, high-risk sexual behavior, illicit drug use, excessive alcohol intake, and chemotherapy (Suman & Carey, 2006).

In North America and Europe, most hepatic resections are performed for metastatic disease. The operative outcome for hepatobiliary surgery is linked to severity of hepatic parenchymal disease and the extent of postoperative functional reduction (see Chapter 2). In patients with mild or well-compensated chronic hepatic disease, operative outcome is likely to be indistinguishable from the outcome in the general population. Patients with hepatocellular carcinoma (HCC) have poorer outcome than those with metastatic disease given the propensity of HCC to develop in the cirrhotic liver (Fattowich, 2003).

The goal of preoperative screening is to determine the presence of preexisting liver disease without the need for extensive or invasive monitoring. Liver function tests can measure different aspects of hepatic function, but as a group of tests, they lack specificity and are often affected by nonhepatic function. These biochemical markers cannot quantify the hepatic disease. Another issue is finding abnormal hepatic function test results in asymptomatic patients. In general, for asymptomatic patients with mildly elevated alanine and aspartate aminotransferase levels and a normal bilirubin concentration, cancellation of surgery is rarely indicated. In patients with significant abnormalities, detailed investigation is warranted to evaluate for underlying cirrhosis, given the high perioperative risk observed in patients with cirrhosis. The need for further investigation in these patients is highlighted by studies that report an incidence of undiagnosed cirrhosis of 34% in asymptomatic patients with abnormal liver function results (Hay et al, 1989; Hultcrantz et al, 1986). It is important to identify patients with underlying hepatic impairment, because they may be at increased risk for further injury from alterations in splanchnic blood flow that occur during anesthesia and intraabdominal surgery.

Measurement of metabolic liver function would provide the necessary predictive information to assess this risk. Metabolic liver function tests (see Chapter 2), such as the aminopyrine

breath test and indocyanine green clearance, may have predictive value in this regard but are not routinely performed. To date, risk assessment has been primarily performed in patients with known liver disease (Child-Turcotte-Pugh score), but the quantification of risk in asymptomatic patients should not be extrapolated from these studies. The risk of postoperative hepatic insufficiency is closely related to the volume and function of the remnant liver, and several methods for liver volume determination are available. Most use computerized tomography (CT) combined with three-dimensional CT volumetry (Denys et al, 2002). When the functional liver remnant volume is below a certain threshold, generally 25% to 30% for normal liver and 40% for diseased liver, the risk of postoperative hepatic failure is high, and portal vein embolization may be indicated prior to hepatic resection (Vauthey et al, 2000).

Bloodless Surgery

In the early years of hepatic resection, major intraoperative blood loss was common, transfusion of blood products was routine, and morbidity and mortality were unacceptably high (Foster & Berman, 1977). General improvements in hepatic resection techniques have reduced intraoperative blood loss and transfusion rates; nevertheless, perioperative transfusion remains a potent predictor of increased perioperative morbidity and mortality (Jarnagin et al, 2002). In recent years, liver resection without the need for blood transfusion has become increasingly possible (Belghiti et al, 2000; Cunningham et al, 1994; Fan et al, 1999; Jarnagin et al, 2002). Patient blood management is based on three pillars: 1) detecting and treating preoperative anemia, 2) reducing the loss of red blood cells perioperatively, and 3) optimizing the treatment of anemia (Spahn et al, 2008).

Thorough preoperative planning is essential to avoid perioperative allogeneic transfusion. Any history of bleeding disorders and management of anticoagulation must be evaluated, including discontinuation of drugs that adversely affect clotting (e.g., acetylsalicylic acid, nonsteroidal antiinflammatory drugs, and anticoagulants). In patients with anemia, recombinant human erythropoietin or iron therapy may optimize the starting operative hemoglobin (Monk, 1996). Preoperative autologous donation also has been used to reduce the need for allogeneic red blood products (Brecker & Goodnough, 2001). Preoperative autologous donation may not avoid allogeneic blood, however, because almost half of the patients who donate blood before surgery are anemic on the day of operation, and preoperative strategies to augment the red blood cell mass require more time than is generally reasonable for optimal efficacy. Patients with low hemoglobin levels at the start of surgery are at an increased risk of receiving allogeneic blood (Armas-Loughran et al, 2003). In addition, preoperative autologous donation is costly; it can be associated with clerical errors; and for every 2 units donated, usually only 1 unit gets transfused (Goldman et al, 2002). If the patient is optimized and surgery is bloodless, the autologous units are discarded. Other blood conservation strategies, such as intraoperative blood salvage (cell saver) and acute normovolemic hemodilution (ANH) have been used successfully for hepatobiliary surgery in Jehovah's Witness patients (Jabbour et al, 2005). ANH has been shown in two prospective studies to reduce the amount of red blood cells transfused per patient in major liver resections (Matot et al, 2002a; Jarnagin et al, 2008).

INTRAOPERATIVE MANAGEMENT

Hepatic blood flow in surgical patients can be altered by a variety of factors, including arterial blood pressure, posture changes, carbon dioxide levels, intravascular volume shifts, positive pressure ventilation, positive end-expiratory pressure, regional anesthesia, and volatile anesthetics (Gelman, 1992). Surgical stimulation and manipulation of the liver markedly increases hepatic oxygen extraction ratio and splanchnic vasoconstriction (see Chapter 4) (Kainuma et al, 1991; Whittle & Moncada, 1998). A 16% decrease in hepatic blood flow is associated with anesthesia and mechanical ventilation (Gelman, 1976), and a further 40% decrease is seen with splanchnic surgery. This decrease may be the direct effect of sympathetic control of the hepatic venous bed mediated through the hepatic innervation (Greenway et al, 1986).

Positive end-expiratory pressure decreases hepatic blood flow in a stepwise manner. The response cannot be explained by a decrease in cardiac output alone; investigators postulate a vasoconstrictive response in the preportal vasculature. Intraperitoneal insufflation and head-up tilt result in impairment of hepatic blood flow secondary to decreases in cardiac output (Berendes et al, 1996b; Eleftheriadis et al, 1996). The hepatic blood flow decrease caused by hypotensive spinal anesthesia is attenuated by ephedrine administration (Nakayama et al, 1993). Two human studies using the indocyanine green plasma disappearance rate to evaluate the effects of high lumbar epidural anesthesia (EDA) on hepatic blood flow have found a decrease of 25% to 35% despite a constant cardiac output (Kennedy et al, 1971; Tanaka et al, 1997). Patients treated with norepinephrine to compensate for the EDA-induced decrease in arterial blood pressure had an additional marked decrease in hepatic blood flow (Meierhenrich et al, 2009).

It is controversial whether catecholamines increase hepatic blood flow and oxygen supply, but dobutamine does not cause a significant increase in hepatic arterial blood flow (Kainuma et al, 1992). Total hepatic blood flow and portal venous blood flow are increased, however, resulting in an augmentation of hepatic oxygen delivery. The increase in hepatic oxygen delivery is countered by an increase in hepatic oxygen uptake with no overall improvement in hepatic oxygen supply–uptake ratio. Dopamine and norepinephrine increase hepatic venous oxygen saturation, suggesting that the vasoactive treatment of patients in septic shock may not compromise splanchnic oxygenation (Ruokonen et al, 1991, 1993). Hepatic portal flow does not decrease despite a 20% to 60% reduction in blood pressure as long as cardiac index is maintained during sodium nitroprusside hypotension (Chauvin et al, 1985). A well-planned anesthetic maximizes the relationship between oxygen transport and oxygen use with the premise that reductions in systemic pressure would reduce hepatic blood flow. Anything resulting in significant reductions of systemic pressure and cardiac output–induced hypotension, hypovolemia, and anesthetic overdoses should be avoided.

Volatile Anesthetics

Anesthetic Hepatotoxicity

Fulminant hepatic necrosis and jaundice after halothane, so-called halothane hepatitis, is rare—one in 6000 to 35,000 anesthetics—but often fatal. Halothane hepatitis is an

immunologic phenomenon initiated by halothane metabolism and the binding of its metabolite to liver proteins to form trifluoroacetylated proteins, which stimulate antibodies in susceptible individuals. Upon subsequent halothane reexposure, these antibodies mediate massive hepatic necrosis. Because the extent of metabolism of enflurane, isoflurane, and desflurane is so much less than that of halothane, fulminant hepatitis from these anesthetics is far less common than with halothane (Elliot & Strunin et al, 1993). In 1987, the U.S. Food and Drug Administration determined that there was no conclusive association between isoflurane exposure and postoperative hepatitis (Shingu et al, 1983; Stoelting et al, 1987). Sevoflurane metabolism is different from that of the other volatile anesthetics, however, because it does not result in trifluoroacetyled liver proteins, and immune-based hepatitis after sevoflurane has not been reported. With the disappearance of halothane and enflurane from clinical practice in developed countries, and lack of hepatotoxicity from either isoflurane, desflurane or sevoflurane, anesthetic volatile hepatotoxicity is not a significant concern (Elliot & Strunin, 1993).

Hemodynamics

Volatile anesthetics reduce hepatic blood flow in a dose-dependent fashion by affecting cardiac output and systemic pressure. Surgical manipulation causes an additional decrease in estimated hepatic blood flow. Isoflurane has been considered the agent of choice in cases in which preservation of splanchnic blood flow is required, and liver blood flow and the hepatic artery buffer response are maintained better in the presence of isoflurane than with any other volatile anesthetic agent (Berendes et al, 1996a). In addition, isoflurane is shown to attenuate the increases in hepatic oxygen consumption associated with surgery and liver manipulation.

Desflurane is shown to have no deleterious effects on liver function and hepatocyte integrity, and it is associated with significantly greater gut blood flow than equipotent isoflurane. This difference cannot be explained by systemic hemodynamics alone. There is no difference in total hepatic flow between isoflurane and desflurane groups, however, which suggests that an intact hepatic arterial supply buffers response with desflurane (O'Riordan et al, 1997). Sevoflurane is similar to isoflurane and desflurane with a few exceptions (Ebert et al, 1995). Indocyanine green clearance is better preserved during sevoflurane anesthesia. In Beagles subjected to sevoflurane anesthesia and ligation of the hepatic artery, hepatic oxygen supply–uptake ratio, hemoglobin oxygen saturation, and oxygen partial pressure in hepatic venous blood were significantly lower than with halothane or isoflurane.

Nitrous oxide is used extensively in patients with hepatic disease (Khalil et al, 1994; Lampe et al, 1990). Although it has not been shown to contribute to hepatic disease exacerbation, the sympathomimetic effects of nitrous oxide may increase hepatic metabolic requirements.

Intravenous Anesthetics and Muscle Relaxants

Inhaled anesthetics supply all the aspects needed for anesthesia in one package, but today most anesthesiologists choose multiple drugs to reach their goals: immobility, amnesia, suppression of autonomic reflexes, muscle relaxation, and analgesia. Over the past several decades, dramatic advances have been made in intravenous anesthesia with the result that total intravenous anesthesia is now a workable alternative to the traditional inhalation anesthetic. Anesthesiologists using multiple drugs take advantage of interactions among drugs that have different mechanisms of action but similar therapeutic effects. The therapeutic goal of the anesthetic can often be achieved with less toxicity and faster recovery than when individual drugs are used alone in higher doses. The safety of intravenous anesthetics and muscle relaxants in patients having hepatobiliary surgery is well documented (Gelman, 1992).

The main mechanisms that affect hepatic elimination of a drug are changes in hepatic blood flow and changes in the ability of the liver cells to biotransform and/or excrete a drug. These two mechanisms, hepatic blood flow and hepatocyte function, play an important role in the choice of anesthetics for patients undergoing hepatobiliary surgery. High-extraction drugs (ketamine, flumazenil, morphine, fentanyl, sufentanil, lidocaine) are directly related to liver blood flow and are essentially cleared as they pass through the liver. Protein binding, enzymatic induction, intrahepatic shunting, and the effect of anesthetics on liver blood flow may influence the elimination of drugs with a high extraction rate. Reduced metabolic clearance results in increased peak drug level with minimal change in the elimination half-life. Drugs with a low extraction rate (benzodiazepines) differ from high-extraction drugs in that concentration changes little after passage through the liver, and intrinsic clearance depends on hepatic metabolic function as determined by liver size and total enzyme capacity (Colli et al, 1988). In patients with impaired liver function, such drugs have a prolonged length of activity with no increase in peak levels.

SPECIAL ANESTHETIC CONSIDERATIONS

Anesthesia for Hepatectomy

Fluid loading before resection is commonly practiced in preparation for hepatic resection. This fluid loading often results in a distended and tense vena cava and dilated hepatic veins, both of which contribute to increased blood loss during liver mobilization and parenchymal transection. A relationship exists between extent of intraoperative blood loss and morbidity; blood loss greater than 5 L in an adult is associated with prohibitive mortality (Yanaga et al, 1988). Inadvertently, fluid loading to provide hemodynamic stability during episodes of uncontrolled bleeding may cause technical difficulties and handicap repair of venous injuries.

Another approach, low central venous pressure (CVP) anesthesia, is designed to preclude vena caval distension to facilitate mobilization of the liver and dissection of retrohepatic vena cava and major hepatic veins (Cunningham et al, 1994; Melendez et al, 1998). This surgical anesthetic technique compares favorably with other techniques for major hepatic resection (Delva et al, 1989; Segawa et al, 1993; Yanaga et al, 1988). Low CVP anesthesia is performed in combination with surgical inflow and outflow vascular control before parenchymal transection. Such an approach requires close cooperation between the anesthesiologist and the surgeon. Low CVP anesthesia minimizes hepatic venous bleeding during parenchymal transection and facilitates control of inadvertent venous injury. The blood loss resulting from a vascular injury is directly proportional to the pressure gradient across the vessel wall and the fourth power of the radius of the injury. If the CVP is lowered from 15 mm Hg to

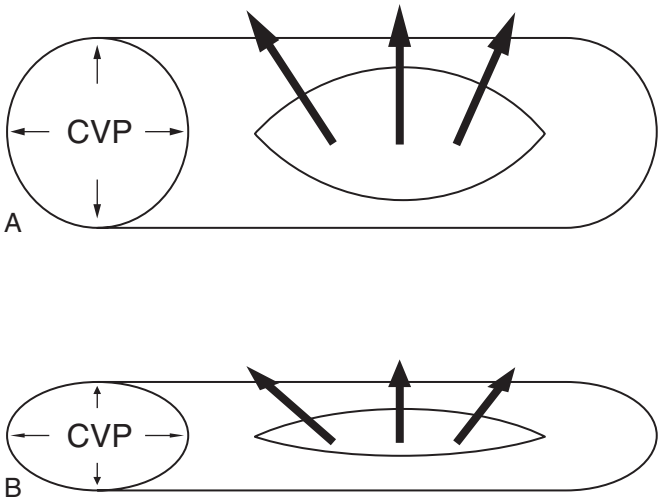


FIGURE 22.1. Vena caval injury profile under various central venous pressure (*CVP*) conditions. **A,** High CVP. **B,** Low CVP. Increased CVP leads to distension of the vena cava with ensuing enlargement in diameter of injury and increase in the bleeding driving pressure.

3 mm Hg, the blood loss through a vena caval injury consequently falls by a factor greater than 5. Lowering CVP lessens the pressure component of the equation and also minimizes the radial component of flow by reducing vessel distension (Fig. 22.1).

Fluid restriction is an important aspect of the low CVP anesthesia technique. Preoperative overnight fluid replacement, a maneuver commonly performed before or immediately after the induction of general anesthesia, is withheld. Strict fluid restriction is practiced until the liver resection is completed. Intermittently, small fluid boluses may be given to maintain hemodynamic stability. To guarantee the safety of patients, appropriate cannulation is carried out, and a high level of vigilance is maintained. Transfusion equipment, such as the Woods pump coupled to a level 1 system, is an important aid to emergency fluid resuscitation, although this is infrequently needed. Intravascular hypovolemia is counteracted with 15-degree head-down tilt. Steep head-down tilt preserves hemodynamic stability and renal function by improving venous return. In animals, head-down tilt increases glomerular filtration rate, sodium excretion, and urine output lasting 8 hours (McCombs et al, 1996). Prolonged head-down tilt improves venous return and yields a 70% increase in plasma atrial natriuretic protein (Hughson et al, 1995; Terai et al, 1995). Although some investigators report intraoperative oliguria during low CVP anesthesia, no increase in the incidence of postoperative renal failure has been observed (Melendez et al, 1998).

Anesthesia is maintained with a combination of isoflurane in oxygen and narcotics, because isoflurane provides vasodilation with minimal myocardial depression (Schwinn et al, 1990). Elimination of nitrogen from the anesthetic gas mixture is necessary to permit expiratory nitrogen monitoring for air emboli. Restriction of nitrous oxide in the gas mixture prevents the diffusion-mediated increase in the volume of circulating air. Consistent with its minimal effect on cardiac output and systemic pressure, fentanyl has no effect on liver blood flow and oxygen delivery. In combination with isoflurane, fentanyl has the least effect on hepatic hemodynamics of any opiate, making it the narcotic of choice for anesthetics. In most patients, fentanyl is the ideal narcotic to aid in the maintenance of anesthesia, providing analgesia with minimal hypotension (Rosow et al, 1982). In a small group of patients, the anesthetic is supplemented with morphine to achieve the desired CVP. Morphine reduces CVP by inducing venous vasodilation caused by histamine release and μ_3 receptor activation (Grossman et al, 1996; Rosow et al, 1982; Stefano et al, 1995). The combination of these anesthetics readily provides the favorable low CVP environment for hepatic resection. With this technique, intravenous nitroglycerin to lower CVP to less than 5 mm Hg is rarely necessary.

The risk of intraoperative air emboli is likely to increase under low CVP anesthesia. Transesophageal echocardiography can be used to monitor air emboli, but this technology is sensitive and overdiagnoses clinically insignificant events. With surgical vigilance and rapid occlusion of open venous channels (see Chapters 90A and 92), low CVP anesthesia results in a low incidence (0.4%) of clinically significant air emboli. More complex low CVP anesthesia management techniques have been described (Rees et al, 1996). They employ epidural blockade and intravenous nitroglycerin. These patients may require intraoperative dopamine for systemic pressure support, a technique this is cumbersome and adds an unnecessary level of complexity to an already challenging situation.

Bloodless Surgery

Red blood cell transfusions are indisputably associated with an increase in mortality, major adverse cardiac and noncardiac outcome, acute lung injury, nosocomial infection, tumor growth, duration of hospitalization, and cost (Murphy et al, 2007; Beattie et al, 2009; Kulier et al, 2007; Marik et al, 2008; Atzil et al, 2008; Shander et al, 2007). Therefore it is important not to confuse the momentary helpful effect of red blood cell transfusion on hypotension and hypovolemia with an outcome benefit. Intraoperative blood cell salvage, hemodilution, and tolerance of normovolemic anemia (Gozzetti et al, 1995) all may contribute to reduced allogeneic red blood cell transfusion in major liver surgery. Autologous blood cell salvage (intraoperative autotransfusion) involves recovery of the patient's shed blood from a surgical wound. The blood is then washed or filtered and reinfused into the patient. Hepatectomies often are performed for cancer but previously, cell salvage had been excluded in oncologic surgery because of the concern for potential dissemination of cancer cells. This concern has been challenged because of the availability of leukocyte-depleting filters and irradiation of blood removed during cancer surgery (Hansen et al, 1999).

Another transfusion-sparing technique is acute normovolemic hemodilution (ANH), a recycling technique that can be performed intraoperatively by the anesthesiologist. Blood is removed from the patient after induction and is replaced with crystalloid or colloid fluid. By removing the patient's blood and replacing it with acellular fluid, the blood loss is diluted. The previously removed blood is stored at room temperature in the operating room and is returned to the patient at the conclusion of the operation. Two randomized studies of ANH in major hepatic resection showed a significant reduction in the percentage of patients requiring allogeneic red blood cell transfusion (Matot et al, 2002a; Jarnagin et al, 2008).

Epidural Anesthesia and Analgesia

Epidural block is widely used to manage major abdominal surgery and postoperative analgesia, but its risks and benefits are uncertain. Studies do not support the routine use of epidural anesthesia (EDA), rather than parenteral analgesia, to prevent postoperative mortality (Fanzca et al, 2002; Park et al, 2001; Wijeysundera et al, 2008). There are, however, other reasons to prefer EDA, including better postoperative pain relief and reduced pulmonary complications (Fanzca et al, 2002). In contrast to EDA for other abdominal surgery, the use of an indwelling epidural catheter and the timing of its removal in patients undergoing liver resection remain controversial (Matot, et al, 2002b).

The hemostatic abnormalities associated with liver resection are not always predictable and/or reversible. Significant disturbances of prothrombin time (PT) can be seen in patients undergoing uncomplicated liver resection. In patients who undergo minor liver resections, the PT usually returns to control levels within 1 day. In patients having major liver resections, the disturbances in PT can be prolonged and, as a result, the epidural catheter cannot be removed without administering fresh frozen plasma to normalize the coagulation profile because of a theoretically increased risk of spinal hematoma (Siniscalchi et al, 2004). In addition, thoracic EDA is associated with a decrease in hepatic blood flow and, if combined with continuous infusion of norepinephrine to counteract the EDA-related decrease in systemic arterial blood pressure, hepatic blood flow is decreased further (Meierhenrich et al, 2009; Tanaka et al, 1997). Hepatic hypoperfusion is regarded as an important factor in the alteration of hepatic oxygen balance and metabolic activity and the pathophysiology of perioperative liver injury. Furthermore, it has been hypothesized that hypoperfusion of the liver may initiate or contribute to the development of a systemic inflammatory response syndrome that may lead to multiple organ failure (Maynard et al, 1997). The decision to insert an epidural catheter for either intraoperative anesthesia or postoperative analgesia in patients undergoing hepatic resection should be made with care.

Obstructive Jaundice

Bile duct obstruction affects hepatic hemodynamics. Acute biliary obstruction is associated with an increase in liver blood flow (see Chapter 4), but flow is decreased with chronic obstruction. Relief of long-term obstruction is not associated with a return to normal pressures and may be associated with hemodynamic embarrassment and shock. The exact cause of hemodynamic derangement in the face of biliary obstruction is unknown, but increased portal resistance is believed to play a role. Biliary sepsis may contribute to the exacerbation of the hemodynamic embarrassment. In these cases, aggressive hemodynamic monitoring may be lifesaving. Either by percutaneous or endoscopic approaches, preoperative biliary drainage does not necessarily improve the perioperative morbidity of patients who show no evidence of infection, and it is therefore not recommended as a routine (Lai et al, 1994; see Chapter 50). When there is clinical concern for the development of acute cholangitis, rapid biliary decompression and intravenous antibiotics should be administered preoperatively, and surgery should be delayed until the infection resolves (Lai et al, 1992).

ANESTHESIA FOR VASCULAR ISOLATION (SEE CHAPTER 91)

Prolonged inflow occlusion with or without hepatic vascular isolation is an alternative surgical approach for liver resection. Hepatic vascular isolation induces significant hemodynamic changes. The anesthetic management is more complex, and many patients require pulmonary artery catheters during the procedure. Hepatic vascular isolation typically causes a decrease in venous return with a resultant decrease in cardiac index and an increase in systemic vascular resistance. Mean arterial pressure is maintained by infusing large volumes of fluid to keep the CVP high. Some patients require vasopressor support to maintain adequate perfusion during the cross-clamping period. Most patients tolerate these hemodynamic changes reasonably well, although in some cases, persistent hypotension or low cardiac index or both demand that the procedure be abandoned. Several studies of hepatic vascular isolation are summarized in Table 22.1 (Belghiti et al, 1996; Delva et al, 1989; Emond et al, 1995; Emre et al, 1993; Habib et al, 1994; Hannoun et al, 1993; Melendez et al, 1998). In these studies, blood loss and transfusion requirements were greater than those reported by the authors using portal triad clamping with extrahepatic control of the hepatic veins. Hepatic vascular isolation is more complex and has not yielded better results than portal triad clamping and extrahepatic control of the hepatic veins (Belghiti et al, 1996; Cunningham et al, 1994).

POSTOPERATIVE CARE

Mortality and morbidity after hepatobiliary surgery have decreased as a result of surgical and anesthetic advances and a better understanding of hepatic physiology (Belghiti et al, 2000; Jarnagin et al, 2002; Melendez et al, 1998; Ryan et al, 1982). Hepatobiliary surgery is increasingly common at major medical centers, and postoperative recovery is becoming indistinguishable from that after other major abdominal surgery. At Memorial Sloan-Kettering Cancer Center, most patients recover after major surgery in the postanesthesia care unit (day 1) and then are transferred to the general ward without any need for intensive care.

Immediate Postoperative Concerns

Some of the problems that cause metabolic and functional changes after hepatobiliary surgery are common to all major intraabdominal procedures (Aronsen et al, 1969). Others are unique and require an in-depth understanding of liver physiology. Immediate postoperative concerns are bleeding, intravascular volume, renal function, and oxygenation. Important laboratory tests are hematocrit, electrolytes, serum creatinine, blood urea nitrogen, PT/partial thromboplastin time, liver enzymes, and chest radiograph.

At least three mechanisms contribute to impaired pulmonary function in the postoperative period: 1) respiratory muscles disrupted by surgical transection of the abdominal muscles will not function normally; 2) patients may limit motion of respiratory muscles to minimize postoperative pain; and 3) stimulation of the visceral afferent nerves markedly changes the activation of respiratory muscles. For example, removal of the gallbladder activates vagal efferents that produce a reflex inhibition of

Table 22.1

Comparison of Operative Parameters Between HVI and LCVP Anesthesia-Aided Hepatectomy

Reference	Technique	Total Cases	Major Resections*	BLOOD LOSS (mL)		Transfusions (units or mL)†
				Mean†	Median	
Delva et al, 1989‡	HVI	35	35	–	–	8 ± 8.3
Emre et al, 1993	HVI	16	13	1866 ± 1683	1325	–
Hannoun et al, 1993	HVI	15	15	–	–	5.8 ± 4.7
Habib et al, 1994	HVI	56	33	1651 ± 1748	1200	930 ± 750
Cunningham et al, 1994	LCVP	100	69	1012 ± 9640	1000	1.4 ± 2.1
Emond et al, 1995	HVI	48	44	1255 ± 1291	–	1.9 ± 2.6
Belghiti et al, 1996	HVI	24	24	1195 ± 1105	–	2.5 ± 3.4
Melendez et al, 1998‡	LCVP	496	357	849 ± 972	618	0.9 ± 1.8

*Major resections include all lobectomies and extended lobectomies.
†Values are reported in mean ± SD.
‡Denotes inclusion of cirrhotic patients in series.
HVI, hepatic vascular isolation; LCVP, low central venous pressure

diaphragmatic activity. Of note, laparascopic surgery may ameliorate the first two mechanisms but not the third, and significant decrements in pulmonary function may still be observed after laparascopic surgery.

The nature and magnitude of the patient's preexisting respiratory condition determine the effect of a standard anesthetic on respiratory function. Anesthesia results in a decrease in mucus transfer and reductions of the functional residual capacity/closing capacity ratio. Airway closure can occur with mild, active expiration in patients with emphysema, bronchitis, and asthma. In addition, inflammation and scarring can compromise bronchial structural integrity and increase further the risk of alveolar collapse. In patients with asthma or obstructive lung disease, high airway resistance favors deep, slow respiration; this may not be possible in patients with large abdominal incisions. Anticipated respiratory compromise after upper abdominal surgery may preclude early extubation, especially in combination with any baseline abnormality in gas exchange.

Unique postoperative concerns in patients after hepatobiliary surgery include phosphorus replacement, anesthetic elimination, drug metabolism, coagulation, and postoperative pain control. Data suggest that hepatocellular regeneration may be critically dependent on cellular ATPase stores (Campbell et al, 1990; Greene, 1981). Liver regeneration after partial hepatectomy involves rapid cell division 24 to 72 hours after liver resection. Standard therapy for posthepatic resection should include the supplementation of intravenous fluids with sodium or potassium phosphate. Particular attention must be paid to anesthetic elimination and residual drug effect—especially sedative, analgesic, and neuromuscular blockers—in patients who have altered drug pharmacodynamics and pharmacokinetics. Postoperative pain management must be adapted to this population. Patient-controlled analgesia, commonly employed for postoperative pain management, should be employed initially without a basal narcotic infusion rate. After hepatic resection, patients experience an unpredictable reduction in the metabolism of narcotics.

The half-life of coagulation factors is 6 hours, so coagulation factor deficiency is likely to evolve rapidly. Routine parenteral administration of vitamin K commonly corrects the coagulation abnormalities within 48 hours. More rapid correction may be accomplished by fresh frozen plasma but is rarely needed, unless the PT or international normalized ratio (INR) exceeds 2, or if there are concerns of ongoing postoperative blood loss (Martin et al, 2003).

Delayed Perioperative Complications

Identifying patients at high risk for complications is an important but difficult component of the overall management strategy. A study from Memorial Sloan-Kettering Cancer Center showed that when postoperative hepatobiliary patients required admission to the intensive care unit, mortality ranged from 37% to 79% regardless of admission diagnosis (Melendez et al, 1998). A systematic proactive approach that identifies early deviations from the norm would be preferable to having to treat organ failure (Sesto et al, 1987).

Jaundice

The differential diagnosis of postoperative jaundice is listed in Table 22.2. Mild jaundice in the early postoperative period after partial hepatectomy is relatively common, particularly in patients who undergo a major resection and have a transient, self-limited hyperbilirubinemia in the first few days after operation, which may be exacerbated by hematoma reabsorption and hemolysis of transfused blood. Progressive jaundice that does not resolve portends a more significant problem.

One suggested definition of postoperative hepatic insufficiency is a peak bilirubin greater than 7 mg/dL. In a cohort of 1059 noncirrhotic patients undergoing hepatic resection, a postoperative bilirubin greater than 7 mg/dL was associated with 30% chance of dying of hepatic insufficiency (Mullen et al, 2007). On the other hand, in the same cohort, 70% survived; this highlights the importance of identifying any correctable problem that may be contributing to the hyperbilirubinemia.

It is prudent to be suspicious of a bile duct injury at the time of surgery when faced with postoperative extrahepatic obstructive jaundice. Hemobilia may occur with temporary obstruction

Table 22.2

Differential Diagnosis of Postoperative Jaundice

Increased Bilirubin Load	Biliary Obstruction	Hepatocellular Injury
Blood transfusion	Intrahepatic cholestasis	Hepatic hypoxemia
Hematoma	Drug induced	Exacerbated chronic hepatitis
Hemolytic anemia	Infection induced	Acute hepatitis
Extracorporeal circulation hemolysis	Extrahepatic cholestasis	Viral
	Bile duct injury	Alcoholic
	Pancreatitis	Gilbert disease
	Retained gallstones	Sepsis
		Trauma
		Toxins, drugs

Modified from Brown BR, 1988: Postoperative jaundice. In Brown BR (ed): Anesthesia in Hepatic and Biliary Disease. Philadelphia, FA Davis, pp 265-273; and Gelman S, 1992: Anesthesia and the liver. In Barash PG, et al, (eds): Clinical Anesthesia, 2nd ed. Philadelphia, Lippincott, pp 1185-1214.

of the bile ducts by blood clots, and the possibility of a bile leak also must be considered. Hepatocellular injury is another possibility in the differential diagnosis of postoperative jaundice. Sepsis is a common condition causing a low-flow state to the liver, and infectious hepatitis may manifest as postoperative jaundice, often related to intraoperative blood transfusions; in some cases, the responsible virus has no serologic marker. Postoperative hepatic failure from excessive sacrifice of functional parenchyma or vascular embarrassment also must be included in this differential diagnosis. In developed countries, halothane is not used, so anesthetic-induced liver failure rarely should be included in the differential diagnosis.

Ascites

Ascites (see Chapter 74) occurs as a result of several factors: 1) impaired albumin and protein synthesis; 2) increased hydrostatic pressure in hepatic sinusoids and splanchnic capillaries; 3) overproduction of hepatic and splanchnic lymph, leading to a transudation of lymph into the peritoneal space; 4) limited or reduced reabsorption of water and protein by peritoneal lymphatics; 5) sodium retention by the kidney secondary to hyperaldosteronism, increased sympathetic stimulation, and alterations in metabolism of prostaglandins and kinins; and 6) impaired renal water excretion, partially owing to increased concentrations of antidiuretic hormone. The decreased serum albumin 1 to 2 weeks after hepatobiliary surgery, by itself, is generally unimportant clinically (Grundmann & Heistermann, 1985), and even in the presence of severe hypoalbuminemia, albumin infusion has no beneficial effect.

The medical management of ascites emphasizes bed rest and sodium restriction. If a spontaneous diuresis does not occur, therapy is begun with the aldosterone antagonist spironolactone. In patients with ascites, contraction alkalosis and electrolyte abnormalities, such as hyponatremia, hyperkalemia, hypochloremia, and hypokalemia, are commonly encountered. If ascites is refractory to medical management, paracentesis may offer temporary palliation. If life-threatening complications such as cardiac or respiratory compromise occur, patients should be transferred to the ICU.

Renal Failure

After hepatobiliary surgery, rapidly progressive renal failure may occur (see Chapter 23), although this is uncommon after routine resections (Belghiti et al, 2000; Jarnagin et al, 2002; Melendez et al, 1998). Hepatic resection using low CVP anesthesia is associated with a very low incidence of postresection renal dysfunction, as shown by Melendez and colleagues (1998). The principal differential diagnoses include acute tubular necrosis, prerenal azotemia, and hepatorenal syndrome, which is the development of otherwise unexplained renal failure in patients with advanced liver disease.

In hepatorenal syndrome, urine sodium is typically less than 10 mEq/L with hyperosmolar urine, oliguria (<400 mL/24 h), fractional excretion of sodium less than 1, and urine creatinine/plasma creatinine ratio greater than 30:1. The pathophysiology of hepatorenal syndrome is based on the pooling of blood in the splanchnic bed and decreasing plasma volume (Hartleb et al, 1997). The kidney perceives a decreased glomerular filtration rate, and the resulting vasoconstriction shunts blood away from the renal cortex. In some cases, the precipitating event can be attributed to hemodynamic instability, nephrotoxic drugs, infection, or overzealous diuresis and paracentesis. Although no specific treatment for hepatorenal syndrome is available, it should always be assumed that the primary pathophysiologic event is circulatory, which requires transfer of the patient to the ICU.

Pulmonary Care

Minor pulmonary complications, such as atelectasis or pleural effusion, are common after liver resection. With aggressive postoperative pulmonary toilet and early mobilization, such problems resolve without the need for further intervention. Perioperative pulmonary complications include pneumonia, bronchospasm, atelectasis, hypoxemia, exacerbation of underlying chronic lung disease, and respiratory failure, usually defined as the need for mechanical ventilatory support. Patients with significant hepatic parenchymal disease are at potential risk for hepatopulmonary syndrome, which is defined as a triad of signs that comprise 1) liver disease, 2) increased alveolar-arterial gradients, and 3) evidence of intrapulmonary vascular resistance (Krowka & Cortese, 1994). Autopsy specimens of human and animal lung have shown precapillary pulmonary dilations and direct arteriovenous communications. Hepatopulmonary syndrome is rare after hepatic resection, and these patients generally require management in the ICU.

Glucose Metabolism

Glucose deprivation leads to hepatic glycogenolysis to provide glucose. After glycogen stores in the liver are exhausted (12 to 24 hours), the liver must synthesize glucose from other substrates (gluconeogenesis). The hormones insulin, glucagon, and epinephrine are important modulators of these processes. On balance, the postoperative patient would seem to be prone to hypoglycemia secondary to diminished glycogen reserves, increased insulin levels, and impaired gluconeogenesis; but dangerous hypoglycemia is rare, and its presence must raise the suspicion of acute hepatic failure. In most resections, isotonic saline solutions without dextrose can be used during the first 12 to 24 hours after resection, following which routine dextrose solutions should be ordered and glucose levels monitored.

Coagulation

After routine liver resections, transient and self-limited prolongation of PT that commonly occurs usually resolves without the need for transfusion of fresh frozen plasma or

administration of other agents. The liver synthesizes vitamin K–dependent factors II (prothrombin), VII, IX, and X; protein S; and protein C. Improvements in coagulation may be achieved with vitamin K (10 mg/day). If this treatment fails to correct a prolonged INR or PT after 2 to 3 days, vitamin K administration should be stopped and additional causes should be sought.

In addition to the vitamin K–dependent factors, the liver also synthesizes antithrombin III and factor I (fibrinogen). In this setting, fresh frozen plasma may be administered at a dose of 12 to 20 mL/kg (2 to 6 U) with the goal of decreasing the PT to within 3 seconds of control. If coagulopathy persists, dysfibrinogenemia should be considered. Patients with liver disease who do not respond to standard corrective measures may respond to vasopressin. Vasopressin is a synthetic peptide that increases factor VIII concentrations and shortens PT, and it may be used in concert with fresh frozen plasma. After hepatectomy, persistent INR greater than 2 and thrombocytopenia less than 100,000 have been identified as warning signs for hepatic insufficiency.

Sepsis

Mortality after hepatic resection is often caused by abdominal sepsis (Bozzetti et al, 1992). In one series, 6 of 14 deaths were the result of intraabdominal sepsis (Melendez et al, 1998). Biliary manipulation and placement of biliary stents, culture-positive bile, retained gallstones, ascites, and blood loss all may predispose to abdominal sepsis. Patients undergoing hepatic resection for hilar cholangiocarcinoma are at particular risk for postoperative infective complications. Other sources of sepsis include the respiratory and urinary systems. Upper abdominal incision, pleural effusion, chronic obstructive pulmonary disease, and poor pulmonary toilet may promote the development of pneumonia, so wound inspections and central line catheter changes should be performed routinely.

Gastrointestinal Bleeding

Although the incidence of stress-related gastric mucosal lesions is high, the actual incidence of bleeding ulcers is 5% with a mortality of 50% reported. In practice, clinically significant gastrointestinal bleeding after hepatic resection is rare (Jarnagin et al, 2002). Endoscopy allows identification of the bleeding site, and treatment is largely supportive with transfusions, antacids, and H_2 blockers. Prophylactic therapy for prevention of stress ulceration should be considered in all patients after major hepatobiliary procedures.

Encephalopathy

A sudden change in a patient's mental status and the onset of asterixis, a flapping tremor related to loss of extensor tone, are signs of hepatic insufficiency that should precipitate a search for the cause and the start of therapy for hepatic encephalopathy (Gitlin, 1998). Precipitating factors include gastrointestinal bleeding, infection, drugs, diet, and dehydration. The exact pathogenesis of hepatic encephalopathy is unknown, but accumulation of endogenous ammonia is associated with the onset of encephalopathy and has been suggested as causative. Other possible contributory factors include 1) changes in the blood–brain barrier permeability, 2) abnormal neurotransmitter balance, 3) altered cerebral metabolism, 4) impairment of neuronal Na^+-K^+-ATPase activity, and 5) increased endogenous benzodiazepines. Standard therapy is designed to reduce levels of ammonia and other potentially toxic metabolites, and short-term benefit from flumazenil administration has been reported (Ferenci et al, 1989). Dietary protein restriction and lactulose, however, remain the gold standard of care.

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CHAPTER 23

Perioperative critical care in hepatopancreatobiliary patients

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OVERVIEW

Patients with cirrhosis or decompensated liver disease (see Chapters 2, 70B, 72, 73, 74, 75A, 75B, and 75C) are at particularly high risk for perioperative morbidity and mortality after major surgery, often necessitating admission to the intensive care unit (ICU). Compared with noncirrhotic patients, patients with cirrhosis who are admitted to the ICU have higher rates of complications and hospital mortality, extended lengths of stay, and greater resource use (Aggarwal et al, 2001; Cholongitas et al, 2006). Combined respiratory and renal failure requiring the use of mechanical ventilation and renal replacement therapy carries a mortality rate ranging from 61% to 89% (Arabi et al, 2004; Cholongitas et al, 2009). Meticulous perioperative assessment, planning, and care are essential to minimize complications and decrease mortality rates in these patients. Although this chapter addresses the special perioperative concerns of cirrhotic patients, unless otherwise specified, the data are applicable to all types of chronic liver disease, including chronic infections with hepatitis B or C virus, chronic autoimmune hepatitis, biliary cirrhosis, sclerosing cholangitis, and hemochromatosis.

PREOPERATIVE ASSESSMENT AND CARE

Global Assessment

The loss of hepatic reserve capacity and the associated systemic derangements that result from liver dysfunction cause patients with chronic liver disease to have an inappropriate response to surgical stress. Increased surgical risk has been reported for various types of surgery in cirrhotic patients, including cardiac operations, open cholecystectomy, hysterectomy, nephrectomy, and transurethral resection of the prostate (Shaheen et al, 2009; Hayashida et al, 2004; Thulstrup & Sorensen, 2001; Lund et al, 2003; Nielsen et al, 2001, 2002). Emergency surgery and unscheduled laparotomy for trauma carry a high mortality rate (Pronovost et al, 1999; Carbonell et al, 2005; Wahlstrom et al, 2000; Demetriades et al, 2004). In contrast, patients with cirrhosis who undergo laparoscopic cholecystectomy have generally favorable outcomes (Morino et al, 2000; Pavlidis et al, 2009).

Two risk-stratification scoring systems have been developed to evaluate the preoperative severity of liver dysfunction and to predict postoperative outcome in cirrhotic patients. The Child score and its modification, the Child-Turcotte-Pugh (CTP) score, has been most commonly used. In the CTP score, a composite score of the degree of hepatic synthetic dysfunction (based on prothrombin time and serum levels of albumin and bilirubin), degree of ascites, and presence of hepatic encephalopathy yields a total score that ranges from well-compensated cirrhosis (class A, 5 to 6 points) to mild (class B, 7 to 9 points) and severe (class C, 10 to 15 points) decompensation. Cirrhotic patients undergoing elective or emergency extrahepatic surgery have a mortality rate ranging from 0% to 7.1% for class A to 84% to 100% for class C (Franzetta et al, 2003). Other risk factors for perioperative complications and mortality among cirrhotic patients undergoing surgery include male gender, preoperative infection or upper gastrointestinal bleeding, elevated creatinine concentration, and thrombocytopenia (Ziser et al, 1999).

In 2000, the Model for End-Stage Liver Disease (MELD) score was developed and proved to be superior to the CTP score in predicting the 3-month survival of patients undergoing transjugular intrahepatic portosystemic shunt (TIPS) (Malinchoc et al, 2000; Salerno et al, 2002). The MELD score is based on the prothrombin time–international normalized ratio (PT-INR) and serum bilirubin and creatinine levels, and it is calculated as follows:

$$\text{MELD Score} = 3.8[\text{Ln Serum bilirubin (mg/dL)}] + 11.2[\text{Ln INR}] + 9.6[\text{Ln Serum creatinine (mg/dL)}] + 6.4$$

The MELD score has been shown to correlate well with the CTP score in predicting postoperative mortality in cirrhotic patients undergoing elective and emergent surgery (Farnsworth et al, 2004). Other studies have shown that high MELD scores predict a poor outcome after hepatic resection for hepatocellular carcinoma (HCC) and following abdominal nonhepatic surgery in cirrhotic patients (Befeler et al, 2005; Teh et al, 2005). Finally, functional assays, such as the monoethylglycinexylidide (MEGX) test and indocyanine green clearance, may be used to assess hepatic functional reserve to predict postoperative morbidity and mortality prior to liver resection (Ercolani et al, 2000; Oellerich & Armstrong, 2001; Ravaioli et al, 2003; Lorf et al, 2008).

Risk Assessment (See Chapter 2)

Although surgical and anesthetic risks are largely related to the severity and not the cause of cirrhosis, determination of the etiology of the liver disease may be helpful in guiding the perioperative management and the timing of surgery (Table 23.1). A

Table 23.1

Risk Factors for Surgery and Preventive and Therapeutic Interventions

Risk Factors	Detrimental Effects	Interventions
Active alcohol use	Acute alcohol hepatitis	Cancel elective surgery
	Increased tolerance to sedatives and anesthetics	Prolonged alcohol abstinence
	Alcohol withdrawal and delirium	Use sedative and defer elective surgery
Iron overload	Cardiomyopathy and arrhythmias	Therapeutic phlebotomies
Hepatitis B infection	Flare of hepatitis	Antiviral agents
Autoimmune hepatitis	Flare of hepatitis	Stress-dose steroids

Table 23.2

Preoperative Risk Factors and Recommendations

Risk Factors	Evaluation and Management
Esophageal varices	Esophagogastroduodenoscopy Nonselective β-blockers Band ligation
Ascites	Abdominal ultrasound Paracentesis to rule out spontaneous bacteral peritonitis Sodium restriction Diuretics
Refractory ascites with low MELD score	TIPS
Hepatopulmonary syndrome	Arterial blood gas and bubble electrocardiogram Quantitative tagged microaggregated lung perfusion scan Echocardiogram Right heart catheterization for confirmation

MELD, Model for End-Stage Liver Disease; TIPS, transjugular intrahepatic portosystemic shunt

history of alcohol use should be obtained for all cirrhotic patients. Surgery should be deferred, if possible, in patients who are actively drinking alcohol because alcohol increases tolerance to narcotic and anesthetic agents, increases the risk of general anesthesia, and predisposes patients to alcohol withdrawal in the postoperative period (May et al, 2001; Spies et al, 2001). Prolonged alcohol abstinence (≥6 months) may lead to a significant reduction in the severity of portal hypertension and improvement in synthetic function in patients with alcoholic hepatitis. However, postponing surgery to allow alcohol abstinence is generally not practical in case of surgery for trauma or liver cancer.

Similar to active alcohol use, chronic viral and autoimmune hepatitis increase the risk of perioperative complications. Among patients undergoing hepatectomy for hepatocellular carcinoma, the presence of high-grade inflammation of the remaining healthy liver is associated with postoperative hepatic dysfunction (Nanashima et al, 2003). Patients with cirrhosis as a result of chronic hepatitis B may benefit from antiviral and immunologic agents such as lamivudine, adefovir, entecavir, telbivudine, tenofovir, interferon alfa-2b, and peginterferon alfa-2a before surgery (Keeffe et al, 2008; Lau et al, 2005; Hadziyannis et al, 2005, 2006; Schalm et al, 2000; Chan et al, 2005). Patients with chronic autoimmune hepatitis who have been on long-term steroid therapy should receive stress-dose steroids in the perioperative period, and adjunctive immunomodulatory agents should be resumed as soon as possible (Czaja, 2009).

Portal Hypertension, Varices, and Ascites (See Chapters 70A, 70B, 74, 75A, 75B, and 75C)

The severity of portal hypertension, as manifested by ascites and varices, is a major concern in the preoperative evaluation of cirrhotic patients. Preoperative endoscopy and measurement of hepatic venous pressures identify patients with severe portal hypertension who are at risk for variceal bleeding (Dittrich et al, 2003). Elevated hepatic venous pressures may portend the development of postoperative complications and higher hospital mortality in cirrhotic patients undergoing various surgical procedures including cholecystectomy, coronary artery bypass grafting, abdominal aortic aneurysm repair, and colorectal surgery (Csikesz et al, 2009; Nguyen et al, 2009). A platelet count of less than 100,000/μL is another useful surrogate marker of severe portal hypertension and of eventual hepatic decompensation (Zaman et al, 2001).

In patients with significant risk factors for variceal hemorrhage, nonselective β-blockers, such as propranolol or nadolol, are recommended to decrease the resting heart rate by 25% of pretreatment level or to approximately 50 to 60 beats/min. These agents, used either alone or in combination with nitrates, may reduce the variceal bleeding rate by half (Bureau et al, 2002; Patch et al, 2002). Alternatively, esophageal variceal band ligation or TIPS placement (see Chapter 76E) could be considered (Escorsell et al, 2002; Lo et al, 2002).

Ascites predisposes to bacterial peritonitis, respiratory compromise as a result of reduced lung expansion, and delayed wound healing. Adequate control and evaluation of ascites is important in cirrhotic patients scheduled to undergo abdominal surgery. In general, control of ascites may require several months and can be achieved with a low-sodium diet, diuretics, and/or large volume paracentesis (Table 23.2). In approximately two thirds of patients with ascites that is refractory or intolerant to diuretics, TIPS may be beneficial. Doppler ultrasound is advocated prior to TIPS procedure, as findings of abnormal blood flow in the portal venous system correlate well with increased mortality (Harrod-Kim & Waldman, 2005). Patients who undergo TIPS are also at increased risk for hepatic encephalopathy and should be monitored closely (Sahagun et al, 1997; Maleux et al, 2004). Patients with high MELD scores (>15) are at high risk for 30-day mortality and should not undergo TIPS for refractory ascites (Ferral et al, 2004; Schepke et al, 2003). In general, cirrhotic patients whose ascites is refractory to diuretics or TIPS should avoid abdominal surgery because of the high rates of postoperative morbidity and death. Finally, a high MELD score and use of a proton pump inhibitor are also associated with increased risks of spontaneous bacterial peritonitis (Bajaj et al, 2009; Obstein et al, 2007).

Avoiding preoperative intravascular volume depletion is important, as hypovolemia can lead to intraoperative and postoperative hypotension and shock, particularly in cases of surgery for emergent or life-threatening indications. Paracentesis and diuretics should be used judiciously, because they can trigger hypovolemic shock. Paracentesis may be performed with concomitant intravenous administration of selective colloid solutions. Albumin solutions are the preferred colloids used for resuscitation, as isotonic saline or dextran solutions may lead to ongoing accumulation of ascites (Garcia-Compean et al, 2002; Planas et al, 1990).

Nutrition (See Chapter 24)

Severe malnutrition affects up to 40% of cirrhotic patients and is associated with a high incidence of morbidity and mortality in patients with cirrhosis who are undergoing surgery (Kalaitzakis et al, 2007; Merli et al, 2002; Sam & Nguyen, 2009). In patients with advanced cirrhosis, several of the common parameters of nutritional status—such as body weight, body mass index, and albumin level—are not valid and reliable tools for assessment.

Perioperative interventions to enhance the nutritional status of cirrhotic patients may be associated with improved outcomes. Although special supplements with branched-chain amino acids are available and may reduce the risk of hepatic encephalopathy (Marchesini et al, 2003), in practice, their benefit is at most marginal. Nutrition via the enteral route is advocated, and nasogastric tubes can be employed safely in patients with esophageal varices. Total parenteral nutrition may be difficult to administer in cirrhotic patients because of concerns with fluid overload and infection.

Anemia

Bleeding, hemolysis, splenic sequestration, malnutrition, and underlying liver disease are among the multifactorial causes of anemia in cirrhotic patients. Longitudinal studies of patients with compensated cirrhosis without esophageal varices demonstrate that anemia may develop an average of 39 months after the onset of cirrhosis (Qamar et al, 2009). In 20% to 40% of patients with advanced cirrhosis of nonbiliary origin, a spur-cell hemolytic anemia associated with iron overload may become evident. Iron should be administered only in the presence of documented deficiency. In patients scheduled for partial hepatectomy for HCC, autologous blood transfusion and erythropoietin therapy have been used successfully to prevent the need for red blood cell transfusions (MacLaren et al, 2004; Shinozuka et al, 2000; Kajikawa et al, 1994).

Coagulopathy

Coagulation abnormalities are frequently found in cirrhotic patients undergoing surgery. Etiologies include decreased hepatic synthetic function, abnormal synthesis of coagulation factors, malnutrition, vitamin K deficiency, thrombocytopenia, and dysfibrinogenemia (Amitrano et al, 2002; Qamar et al, 2009; Richard et al, 2007). The degree of coagulopathy is proportional to the severity of cirrhosis. For patients with prolonged PT-INR and suspected vitamin K deficiency, a 3-day trial of vitamin K is recommended to determine whether the coagulopathy is correctable. Intravenous administration of vitamin K is the favored method in the ICU: subcutaneous administration has an inconsistent rate of absorption, and intramuscular injection carries the risk of hematoma formation. Oral menadiol, the water-soluble formulation of vitamin K, is effective for patients with cholestasis. If the PT-INR fails to correct with vitamin K, mixing studies may help identify possible inhibitors and guide therapy with fresh frozen plasma (FFP) or recombinant factors. Of note, the number of units of FFP commonly used in clinical practice infrequently corrects the coagulopathy (Youssef et al, 2003). In general, administration of cryoprecipitate is recommended when serum fibrinogen levels are less than 100 mg/dL, particularly in the presence of bleeding.

Excessive plasma transfusions can lead to volume overload and may exacerbate ascites. Human recombinant activated factor VIIa (rFVIIa) has been shown to be beneficial as an alternative to plasma. Rapid correction of the PT-INR has been documented within 15 minutes of a small, single intravenous dose of rFVIIa (Surudo et al, 2003), and rFVIIa has been used successfully in cirrhotic patients with coagulopathy to achieve hemostasis for colonic polypectomy, liver biopsy, dental extraction, and bleeding esophageal varices refractory to standard endoscopic therapy (Anantharaju et al, 2003; Berthier et al, 2002; Carvalho et al, 2002; Ejlersen et al, 2001; Romero-Castro et al, 2004). Transfusion of platelets is recommended before invasive procedures. A platelet count of less than 50,000/μL is the usual trigger for transfusion (Rebulla, 2001). Finally, desmopressin may be considered for refractory hemorrhage, particularly when azotemia is present.

Cardiorespiratory Evaluation

Patients with advanced cirrhosis typically have a hyperdynamic hemodynamic profile similar to the systemic inflammatory response syndrome: high cardiac output and vasodilatation of the pulmonary, splanchnic, and peripheral beds (Cazzaniga et al, 2009). Patients with alcoholic liver disease and iron overload are predisposed to cardiomyopathy and cardiac arrhythmias (Moller & Henriksen, 2008). Patients with cirrhosis also are at risk for coronary artery disease because of a high prevalence of cigarette smoking and diabetes mellitus (Hickman & Macdonald, 2007).

Hypocapnia is the most frequent gas-exchange abnormality in patients with cirrhosis (Aller et al, 1999), and pulmonary function can be compromised by tense ascites. Large-volume paracentesis may lead to improvement in the forced expiratory volume in 1 second (FEV_1), functional residual capacity (FRC), and arterial oxygenation (Gupta et al, 2000).

Patients with cirrhosis are also at risk for the development of hepatopulmonary syndrome (HPS) (Gupta et al, 2001). Subclinical or overt HPS is often associated with portopulmonary hypertension and causes significant pulmonary abnormalities as a result of alterations in the pulmonary vasculature by various toxins that accumulate and bypass the cirrhotic liver. Patients with HPS are seen with hypoxemia, platypnea, orthodeoxia, clubbing, and spider angiomata. The predictive value of the alveolar-arterial oxygen gradient in identifying patients with HPS remains a matter of controversy (Schenk et al, 2002; Lima et al, 2004); however, transthoracic echocardiography can be performed to screen for HPS and portopulmonary hypertension; bubble contrast echocardiography identifies the presence of intrapulmonary shunts indicative of HPS (see Table 23.2).

The presence of HPS worsens the overall prognosis of patients with liver cirrhosis (Schenk et al, 2003). The severity of HPS can be quantified with a tagged, macroaggregated albumin lung perfusion scan and arterial blood gas analysis. Postoperative mortality from cardiorespiratory complications

can be estimated by a preoperative Pao_2 of 50 mm Hg or a macroaggregated albumin scan quantification shunt fraction of 20% or higher (Arguedas et al, 2003). General anesthesia for hepatic and extrahepatic procedures in patients with HPS is associated with increased perioperative risk (Mazzeo et al, 2004).

Portopulmonary hypertension, an integral component of HPS, is often asymptomatic and difficult to diagnose; however, this syndrome predisposes to intraoperative cardiac arrhythmias and cardiac arrest. Mortality of portopulmonary hypertension is high, with 1- and 5-year survival rates of 54% and 14%, respectively (Swanson et al, 2008). Although transthoracic echocardiogram may be the initial study performed, right heart catheterization is the best diagnostic tool for portopulmonary hypertension, and it helps discriminate this process from other causes of pulmonary hypertension (Krowka et al, 2006). Elective surgery under general anesthesia in patients with severe HPS-associated pulmonary hypertension should be deferred until the pulmonary hypertension is controlled with vasodilator agents.

Electrolytes

Hyponatremia is quite common in patients with cirrhosis because of their impaired ability to excrete free water, and it is associated with increased mortality (Borroni et al, 2000). Hyponatremia often occurs in the setting of severe ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome (Angeli et al, 2006). Hyponatremia and other electrolyte abnormalities, such as hypokalemia and hypomagnesemia, can result from the use of loop diuretics and as a consequence of the chronic respiratory alkalosis associated with cirrhosis. Patients with active alcohol use are also at increased risk of hypophosphatemia. Electrolyte imbalances should be evaluated and corrected before surgery to limit cardiac arrhythmias, peritonitis, and hepatic encephalopathy.

Infection

Spontaneous bacterial peritonitis (SBP) develops in 20% of hospitalized patients with cirrhosis. Risk factors for SBP include gastrointestinal hemorrhage, metabolic alkalosis, dehydration, hyponatremia, and a high MELD score (Obstein et al, 2007). SBP carries an increased mortality rate, which can be worsened by age, renal dysfunction, bacteremia, and elevated MELD score (Perdomo Coral & Alves de Mattos, 2003; Nobre et al, 2008; Cho et al, 2007). It is prudent to have a low threshold to perform a diagnostic paracentesis if SBP is suspected, especially in the setting of large-volume ascites (Kuiper et al, 2007). If SBP is present, elective surgery should be deferred until the infection has been adequately controlled. Prophylactic antimicrobial intestinal decontamination can prevent SBP in hospitalized patients with cirrhosis who have gastrointestinal hemorrhage or a low protein level in the ascitic fluid (Loomba et al, 2009; Terg et al, 2008).

INTRAOPERATIVE MANAGEMENT

Intraoperative management of cirrhotic patients involves careful selection of anesthetic, narcotic, and sedative agents; maintenance of intravascular volume in the setting of fluid losses and shifts; and adjustment to blood losses in the setting of relative anemia and coagulopathy.

Anesthesia

The degree of impairment in hepatic synthetic function and other hepatic functions has to be strongly considered when selecting anesthetics, muscle relaxants, analgesics, and sedatives in the perioperative period. General anesthesia, which is required during hepatic surgery, decreases total hepatic blood flow. Inhalational agents such as isoflurane and sevoflurane, which undergo less hepatic metabolism, continue to be the preferred anesthetic agents in patients with liver disease Although significant increases in liver transaminases and alkaline phosphatase were observed when isoflurane was used compared with sevoflurane (Nishiyama et al, 2004), isoflurane continues to be favored because of its minimal effects on hepatic blood flow. Halothane is not used because of the high risk of hepatotoxicity (Golembiewski, 2004). Endotracheal intubation and induction are achieved in patients with liver disease similar to that in the general population. Atracurium and cisatracurium are the preferred neuromuscular blocking agents to facilitate intubation, because they are not metabolized through the hepatic or renal system.

Low doses of intravenous agents, such as fentanyl and midazolam, are generally used for induction and sedation. Midazolam may exacerbate hepatic encephalopathy, an adverse effect that is still evident several hours after surgery or an endoscopic procedure (Assy et al, 1999). Decreased protein binding and increased volume of distribution hinder the clearance of midazolam in cirrhotic patients, and significant delays in the elimination of midazolam and decreased psychomotor function have been shown in patients with severe alcohol-induced cirrhosis. Midazolam and meperidine are extensively metabolized by hepatocytes, and their half-life is altered in liver disease (Delco et al, 2005), therefore it is recommended that the doses of midazolam and meperidine be reduced by 50% in cirrhotic patients. Cirrhosis delays the elimination of alfentanil, whereas the metabolism of fentanyl, sufentanil, and remifentanil does not seem to be affected (Lentschener & Ozier, 2002). Nonetheless, opioids are avoided intraoperatively.

Ventilation

Patients with chronic liver disease are at increased risk of hypoxemia because of diffusion abnormalities, ventilation/perfusion mismatch, and decreased functional reserve capacity. Muscle relaxants and inhaled anesthetic agents may reduce the oxygen debt. From a ventilatory perspective, large–tidal volume ventilation may increase intraabdominal pressure, exacerbate respiratory alkalosis, lead to barotrauma, reduce ventricular preload, and result in systemic hypotension and organ injury. Cirrhosis is a relative contraindication to the use of carbon dioxide during exploratory laparoscopy.

Hemodynamic Parameters

Alterations in volume status may be a significant intraoperative problem. Decreased effective circulatory volume is frequently present despite the presence of total body fluid overload. The initial periods of surgery may be associated with significant fluid shifts resulting from the removal of ascites when the peritoneal cavity is accessed. The administration of fluid in the immediate preoperative period may reduce the hemodynamic perturbations and prevent other complications related to

hypovolemia, such as hepatic encephalopathy and postoperative renal failure.

During surgery, the mean arterial blood pressure should be maintained above 70 mm Hg to avoid organ injury. Surgery may be complicated by excessive intraoperative hemorrhage resulting from the presence of portal hypertension and coagulopathy. As a result, it is often necessary to infuse large volumes of blood products or intravenous fluids during a limited time to maintain hemodynamic stability; this may result in exacerbation of portal hypertension and volume overload. To avoid excessive fluid overload, colloid solutions such as albumin should be administered. Permissive hypotension and ischemic conditioning are relatively contraindicated in cirrhotic patients (Clavien et al, 2003), and intraoperative blood transfusion is a significant factor related to morbidity and mortality in patients undergoing hepatic resections. Despite the lack of randomized trials, rFVIIa may limit bleeding and the need for red blood cells, plasma, and platelets transfusions (Franchini et al, 2008; Tsochatzis et al, 2007).

Electrolytes

Correction of electrolyte abnormalities is important to prevent arrhythmias and hemodynamic compromise. Administration of calcium should be considered, because hypocalcemia develops after transfusion of large volumes of blood as a result of high citrate load. Intraoperative and postoperative serum levels of potassium, calcium, magnesium, and phosphorus should be obtained, and abnormalities should be corrected.

POSTOPERATIVE MANAGEMENT

Admission to the ICU may become necessary for postoperative patients with underlying cirrhosis given the high risk of complications and mortality in these patients. Among the important critical care issues requiring careful postoperative assessment are fluid derangements, abdominal compartment syndrome, renal failure and hepatorenal syndrome, hepatic encephalopathy, venous thromboembolism, and bleeding as a result of coagulopathy and thrombocytopenia. Once a patient is admitted to the ICU, postoperative mortality rises with increasing length of stay (Povoski et al, 1999).

Fluid Management and Abdominal Compartment Syndrome

Postoperatively, cirrhotic patients are prone to transient hypotension, vasodilation, and fluid shifts. Oliguria also may occur because of reaccumulation of ascites at the expense of the intravascular space. Ascites may occur even in stable cirrhotic patients without documented preoperative ascites. Maintenance of normal renal function is paramount (Cholongitas et al, 2006). Colloid rather than crystalloid fluids should be administered (Garcia-Compean et al, 2002; Planas et al, 1990), and fluid replacement may be guided by the volume of peritoneal fluid drained intraoperatively. If hypotension develops that is refractory to the administration of colloids, vasopressor agents such as norepinephrine may be necessary (Saner et al, 2003). The goal is to limit ascites formation as much as possible. In general, oliguria should not be an indication for diuretic therapy in the setting of significant peritoneal fluid drainage, but rather an indication for fluid (colloids) and vasopressor support, especially if the patient is hemodynamically unstable (Moreau et al, 2002; Appenrodt et al, 2008).

The development of tense ascites may predispose to surgical wound dehiscence, renal failure, peritonitis, and abdominal compartment syndrome (ACS). ACS is characterized by an acute and progressive elevation of the intraabdominal pressure to more than 20 mm Hg in association with failure of one or more organs (Malbrain et al, 2007). The 24-hour fluid balance and peak airway pressure are two independent variables predictive of the development of ACS in nontrauma surgical patients (McNelis et al, 2002). Patients with ACS may have hypotension resulting from decreased venous return, hypoxemia from decreased FRC and ventilator dyssynchrony, and laboratory and radiologic abnormalities from renal failure and bowel ischemia. Measurement of intraabdominal pressure using the bladder is the current mainstay of diagnosis. Excessive fluid administration should be avoided by establishing appropriate endpoints of resuscitation (An & West, 2008). Paracentesis and, in extreme situations, surgical decompression may be necessary to prevent organ injury and wound dehiscence.

Acute Renal Failure and Hepatorenal Syndrome

Acute renal failure (ARF) after liver resection occurs in more than 15% of cases with an attributed mortality rate of 4.2% (Slankamenac et al, 2009). In contrast, ARF is uncommon after cardiac and noncardiac surgery with an overall incidence of 0.85 to 1.7% (Thakar et al, 2005; Kheterpal et al, 2007). A recent scoring system using four criteria—1) cardiovascular disease, 2) elevated alanine aminotransferase (ALT), 3) underlying renal disease, and 4) diabetes mellitus—demonstrated an increased risk of ARF after hepatic resection (Slankamenac et al, 2009). Postoperative ARF in patients with cirrhosis may be caused by parenchymal renal disease, administration of nephrotoxic drugs in the perioperative period, hypovolemia, and hepatorenal syndrome (HRS) (Gines & Schrier, 2009). Management of ARF varies with the etiology and ranges from providing fluid resuscitation in cases of hypovolemia-induced renal failure to renal replacement therapy (Table 23.3).

HRS represents the most dreadful postoperative renal complication in patients with underlying liver disease, and it develops in the setting of advanced cirrhosis, when splanchnic and peripheral vasodilation lead to decreased effective intravascular volume, impaired renal perfusion, and increased reabsorption of sodium (Kramer & Horl, 2002). HRS can be precipitated by infection or intravascular volume depletion as a result of perioperative peritoneal fluid drainage or diuretic administration. Subsequent renal ischemia and tubular injury can progress to renal failure. HRS is characterized by oliguria and a low urine sodium concentration.

Acute tubular necrosis (ATN) may be indistinguishable from HRS, as both conditions share similar clinical presentations and findings on urinalysis. The diagnosis of HRS can be established using the criteria of the International Ascites Club (Arroyo et al, 1996). When HRS is documented, the presence of infection, especially peritonitis, should be considered; empiric antibiotic therapy should also be considered, and peritoneal fluid cultures should be monitored (Fernandez et al, 2007). Administration of vasoconstrictors, such as vasopressin or terlipressin, has been shown to improve renal function and reverse HRS (Sanyal et al, 2008; Sharma et al, 2008; Alessandria et al, 2007; Gines et al, 2004). Randomized controlled

Table 23-3

Postoperative Issues and Management in Hepatobiliary Surgery

Issues	Evaluation and Management
Fluid derangements	Maintenance of normal renal function Use colloid rather than crystalloid fluids Use vasopressor agents for refractory hypotension
Abdominal compartment syndrome	Measure intraabdominal pressure Avoid excessive fluid administration Paracentesis, surgical decompression
Renal failure and hepatorenal syndrome	Avoid intravascular depletion, excessive diuresis Renal replacement therapy Vasopressin or terlipressin for HRS Consider antibiotics for peritonitis-induced HRS
Bleeding due to coagulopathy and thrombocytopenia	RBCs, platelets, plasma transfusion Erythropoietin rFVIIa Octreotide and vasopressin or terlipressin for variceal hemmorhage
Hepatic encephalopathy	Use sedatives and analgesics judiciously Avoid NSAIDs Remifentanil is preferred narcotic Propofol preferred for sedation in mechanically ventilated patients Lactulose or lactitol enemas Oral antibiotics (neomycin, metronidazole, rifaximin)
Venous thromboembolism	Early mobilization Pneumatic compression devices and/or GPS UFH or LMWH

HRS, hepatorenal syndrome; RBCs, red blood cells; rFVIIa, recombinant factor VIIa; NSAIDs, nonsteroidal antiinflammatory drugs; GPS, graduated pressure stockings; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin

studies are notably absent, but most reports indicate slow improvement of renal function in approximately two thirds of cases after several days of therapy with terlipressin (Halimi et al, 2002).

Anemia and Hemorrhage

Postoperative bleeding, variceal hemorrhage, and anemia are usually caused by cirrhosis-induced coagulopathy and thrombocytopenia. The risk of postoperative variceal rupture and bleeding is increased by large-volume ascites, excessive blood transfusion, increased portal pressure, and infection. Paracentesis may reduce the hepatic venous pressure gradient, the variceal pressure, and the wall tension in patients with ascites. Infection increases portal pressure, especially peritonitis, through endotoxin and cytokine-mediated responses (Bambha et al, 2008; Hou et al, 2004); this adversely affects coagulation in cirrhotic patients as a result of a heparin effect (Montalto et al, 2002; Zambruni et al, 2004). Octreotide alone or in combination with diuretics may prevent rebleeding by limiting portal hypertension (Morales et al, 2007; Kalambokis et al, 2006).

Anemia and the need for blood products may be prevented by the administration of recombinant erythropoietin if initiated on arrival in the ICU. Administration of FFP is commonly used to treat the coagulopathy; however, volume overload is a major limitation of FFP. Also, rFVIIa may be used to rapidly correct the coagulopathy of postoperative cirrhotic patients, who would need a large volume of FFP otherwise (Ejlersen et al, 2001; Romero-Castro et al, 2004; Bosch et al, 2004). In addition to blood transfusion, acute management of variceal hemorrhage and anemia includes administration of octreotide, vasopressin, and terlipressin (Morales et al, 2007; Abid et al, 2009; Escorsell et al, 2000; Feu et al, 1996; Ioannou et al, 2003).

Sedative and Pain Management and Hepatic Encephalopathy

Sedatives and pain medications should be used judiciously in postoperative patients with cirrhosis to prevent an exacerbation of hepatic encephalopathy. In cirrhotic patients, the pharmacokinetics and pharmacodynamics of sedative and narcotic agents are altered with prolongation of their elimination half-lives as a result of decreased clearance and increased volume of distribution (Delco et al, 2005; MacGilchrist et al, 1986). By impairing respiratory drive and delaying extubation, narcotics and sedatives may predispose to atelectasis, aspiration, and postoperative pneumonia. Among the narcotic agents available, remifentanil is preferred because of its limited hepatic metabolism. Propofol is a better choice than benzodiazepines for sedation because of its shorter recovery time, which may allow for more reliable serial neurologic assessment (Weston et al, 2003; Schilsky et al, 2009). Nonsteroidal agents should be avoided because of the potential for peptic ulceration, fluid retention from inhibition of renal prostaglandin synthesis, and precipitation of hepatorenal syndrome. Hepatic encephalopathy is commonly treated with lactulose orally or with lactitol enemas (Wright & Jahan, 2007). Side effects of lactulose include gaseous distension, abdominal cramps, and anorexia, which may result in higher narcotic requirements and a self-perpetuating cycle. To prevent these complications, simethicone and a polyethylene glycol laxative may be employed. Second-line agents for the treatment of hepatic encephalopathy include oral antibiotics such as neomycin, metronidazole, and rifaximin (Al Sibae & McGuire, 2009).

Prophylaxis against Venous Thromboembolism

The general guidelines for prophylaxis against venous thromboembolism (VTE) include early mobilization, use of intermittent pneumatic compression devices and/or graduated compression stockings, and pharmacologic thromboprophylaxis. Mechanical thromboprophylaxis should be used primarily in patients at high risk of bleeding. In postoperative cirrhotic patients, pharmacologic thromboprophylaxis with unfractionated heparin or low-molecular-weight heparins (LMWHs) must be applied judiciously, because these patients already are predisposed to bleeding (Geerts et al, 2008). The clinical advantages of LMWHs over unfractionated heparin include its once-daily administration and the lower risk of heparin-induced thrombocytopenia (Martel et al, 2005). When the high bleeding risk decreases postoperatively, pharmacologic thromboprophylaxis should be substituted for or added to the mechanical prophylaxis. Renal function must be considered when making decisions regarding the use of LMWHs, as these agents are cleared by the kidney.

References are available at expertconsult.com.

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CHAPTER 24

Preoperative and postoperative nutrition in hepatobiliary surgery

Christine Van Cott, Randall Zuckerman, and William S. Helton

GOALS OF NUTRITIONAL SUPPORT IN HEPATOBILIARY SURGERY

The general objective of nutritional support in patients undergoing hepatobiliary surgery are the same as for any other patient undergoing surgery: to decrease postoperative morbidity and mortality. Nutritional intervention should attempt to maintain or restore immunity, support anabolism, and attenuate the catabolic response to injury. In addition, nutritional intervention should strive to restore specific hepatocellular functions, attenuate hepatocellular injury in response to ischemia and reperfusion (I/R), and optimally support hepatocellular function and regeneration after transplantation or resection.

In addition to providing the basic components to correct protein-calorie malnutrition, nutritional strategies have tried to identify and provide disease-specific nutrient requirements for individual organs, cells, and tissues. This new direction or application of nutritional science has been termed *nutritional pharmacology*, and it is based on the observation that individual components of the immunoinflammatory response to injury and infection can be influenced and manipulated by the timely administration of specific nutrients, in specific concentrations, and by specific routes of feeding. Using the principles of nutritional pharmacology, clinicians and scientists have observed that liver structure and function in health and disease can be influenced significantly by nutritional means. This chapter discusses preoperative and postoperative applications of nutrition in hepatobiliary surgery, integrating more recent developments with established practices.

ALTERATIONS IN LIVER METABOLISM THAT AFFECT NUTRITIONAL STATUS

The liver plays a crucial role in the metabolism and assimilation of nutrients, and it is central in the orchestration of protein and carbohydrate metabolism. Any defect or disease of the liver results in significant metabolic derangements. Progression of liver dysfunction results not only in metabolic derangement from a decrease in the number of functioning hepatic cells but also in shunting of portal blood, which decreases the delivery of nutrients, growth factors, and hormones to the remaining cells. Patients with advanced liver disease and cirrhosis also have increased circulating serum levels of growth hormone, glucagon, epinephrine, and cortisol. The cause of this altered hormonal pattern is not completely understood but is typical of a catabolic state and results in carbohydrate intolerance and muscle proteolysis (Eigler et al, 1979; Sherwin et al, 1974). It is speculated further that the catabolic profile of patients with cirrhosis and ascites may be due in part to a defective gastrointestinal (GI) mucosal barrier, which leads to the escape of endotoxin from the lumen of the bowel into the peritoneal cavity (Helton, 1994). The transmigrated endotoxin stimulates peritoneal mononuclear phagocytic cells and Kupffer cells in the liver to release proinflammatory cytokines and mediators (interleukin [IL]-1, tumor necrosis factor [TNF], IL-6, eicosanoids, and nitric oxide). These mediators and cytokines modulate numerous metabolic functions of the liver, including amino acid, protein, lipid, carbohydrate, and trace mineral metabolism (Andus et al, 1991). The proinflammatory cytokines are produced by cells in the intestine and liver to mediate anabolic and catabolic functions and regulate hepatic blood flow, bile flow, liver regeneration, and the response to I/R injury.

TNF is the proximal cytokine signal produced by hepatic Kupffer cells in response to endotoxin or I/R injury. TNF initiates a cascade of inflammatory events that are important in the pathogenesis of many types of surgically induced liver injury, such as I/R injury that occurs with liver resection and transplantation. Endotoxemia occurring in response to manipulation of the biliary tree in patients with biliary obstruction also stimulates the release of TNF, which is believed to mediate in part the systemic sepsis response and subsequent increased organ failure rate associated with operating in the setting of biliary obstruction and infection (Nolan, 1981; Wilkinson et al, 1976). TNF and IL-6 cause a reprioritization of hepatic protein synthesis, a process involving accelerated production of acute-phase proteins at the expense of constitutive proteins. Some indirect evidence suggests that parenteral nutrition also weakens the intestinal barrier, allowing endotoxin to escape from the gut, where it then primes Kupffer cells for cytokine release in response to later infection (Fong et al, 1989).

Increased skeletal muscle proteolysis and muscle wasting in advanced cirrhosis may be related in part to the fact that the cirrhotic liver does not respond appropriately to growth hormone because of low levels of growth hormone–binding protein (Hattori et al, 1992). Growth hormone normally binds to growth hormone–binding protein on hepatocytes and stimulates the production of insulin-like growth factor-1 (IGF-1), the principal mediator of growth hormone–induced protein synthesis and IGF-1 binding proteins. Patients with advanced cirrhosis have low circulating plasma levels of IGF-1 and IGF-1 binding proteins (Hattori et al, 1992; Poggi et al, 1979). The net effect of this metabolic derangement is impaired glucose disposal by skeletal muscle and impaired skeletal muscle protein synthesis. Simultaneously, there is decreased protein synthesis by the diseased liver for the major secretory proteins, such as albumin, and proteins in the coagulation cascade (Nachbauer &

Fischer, 1983). As a result of the aforementioned alterations, the administration of recombinant IGF-1, but not growth hormone, may enhance protein synthesis (Inaba et al, 1994) and may be an important adjunct to improving the nutritional state of patients with liver disease who are undergoing operation (Sato et al, 1994).

Subclinical steatorrhea is common in patients with cirrhosis or obstructive jaundice and leads to fat-soluble vitamin and trace element deficiencies (Gitlin & Heyman, 1984). These deficits are underappreciated in the nutritional assessment of patients with hepatobiliary disease who are undergoing surgery, and such deficits should be corrected.

IDENTIFICATION OF PATIENTS AT RISK FOR POSTOPERATIVE COMPLICATIONS

To use nutritional support appropriately in a cost-effective and clinically efficacious manner, it is necessary to identify which patients are at risk for nutritionally related complications and which would benefit from nutritional intervention. Malnutrition is recognized as an important predisposing factor in the morbidity and mortality of patients undergoing major abdominal surgery (Table 24.1; Mullen et al, 1979). Approximately 48% to 70% of patients with obstructive jaundice (Foschi et al, 1986; Pitt et al, 1981; Padillo et al, 2001) and nearly all patients with advanced cirrhosis undergoing operation have significant malnutrition and are at risk for postoperative complications. Infection is the most common complication in patients undergoing liver and biliary surgery and occurs in 22% to 40% of all patients (Dixon et al, 1983; Foschi et al, 1986; McPherson et al, 1984; Pitt et al, 1981; Smith et al, 1985; Stimpson et al, 1987). Sepsis and sepsis-induced multiple organ failure are the most common causes of death in liver transplant recipients (Colonna et al, 1988; Yokoyama et al, 1989; Torbenson et al, 1998) and in patients with jaundice and cirrhosis undergoing abdominal operations (Armstrong et al, 1984; McPherson et al, 1984; Pitt et al, 1981, 1985). Because most patients with severe liver disease or jaundice are malnourished, and because malnutrition leads to infection, nutritional intervention and repletion may decrease postoperative morbidity and mortality rates in patients undergoing hepatobiliary surgery.

Several prognostic scoring systems have been developed to identify malnourished patients at risk for developing postoperative complications (Buzby et al, 1980). Although no consensus has been reached on the best method for assessing the nutritional status of hospitalized patients, the Nutritional Risk Index (NRI), Maastricht Index (MI), Subjective Global Assessment (SGA), and Mini Nutritional Assessment (MNA) can all be safely applied in the clinical setting with no significant difference in predictive value (Kuzu et al, 2006; Clugston et al, 2006). Although the use of such scoring systems allows prediction of postoperative complications in specific patient groups, their applicability in patients with significant liver disease or cirrhosis is not well established (Shronts, 1988). The most recent (2009) guidelines from the European Society for Clinical Nutrition and Metabolism (ESPEN) recommend the use of simple bedside methods, such as the SGA, for patients with either liver or pancreas disease. Because conventional markers, such as weight status and serum protein levels, are altered and depend on nonnutritional factors, other subjective measures must be relied upon. A dietary and medical history combined with physical examination continues to be the most sensitive means of assessing nutritional risk in patients undergoing hepatobiliary surgery.

The evaluation of a patient's nutritional status should begin with an initial baseline evaluation and continue throughout the patient's course of treatment. A complete nutritional assessment includes 1) physical examination and clinical evaluation, 2) assessment of muscle mass and strength, 3) evaluation of serum albumin and C-reactive protein, 4) assessment of vitamin and mineral deficits, and 5) determination of nutrient requirements (Table 24.2; Shronts, 1988). Historical questions should focus on the patient's nutritional intake, the degree and rate of weight loss over the previous 6 months (Windsor, 1993), use of alcohol, length of time with jaundice, and problems with diarrhea, which may indicate fat malabsorption and steatorrhea. This assessment, although not clinically tested in prospective trials in patients undergoing liver surgery, is similar to the global

Table 24.1

Causes of Malnutrition in Cirrhosis

Poor Dietary Intake
Anorexia, nausea, alcohol abuse, dietary restrictions (protein, fat, sodium, fluid)
Malabsorption/Maldigestion
Cholestasis, intraluminal bile deficiency, coexisting pancreatic exocrine insufficiency, fat malabsorption
Increased Catabolism
Muscle proteolysis
Decreased Protein Synthesis
Decreased hepatocyte growth hormone receptor, IGF-1 and IGF-BP, hepatic transport proteins, fibrinogen, coagulation factors, lipoproteins
Drug Therapy Effects
Neomycin: villous atrophy, diarrhea, zinc deficiency Lactulose: diarrhea, zinc deficiency Diuretics: potassium, magnesium, zinc deficiency Cholestyramine: diarrhea, fat-soluble vitamin deficiency

IGF, insulin-like growth factor; BP, binding protein

Table 24.2

Nutritional Assessment

Clinical Evaluation
Dietary and medical history Physical activity Weight loss over past 6 months
Physical Examination
Body weight Skin changes Ascites Muscle mass and strength
Protein Synthetic Function
Albumin, transferrin Prealbumin, prothrombin time C-reactive protein
Vitamin, Mineral, Trace Element Deficits
Vitamins A, D, E, K, B_6, niacin, folate, B_{12} Thiamine, magnesium, potassium, zinc, iron, phosphorus

Table 24.3

Nutritional Risk Factors for Postoperative Complications in Hepatobiliary Surgery

Weight loss >4% of lean body mass weight over previous 6 months
Serum albumin <3 g/dL
Hematocrit <30%
Skin test allergy
<25th percentile for mid-arm circumference and triceps skin fold
Total body potassium <85% normal

Data from Halliday A, et al, 1988: Nutritional risk factors in major hepatobiliary surgery. J Parenter Enteral Nutr 12:43-48; Harrison J, et al, 1997: A prospective study on the effect of recipient nutritional status on outcome in liver transplantation. Transplant Int 10:369-374; and Pitt H, et al, 1981: Factors affecting mortality in biliary tract surgery. Am J Surg 141:66-71.

nutritional assessment scale of Baker and Detsky (Baker et al, 1982; Detsky et al, 1987) and should provide a sensitive means of detecting patients at risk for nutrition-related problems after surgery. Dixon et al (1983), Pitt (1981), and Halliday et al (1988) and their colleagues identified several nutritional risk factors in patients undergoing biliary tract surgery that were predictive of postoperative morbidity and mortality (Table 24.3). If these factors are identified in a patient being considered for an elective operation, preoperative nutritional repletion is probably indicated.

ANTIOXIDANT NUTRIENT DEPLETION IN THE PATHOGENESIS OF LIVER INJURY

Patients with liver disease, biliary obstruction, bacterial or viral infection, or malnutrition have impaired antioxidant defenses coupled with increased oxidant stresses (Bell et al, 1992; Burra et al, 1992). Additional factors that deplete hepatic antioxidants include smoking, alcohol ingestion, general anesthesia, and surgery (Bulger & Helton, 1998; Goode et al, 1994). This antioxidant depletion likely contributes to increased risk for postoperative infection and multiple organ dysfunction in this patient population. Data from animal studies suggest that a major pathophysiologic event in hepatocellular injury is depletion of endogenous antioxidants (Bell et al, 1992; Burra et al, 1992) at the time of increased oxidative stress from infection (Sugino et al, 1987, 1989), liver resection (Ouchi et al, 1991), or transplantation (Serino et al, 1990).

Patients with chronic liver disease are at particularly high risk for having depleted stores of fat-soluble vitamins. Patients with chronic liver disease (see Chapter 2) have altered bile salt pools and enterohepatic circulation of bile salts, leading to impaired micelle formation, which leads to malabsorption of fat and fat-soluble vitamins A, D, E, and K. Patients with advanced cirrhosis were found to have markedly depleted preoperative plasma levels of vitamin E, vitamin A, and carotene, and these decreased even further after transplantation (Goode et al, 1994).

Patients with cirrhosis have lower antioxidant defenses, which compounds the insult of reperfusion injury by oxygen free radicals. Also, plasma levels of vitamin E decrease significantly in the first hours after surgery or acute injury; a significant reduction in the levels of liver α-tocopherol, an active form of vitamin E, was observed during the first hour of reperfusion in a rat model of liver ischemia (Marubayashi et al, 1984; Maderazo et al, 1990, 1991). Low levels of vitamin E also have been reported in patients with varying levels of chronic liver damage (Goode et al, 1994). Obstructive jaundice often is associated with endotoxemia (Bailey, 1976; Ding et al, 1992), which leads to Kupffer cell production of oxygen free radicals and nitric oxide, which inhibit protein synthesis (Curran et al, 1990). Endotoxemia also reduces endogenous levels of the antioxidants glutathione, vitamin E, and coenzyme Q (Marubayashi et al, 1986).

Two of the most important components of the human antioxidant system are ascorbic acid (vitamin C) and α-tocopherol. Ascorbate is required as a cofactor for many enzymes involved in the scavenging of many free radicals; α-tocopherol has the ability to scavenge intermediate peroxyl radicals and therefore interrupt the chain reactions of lipid peroxidation (Birlouez-Aragon et al, 2003; Halliwell et al, 1990; Traber, 1994), and it is the most important inhibitor of the free-radical chain reaction of lipid peroxidation. Studies in rodents show that supplemental vitamin E significantly attenuates liver I/R injury and hepatic lipid peroxidation (Sugino et al, 1989). In vitro, physiologic concentrations of vitamin E inhibit lipopolysaccharide-stimulated TNF secretion by Kupffer cells, suggesting that subnormal tissue or plasma levels of vitamin E may potentiate macrophage cytokine release (McClain et al, 1994; see Chapters 9 and 10).

Vitamin E has a variety of protective effects on the hepatobiliary system (Leo et al, 1995). It attenuates endotoxemia (Powell et al, 1991; Sugino et al, 1989) and hepatocellular membrane lipid peroxidation and cellular damage after I/R injury (Lee & Clemens, 1992; Marubayashi et al, 1986). In rodents with bile duct obstruction, the concentrations of vitamin E and other antioxidants are reduced in liver tissue (Singh et al, 1992; Sokol et al, 1991). Large doses of enterally administered vitamin E inhibit the release of TNF in models of infection (Bulger et al, 1997; Marubayashi et al, 1989). Under these conditions, vitamin E supplementation improves survival after a septic challenge (Yoshikawa et al, 1984). Pretreatment with α-tocopherol improved adenosine triphosphate (ATP) levels, prevented the increase in lipid peroxidation products, and decreased the loss of hepatic glutathione during the early phase of reperfusion after warm ischemia in rats (Giakoustidis et al, 2002); α-tocopherol also increased the survival of rats with steatotic liver that underwent warm liver ischemia, and it has shown beneficial effects in cold I/R injury (Gondolesi et al, 2002; Eum et al, 2002). These animal studies show a protective effect of vitamin E on liver function and survival during conditions commonly encountered in patients undergoing hepatobiliary surgery.

Vitamin C deficiency is evident in 50% of patients with alcoholic liver disease (Muller, 1995) and is probably even lower in alcoholics who smoke. Vitamin C recycles reduced α-tocopherol and is intimately linked to vitamin E's ability to quench free radical–mediated cellular damage (Sardesai, 1995). The simultaneous administration of ascorbate and α-tocopherol is more effective in inhibiting oxidation than either alone (Niki et al, 1995). Ascorbate and vitamin E are located in different domains; vitamin C acts as a first defense, when the radicals are generated in the plasma, with vitamin E breaking the chain propagation at the cellular membrane level. The synergistic protective effects of vitamin C and vitamin E in preventing lipid peroxidation and cellular damage suggest that these vitamins should be administered together for maximal potential benefit (Bulger & Helton, 1998). A prospective randomized study in patients undergoing

liver resection using an infusion containing 10 mg α-tocopherol acetate and 1 g ascorbate administered prior to reperfusion demonstrated that in the treated group, less plasma lipid peroxidation and acute liver damage occurred as assessed by measurement of the prothrombin time (PT) and aminotransferase levels. The treated group also had fewer postoperative complications (Cerwenka et al, 1999).

The administration of fish oils or omega-3 fatty acids also can influence cytokine and prostanoid release by the intestine (Ogle et al, 1995) and Kupffer cells of the liver (Bankey et al, 1989; Billiar et al, 1988). These observations show that hepatocellular function before and after hepatobiliary operations can be modulated by the administration of specific nutrients and vitamins (Helton, 1994; Marubayashi et al, 1989) and provide a potential opportunity whereby the hepatobiliary surgeon can influence patient outcome by nutritional means. In mice models, administration of omega-3 fatty acids demonstrates trends toward biochemical protection and a marked reduction of necrosis and inflammation after bile duct ligation (Lee et al, 2008). No clinical trials to date have shown that diets supplemented with fish oil, omega-3 fatty acids, or vitamin E improve the outcome of patients undergoing hepatobiliary operations, but this is an area of nutritional support that should be studied in patients undergoing hepatobiliary operations.

SPECIFIC NUTRITIONAL PROBLEMS IN PATIENTS WITH HEPATOBILIARY DISEASES

Obstructive Jaundice

Patients with significant jaundice (see Chapters 2 and 7) often have anorexia and lose weight because of decreased oral intake. Approximately 45% to 70% of patients with obstructive jaundice present with malnutrition as evidenced by greater than 10% weight loss, albumin less than 3 g/dL, decreased triceps skin fold, and impaired delayed hypersensitivity reactivity (Foschi et al, 1986). The NRI is simple to use and can define a high-risk subgroup of patients with obstructive jaundice; an NRI less than 83.5 has been found to be significantly associated with an increased mortality risk and longer duration of hospital admission but not an increased complication rate in this population subgroup (Clugston et al, 2006). The primary nutritional deficit resulting from obstructive jaundice is malabsorption of fat and fat-soluble vitamins. In addition, there is loss of trace minerals, such as phosphate, calcium, magnesium, and zinc, owing to salt formation from unabsorbed dietary fat (Shronts, 1988).

Patients with obstructive jaundice may have ascites secondary to decreased serum albumin levels, but the metabolism of carbohydrates and proteins is rarely altered (Flannigan et al, 1985). Biliary sepsis in a patient with obstructive jaundice contributes to malnutrition by shifting protein synthesis from anabolic protein synthesis to acute-phase protein synthesis (O'Neill et al, 1997). This reprioritization of protein synthesis occurs as a result of endotoxin-stimulated Kupffer cell production of TNF, IL-6, eicosanoids, nitric oxide, and other inflammatory mediators that directly inhibit protein synthesis (Curran et al, 1990; Heinrich, 1990; see Chapters 9 and 10). Because of these derangements, some authors have advocated preoperative biliary drainage (PBD) in both liver and pancreas surgery. A Cochrane 2008 analysis demonstrated that PBD is not recommended in patients who need surgery for obstructive jaundice. However, another recent Cochrane review showed no evidence to support or refute routine endoscopic retrograde cholangiopancreaticography (ERCP) with stenting in patients with malignant pancreaticobiliary diseases awaiting surgery (Wang et al, 2008; Mumtaz et al, 2007). PBD in pancreatic adenocarcinoma should not be routine practice, as it is associated with a stent-related complication rate of 23% and has resulted in a twofold increase in postpancreatectomy infectious complications (Mezhir et al, 2009); however, trials have supported PBD in extended hepatectomy for hilar colangiocarcinoma, if the future liver remnant volume is anticipated to be less than or equal to 30%. To reverse the catabolic effects of chronic endotoxemia and restore hepatic protein synthesis, patients with biliary infection should be treated with biliary decompression for at least 4 weeks before major hepatobiliary surgery to allow hepatocytes to recover their protein synthetic capacity.

Cirrhosis and Liver Failure

Patients with cirrhosis (see Chapters 70, 73, and 74) provide the clinician with a major challenge, as they have multiple hormonal and metabolic alterations (see Chapter 2). Characteristics of cirrhotic patients include wasting symptoms, especially loss of fat and muscle mass; growth failure; glucose intolerance; hyperinsulinemia; insulin resistance; increased plasma glucagon and catecholamines; elevated serum free fatty acids; elevated glycerol; hypoproteinemia; hyperammonemia; hypophosphatemia; and alterations in plasma and cerebrospinal fluid amino acid profiles (Achord, 1987; Henriksen et al, 1985; Petrides & De Fronzo, 1989; Riggio et al, 1984). These hormonal and metabolic aberrations lead to altered metabolism of all three macronutrients: fat, protein, and carbohydrate. The hormonal and metabolic changes seen in cirrhosis also lead to an increased skeletal muscle proteolysis for energy provision, which leads to eventual muscle wasting. In addition, there is increased peripheral lipolysis with a decreased ability to use fat and carbohydrate, which leads to hyperglycemia and hyperlipidemia (Katz, 1986).

Compounding these metabolic alterations are issues that predispose patients with cirrhosis to malnutrition, including decreased dietary intake owing to nausea and vomiting, and the common practice of imposing protein restriction in an effort to prevent encephalopathy. This practice of protein restriction is questionable in an already malnourished patient. Protein restriction exacerbates the problems inherently associated with malnutrition and prohibits the goal of liver regeneration. An alteration of plasma and cerebrospinal fluid amino acid profiles caused by catabolism, impaired hepatocellular function, and portal shunting leads to decreased levels of branched-chain amino acids (BCAAs) valine, leucine, and isoleucine and preferred uptake into the brain of aromatic amino acids phenylalanine, tyrosine, and tryptophan. The increased uptake of aromatic amino acids is thought to alter the production of neurotransmitters, resulting in encephalopathy. This theory led to the use of BCAA as dietary treatment for patients with liver disease (Marchesini et al, 2005). Correcting the serum amino acid profile by BCAA administration aims to reverse mental status changes and promote anabolism (Fischer et al, 1976). Oral supplementation with a BCAA preparation that can be administered for a long period improves event-free survival, serum albumin concentration, and quality of life in patients with decompensated cirrhosis (Bianchi et al, 2005; Marchesini et al, 2003; Muto et al, 2005). Changes in Model for End-Stage Liver Disease (MELD) and Child-Turcotte-Pugh (CTP) scores were

smaller in a BCAA-administered group than in a control group, and serum total bilirubin and serum albumin were better preserved. The incidence of major cirrhotic complications was also lower in the BCAA group than in the control group (Kawamura et al, 2009). ESPEN upgraded the recommendation of BCAA supplementation in decompensated liver cirrhosis in the latest revision of its guidelines in 2006. Recent work has demonstrated that BCAA may affect microinflammation in hepatitis C–positive patients with cirrhosis, reducing the production of oxidative stress and possibly leading to a decrease in the occurrence of hepatocellular carcinoma (HCC) (Ohno et al, 2008). More studies are needed to identify those who might benefit and what the benefit may be from BCAA supplementation.

Liver Resection

Metabolic alterations occur in the regenerating liver after liver resection (Diehl, 1991; see Chapters 5 and 64). Krebs cycle activity is depressed, as is the reduction–oxidation state of the hepatic mitochondria, with a switch from the use of glucose to fat as the preferred source of energy by way of β-oxidation (Nakatoni et al, 1981). Because hyperglycemia and hyperinsulinemia suppress the release of fatty acids from adipose tissue and decrease ketone body production by the liver (Riou et al, 1986), hypertonic glucose infusions and insulin administration should be avoided in the immediate (<6 hours) postoperative period (Ozawa, 1992).

These observations indicate that selective administration of fat or ketone bodies shortly after liver resection or transplantation may be beneficial. In rodents, the provision of intravenous fat (30% of total nonprotein calories) (Hamada, 1993; Nishiguchi et al, 1991) or the ketone body monoacetoacetate (Birkhahn et al, 1989) immediately after liver resection accelerates liver regeneration. The administration of medium-chain triglycerides after liver resection results in better hepatic energy charge and decreased lipid peroxidation compared with the effects of intravenous glucose or long-chain triglyceride infusions (Hamada, 1993).

Sarac and colleagues (1994) hypothesized that increasing fat oxidation preoperatively via fasting would improve liver function after extensive liver resection in rats. Rats subjected to 90% hepatectomy had improved survival to almost 100% when fasted 24 hours before operation and fed oral glucose immediately after operation. Greater use of ketone bodies was observed in the liver of fasted rats, suggesting that the enzyme machinery for using free fatty acids was induced by the previous fast. This and many animal models have demonstrated that glycogen is essential to maintaining hepatocellular integrity and function by supplying glucose for ATP generation. A recent trial that administered high concentrations of glucose to patients intravenously 24 hours before hepatic lesion resection with portal clamping found significantly improved liver function on the first and fifth days postoperatively by reducing liver I/R injury (Tang et al, 2007).

The regenerating liver has an increased demand for specific amino acids, and provision of these in the diet accelerates regeneration. Immediately after liver resection, an abrupt increase is seen in the synthesis of the system A amino acid transporter—which transports alanine, serine, and methionine—but not those of system N (glutamine, histidine, asparagine) or system ASC (e.g., cysteine) (Fowler et al, 1992). Increased system A activity depends on portal glucagon and insulin secretion and substrate amino acid supply (Dolais-Kitabgi et al, 1981); system N and system ASC are not similarly regulated (Fowler et al, 1992). This fact supports the argument by many liver surgeons that enteral administration of glucose is the preferred route of feeding because of the effect on insulin release, which is vital to the function of the regenerating liver (Ozawa, 1992; Ozawa et al, 1974).

Provision of adequate protein and calories is important to ensure adequate liver regeneration. Rats subjected to 50% of normal daily caloric intake for 1 week before and after liver resection had significantly impaired liver regeneration, even when administered exogenous IGF-I, compared with normally fed rats (Sato et al, 1994). Specific types of protein-supplemented diets, such as a nucleoside-nucleotide supplemented total parenteral nutrition (TPN) solution, may improve protein synthesis after hepatectomy (Ogoshi et al, 1989).

John and colleagues (1992) reported that postoperative TPN consisting of 45% fat calories significantly impaired hepatic regeneration and albumin synthesis, caused cholestasis, and increased mortality compared with the same diet administered by the enteral route after 70% hepatectomy in rats. Mortality was 68% in rats fed TPN, 9% in rats fed enterally, and 8% in rats fed chow. This increased mortality rate in TPN-fed rats could be due to increased bacterial translocation and lipopolysaccharide migration across the gut, which overwhelms the limited phagocyte capacity of the remnant Kupffer cell mass (van Leeuwen et al, 1991). The increased mortality rate may also be due to excessive administration of intravenous glucose calories, which adversely affects liver substrate metabolism (Ozawa, 1992; Ozawa et al, 1976). Investigators subsequently showed that the lethal consequences of parenteral nutrition after liver resection in rats could be ameliorated by decreasing the caloric and amino acid load (Delany et al, 1994). A more recent study has demonstrated that increased parenteral caloric intake, and not hyperglycemia, is an independent risk factor for bacteremia in patients receiving TPN (Dissanaike et al, 2007).

Transplantation

In the first 6 hours after liver transplantation (see Chapters 97 and 100), glucose use by the transplanted liver is impaired until the redox state of the mitochondria improves (Ozaki et al, 1991). During this time, the liver preferentially uses fatty acid oxidation for ATP generation (Ozaki et al, 1991; Takada et al, 1993). After 6 hours, normally functioning liver allografts shift substrate use from fat to glucose, whereas failing livers continue to use fat. This shift in metabolism can be followed by measuring the plasma concentration of total ketone bodies and arterial ketone body ratio (Takada et al, 1993). Based on these observations, Takada and colleagues suggested that glucose should be administered in small quantities in the immediate postoperative period without insulin to avoid suppressing peripheral fat mobilization. Glucose infusion should be increased steadily, as mitochondria respiration recovers and the Krebs cycle becomes active. When the redox state of mitochondria is sufficiently improved (e.g., arterial ketone body ratio approximately 0.7), amino acids and increased amounts of glucose can be administered. It has been demonstrated that intraportal insulin administration augments liver regeneration during the first postoperative transplant week by improving hepatic function in live-donor liver transplant recipients (Xu et al, 2009).

The nutritional status of the donor liver may be an important factor affecting posttransplant allograft function. Initially, it

was believed that liver allografts obtained from fasted subjects were more susceptible to anoxic liver injury than allografts obtained from subjects being administered glucose up to the time of liver donation because of an absence of glycogen as a source of glucose from glycolysis in the fasted group (Bradford et al, 1986). In addition, it was shown that livers from fasted animals had enhanced generation of oxygen radicals by Kupffer cells (Gasbarrini et al, 1993). Subsequent work in animal liver transplant models (Astarcioglu et al, 1991; Palombo et al, 1988) and human liver donors (Cywes et al, 1992) showed that glucose administration to the donor increases liver glycogen and ATP content before cold preservation and attenuates liver injury after transplantation.

Work by Sumimoto and colleagues (1993) shows, however, that the effects of fasting and feeding on liver allograft function after cold preservation and reperfusion are more complex. They reported no relationship between hepatic glycogen content and posttransplant function after cold preservation. The same investigators also showed that livers from fasted rats undergo two changes, one that sensitizes it to preservation and reperfusion injury (short-term fast [1-3 days]) and one that increases its tolerance to preservation injury (long-term fast [4 days]). Long-term fasting improves subsequent liver allograft function in rats (Sumimoto et al, 1993). The mechanisms for this protection are unclear, but it may be related to the accumulation of metabolites within the liver that are readily used as a source of energy or to the decreased apoptosis of sinusoidal endothelial cells. A study comparing rats that were orthotopically transplanted with donor rat livers, either fasted or fed, found that the number of apoptotic sinusoidal edothelial cells was significantly higher in the fed group than in the fasted group, suggesting that donor fasting decreases sinusoidal endothelial cell apoptosis after reperfusion, leading to the protection of the liver graft from reperfusion injury (Sun et al, 2001). The latter change may explain why livers from rats subjected to prolonged periods of fasting generate fewer oxygen radicals after reperfusion.

Hepatic Cancer

Hepatic cancer (see Chapters 80 and 81) is commonly accompanied by progressive weight loss, anorexia, and malnutrition. Patients with hepatocellular carcinoma (HCC) usually have advanced cirrhosis, and for that reason, their malnutrition is often more pronounced (see Chapters 2, 70, 72, and 73). Inefficient energy use resulting from increased Cori cycle activity (Holroyde & Reichard, 1981) and other common occurrences with liver damage may be seen, such as increased protein turnover rates with altered amino acid profiles, increased gluconeogenesis, and increased lipid oxidation (Holroyde & Reichard, 1981; Waterhouse et al, 1979; Young, 1977). If jaundice is present, fat malabsorption often occurs in these patients. Profoundly malnourished patients with cirrhosis or chronic active hepatitis and HCC usually are seen initially in an advanced clinical stage, such as Okuda class III. These patients generally should not undergo operation because of a prohibitive operative mortality (Okuda et al, 1985).

Pancreatic Cancer

Pancreatic cancer (see Chapter 58) is associated with a severe metabolic derangement referred to as the *cancer anorexia-cachexia syndrome* (Ryan et al, 1998; Inui, 2002). This syndrome is associated with anorexia tissue wasting, malnutrition, weight loss, and a loss of compensatory increase in feeding. The pathogenesis is dependent on disorders of carbohydrate, protein, lipid, and energy metabolism mediated by cytokine elaboration (IL-1, IL-6, TNF, interferon [IFN] γ, leukocyte-inhibiting factor [LIF], TGF-β) and an overall increase in leptin levels (Bruera et al, 2000; Walker, 2001). Pancreatic cancer has the highest incidence of cachexia among patients with cancer, and up to 80% of such patients have cachexia at the time of their initial diagnosis. For this reason, patients with pancreatic cancer are perhaps the most likely of all patients undergoing hepatopancreatobiliary surgery to benefit from nutritional support strategies.

NUTRITIONAL MANAGEMENT IN PATIENTS UNDERGOING HEPATOBILIARY SURGERY, INCLUDING LIVER TRANSPLANTATION

The primary indication for nutritional support in any patient before and after hepatobiliary surgery is to decrease the incidence of postoperative complications by repleting nutrient deficits that occurred as a result of anorexia, malabsorption, and catabolic states. In addition, nutritional support strives to preserve protein synthesis, prevent hepatocellular dysfunction and injury, and provide a favorable environment for liver cell repair and regeneration. No data support the routine use of nutritional support in well-nourished patients undergoing hepatobiliary surgery. The administration of parenteral nutrition to well-nourished patients undergoing surgery is associated with a higher incidence of postoperative complications (Brennan et al, 1994; Buzby, 1991). Conversely, patients who are profoundly malnourished or deficient in specific vitamins probably benefit from preoperative and postoperative nutritional support (Buzby, 1991; Halliday et al, 1988; Helton, 1994).

Several methods are available to provide patients nutritional support. Most common and most physiologic is an oral diet tailored to the patient's specific needs. If the patient is unable to consume an oral diet or meet the estimated caloric needs orally, a soft silicon nasogastric or nasoduodenal feeding tube should be placed, even in the presence of known esophageal varices. If the patient is unable or unwilling to accept a nasoenteric feeding tube, placing a feeding jejunostomy or gastrostomy tube using the laparoscopic approach should be considered (Duh & Way, 1993); placement of a percutaneous endoscopic gastrostomy tube is associated with a higher risk of complications and is not recommended (ESPEN guidelines, 2006). Lastly, in the rare event that a patient can tolerate oral and enteral nutrients but cannot meet his or her total nutritional needs by oral intake alone, combination diets using partial enteral feeding or partial parenteral feeding are appropriate. Standard parenteral solutions usually are acceptable in these patients. The increased infectious complications and costs associated with parenteral nutrition mandate that this route of feeding be used only when the enteral route is unavailable. Profoundly malnourished patients with malabsorption who develop diarrhea in response to enteral feeding can receive partial enteral nutrition with the balance of calories, protein, fat, trace elements, and vitamins administered by the peripheral intravenous route (Benya et al, 1990).

An enteral formula should be chosen based on the patient's ability to digest and absorb nutrients. For most patients, a

Table 24.4

General Guidelines for Nutritional Support

Oral route > enteral > PICC > TPN
kcal: 30 kcal/kg/day
Nitrogen: 1-1.5 g/kg/day
Glucose: ≤5 mg/kg/min
Fat calories: ≤30% of total calories

PICC, percutaneous indwelling central catheter; TPN, total parenteral nutrition.

standard enteral diet is sufficient. General guidelines for feeding are listed in Table 24.4, and these guidelines are sufficient for most patients. In a few situations, modified specially formulated diets may be beneficial for a patient with hepatobiliary disease or pancreatic insufficiency. In theory, modulating the inflammatory and cytokine systems before operation by the administration of fish oils alone or in combination with antioxidants has the potential to improve patient outcomes (Ok et al, 2003; Persson et al, 2005) but has not been studied to date.

Obstructive Jaundice (See Chapter 7)

If patients are profoundly malnourished, and preoperative nutritional repletion is indicated, an argument can be made for reestablishing bile flow by placing a biliary stent for decompression of the biliary tree before proceeding with a major operation. Before undertaking this step, however, patients should be assessed for their ability to tolerate fat, and dietary recommendations should be made based on this assessment. Generally, restoration of bile flow improves absorption of fat and fat-soluble vitamins. Foschi and colleagues (1986) reported a prospective randomized trial in which patients with obstructive jaundice were randomized to biliary decompression followed by operation or biliary decompression combined with 2 weeks of alimentation followed by operation. Malnutrition was present in 70% of the patients. Of the patients receiving alimentation, 85% received at least partial enteral feeding. Patients receiving alimentation for 2 weeks had lower morbidity (17% vs. 46%), mortality (3.5% vs. 12.5%), and postoperative infection (14% vs. 28%) rates compared with patients receiving only biliary decompression.

When bile flow is not reestablished in patients with biliary obstruction who require nutritional support, ability to tolerate fat in the diet is impaired. These patients should ingest a low-fat diet supplemented with water-soluble forms (e.g., Aquasol E, vitamins A, D, E, and K) of the fat-soluble vitamins. They also should receive supplements of calcium, phosphorus, and magnesium (Shronts, 1988). Rather than struggle with the problems of inadequate oral intake in these anorectic patients, they are more easily and effectively repleted nutritionally by tube feedings because of the ability to administer more physiologically appropriate diets, containing predigested protein (dipeptides and tripeptides) and a blend of medium-chain triglycerides and long-chain triglycerides. These specialized diets help avoid diarrhea from fat maldigestion and malabsorption, because the absorption of medium-chain triglycerides depends on neither bile salts nor pancreatic lipase, as does absorption of long-chain triglycerides (McCullough et al, 1989; Snopko et al, 1991).

Patients with obstructive jaundice require approximately 25 to 35 kcal/kg dry weight to maintain nitrogen balance, and it is recommended that 25% to 40% of total calories be provided by fat as tolerated, but this is unlikely without biliary decompression (McCullough et al, 1989). Patients with externally draining biliary catheters represent a particularly difficult problem, because they not only have problems related to biliary obstruction but also suffer under the added insult of continuous fluid, electrolyte, and protein loss. This situation has become increasingly less common as interventional radiologists and gastroenterologists have gained greater proficiency with biliary drainage procedures.

Cirrhosis and Hepatic Failure (See Chapters 70, 72, and 73)

The following discussion summarizes the essentials of nutritional management of cirrhotic patients. For more detailed discussions, the interested reader is referred to other authors on this topic (Cabre & Gassull, 2001; McCullough & Tavill, 1991; Nompleggi & Bonkovsky, 1994; Shronts, 1988). Hospitalized patients with cirrhosis requiring operation have substantial morbidity and mortality (Rice et al, 1997; Alberino et al, 2001). Because malnutrition is a major problem in these patients, aggressive nutritional support should be undertaken when surgery is being contemplated or carried out. Prospective, randomized clinical trials have shown that hospitalized patients with cirrhosis do not meet their nutritional needs with aggressive daily dietary counseling and have reduced hospital mortality and morbidity when fed via nasogastric or duodenal tubes (Cabre et al, 1990). It is recommended that all hospitalized cirrhotic patients undergoing emergency operation be fed via the enteral route unless otherwise contraindicated; use of parenteral nutrition in these patients is not indicated if the GI tract is functional.

Because the metabolic derangement of advanced liver disease affects all three macronutrients, any dietary intervention needs to supplement all three. The caloric needs of patients with liver disease are increased (35 to 40 kcal/kg body weight/day), particularly if they have ascites (McCullough & Tavill, 1991; ESPEN guidelines, 2006). Protein needs depend on the patient's current nutritional status, ability to tolerate protein, and history or presence of encephalopathy. In a nonencephalopathic patient, 1 to 1.5 g protein/kg dry weight is recommended. If encephalopathy is present, a thorough diet history should be taken to determine the tolerable amount of protein with recommendations to supply at least a minimum 0.5 to 0.7 g/kg dry weight per day.

Fluid and sodium restriction is often necessary, depending on the severity of ascites and edema. A level of at least 2 g of sodium per day is recommended, because lower levels are unpalatable and usually decrease dietary intake further, exacerbating the patient's malnutrition. In cases of intractable ascites, some nutritional support experts (Shronts & Fish, 1993) have recommended a 500 to 1000 mg sodium diet and 1 to 1.5 L of fluid. The authors believe, however, that treatment of massive ascites should rely more on aggressive diuretics rather than drastic limits on fluid intake. Patients with cirrhosis and those with hepatic failure commonly have micronutrient deficiencies of phosphate, magnesium, and zinc; these should be measured, monitored, and aggressively repleted as necessary by the intravenous route (Shronts, 1988). As stated earlier, the use of BCAA-enriched formula should be used in patients with encephalopathy and decompensated cirrhosis, leading to

improved long-term event-free survival and decreased major complications.

Preliminary data suggest that use of recombinant growth hormone may improve nutritional recovery and liver regeneration in cirrhotic patients (Luo et al, 2004). A smaller study demonstrated increased albumin levels and energy metabolism in patients with cirrhosis after a 4-month administration of IGF-I (Conchillo et al, 2005). More recently, patients treated with parenteral nutrition and recombinant growth hormone versus parenteral nutrition alone were found to have increased levels of serum prealbumin, growth hormone, IGF-1, IGF binding protein (IGF-BP)-3, hepatic IGF-1 mRNA, IGF-BP-3 mRNA, and liver Ki67 labeling index (Cao et al, 2007). Although these studies resulted in no actual clinical improvements, this data would encourage further testing of growth hormone in this subgroup of patients.

Liver Resection

Most patients in Western countries undergoing liver resection (see Chapters 90, 91, and 92) have no associated cirrhosis and no need for specialized nutritional support preoperatively or postoperatively. Most can begin an oral diet safely on the first or second postoperative day, and most are able to tolerate a full regular diet within 5 days. Malnourished patients being considered for elective liver resection should receive nutritional repletion preoperatively and postoperatively by the oral or enteral route. In addition, patients undergoing extensive liver resection, particularly patients with compromised preoperative hepatocellular function (e.g., steatosis, chronic viral hepatitis, or cirrhosis), may benefit from specialized nutritional support.

Based on the physiology discussed previously, it is strongly recommended that patients not receive hypertonic glucose infusions in the immediate (<6 hours) postoperative period, because this can interfere with the liver's preferential use of fatty acids for energy and hepatic regeneration. If nutritional support is initiated within 24 or 48 hours after liver resection, it should be administered via the enteral route through a nasoduodenal or jejunal tube. If the patient is profoundly malnourished preoperatively, and the surgeon intends to administer postoperative nutrition, placement of a feeding jejunostomy tube at the time of surgery should be considered.

Nutritional therapy has the potential to attenuate damage to the residual liver in patients scheduled to undergo elective liver resection by preventing further reductions in endogenous antioxidants and by repleting deficient antioxidant defenses. Patients at risk for depleted hepatic antioxidant defenses are alcoholics, smokers, and patients with a long history of obstructive jaundice, chronic biliary infection, or chronic active viral hepatitis (Bulger & Helton, 1998; Helton, 1994). It is imperative that all patients stop smoking and cease ethanol ingestion approximately 2 weeks preoperatively to replete their intrinsic antioxidant defenses and avoid further oxidation stress and lipid peroxidation after operation. It can take 2 weeks of oral vitamin E supplementation to increase vitamin E content significantly in some tissues (Yau et al, 1994). Patients at risk for vitamin E deficits should receive supplements for 2 weeks preoperatively when possible.

A prospective randomized trial evaluated the effect of an antioxidant vitamin infusion (Omnibionta) that included 10 mg of α-tocopherol acetate, 2 mg of dl-α-tocopherol, and 1 g of ascorbate in patients undergoing liver surgery (Cerwenka et al, 1998). An antioxidant protective effect was shown by significantly less postischemic increases in transaminases and prothrombin time (PT) compared with patients who did not receive the vitamin infusion. A 2005 placebo-controlled double-blind study of 47 patients who underwent partial liver resection again demonstrated that the group receiving infusions containing vitamin E had a significantly shorter length of stay in the intensive care unit (ICU) and showed improvement in aspartate aminotransferase, alanine aminotransferase, and glutamic dehydrogenase (Bartels et al, 2004). When considering the fact that vitamins are cheap, safe, and readily available and that patients undergoing hepatobiliary operations are at risk for oxygen radical–mediated injury, it is reasonable to consider administration of vitamin E and vitamin C for several days preoperatively in patients at risk for postoperative complications.

To explore the hypothesis that the remnant liver after liver resection has limited capacity to metabolize glucose, Nishizaki and colleagues (1996) randomized patients after liver resection to receive peripheral glucose infusion (10 kcal/kg body weight/day) or hypertonic glucose via a central catheter for 7 days; both groups were allowed ad libitum food intake when tolerated. The average caloric intake of the two groups was 20 kcal/kg body weight/day (peripheral dextrose) and 30 kcal/kg body weight/day (hypertonic glucose) with no untoward effects from the hypertonic glucose infusion (Nishizaki et al, 1996); patients in that group had improved prealbumin, decreased urinary 3-methylhistidine excretion, and improved nitrogen balance compared with those who received peripheral glucose. The results of this study showed that the remnant liver is not harmed by increased loads of glucose.

A 2006 systematic review of nutritional support after open liver resection concluded that early enteral nutrition is safe, resulting in a significantly lower rate of wound infection and catheter-related complications when compared to parenteral nutrition; however, no differences in mortality were found with either enteral or parenteral nutrition, but patients who received enteral nutrition did show an improved postoperative immune competence (Richter et al, 2006).

Liver Transplantation (See Chapters 97 and 100)

Clinical and experimental observations show that nutrition plays an extremely important role in just about all aspects of liver transplantation. The status of the donor, the function of the transplanted liver, the overall health of the recipient, the rejection process, the absorption and metabolism of immunosuppressive drugs, and a variety of metabolic pathways are influenced by nutrients and how they are administered. Clinical observations show that malnourished patients undergoing liver transplantation have a significantly poorer outcome than well-nourished patients (Porayko et al, 1991; Shaw et al, 1985). Pretransplant nutritional status, hemoglobin levels, and disease severity were independently associated with the number of infectious episodes during hospitalization (Meril et al, 2009). Degree of malnutrition correlates significantly with days spent in the ICU, days spent mechanically ventilated, and length of hospital stay, and it also correlates significantly with mortality after transplantation (Pikul et al, 1994; Meril et al, 2009). Patients who were seen initially at less than 90% of ideal body weight had a longer hospital stay, needed longer ventilatory

support, and had a higher rate of infectious complications; and conversely, patients who were obese also required a longer period of support (Hade et al, 2003).

Liver transplant recipients are predisposed to postoperative infectious complications not only because of severe preoperative protein calorie malnutrition but also because of immunosuppressive drug therapy (O'Keefe et al, 1980, 1981). Profoundly malnourished recipients have an incidence of infectious morbidity and 3-month mortality rates twice that of well-nourished patients undergoing liver transplant (Harrison et al, 1997).

Several studies have investigated the effects of nutritional support in liver transplant patients (Charlton et al, 1992; Chin et al, 1990; Harrison et al, 1997; Hasse et al, 1995; Martin et al, 1993; Mehta et al, 1995; Reilly et al, 1990; Wicks et al, 1994). Based on these studies, patients awaiting transplantation who are malnourished should receive aggressive nutritional counseling and support (Cabre & Gassull, 2001; Harrison et al, 1993, 1997; Plauth et al, 1997). Nutritional supplements, including vitamins, should be taken in an effort to attenuate further nutritional deficits and to replenish losses. Patients who ingest inadequate amounts of calories should be fed via a soft nasogastric feeding tube. In contrast to what most people and physicians believe, these tubes are well tolerated and can be used for months without much difficulty or patient discomfort.

Reilly and colleagues (1990) prospectively studied the effects of three intravenous diets in hypoalbuminemic patients after liver transplantation. The three diets were a BCAA-based TPN solution, a standard TPN diet, and intravenous glucose (Reilly et al, 1990). Both TPN diets provided 1.5 g protein/kg body weight/day and 35 kcal/kg body weight/day. Glucose was limited to 5 mg/kg body weight/min, and the balance of energy was provided as Intralipid 10%. Patients in both TPN groups were extubated and discharged from the ICU a mean of 2.3 days earlier compared with patients receiving only glucose. In addition, overall hospital charges were estimated to be $21,000 less in the patients who received either standard TPN or BCAA-based TPN. The investigators concluded that malnourished patients undergoing transplantation can and should receive postoperative TPN.

Numerous transplant centers subsequently showed that liver transplant patients can be fed successfully and safely by a nasoduodenal or nasojejunal tube within hours after transplantation (Hasse et al, 1995; Martin et al, 1993; Mehta et al, 1995; Sekido et al, 2003; Wicks et al, 1994). Enteral nutrition as early as 12 hours after surgery seemed to improve nutritional parameters and measures of immune function such as total lymphocyte count (Bengmark, 2002; Sekido et al, 2003). In three studies, early initiation of feeding after operation (<24 hours) was associated with a postoperative infection rate that was lower than expected (Hasse et al, 1995; Martin et al, 1993; Mehta et al, 1995; Wicks et al, 1994). In the prospective, randomized study reported by Hasse and colleagues (1995), the enterally fed patients had no viral infections in the first 2 postoperative weeks compared with 17% of patients fed intravenously ($P < .05$). Bacterial and overall infection rates also were decreased in the enterally fed group (14% vs. 29% and 21% vs. 41%, respectively), although the differences did not reach statistical significance. Mehta and colleagues (1995) reported that postoperative liver transplant patients fed immediately via the enteral route had decreased incidence of postoperative ileus (5% vs. 28%; $P < .01$) and started on oral feedings much sooner (8 days vs. 12 days; $P = .07$) than patients fed intravenously. Based on these studies, postoperative nutritional support should be administered via a nasoduodenal or jejunal tube if indicated for nutritional repletion or maintenance.

Based on the hypothesized benefits of increasing glycogen levels of the liver before cold preservation, the University of Toronto Liver Transplant Group carried out a prospective, randomized trial investigating treatment of the donor liver before procurement with a short-term intraportal glucose and insulin infusion (Cywes et al, 1992). This study showed that increasing liver glycogen content decreased preservation and reperfusion injury compared with untreated livers. The protective effect of glycogenation was not clinically apparent and manifested only as differences in serum transaminase levels. The protective effects were predominantly evident in patients with prolonged warm ischemia times, suggesting that the extra glycogen provided substrate for anaerobic glycolysis as the liver rewarmed before reperfusion. Another area under investigation is the use of both prebiotics and probiotics to enhance the GI immune response. A prospective, randomized, double-blind trial treated all postoperative liver transplant recipients with enteral nutrition and a combination of lactic acid bacteria and fibers, thereby reducing bacterial infection rates from 48% to 3% following liver transplantation (Rayes et al, 2005).

Hepatic Cancer

Many liver cancer patients experience major metabolic alterations coupled with some degree of wasting. Each individual patient should be evaluated for current nutritional status, and an individual nutritional plan should be devised to maintain or replete the patient's nutritional status. This includes increased calorie and protein provision when necessary (35 kcal/kg dry weight/day, 2 g protein/kg dry weight/day, and micronutrient supplementation as needed; Fan et al, 1994). Dietary restrictions of any kind should be avoided if at all possible in these patients, including sodium and fluid restrictions.

Fan and colleagues (1994) showed the utility of preoperative and postoperative TPN in patients undergoing elective liver resection for HCC. In this study, the authors randomized 120 patients to one of two groups: standard oral diet preoperatively and intravenous dextrose postoperatively or TPN in addition to oral diet preoperatively and postoperatively. Perioperative nutritional therapy consisted of a solution enriched with 35% BCAA, dextrose, and lipid emulsion (50% medium-chain triglycerides), given intravenously for 14 days (7 days preoperatively for 12 h/day and 7 days postoperatively continuously). The TPN diet provided 30 kcal/kg body weight/day and 1.5 g amino acid/kg body weight/day. The TPN-supplemented group of patients had a reduction in overall postoperative morbidity compared with the control group (34% vs. 55%), predominantly because of fewer septic complications (17% vs. 37%). In addition, less deterioration of liver function was seen, as measured by the change in the rate of clearance of indocyanine green, and less ascites. Postoperative mortality in the perioperative TPN group also was 45% less than in the control group.

Two important aspects of this study are that 90% of the patients had either cirrhosis or chronic active hepatitis, and the average nutritional status of patients in both groups was adequate. The complication rates and deaths were not stratified according to the preoperative severity of malnutrition, and it is

unknown whether the beneficial treatment effect of perioperative TPN was beneficial to all patients or only for patients with malnutrition. Nevertheless, the general conclusion of this well-conducted study was that patients with cirrhosis or chronic active hepatitis with HCC who undergo liver resection seem to benefit from perioperative parenteral nutrition. Postoperative parenteral nutrition with solutions enriched with BCAAs in major liver resections for colorectal metatasis has a positive impact on liver function tests during the postoperative period (Vyhnánek et al, 2008).

Pancreatic Cancer

Although the pathogenesis of the cancer anorexia–cachexia syndrome is better understood, few clinical studies have addressed prevention or treatment of this syndrome in patients with pancreatic cancer. A 2005 Cochrane Database meta-analysis demonstrated a benefit of megastrol as compared with placebo for increased weight gain and appetite in anorexia-cachexia related to cancer, AIDS, and other pathologies (Berenstein et al, 2005). Omega-3 fatty acids have been shown to modulate both proinflammatory cytokines and acute-phase reactants. In pancreatic cancer patients, n-3 fatty acids have decreased the acute-phase protein response and increased serum albumin and fibrinogen (Barber et al, 2004). Eighteen patients with advanced pancreatic cancer received oral supplementation with fish oil and after 3 months had an increase in weight, a significant reduction of acute-phase proteins, and stabilization of resting energy expenditure (Wigmore et al, 1996). Similarly, a report of 20 patients receiving eicosapentaenoic acid, an n-3 fatty acid, also showed a benefit in terms of weight gain and an improvement in performance status and appetite (Barber et al, 1999). Barber and colleagues also found a decrease in IL-6, a rise in insulin, and a fall in the cortisol–insulin ratio in patients with pancreatic cancer who received a nutritional supplement (600 kcal/day and 2 g/day of EPA; Barber et al, 2001).

A prospective, randomized, double-blinded clinical trial showed, in the post ad hoc analysis, that although a diet enriched with n-3 fatty acids did not provide a clear-cut therapeutic advantage, a correlation was found between supplement intake and weight gain, lean body mass gain, and quality of life as compared with intake of an isocaloric control diet not rich in omega-3 fatty acids (Fearon et al, 2003). Further investigations need to be made into the above supplements in pancreatic cancer patients to clarify a possible role in improving survival benefit and quality of life.

SUMMARY

Careful attention must be paid to the hepatobiliary patient's overall clinical condition, inadequacy of diet, and degree of malnutrition to determine the appropriate level, if any, of nutritional support. Inappropriate therapy can result in further metabolic abnormalities and harm to the patient. Increasing evidence shows that specific nutrients administered under specific conditions to selected patients can modulate metabolic events in patients with hepatobiliary disease. Before prescribing nutritional therapy to a patient, a clinician or dietitian with experience and expertise in liver metabolism should be consulted to evaluate the patient, provide recommendations for a diet, and monitor the patient's course.

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CHAPTER 25

Postoperative complications requiring intervention, diagnosis, and management

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OVERVIEW

The literature regarding postoperative adverse events is difficult to interpret, because most reports are retrospective in nature, and the definitions of adverse events vary among institutions. Complication rates may vary by how hard one looks and by what definition an individual surgeon uses to declare a postoperative event as a complication rather than normal postoperative recovery. This is particularly true for retrospective analyses, which likely overlook many events. Over the past decade these difficulties have been addressed through the development of more carefully defined systems for documenting and grading perioperative complications to improve reporting and provide more uniform methods for comparing outcomes across institutions and countries (Bassi et al, 2005a; Clavien et al, 2009; DeOliveira et al, 2006; Grobmyer et al, 2007; Vin et al, 2008). These systems of standardized grading and reporting of adverse events have become the norm in medical oncology trials and are becoming so in prospective surgical trials. Such standardization should improve our ability to define the morbidity of a procedure and to compare morbidity among approaches and institutions.

Over the last 15 years, major hepatic and pancreatic resections have been performed with increasing frequency (Allen, 2007; Brennan et al, 2004; Cameron et al, 2006; Jarnagin et al, 2002; Nguyen et al, 2009; Riediger et al, 2007; Balcom et al, 2001). This increase has been most apparent at high-volume institutions and may be secondary to a trend in specialization. Multiple reports have shown a link between high-volume surgeons and institutions and decreased postoperative mortality for both pancreatic and liver resection (Begg et al, 1998; Birkmeyer et al, 2003; Eppsteiner et al, 2008, 2009; Lieberman et al, 1995). Despite the observed decrease in postoperative mortality, morbidity remains statistically unchanged over time with most large series reporting a 35% to 45% major complication rate following either pancreatic or hepatic resection (Ho et al, 2005; Simons et al, 2009; Turaga et al, 2008).

This apparent improvement in postoperative mortality without an observed decrease in morbidity suggests an improved ability to successfully rescue patients who experience significant postoperative complications. Management of serious complications following pancreatectomy and liver resection has shifted from operative reexploration to interventional or endoscopic procedures (Vin et al, 2008). High-quality imaging and increasing familiarity with the specific perioperative events has led to earlier detection and intervention and a subsequent reduction in the need for reoperation. Percutaneous drainage procedures are now the typical approach to postpancreatectomy leak or abscess, and they can be performed with minimal sedation and low morbidity.

This chapter seeks to outline the most commonly reported postoperative events following pancreatic and hepatic resection and the trials designed to assess technical approaches to reduce these events. We review the current definitions and grading systems for the reporting of these events; outline the management of the most common events, pancreatic leak and perihepatic fluid collection; and provide a detailed discussion of interventional techniques.

PANCREATECTOMY

The mortality associated with pancreatectomy has significantly improved over the last 20 years; however, the morbidity has remained essentially unchanged. Operative mortality following pancreatic resection in large series reported since 2000 is presented in Table 25.1. The overall perioperative mortality has ranged from 2% to 9% for pancreaticoduodenectomy (PD), and reported morbidity rates are between 35% and 43% (Buchler et al, 2000; Mezhir et al, 2009, Muscari et al, 2006; Winter et al, 2006a). Recent studies show significantly improved mortality rates compared with reports from the 1980s and 1990s. This trend is illustrated in perioperative mortality data over a span of more than 25 years at Memorial Sloan-Kettering Cancer Center (MSKCC; Fig. 25.1). In a 5-year period between 1983 and 1990, the mortality rate was 10% in 125 pancreatic resections; between 2006 and 2009, the operative mortality rate was 1.7% in 694 pancreatic resections. The operative mortality rates presented in Table 25.1 are remarkably similar despite the fact that these data are from different institutions around the world.

Complications may occur at the operative site (hemorrhage, leak, obstruction) or remotely (deep venous thrombosis, cardiac arrhythmia, pneumonia). Despite efforts to optimally manage comorbid conditions preoperatively, cardiac and pulmonary events occur following major surgeries. In addition, the combination of prolonged operative time, fluid volume, and underlying malignancy may increase the risk of certain complications unrelated to technique, such as pulmonary embolus, atrial

Table 25.1

Morbidity and Mortality Rates According to Pancreatectomy Procedure

Study	Years Inclusive	N	Morbidity N (%)	Mortality N (%)
Pancreaticoduodenectomy				
Buchler et al, 2000	1993–1999	331	127 (38)	7 (2)
Muscari et al, 2006	1995–1999	300	117 (39)	28 (9)
Winter et al, 2006	1970–2006	1175	415 (35)	26 (2)
Mezhir et al, 2009*	2000–2005	340	147 (43)	9 (3)
Distal Pancreatectomy				
Kooby et al, 2008*†	2002–2006	342	334 (98)	1 (0.3)
Kleef et al, 2007	1993–2006	302	105 (35)	6 (2)
Goh et al, 2008	1986–2006	232	107 (46)	7 (3)
Nathan et al, 2009	1984–2006	704	232 (33)	7 (1)
Central Pancreatectomy				
Sauvanet et al, 2002†	1990–1998	53	22 (42)	1 (2)
Roggin et al, 2006	1993–2005	10	6 (60)	0 (0)
Crippa et al, 2007†	1990–2005	100	58 (58)	9 (9)
Adham et al, 2008	1987–2005	50	18 (36)	0 (0)
Ocuin et al, 2008	2000–2007	13	12 (92)	1 (8)
Hirono et al, 2009	1999–2008	24	12 (50)	1 (4)
Total Pancreatectomy				
Karpoff et al, 2001	1983–1998	28	15 (54)	1 (4)
Billings et al, 2005‡	1985–2002	99	32 (32)	5 (5)
Muller et al, 2007	2001–2006	100	38 (38)	6 (6)
Reddy et al, 2009	1970–2007	100	69 (69)	8 (8)

*Matched case-control study
†Multiinstitutional study
‡Included completion pancreatectomy patients

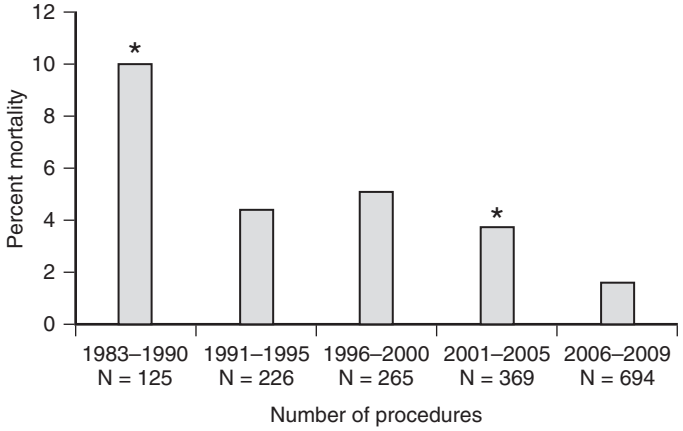


FIGURE 25.1. Trend in 90-day operative mortality rates after pancreatectomy from 1983 to 2009 at Memorial Sloan-Kettering Cancer Center. *P = .01.

dysrhythmia, and pneumonia. The most common severe complications following pancreatic and hepatic resection are directly related to the technical aspects of the operation itself. The frequency of the most commonly reported major complications following pancreatectomy are listed in Table 25.2. These include delayed gastric emptying (DGE), intraabdominal fluid collection or abscess, hemorrhage, wound infection, and anastomotic fistula. A comprehensive list of complications taken from a series of 204 consecutive pancreaticoduodenectomies at MSKCC from 2001 to 2003 is presented in Table 25.3 (Grobmyer et al, 2007).

Pancreatic leak/fistula continues to be one of the most common and most difficult complications following pancreatectomy. Multiple studies have reported pancreatic fistula to be more common following central or distal pancreatectomy compared with pancreaticoduodenectomy (Pratt et al, 2006; Goh et al, 2008; Kleeff et al, 2007; Kooby et al, 2008; Nathan et al, 2009; Ferrone et al, 2008; Reid-Lombardo et al, 2007). The series reported in Table 25.1 also demonstrate that central pancreatectomy (Adham et al, 2008; Crippa et al, 2007; Hirono et al, 2009; Ocuin et al, 2008; Roggin et al, 2006; Sauvanet et al, 2002) and total pancreatectomy (Billings et al, 2005; Karpoff et al, 2001; Muller et al, 2007; Reddy et al, 2009) are procedures associated with slightly higher overall morbidity than PD and distal pancreatectomy, and total pancreatectomy is associated with a slightly higher mortality rate than PD.

Defining and Grading Complications After Pancreatectomy

Accurate identification and reporting of perioperative complications are vital to improve quality of care and to compare outcomes among different institutions and time periods. Without a standardized system for complication recording, there is a significant risk of inaccuracy and underreporting. Recently, several institutions have implemented specific classification and grading systems for surgical complications (Clavien et al, 1992, 2009; DeOliveira et al, 2006; Grobmyer et al, 2007). These systems have developed simplified definitions of postoperative complications and a grading system for severity using therapy-oriented grading schema.

This approach to defining and grading adverse events has been well established in medical oncology. The Common Terminology Criteria for Adverse Events (CTCAE) developed by the National Institutes of Health Cancer Therapy Evaluation Program (CTEP) has been utilized in clinical trials since 1982 (National Cancer Institute's Cancer Therapy Evaluation Program). CTCAE is an example of a universally employed terminology system for complication reporting that has been utilized across medical disciplines. This system also includes a limited schema for postoperative complications. Table 25.4 demonstrates an example of the grading system for common complications following pancreatectomy. The grade of the complication increases with the invasiveness of the treatment required.

Among the complications listed, pancreatic fistula is one of the most severe that can occur after pancreatectomy. The reporting of this complication is arguably the most problematic, as definitions have varied. Pancreatic fistula often precedes other complications, such as abscess and hemorrhage. Inherent to its cause, complications from pancreatic leak, or any anastomotic leak for that matter, often overlap (see Management of Fistula, Leak, and Abscess below). When a postoperative patient

Table 25.2

Common Complications Associated with Pancreatectomy

Study	N	Patients with Complications N (%)	Fistula N (%)	Intraabdominal Collection or Abscess N (%)	DGE N (%)	Hemorrhage N (%)	Wound Infection N (%)	Reoperation Rate N (%)
Pancreaticoduodenectomy								
Buchler et al, 2000	331	127 (38)	7 (2)	4 (1)	54 (16)	12 (4)	13 (4)	13 (4)
Muscari et al, 2006	300	117 (39)	50 (17)	15 (5)	—	18 (6)	—	—
Winter et al, 2006	1175	415 (35)	52 (4)	38 (3)	161 (14)	—	91 (8)	35 (3)
Reid-Lombardo et al, 2007*	1507	—	196 (13)	97 (6)	187 (12)	54 (4)	—	53 (4)
Mezhir et al, 2009†	340	147 (43)	20 (6)	23 (7)	29 (9)	12 (4)	46 (14)	—
Distal Pancreatectomy								
Kooby et al, 2008*†	342	170 (50)	99 (29)	—	—	—	36 (11)	6 (2)
Kleef et al, 2007	302	105 (35)	35 (12)	14 (5)	14 (5)	10 (3)	8 (3)	26 (9)
Goh et al, 2008	232	107 (46)	72 (31)	—	—	—	17 (7)	11 (5)
Nathan et al, 2009	704	232 (33)	203 (29)	36 (5)	—	—	—	40 (6)
Central Pancreatectomy								
Sauvanet et al, 2002*	53	22 (42)	16 (30)	3 (6)	1 (2)	2 (4)	2 (4)	3 (6)
Roggin et al, 2006	10	6 (60)	3 (30)	—	—	1 (10)	—	1 (10)
Crippa et al, 2007*	100	58 (58)	44 (44)	15 (15)	2 (2)	1 (1)	—	0 (0)
Adham et al, 2008	50	18 (36)	4 (8)	7 (14)	—	3 (6)	—	6 (12)
Hirono et al, 2009	24	12 (50)	15 (63)	1 (4)	1 (4)	0 (0)	1 (4)	0 (0)
Total Pancreatectomy								
Billings et al, 2005‡	99	32 (32)	NA	6 (6)	8 (8)	—	4 (4)	2 (2)
Muller et al, 2007	100	38 (38)	NA	2 (2)	8 (8)	2 (2)	2 (2)	15 (15)
Reddy et al, 2009	100	69 (69)	NA	—	11 (11)	14 (14)	18 (18)	—

*Multiinstitutional study
†Matched case-control study
‡Included completion pancreatectomy patient
DGE, delayed gastric emptying; NA, not applicable; —, not available

has fever, tachycardia, and leukocytosis and cross-sectional imaging reveals a perianastomotic fluid collection, the etiology of this collection is likely an anastomotic leak. When the collection is drained, if it is infected, it may be recorded or defined as an abscess. If the fluid is amylase rich, one investigator may report it as a pancreatic fistula and another may report it as a pancreatic leak. This ambiguity is reflected in reports that reflect rates of intraabdominal abscess for pancreatectomy ranging from 1% to 15%. Moreover, the incidence of fistula ranges from 2% to 27% for PD and 12% to 31% for distal pancreatectomy in part as a result of the inconsistent definitions utilized in studies from different institutions.

Toward a Unifying System for Reporting Pancreatic Fistula

Pancreatic fistula has been recently defined by the International Study Group of Pancreatic Fistula (ISGPF; Bassi et al, 2005a). This system has served as a foundation for defining and reporting pancreatic fistula among numerous studies and is an example of the efforts to unify complication reporting. The study group comprised an international panel of pancreatic surgeons working in high-volume centers, and it aimed to develop a simplified and universal definition of pancreatic fistula with a grading system based on clinical impact. *Fistula* was defined as "drain output of any measurable volume of fluid on or after postoperative day 3 with amylase content greater than three times that of normal serum amylase." Three grades were applied according to clinical impact, from grade A (none) to grade C (significant; Table 25.5). As demonstrated in Table 25.6, many institutions have implemented this system for reporting the rates and outcomes of pancreatic fistula.

Independent prospective validation of the ISGPF definition and grading system has been reported. Pratt and others (2006) prospectively analyzed postoperative complications in 176 consecutive patients after pancreaticoduodenectomy. There were 53 patients with confirmed fistulae (30% incidence), categorized in the various grades: 26 patients (15%) were grade A, 21 (12%) were grade B, and 6 (3%) were grade C. No deaths were related to fistula in this study. Patients with grade A fistulas had shorter hospital stays and fewer secondary complications than patients with grade B and C fistulas, although the overall rate of secondary complications between grade B and C fistulas was not significantly different (76% vs. 100%, respectively, $P = .2$). Patients with grade C fistulas had a higher frequency of intensive care unit (ICU) transfer and blood transfusions and longer hospital stays compared with those who had grade B fistulas, and five of the six patients with a grade C fistula were discharged to a rehabilitation facility, significantly more than patients with grade A and B fistulae.

In an economic assessment, the authors reported a correlation between increased health care costs and increase in fistula

Table 25.3

Complications After Pancreaticoduodenectomy

Complication	N	%
Anastomotic leak, pancreas	24	12
Wound infection	22	11
Delayed gastric emptying	14	7
Hemorrhage	10	5
Intraabdominal abscess	8	4
Fascial dehiscence or evisceration	7	3
Supraventricular arrhythmia	7	3
Urinary tract infection	6	3
Anastomotic leak, biliary	6	3
Hypotension, shock	5	2
Cellulitis	3	1.5
Clostridium difficile colitis	3	1.5
Congestive heart failure, left ventricular dysfunction	3	1.5
Myocardial infarction	3	1.5
Renal failure	3	1.5
Apnea or hypoxia	2	1
Atelectasis	2	1
Catheter-related infection	2	1
Deep venous thrombosis	2	1
Dehydration	2	1
Anastomotic leak, intestinal	2	1
Gastrointestinal bleeding	2	1
Pleural effusion	2	1
Pneumonitis	2	1
Sepsis	2	1
Small bowel obstruction	1	0.5
Angina, cardiac ischemia	1	0.5
Aspiration	1	0.5

Modified from Grobmyer SR, et al, 2007: Defining morbidity after pancreaticoduodenectomy: use of a prospective complication grading system. J Am Coll Surg 204(3):356-364.

grade. This study validated the ISGPF classification scheme by demonstrating no clinical consequence of grade A fistulas, whereas grade B and C fistulas led to more complications, longer hospital stays, and higher health care costs.

Randomized Controlled Trials Aimed at Reducing Complications

Multiple prospective randomized controlled trials have been performed to evaluate technique and complications following pancreatic resection. Selected prospective trials published since 2000 are presented in Table 25.7. In general, these studies have reported conflicting outcomes with no specific technique demonstrating superiority. The interpretation of surgical technique trials is difficult, as most trials randomize patients between "the standard technique" at a given institution and a "new," perhaps less familiar technique. These studies are often underpowered, and it is therefore not surprising that equivalency is concluded. Fortunately, none of the reported techniques have been shown to be inferior from an oncologic standpoint, and therefore any of these reported techniques may be considered acceptable in the appropriately selected patient.

Routine preoperative biliary drainage (PBD) has been evaluated in multiple prospective randomized trials. These trials have evaluated both percutaneous external and endoscopic internal drainage (see Chapters 27 and 28). These studies, as well as multiple retrospective case-matched reports, have documented an increase in perioperative complications in patients undergoing PBD (Mezhir et al, 2009; Povoski et al, 1999). A recent prospective, controlled clinical trial randomized patients with serum bilirubin levels between 2.3 and 14.6 mg/dL to PBD or no PBD prior to pancreaticoduodenectomy (van der Gaag et al, 2010). The authors reported 39% significant complications in the no PBD group compared with 74% in the PBD group ($P < .001$). These data support previous prospective and retrospective studies and do not support routine PBD in patients with moderately elevated bilirubin.

Pylorus preservation has been evaluated as a technique to decrease the morbidity of PD (see Chapter 62A). Standard PD with partial gastrectomy versus pylorus-preserving PD (PPPD), with or without extended lymphadenectomy, has also been investigated in randomized trials. As demonstrated in Table 25.7, no benefit was demonstrated for either approach in regard to operative or long-term oncologic outcomes, but extended lymphadenectomy was associated with increased perioperative morbidity, including DGE and pancreatic fistula (Yeo et al, 2002; Seiler et al, 2005).

Pancreatic fistula rates have been assessed according to anastomotic technique in an attempt to reduce postoperative pancreatic fistula. Randomized comparisons have been made between pancreaticojejunal invagination to direct duct-mucosa anastomosis and pancreaticojejunostomy (PJ) to pancreaticogastrostomy (PG). Berger and colleagues (2009) performed a two-institution randomized controlled trial comparing pancreatic invagination to duct–mucosa anastomosis with patients stratified based on the texture of the pancreas. A significant reduction in fistula rates were seen when using the invagination technique (12%) compared with duct-mucosa anastomosis (24%), and leak rates were significantly higher overall in soft glands. Bassi and colleagues (2005b) showed a decrease in DGE, biliary fistula, and abdominal collections with PG; however, these findings have not been replicated by other groups (Duffas et al, 2005; Yeo et al, 1995). No study to date has demonstrated convincingly an optimal method for pancreatic stump closure following distal pancreatectomy (Knaebel et al, 2005); the results of an ongoing, large, multiinstitutional randomized trial may provide some guidance (Diener et al, 2008).

Other adjuncts to reduce pancreatic leak have included somatostatin analogs, stents, and tissue glues. The perioperative use of somatostatin analogs was found to reduce fistula rates in several European trials (Montorsi et al, 1995; Buchler et al, 1992; Friess et al, 1995). However, these findings have not been reproduced in recent large, single, and multiinstitutional studies performed in the United States (Sarr, 2003; Suc et al, 2004; Yeo et al, 2000). Fibrin glue has been applied in two settings to determine its role for reducing pancreatic fistula, applied in a perianastomotic fashion (Lillemoe et al, 2004) or as a plug into the pancreatic duct prior to anastomosis (Suc et al, 2003). Neither study showed a reduction in fistula rates. Two prospective trials evaluated pancreatic stent placement at the time of anastomosis; in one study, a pancreatic duct stent significantly reduced the rate of pancreatic fistula (Poon et al,

Table 25.4

Definitions and Grading of Complications According to CTCAE: Example

Adverse Event and Definition	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Gastroparesis					
An incomplete paralysis of the muscles of the stomach wall, resulting in delayed gastric emptying into the small intestine	Mild nausea, early satiety, and bloating; able to maintain caloric intake on regular diet	Moderate symptoms; able to maintain nutrition with dietary and lifestyle modifications; may need pharmacologic intervention	Weight loss refractory to medical intervention; unable to maintain nutrition orally	—	—
Abdominal Infection					
An infectious process involving the abdominal cavity	—	—	IV antibiotic indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Intraabdominal Hemorrhage					
Bleeding in the abdominal cavity	—	Medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Wound Infection					
An infectious process involving the wound	—	Localized; local intervention indicated (e.g., topical antibiotic)	IV antibiotic indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Pancreatic Fistula					
An abnormal communication between the pancreas and another organ or anatomic site	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

Antibiotic intervention includes antifungal and antiviral therapy.
CTCAE, Common Terminology Criteria for Adverse Events; IV, intravenous; GI, gastrointestinal; TPN, total parenteral nutrition

Modified from http://www.ctep.info.nih.gov.

Table 25.5

International Study Group of Pancreatic Fistula Grading System

Clinical Variable	Grade A	Grade B	Grade C
Clinical condition	Well	Often well	Ill-appearing/ bad
Supportive treatment: PPN/ TPN/enteral nutrition; antibiotics; somatostatin analog	No	Yes/no	Yes
Imaging results (if obtained)	Negative	Negative/ positive	Positive
Persistent drainage ≥3 weeks (± drain in place)	No	Usually yes	Yes
Reoperation	No	No	Yes
Death related to fistula	No	No	Possibly yes
Clinical signs of infection	No	Yes	Yes
Sepsis	No	No	Yes
Readmission	No	Yes/no	Yes/no

Pancreatic fistula is defined as drain output of any measurable volume of fluid on or after postoperative day 3 with amylase content >3 times normal serum activity. Once this criterion has been met, the grading system is applied.
PPN, partial parenteral nutrition; TPN, total parenteral nutrition

Modified from Bassi C, et al, 2005: Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 138(1):8-13.

2007), but the other study did not demonstrate any difference in fistula rates or overall complications (Winter et al, 2006b).

The routine use of intraperitoneal drains following elective pancreatic surgery remains an area of debate. Conlon and colleagues (2001) randomized 179 patients after pancreatic resection (PD or distal pancreatectomy) to placement of intraperitoneal drains or no drains, demonstrating no benefit to routine drainage. Moreover, patients in the drainage group were more likely to have an intraabdominal abscess, collection, or fistula.

Management of Postpancreatectomy Complications

Pancreatic Leak, Fistula, and Abscess

Vin and colleagues (2008) reported a series of 908 pancreatic resections and the rate and management of pancreatic fistula, leak, and abscess. As demonstrated in Figure 25.2, a significant overlap was found among these three separately defined complications in the 158 patients in which they occurred. This further highlights the difficulty in defining discrete complications, the crossover between different definitions, and the clinical relevance of complication grading. In this study, a *pancreatic fistula*, defined as clinical signs or symptoms with amylase-rich drainage greater than 50 mL/day beyond postoperative day 10, was identified in 92 patients; however, in 63 of these (69%), the

Table 25.6

Fistula Rates After Pancreatectomy

Study	N	Definition of Pancreatic Fistula	Fistula N (%)
Pancreaticoduodenectomy			
Buchler et al, 2000	331	≥30 mL amylase-rich fluid (>5000 U) for >10 days	7 (2)
Muscari et al, 2006	300	Fluid with amylase 4 × normal for 3 days or evidenced by imaging	50 (17)
Winter et al, 2006	1175	Drainage of >50 mL amylase-rich fluid on or after postoperative day 10	52 (4)
Reid-Lombardo et al, 2007*	1507	ISGPF classification	320 (21)
Mezhir et al, 2009†	340	Sarr's definition (≥5 days, amylase 5 × normal, >30 mL) drainage of >50 mL amylase-rich fluid on or after postoperative day 10	141 (42)
Distal Pancreatectomy			
Kooby et al, 2008*†	342	Amylase-rich fluid (>350 mg/dL) in any drain and clinical sequelae	99 (29)
Kleef et al, 2007	302	≥30 mL amylase-rich fluid (>5000 U) for >10 days	35 (12)
Goh et al, 2008	232	ISGPF classification	72 (31)
Ferrone et al, 2008	462	ISGPF classification	133 (29)
Nathan et al, 2009	704	ISGPF classification	203 (29)
Central Pancreatectomy			
Sauvanet et al, 2002*	53	Amylase-rich fluid after postoperative day 5	16 (30)
Roggin et al, 2006	10	Drainage of >50 mL amylase-rich fluid on or after postoperative day 10	3 (30)
Crippa et al, 2007	100	ISGPF classification	44 (44)
Adham et al, 2008	50	Clavien classification	4 (8)
Ocuin et al, 2008	13	ISGPF classification	8 (62)
Hirono et al, 2009	24	ISGPF classification	15 (63)

*Multiinstitutional study
†Matched case-controlled study
ISGPF, International Study Group of Pancreatic Fistula

fluid that was drained was culture positive. These patients could therefore have been defined as having either or both a pancreatic fistula and postoperative abscess. Regardless of the definition, patients who develop a pancreatic fistula, leak, or abscess will often evidence similar findings and be treated in a similar fashion. Importantly, the type of complication (fistula, leak, or abscess) was not associated with presentation (fever, leukocytosis) or overall morbidity (duration of drainage, length of stay, ICU admission); however, these factors were similar in patients who had a similar grade of complication.

Vin and colleagues (2008) reported a 90-day mortality rate of 5% in patients who developed fistula, leak, or abscess. These complications were more common in men and in patients undergoing treatment for bile duct, ampullary, and duodenal tumors (63 [31%] of 206) compared with pancreatic tumors (95 [14%] of 702; $P < .001$). Type of resection (PD vs. distal pancreatectomy), tumor histopathologic subtype, and PBD were not associated with occurrence of fistula, leak, or abscess. Surgical drains were placed in 88 patients with these complications. The surgical drain alone, without additional interventional radiologic management, was successful for treatment in 16 (18%) of 88 patients, and 133 patients were managed with percutaneous drainage alone.

Duration of drainage was defined as the time from initial drain placement when performed percutaneously, the date of operation for drains placed intraoperatively, or the date of reoperation for collections requiring operative drainage to the time of drain removal. Mean duration of drainage was 38 days (range, 3 to 228 days). Factors associated with drainage for more than 30 days on multivariate analysis included distal pancreatectomy (odds ratio [OR], 4.3; $P = .01$) and drain output greater than 200 mL during the first 48 hours (OR, 2.9; $P = .02$). In this study, PD patients more often had initial fever, culture-positive collections, and drainage more than 30 days compared with distal pancreatectomy patients. Those in the latter group, by contrast, were more often readmitted, had initial drainage on readmission, and were more likely to have prolonged drainage.

Delayed Gastric Emptying

Delayed gastric emptying (DGE) after PD is common (see Table 25.2) and is typically reported in 9% to 16% of patients. A review of randomized controlled trials for treatment of DGE has been recently published (Traverso & Hashimoro, 2008), examining the literature for level I evidence, and four trials were identified that focused on the prevention of DGE. The largest study from Yeo and others (1993) randomized patients to erythromycin or control and found no reduction in the incidence of DGE. In a separate study, erythromycin did significantly reduce postoperative DGE, but the study was very small, and DGE occurred in 57% of patients in the control arm (Ohwada et al, 2001). Tani and colleagues (2006) randomized patients to retrocolic or antecolic gastrojejunostomy and found a significantly lower rate of DGE with the antecolic approach.

Although DGE and pylorus preservation have been a concern, to date no study has found a difference in the

Table 25.7

Prospective Randomized, Controlled Trials Aimed at Reducing Perioperative Complications After Pancreatectomy

Clinical Variable	Study	Randomization	N	Fistula N (%)	Outcome
PBD	van der Gaag, 2010	PBD	106	8 (8)	46% complication rate from PBD procedures
		Surgery alone	96	11 (12)	No difference in operative complications
Extent of resection	Seiler et al, 2005	PPPD	64	2 (3)	No difference in complications or quality of life
		Standard PD	66	1 (1)	
	Yeo et al, 2002	PPPD	148	9 (6)	Increase in overall complications, DGE, and fistula rates in radical surgery group; no difference in survival
		Standard PD + ELND	146	19 (13)	Statistically significant decrease in fistula rate in patients randomized to invagination
Anastomotic technique	Berger et al, 2009	Invagination	100	12 (12)	No difference in overall complications
		Duct to mucosa	97	23 (24)	
	Bassi et al, 2005	PG	69	9 (13)	DGE, biliary fistula, and abdominal collections favors PG
		PJ	82	13 (16)	
	Duffas et al, 2005	PG	81	13 (16)	No difference in complications
		PJ	68	14 (21)	
	Yeo et al, 1995	PG	73	9 (12)	No difference in complications
		PJ	72	8 (11)	
Somatostatin analogs	Suc et al, 2004*	Perioperative octreotide (10 days)	122	21 (17)	No difference in complications
		No octreotide	108	20 (19)	
	Sarr, 2003†	Perioperative vantreotide (7 days)	135	37 (27)	No difference in complications
		Placebo	140	29 (21)	
	Yeo et al, 2000	Perioperative octreotide (7 days)	104	11 (11)	No difference in complications
		Placebo	107	10 (9)	
Fibrin glue	Suc et al, 2003	Fibrin duct occlusion	102	17 (17)	No difference in complications
		Surgery alone	80	12 (15)	
	Lillemoe et al, 2004	Glue applied topically to PJ	59	15 (25)	No difference in complications
		Surgery alone	66	20 (30)	
Pancreatic duct stent	Poon, 2007	Pancreatic duct stent	60	4 (7)	Significant reduction in fistula rate and hospital stay in stented group
		Surgery alone	60	12 (20)	
	Winter et al, 2006	Pancreatic duct stent	115	13 (11)	No difference in complications
		Surgery alone	119	9 (8)	
Intraperitoneal drainage	Conlon et al, 2001*	Closed suction drainage	88	11 (13)	No difference in overall complications
		No drain	91	– (–)	Increased overall incidence of any complication (fistula, leak, or abscess) in drained group

*Included patients treated with distal pancreatectomy and PD

†Included distal pancreatectomy, central pancreatectomy, and PD

PBD, preoperative biliary drainage; PPPD, pylorus-preserving pancreaticoduodenectomy; PD, pancreaticoduodenectomy; ELND, extended lymph node dissection; PG, pancreaticogastrostomy; PJ, pancreaticojejunostomy; DGE, delayed gastric emptying

incidence of DGE following conventional compared with pylorus-preserving procedures (Diener et al, 2007). As discussed earlier in this chapter, and as highlighted in Table 25.7, the reported incidence of DGE was lower in two studies analyzing anastomotic technique. Bassi and colleagues (2005b) found a statistically significant reduction in DGE in patients who had PG compared to PJ. In the study by Yeo and others (2002), comparing radical with standard PD, an increase in DGE was seen in the radical group. It is important to note, however, that neither study had DGE as the primary end point.

Among these studies, significant variability was observed in the range of reported incidence of DGE. As with pancreatic fistula, part of the variability in incidence across studies was from the variation in definition. The ISGPF recently devised a formal grading system for DGE based on duration of nasogastric tube placement and the timing of patients' tolerance of solid food (Wente et al, 2007).

The authors' current management strategy for patients with significant DGE—that is, the inability to tolerate solid food or prolonged nasogastric tube requirement—is to perform cross-sectional imaging to exclude secondary causes, such as fistula, leak, or abscess. As initial treatment, intravenous metoclopramide is given with or without the addition of oral erythromycin. The possibility of an underlying structural abnormality should be investigated with upper gastrointestinal (GI) series or esophagojejunoscopy, which has the potential to evaluate and treat an anastomotic abnormality. In the setting of prolonged DGE, endoscopic placement of a feeding jejunostomy may be

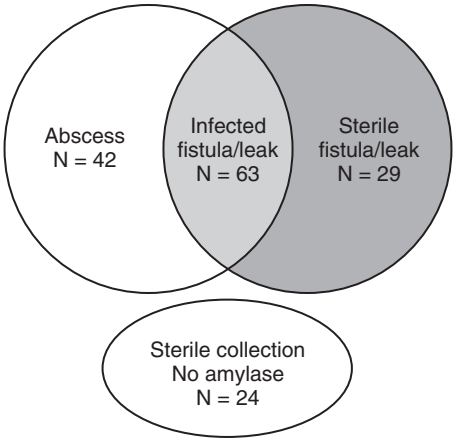


FIGURE 25.2. Categories of 158 postpancreatectomy complications following 908 pancreatic resections at Memorial Sloan-Kettering Cancer Center from 2000 to 2005. *(Modified from Vin Y, et al, 2008: Management and outcomes of postpancreatectomy fistula, leak, and abscess: results of 908 patients resected at a single institution between 2000 and 2005. J Am Coll Surg 207[4]:490-498.)*

required, but reoperation is reserved for patients who fail to progress after prolonged parenteral nutrition and medical therapy.

Hemorrhage

Postoperative hemorrhage is a potentially lethal complication after pancreatectomy, and it can occur in the immediate postoperative period (<7 days) or in a delayed fashion (>14 days). Management is often guided first by the patient's hemodynamic stability. Any unstable patient should be transfused and taken for reexploration. Patients who can be easily stabilized may be candidates for endoscopic or interventional radiologic management. Intraluminal bleeding is most commonly from the gastrojejunal anastomosis and can often be managed with endoscopic therapy. Extraluminal bleeding from arterial pseudoaneurysm (Fig. 25.3) or vascular erosion from a pancreatic fistula typically occur later, following operation, and these can be approached via angiographic embolization in stable patients. A high index of suspicion is critical, as mortality from late postoperative hemorrhage is significant (Brodsky & Turnbull, 1991).

Yekebas and others (2007) analyzed the treatment and outcome of 87 patients who had postoperative hemorrhage in a series of 1669 pancreatic resections in 1524 patients (overall hemorrhage rate, 6%). Hemorrhage was classified as mild in 36 patients (41%) and severe in 51 patients (59%); 29 patients (33%) had a sentinel bleed. The bleeding site was extraluminal in 51 (59%) and intraluminal in 36 (41%); 17 patients had what appeared to be extraluminal hemorrhage, but further evaluation confirmed bleeding from the transected pancreas or resection cavity; and 34 patients (39%) had pancreatic fistula that preceded hemorrhage.

Treatment included endoscopy, angiography with coil embolization, and reoperation. Endoscopic treatment was successful in three (20%) of 15 patients with intraluminal hemorrhage. Any patient with true extraluminal hemorrhage required reoperation, and 17 patients had bleeding from the pancreatic anastomosis and had a secondary anastomotic leak. Among 25 patients treated with coil embolization by angiography, coiling was successful in 20 (80%). Reoperation was performed in 60 patients; in 33, surgery was the first-line treatment of hemorrhage, and the remaining 27 were for failure of nonoperative measures. This included patients with pancreatic fistula (13 patients) and/or vascular abnormalities such as pseudoaneurysm and erosions (12 patients). Fourteen patients died from hemorrhage, for a mortality rate of 16%. All of the mortalities were in the group with delayed hemorrhage, which occurred after postoperative day 5.

This and other studies have demonstrated that significant morbidity and mortality are associated with postoperative hemorrhage, especially when delayed beyond postoperative day 5 (Choi et al, 2004). These patients often require reoperation or interventional radiology procedures to halt life-threatening hemorrhage. Furthermore, patients who experience a postoperative hemorrhage often have underlying complications that require treatment, such as pancreatic fistula. If angiographic embolization successfully treats hemorrhage, cross-sectional imaging should be performed to assess for the presence of leak, fistula, or abscess that would require drainage.

IMAGING AND INTERVENTIONAL THERAPY OF COMPLICATIONS AFTER PANCREATIC SURGERY

Imaging of Complications After Pancreatic Surgery

Imaging plays an important role in identifying complications and directing therapy in patients who have recently undergone pancreatic resection. The observation that 22% of patients undergoing a PD over a 12-year period required percutaneous interventions highlights the importance of imaging and image-guided interventions in the postoperative management of these patients (Zink et al, 2009). Transabdominal ultrasound (US) is a commonly available imaging tool that enables detection of focal, encapsulated, or free intraperitoneal fluid collections, but gastrointestinal gas and/or postoperative pneumoperitoneum superimposition represents the major disadvantage of US in the evaluation of the pancreas (see Chapter 13).

Computed tomography (CT) is the most effective imaging modality for evaluation of the pancreas after surgery (Johnson et al, 2002; see Chapter 16). It allows detection of the normal features as well as postoperative complications such as bleeding, anastomotic leakage, abscess, or fistula formation (Johnson et al, 2002; Scialpi et al, 2005). CT is performed when there is clinical or biochemical suspicion of complications in the early postoperative period (Scialpi et al, 2005). The data sets obtained with modern multidetector-row CT scanners provide voxels that are both submillimeter in dimension and isotropic, enabling reformations in any desired plane with spatial resolution similar to that in the transverse plane. Ideally the multiphase scan protocol includes good oral contrast with unenhanced CT as well as intravenous contrast-enhanced CT, including images acquired during the arterial phase and portal venous phase.

One potential advantage of MRI over CT imaging is the option to perform both contrast-enhanced MRI and magnetic resonance cholangiopancreatography (MRCP) using thick-slab and thin-slab, highly T2-weighted imaging (see Chapter 17). Ishizu and colleagues (1997) reported visualizing the pancreatic duct with MRCP in 91% of patients (69% complete duct visualization and 23% partial duct visualization) who had previous pancreatic surgery. This feature may enable improved



FIGURE 25.3. After Whipple procedure for pancreatic adenocarcinoma, a 63-year-old female patient had clinical evidence of bleeding 3 weeks after surgery. **A,** Abdominal computed tomography during the arterial phase revealed a large hematoma (*arrowheads*) centered in the subhepatic space with central highly enhancing components within this hematoma consistent with the lumen of a pseudoaneurysm at the origin of the gastroduodenal artery (*arrows*). **B,** Conventional angiography confirmed a pseudoaneurysm of the gastroduodenal artery (*arrow*), which was isolated by occluding the proper hepatic (outflow) and common hepatic artery (inflow) with multiple stainless steel coils. **C,** The angiogram after occlusion showed coils in the hepatic arteries (*arrows*) with lack of enhancement of the hepatic arteries and the pseudoaneurysm of the gastroduodenal artery. **D,** After placement of a covered stent (*between arrows*) into the hepatic artery in a 46-year-old male who had gastroduodenal artery stump bleeding after Whipple procedure. Covered stent placement is an alternate treatment to coils that allows preservation of hepatic artery flow.

management of leaks; however, the use of magnetic resonance imaging (MRI) must be balanced by its lower spatial resolution and reduced accessibility compared with CT.

On imaging studies, postoperative fluid collections are the most commonly seen complication of pancreatic surgery. An infected collection (abscess) is characterized by a complex fluid collection, representing pus and detritus, surrounded by a thick rim of contrast enhancement, representing inflammatory tissue (Fig. 25.4). Septations and gas inclusions may also be present. However, a clear differentiation between uninfected postoperative fluid collections with surrounding granulation tissue and abscess cannot be reliably done by imaging, and fine needle aspiration (FNA) is necessary when infection is suspected. Fluid collections after pancreatic surgery may occur in either retroperitoneal or intraperitoneal locations. The location of the fluid collection may suggest its origin. It has been observed that fluid collections around the PJ site were significantly more frequently associated with a pancreatic fistula. Fluid collections around the pancreas have shown elevated amylase values compatible with leakage in 82% of cases, in contrast to perihepatic collections, which have elevated fluid amylase values in only 46% of the collections (Zink et al, 2009; Hashimoto et al, 2007).

One of the most challenging imaging interpretations in the PD patient is distinguishing the jejunal anastomotic loop from a postsurgical fluid collection. The course of the normal loop can usually be followed from its origin to the pancreatic and biliary anastomoses in the right upper quadrant. Rarely, oral contrast refluxes into the loop, which can help identify its

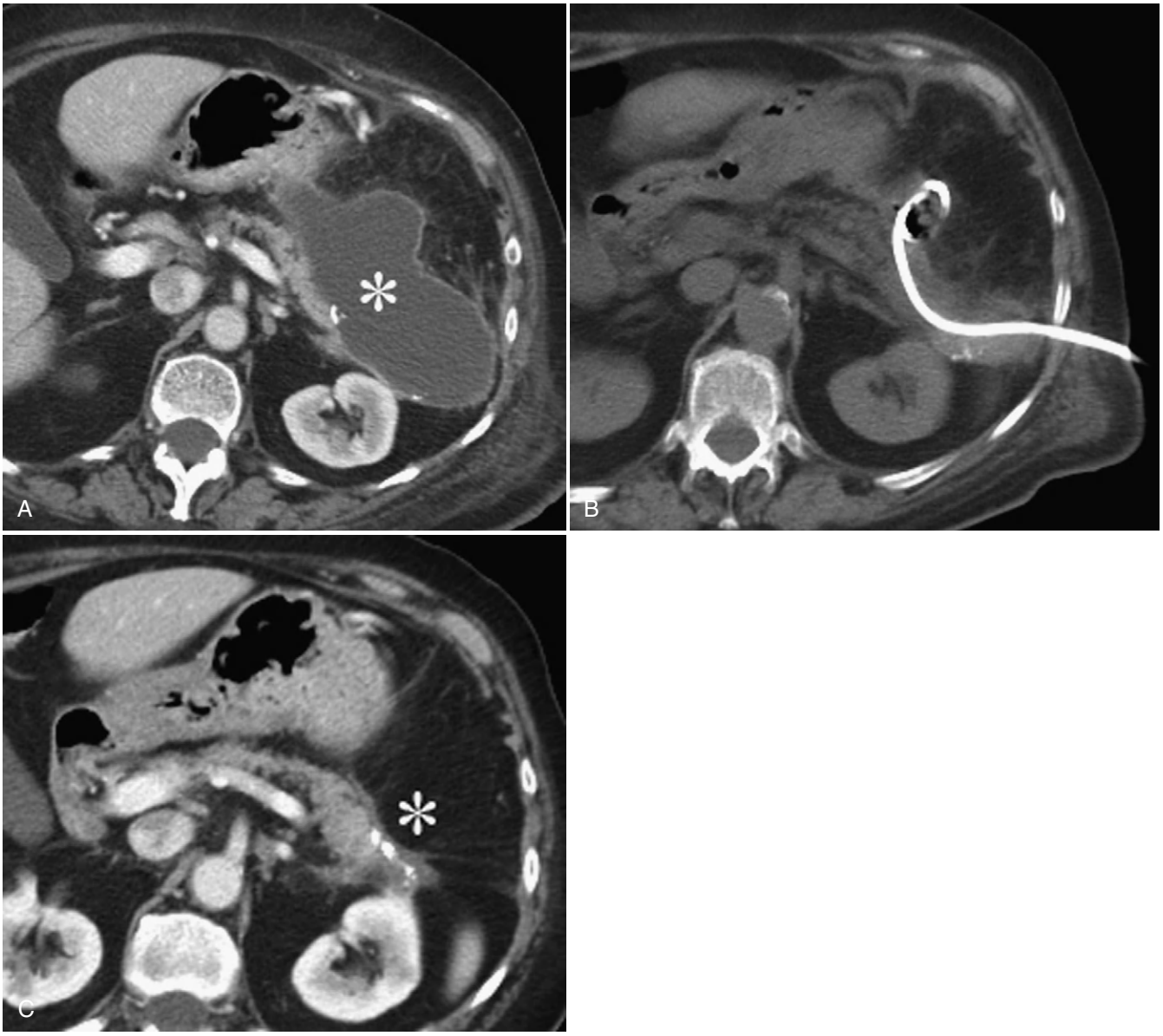


FIGURE 25.4. A 77-year-old female patient after distal pancreatectomy for resection of a neuroendocrine tumor of the pancreatic tail. **A,** Postoperative development of a 14 × 6 cm rim-enhancing fluid collection in the operative bed suspicious for abscess vs. postoperative seroma/pseudocyst (*asterisk*). **B,** Computed tomography (CT)-guided drainage of the fluid collection with a 10-Fr drainage catheter. Rust-colored fluid was aspirated and sent for analysis, which was suggestive of fistula. Culture was negative, and the catheter was removed after the output had diminished. **C,** CT follow-up 10 months after removal of the catheter showed resolution of the fluid collection (*asterisk*).

presence. In some cases, needle puncture of the possible collection with subsequent contrast injection may be necessary to differentiate a postsurgical fluid collection from the normal postsurgical jejunal loop (Gervais et al, 2001).

A fluid-containing pancreatic fistula presents as a tubular tract communicating with the main pancreatic duct, often surrounded by a rim of contrast enhancement. At MRCP, a fistula often shows a highly hyperintense T2 signal because of the pancreatic juice. Fistula can often be demonstrated with CT and MRI/MRCP. It has been reported that with CT, the site of pancreatic fistula, may be identified in 75% of patients compared with 93% with MRI and MRCP (O'Toole et al, 2007).

Finally, hematomas and pseudoaneurysms are important imaging findings after pancreatic surgery. Hematomas may appear as dense collections on CT, and active bleeding may be seen as contrast extravasation. Pseudoaneurysms may be the result of direct injury related to the dissection or to pancreatic fluid eroding a vessel; often they do not occur until several days to months after surgery (Sugimoto et al, 2001). Imaging with CT, Doppler ultrasound (US), or MRI may identify these pseudoaneurysms and help guide intervention (see Chapter 19; see Figure 25.3).

Interventional Radiology Techniques for the Postpancreatic Surgery Patient

Interventional radiology (IR) techniques have become the first-line management choice for many postpancreatectomy complications. Image-guided drainage of intraabdominal fluid collections, percutaneous biliary drainage (PBD), and angiography with vessel embolization permit a less invasive approach to postsurgical complications and frequently mitigate the need for reoperation. Sohn and colleagues (2003) reported the use of postoperative IR procedures in 12% of 1061 patients undergoing PD. And according to Baker and others (2008), these postoperative IR procedures were for intraabdominal abscess drainage (72%), PBD (18%), and angiography with or without embolization (10%).

Image-Guided Abdominal Drainage

One of the major advances in the management of postoperative fluid collections and abscesses over the past 2 decades has been the introduction of image-guided percutaneous drainage procedures, which have changed the management of patients previously requiring an urgent reexploration. Small fluid collections at the resection site are common in the immediate postprocedural period and usually resolve spontaneously. These collections generally do not require an interventional procedure, but they can be aspirated with a needle if there is clinical suspicion for infection (Gervais et al, 2001). Abscess drainage can be performed with US but is done more often with CT guidance (see Fig. 25.4). The technical success rate has been reported to be 96% to 100% (Betsch et al, 2002; Lagan et al, 2008; Zink et al, 2009). The complication rate of interventional drainage of fluid collections is low, however, bleeding and bowel perforation have been reported (Lambiase et al, 1992; Betsch et al, 2002; Lagan et al, 2008; Zink et al, 2009).

There are two widely used techniques of imaging-guided abscess drainage: the *trocar technique* and the *Seldinger technique*. The trocar technique is performed by direct puncture of the abscess using a trocar needle, which is covered by the catheter, and by removal of the trocar needle after the catheter is in position. The Seldinger technique is performed by puncture of the abscess using a coaxial needle, through which a guidewire is inserted into the fluid collection. The needle is then removed, leaving the guidewire in situ. The needle tract is serially dilated by exchange of dilators and guidewires. Finally, a drainage catheter is inserted into the abscess over the guidewire. The advantage of the Seldinger technique is that it is less traumatic to the surrounding tissue because of the initial use of small needles and the subsequent dilation with dilators, until the size of the catheter is reached. The advantage of the trocar technique is that this procedure is easier and faster to perform. Independent of the technique, a wide range of drainage catheters is available, ranging from 6 to 14 Fr in diameter (Gerzof et al, 1978; Goletti et al, 1993; vanSonnenberg et al, 1984). Although no difference has been seen comparing 7 and 14 Fr drainage (Roethlin et al, 1998), the diameter of the catheter may be chosen on the basis of viscosity of the content.

After catheter placement, the abscess is emptied, and specimens are sent for bacteriologic examination and culture and for evaluation of amylase levels. Postprocedural drain care includes local protection of the skin incision and flushing of the drain with gentle saline solution two to three times a day to prevent drain clogging. Documentation of the daily output volume is mandatory to evaluate drain function.

Percutaneous drainage of abdominal fluid collections has been reported to be as effective as operative drainage. No significant differences have been reported in mortality or morbidity, and the duration of hospital stay has been similar when patients were matched for age, sex, diagnosis, and abscess etiology and location (Hemming et al, 1991; Olak et al, 1986).

The earliest experiences with CT-guided percutaneous drainage of abdominal abscesses were reported in the late 1970s (Gerzof et al, 1978). Since then, the efficacy of the procedure has been confirmed in several studies, in which success rates of drainage of abdominal fluid collection or abscesses were 62% to 96% (Zink et al, 2009; Betsch et al, 2002; Lagan et al, 2008; Lambiase et al, 1992; Gerzof et al, 1978; vanSonnenberg et al, 1984; Cantasdemir et al, 2003; Cinat et al, 2002; Freeny et al, 1988). Multiple drainage procedures may be necessary in the same patient to achieve clinical success (Zink et al, 2009; Cinat et al, 2002).

A similar high rate of successful imaging-guided drainage can be achieved in patients with accompanying pancreatic fistula. The reported success rates in patients with accompanying fistulas have been 67% to 89% (Zink et al, 2009; Aassar et al, 1999; Kerlan et al, 1985; Singh et al, 2006). One important prognostic factor associated with decreased success of percutaneous drainage is the presence of yeast in the abscess fluid (Cinat et al, 2002).

Although studies have shown that fluid collections with pancreatic fistulae have similar drainage success compared with fluid collections without an active pancreatic leak, fluid collections with pancreatic fistulae require longer drainage. Zink and others (2009) reported the median duration of drainage in patients with abscess was 29 days compared with 11 days in patients with a sterile fluid collection. Patients with a pancreatic leak had median drain duration of 30 days (Zink et al, 2009).

Percutaneous Biliary Drainage

Biliary obstruction or leak is another example of a complication that can occur after pancreatic surgery that can be managed

using nonoperative techniques. Endoscopic management is possible but frequently difficult because of the alteration in the anatomy as a result of surgery. Malignant strictures can be palliated with a biliary drainage catheter, and metallic stents may be useful, but they frequently occlude in less than a year (Dahlstrand et al, 2009). Therefore, the decision to pursue metallic stenting often hinges upon a patient's life expectancy. Benign strictures can be relieved with balloon dilation but may also recur and require repeated dilations (Kocher et al, 2007). Bile leaks at the hepaticojejunostomy usually require both drainage of the bile fluid collection and PBD to divert bile and allow for the leak to heal (Gervais et al, 2001; Dorico et al, 2008).

Angiography and Embolization (See Chapter 19)

Postoperative bleeding pseudoaneurysms usually occur relatively late after surgery and are associated with a high mortality rate (Rumstadt et al, 1998). In a report by Otah and colleagues (2002), the average presentation was 19 days after surgery, and the majority of patients were already discharged home. All patients in this report first had a sentinel bleed with minimal blood seen in drains or in the GI tract. *Sentinel bleeds* were defined as the appearance or paradoxical increase in the amount of blood from the abdominal drains or GI tract combined with a decrease in hemoglobin of 2 g/dL at least 3 days after surgery (Tien et al, 2008). This has led some to take a very aggressive approach to the presence of even minimal bleeding beyond 3 days after resection. CT angiography can sometimes identify the vessel of interest, however, this potential benefit must be weighed with the additional contrast dose needed to perform CT. Given that the likely bleeding source will be identified on angiography, the CT may not be beneficial, especially in patients with borderline renal function. Many believe angiography with possible embolization should be pursued in the presence of a sentinel bleed, with reoperation reserved only for the presence of active, massive bleeding or failed embolization (Otah et al, 2002; Blanc et al, 2007). The success rate is approximately 85% (Tsai et al, 2007).

Pseudoaneurysms after pancreatic surgery occur in the gastroduodenal artery most commonly, followed by the hepatic artery, superior mesenteric artery, and splenic artery (Tien et al, 2008). Selective coil embolization across the pseudoaneurysm is successful in approximately 85% of patients (Tsai et al, 2007). More recently, however, some have reported the use of covered stents, instead of coils, to exclude the pseudoaneurysm while preserving flow to distal structures supplied by the injured vessel (Narumi et al, 2007; Suzuki et al, 2009; Wallace et al, 2007). A demonstration of these images and techniques is shown in Figure 25.3.

Drain Management

After catheterization of the abscess, a specimen is obtained for microbiology and chemistry studies (amylase, bilirubin). The collection is drained before gentle contrast injection to limit possible bacteremia that might occur in a distended collection during injection. Contrast injection can identify fistulae and may show additional pockets of drainable fluid. Once drainage is complete, imaging should be obtained to document a collapsed cavity. The catheter should be marked at the skin site as an indicator of possible migration during the patient's follow-up management. Saline flushes should be used two to three times daily to maintain a patent tube.

After patients have defervesced and otherwise improved clinically, they may be eligible for discharge with their catheters for home management. Whether the patient is in the hospital or at home, the catheter output should be carefully monitored. If the daily net output remains high (>50 mL) for several days, an ongoing fistula or leak may be present. If the daily net output diminishes to fewer than 10 mL, consideration should be given for a tube study to evaluate for a functional tube, particularly if any systemic signs of recurrent infection are evident. A saline flush should be easily injected into the tube with the complete volume returned upon aspiration. If the tube is functional and has not been dislodged, and the patient is not having pain or fever, then it may be removed. On the other hand, if the saline flush cannot be completely aspirated, the tube has been moved from its skin marking, or the patient's clinical condition has changed, then the tube should be imaged.

Imaging method depends on physician preference: some prefer a fluoroscopic tube injection; others prefer a CT scan, and others still prefer both studies. The fluoroscopic contrast injection will show the remaining cavity size and the presence of fistula. The CT can also show the cavity size but not necessarily a fistula. If the CT shows a collection remaining around the catheter, a malfunctioning tube must be suspected, as functional tubes should have no collection around the tube. If imaging demonstrates nondraining locules, some prefer to try an intracavitary tissue-type plasminogen activator (TPA). One report showed an 89% success rate using TPA to drain abscess refractory to simple catheter drainage (Beland et al, 2008). The risk of bleeding should be carefully considered prior to the use of TPA in a postpancreatectomy patient, and this should be utilized only in carefully selected patients.

Postpancreatic drains may be present for several weeks. The study by Vin and colleagues (2008) demonstrated a mean duration of 38 days (range, 3 to 228 days). Pancreatic drains ideally require an active participation by the patient or patient's caregivers.

Supportive Management of Pancreatic Fistula

Patients with infected fluid collections are typically treated with broad-spectrum antibiotic therapy until clinical signs and symptoms of infection resolve. To date, no strong clinical evidence is available to show that somatostatin analogs enhance fistula closure (Stojadinovic et al, 2003). A recent prospective trial randomized patients with pancreatic or enterocutaneous fistulae to intramuscular injection of 30 mg of a sustained-release somatostatin analog, lanreotide, or placebo (Gayral et al, 2009). The investigators found a significant reduction in fistula output within 72 hours of injection (primary end point), however, no difference was found in fistula closure rates (secondary end point).

To date, no evidence of any benefit has been shown for supplemental parenteral or enteral nutrition in patients with pancreatic leak who can tolerate oral intake. It is our general practice to allow patients ad libitum feeding as tolerated. More aggressive supportive care, such as total parenteral nutrition, is reserved for patients with secondary complications precluding oral intake or extremely high output that is responsive to initial bowel rest. Patients are managed in the hospital until they have return of oral intake and bowel function and can reliably manage their drain with or without nursing assistance.

Reoperation

Improvements in interventional and endoscopic techniques have reduced the need for reoperation in many patients after

pancreatic resection. Reoperation is still necessary, however, in 3% to 5% of patients following pancreatic or liver resection, and it should be considered in patients with clinical deterioration from hemorrhage, abscess, leak/fistula, or intestinal ischemia. Reoperation rates, as seen in Table 25.2, range from 4% to 15% and vary according to type of pancreatic resection. Standop and others (2009) reported their series of 31 patients (11% of 285 consecutive PDs) who required reoperation. The most common indications for reoperation were hemorrhage (29%) and intraabdominal abscess (23%). Among patients who required reoperation, 45% required a second operative procedure. The mortality rate among patients requiring reoperation was 13% compared with 2% for the cohort of patients that did not require reoperation. Significant mortality in patients requiring reoperation is as high as 60% in some series, indicating the critically ill nature of these patients (Hoshal et al, 2004).

HEPATECTOMY

A large series of hepatic resection reveals that the morbidity associated with open resection ranges from 14% to 45%, and the reported mortality ranges from 0% to 3% (Table 25.8; Jarnagin et al, 2002; Adam et al, 2006; Cescon et al, 2009; Huang et al, 2009; Imamura et al, 2003, Palavecino et al, 2010; Poon et al, 2004; Rees et al, 2008; Koffron et al, 2007). The outcome following hepatic resection has significantly improved over the last 20 years. In 1977, Foster and Berman first reported a multicenter analysis of 621 hepatic resections. In this report, the overall mortality was 13%, and it was more than 20% in patients who had major hepatic resection. The most common cause of operative mortality was hemorrhage. Large series from high-volume centers published in the late 1990s have reported mortality rates of less than 5% (Fan et al, 1999; Gayowski et al, 1994). The significant improvements are multifactorial and include a better understanding of hepatic anatomy, modern cross-sectional imaging, improved anesthetic techniques, improved patient selection, and the use of parenchymal-sparing resections. These innovations have significantly reduced the incidence of massive hemorrhage, which is no longer the dominant cause of death after hepatic resection. The perioperative mortality rate over the last 20 years at MSKCC reflects this trend, with operative mortality rate decreasing from 4.3% from 1996 to 1997 to 1.3% in 2000 to 2001 ($P < .001$). From September 2001 to September 2009, we performed 1877 hepatic resections, and the 90-day mortality rae remained at 2.1%. Over the past 8 years, median estimated blood loss was slightly lower (300 mL), but mean hospital stay remained the same (9 days). With this reduction in hemorrhage, a shift has been seen toward hepatic failure and infectious complications being the leading causes of death after hepatic resection.

The most commonly reported complications following hepatectomy are presented in Table 25.8. In the series of 1803 patients reported by Jarnagin and others (2002), the most common complications arose from the liver and biliary tract that included perihepatic abscess, hepatic failure, sterile perihepatic fluid collection, and bile leak or biloma. Pulmonary complications were the second most frequent complication and included symptomatic pleural effusion, pneumonia, and atelectasis. These findings are similar to other large series that have carefully documented complications by system; these are presented in Table 25.9 (Cescon et al, 2009; Imamura et al, 2003; Jarnagin et al, 2002; Poon et al, 2004).

Factors associated with the development of perioperative complications after hepatectomy have been examined in large series. In the series reported by Jarnagin and colleagues (2002), one of the patterns noted over time was a significant increase in parenchymal-sparing segmental resections and a decrease in the number of hepatic segments resected. This corresponded to a decrease in blood loss, decreased use of blood products, and shortened hospital stay (Table 25.10). On multivariate analysis,

Table 25.8

Morbidity and Mortality Rates After Hepatic Resection from Large, Single-Institution Series

Study	Years Inclusive	N	Primary Hepatic or Biliary Tract Cancer N (%)	Metastatic Disease N (%)	Benign Disease N (%)	Major Hepatectomy N (%)*	Morbidity N (%)	Mortality N (%)
Primary and Metastatic Disease								
Jarnagin et al, 2002	1991–2001	1803	375 (21)	1249 (69)	161 (9)	1568 (87)	817 (45)	55 (3)
Imamura et al, 2003	1994–2002	1056	522 (49)	188 (18)	205 (19)	305 (29)	208 (20)	0 (0)
Poon et al, 2004	1989–2003	1222	878 (72)	156 (13)	188 (15)	757 (62)	396 (32)	39 (3)
Koffron et al, 2007†	2001–2006	300	43 (14)	60 (20)	177 (59)	119 (40)	27 (9)	NR
Huang et al, 2009	1986–2005	2008	1663 (83)	128 (6)	834 (42)	638 (32)	281 (14)	12 (0.6)
Cescon et al, 2009	1985–2007	1500	673 (45)	532 (36)	295 (20)	479 (32)	337 (23)	45 (3)
Palavecino, 2010	1998–2007	1557	247 (16)	1249 (80)	61 (4)	958 (62)	407 (26)	15 (1)
Metastatic Disease Only								
Rees et al, 2008	1987–2005	929	Colorectal metastases	—	—	605 (65)	242 (26)	14 (2)
Adam et al, 2006	1983–2004	1452	NCNN metastases	—	—	799 (55)	320 (22)	32 (2)

*Hepatectomy or extended hepatectomy
†Laparoscopic resections only
NR, not reported; NCNN, noncolorectal nonneuroendocrine

Table 25.9

Common Complications Associated with Hepatectomy

Study	N	Patients with Complications N (%)	Required Transfusion N (%)	Liver Failure N (%)	Perihepatic Abscess N (%)	Bile Leak/ Biloma N (%)	Sterile Perihepatic Collection N (%)	Pulmonary Complication N (%)	Pleural Effusion N (%)	Wound Infection N (%)
Jarnagin et al, 2002	1803	817 (45)	880 (49)	99 (6)	110 (6)	47 (3)	97 (5)	344 (19)	154 (9)	94 (5)
Imamura et al, 2003	1056	208 (20)	230 (22)	1 (.1)	87 (8)	97 (9)	NR	274 (26)	194 (18)	43 (4)
Poon et al, 2004	1222	396 (32)	414 (34)	47 (4)	33 (3)	NR	NR	164 (13)	63 (5)	115 (9)
Cescon et al, 2009	1500	337 (23)	548 (37)	86 (6)	41 (3)	56 (4)	NR	NR	97 (7)	NR

NR, not reported

two factors predictive of morbidity and mortality included the number of hepatic segments resected (Fig. 25.5) and operative blood loss. Retrospective data from MSKCC, as well as those from other institutions, have shown that a parenchymal-sparing approach is associated with less perioperative morbidity without compromising oncologic outcome in appropriately selected patients (Gold et al, 2008; de Haas et al, 2008). Independent predictors of morbidity following hepatic resection in the series from Jarnagin and colleagues (2002) included major concomitant biliary procedure or vascular resection, lower preoperative albumin, and elevated preoperative creatinine. Additional factors associated with increased mortality included elevated preoperative bilirubin, complex hepatic resection, a lower preoperative platelet count, and increased age.

Attempts to reduce complications following hepatic resection have been aimed at techniques to reduce blood loss, operative time, and the requirement for transfusion (see Chapter 22). One major advance in liver surgery has been the concept of low central venous pressure (CVP) anesthesia during resection. It has been demonstrated from retrospective (Melendez et al, 1998) and prospective randomized controlled trials (Wang et al, 2006) that maintaining a low CVP (<5 mm Hg) results in reduced blood loss, lower morbidity, and increased preservation of renal function after hepatic resection.

Techniques for parenchymal transection and their association with postoperative complications have been extensively studied (Pamecha et al, 2009; Poon, 2007). Techniques for parenchymal division include crush clamping, stapling, vessel sealing systems (i.e., LigaSure, Covidien, Boulder, CO), and multiple options for ultrasonic dissection with or without intermittent inflow occlusion. Among the numerous techniques studied in randomized trials, there does not appear to be a single "best" option. Since most studies are performed by high-volume, experienced liver surgeons, it may be difficult to show small differences among techniques (Palavecino et al, 2010; Arita et al, 2005; Ikeda et al, 2009; Patrlj et al, 2010). A recent Cochrane review analyzed seven randomized controlled trials comparing methods for parenchymal division, which included

Table 25.10

Trends in Operative Results After Hepatectomy at Memorial Sloan-Kettering Cancer Center (1983–2001)

Variable	1992–1993 (259)	1994–1995 (339)	1996–1997 (393)	1998–1999 (420)	2000–2001 (392)	*P* value
Three or more segments resected (%)	70	66	58	61	57	.004
Segmental resections (%)	16	27	32	32	33	<.001
Blood loss (mL, median)	810	750	600	500	500	<.001
Blood loss (mL, mean)	1180 ± 70	1125 ± 70	878 ± 54	710 ± 44	641 ± 35	<.001
Operating time (hours, median)	3.8	4.0	4.2	4.1	4.1	<.001
Hospital stay (days, mean)	11.7 ± 0.4	10.9 ± 0.4	10 ± 0.4	10.1 ± 0.5	9.5 ± 0.3	<.001
Morbidity (%)	50	41	47	46	44	.67
Mortality (%)	3.5	4.1	4.3	2.4	1.3	.01

Modified from Jarnagin WR, et al, 2002: Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. Ann Surg 236(4):397-406.

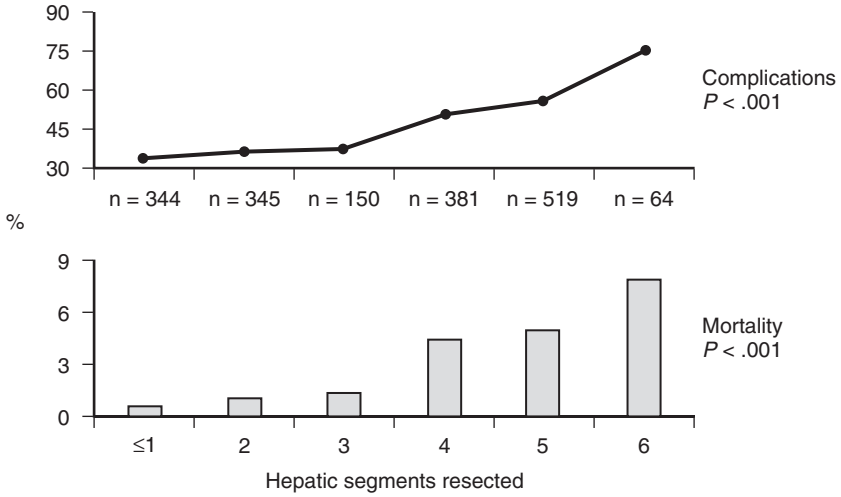


FIGURE 25.5. Perioperative complications and mortality rate stratified by the number of hepatic segments resected. *(Reproduced from Jarnagin WR, et al, 2002: Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. Ann Surg 236[4]:397-406.)*

556 patients (Pamecha et al, 2009). The authors concluded that the crush-clamp technique was the procedure of choice, because the parenchymal transection devices offered no improvement in time or reduction in blood loss compared with crush clamping. In addition, the crush-clamp technique was faster in many of the studies examined. In one positive randomized controlled trial, Lesurtel and colleagues (2005) found that the crush-clamp technique with intermittent vascular inflow occlusion was more effective in terms of reduced time and blood loss and more cost efficient than ultrasonic dissection devices.

An additional technique to potentially reduce the need for perioperative blood and plasma transfusion is intraoperative acute normovolemic hemodilution (ANH), which has recently been studied in a prospective randomized trial at MSKCC (Jarnagin et al, 2008), where 136 patients undergoing major hepatectomy (three or more segments) were randomized to ANH or standard low-CVP anesthesia techniques. Patients randomized to the hemodilution arm had a reduction in the overall perioperative transfusion rate, but this did not reach statistical significance (50% vs. 25% in the standard arm; $P = .067$). ANH patients did have a statistically significant decrease in intraoperative transfusions and had higher postoperative hemoglobin levels compared with the control arm. Furthermore, where intraoperative blood loss was 800 mL or greater, hemodilution patients had a statistically significant decrease in both red cell and plasma transfusion rates. Hemodilution was safe and effective, yet the ideal patients for routine use are currently not defined.

In an effort to better predict the need for intraoperative transfusion, Sima and colleagues (2009) developed a nomogram for perioperative transfusion risk. Factors such as number of segments in the planned resection, malignant versus benign diagnosis, anticipation of extrahepatic resection, and decreased preoperative hemoglobin and platelet count predict the risk for potential transfusion, and blood conservation techniques such as acute normovolemic hemodilution may be planned preoperatively.

The need for routine intraperitoneal drains following hepatic resection has been studied in a prospective manner. Fong and colleagues (1996) randomized 120 patients to drain or no drain following hepatic resection; patients were stratified based on extent of resection, and no difference was found in overall morbidity, perioperative mortality, or requirement for percutaneous drainage between groups. The authors reported that in the 50 subsequent hepatic resections following completion of the trial, only four patients (8%) required percutaneous drainage. These results were concordant with a recent Cochrane review, which demonstrated no evidence for routine placement of intraperitoneal drains following elective hepatectomy (Gurusamy et al, 2007). Currently, it is our practice to drain selectively, and we consider routine drainage only in those patients who have ongoing biliary leakage from the hepatic transection surface and/or a bilioenteric anastomosis created at the time of resection.

Imaging and Interventional Therapy of Bile Leaks and Abscesses After Hepatectomy

Imaging

US, helical CT, and MRI/MRCP are the noninvasive diagnostic procedures widely applied to the liver and biliary system. Ordinary postoperative fluid collections, bilomas, hematomas, and abscesses can be detected with these modalities. Acute and subacute hemorrhage usually shows a typical high density in CT and can therefore be reliably diagnosed with this modality. In addition, active bleeding can be demonstrated by contrast media extravasation on contrast-enhanced CT. In particular, the typical appearance of biloma on imaging is that of an encapsulated mass with space-occupying and space-conforming characteristics contiguous with the liver resection plane or biliary structure (Vujic & Brock, 1982). Repeated imaging may be necessary to clearly differentiate between uninfected postoperative fluid collections and abscesses because of overlapping. In addition, an ordinary postoperative fluid collection may progress to become an abscess. FNA may be necessary to rule out infection when a patient's condition is suspicious for infection and imaging shows an equivocal fluid collection.

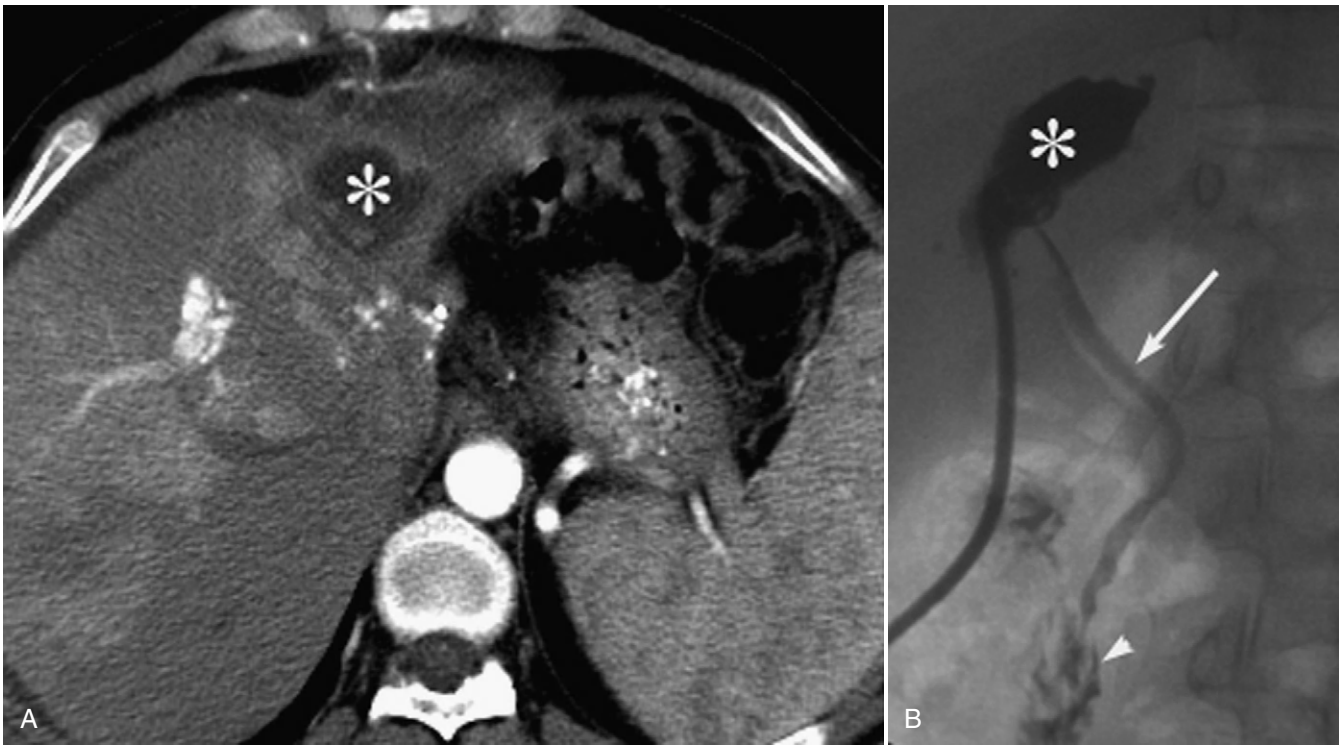


FIGURE 25.6. A 46-year-old male patient with HIV and hepatitis B infection after partial left hepatectomy as a result of hepatocellular carcinoma. **A,** Postoperative follow-up computed tomography revealed a fluid collection at the liver resection site (*asterisk*); it was treated with percutaneous catheter placement. **B,** Contrast injection into the cavity under fluoroscopy revealed the small cavity (*asterisk*) communicating with the common hepatic bile duct (*arrow*). Contrast media is noted in the duodenum (*arrowhead*). Endoscopic retrograde cholangiopancreatography was performed, and a plastic stent was placed into the common bile duct to decrease the output of the fistula.

Interventional Procedures for Treating Posthepatectomy Patients

Hepatic Abscess Drainage

Percutaneous drainage of a hepatic abscess is a minimally invasive, image-guided procedure that carries lower morbidity and is less expensive compared with surgical treatment (Ferraioli et al, 2008). Preparation for the procedure includes evaluation for coagulopathy, choosing the imaging modality for guidance during the procedure (US or CT), and choosing the appropriate route of access. Single abscesses may be drained with US guidance, whereas multiple abscesses may require CT guidance and placement of multiple catheters (vanSonnenberg et al, 2001).

The technical success rate of US- and CT-guided hepatic catheter drainage has been reported to be 94% to 96% (Liu et al, 2009). Abscesses located near the dome of the diaphragm may be technically more difficult to drain without transgressing the pleura, but clinical success rates for percutaneous drainage of intrahepatic abscesses of 70% to 100% have been reported (Akinci et al, 2005; Attar et al, 1986; Dondelinger et al, 1990; Gerzof et al, 1985; Giorgio et al, 2006; Rajak et al, 1998; Mezhir et al, 2010). We reported that yeast in culture and the presence of an obstructed biliary tree were independent predictors of failure of percutaneous drainage of pyogenic hepatic abscess (Mezhir et al, 2010). When biliary obstruction is present, relief of the obstructed biliary tree is mandatory for successful abscess treatment (Fig. 25.6). Size and the presence of loculations did not preclude successful percutaneous drainage in this study.

Although single, small abscesses are generally adequately treated by percutaneous drainage, debate continues on the optimal treatment of large, multiloculated abscesses. Nonetheless, similar clinical success rates of 82% to 92% have been reported for single and multiple abscesses and for single multiloculated and multiple multiloculated abscesses (Liu et al, 2009; Ogawa et al, 1999). Other authors have reported higher success rates for unilocular abscesses and have proposed a treatment algorithm, with small abscesses being treated with antibiotics alone; large, unilocular abscess with percutaneous drainage plus antibiotics; and large, multiloculated abscessed treated with surgical therapy (Hope et al, 2008). It has been reported that repeated catheter drainage improves the success rate (Hope et al, 2008). The clinical success rate for treatment of unilocular abscesses was 83% if a single drainage was performed and 100% if repeated drainages were performed. The success rate for treatment of multilocular abscesses was 33% for single drainage and 50% if repeated drainages were performed (Hope et al, 2008). Some suggest use of intracavitary TPA to aid with multiloculated collections refractory to simple percutaneous drainage (Beland et al, 2008).

Several studies have shown the superiority of percutaneous catheter drainage over needle aspiration. For abscesses, needle aspiration was successful in 60% to 92% of patients, whereas percutaneous catheter drainage was successful in 97% to 100% of patients (Giorgio et al, 2006; Rajak et al, 1998; Singh et al, 2009; Zerem & Hadzic, 2007). Among the successfully treated patients, the average times for clinical improvement, hospital stay, and total resolution of the abscess were similar in the two

treatment groups (Giorgio et al, 2006; Rajak et al, 1998; Singh et al, 2009; Zerem & Hadzic, 2007). In one study no significant difference in the success rate between aspiration and drainage was reported, but multiple aspirations were required in the aspiration group to achieve success (Yu et al, 2004).

Interventional Management of Bilomas and Bile Leaks

Hepatic tumor surgery may also be complicated by biliary leak. It is known that a large number of ordinary postsurgical bile leaks heal spontaneously (Czerniak et al, 1988), but many perihepatic bilomas require percutaneous drainage, particularly those that become infected (Christoforidis et al, 2007). In cases of persistence of a fistula, patients may have prolonged hospital stays (Czerniak et al, 1988). Endoscopic transpapillary drainage or PBD may serve to decompress the biliary system and divert bile flow from the defect in the bile ducts, which may lead to healing of the fistula without need for repeat surgery.

Percutaneous transhepatic biliary drainage has been proven as a low-risk procedure that provides a considerable reduction in repeat laparotomy (Cozzi et al, 2006; Funaki et al, 1999; Kaufman et al, 1985; Vaccaro et al, 1991). It has been reported that percutaneous transhepatic bile drainage was successful in patients with bile leaks in 81% to 90% (Cozzi et al, 2006, Funaki et al, 1999, Ernst et al, 1999) and that technical success was achieved in 90% to 100% when the bile ducts were not dilated (Cozzi et al, 2006; Funaki et al, 1999). Several authors have reported that the success rate of percutaneous or endoscopic treatment depends on bile leak location: success rates are higher when bile leaks are located at the resection plane of the liver, and they are lower when bile leaks occur in the area of the main bile ducts (Fragulidis et al, 2008; Lo et al, 1998).

Supportive Management

Patients are managed using pathway constructs following hepatectomy at MSKCC. This includes daily measurement of white blood cell count, hemoglobin, platelets, and electrolytes including phosphate levels, liver function tests, and international normalized ratio. Especially after major hepatectomy, there can be significant phosphate depletion in the early postoperative period. In addition, aggressive pulmonary toilet and early mobilization is critical to prevent pulmonary complications in patients following hepatic resection.

Supportive management after intervention for bile leak or perihepatic abscess is similar to that for complications after pancreatectomy. Patients who tolerate adequate oral intake and who are able to manage their abscess drain independently or with nursing care can be sent home.

References are available at expertconsult.com.

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CHAPTER 26

Quality of life and hepatopancreatobiliary tumors

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QUALITY OF LIFE

Quality of life (QoL) is a clinically and biologically meaningful outcome for the oncologic patient. Historically, surgical, procedural, and interventional outcomes have been measured in clinical and objective terms using end points such as morbidity, mortality, and disease-free survival. In the 1990s, there was increased recognition of the need to evaluate the patient's subjective experiences, how they felt and functioned. Measurement of a patient's QoL throughout the clinical course should be standard practice. A surgeon often manages the care of a hepatopancreatobiliary cancer patient beyond the surgical procedure alone. Management includes orchestrating diagnostic tests, biliary interventions, and percutaneous ablative therapies. For any of these procedures, the goal of the physician is to minimize the impact on a patient's function and to improve overall QoL (Langenhoff et al, 2001; Miner et al, 2002; Blazeby & Vickery, 2001; Sajid et al, 2008; Pallis & Mouzas, 2004; Sun et al, 2008).

Surgical resection of malignant tumors of the liver, bile ducts, gallbladder, and pancreas is performed for both curative and palliative reasons. Hepatopancreatobiliary surgical outcomes have continued to improve, because advancements in presurgical imaging and surgical techniques have resulted in better patient outcomes, fewer complications, and higher survival rates. After recovery from surgery, while a patient remains disease free, QoL is usually excellent. For those patients who are not candidates for a curative resection, palliation is the major treatment goal (Sun et al, 2008; Abraham et al, 2002; Singhal et al, 2005). Indications for palliative surgical resection include locoregional disease control and surgical bypass to relieve biliary or gastrointestinal obstruction (Nakakura & Warren, 2007; Koninger et al, 2007). Resolution of symptoms such as pruritus, anorexia, fatigue, and pain and improvement of QoL are the major treatment goals.

In the past 10 years, QoL data in the literature have grown significantly. These data can facilitate physician-patient conversations regarding treatment options, especially in the palliative setting. Most of the reports in the literature provide insight into procedural outcomes and their effect on symptoms and QoL. The end result is a more robust clinical understanding of the trajectory of the disease process and of the differing effectiveness of the treatment options. Even though the importance of QoL and symptom assessment is increasingly recognized, much research has yet to be done. Current literature does not delineate well between outcomes in different subgroups; for many procedures, it is not clear what patient characteristics predict a better outcome versus no significant gain or a decline in QoL. As more information becomes available, our understanding of clinical QoL assessment outside of a research setting will be better, with a more direct application to patient care.

This chapter defines and describes QoL as it pertains to patients with hepatopancreatobiliary cancers. Questionnaires commonly used to assess QoL are reviewed, and guidelines for designing QoL studies in this population are presented. An overview of currently available QoL studies is presented to allow for more focused discussions by disease type and procedure. Finally, the future of QoL investigations in hepatopancreatobiliary patients is discussed.

Definition of Quality of Life

In 1947, the World Health Organization (WHO) broadened the definition of health to include not only the absence of disease but also "the complete physical, mental, and social well-being of a person" (WHO, 1947). Karnofsky and Burchenal (1949) subsequently outlined basic criteria for evaluation of new chemotherapeutic agents, describing a simple scale to measure the effect of nitrogen mustard on patients with lung cancer. In the years following, numerous anticancer therapies emerged that increased survival, but toxicities were significant. Izsak and Medalie (1971) sought to identify the "costs of survival" among cancer patients. Noting that a growing number of patients with cancer were surviving longer, they began looking at the lives of the survivors from multiple angles, namely the psychological, behavioral, and environmental aspects. This new insight into patient health care caused a dramatic increase in interest in the new field of QoL research (Aaronson, 1988). One event that placed QoL end points in the spotlight was the controversial approval of gemcitabine for the treatment of pancreatic cancer on the basis of a beneficial clinical response. The "surrogate end point" of clinical benefit was likened to improvement in QoL based on the parameters of pain intensity, analgesic consumption, performance status, and weight gain (Burris et al, 1997). The concept of clinical benefit has increased dialogue about pancreatic cancer and QoL and undoubtedly has raised awareness of the importance of QoL assessment in palliative care settings.

In an effort to better describe clinical benefit, the term *health-related quality of life* emerged and has come to include the aspects of QoL that are most influenced by health and health care interventions (Kassa & Loge, 2002). The terms *quality of life* and *health-related quality of life* are often used interchangeably, but no single definition of either exists. There is consensus, however, that QoL is multidimensional and at a minimum encompasses physical symptoms, treatments, functional ability, family factors, emotional well-being, intimacy, and social aspects (Cella, 1998).

The broad overuse of the term *quality of life* has led to the misleading notion that measurements of performance status (e.g., Karnofsky and Eastern Cooperative Oncology Group, 1949), clinical indicators (e.g., bilirubin level), or symptom checklists adequately reflect QoL (Blazeby & Vickery, 2001). Other clinical factors—including laboratory values, postoperative complications, and time spent in the hospital—also have been translated into QoL results. Although these assessments have value in clinical care and research, care must be taken not to mistake or substitute them for proper QoL measurement.

Applications of Quality of Life Assessments in Surgery

In the past, informal feedback from patients regarding symptoms and functional status combined with the clinician's objective assessment was considered sufficient for making judgments about patients' QoL. Over the past few decades, a demand for more information about the broader effects of treatment and illness has required more formal definitions and evaluations of QoL (Blazeby & Vickery, 2001; Gouma et al, 1999; Barbarisi et al, 2001). In addition to defining the patient's physical, psychological, and functional problems, QoL assessments also evaluate surgical outcomes, compare treatment options, aid preoperative selection of patients, predict prognosis, and monitor quality of care. In the case of neurosurgical measurements of QoL, the standard remains the Karnofsky Performance Status (KPS) set by Karnofsky and Burchenal (1949), which only addresses three variables of QoL: 1) work, 2) activity, and 3) self-care (Meyers & Weitzner, 1995).

Quality of Life as an Outcome

Outcomes research is a new and interesting field in clinical research and in daily clinical practice. In 1996, the American Society of Clinical Oncology published a special article to clarify effectiveness of cancer treatments (ASCO, 1996). Outcomes were divided into cancer outcomes (response rate) and patient outcomes (survival and QoL). As a surgical outcome, QoL has become an issue of increasing importance. The American College of Surgeons has dedicated a section of its Surgical Forum to QoL and outcome studies since 1996 (Tassinari et al, 2003; Velanovich, 2001). More holistic patient outcomes can be given priority over cancer outcomes in several situations. Examples of surgical trials in which consideration should be given to QoL data are 1) adjuvant trials in which a moderate risk of disease recurrence is present; 2) trials in which survival is not expected to differ between treatment arms, but QoL might be affected; 3) trials in which the primary intent is palliative; and 4) equivalency trials in which lesser surgical procedures are done with the expectation that survival and tumor control will be equal (Whalen & Ferrans, 2001).

Comparing Treatment Options

Along with the morbidity and mortality statistics given to patients during discussion of treatment options, QoL data should be included to provide concrete information about severity and duration of side effects and possible functional limitations. This information may be particularly helpful when presenting the option of adjuvant therapy. Considering the multiple factors that must be weighed when recommending appropriate palliation, QoL results may help or even be the deciding factor in treatment decisions. Frank discussions between physicians and patients about what to expect could lead to more informed decision making.

Psychological Screening

For many patients with newly diagnosed cancer, the psychological trauma can be quite intense. This is particularly true for patients with hepatopancreatobiliary cancer, most of whom face an uncertain future, with much of their remaining time consumed by oncologic treatment. The psychological impact of receiving such a diagnosis and living with the disease is profound. Depression and anxiety have been reported in 50% of patients with pancreatic cancer before their diagnosis, and several studies have suggested hormonal and neuropsychiatric links to explain this phenomenon (Holland et al, 1986; Passik & Breitbart, 1996; Passik & Roth, 1999). Attention to the emotional sequelae of hepatopancreatobiliary cancer may improve QoL and treatment adherence significantly. QoL questionnaires and/or psychological questionnaires may be used early in the diagnosis to identify problems that may not otherwise be detected during routine evaluation. Linden and colleagues (2005) found the Psychological Screen for Cancer to be an important tool in screening and for "following changes in patient distress throughout the cancer care trajectory." Early identification of depression or anxiety allows for prompt evaluation by a mental health professional. Subsequent intervention with psychotherapy and/or medication may result in better psychological outcome for many patients.

Prognostic Indicators

QoL data have been shown to have prognostic value in several chemotherapeutic trials in patients with advanced metastatic colorectal cancer. Earlam and colleagues (1996) reported physical symptom scores were better predictors of survival than tumor size. In three large studies, QoL scores were independent predictors of survival; QoL was a stronger predictor of survival than clinician-rated performance status in two of these studies (Earlam et al, 1996; Schoffski et al, 1996; Maisey et al, 2001). One author concluded that QoL measurement may help stratify patients in clinical trials and may facilitate comparisons between studies (Blazeby & Vickery, 2001; Conroy & Blazeby, 2003). Pretreatment QoL was found by de Graeff and others (2001) to be a strong predictive indicator in the assessment of cancer survival in which performance status, physical functioning, and well-being were the QoL variables. For many patients with primary liver cancer or metastatic neuroendocrine cancer in the liver, treatment is often palliative and multimodal in nature, consisting of surgical, hormonal, ablative, and chemotherapeutic approaches. QoL assessment as a prognostic indicator and stratification tool may be useful for treatment algorithms and may help patients with poor performance status avoid futile treatments.

Physician-Patient Communication and Decision Making

The surgical oncologist is responsible for explaining surgical and ablative treatment options and for discussing treatment side effects, potential for cure, and impact of treatment on QoL. Physicians should have open discussions with patients as they advise them in these important treatment decisions. The physician opens the door for better communication by first trying to understand the value each patient places on issues such as survival, toxicity, disease-free interval, and impact on functional status; by matching treatment options to the patient's value

system, the physician can become more effective. Research has shown that patients differ greatly in how they view risk/benefit ratios. A study evaluating treatment options for elderly patients found that meetings with a facilitator along with written information allowed the patient and the family to make decisions better suited to their QoL needs (Matulonis, 2004). Knowledge of and effective communication of QoL results may lead to better informed, shared decision making and ultimately may improve the physician–patient relationship and the outcome (D'Angelica et al, 1998).

QUALITY OF LIFE AFTER HEPATOPANCREATOBILIARY SURGERY

Over the past 10 years, hepatopancreatobiliary operations have moved from high morbidity and high mortality procedures to procedures that are safe and effective in an experienced surgeon's hands. When procedures are performed with the intent to cure, patients are usually accepting of a short-term decline in QoL as a part of recovery from surgery or as a surgical or procedural complication (Perez et al, 1997). When consenting for a procedure, patients usually assume the risks of the surgery willingly as the price of a cure. In this setting, assessment of QoL improves understanding of the impact of a surgery. On the other hand, for both procedural and surgical palliative interventions, patients are less forgiving of postprocedure complications that cause a decline in QoL in the face of an imminently diminishing life span. Therefore QoL becomes an important outcome to include when evaluating a palliative intervention.

Miner and others (2002) offer insight into outcomes after palliative surgeries for advanced malignancy. Their study, limited by a small number of subjects (n = 36) and early mortality (median survival, 108 days), found that 54% of the patients who underwent palliative operations for unresectable disease experienced no clinical improvement after surgery, and these patients died significantly sooner than those who experienced a benefit. For those who did experience an improvement in QoL, duration of improvement was a median of 3.4 months. The surgeon's preprocedure predictions regarding ability to relieve symptoms were correct 78% of the time for those with positive outcomes, while he or she only mistakenly thought they could ameliorate 1 (7%) of the 14 patients who did not improve. The reasons for the surgeon proceeding with the surgery in the belief of a poor clinical outcome were not discussed. Prior to surgery, 26% of patients expressed fear that they did not expect to survive the surgery; patients also reported a strong relationship with their surgeon before the surgery, and this did not change significantly afterward.

Unfortunately, the study found that 46% of patients undergoing palliative surgery expressed hope that their physician would find no evidence of disease at the time of surgery (Miner et al, 2002). This belief cannot simply be attributed to optimism, hope, or a delusional process; however, it is likely that these patients harbored misconceptions regarding the procedure that were not corrected during the consenting process. It is critical that patients understand that a palliative procedure is being done *only* to improve QoL; a cure cannot be achieved, and there will still be evidence of disease. Furthermore, patients should have a realistic expectation as to whether the goal of palliation is achievable. Surgeons should trust their clinical judgment regarding their ability to bring about a favorable clinical outcome as well as the potential for futility. These opinions should be discussed with patients, and such discussions are likely to be in depth and difficult; but the end goal of more realistic patient expectations should not be undervalued, and this is an important topic in palliative medicine that should be further explored.

Existing research is deficient in taking QoL analysis to the next step, in which data are used to identify subsets of patients who are more likely to experience a QoL benefit from various procedures. Currently, QoL data offer insight into the patient experiences at one moment in time, or if collected at more that one time point, how their perspective changes over time. This information fills in the clinical picture, but in a clinical trial, the data are often presented as a stand-alone component, not linked to other outcomes. If QoL analysis is considered to be equivalent to a clinical parameter, such as decline in serum bilirubin, it will provide a more balanced view of surgical outcomes. This information can then be correlated with preprocedural characteristics to provide clinicians with information for evidence-driven decisions regarding clinical recommendations.

Measurement and Interpretation of Quality of Life End Points

It has been established that QoL is an important outcome that should be incorporated into surgical oncology, but the problem remains: How should it be measured? Specifically, what should be measured? First, the concept needs to be clearly defined, because a great deal of variability surrounds the way QoL might be measured in a clinical trial. In a review of QoL studies in six major surgical journals, Velanovich (2001) found that many studies made errors in conceptually defining QoL and in choosing QoL questionnaires. Passik and Kirsch (2000) suggested a "levels of evidence" approach to understanding QoL end points in clinical trials. Such an approach is based on the type and sophistication of the questionnaire chosen for the trial and the conclusions one can make from the resulting data. This approach may be helpful in interpreting QoL conclusions made by authors and in aiding investigators in trial design (Table 26.1). The European Organization for the Research and Treatment of Cancer (EORTC) has placed the evaluation of QoL on questionnaires such as the QLQ-C30, SF-36, and the Rotterdam Symptom Checklist and on modules specific to the disease and treatment (Giannakopoulos et al, 2005). Better understanding of the QoL concept would help the investigator design a study, and it would help to make the published results more meaningful (Koller & Lorenz, 2002; Sprangers, 2002).

Types of Quality of Life Instruments

QoL instruments can be broken down into three general categories: 1) generic, 2) cancer specific or symptom specific, or 3) modular. Generic instruments are multiitem scales designed for use in a wide range of chronic diseases. Examples include the Nottingham Health Profile (NHP), Medical Outcomes Short Form Health Survey (SF-36), and the Sickness Impact Profile (SIP). These are well-validated instruments best suited for comparisons of QoL results across different chronic health conditions. They are generally not sensitive enough to detect changes after interventions for cancer. Cancer-specific or symptom-specific instruments address problems specific to cancer patients. Examples of these are the Spitzer QoL Index (QLI), the Functional Living Index-Cancer (FLIC), and the

Table 26.1

Levels of Evidence for the Determination of QoL in Clinical Trials

Level of Evidence	Approach Taken	Explanation
Low	Single items	This approach includes the use of face-valid items only. Typically, these are designed by researchers for a particular study and have not been piloted or validated by any formal psychometric means.
Middle (A)	Conversion of existing tools	This approach is highlighted by the adaptation of tools from traditional psychology and psychiatry to oncology and assuming that they will be valid and reliable indicators for cancer patients (e.g., Ways of Coping population questionnaire).
Middle (B)	Assessment of a singular domain of QoL	The middle level of evidence also may focus on measuring a single domain of QoL. Typically, the focus is placed on physical well-being and measurement of side effects of treatment (e.g., toxicity ratings of treatments).
High	Multidimensional assessment of QoL	The highest level of evidence requires a multidimensional approach. This should cover the domains of physical, psychological, social, and functional well-being (e.g., FACT, FLIC, CARES).

QoL, Quality of life; FACT, Functional Assessment of Cancer Therapy; FLIC, Functional Living Index-Cancer; CARES, Cancer Rehabilitation Evaluation System

From Passik S, Kirsch K, 2000: The importance of quality-of-life endpoints in clinical trials to the practicing oncologist. Hematol Oncol Clin North Am 14:877-886.

Gastrointestinal Quality of Life Index (GQLI). These scales assess QoL issues common to cancer patients in general but usually lack disease or treatment specificity. Many single-symptom scales abound and include the McGill Pain Questionnaire, the Constipation Assessment Scale, the Piper Fatigue Scale, and numerous others.

Perhaps the gold standard of QoL instruments for cancer patients is the modular questionnaire. Two examples are the Functional Assessment of Cancer Therapy (FACT), also known as the Functional Assessment of Chronic Illness Therapy (FACIT), and the EORTC QLQ-C30. They combine assessment of overall QoL domains—physical, social, functional, and emotional well-being—with disease-specific subscales or "modules." This approach often eliminates the need for multiple instruments yet results in general and disease-specific or treatment-specific QoL information. The FACT and QLQ-C30 are multilingual and are widely used around the world. They are considered by many experts to be the most valid and standardized instruments for QoL assessment in cancer patients, and each has disease-specific subscales developed for use in patients with hepatopancreatobiliary cancer, such as the FACT-HEP (Blazeby et al, 2004; Fitzsimmons et al, 1999; Heffernan et al, 2002; Kavadas et al, 2003; Pallis & Mouzas, 2004). The FACT-HEP is shown in Figure 26.1, and the QLQ-C30 is shown in Figure 26.2. Disease-specific subscales for the QLQ-C30 include the QLQ-LMC21 (metastatic colorectal cancer), PAN-26 (pancreatic cancer), and HCC-18 (hepatocellular carcinoma).

Questionnaire Selection

Since the inception of QoL research in the 1970s, there has been a proliferation of questionnaires, also known as *instruments* or *measures.* Many studies in the past experienced pitfalls with instrument selection and in some cases used instruments designed by the investigator for the purpose of the study without proper validation. In some published studies, the questionnaire is not well described or is simply left unidentified. Other studies report that QoL was improved or worsened based on performance status ratings such as Karnofsky or Eastern Cooperative Oncology Group. These functional performance scores are clinician rated and are not considered to be QoL scores.

Several points must be taken into consideration when deciding which QoL instrument to choose for a particular study. It is generally accepted that QoL is best measured from the patient's perspective, and instruments designed for self-completion are considered to be the most accurate. The instrument should have proven psychometric properties, such as validity (measuring what the user believes it is measuring), reliability (eliciting the same responses from the same patients the second time it is administered when no change would be expected), and sensitivity to changes over time (how likely a change in scores is going to reflect a change in the patient's condition). The instrument should be multidimensional, covering at least four domains of well-being: 1) physical, 2) functional, 3) emotional, and 4) social. The test should be able to elicit a total or global QoL score from the four domains being measured, and a disease-specific or treatment-specific dimension also is useful to obtain information about side effects that are unique to a specific disease or treatment.

The length of an instrument is an important consideration, because although it is important to be thorough, the burden on the patient and staff is a practical concern. Missing data would be more common if the patient were handed a thick packet of papers, and the time required to complete paperwork may affect a patient's willingness to continue in the study. These are crucial considerations if longitudinal assessments are in the study design, or if the patient's condition is expected to deteriorate.

Methodology is important to consider during the design stage of a study. Will the patient complete the questionnaire in the outpatient clinic, or will a research nurse or study assistant complete it over the phone with the patient? Will it be completed at home and mailed back? Will proxy completion be allowed? Was the questionnaire validated for the form of administration the physician plans to use? A multilingual instrument should be considered, depending on the population to be studied. The QLQ-C30 and the FACT have been translated into multiple languages using a rigorous, well-described translation and revalidation method. Selecting the right QoL questionnaire for a study can be a challenge given the enormous number of available QoL questionnaires. Some are more reliable or more valid than others, and some are more sensitive. Some questionnaires have been developed for a certain population of patients or for assessment of a specific condition.

The first step is to decide if QoL is an end point and if changes in QoL are expected. Groenvold (1999) presented four criteria that can be used in the evaluation of QoL as an end point in clinical trials: 1) inclusion of "relevant QoL issues in the questionnaire," 2) large sample size "to detect meaningful differences," 3) timing, and 4) the questionnaire must be free of missing data. A trial meeting these four criteria produces

FACT-HEP (VERSION 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

	Physical well-being	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4
	Social/family well-being	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box ☐ and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4
	Emotional well-being	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4
	Functional well-being	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

A

FIGURE 26.1. FACT-HEP QoL questionnaire. *(Courtesy Dr. David Cella at www.FACIT.org, copyright 1987, 1997. Permission for use must be obtained by contacting Dr. David Cella at www.FACIT.org or d-cella@northwestern.edu.)*

high-quality data, otherwise the results of that trial may be invalid (Groenvold, 1999).

Questionnaire selection and study design depend on the research question being asked. An excellent resource that is dedicated to helping investigators with QoL research is the Mapi Research Institute. This institute has developed a patient-reported outcome and QoL instruments database, which contains valuable information regarding patient-reported outcomes research and an index of QoL questionnaires (www.PROQOLID.org).

Table 26.2 lists basic issues to consider or questions to ask when designing a study with QoL as an outcome, modified

FACT-HEP (VERSION 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	Additional concerns	Not at all	A little bit	Some-what	Quite a bit	Very much
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
C4	I can digest my food well	0	1	2	3	4
C5	I have diarrhea	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
Hep 1	I am unhappy about a change in my appearance	0	1	2	3	4
CNS 7	I have pain in my back	0	1	2	3	4
Cx6	I am bothered by constipation	0	1	2	3	4
H17	I feel fatigued	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
Hep 2	I am bothered by jaundice or yellow color to my skin	0	1	2	3	4
Hep 3	I have had fevers	0	1	2	3	4
Hep 4	I have had itching	0	1	2	3	4
Hep 5	I have had a change in the way food tastes	0	1	2	3	4
Hep 6	I have had chills	0	1	2	3	4
HN 2	My mouth is dry	0	1	2	3	4
Hep 8	I have discomfort or pain in my stomach area	0	1	2	3	4
Hep 9	I am bothered by swelling in my legs	0	1	2	3	4
Q6	Do you have a hepatic artery infusion pump? *(Check one box)*	☐ No or ☐ Yes				
	***If yes**, please answer the following question:*					
Hep 10	My hepatic artery infusion pump interferes with my usual daily activities	0	1	2	3	4
Q7	Do you have an external biliary drainage tube? *(Check one box)*	☐ No or ☐ Yes				
	***If yes**, please answer the following questions:*					
Hep 11	Biliary tubes, or bags, interfere with my usual daily activities	0	1	2	3	4
Hep 12	Biliary tubes, or bags, interfere with intimacy	0	1	2	3	4
Hep 13	I am embarrassed by my biliary drainage tubes or bags	0	1	2	3	4
Hep 14	Caring for my biliary tubes is difficult	0	1	2	3	4

B

FIGURE 26.1. Cont'd

EORTC QLQ-C30 (VERSION 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |_|_|_|_|

Your birthdate (day, month, year): |_|_|_|_|_|_|_|_|

Today's date (day, month, year): 31 |_|_|_|_|_|_|_|_|

	Not at all	A little bit	Quite a bit	Very much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at all	A little bit	Quite a bit	Very much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

FIGURE 26.2. EORTC QLQ-C30. (A user's agreement is required to use this scale and can be accessed through the website www.eortc.be/home/qol/downloads/index.html.)

Table 26.2

Questions to Consider when Designing a QoL Study

Conceptual

Is QoL defined?
Is there a predefined QoL end point?
What domains of QoL will be measured?
Are there expected changes from specific treatment?

Questionnaire Selection

Is there a rationale for using a specific questionnaire?
Is the questionnaire valid, reliable, and sensitive to change?
Was it validated for the study population you intend to use it for?
Does it cover at least the main dimensions relevant for cancer patients?
Is it relatively short and simple?
Is it completed by the patient?
Is it available in other languages relevant to the study population?
Are there disease-specific or treatment-specific questions?
Can a global QoL score be obtained from the results?

Methodology

In what setting will the study be conducted (inpatient, outpatient, home)?
Is a baseline assessment included?
Will timing of assessments reflect change in health-related QoL owing to disease or treatment?
How will it be administered (self-completion with/without research staff's assistance, mailed questionnaires, or phone completion)?
Will proxy completion be allowed?
Is there a research nurse or research assistant responsible for collecting data?
Will reasons for missed data be recorded?

Interpretation of Results

How will missing data be handled?
What clinical factors will be considered (e.g., type of operation, complications, laboratory results, length of hospital stay, preoperative and postoperative treatment)?
Are results likely to be clinically and statistically significant?
How will the results be used?

QoL, quality of lift

Modified from Efficace F, et al, 2003: Beyond the development of health-related quality-of-life (HRQOL) measures: a checklist for evaluating HRQOL outcomes in cancer clinical trials—does HRQOL evaluation in prostate cancer research inform clinical decision making? J Clin Oncol 21(18):3502-3511.

from a combination of two sources: the minimum standard checklist from Efficace and colleagues (2003) and the Gill and Feinstein Criteria for Assessment of Quality of Life studies (Gill & Feinstein, 1994). Table 26.3 lists questionnaires that are relevant for use in hepatopancreatobiliary patients, limited to QoL and symptom questionnaires for patients with cancer or those that address the symptoms associated with diseases of the hepatopancreatobiliary tract. The list is not exhaustive, and questionnaire selection depends on study design and the research question being asked (Mapi Research Trust, QoL Instrument Database; www.PROQOLID.org).

Quality of Life Studies in Hepatopancreatobiliary Cancer

The literature of QoL studies in hepatopancreatobiliary cancer, and particularly pancreatic cancer, has grown significantly since the turn of the century. In the past, authors of research articles discussed QoL in terms of a practitioner's subjective observations, but these conclusions were not grounded in evidence supported by a validated instrument. The discussion of QoL studies in specific disease states that follows is limited to those studies that utilized a validated instrument. The results of these studies are summarized in Table 26.4.

Pancreas Resection

It is commonly known that patients with pancreatic cancer, who experience symptoms of pain and fatigue among others, have impaired QoL compared with the norms in a population (Muller-Nordhorn et al, 2006; see Chapter 58B). Crippa and others (2008) demonstrated that surgical intervention for pancreatic cancer has a favorable impact on QoL. The literature on QoL after pancreatic resection is the most robust collection of all the subgroup analyses, and the group of studies in Table 26.4 include two randomized pancreatic cancer studies, which is comparatively more than for any of the other disease subsets discussed in this chapter (Van Heek et al, 2003; Nguyen et al, 2003). For many other studies in this group, comparisons were made in a nonrandomized setting, which minimizes the scientific rigor of the comparison (Scheingraber et al, 2005).

Many studies have compared the various surgical approaches to pancreatoduodenectomy (PD) including the pylorus-preserving PD (PPPD), Whipple procedure, standard PD (SPD), classical partial PD (CPPD), and total PD (TPD; see Chapter 62A). For patients undergoing surgical resection with a curative intent, an initial decline from baseline was seen in the first 3 postoperative months (Schniewind et al, 2006; Nieveen van Dijkum et al, 2005). Various surgical approaches were compared, but only Nguyen and colleagues (2003) evaluated randomized patients postoperatively. The authors found no differences in QoL and gastrointestinal function between PD and radical PD at a mean of 2.2 years after resection. In related cross-sectional studies, similar global QoL scores were found in patients who had PD with pancreatogastrostomy or pancreatojejunostomy reconstruction and those who underwent PD for multiple endocrine neoplasia type 1, compared with the general population (You et al, 2007; Schmidt et al, 2005).

Total pancreatectomy (TP) generally has been avoided, because it creates an iatrogenic chronic disease process in which patients are dependent on pancreatic enzymes and high doses of insulin. Billings and colleagues (2005) compared 27 TP patients at a mean of 7.5 years after resection with a national database. TP patients experienced an impact on their QoL and health status compared with the general population (Billings et al, 2005). Prior to undergoing a TP, it is advised that patients be thoroughly advised regarding not only the procedure but the expected outcomes, as well as being meticulously educated, prudently selected, and ascertained of adequate medical support in the future.

Palliation of unresectable pancreatic cancer is a worthwhile area of QoL exploration, because the goal of palliation is impacted by a major surgical procedure (see Chapter 63B). Van Heek and colleagues (2003) found in a randomized study that double bypass—hepaticojejunostomy and a retrocolic gastrojejunostomy—reduced the need for reoperation and creation of a gastrojejunostomy by 18%, and it significantly lowered the risk of postoperative gastric outlet obstruction over a single bypass (hepaticojejunostomy; Van Heek et al, 2003). No difference in postoperative QoL was reported between the groups. These QoL results were similar to the results of Shaw and others (2005), who compared PD to open cholecystectomy and found no difference in global QoL between the two groups, although differences were seen in subscales and item analysis (see Table 26.4; Shaw et al, 2005). In a different area of palliative care,

Table 26.3

Quality of Life Questionnaires

Questionnaire	First Author	Type	Description	Mode of Administration	No. Items	Translation	Comments
Edmonton Symptom Assessment System (ESAS)	Bruera, 1991	Symptom/general oncology	Visual analog scale that assesses common symptoms in terminal cancer patients	S, P, C	9	Yes	Useful in hospice/ palliative care settings
Functional Assessment of Chronic Illness Therapy Measurement System or Functional Assessment of Cancer Therapy (FACIT-G, FACT-G) Version 4	Cella, 1993	QoL, general oncology, and chronic illnesses	Assesses four domains of health-related QoL, five domains when disease-, treatment-, or symptom-specific module is used; used worldwide	S, I, T	27 in FACT-G (core or general)	Yes	40 disease-specific subscales available (e.g., hepatopan-creatobiliary [FACT-HEP]); computer scoring programs available
Functional Assessment of Cancer Therapy Hepatoobiliary Symptom Index–8-item (FHSI-8)	Yount, 2002	Brief symptom scale	Assesses common symptoms in patients with advanced hepatopancreatobiliary cancer	S, I, T	8	Yes	Derived from the FACT-HEP
Quality of Life Questionnaire Core 30 Item (QLQ-C30)	Aaronson, 1993	QoL, general oncology with disease-specific modules	Used worldwide in a wide range of cancer patient populations; may be supplemented by disease-specific modules	S	30	Yes	Disease-specific modules available for pancreatic (PAN-26), metastatic colorectal (QLQ-LMC21), and primary liver (HCC-18) cancers
Functional Living Index: Cancer (FLIC)	Schipper, 1984	QoL, general oncology	Assesses the effect of disease and treatment-related symptoms of cancer on patient's function	S	22	Yes	
M.D. Anderson Symptom Inventory (MDASI)	Cleeland, 2000	Symptoms, functioning, general oncology	Assesses the severity and impact of cancer-related symptoms	S, I	19	Yes	
Memorial Symptom Assessment Scale (MSAS)	Portenoy, 1994	Symptoms, general oncology	Provides multidi-mensional information about a diverse group of common symptoms	S	32	No	Short form available (MSAS-SF)
Quality of Life Index (QLI)	Spitzer, 1981	QoL, general oncology	Assesses health outcomes in patients with cancer and other chronic diseases	P, S	5	Yes	
Ferrans and Powers Quality of Life Index (QLI)	Ferrans, 1992	QoL, general population, satisfaction	Measures QoL in terms of satisfaction with life	S	66	Yes	

Table 26.3

Quality of Life Questionnaires—cont'd

Questionnaire	First Author	Type	Description	Mode of Administration	No. Items	Translation	Comments
Quality of Life Scale–Cancer 2 (QOL-CA)	Padilla, 1983	QoL, general oncology	Measures health-related well-being of patients with cancer	S	30	No	
Rotterdam Symptom Checklist (RSCL)	de Haes, 1998	QoL	Measures psychological and physical distress in cancer patients	S, P, I	30, plus 8 items on ADLs	Yes	
Symptom Distress Scale (SDS)	McCorkle, 1978	Symptoms, functioning	Assesses symptom distress in cancer patients	S	13	Yes	
Gastrointestinal Quality of Life Index (GIQLI)	Eypasch, 1993	QoL, general gastroenterology	Assesses QoL in patients with gastroenterologic, hepatic, and pancreatic diseases	S	36	Yes, original in German	Not cancer specific

C, caregiver; I, interviewer; P, proxy; S, self; T, telephone; ADLs, activities of daily living; QoL, quality of life

Wehrmann and colleagues (2005) found that pancreatic duct stenting for obstruction relieved pain symptoms by 4 weeks, lasting for 12 weeks, and improved QoL at the 4-week time point before returning to baseline levels at 12 weeks.

Hepatic Resection

QoL after hepatic resection has been understudied and underreported in the literature despite the frequency that hepatic resections are performed and the improved outcomes (see Chapters 80 and 81 and Part 7, Subsection). Available studies do demonstrate consistent findings among the population. For those who have a survival duration beyond several months, an improvement is seen in QoL. Poon and colleagues (2001) reported on 66 patients who underwent surgical resection of hepatocellular carcinoma (HCC). Although 33 patients had recurrence, mean QoL scores were higher for all patients at 3 months after surgery than at baseline. For those who remained free of recurrence over the 2-year study, QoL measures demonstrated a sustained improvement. This finding was echoed by Chen and others (2004), who demonstrated that after a surgical resection for a primary liver cancer, an initial decline in QoL was seen for the first 10 weeks. After that, an improvement over baseline scores was noted among survivors. The patients who underwent a major hepatectomy experienced a greater decline in QoL immediately following the surgery. Similarly, other studies have reported the return to baseline physical and functional well-being after surgical resection to be 6 weeks for a minor hepatectomy (two segments or less) and 3 months for a major hepatectomy (Martin et al, 2007; Eid et al, 2006). Banz and colleagues (2009) compared those who underwent hepatectomy for benign and malignant disease and found no difference in general and global QoL. Unlike many other populations discussed in this chapter, the surgical procedure, not the disease burden, has the most significant impact on QoL.

Hepatic Artery–Directed Therapies

Regardless of the population treated or the method—transarterial chemoembolization (TACE), bland embolization, or use of yttrium 90 microspheres (^{90}Y)—hepatic artery–directed treatments (see Chapters 83 and 84A) have not been well investigated from a QoL standpoint. Since 2000, only four studies have been published investigating QoL in patients undergoing hepatic artery embolization (HAE) (Gray et al, 2001; Steel et al, 2004, 2006; Kalinowski et al, 2009). All of these studies involve the use of ^{90}Y, they had limited subjects, and the conclusions were divergent. In overlapping populations, Steel and colleagues (2004, 2006) found a decline in QoL for those undergoing TACE or ^{90}Y at 3 months postprocedure, but the directionality diverged at 6 months between the two studies. Gray and colleagues (2001) used a little-researched tool, and Kalinowski and colleagues (2009) reported on only nine patients, so their findings of improvement of QoL postprocedure at 18 and 6 weeks, respectively, are limited.

Although not a traditional QoL assessment, symptom assessment offers value in understanding the impact of a treatment on a population. The Carcinoid Symptom Severity Score (CSSS) was developed to quantify symptoms of patients with neuroendocrine tumors. Neuroendocrine cancer patients have slowly progressing disease, but the symptoms caused by their tumor can negatively impact their QoL. The CSSS categorizes symptom presence, frequency, and effects on lifestyle into five different levels of symptoms (Schell et al, 2002; Wessels & Schell, 2001). Schell and others (2002) demonstrated an improvement in symptoms after HAE with lipiodol/Gelfoam utilizing the CSSS. Current clinical practice and research endeavors would benefit from use of this CSSS tool to consistently and succinctly summarize the impact of symptoms on this population.

Treatment of Gastric Outlet Obstruction

Gastric outlet obstruction (GOO) is a debilitating problem for those with advanced malignancies, particularly pancreatic and gastric cancers. Palliative interventions that relieve the symptoms of dysphagia, nausea, emesis, reflux, abdominal pain, and impaired eating stand to improve QoL for this population. Currently, the palliative treatment options are surgical bypass—gastrojejunostomy or laproscopic gastrojejunostomy (LGJ)—percutaneous gastrostomy, percutaneous jejunostomy, or duodenal stenting (DS). Only three reports include a QoL component, and study populations are small, but the initial results are promising for minimally invasive techniques. DS was shown to improve QoL and to decrease nausea and emesis for

Text continued on page 434

Table 26.4

Quality of Life Studies in Hepatopancreatobiliary Cancer Patients

Study	Patient Population (N)	Study Purpose/QoL End Point	Study Design and Assessment Points	QoL Instrument	QoL Results	Comments
Palliation of Obstructive Jaundice						
Abraham et al, 2002	MBO without liver metastasis who were not surgical candidates (N = 50)	Document change in QoL 1 month after ERCP with endoscopic stent placement	Prospective cohort design	SF-36 Health Survey Questionnaire	Improvement in total bilirubin was significantly associated with improvements in QoL, particularly social function and mental health. Bilirubin level >14 at baseline was associated with lack of improvement in social function at 1 month and a 25% mortality rate at 1 month.	Completion rates: baseline, 100%; 1 month, 52% (26/50)
Artifon et al, 2006	MBO from metastatic pancreatic cancer with liver metastasis but without gastric outlet obstruction (N = 30)	Primary outcome was comparison of cost of care Secondary outcome was comparison of QoL after surgical drainage (choledochojejunostomy) and endoscopic drainage with stent placement	Prospective randomized design comparing surgical drainage against endoscopic drainage; assessed at baseline, 30, 60, and 120 days after drainage	SF-36 Health Survey Questionnaire	QoL scores improved postprocedure at 30 and 60 days and returned to preprocedure levels at 120 days. Endoscopic stent patients had a significantly higher QoL than those with surgical drainage at 30 and 60 days. No difference was found in survival or complication rates between the groups.	SF-36 data not presented. Instrument completion rates not presented.
Berr et al, 2000	Nonresectable bile duct cancer, Bismuth III and IV (N = 23)	Investigate survival impact of photodynamic therapy on survival; secondary outcome was to explore change in QoL	Prospective, phase II trial, single-arm study design; assessed every 3 months after procedure	Spitzer QLI Score	QoL scores improved by 15% and stabilized for 15 months. Time frame improvement first noted, not documented.	QoL score secondary end point and details described in text were limited.
Chan et al, 2005	Patients with obstructive jaundice secondary to unresectable malignancy without having a previous drainage procedure (N = 94)	Primary end point was to evaluate stent patency; secondary end points were morbidity, mortality, and QoL assessment	Randomized, double-blind study comparing ciprofloxacin vs. placebo used for and after stent placement for malignant biliary obstruction; assessed at baseline and 1 month	SF-36 Health Survey Questionnaire	No difference in QoL between groups was found except for significant improvement in social functioning in ciprofloxacin group. Lack of differences in groups was found in the setting of no difference in stent patency but significant improvement in cholangitis frequency with ciprofloxacin group: 10 vs. 21 episodes in placebo ($P = .17$).	Completion rates: ciprofloxacin group 15/44 (34%) and placebo group 16/50 (32%) completed both baseline and 1-month assessment. Only patients who completed both assessments were evaluated.
Ortner et al, 2003	Unresectable cholangiocarcinoma with a >3 cm tumor (N = 39)	Compare survival impact of endoscopic stenting plus PDT with stenting alone on survival; explore change in QoL and cholestasis	Prospective, unblinded, randomized, multicenter study with a group sequential design (block size of 4); group A: PDT after plastic stenting; group B: plastic stenting alone	EORTC QLQ-C30	Post PDT, group A scores significantly improved in physical functioning and emotional and global QoL. Compared with group B, significant difference was noted in physical function, cognitive function, role, and global QoL. Group A had a significantly prolonged survival compared with group B. Only 21% of patients in both groups had successful drainage.	Completion rates were 100% at two reported time points. Length of time between drainage and second time point not clearly defined. Study limited by the possibility of inadequate stenting, creating a bias in favor of the PDT group.
Robson et al, 2010	Malignant biliary obstruction (N = 109)	Evaluate QoL, symptoms, and outcomes PBD	Prospective, longitudinal, cohort study; assessed at baseline, 1 week, and 4 weeks after drainage	FACT-HEP and VASP	Mean FACT-HEP scores declined significantly at 1 and 4 weeks after drainage. VASP scores improved significantly over time. Mortality rates were high: 28% by 8 weeks, 4.74-month median survival.	Completion rates: baseline, 100%; 1 week, 59% (64) of survivors; 4 weeks, 40% (43) of survivors.

Saluja et al, 2008	Gallbladder carcinoma with hilar obstruction (N = 54)	Comparison of endoscopic plastic stent placement with percutaneous plastic stent placement; primary outcome measures were QoL and successful drainage	Prospective, randomized design; assessed at baseline, 1 month, and 3 months after procedure (27 patients per study arm)	WHO-QOL BREF-26 and EORTC QLQ-C30	Neither arm demonstrated a significantly improved QoL 1 month after procedure. Symptoms of insomnia, fatigue, constipation, and appetite improved at 1 month in the PBD group. The endoscopic arm demonstrated improvement in the symptoms of pain, fatigue, and constipation. Mortality rates were high: PBD group, 60 days (range, 43-77); endoscopic stent group, 60 days (range, 28-92).	Completion rates: baseline, 100%; 1 month, 89% (48/54); 3 month, 33% (18/54). Small group. Pruritus was not assessed.
Wiedmann et al, 2004	Unresectable hilar cholangiocarcinoma (N = 23)	Examine survival after PDT with assessment of QoL as secondary end point	Prospective longitudinal cohort study; assessed at baseline and every 6 months until 42 months	Spitzer QLI Score	All patients except one reported an improved QoL over baseline that continued through the 42-month assessment point. Estimated 1-year survival for those with M0 disease: 47%; 4-year estimate: 5%.	Completion rates: baseline, 100%; 6 months, 74% (n = 17) of survivors; 12 months, 39% (n = 9); 18 months, 26% (n = 6); 42 months, 9% (n = 2).
Hepatic Artery–Directed Therapy						
Gray et al, 2001	Unresectable liver metastases from resected large bowel adenocarcinoma randomized to HAC with floxuridine or HAC with ^{90}Y microspheres (N = 74)	Assess tumor response parameters and treatment toxicity; QoL and survival were secondary end points	Phase III randomized clinical trial; QoL assessed before treatment and at 3-month intervals	Priestman and Baum's 11-question linear self-assessment scale	QoL between groups equivalent. Only sexual interest/ability reportedly deteriorated over 18-month posttreatment period. Patient-reported treatment regimens tended to improve, not deteriorate, QoL.	QoL data or statistics not reported.
Kalinowski et al, 2009	Unresectable neuroendocrine cancer with liver metastases undergoing ^{90}Y microsphere embolization (N = 9)	Assess safety and efficacy of ^{90}Y microsphere embolization; assessment of QoL in this population was a secondary end point	Prospective, longitudinal, cohort design; assessed QoL before procedure and at 3, 6, 9, and 12 months after procedure	EORTC QLQ-C30 and QLQ-LMC21	Postprocedure scores decreased in 6 of 9 patients. At 6 months, 6 of 7 experienced significant improvement in QoL scores.	It does not appear in the graphs that QoL score improved over initial assessments. Completion rates of instruments unknown. QoL methods and results not clearly defined.
Steel et al, 2006	Patients with biopsy-proven hepatopancreatobiliary carcinoma who underwent treatment with transarterial chemoembolization or ^{90}Y microsphere infusion (N = 158)	Confirm reliability of FACT-HEP in this heterogeneous population, test sensitivity of FACT-HEP to selected biomarkers, and determine MID estimates	Prospectively assessed QoL at baseline (before embolization), 3 months, and 6 months	FACT-HEP	Reliability of FACT-HEP confirmed. Decline in QoL scores from baseline to 3 months seen in all subscales and general scores. Slight improvement observed at 6 months, with only functional well-being returning to baseline level.	MID estimates established by study provide benchmark scores useful in interpreting changes in QoL. Completion rates: baseline, 100%; 3 months, 35% (n = 55); 6 months, 17% (n = 27).
Steel et al, 2004	Patients diagnosed with HCC undergoing treatment with hepatic arterial infusion of cisplatin (HAI) or ^{90}Y microspheres (N = 28)	Examine the difference between health-related QoL and survival in patients diagnosed with HCC	Nonrandomized, parallel cohort study; QoL assessed at baseline, 3, 6, and 12 months	FACT-HEP	Overall decline in QoL scores in all categories from baseline to 6 months; 3-month FWB scores and overall QoL scores were higher with ^{90}Y compared with HAI. Difference in FWB scores in groups continued to 6 months.	Instrument completion rates: baseline, 100% (n = 28); 3 months, 100% (n = 28); 6 months, 50% (n = 14); data from 12 months not presented.

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Table 26.4

Quality of Life Studies in Hepatopancreatobiliary Cancer Patients—cont'd

Study	Patient Population (N)	Study Purpose/QoL End Point	Study Design and Assessment Points	QoL Instrument	QoL Results	Comments
Gastric Outlet Obstruction						
Mehta et al, 2006	Malignant gastric outlet obstruction randomized to DS or LGJ (N = 25) Predominant diagnosis was pancreatic cancer (n = 15)	Evaluate complications, pain, and QoL after minimally invasive techniques used for palliation of gastric outlet obstruction	Randomized, nonblinded design; pain assessed at baseline and 1 day after procedure; QoL assessed at baseline and 1 month after procedure	SF-36 Health Survey Questionnaire	A significant increase in pain was reported at day 1 after the procedure in the LGJ group ($P = .05$); no difference was noted in the DS group. Only significant change in QoL was an increase in the mean physical health score in the DS group 1 month after procedure.	Completion rates of QoL instruments: baseline, 100%; 1 month, 24% in LGJ group (6 patients); 7% in DS group (7 of those successfully stented).
Miner et al, 2002	Advanced malignancies undergoing palliative surgeries with general anesthesia for palliation of disease related symptoms (N = 26)	Identify items associated with improved outcomes after surgical palliation	Mixed-method, prospective, cohort study with monthly postprocedure assessments until death	FACT-general; Memorial Pain Assessment Card	Of the 26 patients, 8 had indications of gastric outlet obstruction. Surgeries performed were gastrostomy (n = 1), gastrojejunostomy (n = 6), and subtotal gastrectomy (n = 1). Of these patients, 3 had an improvement in symptoms and QoL and 5 did not.	Completion rates: 18 (69%) were assessed monthly until death. Interesting analysis of the patient, family, physician interactions when discussing palliation.
Schmidt et al, 2005	Gastric outlet obstruction secondary to metastatic cancer or unresectable primary cancer (N = 47)	Investigated outcomes after palliative interventions, including surgical bypass, PEG, PEJ, or endoscopic stent	Prospective, longitudinal cohort study; QoL assessed at baseline, 1 month, and 3 months after intervention	EORTC QLQ-C30 and QLQ-STO22	Despite high mortality rates (median survival, 64 days), stent and surgical bypass patients reported improvements in QoL after procedure and at 3 months with a decline in nausea and vomiting.	Completion rates: 1 month, 26/41 (63%) patients living; 3 months, 12/19 (63%) patients living.
RFA						
Ruers et al, 2007	Colorectal cancer with liver metastasis; only patients who underwent an attempt at curative laparotomy, divided into three groups based on outcome: (1) radical resection of metastasis, (2) candidates for local ablative therapy with or without resection, (3) candidates for chemotherapy (N = 201)	Evaluate survival and QoL of the three groups with a specific interest in the value of ablative therapies over chemotherapy	Comparative, prospective, consecutive cohort study: 117 had surgical resection, 45 had ablation, and 39 had chemotherapy; QoL evaluated at baseline and every 3 months for randomly selected members of the cohort (n = 109)	EuroQoL-5D and EORTC QLC-C30	The resection group had a significant increase in survival over the other two groups. All groups experienced a decline in QoL and physical function 3 months after procedure. The surgical group and the RFA group returned to baseline at 1 year. QoL for the chemotherapy group remained below baseline.	QoL assessment was not completed by all members of the cohort. Method for randomly selecting those to compete instruments was not discussed. Instrument completion rates were not included in report.
Wang et al, 2007	HCC patients undergoing TACE alone or TACE followed by RFA (N = 83)	Evaluate outcomes and QoL after TACE and TACE + RFA	Prospective, nonrandomized cohort, longitudinal design; 43 received TACE, 40 received TACE + RFA; QoL assessed at baseline and 3 months	FACT-general, translated into Chinese	The TACE + RFA group had higher overall general FACT scores as well as higher social well-being and FWB scores 3 months after treatment. Predictors of QoL scores were the Child-Pugh class scores and incidence of tumor recurrence.	Completion rates of instruments were not included.

Hepatic Resection

Banz et al, 2009	Patients having undergone hepatic resection for benign or malignant disease >6 months before analysis (N = 135)	Evaluate whether a postoperative diagnosis was associated with differences in long-term QoL	Cross-sectional study; 89 (66%) had malignant disease, 46 (34%) had benign disease	EORTC QLQ-C30 and EORTC LMC21	QoL was assessed a mean of 26.5 months after surgery. Patients who underwent liver resection for malignant disease had similar general, global, and self-assessed QoL to those who had benign disease. Physical function, pain, and social function scores were worse in the malignant group.	Time points for assessment of QoL were inconsistent. Preprocedure QoL scores were not available for comparison. Results were biased in favor of patients undergoing resection for malignancy with better survival.
Chen et al, 2004	Primary liver cancer (predominately HCC) treated with surgical resection (segmentectomies, lobectomies, combined segmentectomies) (N = 36)	Assess QoL after liver resection	Longitudinal, prospective cohort study; QoL assessed before procedure and at weeks 2, 5, and 10; months 4, 6, and 9; and years 1, 1.5, and 2	GQLI	Initial significant decrease postoperatively between baseline and 2- and 10-week time points. Patients undergoing lobectomy and combined segmentectomy had significantly greater declines in reported QoL than those with segmentectomies alone at 2 weeks. At 9 months, the 19 survivors (53%) reported significantly higher QoL scores than baseline ($P < .05$).	100% of patients completed the baseline and 2-week QoL assessments, with a subsequent decline at all points to 36% (13/36) completing 2-year assessment.
Martin et al, 2007	Cholangiocarcinoma, HCC, or metastatic colorectal cancer undergoing major (>2 segments) or minor hepatectomy (N = 32)	Evaluate the time to return to baseline QoL after resection	Prospective, longitudinal design; assessed at consent, discharge, first postoperative visit (2-3 weeks), 6 weeks, and 3, 6, and 12 months; total of 24 had major hepatectomy; 8 had minor hepatectomy	FACT-HEP, FACT-FHSI-8, EORTC, Profile of Mood scale (brief POMS), EORTC QLQ PAN26, Global rating scale	Patients undergoing major resection had a return to baseline QoL (physical well-being, FWB) after initial decline at 3 months with progressive improvement at 6 months. Those undergoing minor resection had a return to baseline functioning at 6 weeks.	Completion rates: 100% for all time points. FACT-HEP instrument was predominately evaluated, with supportive data provided from other instruments.
Poon et al, 2001	HCC patients undergoing resection who met the criteria of no extrahepatic disease, no main portal vein thrombosis, Child-Pugh class A or B liver function, and anatomically resectable disease (N = 66)	Measure QoL outcomes after curative resection for HCC	Prospective, longitudinal design; QoL assessed at 3, 6, 9, 12, 18, and 24 months	FACT-general, translated into Chinese	Postoperative QoL scores (general, physical, social, emotional well-being) were significantly higher at 3 months ($P < .001$). In the 2-year period, 20 of 66 patients died from recurrence; these patients maintained mean QoL scores that were higher than baseline up to 18 months. All 46 patients who completed all time points had mean QoL scores higher than before the procedure at all time points. Thirteen of these 46 had recurrence and a significant decline in QoL over time ($P < .001$). No significant change was seen in QoL over time in the recurrence-free group.	Instrument completion rates were 100% at baseline and 3 months. All time points were completed by 100% of survivors. An analysis of 10 patients who were unresectable and went on to chemoembolization was included as a control group, but considering the small number, this group was not included in this discussion.

Pancreatic Cancer

Billings et al, 2005	Disease requiring TP matched by age and gender with national database and insulin-dependent patients with diabetes	Evaluate QoL after TP	Cross-sectional matched-design; 99 patients who underwent TP were identified, 34 survived; of these, 27 completed questionnaires	SF-36 Health Survey Questionnaire, ADD QoL, EORTC PAN26	Mean follow-up time: 7.5 years after surgery. Pancreatic patients had SF-36 role physical and general health scores ($P < .5$) and ADD-QoL scores ($P < .1$) significantly lower than the national controls. The ADD-QoL scores were not significantly different from other insulin-dependent patients with diabetes.	

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Table 26.4

Quality of Life Studies in Hepatopancreatobiliary Cancer Patients—cont'd

Study	Patient Population (N)	Study Purpose/QoL End Point	Study Design and Assessment Points	QoL Instrument	QoL Results	Comments
Crippa et al, 2008	Newly diagnosed pancreatic adenocarcinoma at various stages (N = 92)	Evaluate QoL and survival in this population	Prospective, longitudinal design; divided into groups: (1) apparently localized cancer treated surgically (n = 28, 30.5%); (2) locally advanced cancer (n = 34, 37%); (3) metastatic cancer (n = 30, 32.5%). QoL assessed at baseline, 3, and 6 months	FACT-HEP	Group 1, all of whom underwent surgical resection, had improved QoL. Group 2 experienced no change, and group 3 experienced a decline. Median survival was 9.8 months after diagnosis with a significant difference in survival among the groups.	Groups 2 and 3 were heterogeneous treatment groups and were treated with chemotherapy ± radiation or no treatment. Completion rates were 56% (63% of survivors) at 3 months and 48% (59% of survivors) at 6 months.
Han et al, 2007	Pancreatic mass that survived >3 years with no clinical evidence of recurrence after SPD or PPPD (N = 67)	Evaluate nutritional status, gastrointestinal symptoms, pancreatic function, and QoL postoperatively	Retrospective chart review with cross-sectional analysis of symptoms and QoL (23 had SPD and 44 had PPPD)	EORTC QLQ-C30	QoL was higher in the PPPD group ($P < .05$). SPD patients reported fewer steatorrhea and diabetic symptoms but more flatus, diarrhea, and fatigue then did the PPPD patients.	This study excluded those who underwent pancreaticogastrostomy and combined liver resection.
Kostro et al, 2008	Pancreatic cancer undergoing surgical resection including PD, DBP, and laparotomy (N = 54)	Assess QoL postoperatively	Comparative, longitudinal, prospective, cohort study; 26 had PD,17 had DBP,11 had laparotomy; assessed at baseline and postoperatively at 1, 2, 3, and 6 months	EORTC QLQ-C30 and EORTC PAN26	No significant differences in were found in global health status among the groups. Palliative options (DBP and laparotomy) controlled symptoms with acceptable QoL, but 8 weeks before death QoL rapidly declined.	Completion rates were baseline, 100%; 1 month, 85% (n = 46); 2 months, 78% (n = 42); 3 months, 57% (n = 31); and 6 months, 41% (n = 2).
Muller-Nordhorn et al, 2006	Pancreatic cancer (various stages) admitted to hospital (N = 45)	Compare QoL with established population norms	Cross-sectional evaluation	EORTC and EuroQol (EQ-5D)	QoL was significantly impaired compared with population norms. Fatigue and pain were significantly associated with impaired QoL.	
Nguyen et al, 2003	Periampullary adenocarcinoma undergoing PD (n = 55) or radical PD (n = 50)	Assess QoL of patients postoperatively	Cross-sectional evaluation of 105 randomized patients	FACT-HEP	Assessments were completed a mean 2.1 years after surgery. No differences at long-term follow-up in QoL and gastrointestinal functional status between PD and radical PD. Radical PD patients had significantly higher postoperative complication rates (43% vs. 29%, $P = .01$). No survival differences were noted between the groups.	
Nieveen van Dijkum et al, 2005	Pancreatic or periampullary surgery undergoing PD or DBP (N = 114)	Evaluate QoL postoperatively	Prospective, longitudinal study with 72 undergoing PD and 42 undergoing DBP; assessed at baseline; 2, and 6 weeks; and 3, 6, 9, and 12 months after surgery (with 59 patients completing weekly assessments)	MSO-24 and GIQLI	QoL scores returned to baseline for both groups 3 months postoperatively. The return for the DBP group was only brief before a decline began again. Rapid decline in QoL was seen 8 weeks before death.	Compliance varied: baseline compliance was 91% in the PD group, 92% in the DBP group. At 6 weeks, both groups had compliance at the low end of 50%. The response recovered to 83% and 89% at 12 months for PD and DBP, respectively.

Schmidt et al, 2005	Benign and malignant disease undergoing PD with PG or PJ for reconstruction (N = 104)	Explore effects on QoL and long-term morbidity	Cross-sectional analysis of QoL before and after surgery	EORTC QLQ-PAN26	Mean assessment was 6.4 years after surgery. Global QoL was the same in both groups. PG group had significant reduction in gastric acid reflux, gastrointestinal ulcers, and pain compared with preoperative state but an increase in steatorrhea, early satiety, and food aversion. PJ patients only reported a difference in jaundice postoperatively.	
Schniewind et al, 2006	Adenocarcinoma of pancreatic head undergoing classic partial PD or PPPD (N = 91)	Examined effects of QoL postoperatively	Prospective, longitudinal design with 34 undergoing PD, 57 undergoing PPPD; assessed at baseline, 3, 6, 12, and 24 months	EORTC QLQ-C30	The 5-year survival was 18% for all patients. QoL was impaired for 3 to 6 months postoperatively. No difference was reported in global QoL between groups. Patients who had a lymphatic resection reported increased diarrhea and pain.	Response rates: 56% preoperatively, peaked at 72% of survivors at 3 months, and fell to 56% of survivors at 24 months.
Shaw et al, 2005	Pancreatic tumors undergoing PD (Whipple and total) matched with patients undergoing a benign open cholecystectomy (N = 49)	Examine long-term QoL between groups	Cross-sectional matched design on age and gender studied over a 9-year period	EORTC QLQ30 and PAN26	Mean assessment at 42 months after procedure. Global health status between groups was similar. The malignant group had deficits in physical and role functioning, expressed concern for future health, and had a greater incidence of fatigue, muscle weakness, and failure to gain weight.	Matched design is a worthwhile study design for comparisons.
Van Heek et al, 2003	Periampullary cancer found to be unresectable during exploration randomized to undergo a DBP or SBP (N = 65)	Primary end point was to assess the development of GOO with secondary end points of morbidity, mortality, length of hospital stay, survival, and QoL	Randomized study design; assessed at baseline, discharge, and monthly thereafter for 6 months (36 in DBP group, 29 in SBP group)	EORTC-C30 and PAN26	Two of 36 DBP and 12 of 29 SBP patients developed GOO ($P = .001$). No difference was reported in length of hospital stay, survival, or change in QoL between the groups. QoL returned to baseline by 4 months after procedure.	Completion rates were >90% in both groups for the first 4 months postoperatively and 75% in the last 2 months.
Wehrmann et al, 2005	Unresectable cancer, pancreatic duct obstruction, and postprandial epigastric pain (N = 20)	Evaluate pain and QoL before and after treatment	Prospective longitudinal cohort; assessed at baseline, 4 weeks, and 12 weeks	Spitzer QLI Score	Successful procedure in 19 patients. Patients reported a significant improvement in pain and QoL at 4 weeks, but scores decreased again at 12 weeks to a level closer to preprocedure.	Total of 100% of patients completed the baseline and 4-week QoL assessments; 16 (84%) of 19 completed the 12-week assessment.
You et al, 2007	Patients with a diagnosis of MEN-1 who underwent surgical treatment of pancreatoduodenal neoplasms (N = 28)	Evaluate the effect of PD resection on perioperative complications, function, and QoL	Retrospective chart review with a cross-sectional evaluation of postoperative QoL	EORTC QLQ-C30 and a unique symptom index	Assessed QoL a mean 5.4 years postoperatively. Patients reported QoL no different than those of the general population. Insulin-dependent diabetes developed in 20% of patients.	

DBP, double-bypass procedure; DS, duodenal stenting; ERCP, endoscopic retrograde cholangiopancreatography; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Core Questionnaire; FACT-HEP, Functional Assessment of Cancer Therapy Hepatobiliary Subscale; FWB, functional well-being; GIQLI, Gastrointestinal QoL Index; GOO, gastric outlet obstruction; HAC, hepatic artery chemotherapy; HCC, hepatocellular carcinoma; LGJ, laparoscopic gastrojejunostomy; ADD-QOL, Audit of Diabetes-Dependent QoL; MBO, malignant biliary obstruction; MEN-1, multiple endocrine neoplasia type 1; MID, minimally important difference; MSO-24, Medical Outcomes Study; PBD, post percutaneous biliary drainage; PD, pancreatoduodenectomy; PDT, photodynamic therapy; PEG, percutaneous gastrostomy; PEJ, percutaneous jejunostomy; PG, pancreatogastrostomy; PJ, pancreatojejunostomy; PPPD, pylorus-preserving pancreatoduodenectomy; QLI, Quality of Life Index; QoL, quality of life; RF, radiofrequency ablation; SBP single-bypass procedure; SPD, standard pancreatoduodenectomy; TACE, transcatheter arterial chemoembolization; TP, total pancreatectomy; VASP, Visual Analog Scale for Pruritus Assessment; WHO-QOL BREF-26, World Health Organization Quality of Life BREF-26; 90Y, yttrium-90

up to 3 months afterward, although success rates varied from 71% to 90% among the groups (Schmidt et al, 2005; Mehta et al, 2006; Kim et al, 2001). Schmidt and colleagues (2005) reported an improvement in QoL in their surgical bypass group as well. Miner and others (2002) presented data for a heterogenous group of patients undergoing surgical palliations; eight in that group underwent a palliative surgery for GOO, and three of eight patients experienced an improvement in all measured parameters; five did not. LGJ was not shown to be superior to DS in one small, randomized study (Mehta et al, 2006).

The value of DS in relieving symptoms related to GOO and improving QoL seems to be an emerging theme in the literature, but current sample sizes are too small, and the groups are too heterogenous to indicate one procedure's superiority over another at this time.

Palliation of Malignant Biliary Obstruction

In most cases, relief of malignant biliary obstruction (MBO) is a palliative intervention (see Chapters 18, 27, 28, 29, 49, 50A, 50B, 50C, 50D, 63A, and 63B). Endoscopic stenting (ES), surgical bypass, and percutaneous biliary drainage (PBD) are all capable of relieving jaundice; however, the topic has not been sufficiently explored to offer clear direction regarding which procedure is best suited for the spectrum of diseases and presentations. Advances have been made, and today palliative surgical bypass is infrequently performed because of the availability and technical successes of the less invasive ES and PBD.

Current literature is restricted to a handful of articles discussing QoL in patients with MBO who have undergone ES, PBD, surgical bypass, or photodynamic therapy (Berr et al, 2000; Abraham et al, 2002; Ortner et al, 2003; Wiedmann et al, 2004; Chan et al, 2005; Artifon et al, 2006; Saluja et al, 2008; Robson et al, 2010). Saluja and colleagues (2008) investigated QoL as a primary end point; the other authors assessed QoL secondarily. Beyond the common indication of relief of MBO, the populations in these studies varied, from those with specific cancers—pancreatic, gallbladder, and bile duct carcinomas—to more general malignant populations with MBO. For that reason it is difficult to make generalized conclusions from these studies. In addition, all of the discussed studies struggle with confounding variables from advancing disease and low response rates as a result of morbidity and mortality, which limit the ability to draw meaningful conclusions.

Patients were evaluated either longitudinally, to assess change in QoL after an intervention, or they were randomized for treatment comparisons. In one longitudinal study, Abraham and others (2002) found that hyperbilirubinemia and weight loss were predictive of poor QoL prior to ES, and ES was found to bring about an improved QoL in this population 1 month after ES placement, especially for those whose initial bilirubin was less than 13 mg/dL. Artifon and colleagues (2006) took evaluation of ES a step further and compared patients who had ES to those who underwent surgical resection. Both groups experienced an improvement in QoL scores at 30 and 60 days postprocedure with a decrease to below preprocedure levels at 120 days. The improvement at 30 and 60 days was significantly greater in the endoscopic group when compared with the surgical group ($P = .05$).

In another longitudinal study, Robson and colleagues (2010) studied the largest cohort in this subset (n = 109), looking at patients with MBO who presented for PBD who were not ES candidates. The patients reported a significant decline in QoL in the overall FACT-HEP scale over the 4-week assessment period but noted a significant improvement in pruritus during this time. The authors concluded that PBD did not improve QoL in the population in the face of a high rate of mortality (28% at 8 weeks postdrainage) (Robson et al, 2010). Saluja and colleagues (2008) randomized gallbladder carcinoma with hilar obstruction patients to either a percutaneously placed plastic stent or an endoscopically placed plastic stent. Neither group had a significant improvement in QoL, but PBD offered better technical success, and the ES group had a lower incidence of cholangitis over the PBD group. In light of these studies, the role of drainage, either ES or PBD, in decreasing the rate of clinical decline in these populations should be considered.

Improvement of QoL after photodynamic therapy (PDT) with ES placement is an emerging theme in the literature. In both prospective and randomized trials, patients experienced an improved QoL after undergoing PDT (Berr et al, 2000; Ortner et al, 2003; Wiedmann et al, 2004). Ortner and colleagues (2003) reported an associated improvement in survival over the stenting group. These reports offer the most positive outcomes from the prospective of improving QoL in a population.

The literature, as expanded on above, is more robust in clarifying which populations benefit from drainage of MBO. How each of these procedures independently alters QoL in the face of progressive disease needs to be clarified further to offer guidance on how to best palliate MBO in a patient whose clinical condition is already in decline.

Radiofrequency Ablation

Radiofrequency ablation (RFA) can be done intraoperatively and percutaneously (see Chapter 85C). Percutaneous RFA programs have expanded dramatically over the past 10 years. The percutaneous approach avoids complications related to an open or laparoscopic surgical procedure while still treating the disease and its symptoms, but these benefits have not been fully evaluated from a QoL perspective in the literature (Cho et al, 2010). Current literature on RFA is limited to two studies evaluating QoL in the setting of HCC or colorectal cancer with liver metastasis, the former utilizing percutaneous RFA, the latter operative RFA (Wang et al, 2007; Ruers et al, 2007). In the HCC study, Wang and others (2007) found a higher sustained QoL after transcatheter arterial embolization (TACE) with RFA than with TACE alone. They also found Child-Pugh class and rates of tumor recurrence were predictors of higher QoL scores.

Ruers and colleagues (2007) evaluated QoL after laparotomy for attempted resection of colorectal liver metastases. Expectedly, those patients who had successful resection of the metastasis had a better survival than those who could not be resected and instead had an intraoperative RFA or were closed and given postoperative chemotherapy. After an initial decline in all groups, QoL returned to baseline at 1 year for the resection and RFA groups, but the chemotherapy group's QoL remained low. This study design was complex and compared heterogenous populations. These results will be clarified better when the Belgium CLOCC trial (EORTC 40004, chemotherapy and local ablation versus chemotherapy) is published. That trial compares RFA with chemotherapy and chemotherapy alone in patients with liver metastases from colorectal cancer. These studies offer promising results: that percutaneous RFA may have the potential to improve QoL over standard treatment options. As minimally invasive RFA applications expand, it is

essential that QoL outcomes be evaluated along with clinical outcomes to further substantiate this procedure as a valid therapeutic option in palliative and curative settings.

CHALLENGES IN QUALITY OF LIFE RESEARCH

QoL has become a field of research unto itself and has drawn attention to the human side of cancer (Passik & Kirsh, 2000). It is far from a perfect science and comes with its own unique set of challenges. Aside from methodologic issues such as proxy completion, missing data, and attrition in terminal or very sick populations of cancer patients, many obstacles exist in the interpretation and applicability of QoL data. One problem faced by QoL researchers and clinicians is the translation of statistically significant changes in QoL scores to clinically meaningful changes. Many tests for QOL assessment have come under harsh criticism, as they tend to rely on mathematical data that "offer such narrow insights into a complex disease and into life when facing cancer" (Corner, 1999). A recently described dilemma that can complicate data integrity is the *response-shift phenomenon.* This occurs when a patient reports stable QoL over time, when clinically they are sicker, because the patient's internal standard adapts to the illness (Sprangers, 2002). The new "surrogate end points" in which clinical benefit is claimed from certain cancer therapies without the use of properly validated instruments poses yet another challenge.

CONCLUSION

The evaluation of QoL reported in the literature has increased dramatically in recent years. As more is learned about QoL, study designs are becoming more robust, and commonly used instruments are more easily recognized by clinicians. These steps are critical for integration of routine QoL assessment into clinical practice, and this chapter has sought to demonstrate the value of assessing QoL and the information that can be obtained through such studies.

There is still more work to be done. As Levine and Ganz (2002) reported, despite the fact that thousands of patients have had QoL measured by multiple instruments in clinical trials, there are only a few examples of outcomes that have influenced individual patients' decision-making or treatment policies. The bridge across the gap between QoL research and clinical practice is the challenge of the future. The conversion of a number into a true understanding of a patient experience is not realistic, but there are merits to utilizing scores to evaluate a patient against established population norms or to deepen the understanding of a person's clinical presentation.

The studies presented here, with their strengths and limitations, provide invaluable information for planning future work. Combine this with the growing interest and clarification of the concept of QoL in procedural settings, and it will undoubtedly lead to more formal evaluations and comparisons utilizing well-designed studies. An increase of current knowledge in this field will lead to a more grounded, realistic, and transparent understanding of the patient's experience of life.

References are available at expertconsult.com.

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CHAPTER 27

Interventional endoscopy: technical aspects

William R. Brugge

OVERVIEW

The field of therapeutic biliary and pancreatic endoscopy has evolved rapidly since the first reports of endoscopic sphincterotomy in 1974. A spectrum of interventional procedures has gained widespread acceptance as therapeutic alternatives to operative management (Table 27.1; Brugge & Van Dam, 1999). The minimally invasive nature of endoscopic retrograde cholangiopancreatography (ERCP) coupled with its ability to be performed under conscious sedation have resulted in its rapid dissemination around the world. Refinements in procedural technique and improvements in accessory equipment have improved results and safety. This chapter focuses on these technical advances. The indications, contraindications, and complications of interventional biliary and pancreatic endoscopy are presented elsewhere (see Chapters 14, 18, 36, 37, 50D, 54, and 63B) and are not directly addressed here.

CANNULATION

Selective cannulation of the bile and pancreatic ducts is a prerequisite for interventional procedures. Cannulation usually can be achieved with a standard cannulating catheter, using contrast injection to confirm successful cannulation. Use of a sphincterotome for cannulation has the advantage of enabling immediate sphincterotomy after cannulation. The sphincterotome also enables upward bowing in a caudocranial axis to assist in selective cannulation of the bile duct (Fig. 27.1). Wire-guided sphincterotome cannulation is associated with a lower rate of pancreatitis (Lee et al, 2009).

If free cannulation with a cannulating catheter fails, guidewire cannulation can be attempted. Hydrophilic guidewires with a special slippery coating are ideal for cannulation, because they minimize trauma to the papilla and more effectively seek out the path to the desired duct. The guidewire is extended several millimeters from the tip of the cannula or sphincterotome, and the papillary orifice is cautiously probed with the wire, until it slips into the duct (Fig. 27.2). When deep cannulation is achieved, the cannulating catheter can be advanced over the wire into the duct.

Precutting

Precutting is a useful technique to achieve selective bile duct cannulation when free or wire-guided approaches fail. The objective of precutting is to incise the roof of the papilla to expose the underlying opening of the bile and pancreatic ducts for selective cannulation. The widely used term *precut papillotomy* is misleading, because the term *papillotomy* has been used interchangeably with the term *sphincterotomy*. The term *papillary roof incision* more accurately describes the procedure of precutting.

Precutting is performed with either a needle-knife catheter (Fig. 27.3, top) or Erlangen-type precut papillotome (Fig. 27.3, bottom). Most of the published experience has been with the needle-knife catheter, which consists of a retractable bare diathermy wire that extends 5 mm from the tip of the catheter; the needle is inserted at or just above the papillary orifice, and the cut is directed upward in the 11 to 12 o'clock position (Fig. 27.4). Biliary cannulation success rates exceeding 90% have been reported (Misra, 2009). The needle knife can also be used to create a supraampullary fistula in patients with biliary obstruction as a result of an ampullary malignancy. Another application is to free an impacted stone at the papilla; an incision is made directly into the most bulging portion of the papilla against the surface of the impacted stone. Higher complication rates with precut sphincterotomy for stone extraction have been reported (Pereira-Lima et al, 2001).

Precutting is not without risk, but some series suggest that in expert hands, it does not increase the risks of pancreatitis (Lawrence et al, 2009). Two large multicenter studies identified precutting as a significant risk factor for postsphincterotomy pancreatitis, and there have been isolated reports of perforation. Practice guidelines have established that precutting requires appropriate training and expertise and should be reserved for patients with a strong indication for sphincterotomy (Carr-Locke, 2004).

Rendezvous Procedure

Biliary cannulation can be aided by a combined percutaneous and endoscopic approach, known as a *rendezvous procedure*. A guidewire is inserted via the percutaneous transhepatic route into the duodenum and is subsequently grasped at the endoscopic end. The guidewire is pulled through the working channel of the endoscope and serves as a guide rail to enable retrograde biliary cannulation, sphincterotomy, and further endoscopic intervention (Calvo et al, 2001).

A rendezvous approach also can be used to accomplish biliary or pancreatic duct cannulation under endoscopic ultrasound guidance (Mallery et al, 2004). The bile or pancreatic duct is punctured transduodenally or transgastrically with a standard fine aspiration needle loaded with a guidewire. The wire is advanced anterogradely across the stricture into the

Table 27.1

Interventional Endoscopy in Biliary and Pancreatic Disease

Sphincterotomy
Stone extraction
Lithotripsy
Mechanical
Shock wave (electrohydraulic, laser)
Chemical dissolution
Stent drainage
Balloon dilation
Sphincter of Oddi manometry
Photodynamic therapy
Papillectomy

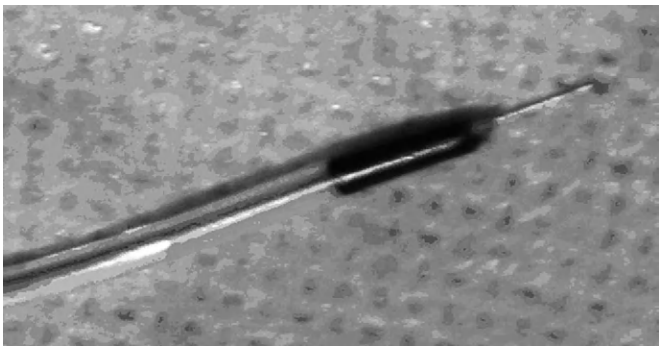


FIGURE 27.3. Needle-knife catheter.

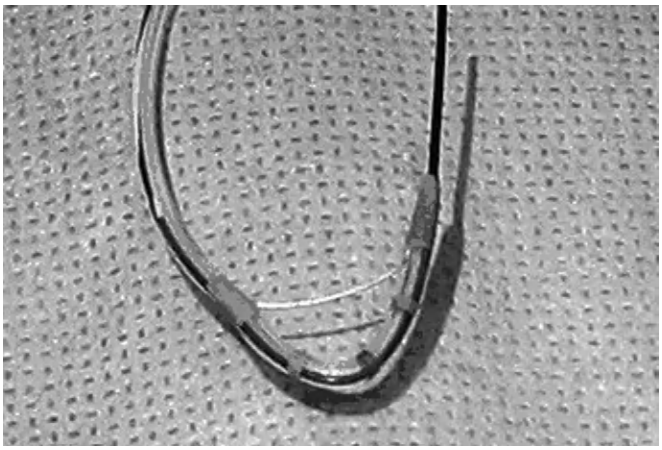


FIGURE 27.1. A bowed sphincterotome for cannulation of the bile duct.

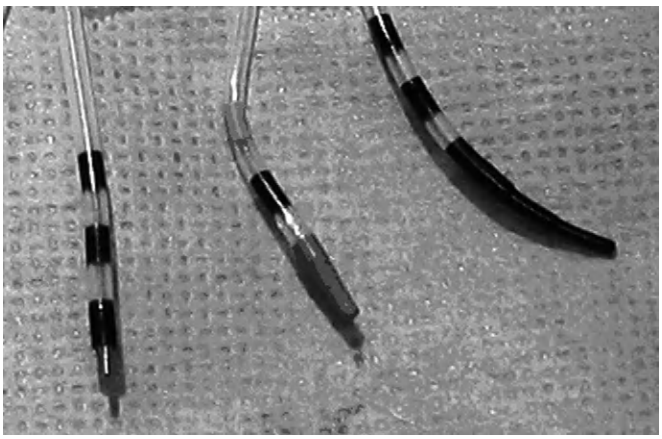


FIGURE 27.2. Cannulating catheters with radiopaque markers.

duodenum (Fig. 27.5), and the stent is placed over the wire in the standard retrograde fashion.

A further variation of the rendezvous approach can be used to achieve cannulation of the pancreatic duct (Bataille & Deprez, 2002). The minor papilla is used to pass a wire from the duct of Santorini into the duct of Wirsung and then across the major papilla. When cannulation of the major papilla is achieved, the wire is rerouted from the minor papilla to the main pancreatic duct (Fig. 27.6).

Juxtapapillary Diverticula

Frequently found in elderly patients, juxtapapillary duodenal diverticula alter the position and anatomic boundaries of the papilla and displace the course of the bile and pancreatic ducts, making cannulation more difficult (Panteris et al, 2008). Accessing the papilla is a problem when it is located within the diverticulum, but various ancillary maneuvers may improve access. Aspirating air from the diverticulum may help "evert" the diverticulum, bringing the papilla into a more favorable position for cannulation. Altering the patient's position and applying abdominal pressure may also be helpful. Failing these, a small depot of normal saline can be injected into the submucosal plane of the mucosa adjacent to the papilla. The injection should be made on the diverticular side of the papilla in an attempt to "tilt" it toward the endoscopist (Fig. 27.7). The use of two accessories, forceps and cannula, inserted together through the working channel to enable the endoscopist to pull the papilla out of the diverticulum and cannulate the papilla simultaneously also has been described (Fujita et al, 1998).

Deep cannulation of the bile duct adjacent to a large juxtapapillary diverticulum may be difficult, because the diverticulum distorts the course of the distal common bile duct. It is helpful to alter the direction of cannulation after entering the biliary orifice according to the anatomy of the diverticulum (Fig. 27.8). The direction of cannulation may be caudal rather than cranial; a guidewire tends to straighten the course of bile and pancreatic ducts and may facilitate deep cannulation (Draganov et al, 2005).

Billroth II Gastrectomy

A patient who has undergone a Billroth II gastrectomy poses a special challenge to the endoscopist. Accessing the papilla is the first obstacle. When the afferent loop is long, it can be difficult to intubate, and the papilla can be difficult to reach. Cannulation of the Billroth II papilla is the second obstacle. Because the endoscope approaches the papilla from below rather than above, the papillary anatomy in a Billroth II patient appears reversed. The bile duct is cannulated by orienting the catheter downward, toward the 5 to 6 o'clock position, rather

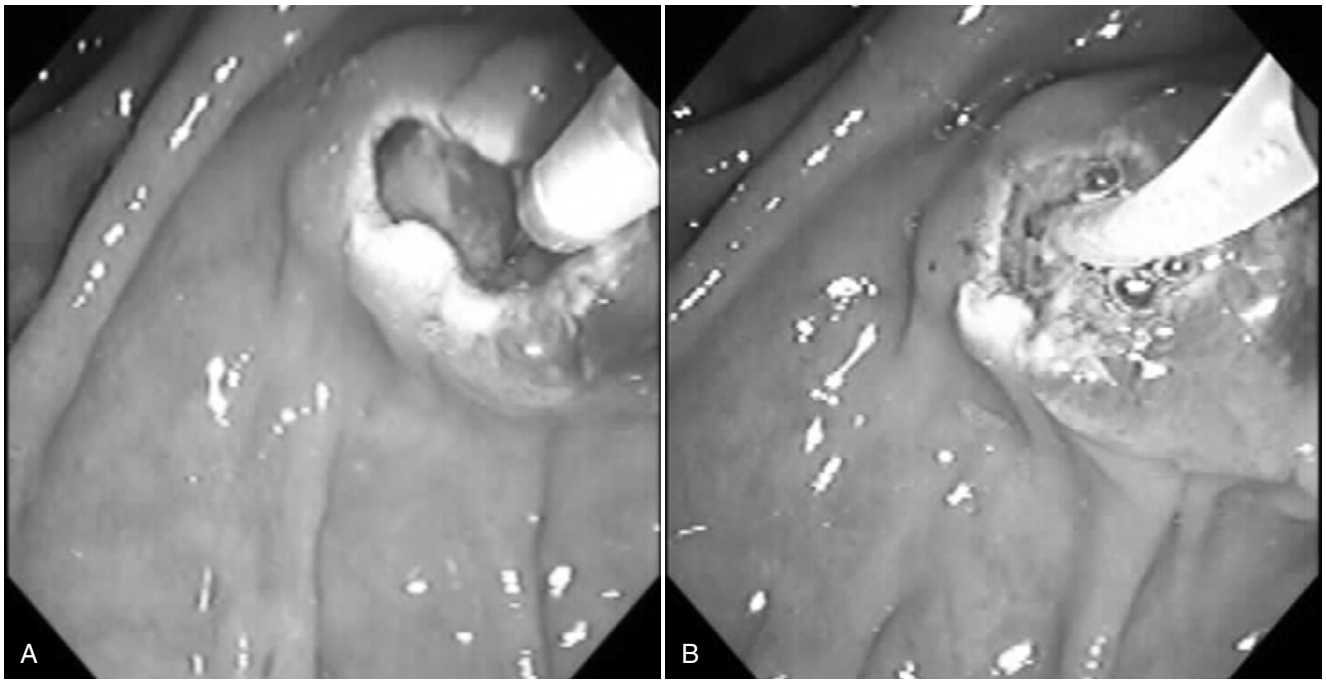


FIGURE 27.4. Precutting technique using a needle-knife catheter. **A,** Insertion of the tip of the precut catheter in the papillary orifice followed by cephalad incision of the papillary roof at the 12 o'clock position with pure-cut current. **B,** The incised roof retracts, exposing the underlying biliary duct orifice. The bile duct is selectively cannulated.

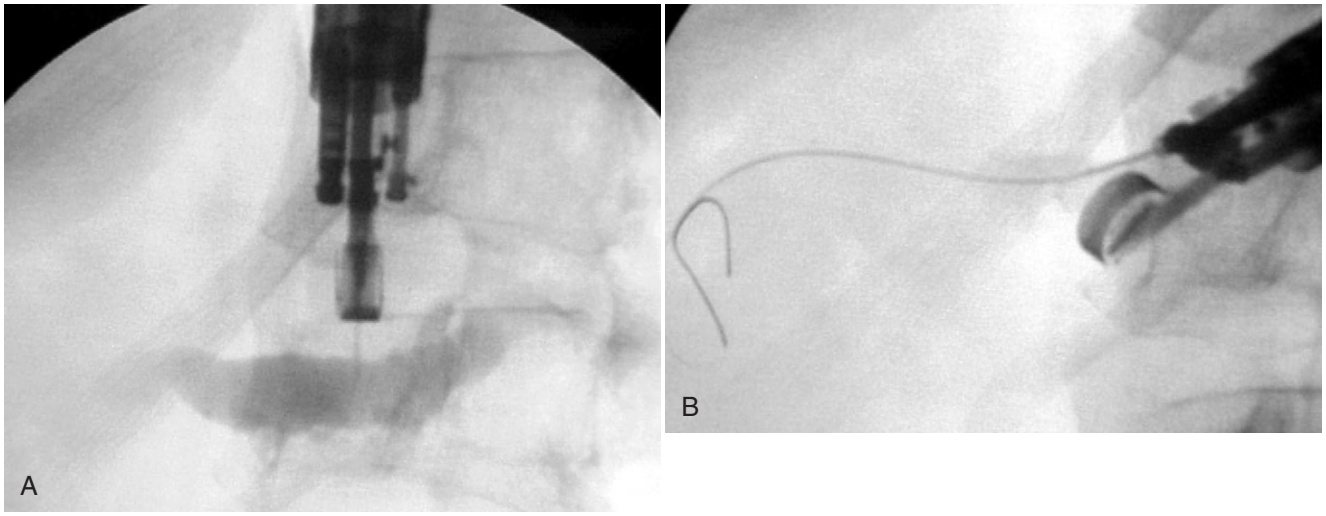


FIGURE 27.5. Radiographs showing transgastric endosonography-guided puncture and injection of the pancreatic duct (**A**) followed by antegrade passage of a wire across the stricture into the duodenum (**B**).

than toward the standard 11 to 12 o'clock position. It is helpful to use a new, straight catheter or mold a downward bow into the catheter to achieve this (Fig. 27.9). A rotatable sphincterotome can also aid in the cannulation of the bile duct (Kim et al, 2008). Cannulation of the pancreatic duct is achieved by inserting the catheter at the 11 o'clock position and aiming it upward in a right-to-left orientation. The bile duct is usually easier to cannulate than the pancreatic duct, because the catheter is automatically directed in the axis of the bile duct. The placement of a guidewire into the bile duct aids in the placement and performance of the sphincterotomy (Dolay & Soylu, 2008).

SPHINCTEROTOMY

Endoscopic sphincterotomy aims at opening the terminal part of the common bile duct or pancreatic duct by cutting the papilla and sphincter muscles. Although not always mandatory for interventional procedures, it greatly facilitates duct access and manipulation.



FIGURE 27.6. Endoscopic image showing a pancreatic rendezvous procedure using the minor papilla to pass a wire anterogradely across the major papilla into the duodenum.



FIGURE 27.9. Cannulation of the bile duct with reversed anatomy after Billroth II gastrectomy.

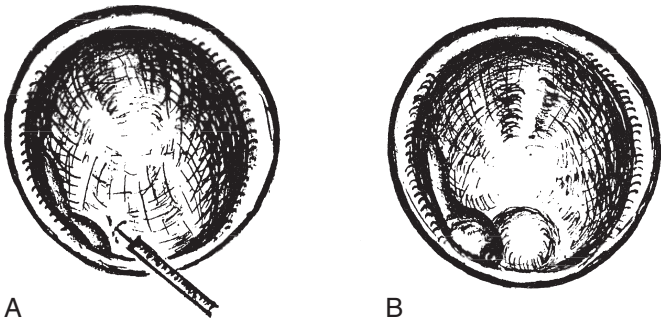


FIGURE 27.7. Technique to improve access to a papilla located on the inner surface of a diverticulum. **A,** With a standard injection catheter, 1 to 2 mL of saline is injected adjacent to the papilla on the diverticular side. **B,** Raised submucosal tissue "tilts" the papilla into view.

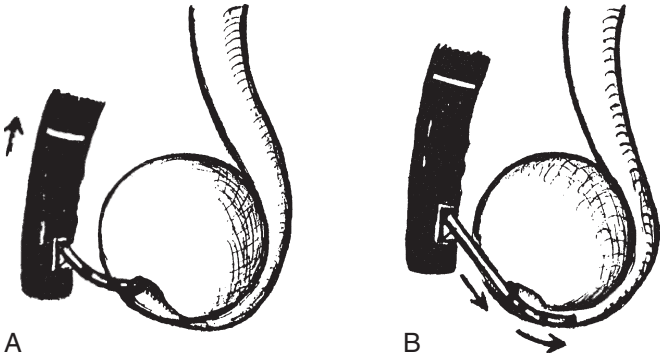


FIGURE 27.8. Technique for deep cannulation of the bile duct in the setting of a large juxtapapillary diverticulum. **A,** Slight withdrawal of the endoscope shifts the angle of cannulation more caudad. **B,** The catheter is advanced while gradually straightening the cannulation angle.

The basic technique of sphincterotomy has changed little since its initial description. The standard sphincterotome, the Erlangen "pull-type" model, consists of a catheter containing a cautery wire exposed 20 to 25 mm near the tip of the instrument. The leading tip distal to the wire, the "nose," is 5 to 10 mm in diameter. After deep bile duct cannulation, the sphincterotome is retracted slowly, until one fourth to one half of the wire length is exposed outside the papilla. The sphincterotome is slightly bowed so that the wire is in contact with the roof, but not excessively, to avoid a "zipper" incision. The incision is made by gently lifting the sphincterotome against the papillary roof using the elevator and up–down controls while applying short bursts of current. The power settings vary according to the type of diathermy unit used. It is debated whether blended or pure-cut current should be used. Theoretically, pure-cut current would be associated with less edema of the ampulla and may decrease the risk of pancreatitis, but the risk of postsphincterotomy hemorrhage might be greater. In a prospective randomized study, the use of pure-cut current was associated with a lower incidence of pancreatitis than with blended-current sphincterotomy (Elta et al, 1998). In addition, the use of blended current after pure cutting reduced the risk of bleeding without increasing the risk of pancreatitis (Gorelick et al, 2001). Another randomized study found that pure-cut current did not reduce the frequency of pancreatitis and was associated with a significantly increased risk of minor bleeding (Macintosh et al, 2004). If blended current is used, the cut should be monitored for excessive tissue blanching and edema, because this is likely to increase the risk of pancreatitis.

The length of a bile duct sphincterotomy should be tailored to the indication. A small incision (≤1 cm) is adequate for stent insertion, whereas stone extraction usually requires a larger incision, depending on the size of the stone to be extracted

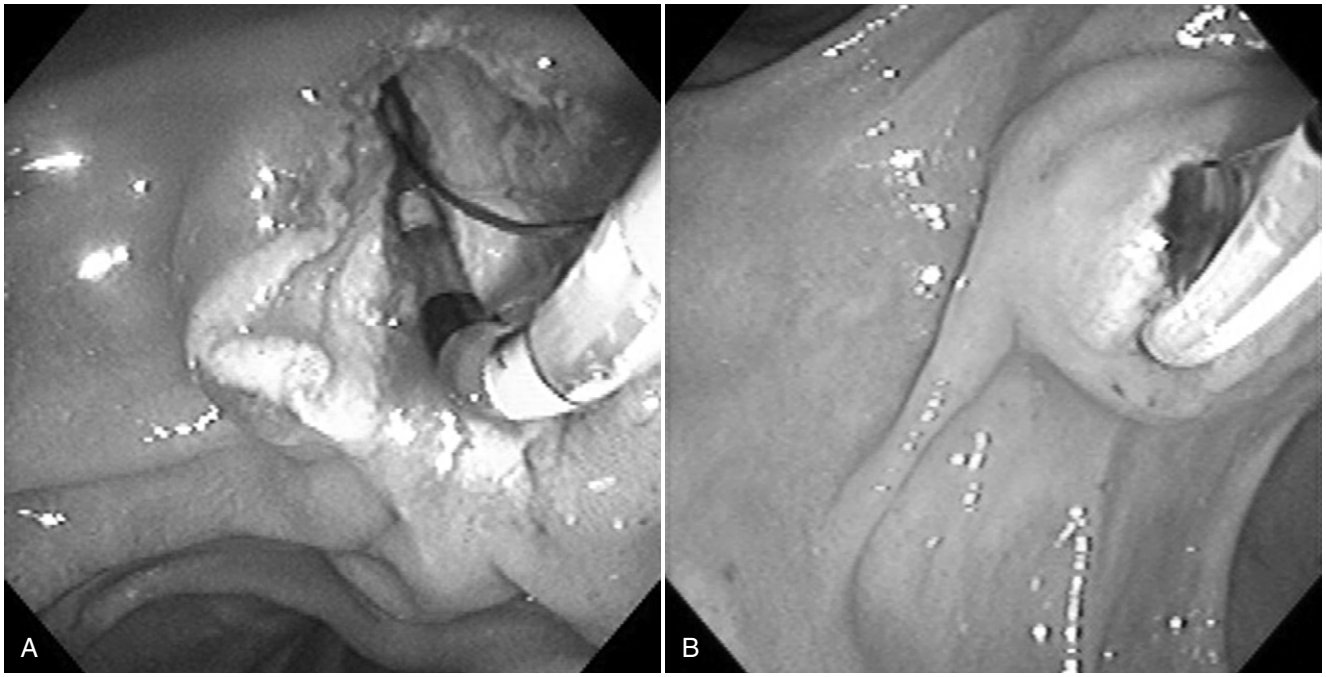


FIGURE 27.10. Biliary (**A**) and pancreatic (**B**) sphincterotomy using a standard sphincterotome.

(Fig. 27.10A). The extent of the sphincterotomy is limited by the length of the intraduodenal portion of the common bile duct. The length of a pancreatic duct sphincterotomy should not exceed 1 cm because of the perpendicular insertion at the ampulla (Fig. 27.10B). In rare cases, a biliary sphincterotomy can be performed with a sphincterotome placed through a percutaneously placed choledochoscope (Itoi et al, 2004). The adequacy of a sphincterotomy can be gauged by the ability to move the bowed sphincterotome across the opening. In the presence of a juxtapapillary diverticulum, the incision should be performed in millimeter increments, paying close attention to the boundaries of the incision and the course of the intraduodenal segment of the bile duct. Late stenosis has been reported to be more common after pancreatic sphincterotomy than after biliary sphincterotomy and is easily treated with repeat endoscopic sphincterotomy (Veldkamp et al, 2007).

In a Billroth II patient, the standard pull-type sphincterotome is unsuited for sphincterotomy because of the difficult approach to the papilla. Special sphincterotomes and techniques have been developed to accommodate this anatomic variation (Dolay & Soylu, 2008). As an alternative to the sphincterotome, a needle knife can be used to perform the sphincterotomy over a previously inserted stent that serves as a guide rail for the incision (Nakahara et al, 2009; Fig. 27.11).

Sphincterotomy of the minor papilla in a patient with pancreas divisum requires greater caution because of the smaller size of the papilla. Wire-guided cannulation will aid in the performance of a minor ampulla sphincterotomy (Maple et al, 2009). The incision length is generally 3 to 5 mm, but it may be larger if the minor papilla is very prominent. The incision is made at the 12 o'clock position. A needle knife can also be used to perform the sphincterotomy over a 5- or 7-Fr stent (Fig. 27.12; Kwan et al, 2008), and balloon dilation sphincteroplasty can be used to aid in the extraction of pancreatic duct stones (Maydeo et al, 2009). A reduction in symptoms and episodes of pancreatitis is often reported after sphincterotomy in older patients with a history of recurrent pancreatitis and a dilated pancreatic duct (Fukumori et al, 2007; Borak et al, 2009).

SPHINCTEROPLASTY

Balloon dilation of the sphincter muscle using high-pressure hydrostatic balloons 6 or 8 mm in diameter has been employed as an alternative to sphincterotomy (Fig. 27.13; MacMathuna et al, 1994). The theoretical advantage of this approach is the preservation of the sphincter function. The drawback of balloon dilation is a more limited size of the papillary opening, which may limit the size of the stone that can be extracted using the balloon or a basket catheter. Stones measuring greater than 8 mm often require mechanical lithotripsy to enable transpapillary extraction. The risk of pancreatitis seems to be higher after a sphincteroplasty compared with a sphincterotomy, but balloon dilation after a limited sphincterotomy does not increase the risk of pancreatitis (Kowalski et al, 2009).

STONE EXTRACTION

Several series have shown that 85% to 90% of bile duct stones can be removed effectively after endoscopic sphincterotomy with a basket and/or balloon catheter (see Chapters 36 and 37). The choice of basket or balloon is largely dictated by stone size: baskets are sturdier and provide better traction for removal of a larger stone (Fig. 27.14); a balloon catheter occludes the lumen and is ideal for removing small stones or sludge (Fig. 27.15).

Several technical points may increase the success rate of stone extraction. The sphincterotomy should be generous enough to enable extraction of the stone. The adequacy of the incision can be assessed by passing an inflated balloon catheter

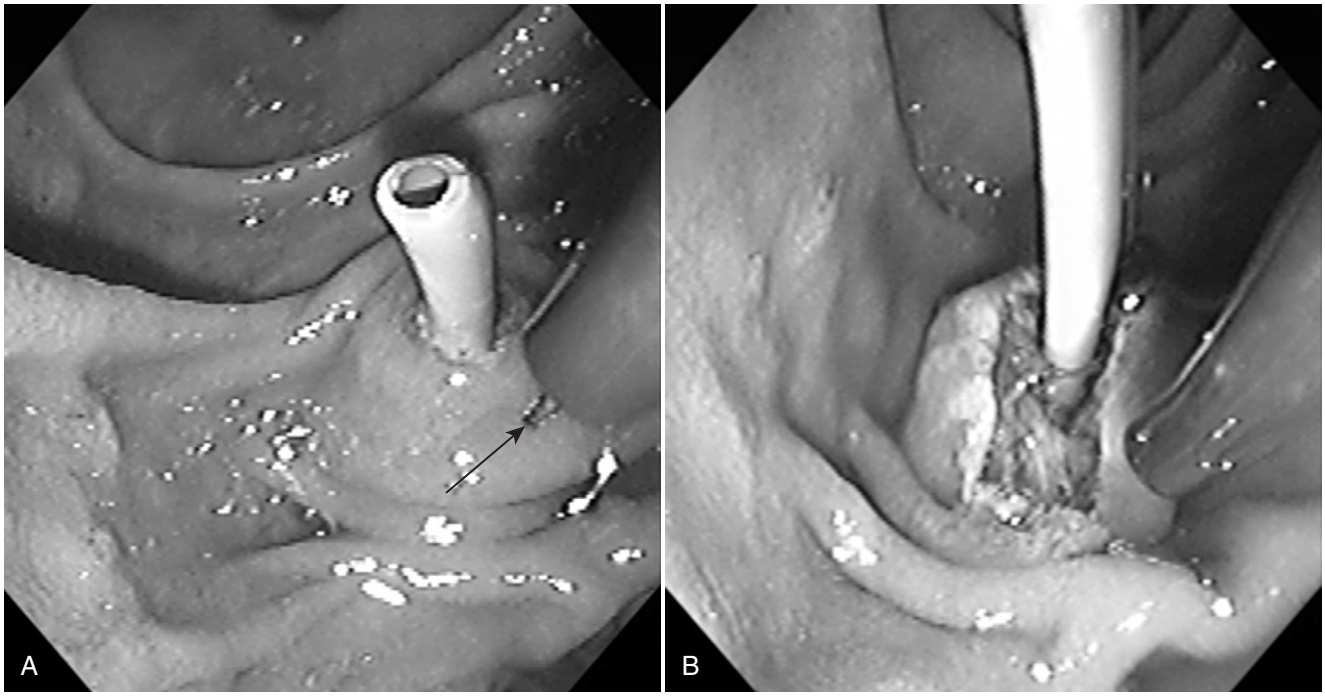


FIGURE 27.11. Sphincterotomy over an indwelling stent in a Billroth II patient. **A,** Needle-knife (*arrow*) positioned for sphincterotomy after stent insertion. **B,** Appearance after completed sphincterotomy.

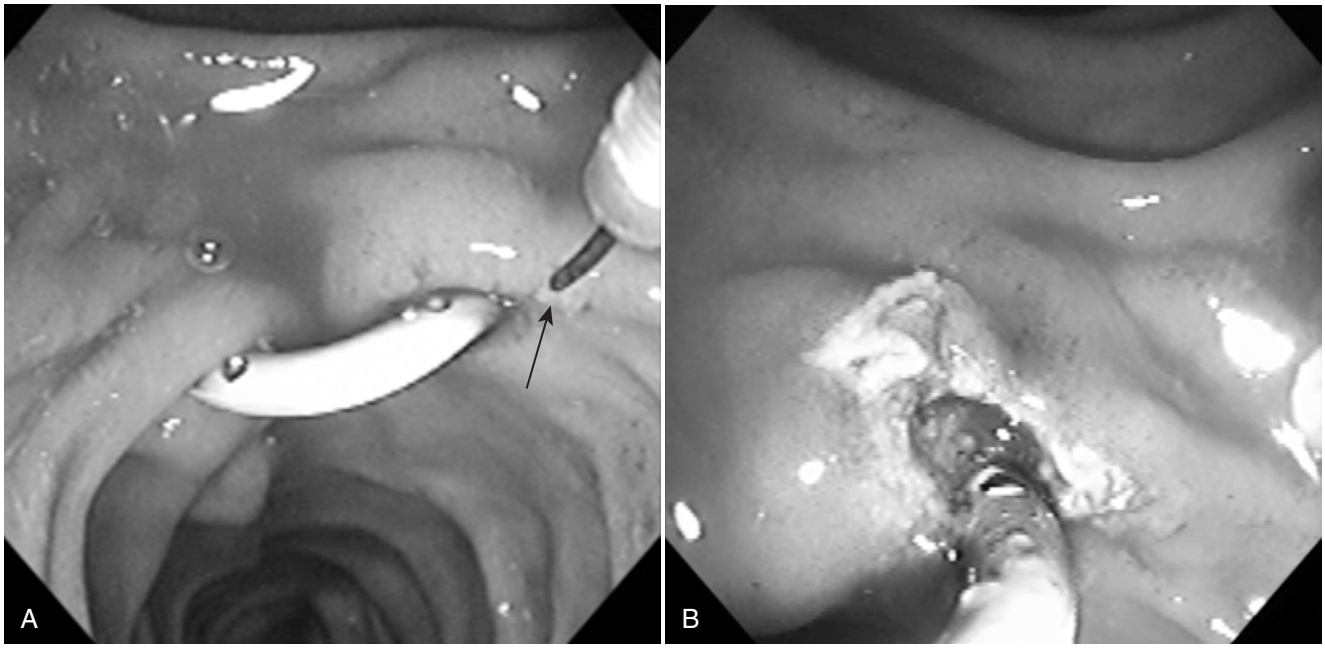


FIGURE 27.12. Sphincterotomy of the minor papilla. **A,** Needle-knife (*arrow*) positioned for sphincterotomy after 7-Fr stent insertion. **B,** Appearance after completed sphincterotomy.

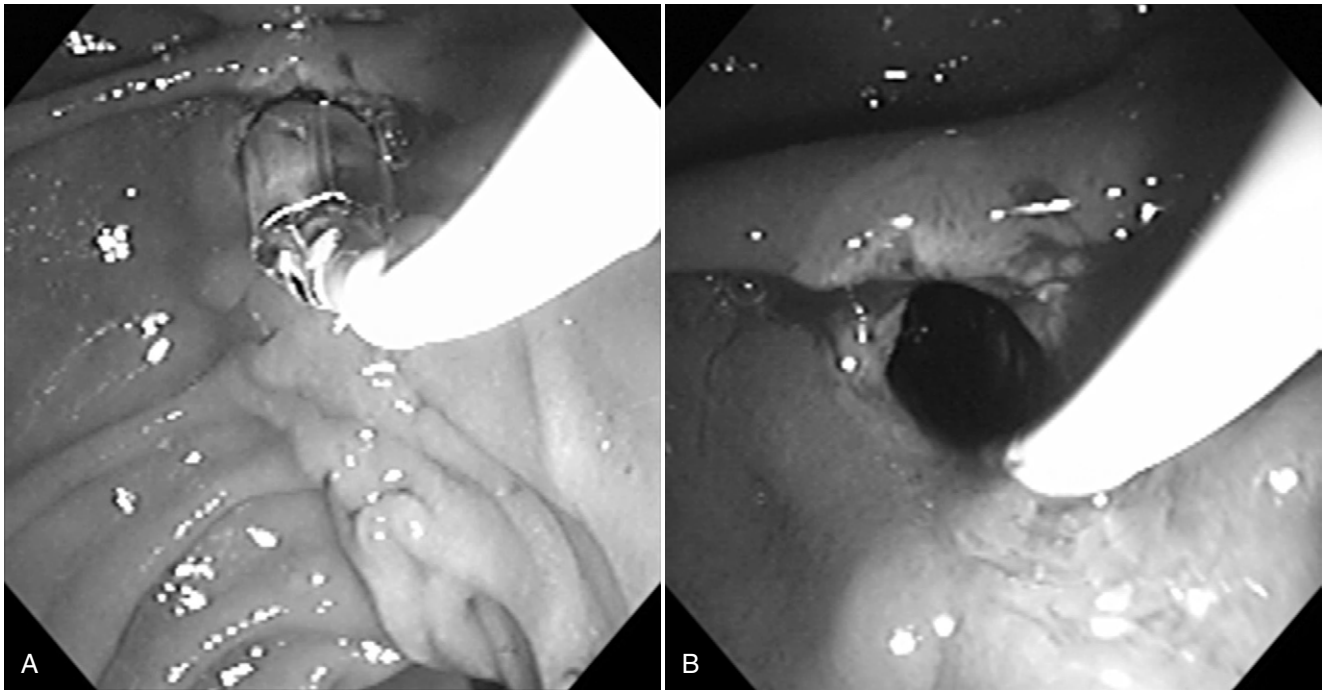


FIGURE 27.13. A, Sphincteroplasty using an 8-mm balloon in a patient with coagulopathy and bile duct stones. **B,** Appearance after sphincteroplasty.



FIGURE 27.14. Extraction of a large stone using a Dormia basket.

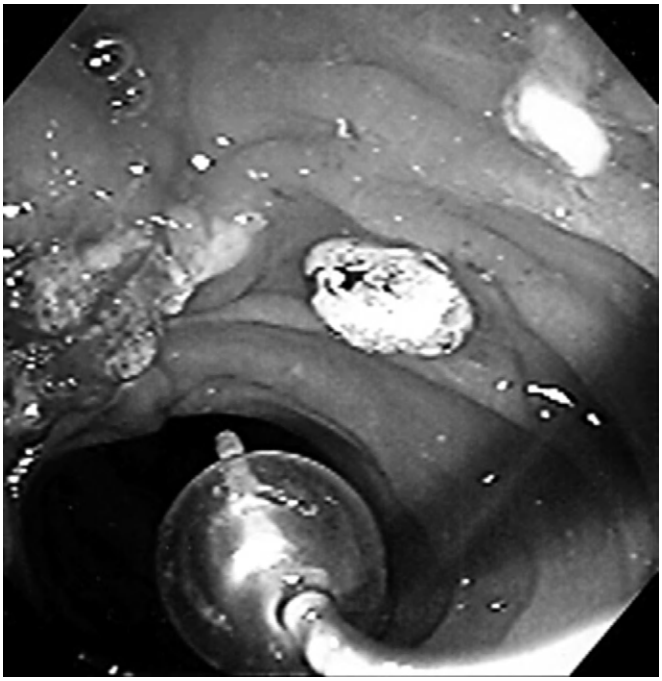


FIGURE 27.15. Extraction of small stones with a balloon catheter.

through the sphincterotomy opening. If multiple medium or large stones are present, it is important to remove stones individually, beginning with the lowermost stone, to avoid stone impaction. If a stone is mistakenly captured, it can be dislodged from the basket by pushing it upward into the hepatic duct confluence, where the basket tends to fold over or advance into the hepatic duct, thereby releasing the stone. When extracting a stone, the direction of traction should be in the axis of the bile duct, which can be verified on fluoroscopy. The success rate of stone extraction after balloon sphincteroplasty is very high (Garcia-Cano et al, 2009). Lithotripsy is indicated for the extraction of stones too large for extraction through the sphincteroplasty (Attasaranya et al, 2008).

Intrahepatic stones pose a special challenge, because they are difficult to access via the retrograde transpapillary route (see Chapters 39 and 44). These stones usually form above strictures and are tightly impacted, and a wire-guided basket may be helpful to gain access to such stones. Intrahepatic stones also can be removed by the percutaneous transhepatic route (see Chapters 28 and 44).

Pancreatic duct stones are a common finding in obstructive chronic pancreatitis. Pancreatic duct stones tend to be firmly impacted or form proximal to a stricture, requiring preliminary fragmentation using lithotripsy techniques. Stone fragments and debris are extracted with a basket or balloon (Fig. 27.16). A recent study comparing surgical and endoscopic treatment of benign pancreatic disease suggests surgery provides a superior long-term outcome (Cahen et al, 2007).

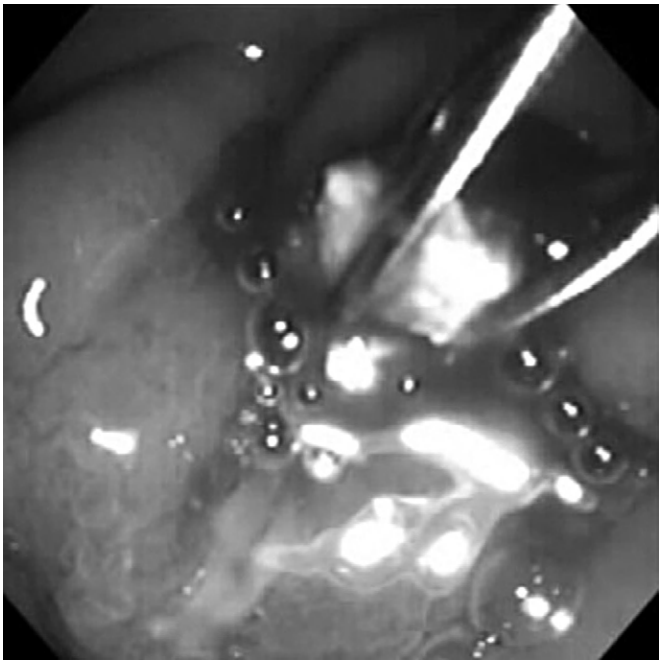


FIGURE 27.16. Extraction of pancreatic stone debris with a basket after extracorporeal shock-wave lithotripsy.

LITHOTRIPSY

Standard stone extraction techniques may fail when a stone is large, impacted, proximal to a stricture, or when stones are multiple. A variety of modalities are currently available to fragment these difficult stones before extraction, including mechanical lithotripsy, intraductal shock-wave lithotripsy, extracorporeal shock-wave lithotripsy, and dissolution therapy.

Mechanical Lithotripsy

Using mechanical lithotripsy, the stone is forcefully crushed in the arms of a Dormia basket after entrapment. This method is the simplest and most cost-effective of the lithotripsy techniques, with success rates of 80% to 90%. There are two variations to the technique of mechanical lithotripsy: a nonendoscopic method and a through-the-endoscope method. Using the nonendoscopic method, the stone is captured within a standard Dormia basket, the basket handle is cut off, and the endoscope is removed. A coiled metal sheath is inserted over the wire, until its tip is in contact with the stone, and mechanical lithotripsy is performed (Fig. 27.17). Using the through-the-endoscope method, a special lithotripsy basket contained within a metal sheath is inserted through the endoscope working channel (Fig. 27.18). The stone is captured in the basket, and lithotripsy is performed. Because the basket is part of a single-unit lithotriptor device, this method presumes that the endoscopist anticipates the need for mechanical lithotripsy before an attempt is made to extract the stone. If stone extraction is attempted with a standard Dormia basket, and the stone and basket become impacted in the bile duct, the endoscopist must use the nonendoscopic method to effect fragmentation.

Intraductal Shock-Wave Lithotripsy

Failure of mechanical lithotripsy is usually due to an inability to capture the stone in the basket, which may occur if the stone is firmly impacted or very large. An alternative modality to achieve stone fragmentation is to use shock waves, which can be delivered intraductally or extracorporeally. Intraductal lithotripsy is performed using flexible probes that can be introduced into the bile or pancreatic duct. The shock waves are generated using electrohydraulic or laser technology and are applied directly to the stone surface. Because shock waves can cause injury to the duct wall, intraductal lithotripsy generally is performed under endoscopic guidance using a "baby scope" inserted into the duct via the duodenoscope, or "mother scope" (Fig. 27.19; Swahn et al, 2009). The lithotripsy probe is inserted through the operating channel of the baby scope, and shock waves are fired under visual guidance, until adequate stone fragmentation is achieved (Fig. 27.20). In patients with an altered anatomy, a nonoperative approach can be taken, using a holmium laser delivered through a choledochotomy (Bark et al, 2009).

Extracorporeal Shock-Wave Lithotripsy

Extracorporeal shock-wave lithotripsy (ESWL) has been shown to be an effective and safe method to fragment bile and pancreatic duct stones that defy endoscopic extraction. The technique can be used for fragmentation of bile duct stones using fluoroscopic or ultrasound guidance (Amplatz et al, 2007). However, if the stone is not visible by fluoroscopy or ultrasound, ESWL is not possible (Merrett & Desmond, 1990). After fragmentation of any stones, the residual fragments must be removed, usually aided by endoscopic sphincterotomy (Tandan et al, 2009). The need for ESWL has decreased as the effectiveness of mechanical lithotripsy has improved. Pancreatic stone fragmentation

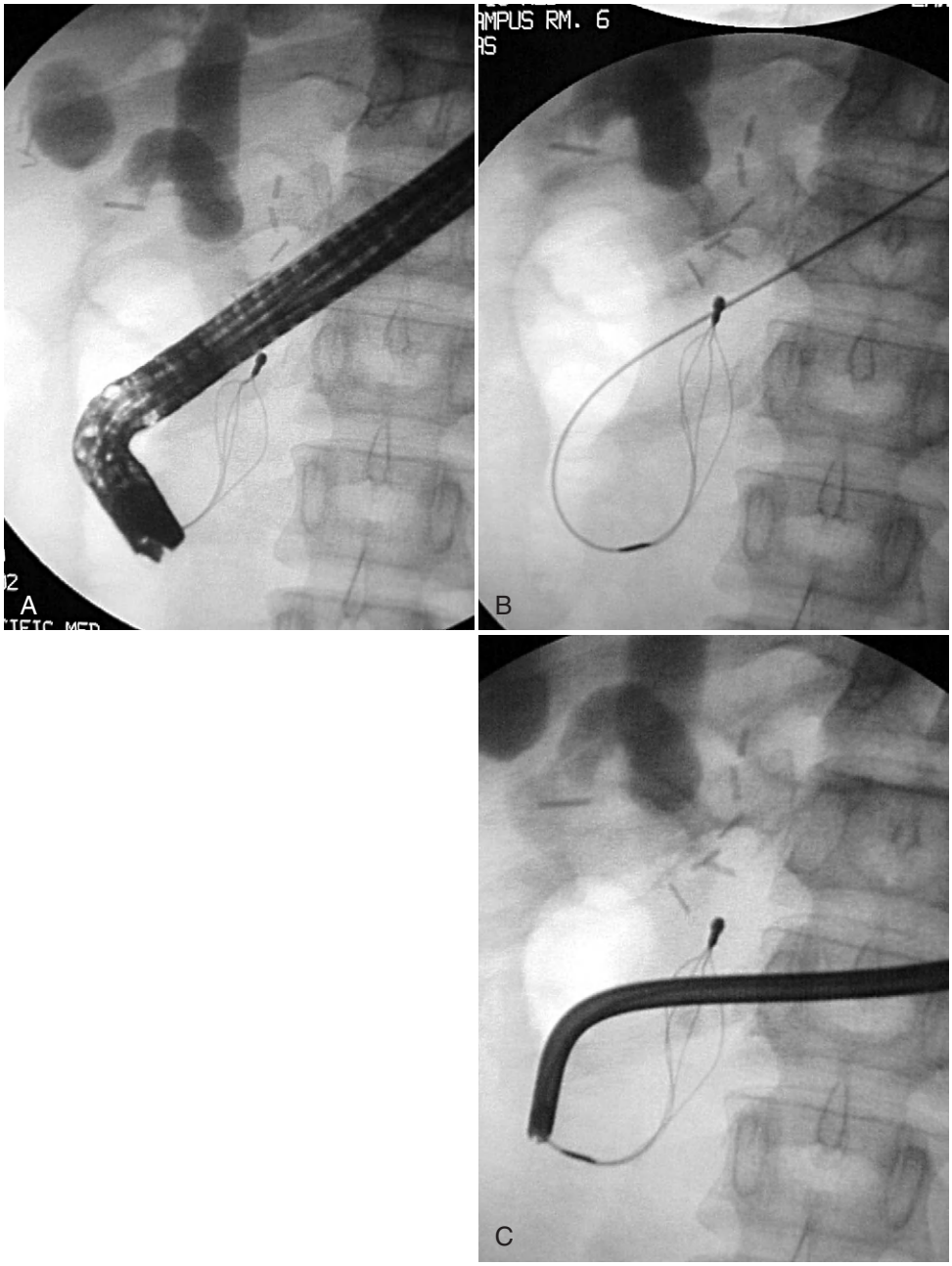


FIGURE 27.17. Radiographs showing intraductal mechanical lithotripsy of a large stone using the nonendoscopic approach. **A,** Impacted stone captured in standard Dormia basket. **B,** Endoscope removed. **C,** Lithotripsy cable sheath advanced to the stone for mechanical lithotripsy.

with ESWL requires multiple sessions and endoscopic management that includes pancreatic sphincterotomy and stent placement (Brand et al, 2000).

Chemical Dissolution

Monooctanoin and methyl tert-butyl ether (MTBE) have been used to dissolve common bile duct stones via nasobiliary drainage catheters and T-tubes (Tandon et al, 1990). Despite encouraging initial reports, this approach has been abandoned because of the cumbersome and time-consuming technique, poor overall results, and adverse effects related to leakage of the solvent into the duodenum. The administration of ursodeoxycholic acid in combination with endoscopic stent placement was shown in one study to soften and decrease the size of common bile stones, facilitating endoscopic extraction (Han et al, 2009). This approach is taken when initial stone extraction and fragmentation is unsuccessful.

STRICTURE DILATION

Stricture dilation can be performed using push-type dilation catheters (bougies) or high-pressure hydrostatic balloons (see Chapter 28). Hydrostatic balloons are commonly used to dilate

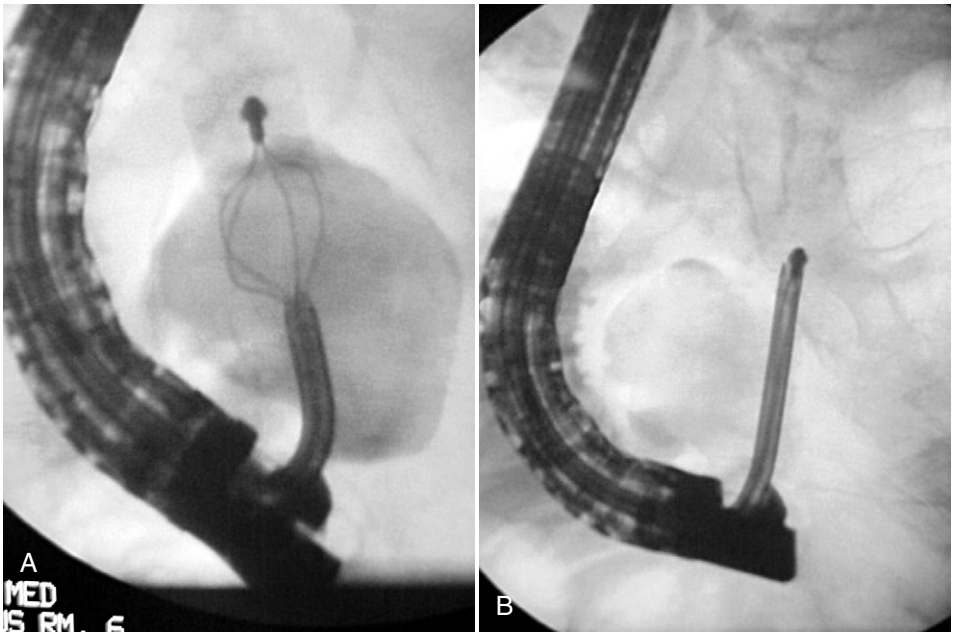


FIGURE 27.18. Radiographs showing through-the-endoscope lithotripsy. **A,** Impacted stone captured in the lithotriopsy basket. **B,** Lithotriopsy cable advanced through the endoscope to perform lithotriopsy.

benign strictures caused by chronic pancreatitis, sclerosing cholangitis, or operative injury (Freeman et al, 2001). When inflated, the balloon applies radial dilating force, and balloons are available in varying lengths (2, 3, and 4 cm) and diameters (4, 6, and 8 mm). The balloon is inflated with diluted contrast material to the maximum atmospheric pressure allowable, and it is kept inflated until the stricture "waist" disappears, generally after 30 to 60 seconds. Dilation is painful, and this may limit the duration of inflation; sequential brief dilations may be better tolerated. Balloon dilation is usually used in conjunction with stent placement except in liver transplantation patients, in whom chronic stenting may be associated with complications (Kulaksiz et al, 2008). The duration of stenting required to achieve a permanent dilation effect varies. Postoperative biliary strictures and pancreatic strictures secondary to chronic pancreatitis may require more than a year of stenting (Weber et al, 2009b), and bile duct strictures associated with chronic calcified pancreatitis are less likely to respond to plastic stenting (Kahl et al, 2003). The placement of multiple stents by adding a stent at 3-month intervals may optimize the dilation effect (Fig. 27.21; Sakai et al, 2009). Similar approaches have been successful for strictures in the ducts of Santorini and Wirsung (Costamagna et al, 2006).

Tight strictures that do not permit passage of a bougie or balloon catheter can be opened with the Soehendra Stent Retriever (Cook Medical, Winston-Salem, NC) (Brand et al, 2000). The device has a threaded tip at its end with a central lumen for coaxial guidewire insertion, and it is rotated to core a path through a high-grade stricture. After placement of a guidewire across the stricture, the Retriever is coaxially inserted until it engages the stricture. The rotational device is rotated clockwise at the handle by the assistant, while the endoscopist advances the device across the stricture (Fig. 27.22). Strictures should be sampled with brushings for cytology or forceps for histologic material (Higashizawa et al, 2002).

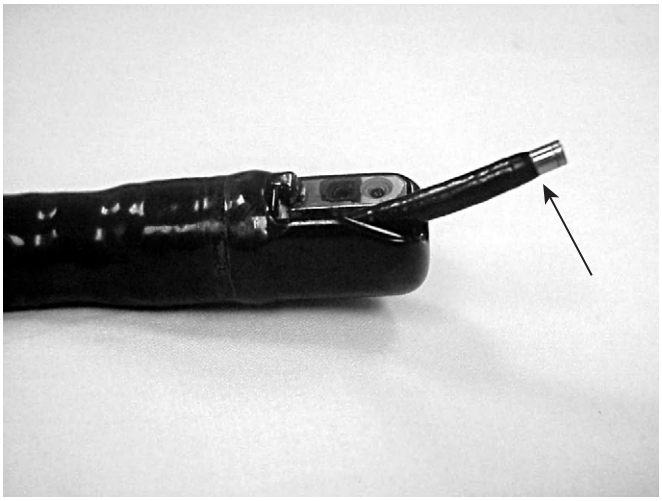


FIGURE 27.19. "Baby scope" (*arrow*) inserted through the working channel of the "mother scope" (duodenoscope).

STENTING

Endoscopic transpapillary stent placement is a well-standardized technique that can be carried out with an overall success rate of greater than 90%. Stenting has become the treatment of choice for the palliative decompression of malignant distal biliary obstruction (see Chapters 50B, 58, 59, and 63B), and it may be an alternative to surgery for the treatment of benign distal biliary and pancreatic strictures, although not all authors agree regarding the long-term efficacy (see Chapter 42). Stenting also has been found to be an effective treatment for bile duct leaks

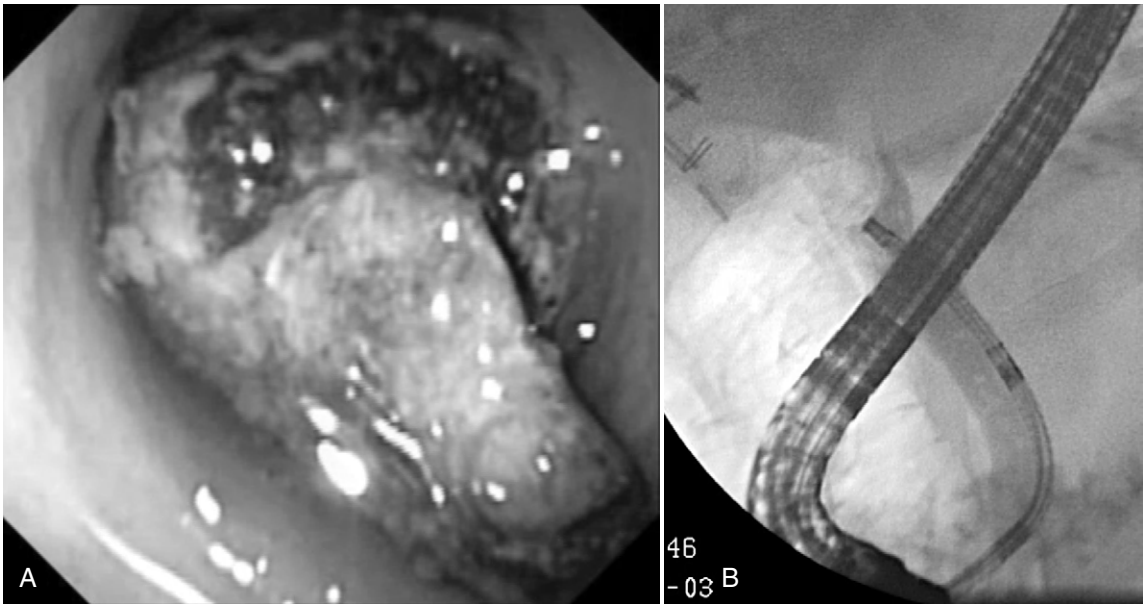


FIGURE 27.20. Intraductal shock-wave lithotripsy. **A,** The video cholangioscope has been inserted into the bile duct to visualize the stone. **B,** Radiographic view showing lithotripsy under direct cholangioscopic vision.

after surgery or trauma (Coelho-Prabhu & Baron, 2009); a biliary sphincterotomy should be performed at the time of the stent placement and may be used as the sole treatment (Aksoz et al, 2009). Pancreatic duct leaks are also effectively treated, particularly with stenting across the duct defect.

Types of Stents

Two types of stents are used, made of either plastic and expandable metal (Fig. 27.23). Plastic stents may be straight, with flaps for anchorage, or they may be a single or double pigtail (Jain et al, 2000). Expandable metal stents may be uncovered or covered. The covering of the expandable stent may block drainage of a neighboring duct, so covered stents should be restricted to distal bile duct strictures and must be used cautiously in patients with a gallbladder. Covered stents may extend patency rates by preventing tumor or hyperplastic tissue ingrowth, but this requires further study. Plastic stent migration out of the stricture is more commonly seen in benign strictures requiring the use of longer stents (Arhan et al, 2009), and the frequency

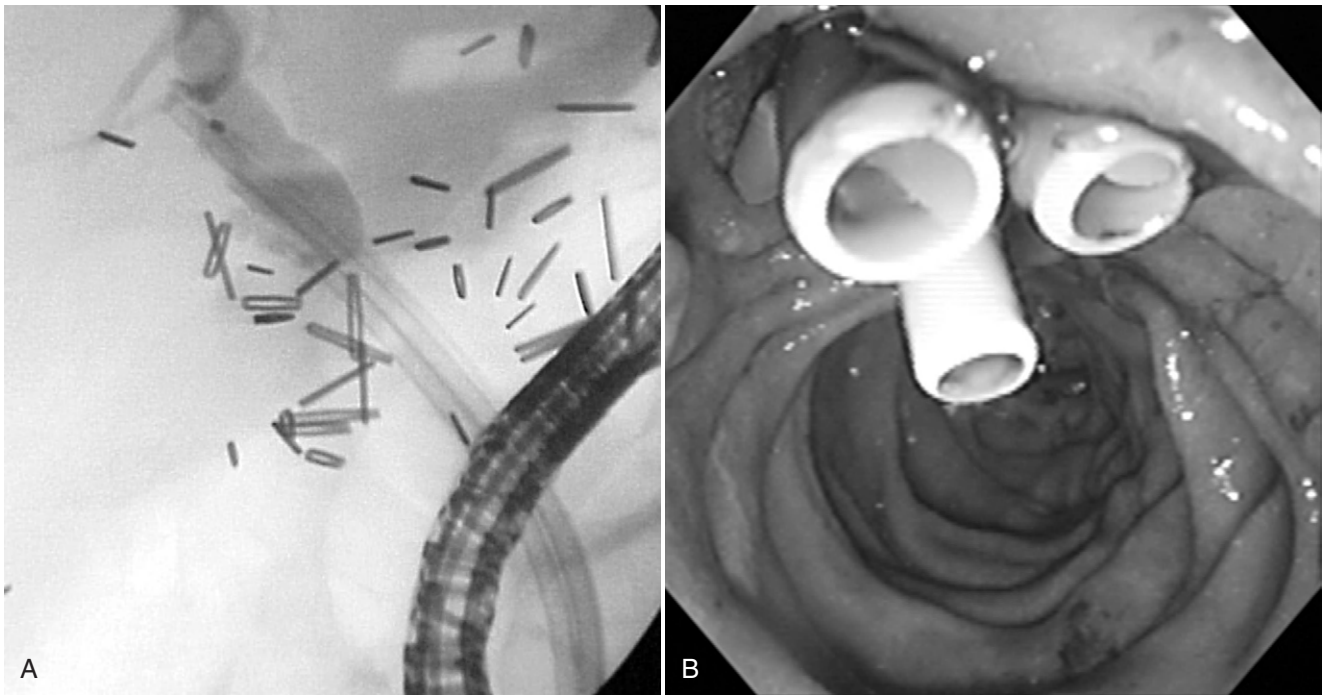


FIGURE 27.21. Radiographic (**A**) and endoscopic (**B**) images of multiple stents dilating a high-grade postoperative bile duct stricture.

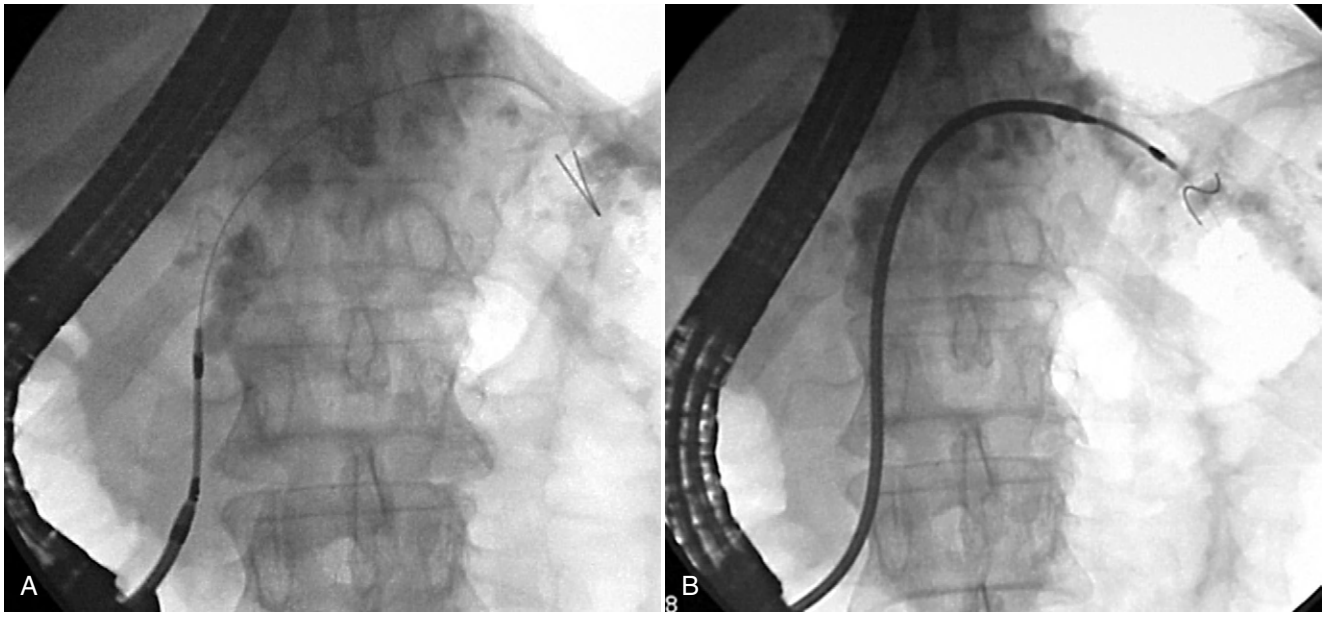


FIGURE 27.22. Radiographs before (**A**) and after (**B**) dilation of a tight stricture in the pancreatic head using the Soehendra Stent Retriever. *(Courtesy Cook Medical, Winston-Salem, NC.)*

of stent occlusion is related to the diameter of the metal stent (Loew et al, 2009). Recently, the use and removal of covered metal stents in benign disease has been demonstrated but is associated with a complication rate of 14%. Special "pancreatic" stents made of soft plastic with multiple side holes for drainage of side branches are used in the pancreatic duct. Pancreatic duct stents with large side holes remain patent for longer periods than stents with small side holes (Buscaglia et al, 2009); however, most pancreatic stents are placed for short-term prophylaxis to maintain sphincter patency (Chahal et al, 2009). Long-term use of fully covered metal stents in pancreatic duct strictures has been reported, but the migration rates are high (Park et al, 2008).

Technique of Stent Placement

After diagnosing the type and site of the obstruction with a diagnostic ERCP, a small sphincterotomy is often performed to facilitate insertion of instruments. The stricture is negotiated with a guidewire; use of short guidewires may decrease the duration of the procedure and time spent on wire exchanges (Reddy & Draganov, 2009). The technical success of stent placement has been enhanced by the use of hydrophilic wires, which allow easier and less traumatic passage through strictures. In addition, various maneuvers may facilitate the negotiation of a tight stricture: The angle of access to the stricture can be changed by adjusting the position of the guide catheter tip, and an angulated guidewire tip may be helpful for negotiating eccentric strictures. For concentric strictures, an inflated balloon catheter inserted over the guidewire centers the guidewire in the lumen. When the stricture is passed with a wire, a dilating catheter is coaxially inserted to dilate the stricture and obtain a complete cholangiogram. Cytology brushings can be obtained at this point to confirm malignant obstruction. A stent (plastic or expandable metal) is inserted using the Seldinger technique. Decompression of the obstructed biliary tree is typically indicated by a gush of dark stagnant bile into the duodenum.

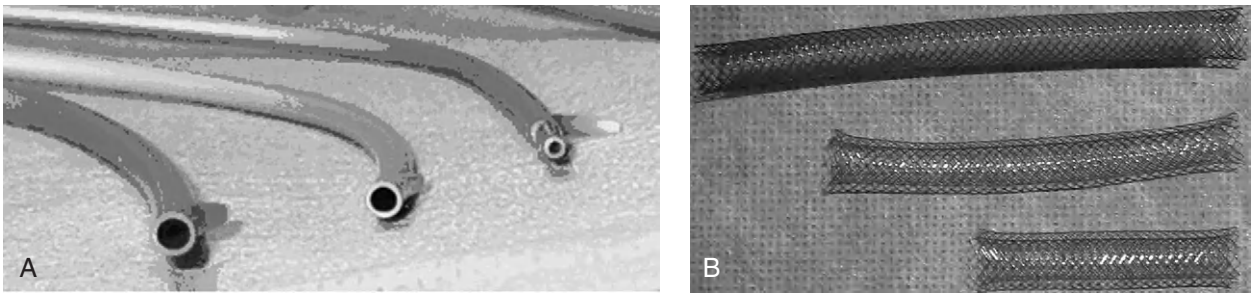


FIGURE 27.23. Straight plastic (**A**) and expandable metal (**B**) stents.

Hilar Strictures

Hilar strictures are often difficult to stent, because they are further away from the endoscope and tend to be tortuous and sclerotic (see Chapters 28 and 50D). For obstructing hilar cholangiocarcinoma (Klatskin tumors), the success rate of transpapillary stenting varies according to the level of obstruction. For type I strictures (involvement of the common hepatic duct), the success rate is around 86%, but it decreases to 45% for type II strictures (involvement of both main hepatic ducts) and 15% for type III strictures (involvement of secondary intrahepatic branches). Controversy exists as to whether both lobes of the liver need to be drained when a bifurcation lesion obstructs both lobes. Although some studies suggest that unilateral stenting is associated with a high frequency of jaundice resolution, two subsequent studies showed bilateral drainage to be associated with a significantly lower complication rate (Naitoh et al, 2009). Both lobes should be drained in type II and III obstruction if contrast medium fills both hepatic ductal systems and fails to drain. Endoscopic transpapillary stenting may need to be complemented by percutaneous transhepatic stenting when drainage is not complete and jaundice fails to resolve adequately (see Chapters 28 and 50D; Paik et al, 2009).

Dual-stent or multiple-stent insertion for hilar strictures requires a clear outline of the ductal anatomy on cholangiography. The anatomy is best appreciated with the patient in the supine position, because the right and left ductal branches are separated. A wire is advanced into each duct for which stent drainage is planned. A super-stiff 0.038-inch Amplatz guidewire (Boston Scientific, Natick, MA) assists stenting of a tight, angulated stricture. After wire placement, the strictures are dilated with a balloon to facilitate subsequent stent insertion; a 6 mm balloon is generally used. If a balloon catheter cannot be negotiated across a tight stricture, a 7-Fr Soehendra Stent Retriever can be used to core a path through the stricture (van Someren et al, 1996). The left hepatic duct should be stented first, because the left duct has a more acute angle of takeoff from the common hepatic duct (Fig. 27.24).

For malignant hilar strictures, self-expandable metal stents have numerous advantages over plastic stents. Drainage is superior because of the larger diameter and open mesh design that provides drainage of side branches. A sphincterotomy is not required when the distal (bottom) ends of metal stents are positioned within the duct, which may reduce the risk of post-stenting cholangitis. Many authors disagree with endoscopic approaches to hilar strictures and advocate intubation for obstruction at this level by percutaneous methods (see Chapter 52; Paik et al, 2009).

Chronic Pancreatitis (See Chapter 55)

Focal strictures of the main pancreatic duct may be stented to improve drainage and provide pain relief (Ponchon et al, 1995). As a rule, large diameter stents should be left in place, until the stricture either resolves or is significantly improved, but only in the face of well-established chronic pancreatitis. Persistent stenting has been used to achieve an adequate dilation effect with normalization of ductal caliber (Fig. 27.25). If the stricture is persistent or recurs, multiple stents can be placed to achieve greater dilation. Despite symptomatic improvement, the use of intraductal stents for prolonged periods is associated with a significant risk of duct damage (Somogyi & Forsmark, 1998). Migrated pancreatic duct stents can be managed with endoscopic balloon retrieval (Price et al, 2009).

Stent Clogging

Clogging of plastic stents is a common problem that necessitates a stent exchange. The mean duration of patency of plastic biliary stents is approximately 5 months. Exploring ways to prolong stent patency has been the subject of considerable research over the years and remains unresolved. Expandable metal stents can be inserted through the duodenoscope in a compressed state and can expand to a diameter threefold that of plastic stents and are less prone to clogging (Weber et al, 2009b). Small diameter metal stents occlude more rapidly than large diameter stents (Loew et al, 2009). Conformable stents do not offer any better patency rate than nonconformable metal stents (Yang et al, 2009); and despite a need for fewer procedures with the use of metal stents, cost savings may not be significant (Yoon et al, 2009). Uncovered metal stents are not removable, which may present a problem if they become occluded, or if surgery is considered at a later time, and expandable stents should be reserved for unresectable malignant strictures. Covered metal stents may be removed, although with a significant complication rate (Mahajan et al, 2009).

Pancreatic stents occlude over time, but only a few patients become symptomatic (Buscaglia et al, 2009). The low incidence of pain or pancreatitis despite stent occlusion suggests that the stent functions as a wick around which pancreatic fluid continues to drain. In contrast to the bile duct, infection of the pancreatic duct (ductitis) is rarely seen as a complication of stent clogging.

Replacement of a clogged plastic stent can be performed by either removing the clogged stent with a snare or forceps and inserting a new stent or by exchanging the stent over a guidewire using a stent retriever (Fig. 27.26; Chaurasia et al, 1999). Foreign body forceps are used for biliary stents impacted in the wall of the duodenum. The metal spiral stent retriever is used when guidewire access to the bile duct is necessary.

Endoprosthesis for Stone Impaction

Failure to clear the duct of stones after sphincterotomy and ductal instrumentation places the patient at substantial risk for ductal infection (cholangitis, pancreatitis) and sepsis. Stent placement provides persistent drainage despite the presence of bile duct stones (Sharma et al, 2009). The placement of a 7- or 10-Fr endoprosthesis may be used as a temporizing measure to maintain drainage and prevent stone impaction pending more definitive management (Sharma et al, 2009). Stent placement also may be preferable to attempting stone extraction in a septic patient; clearance of the duct can be performed when the sepsis has resolved, and the patient's condition has stabilized (Chopra et al, 1996). Stents should not be left in place as definitive treatment or over an extended time, because late complications, mainly cholangitis, have been reported. Surgical treatment of the problem must be considered when endoscopic techniques fail (see Chapters 29, 34, and 35).

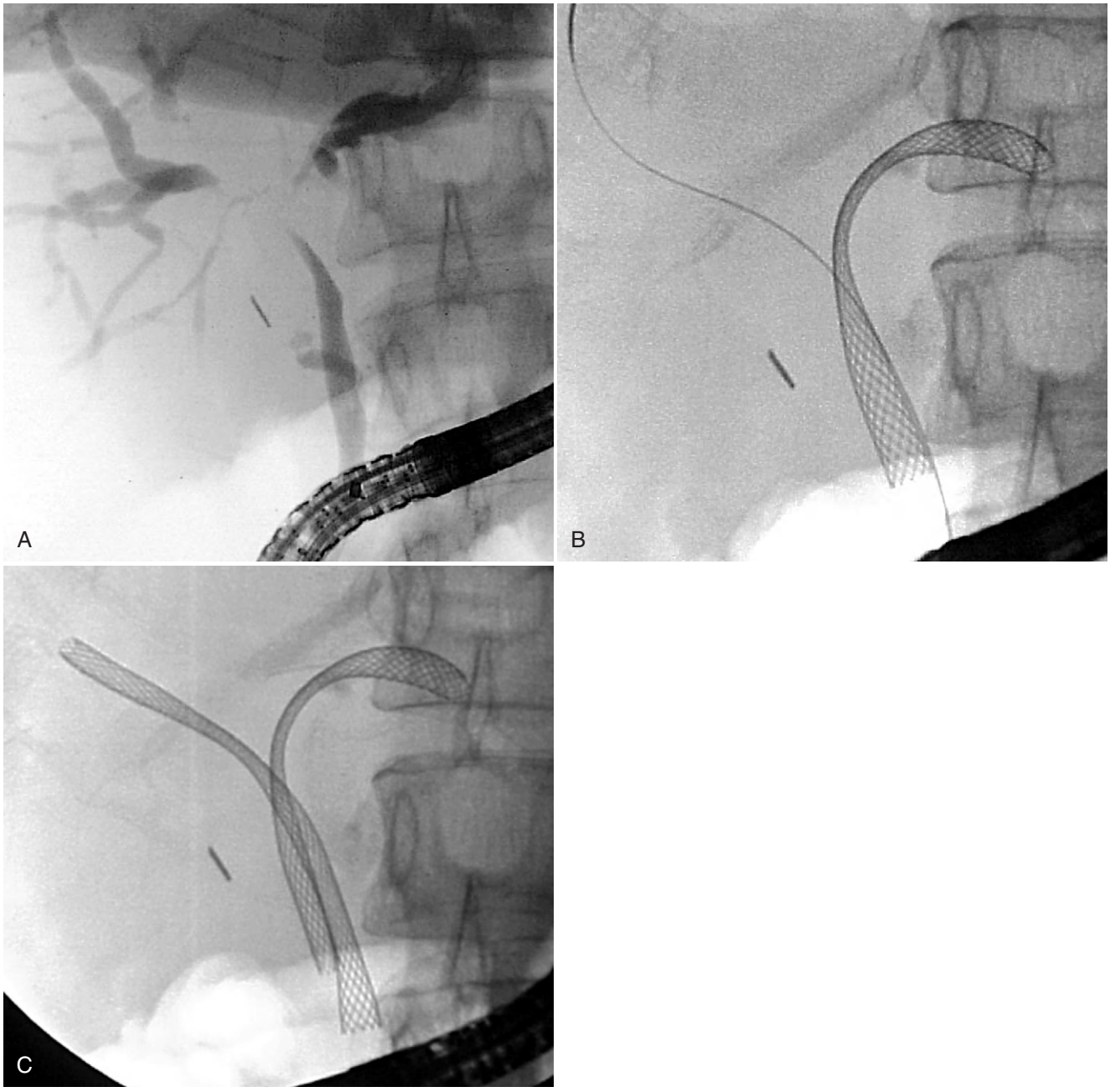


FIGURE 27.24. Radiographs showing type III malignant hilar obstruction with upstream dilation of the right and left hepatic ducts (**A**), placement of a left-sided biliary metal stent to drain the left hepatic lobe (**B**), and placement of a second right-sided biliary metal stent to drain the right hepatic lobe (**C**).

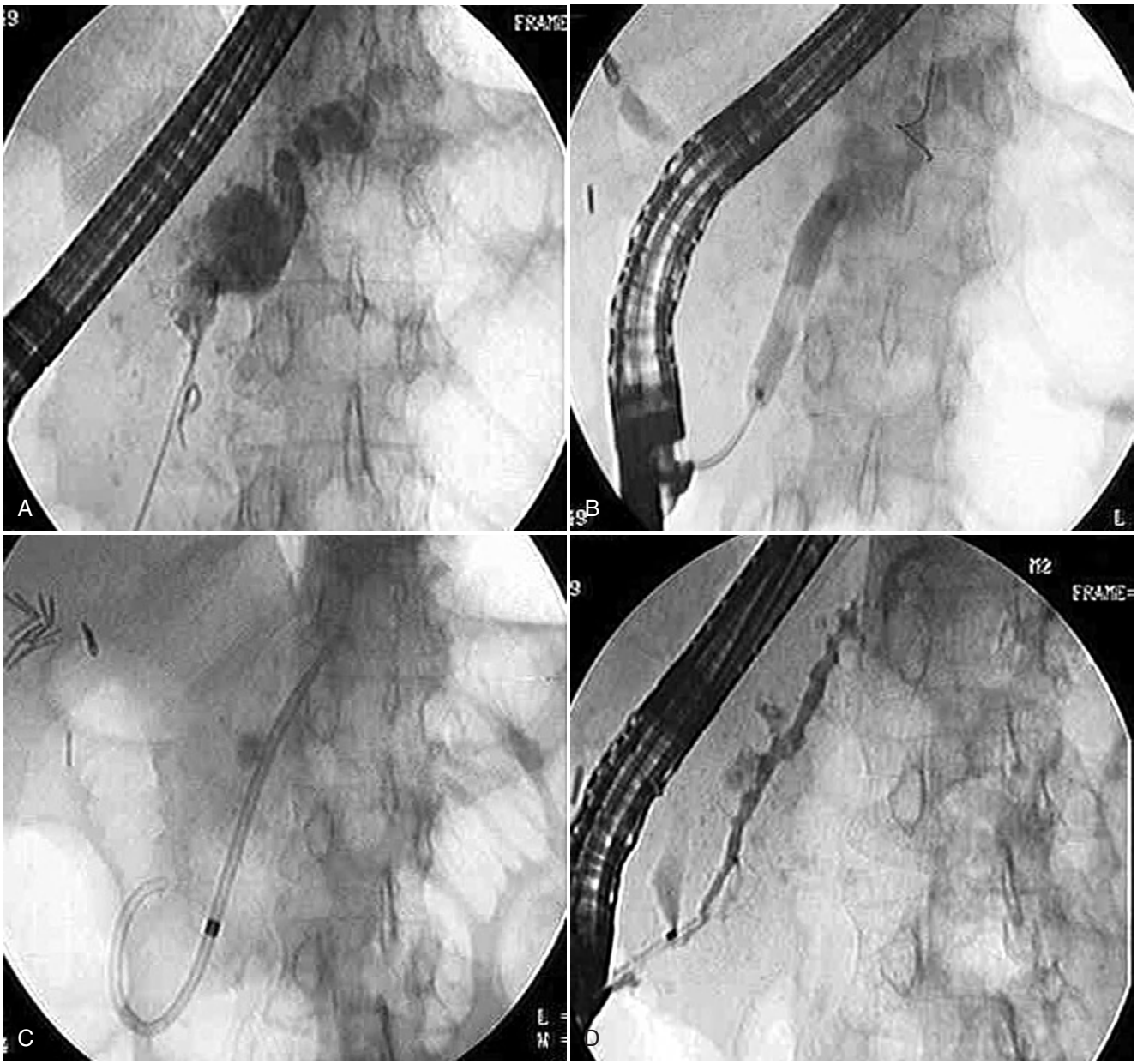


FIGURE 27.25. Radiographs showing a high-grade stricture in the pancreatic head with upstream dilation (**A**) followed by balloon dilation (**B**) and placement of a pancreatic pigtail stent (**C**). Resolution of the stricture and normalization of pancreatic duct caliber after stent removal (**D**).

PHOTODYNAMIC THERAPY

Photodynamic therapy has been used in conjunction with biliary stenting to improve biliary drainage in patients with non-resectable cholangiocarcinoma. A photosensitizing cytotoxic agent is administered intravenously that is selectively taken up by tumor cells. Subsequent exposure to laser light of the proper wavelength activates the photosensitizing agent and results in tumor destruction. Application of laser light is performed with thin laser fibers. A recent randomized trial found that stenting plus photodynamic therapy was superior to stenting alone in prolonging survival in patients with advanced cholangiocarcinoma (Kahaleh et al, 2008). Laser light therapy can be delivered through a metal stent (Wang et al, 2008).

SPHINCTER OF ODDI MANOMETRY (SEE CHAPTER 12)

Sphincter of Oddi manometry is used in some centers to diagnose sphincter of Oddi dysfunction (SOD), a poorly understood entity associated with recurrent abdominal pain and at times with abnormal liver function tests and serum amylase values. The technique of sphincter of Oddi manometry has become fairly standardized, using special endoscopic manometry catheters introduced into the bile or pancreatic duct (Fig. 27.27). Solid-state catheters provide results nearly identical to water-perfused catheters (Draganov et al, 2009); the bile and pancreatic sphincter pressures are measured separately. Sphincterotomy has been shown to result in symptomatic

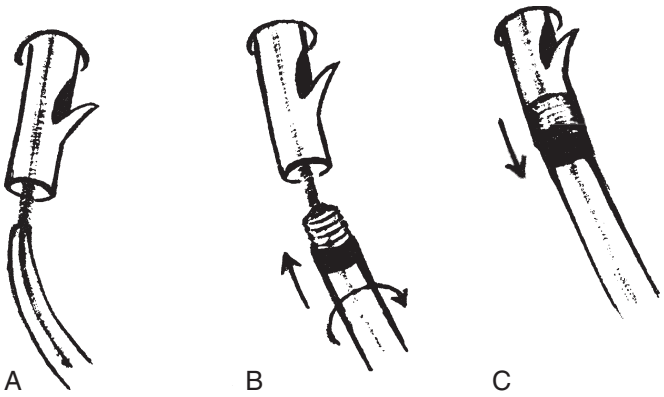


FIGURE 27.26. Stent replacement using the Soehendra Retriever. **A,** With the aid of an endoscopic retrograde cholangioplasty catheter, a conventional 0.035-inch Teflon-coated guidewire is inserted through the prosthesis. **B,** The catheter is removed, and the Retriever is inserted over the wire, until it abuts against the distal end of the prosthesis. The stent is rotated clockwise to screw the Retriever tip into the prosthesis. **C,** The stent is removed over the indwelling guidewire. *(Courtesy Cook Medical, Winston-Salem, NC.)*

improvement of biliary pain in patients documented to have SOD and abnormal liver function tests (Elmi & Silverman, 2009). High-risk patients should have a prophylactic pancreatic stent placement and needle-knife fistulotomy (Madacsy et al, 2009). Small diameter pancreatic duct stents, as small as 3 Fr, are safer and have a higher rate of spontaneous passage (Rashad et al, 2004). Unsuccessful pancreatic stent placements are associated with a high rate of pancreatitis (Freeman et al, 2004).

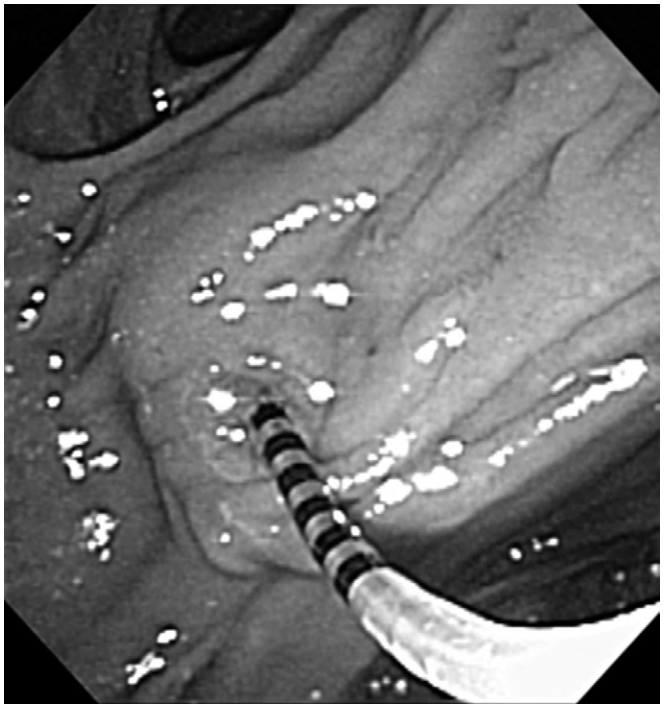


FIGURE 27.27. Endoscopic view of sphincter of Oddi manometry using a standard triple-lumen manometry catheter. *(Courtesy Cook Medical, Winston-Salem, NC.)*

Pancreatic sphincterotomy, often in conjunction with biliary sphincterotomy, is performed for patients with recurrent pancreatitis using a wire-guided papillotome (Joo et al, 2009).

AMPULLECTOMY

Benign adenomas of the papilla of Vater can be removed together with the papilla of Vater using a diathermic snare in an analogous manner to colon polypectomy (snare ampullectomy). Endoscopic ultrasonography may aid in assessing these tumors and for selecting patients suited to this approach (see Chapter 14) The technique entails snaring of the papilla flush with the duodenal wall (Fig. 27.28; Menees et al, 2009). Saline does not need to be injected prior to the ampullectomy. This is an alternative to local surgical resection, if complete excision of the adenoma and ampulla is achieved; however, it is crucial that

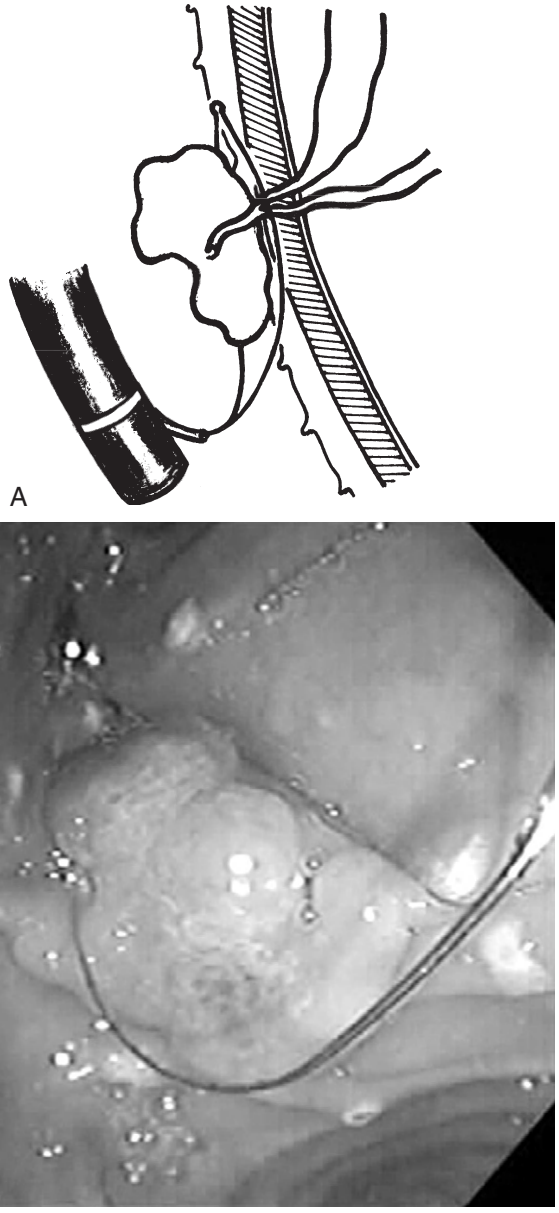


FIGURE 27.28. Schematic (**A**) and endoscopic (**B**) views showing the technique of snare ampullectomy of a benign ampullary adenoma.



FIGURE 27.29. Radiographic views of a pancreatic duct leak at the neck region. **A,** Before stenting. **B,** After stenting.

the excised tissue specimen be retrieved and submitted for complete histologic evaluation. Surgical resection is indicated if the specimen shows malignancy or complete excision cannot be achieved endoscopically (see Chapter 59). Prophylactic pancreatic stent placement is used to prevent pancreatitis (Yamao et al, 2009; Harewood et al, 2005). Periodic endoscopic surveillance is mandatory to evaluate for adenoma recurrence.

Pseudocysts and Leaks

To determine whether a cyst communicates with the pancreatic duct, ERCP may be indicated in patients with pseudocysts that fail to resolve or those that recur (Lakhtakia & Reddy, 2009). Outflow obstruction secondary to a stricture, stone, or ampullary stenosis should be treated with sphincterotomy and/or stenting (Habashi & Draganov, 2009). Stenting also has been found to be effective in the management of partial and complete ductal leaks, fistulas, and ascites (Fig. 27.29; Kozarek et al, 1997). Endoscopic approaches to internal drainage of nonneoplastic pancreatic cysts are described in Chapter 14.

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CHAPTER 28

Radiologic hepatobiliary interventions

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RADIOLOGIC INTERVENTION

Radiologic intervention is applicable for a wide range of hepatobiliary diseases (see also Chapters 12, 19, 25, and 32). The use of these techniques in pancreatic disease is referred to in Chapters 25, 32, 54, 55, and 63.

TREATMENT OF HEPATIC CYSTS

Simple, nonparasitic hepatic cysts (see Chapters 69A and 69B) are the second most common benign lesions that involve the liver, following hemangiomas. They are found in approximately 1% to 2.5% of adults and occur more commonly in women and in the right liver. These cysts are lined with bile duct epithelium, contain clear fluid, and almost never communicate with the biliary tree (Forbes & Murray-Lyon, 1991). Simple cysts can be acquired from processes such as trauma or inflammation, or they may be congenital, such as in polycystic disease (see Chapter 69), with cysts possibly present in the kidneys and pancreas as well.

Typically, simple hepatic cysts are asymptomatic and are discovered incidentally on liver imaging done for other indications. When present, symptoms include nonspecific abdominal discomfort and early satiety, with or without weight loss. Although usually chronic in nature, the symptoms may occur acutely with cyst rupture, intralesional hemorrhage, infection, or torsion of a pedunculated cyst. Infrequently, a patient may be seen initially with jaundice or leg swelling related to the mass effect of a cyst on the bile duct or the inferior vena cava, respectively.

On cross-sectional imaging, the requisite feature of a simple hepatic cyst is a circumscribed, thin-walled, nonseptated lesion with lack of enhancement after intravenous contrast medium administration. Imaging modality–specific features include posterior acoustic enhancement on ultrasound (US), low attenuation on computed tomography (CT), and signal intensity similar to that of free water on magnetic resonance imaging (MRI). Wall thickening, the presence of septations, or lack of enhanced through-transmission on US should raise the question of another pathology, such as cystic metastasis, cystadenoma (see Chapter 79B), or hydatid disease (see Chapter 68), which must be thoroughly investigated (Mortele & Ros, 2001; Nisenbaum & Rowling, 1995). This evaluation is especially important before beginning treatment, and periodic imaging follow-up early in the course of therapy is prudent.

In the absence of symptoms or signs, simple liver cysts require no treatment. Traditional therapy of symptomatic cysts has been surgical, with laparoscopic deroofing currently favored by many surgeons (Gall et al, 2009; Mazza et al, 2009; see Chapter 65). Interventional radiologic techniques such as fine needle aspiration (FNA) and catheter drainage without or with cyst sclerosis have been used to treat simple cysts. With these techniques, symptomatic relief usually is achieved, although recurrence is common with aspiration alone.

Percutaneous chemical sclerosis of cysts with a variety of agents—including alcohol, tetracycline antibiotics, and povidone-iodine—either at the time of initial aspiration or after a period of catheter drainage usually provides successful therapy (vanSonnenberg et al, 1994). In the case of alcohol, it fixes the cells lining the cyst cavity, thereby preventing secretion of cyst fluid and subsequent enlargement (Bean & Rodan, 1985). Tikkakoski and colleagues (1996) described single-session treatment with alcohol for 59 symptomatic hepatic cysts in 25 patients. The cysts were evacuated via a 5-Fr drainage catheter, and absolute alcohol was instilled and left in for 20 minutes with the patient turned in various positions to maximize cyst wall exposure to the agent. In some cases, the procedure was repeated once or twice during the same session, after which the entire volume of injected ethanol was aspirated, and the catheter was removed.

Yoshida and colleagues (2003) successfully treated symptomatic solitary hepatic cysts with multiple minocycline injections and noted complete cyst regression without recurrence. Lopes and colleagues (1998) successfully treated seven patients with hepatic cysts by aspiration followed by instillation of tetracycline with a resultant decrease in all lesions. Kimura and colleagues (2005) performed repeated percutaneous instillations of alcohol after cyst aspiration and achieved subtotal or total cyst regression. Another study compared single-session alcohol sclerotherapy versus prolonged catheter drainage with negative pressure; they reported no differences in average volume reduction, final volume, and cyst regression (Zerem et al, 2008).

Typically, aspiration and cyst sclerosis are done as an outpatient procedure, and the patient is discharged home after a short period of observation. The benefits of this approach are the minimally invasive nature, low risk of complications, short recovery period, avoidance of general anesthesia and a long hospital stay, and cost effectiveness.

Laparoscopic cyst fenestration and deroofing are safe and are currently the most effective surgical approaches for symptomatic simple hepatic cysts. Image-guided (US or CT) hepatic cyst aspiration with chemical sclerosis using tetracycline or alcohol should be the treatment of choice for patients who are poor operative risks (Mazza et al, 2009).



FIGURE 28.1. Pylephlebitis. **A,** Computed tomography (CT) scan showing complex mass in the caudate lobe and portal vein thrombosis. The unusual pattern of parenchymal liver enhancement with central low density is characteristic in patients with portal vein occlusion. **B,** CT scan 1 month after treatment with antibiotics shows that the abscess in the caudate lobe has largely resolved. **C,** Findings of cavernous transformation of the portal vein on ultrasound.

Pyogenic Hepatic Abscess Drainage

Pyogenic hepatic abscesses result in considerable morbidity, and mortality occurs if abscesses are left untreated. Advances in cross-sectional imaging and interventional radiology have revolutionized the diagnosis and therapy of liver abscesses with a dramatic improvement in prognosis (see Chapter 66). Mortality has decreased from 65% (1952–1972) to 31% (1973–1993). This decrease occurred in the face of no significant change in patient characteristics, such as age and sex distribution, or incidence of associated conditions, such as diabetes mellitus, steroid use, chronic liver disease, chronic pancreatitis, and pyelonephritis (Huang et al, 1996). Another study from Denmark found the incidence rate of pyogenic abscesses increased from 6 to 18 per 1 million men and from 8 to 12 per 1 million women, and the 30-day mortality rate decreased from 40% for men and 50% for women to around 10% for both genders (Jepsen, 2005).

The liver is the most common site of abdominal visceral abscesses. Liver abscess is a result of either direct spread of infection from a contiguous focus, such as the biliary tree, or hematogenous seeding of the liver via the portal vein or hepatic artery. Biliary tract pathology is the most common cause of liver abscess. Of the nonbiliary diseases that lead to hepatic abscess, appendicitis with rupture and suppurative pylephlebitis, usually from infection in the female genital tract, are frequent causes (Zaleznik & Kasper, 1998).

The constellation of a liver abscess and portal vein thrombosis with cavernous transformation of the portal vein may mimic the findings seen in hepatocellular carcinoma (HCC; Fig. 28.1). Clues to the correct diagnosis are the clinical and laboratory parameters that suggest infection and the absence of cirrhosis and portal hypertension, both of which are commonly seen with HCC. With successful treatment, complete resolution of both the abscess (see Fig. 28.1B) and the cavernous transformation of the portal vein (see Fig. 28.1C) is seen in many cases.

Hematogenous seeding of the liver via the hepatic arterial system is unusual and should be suspected if nongastrointestinal flora—particularly a single organism, such as *Staphylococcus aureus* or streptococcal species—is isolated from a liver abscess. Cryptogenic abscesses may be seen in diabetic patients; however, a diligent search should always be made for a primary cause, such as diverticulitis.

The microbial flora often reflect the source of the infectious process (see Chapter 11). In a study of 111 patients with pyogenic liver abscesses, *Klebsiella* species and *Escherichia coli* were the most common offenders (Lok et al, 2008). Anaerobes generally are encountered with a previous history of biliary intervention (e.g., surgery or stenting). With nonbiliary

gastrointestinal (GI) sources of infection, polymicrobial gram-negative aerobes and anaerobes predominate, whereas systemic bacteremia is more likely to give rise to a single isolate, often *S. aureus.* Other reported microbes reflect individual patient factors, such as *Entamoeba histolytica* with a history of residence in or travel to endemic areas, and *Candida* species in neutropenic patients.

Clinical symptoms and signs are nonspecific. Of 111 patients with pyogenic liver abscess (Lok et al, 2008), 91% were seen initially with fever, 79% with right upper quadrant pain, 18% with anorexia, and 18% with septic shock. Laboratory abnormalities also are nonspecific. In the same study, 93% had hypoalbuminemia, 75% leukocytosis, 72% elevated alkaline phosphatase, and 59% elevated alanine transaminase.

US and CT are the imaging modalities of choice (Zaleznik & Kasper, 1997). Radionuclide scans (gallium, indium, and technetium) and MRI can provide further diagnostic information, but rarely are necessary.

Decompression of the abscess cavity and systemic antibiotic therapy are the mainstays of treatment for liver abscess. Decompression evacuates the pus and endotoxins and relieves the intracavitary pressure; this ameliorates systemic toxic symptoms by decreasing hematogenous dissemination of toxins. It also allows better penetration of antibiotics into the wall of the abscess. In general, large abscess cavities should be drained, and aspiration alone should only be considered for smaller lesions.

Uncomplicated pyogenic liver abscesses may be single or multiple, often are unilocular, and may be septated (Fig. 28.2). It may be impossible to evacuate complex multiloculated abscesses completely at the time of initial catheter placement (see Fig. 28.2B). Typically, there is free communication between the loculi (see Fig. 28.2C); consequently, most resolve completely when treated with a single catheter (see Fig. 28.2D) and appropriate antibiotics. If in doubt about adequate drainage of multiple locules or multiple abscesses, more than one catheter is indicated. Communication with the biliary tree may be seen when the drainage catheters are injected with contrast material as a part of performing an abscessogram (see Fig. 28.2C). The catheter contrast injections should not be performed until the pus has been evacuated to ensure that septicemia is not provoked iatrogenically.

Regarding the choice of percutaneous needle aspiration versus catheter drainage, opinions vary. Giorgio and colleagues (2006) described their experience with 118 patients treated with US-guided percutaneous needle aspiration and systemic antibiotic therapy. Cure was achieved in all 118 patients, and in 36 instances with only a single puncture. No recurrences were seen at 7 to 42 months of follow-up. The use of percutaneous needle aspiration and antibiotics is simple, less expensive, and more comfortable for the patient than catheter drainage. In practice, however, more than one aspiration is usually necessary for complete treatment with this strategy. Yu et al (2004) performed percutaneous needle aspiration in 64 patients with pyogenic liver abscess and concluded it was probably as effective as continuous percutaneous catheter drainage; however, their data were not statistically significant. Rajak and colleagues (1998) also compared the two methods of percutaneous treatment in 50 patients; they concluded that percutaneous catheter drainage was more effective than percutaneous needle aspiration. A failure of treatment was defined as a lack of response to a second attempt of percutaneous needle aspiration.

A more recent study (Zerem, 2007) also compared the two treatment methods in 60 patients, with the lack of response to percutaneous needle aspiration defined at three attempts. These authors agreed with Rajak and colleagues (1998) and concluded that percutaneous catheter drainage was more effective than percutaneous needle aspiration in the management of liver abscess. They opined that percutaneous catheter drainage is more efficient for multiloculated liver abscesses, and that percutaneous needle aspiration is a valid alternative for abscesses 5 cm or less in greatest diameter. Currently, treatment of pyogenic liver abscess with drainage catheter placement is the most commonly accepted method among interventional radiologists. Percutaneous aspiration without catheter drainage is not recommended except for occasional patients with one or more small liver abscesses that are too small for a catheter.

Surgical intervention for liver abscesses should be reserved for cases with coexisting surgically correctable causes of liver abscess (e.g., biliary tree abnormalities) or for cases of failed percutaneous therapy (see Chapter 66). A recent study demonstrated that partial liver resection is a safe and successful treatment for large, multiloculated complex pyogenic liver abscesses (Hope et al, 2008). Some associated biliary tree abnormalities may be amenable to endoscopic correction. In this subset of patients, endoscopic retrograde cholangiopancreatography (ERCP) might be preferred over surgery (Lam et al, 1999). Another study reported that previous endoscopic sphincterotomy was a good prognostic factor for early resolution of liver abscesses within 6 weeks (Wong et al, 2002).

Empiric antibiotic therapy is initiated on the suspected source of infection, with later adjustment based on the results of culture and sensitivity of the aspirated specimen. Several weeks of therapy may be required. Sending aspirates to the laboratory for aerobic and anaerobic cultures at the time of initial access is crucial for prescribing an appropriate antibiotic regimen.

Amebic Abscess

In a patient with a hepatic abscess and a history of travel to or residence in endemic areas, the possibility of infection with *Entamoeba histolytica* should be considered (see Chapter 67). Hepatic amebic abscess is the most common extraintestinal manifestation of amebiasis. Conditions that affect cell-mediated immunity—such as extremes of age, pregnancy, corticosteroid therapy, malignancy, HIV infection, and malnutrition—also may increase the chance that enteric *E. histolytica* infection results in extraluminal disease with liver involvement. The clinical findings are similar to the findings for pyogenic abscess; in addition, amebic abscesses may have superimposed bacterial infection, and they usually are solitary and most commonly located in the right lobe, adjacent to the liver capsule (Brindicci et al, 2006).

Serologic testing is the most widely used method to diagnose hepatic amebic abscess. Aspiration may be used to establish the diagnosis and to exclude secondary bacterial infection. When aspiration is used for diagnosis, the cavity should be aspirated as completely as possible. Amebic abscesses contain acellular, proteinaceous debris and an "anchovy paste," a chocolate-colored fluid consisting predominantly of necrotic hepatocytes. Antigen tests and polymerase chain reaction on aspirated material may be helpful to confirm the diagnosis. Biopsy of the abscess wall may also establish the diagnosis if the other tests are inconclusive, which is the case in about 10% of patients (vanSonnenberg et al, 1985).

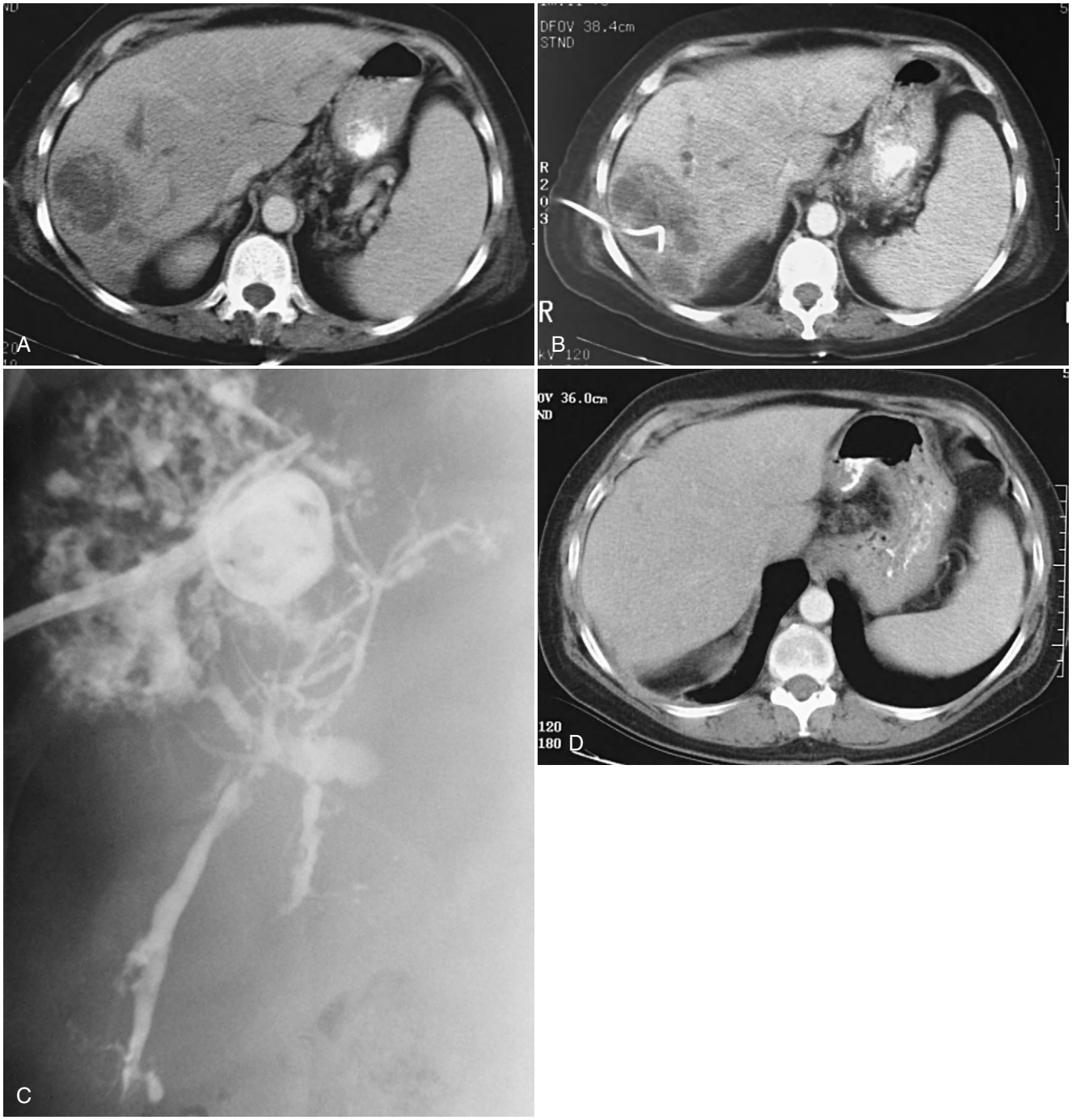


FIGURE 28.2. Liver abscess. **A,** Computed tomography (CT) scan showing multiloculated abscess in right lobe with dilated intrahepatic bile ducts. **B,** CT scan at the time of drainage catheter placement. **C,** Contrast study via the drainage catheter shows typical, irregular, loculated-type appearance and communication with biliary tree. **D,** Follow-up CT scan 3 months after treatment of hepatic abscess shows complete resolution.

Amebic liver abscesses can generally be treated successfully with antibiotics alone (Chavez-Tapia et al, 2009). With clinical suspicion of amebic liver abscess, empiric treatment with metronidazole and a luminal agent (paromomycin or iodoquinol) may be started while awaiting confirmatory tests. Indications for catheter drainage of amebic abscess include failed medical therapy, secondary pyogenic infection, pregnancy, perforated abscess, false-negative serology, and left lobe abscess because of the proclivity to rupture or spread into the pericardium (vanSonnenberg et al, 1985; Ken et al, 1989; Hanna et al, 2000).

Echinococcal Disease

Echinococcal disease is an endemic zoonosis acquired from ingestion of *Echinococcus granulosus* eggs from infected animals (see Chapter 68). The most common location of hydatid cysts is the liver. Echinococcal cysts in the liver have a characteristic

multiloculated or finely multiseptated appearance, and the right lobe is affected in 60% to 85% of cases.

Echinococcosis rarely manifests with an acute illness. Symptoms are unusual before the cyst has reached at least 10 cm in diameter. A large cyst can produce hepatomegaly with or without associated right upper quadrant pain, nausea, and vomiting. *Echinococcus granulosus* cysts can rupture into the biliary tree and produce biliary colic, obstructive jaundice, cholangitis, or pancreatitis. Pressure or mass effect on the bile ducts, portal and hepatic veins, or inferior vena cava can result in cholestasis, portal hypertension, venous obstruction, or Budd-Chiari syndrome. Liver cysts also can rupture into the peritoneum causing peritonitis, or they can rupture transdiaphragmatically into the bronchial tree, causing pulmonary hydatidosis or a bronchial fistula. Secondary bacterial infection of the cysts can result in liver abscesses. Serologic tests are often useful to establish the diagnosis, in conjunction with the typical clinical and radiologic presentation.

Traditionally, surgery has been the recommended treatment for hepatic cysts (World Health Organization, 1996), but the combination of percutaneous drainage with drug therapy is a more recent alternative. Although percutaneous aspiration previously was contraindicated because of the risk of anaphylaxis, this complication has been shown to be rare (Akhan et al, 1996). Bret and associates (1988) demonstrated the safety of aspiration or drainage of these cysts in 13 patients, and none of the patients who underwent drainage was premedicated. If a catheter was placed for drainage, a scolicidal agent was injected into the cyst cavity after cystography. No complications or recurrences were reported 6 months to 1 year after treatment. Khuroo and colleagues (1997) compared percutaneous drainage with surgery for hepatic hydatid cysts and reported that percutaneous drainage, combined with albendazole, is an effective alternative to cystectomy. They demonstrated similar efficacy in cyst regression and disappearance, with advantages of a shorter hospital stay and a lower complication rate. Zerem and Jusufovic (2006) treated 72 patients with univesicular and multivesicular hepatic hydatid cysts with US-guided percutaneous drainage combined with albendazole, and 81% of the cysts in the univesicular group and 63% in the multivesicular group disappeared.

Percutaneous evacuation of cyst content (PEVAC) has been reported as a safe and effective treatment of multivesicular echinococcal cysts with or without cystobiliary fistulas, which contain undrainable material (Schipper et al, 2002). Hydatid cysts commonly have a communication with the biliary tree, which is a contraindication to injection of sclerosing agents, because this may cause diffuse injury to the biliary epithelium (Belghiti et al, 1986).

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT

The concept of transjugular hepatic intervention dates back to 1967, when Hanafee attempted diagnostic cholangiography via the transjugular intrahepatic route as a safer alternative to the percutaneous technique. At times, he inadvertently punctured portal vein radicles (Hanafee & Weiner, 1967). In 1969, Rosch and colleagues explored the transjugular route to visualize the portal venous system as an alternative to other available methods, such as splenoportography. The same year, Rösch and colleagues created the first transjugular intrahepatic portosystemic shunt (TIPS; see Chapter 76E) in dogs, using coaxial catheters to dilate the intrahepatic tract (Rösch et al, 1969, 1971). They discovered that without support, the tract would close; the plastic tubing used to "stent" the tract either thrombosed or migrated. Balloon dilation (Burgener & Gutierrez, 1979) and cryoprobes (Colapinto et al, 1983) were tried, but keeping the intrahepatic tract from shutting down remained a major problem. In the first human application of TIPS, Colapinto and associates (1982) used prolonged balloon inflation for 12 hours to keep the tract patent, but ultimately without success. The technique became a viable clinical option after refinement of metal stent technology in the late 1980s, when Richter and colleagues (1989) performed a landmark TIPS using a balloon-expandable Palmaz stent to maintain tract patency. The availability of Wallstents led to the rapid expansion and acceptance of the procedure.

Indications

The main indication for TIPS is the treatment of acute or recurrent variceal bleeding that has failed or is refractory to medical or endoscopic therapy, or both (see Chapters 75 and 76). This is especially true for patients who are bleeding from gastric or peristomal varices and those with severe portal hypertensive gastropathy. It is the preferred technique as a bridge to liver transplant, compared with surgical portosystemic shunts, because when performed correctly, TIPS does not alter extrahepatic vascular anatomy. It also is indicated for the control of refractory ascites and hepatic hydrothorax. TIPS may be used to treat Budd-Chiari syndrome in patients with moderate disease who fail to improve with anticoagulation (Boyer & Haskal, 2010).

Contraindications

There are several absolute and relative contraindications to TIPS placement. Absolute contraindications include congestive heart failure, sepsis, unrelieved biliary obstruction, severe pulmonary failure, and as the primary prevention of variceal bleeding (Boyer & Haskal, 2010). Relative contraindications to TIPS include the presence of HCC or hepatic metastases along the expected path of TIPS, hepatic vein obstruction, portal vein thrombosis, severe encephalopathy, polycystic disease of the liver, uncorrectable coagulopathy, and thrombocytopenia.

Technique (See Chapter 76E)

Various techniques and different systems are available for performing TIPS (Fig. 28.3). An imaging study using US, intravenous contrast-enhanced CT, or MRI to show a patent portal vein, hepatic veins, and hepatic venous anatomy is required. In an acutely bleeding patient, upper GI endoscopy confirms esophageal varices, excludes other sources of upper GI bleeding, and allows an attempt at endoscopic treatment. TIPS usually is performed under conscious sedation, but general anesthesia also may be used. Right internal jugular access is preferred, and a vascular sheath is placed. A selective catheter is advanced into one of the hepatic veins (see Fig. 28.3A).

The right hepatic vein is most commonly accessed for TIPS creation. Right atrial and free and wedged hepatic venous pressures are obtained, followed by hepatic and wedged hepatic venography. A specially designed needle is passed via the

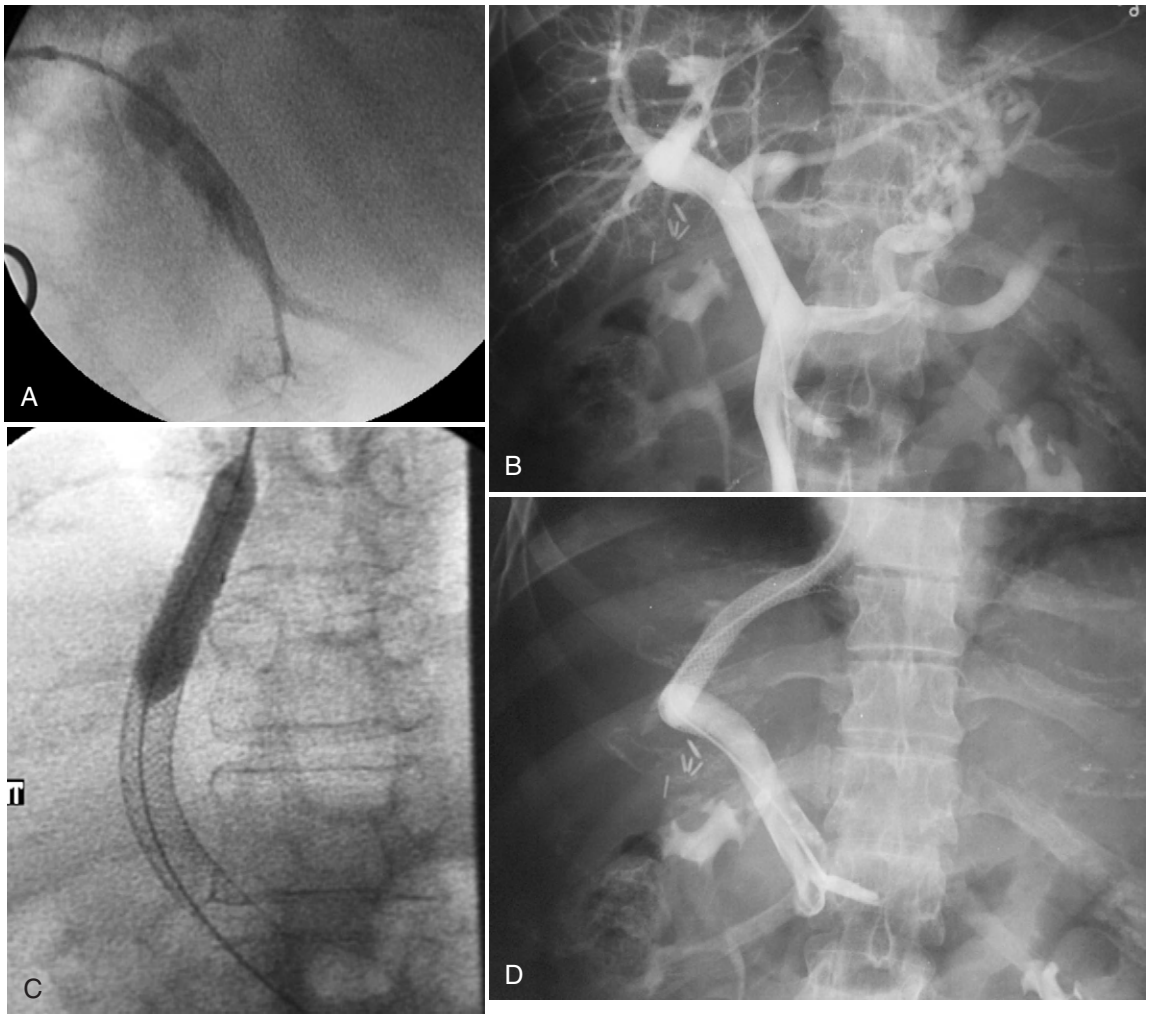


FIGURE 28.3. Transjugular intrahepatic portosystemic shunting. **A,** Right hepatic venogram performed via a transjugular catheter. **B,** Portogram shows enlarged coronary vein with opacification of gastroesophageal varices. **C,** Balloon dilation of the transhepatic tract between the right hepatic and right portal veins. **D,** After shunt placement. The dilated coronary vein and varices are no longer opacified.

transjugular route from the right hepatic vein across the liver parenchyma into the right portal vein 2 to 3 cm from the main portal vein confluence. A guidewire is advanced into the superior mesenteric vein or splenic vein and is used to place a catheter for pressure measurements and venography (see Fig. 28.3B). The tract is predilated with a balloon (see Fig. 28.3C); an appropriately sized (8 to 12 mm) self-expanding bare stent or a specially designed covered stent is deployed, and the balloon is dilated to an appropriate size. Pressures are obtained, with the goal being a portal–systemic gradient of less than or equal to 12 mm Hg. If the gradient is greater than 12 mm Hg, certain stents (Wallstents) may be dilated with a 12-mm balloon. If this dilation does not result in a satisfactory pressure gradient, and collaterals fill persistently, or when stents other than Wallstent have been used, parallel TIPS should be considered. If the result is satisfactory (see Fig. 28.3D), the procedure is concluded, and baseline US studies are performed within the following few days.

Results (See Chapter 76E)

In a review of 1750 patients at nine institutions in the United States and abroad (Barton et al, 1995), the technical success rate of TIPS was 97%. Failures were related to portal vein thrombosis, extremely hard livers, and massive ascites. The procedure controlled acute bleeding in 91% of patients. Rebleeding increased with time, with a 6% incidence at 3 months, 17% at 6 months, and 21% at 1 year. Higher Model for End-Stage Liver Disease (MELD), Acute Physiology and Chronic Health Evaluation (APACHE II), and Child-Pugh scores are associated with decreased survival. The Society of Interventional Radiology states technical success for TIPS should be achieved in 95% of patients, and clinical success should be achieved in more than 90% (Haskal et al, 2003).

Complications include TIPS thrombosis or occlusions, transcapsular puncture, stent migration, exacerbation of hepatic encephalopathy, right heart failure, procedure-related hemorrhage, hemobilia, contrast-induced acute tubular necrosis, hypersensitivity reactions to contrast material, fever, and pulmonary edema. Fatal outcomes were reported in 1.7% of patients, caused by intraperitoneal, retroperitoneal, and mediastinal hemorrhage; laceration of hepatic arteries, portal vein branches, and the liver capsule; and right heart failure (Barton et al, 1995). Mortality rates for TIPS are dependent on the indication and the patient's health status based on the

aforementioned scoring systems. The 1-year survival for TIPS performed for bleeding varices ranges from 48% to 90%, with lower survival rates when performed for refractory ascites (Boyer & Haskal, 2010).

Stenoses and occlusions occurred in 35% to 85% of bare stents (Barton et al, 1995). This wide range reflects differences in follow-up protocol, with some centers using US and some using venography. In addition, routine surveillance was done at some centers, whereas at others, patients were not studied unless they became symptomatic. With repeat intervention, assisted patency of TIPS can be maintained in 95% of patients. The use of specially designed covered stents has dramatically improved the primary patency rates of TIPS (Rossi et al, 2004; Saxon, 2004). Bureau and colleagues (2007) composed a randomized controlled study of 80 patients to compare covered stents with bare stents and showed a primary patency rate of 76% and 36% at 2 years, respectively. Rates of being free of encephalopathy were 67% in the covered-stent group compared with 51% in the bare-stent group; thus, performing TIPS with covered stents is the current recommendation (Boyer & Haskal, 2010).

PORTAL VENOUS EMBOLIZATION

Branches of the portal vein may be embolized to induce ipsilateral atrophy and contralateral liver hypertrophy in the preoperative management of select liver and biliary tumors. The resulting hypertrophy of the future liver remnant reduces the risk of postresection liver failure in selected patients. The role and technique of preoperative portal vein embolization are discussed in detail in Chapters 93A and 93B.

BILE DUCTS AND GALLBLADDER

Percutaneous Transhepatic Cholangiography

Percutaneous transhepatic cholangiography (PTC) is performed much less commonly for diagnostic purposes than in the past (see Chapter 18). Noninvasive imaging of the biliary tree such as with US (Chapter 13), CT (Chapter 16), and MR cholangiopancreatography (Barish & Soto, 1997; see Chapter 17) has greatly reduced the need for invasive PTC to diagnose biliary tract disorders. Indications for PTC have included defining the level of obstruction in patients with dilated bile ducts, to evaluate for suspected bile duct stones, to determine the etiology of cholangitis, to evaluate suspected bile duct inflammatory disorders, and to demonstrate the site of a bile duct leak (Burke et al, 2003). The complications of the procedure are uncommon and include sepsis, cholangitis, bile leak, hemorrhage, or pneumothorax (Burke et al, 2003).

Percutaneous Cholecystostomy

Percutaneous cholecystostomy is indicated for patients with acute calculous cholecystitis who are too ill to undergo cholecystectomy or for patients with acalculous cholecystitis (see Chapters 31 and 32; Welschbillig-Meunier et al, 2005; Akhan et al, 2002; vanSonnenberg et al, 1992). In the case of acute calculous cholecystitis, management depends on patient-related factors. In a patient with a long life expectancy, percutaneous cholecystostomy is a temporizing method to allow the patient to recover from the critical illness. When the patient's condition stabilizes, cholecystectomy can be performed on a nonemergent basis. Conversely, for a patient with limited life expectancy and/or multiple comorbidities, if cystic and common bile ducts are patent, stones may be removed from the gallbladder and/or the common bile duct percutaneously or endoscopically.

Before catheter removal, after the tract has matured, it must be understood that a diseased gallbladder will be left behind. The recurrence rate of acute calculous cholecystitis after percutaneous cholecystostomy is approximately 25% (Van Steenbergen et al, 1990). Some patients with extreme debility and obstructed cystic or bile ducts may require long-term percutaneous cholecystostomy. In such cases, the catheter should undergo periodic exchange to avoid clogging and fragmentation.

Acute acalculous cholecystitis usually is considered in elderly patients with an unexplained sepsis syndrome; such patients often are being managed in intensive care units when imaging, usually US, reveals a distended, tender gallbladder. The facility with which the procedure can be performed, even at the bedside, along with the low complication rate allows percutaneous cholecystostomy to serve a diagnostic and therapeutic function. Even patients with gas within the gallbladder wall can be treated with percutaneous cholecystostomy. A 56% to 80% clinical response to percutaneous cholecystostomy has been reported (Boland et al, 1994). A more recent study (Chuang et al, 2007) reported percutaneous cholecystostomy followed by cholecystectomy as a treatment for emphysematous cholecystitis in four patients, none of whom suffered a complication.

Initially, thick, viscous, dark bile is aspirated from the distended gallbladder in these patients. As inflammation subsides and cystic duct patency is restored, normal-appearing bile begins to drain from the catheter. At that point, a contrast study of the catheter can be performed to document patency of the cystic and the common bile ducts, and the percutaneous cholecystostomy catheter may be clamped. It is important not to remove the catheter until a mature tract to the skin has formed to avoid intraperitoneal leakage of bile. Depending on the nutritional status of the patient and whether a transhepatic or transperitoneal approach was used to enter the gallbladder, catheter removal typically occurs no sooner than week 2 or 3 after the procedure (Hatjidakis et al, 1988; vanSonnenberg et al, 1992).

Percutaneous cholecystostomy also may be performed as a means of relieving distal common bile duct obstruction in patients who are too ill to tolerate another, more definitive procedure; in patients who have minimal or no intrahepatic biliary ductal dilation; or in those who have failed or cannot undergo endoscopic retrograde biliary endoscopy, provided that the cystic duct is patent. Percutaneous cholecystostomy is quicker, easier, and safer than percutaneous transhepatic biliary drainage under these circumstances, and it can be performed at the bedside with US guidance. Patients without significant dilation of intrahepatic ducts can have a percutaneous cholecystostomy catheter placed that can be injected with contrast medium at a later time to opacify the intrahepatic ductal system, facilitating conventional transhepatic access to the biliary tree for a variety of interventions (vanSonnenberg et al, 1990a, 1992).

Interventional Radiologic Management of Bile Duct Stones

Retained common bile duct stones after surgery may be treated successfully via a T-tube tract in most patients or via a transhepatic approach (Fig. 28.4; see Chapters 35, 36, and 39). Stones can be extracted or crushed with baskets, or they can be swept



FIGURE 28.4. Common bile duct calculi. **A,** Note multiple angular filling defects in the common duct, representing stones. **B,** Balloon inflated during dilation of the sphincter at the ampulla of Vater. **C,** Final study obtained after clearance of stones from the common bile duct.

into the bowel with balloon catheters. Balloon dilation of the sphincter (see Fig. 28.4B) is performed to allow for passage of small fragments, typically with a 10-mm balloon. An older, classic study on stone extraction surveyed 39 institutions and reported 5% morbidity and no deaths in 612 extraction procedures (Burhenne, 1976). With the development of more sophisticated devices for minimally invasive procedures—including steerable catheters, cholangioscopes, and contact lithotripsy probes—the success rate for treatment of retained common bile duct stones is even greater. These techniques and devices also can be applied to the transhepatic removal of intrahepatic stones (see Chapter 39 and 44).

The principal drawback to T-tube stone extraction is that a 4- to 6-week period is required for tract maturation. In select cases, attempts can sometimes be made earlier with tract protection by sheaths. Endoscopic sphincterotomy and stone extraction (see Chapter 36) may be performed sooner, typically after 7 to 10 days, with 90% to 95% success rate (Becker et al, 1993; O'Doherty et al, 1986). Complication rates are 4% to 19% with a 0% to 2% mortality rate. Christoforidis and colleagues (2004) stated that the endoscopic technique is a safe and efficient treatment for residual stones after common bile duct exploration with a T-tube insertion, offering immediate cure compared with percutaneous techniques.

The location of bile duct stones and previous surgeries are important factors in deciding the method of treatment. Intrahepatic bile duct stones are more readily accessible by interventional radiologists than gastroenterologists. Furthermore, previous operations such as hepaticojejunostomy make an endoscopic approach impossible, thus percutaneous routes by interventional radiologists are indicated for these patients. A series of six patients with extensive and complicated recurrent pyogenic cholangitis (see Chapter 44) who all had previous biliary surgery underwent numerous percutaneous techniques—basketing, flushing, crushing, balloon occlusion, and chemical dissolution—to remove innumerable retained intrahepatic and extrahepatic stones (vanSonnenberg 1986).

Percutaneous Transhepatic Biliary Drainage

Percutaneous transhepatic biliary drainage (PTBD) is indicated for relief of biliary obstruction, especially of the proximal biliary tree, and is associated with pruritus and cholangitis (see Chapters 20, 26, 27, 42, and 50D). In general, distal biliary disease is addressed by biliary endoscopy. PTBD is indicated in some patients as the initial step in the planned treatment of benign and malignant bile duct strictures, biliary stones, or locoregional treatment of primary and metastatic liver neoplasms. PTBD is also indicated for severe cholestasis but should not be performed solely for the relief of jaundice or for the cosmetic treatment of dilated bile ducts; this is due to the invasiveness of the procedure and its associated potential complications, including bleeding, bile peritonitis, and sepsis. Preoperative biliary decompression in jaundiced but otherwise asymptomatic patients is controversial (see Chapters 50A, 50B, 50C, 50D, and 62A). PTBD also may be indicated for lowering serum bilirubin levels to permit the use of chemotherapeutic agents with biliary excretion routes. Lastly, in select complicated situations, the surgeon may request catheterization of the bile ducts to help identify the ducts to avoid injury at surgery.

In general, surgery, biliary endoscopy, and PTBD all should be weighed as options for each individual patient. A multidisciplinary consensus involving hepatobiliary surgeons, gastroenterologists, and diagnostic and interventional radiologists regarding the need for, and proper technique of, biliary drainage for an individual patient or clinical problem is the optimal approach.

Preprocedure Evaluation

Preprocedure evaluation should include a complete blood cell count (including platelets), prothrombin time, partial thromboplastin time, international normalized ratio, and liver function tests. Diagnostic imaging of the liver and biliary tree is a prerequisite. US is a safe, cost-effective technique to demonstrate biliary obstruction and the level of obstruction. CT and MR cholangiopancreatography (MRCP; see Chapters 16 and 17) are extremely useful to show hepatobiliary anatomy and pathology in great detail. CT is the procedure of choice for procedural planning. Findings such as liver atrophy are readily identified on any cross-sectional imaging modality, but other anatomic considerations—such as colonic interposition and identification of calcifications or surgical clips that may serve as useful fluoroscopic landmarks—are readily evident on CT. Translation of this information into three-dimensional images greatly facilitates the drainage procedure, and three-dimensional postprocessing CT can be performed if desired.

Patients undergoing biliary drainage have a high incidence of bacterobilia, particularly when there has been previous operation or biliary instrumentation (Brody et al, 1998). Prophylactic antibiotics are indicated in all cases of PTBD. Broad-spectrum agents that cover enterococci, streptococci, and aerobic and anaerobic gram-negative bacilli typically are administered before the interventional radiology procedure commences (Lipsett, 1996; see Chapter 11).

Technique

The choice of a right- or left-sided approach for PTBD is based on many factors. Drainage of an atrophic portion of the liver does nothing to conserve or improve hepatic function or to lower serum bilirubin (see Chapter 5). The only reason to drain an atrophic segment would be for unrelenting biliary sepsis after satisfactory drainage of the functional liver parenchyma. In general, high bile duct obstruction is more likely to result in isolation of the right anterior and right posterior sectoral ducts and to extend to involve second-order branches. Such isolation of segmental ducts occurs later on the left, because the left hepatic duct is typically longer compared with the main right duct, which is shorter and has a more palmate branching pattern. In addition, the right posterior sectoral duct joins the left hepatic duct, rather than its anterior right counterpart, in at least 20% of cases (see Chapter 1B).

In high obstruction, in the absence of left portal vein compromise, a left-sided approach may be preferred. Other advantages of left-sided access are a more favorable angle for biliary intervention; better use of US to guide safe puncture of the duct, which is easier to visualize on the left; avoidance of pleura; less discomfort associated with an intercostal route; and less chance of an ascites leak around the catheter with an anterior left subxiphoid approach rather than a right lateral intercostal approach. The advantages of a right-sided approach are decreased exposure of the operator to radiation and in general more operator familiarity with right-sided access. In certain cases, access from both sides may be needed (vanSonnenberg, 1986). In patients who are being considered for operation,

left-sided drainage catheters are often close to or in the line of the intended incision, although this should not be an overriding concern if left-sided drainage is required.

An attempt should be made to puncture a peripheral bile duct; this limits the risk of injuring a major vessel near the hilum and ensures an adequate number of sideholes in the catheter above the obstruction for effective drainage. It is important to avoid puncturing the left ductal system from the right side, and vice versa, because this makes further catheter manipulations difficult. It is usually possible to place an 8-Fr catheter across the obstructed area down into the duodenum at the time of initial drainage, allowing for drainage of bile into the bowel. If this cannot be accomplished initially or in the presence of cholangitis, when undue manipulation within the biliary tree is inadvisable, we leave an external drainage catheter and cross the obstruction a few days later, after the patient has become stable clinically. In most patients, when the inflammatory component of the obstruction has resolved, conversion to an internal/external catheter or placement of a biliary stent is possible.

Patients with high bile duct obstruction frequently exhibit complete or near-complete isolation of the right and left hepatic ducts. In some cases, isolation extends to the sectoral or segmental level, which is more frequent on the right side, as discussed earlier. A single drainage catheter is placed at the initial encounter with the patient. It is necessary to have approximately 30% of the hepatic parenchyma drained and functional to alleviate jaundice; this is frequently accomplished with drainage of either the right or the left ductal system. Pruritus is related to bile salt deposition within the skin and usually responds immediately and dramatically to drainage of any part of the liver. It may take 2 weeks for the bilirubin level to decrease and plateau, particularly in long-standing obstruction, and it is advisable to withhold further intervention until the serum bilirubin has stabilized. If the serum bilirubin does not decline to an acceptable level after this time, or if biliary sepsis is the predominant problem, it may be necessary to place more than one catheter or consider a coexistent medical cause for jaundice as well.

At the time of initial drainage of patients with malignant biliary obstruction and limited life expectancy, placement of an internal biliary endoprosthesis should be considered. Plastic and metal endoprotheses are available. Metal stents have a longer median patency (3.6 to 9.1 months) relative to plastic stents (1.8 to 5.5 months), but there is no difference in median survival (Levy et al, 2004). Tsuyuguchi and colleagues (2008) suggest that metal stents are recommended in patients who are expected to survive longer than 6 months, whereas plastic stents should be used in patients with a suspected survival of less than 6 months. The difference in cost also serves as a factor in this management recommendation, because metal stents are more expensive than plastic stents if reintervention is not required (Davids et al, 1992). Metal stents also may be covered with polyurethane, and these were found to prevent tumor ingrowth and had higher patency, but complications of acute cholecystitis (Isayama et al, 2004) and stent migration also occurred (Yoon et al, 2006). Thus further studies are needed to establish the indications for covered versus bare metal stents.

Metal stents most commonly used for malignant disease within the biliary tree are the Wallstent and Strecker stents. These are nonremovable, self-expanding, flexible, braided, or woven stents that are placed through 7- to 10-Fr sheaths, and they can expand to diameters of 6 to 10 mm. Because these metallic stents are permanent, they should be used only when the patient has no possibility of undergoing curative resection. Hepatobiliary surgical resections are much more difficult after a metal stent has been placed. In patients with mid to distal common bile duct obstruction without signs of infection, and when placement of additional drainage catheters is not a consideration, this approach allows for biliary stenting at the time of the initial biliary drainage procedure. When satisfactory lumen and flow have been restored, the percutaneous access can be removed immediately but preferably the following day.

Patients with high bile duct obstruction or isolated obstructed segments of the liver may require more than one drainage procedure. In such patients and in patients with signs of infection, it is best to wait to consider metal stent placement until the patient shows a clinical response, such as decrease in serum bilirubin and resolution of sepsis, and then devise a clear strategy for treatment. Although drainage catheters and endoprostheses can be placed through the interstices or alongside an existing stent, it is much easier for both operator and patient if the stents are deployed simultaneously in a carefully preplanned manner.

In the case of isolation of the right and left hepatic ducts, management can be accomplished in one of two ways. From one transhepatic approach (Fig. 28.5), a stent can be placed across the confluence of the bile ducts to the contralateral side, and the second stent can be deployed from the ipsilateral side into the common hepatic and/or common bile duct. Alternatively, especially when the patient has failed to respond to a single drainage, the contralateral side can be approached percutaneously (Fig. 28.6), allowing for simultaneous placement of side-by-side stents across the obstruction at the ductal confluence into the distal common bile duct. We agree with Morgan and Adam (1996) that the latter approach is preferable in the event that it is necessary to intervene again for subsequent stent occlusion. For hilar lesions, we are careful to "overstent" (Lammer et al, 1996) in an effort to avoid occlusion related to tumor overgrowth. One way is to predilate and/or postdilate when placing Wallstents. Some patients find balloon dilation to be quite painful, and although general anesthesia is not used routinely, it may be advantageous in select patients. Satisfactory stent expansion typically is achieved within 24 hours (see Figs. 28.5B and 28.6B) without the aid of balloons.

There is a role for balloon dilation if, after deployment, contrast material does not flow promptly across the stent. After stent deployment, the introducer system is removed, and a 4- to 5-Fr end-hole catheter, such as a Kumpe (Cook, Bloomington, IN), is left as a protective catheter. If dual access has been used, two protective catheters are left. These catheters are used for subsequent follow-up cholangiography (see Figs. 28.5C and 28.6C) and to ensure that there has not been asymmetric stent shortening or some other occurrence that would require placement of additional stents or other intervention. In 95% of cases, no other intervention is necessary.

Bile Duct Biopsy

Faced with inoperable, presumed malignant bile duct obstruction, a tissue diagnosis is necessary before initiating brachytherapy or sometimes simply in an effort to give meaningful prognostic information to the patient and family. A diagnosis can be arrived at in several ways. Bile cytology obtained at the time of initial drainage, although insensitive, has been found to

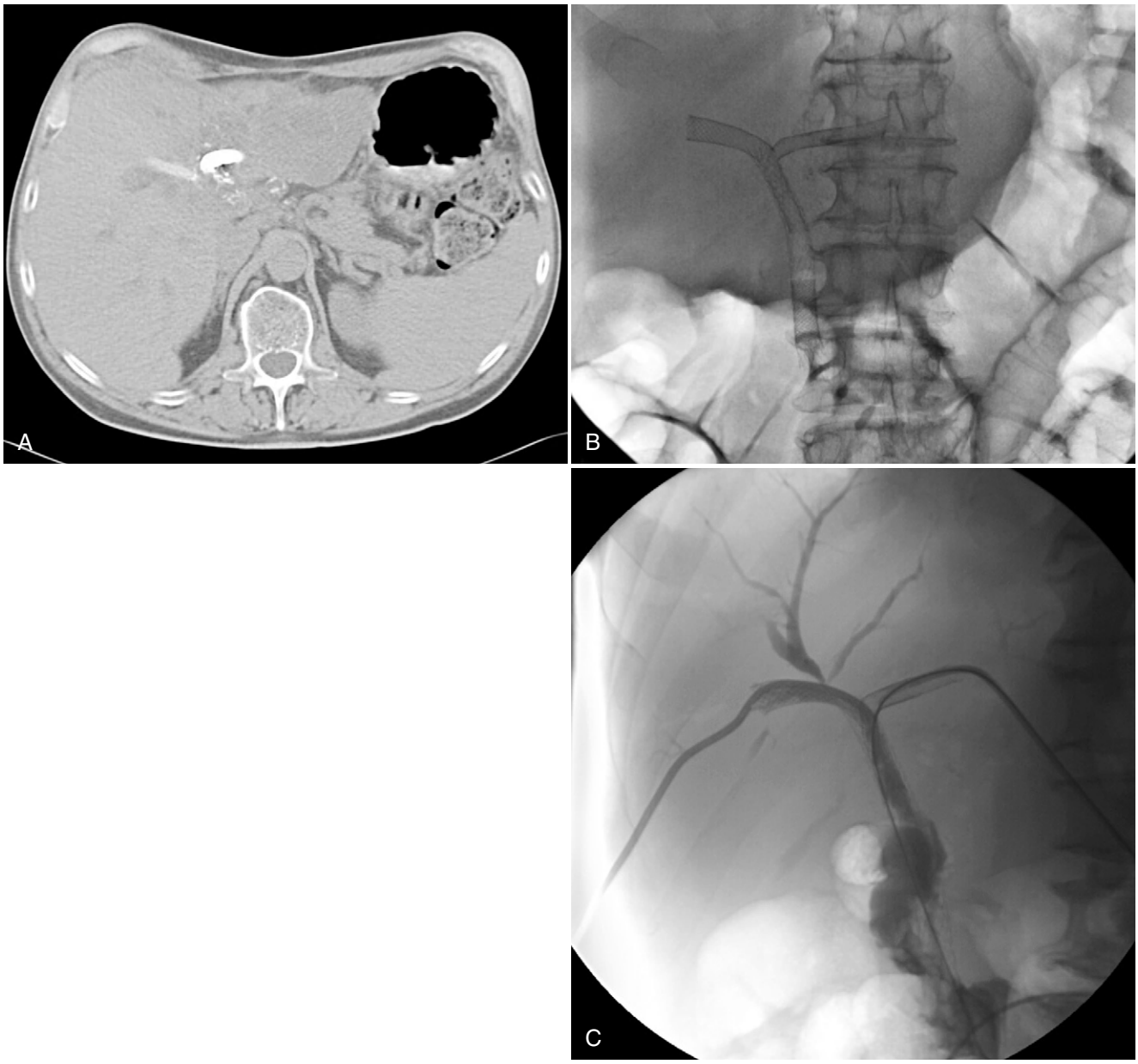


FIGURE 28.5. Wallstents. **A,** Patient with gallbladder cancer and hilar obstruction. Wallstents are deployed simultaneously from the left hepatic duct into the right hepatic duct and from the left hepatic duct into the common bile duct. Right-sided access was performed when cholangitis did not respond to drainage of the left side alone. **B,** Wallstents 24 hours after placement, expanded without balloon dilation. **C,** Right catheter cholangiogram shows the stents to be well positioned and widely patent.

be quite specific (Savader et al, 1988), and there is virtually no disadvantage to sending a specimen. Cytology can be obtained also with intraluminal brushes; the reported sensitivity ranges from 44% to 67% (Ryan, 1991; Cropper & Gold, 1983; Mendez et al, 1980). Percutaneous transluminal forceps biopsy has shown better diagnostic capabilities with a sensitivity of 78.4% and specificity of 100% in cases of malignant biliary obstruction (Jung et al, 2002; see Chapter 20). If these methods fail, a cholangiographically guided percutaneous needle biopsy can be performed, which frequently yields a diagnosis. If a mass is visualized on CT or US, these modalities can be used to guide the biopsy. These options will usually yield a biopsy diagnosis, and the choice is tailored to the patient's situation and the radiologist's preference.

Brachytherapy

Brachytherapy involves the local delivery of radiation to a tumor and can be used percutaneously to treat unresectable or recurrent cholangiocarcinoma (see Chapters 50A, 50B, 50C, and 50D). We also have used this method to treat intraductal metastatic colorectal carcinoma and bile duct carcinoma. Conventional biliary drainage is performed first, placing one or more internal/external catheters. After the

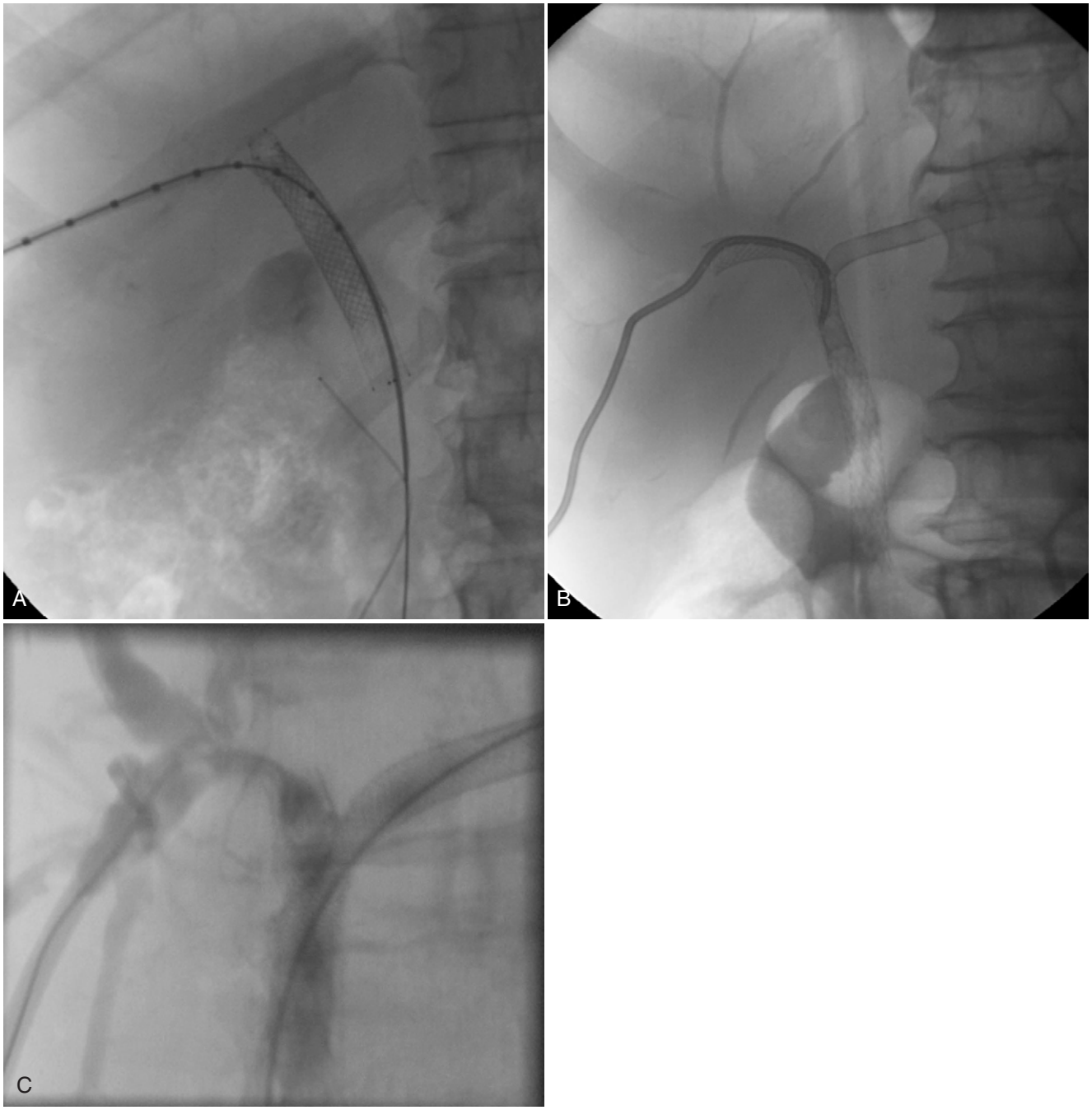


FIGURE 28.6. Wallstents. **A,** Patient with hilar obstruction secondary to cholangiocarcinoma. Bilirubin level was not low enough for chemotherapy after drainage of the right hepatic ducts; the patient subsequently underwent drainage of the left hepatic ducts and side-by-side Wallstent placement. **B,** After 24 hours, the Wallstents are well expanded without balloon dilation. **C,** Cholangiography shows the stents to be well positioned and widely patent.

bilirubin has normalized and any underlying infection has subsided, a Wallstent is introduced to bridge the area of obstruction, and a simulation catheter is positioned through the Wallstent. After dosimetry is performed, the radiation source is loaded within 24 hours and remains in place for a predetermined time, depending on dosimetry calculations. When therapy is complete, the catheter and radiation source are removed at the bedside. This method is not only a means for local tumor therapy but also seems to prolong Wallstent patency by decreasing the rate of tumor ingrowth (Eschelman et al, 1996), at least when combined with external-beam therapy.

Bile Duct Injury

Much of what we know about the role of interventional radiology in the management of traumatic injury to the bile ducts has been learned from complications of iatrogenic trauma, particularly after laparoscopic cholecystectomy (Boland et al, 1996; Lillemoe et al, 1997; Lund & Winick, 1996; vanSonnenberg et al, 1990c).

Similar principles would apply to the treatment of noniatrogenic injuries, although these are rarely seen. Patients with strictures who do not have a previous history of biliary surgery or significant right upper quadrant trauma should be investigated aggressively in an effort to establish that the stricture is not malignant prior to treatment (see Chapters 38, 42A, 42B, and 102).

In general, small postoperative bile leaks typically heal spontaneously, assuming there is no outflow obstruction, and usually all that is required is percutaneous drainage of any collection that may have formed (see Chapters 42A and 42B). Cystic duct leaks after cholecystectomy may respond best to endoscopic placement of a plastic biliary endoprosthesis. Major bile duct injuries consist of duct transection, laceration, and/or partial or complete ligation (vanSonnenberg et al, 1990c). These injuries are categorized according to the anatomic site of injury. Normal anatomic variants also pose challenges. Christensen et al (1992) discussed how aberrant right hepatic ducts are the most common biliary tract anomaly susceptible to injury at cholecystectomy. Complications include biliary leakage and fistulas, bilomas, pain, fever, and sepsis. An accidentally ligated aberrant right hepatic duct may not be appreciated at ERCP. Prudent evaluation with US, CT, MRCP, and PTC of sequestered posterior right hepatic duct dilation is essential for proper diagnosis. A preoperative biliary catheter may aid the surgeon in subsequent ductal reconstruction.

The length of duct available for surgical reconstruction and the integrity of the hepatic duct confluence greatly influence treatment options. Most surgeons and radiologists agree that the best chance for a trouble-free long-term outcome can be expected after primary surgical repair (Boland et al, 1996; Lillemoe et al, 1997). In the study by Lillemoe and colleagues (1997), patients treated surgically showed improved outcomes compared with patients treated with interventional techniques, including drainage and balloon dilation. All of the patients treated with interventional techniques had previous surgical attempts at reconstruction. In the interventional group, patients who presented late and with low (Bismuth type 1; see Chapters 42A and 42B) injuries fared significantly better. These patients require a team approach. Patients who are poor surgical candidates, those who have portal hypertension, and those who have had multiple previous attempts at surgical repair might be treated best with percutaneous drainage and balloon dilation (see Chapters 27, 42A, and 42B).

Mid to distal common bile duct strictures can be dilated with a balloon catheter. Balloons should be sized slightly larger than the duct being dilated, usually 8 to 12 mm, and inflated to eliminate any "waist." When dilating strictures at the hilum (Fig. 28.7), balloon dilation may require two or more catheters, which may be used sequentially to dilate from side to side and into the common hepatic duct, across a biliary-enteric anastomosis (see Fig. 28.7B), or simultaneously. When the simultaneous or "kissing balloon" technique is used, with one balloon placed from the right and one from the left, size should be adjusted appropriately. There is no evidence that prolonged inflation or multiple inflations enhance patency, and some authors believe this may promote ductal ischemia. Occasionally, bile duct rupture occurs (see Fig. 28.7C), and we have seen a related arterial vascular injury (see Fig. 28.7D) that required embolization; however, we have not found it necessary to treat bile duct rupture with anything other than continued drainage (see Fig. 28.7E).

How long a catheter should be left in place after balloon dilation is controversial (Boland et al, 1996). We leave a 10- or 12-Fr drainage catheter in place for 2 to 4-weeks, at which time we reevaluate the patient cholangiographically. If the stricture site is widely patent, we exchange for a drainage catheter above the treated area; if the patient tolerates a clamping trial, this catheter is removed in a few days. If the follow-up cholangiogram shows residual or recurrent narrowing, the site is dilated again with a slightly larger balloon, followed by another 4-week observation period and a cholangiogram. Again, a drainage catheter is left above the dilated site and clamped. If the patient tolerates this "capping trial," the catheter is removed.

Biliary pressure measurements and bile duct perfusion with manometry offer the only real objective information about bile duct dynamics and the status of balloon dilation (vanSonnenberg et al, 1983, 1990b). We utilize manometry and perfusion dynamics if evaluation of the dilatation, patency, and flow dynamics are not straightforward (relatively common). Patients who fail repeated dilations should undergo either continued catheter drainage or surgical treatment. We believe that self-expanding metallic stents should not be used to treat benign strictures, unless the patients are extremely poor surgical candidates or they have limited life expectancy because of comorbid conditions. Surgically treated patients have better outcomes, and when a metallic stent is placed, it makes subsequent surgical repair more difficult (vanSonnenberg et al, 1986). These decisions should always be made with the surgeon and interventional radiologist in concert.

Vascular Injury

Sclafani (1985) showed that angiographic methods could be used to control hemorrhage from injuries to the liver and spleen (see Chapters 19, 50D, 104, and 105). Hagiwara and colleagues (1997) concurred more recently that this method is an effective alternative to surgery. All but the most severe hepatic venous bleeding is self-limiting, and angiographic methods are suitable to treat hemorrhage secondary to blunt or penetrating trauma, including iatrogenic arterial injuries resulting from biliary interventions (Fig. 28.8). When the site of injury is established—by the presence of pseudoaneurysm formation (Fig. 28.8B), extravasation (Fig. 28.9A), abrupt vessel cutoff, or spasm—the injured vessel may be occluded with absorbable gelatin sponge (Gelfoam), metal coils, or both (Fig. 28.8C). If small coaxial catheters are necessary, microcoils or polyvinyl alcohol particles may be used. The dual blood supply to the liver makes it extremely tolerant of arterial occlusion for hemostasis; however, caution must be exercised in jaundiced patients, because significant compromise of arterial inflow can result in hepatic necrosis.

Percutaneous Tumor Ablation

Many percutaneous methods for tumor ablation are currently in use, including heating, freezing, alcohol injection, and combinations of these techniques. Although radiofrequency ablation (RFA) is the most common ablation method in the United States, treatment should be tailored to the individual patient's situation (vanSonnenberg et al, 2005). For example, in a patient with metastatic pheochromocytoma to the liver, a combination of alcohol and RFA was used to synergistically enhance tumor kill (Fig. 28.10; Mamlouk et al, 2009; Shankar et al, 2004). Nonresectional ablation of liver tumors is covered further in Chapters 83, 84A, 84B, 85A, 85B, 85C, and 85D).

References are available at expertconsult.com.

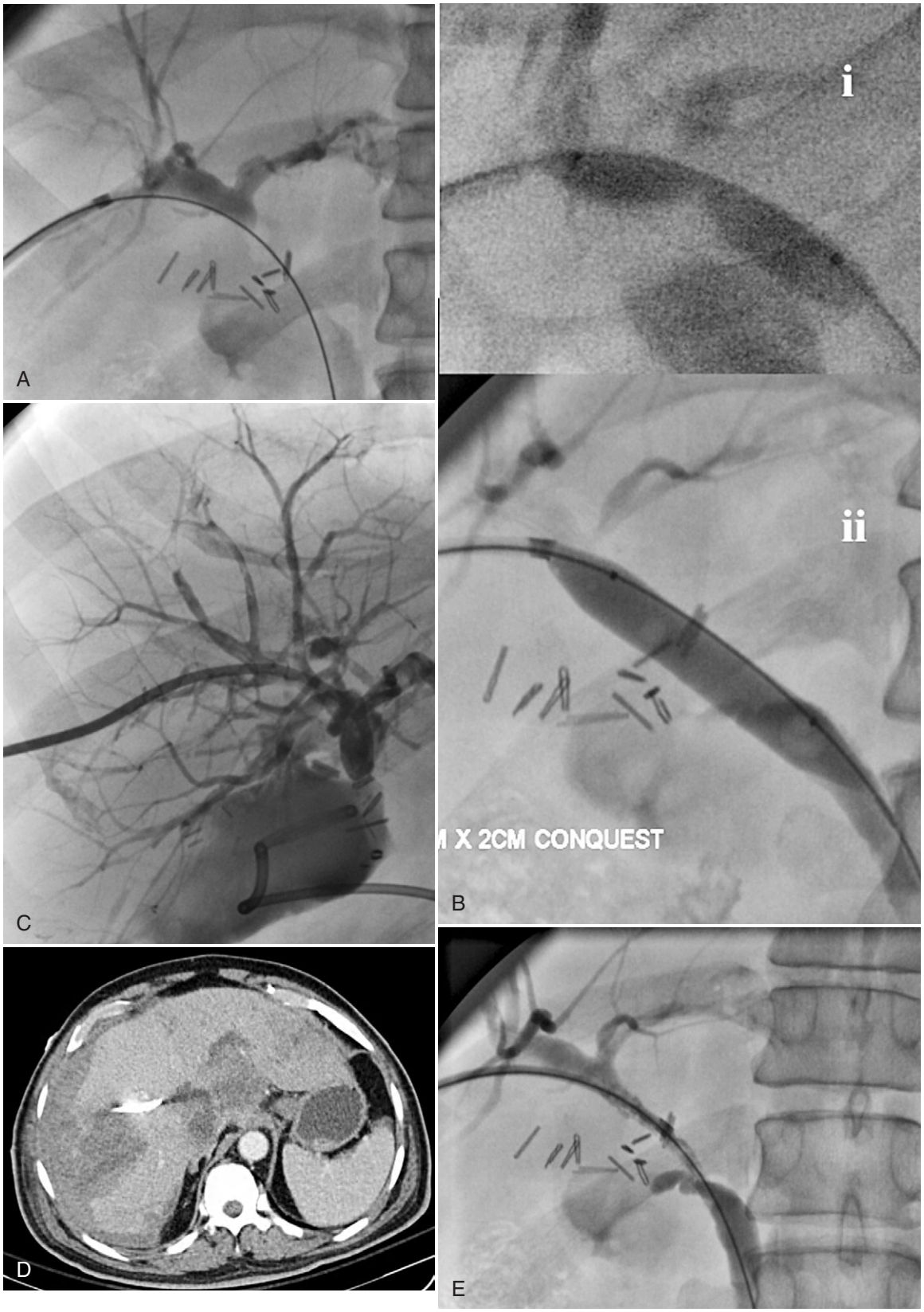


FIGURE 28.7. Bile duct stricture. **A,** Note high-grade narrowing at the hepatobiliary anastomosis, involving the confluence of the right and left hepatic ducts. **B,** Note waist in balloon used to dilate from right hepatic duct to left hepatic duct (*i*); the waist has been eliminated on the second balloon used to dilate across the biliary-enteric anastomosis (*ii*). **C,** Note extravasation of contrast material resulting from bile duct rupture after balloon dilation. **D,** CT scan from the same patient showing a significant intrahepatic hematoma and a subcapsular hematoma. **E,** Follow-up cholangiogram 2 months later shows the hepatic ductal confluence and hepatobiliary anastomosis to be patent.



FIGURE 28.8. Hemobilia. **A,** Cholangiogram shows an intraductal cast secondary to blood clot after biliary drainage of the right hepatic duct. **B,** Pseudoaneurysm of the anterior sectoral division of the right hepatic artery. **C,** After stainless steel coil embolization of the anterior sectoral branch of the right hepatic artery.

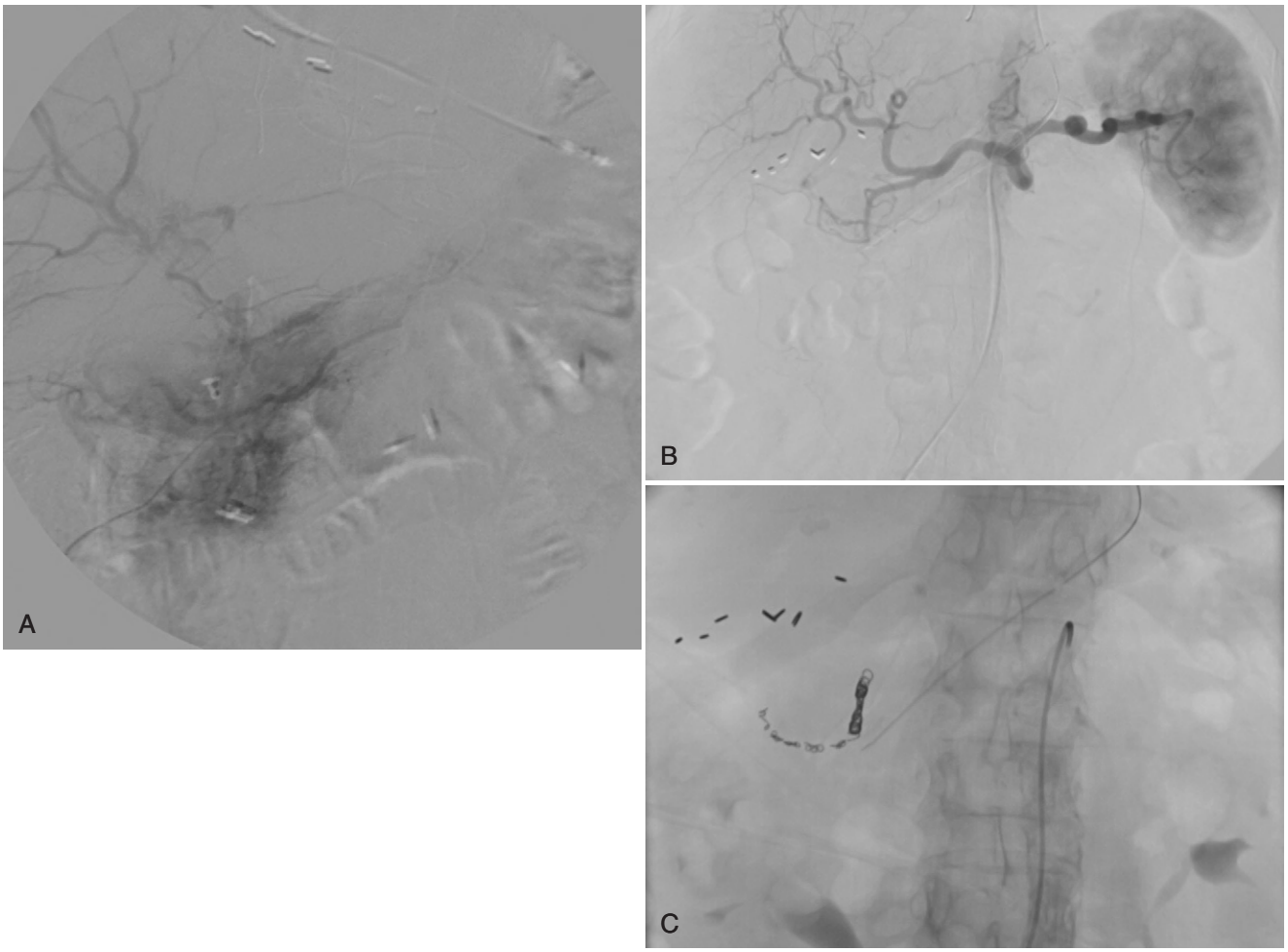


FIGURE 28.9. Vascular trauma. **A,** Patient with a history of bleeding duodenal ulcer initially treated with electrocautery is seen with a rebleed. Injection of contrast material into a catheter in the right hepatic artery opacifies the duodenum. **B,** When the catheter is pulled back and injected again, extravasation of contrast material from the right hepatic artery is seen. **C,** Unsubtracted angiogram after right hepatic artery embolization with stainless steel coils.

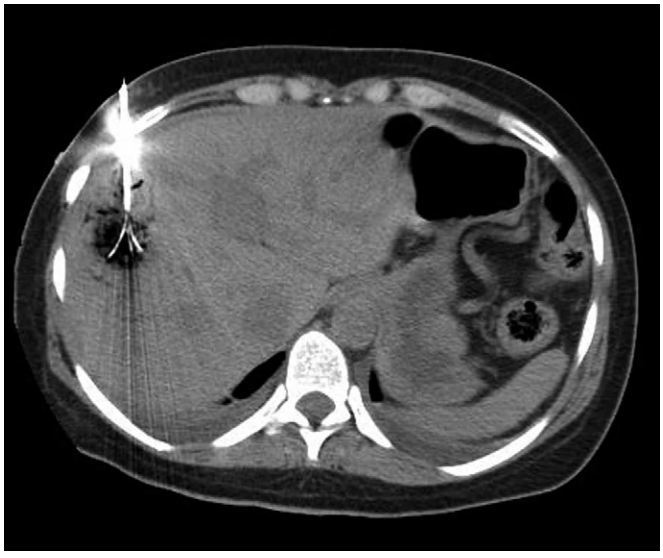


FIGURE 28.10. Radiofrequency ablation (RFA) of a liver tumor in a patient with metastatic pheochromocytoma to the liver. Axial computed tomographic image shows an electrode within the destroyed tumor. Gas represents coagulation necrosis; ethanol was infused immediately before RFA to synergize the necrotic effect. *(From Mamlouk MD, et al, 2009: Radiofrequency ablation and biopsy of metastatic pheochromocytoma: emphasizing safety issues and dangers. J Vasc Interv Radiol 20:670-673.)*

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CHAPTER 29

Bile duct exploration and biliary-enteric anastomosis

Clifford S. Cho and Michael I. D'Angelica

OVERVIEW

Rapid evolution in the management of biliary tract disorders over the past 3 decades has resulted in a number of alternatives to formal operative intervention. Nevertheless, the need for biliary exploration or restoration of biliary-enteric continuity because of obstruction by calculus or tumor remain important indications for surgical intervention. The operative conduct of biliary-enteric anastomosis demands a considerable appreciation for relevant anatomy and alternative technical strategies, which are discussed in this chapter.

ANATOMY

Safe operative planning and technique demand a comprehensive understanding of the extrahepatic biliary anatomy and a thorough appreciation for the common anatomic variants that may be encountered. Hepatobiliary anatomy is discussed at length in Chapter 1B; in this section, we will highlight specific aspects deserving of additional emphasis.

The typically short extrahepatic course of the right hepatic duct makes operative access to the segmental or sectional drainage of the right hemiliver rather difficult. However, the biliary anatomy of the right hemiliver is rather prone to variation, and aberrant drainage from the right anterior or posterior section may assume a long extrahepatic course before joining with the left hepatic ductal system. In comparison, the left biliary system is relatively consistent. Also in contrast to the right, the left hepatic duct invariably has a longer extrahepatic course as it runs along the undersurface of segment IVb (Fig. 29.1). In cases where the base of segment IVb is broad, the left hepatic duct assumes a longer and more transverse course; in cases where the base of segment IVb has a narrower and pyramidal configuration, the course of the left hepatic duct is shorter and more oblique. Drainage from most of segment I enters into the left hepatic duct just before its convergence with the right hepatic duct; drainage from the right portion of segment I typically enters into the right posterior sectoral duct. The left hepatic duct runs along the left portal vein within a peritoneal reflection of the gastrohepatic ligament, and it is best exposed by lowering the hilar plate along the base of segment IVb (Fig. 29.2). These structures are joined by the left hepatic artery as they enter the umbilical fissure, where arterial and venous branches to and biliary ducts from segments II, III, and IV are found. The ligamentum teres along the lower edge of the falciform ligament runs across the umbilical fissure, which is often covered by a bridge of hepatic tissue that crosses from the left lateral section to the base of segment IV. This bridge of tissue must often be divided to permit full exposure of and access to the biliary and vascular structures to and from segments II, III, and IV (Fig. 29.3).

BILE DUCT EXPLORATION

Overview

The most common indication for exploration of the biliary system is the presence of common bile duct stones. Contemporary percutaneous and endoscopic techniques have largely replaced operative interventions for this indication, and nonoperative, laparoscopic, and open operative strategies are addressed in greater detail in Chapters 34, 35, and 36, respectively. In this chapter, we highlight the various operative approaches for open exploration of the bile ducts.

Incision and Exposure

A right subcostal incision generally affords satisfactory exposure of the extrahepatic biliary system. The hepatic flexure of the right hemicolon is mobilized, and the proximal transverse colon is mobilized off the duodenum. Downward retraction of the proximal transverse colon facilitates exposure of the duodenum, whose retroperitoneal attachments are freed with a generous Kocher maneuver. A cholecystectomy is often performed in conjunction with bile duct exploration for patients with calculous disease, and removal of the gallbladder greatly enhances exposure of and access to the porta hepatis. Alternatively, retraction of the mobilized gallbladder can be useful for exposing the junction of the cystic duct and common bile duct. Cephalad retraction of the undersurface of the liver along the base of segment IVb also enhances optimal visualization of the extrahepatic biliary system (Fig. 29.4).

Supraduodenal Exploration (See Chapter 35)

Choledochotomy

Open exploration of the extrahepatic biliary system is best undertaken through a longitudinal distal choledochotomy. Opening the common bile duct distally toward the duodenum facilitates exploration of the distal biliary system and permits easy construction of a choledochoduodenostomy, if necessary. Care must be taken to verify the anatomic relationship between the cystic duct and common bile duct, as low or anterior

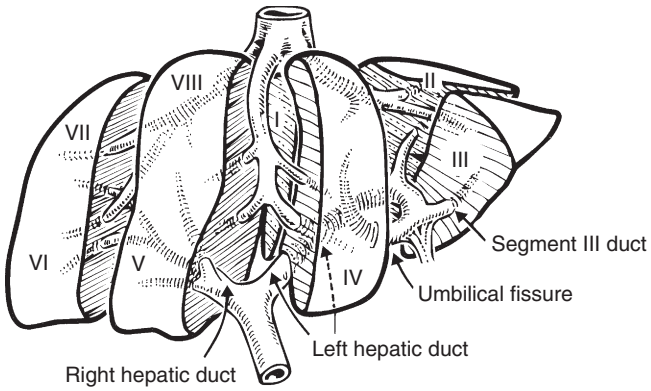


FIGURE 29.1. Diagrammatic expanded view of the liver showing its segmental structure. Elements of the portal triad are distributed to the right and left liver on a segmental basis. The left hepatic duct always pursues an extrahepatic course beneath the base of the quadrate lobe (segment IV) in the groove separating the quadrate from the caudate lobe (segment I; see Fig. 29.2). The ligamentum teres marks the umbilical fissure and runs to join the umbilical portion of the left branch of the portal vein. Each portal triad is composed of hepatic artery, portal vein, and biliary duct. Note the distribution of the left portal triad in the umbilical fissure; major branches recurve to the quadrate lobe medially, and two major branches pursue a lateral course to segments II and III of the left lobe.

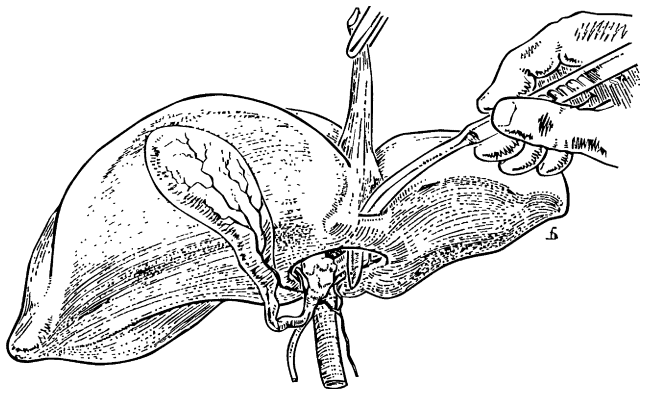


FIGURE 29.3. The bridge of liver tissue frequently present between the base of the quadrate lobe (segment IV) and the left lobe of the liver can be divided. This is conveniently done by passing a curved director beneath it and cutting it with diathermy. Such division can be useful in aiding an approach to the left hepatic duct, particularly if the course of the duct is vertical and the base of the quadrate lobe is short. If the bridge of tissue is present, the maneuver is always necessary to allow dissection of the segment III duct (see Fig. 29.8).

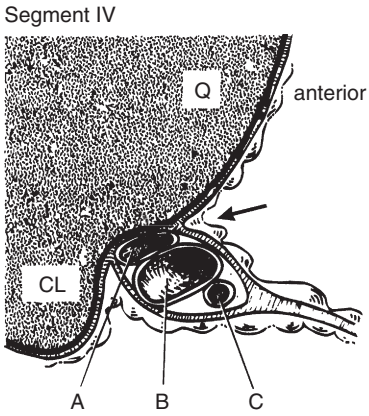


FIGURE 29.2. Sagittal section showing the relationship of the quadrate (*Q*) and caudate lobe (*CL*) to the left portal triad, which is encased within a reflection of the lesser omentum that fuses with the Glisson capsule at the base of the quadrate lobe. The *arrow* indicates the point of incision for the dissection to lower the hilar plate (see also Fig. 29.5). *A,* Left hepatic duct. *B,* Left branch, portal vein. Note the left hepatic artery (*C*) joins the left duct and left branch of the portal vein at the umbilical fissure.

insertion of the cystic duct can result in unintended injury to this structure (Fig. 29.5). Placement of the incision in an anterior location minimizes the risk of injury to the periductal vasculature, which typically runs along the medial and lateral aspects of the common hepatic and common bile ducts. The length of the choledochotomy is dictated by the diameter of the duct and the size of the stones present within its lumen, but length typically ranges between 1 to 2 cm.

A number of options exist for bile duct exploration, and these are discussed in further detail in Chapters 34 and 35;

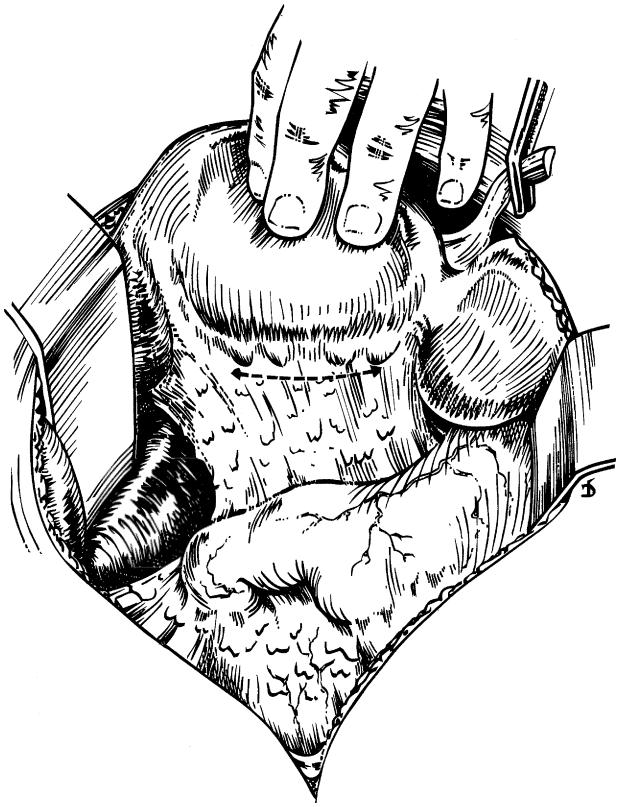


FIGURE 29.4. The initial line of incision for an approach to the left hepatic duct by lowering of the hilar plate. The liver is elevated, and the quadrate lobe is retracted upward. The incision is made at precisely the point at which the Glisson capsule reflects to the lesser omentum (see Fig. 29.2).

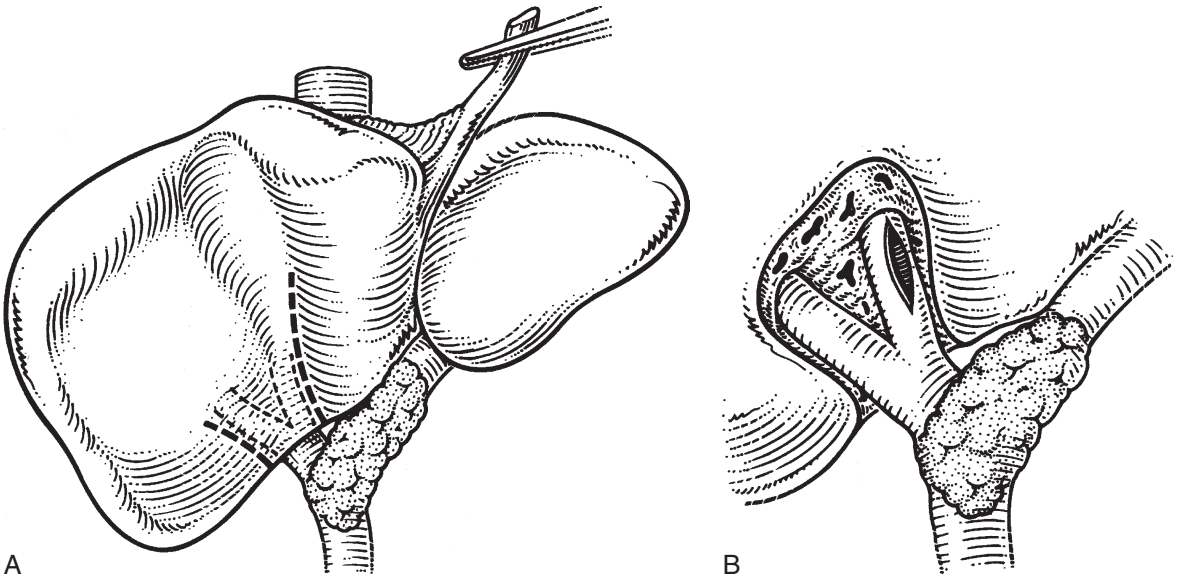


FIGURE 29.5. **A,** Exposure of the right hepatic pedicle. The liver is opened as indicated, and liver tissue is cleared over a small distance. **B,** The relevant duct, usually the anterior sectoral duct, is opened, and anastomosis is carried out.

regardless of the method used, care must be taken to be as atraumatic as possible (Orloff, 1978). Iatrogenic injury to the duct mucosa can result in delayed stricture formation, and inaccurate delivery of rigid instrumentation can create false passages into the duodenum or pancreas. Fiberoptic choledochoscopy permits excellent visualization when saline is infused at a low rate through the endoscope. This is particularly effective for exploring the smaller intrahepatic radicles of the proximal biliary system.

T-Tubes (See Chapter 35)

Following bile duct exploration, the choledochotomy is typically closed over a T-tube. One advantage of T-tube insertion is the ability to ensure adequate decompression of the biliary tree, particularly after manipulation of the papilla. Postprocedural edema or spasm resulting in biliary outflow obstruction can result in bile leakage from the choledochotomy closure site. Another advantage is the ability to directly access the biliary system postoperatively through the T-tube for detection and treatment of retained stones. A 14-Fr or larger T-tube should be used if the size of the common bile duct permits, as this will allow for subsequent cholangiography or choledochoscopy through the T-tube.

Postoperatively, the T-tube is placed to dependent drainage. The volume of drainage should decline as postoperative edema resolves and normal biliary drainage into the duodenum is restored. If high outputs persist through the T-tube, or if bile drainage around the T-tube into the closed suction drain is seen, T-tube cholangiography should be undertaken to evaluate for tube malfunction, dislodgment, or distal obstruction from a retained stone. If no problems are encountered, tube removal can be performed at the bedside as early as 1 week postoperatively, if T-tube cholangiography is normal. If retained gallstones are found, the T-tube can be clamped, with instructions to open the T-tube in the event of fevers, jaundice, or pain, and repeat cholangiography is obtained in 1 month; if choledocholithiasis persists, stone extraction may be undertaken either percutaneously through the T-tube or via endoscopic papillotomy.

Transduodenal Exploration

In unusual cases in which gallstones are impacted at or near the ampulla of Vater, or in patients whose surgically altered anatomy makes endoscopic techniques difficult (e.g., after Roux-en-Y gastrojejunostomy), transduodenal exploration may be warranted. Transduodenal access to the distal biliary system requires operative sphincterotomy, which in turn requires operative sphincteroplasty to avoid postoperative papillary stenosis. Chapter 62C discusses transduodenal resections for neoplastic disease, the details of which are not dissimilar to the approach used for calculous disease (see Chapter 35).

Outcomes After Bile Duct Exploration

Advances in endoscopic and percutaneous approaches have vastly limited the indications for operative bile duct exploration. Nevertheless, it is important to recognize that historical analyses have largely substantiated the safety and efficacy of operative bile duct exploration. In a representative single-center North American series of 100 consecutive, open, supraduodenal common bile duct explorations, no operative mortalities were encountered, and the overall morbidity rate was 15.7%, including a 5.3% rate of retained common duct stones (Pappas et al, 1990). Similar observations have been reported in retrospective analyses of transduodenal sphincteroplasties and common bile duct explorations (Kibria & Hall, 2002; Morgan et al, 2008; Sellner et al, 1988), highlighting low rates of morbidity and recurrent choledocholithiasis.

BILIARY-ENTERIC ANASTOMOSIS

Overview

The operative conduct of the biliary-enteric anastomosis centers around three technical steps: 1) identification of healthy bile duct mucosa proximal to the site of obstruction; 2) preparation of a segment of alimentary tract, most often a Roux-en-Y jejunal limb; and 3) construction of a direct mucosa-to-mucosa anastomosis between these two.

For this reason, preoperative planning must incorporate comprehensive radiographic evaluation of the relevant biliary anatomy; these strategies and techniques are addressed in Chapters 13, 16, 17, and 18. In some cases, preoperative insertion of percutaneous transhepatic biliary stents may facilitate intraoperative identification of the right or left hepatic ducts. However, it is important to recognize that stent insertion is associated with a risk of procedural complications and inevitably results in bacterial contamination of the biliary tree that can lead to cholangitis and periductal inflammatory changes that may delay or hinder operative intervention. Because of these risks, and because the hepatic ducts can be identified without stents at the time of operative exploration, we have not routinely used preoperative biliary stents. When undertaken, caution must be exercised to avoid attempted percutaneous drainage if it is unlikely that the stent can be placed across the obstructing lesion. Insertion of a percutaneous drain into an excluded biliary segment will result in bacterial colonization of static bile; if that hepatic segment cannot be decompressed by a subsequent operative intervention, it will not be possible to remove that external drain without risking refractory cholangitis.

Options for biliary-enteric anastomosis include hepaticojejunostomy, choledochojejunostomy, choledochoduodenostomy, cholecystojejunostomy, and cholecystoduodenostomy. Selection of the proper anastomosis is dictated by the indication for biliary decompression and the anatomic location of the biliary obstruction. The indications for and operative conduct of these surgical options are detailed below.

Incision and Exposure

A right subcostal incision with or without an upper midline extension or left subcostal extension provides adequate exposure for construction of the biliary-enteric anastomosis. Use of retractors capable of upward elevation and cephalad retraction of the costal edges are quite valuable for optimizing visual exposure of the relevant hilar anatomy. Division of the ligamentum teres and mobilization of the falciform ligament off the anterior surface of the liver also facilitate operative exposure; anterocephalad retraction of the ligamentum teres and division of the bridge of tissue overlying the umbilical fissure are critical for optimal visualization of the vascular inflow and biliary drainage of segments II, III, and IV (see Fig. 29.3).

If direct surgical decompression of the gallbladder is not to be undertaken, cholecystectomy will also facilitate access to the extrahepatic biliary system by exposing the cystic duct, which can be followed to its origin off the common hepatic duct or right hepatic duct. Cholecystectomy also exposes the cystic plate, which runs in continuity with the hilar plate. Lowering of the hilar plate permits exposure of the left hepatic duct as it courses along the base of segment IVb. In cases of unilateral hepatic atrophy as a result of long-standing biliary obstruction or preoperative portal vein embolization, it is critical to understand that the normal anatomic relationships of the portal structures are altered. In the more common circumstance of right-sided atrophy, the portal and hilar structures are rotated posteriorly and to the right; as a result, the portal vein, which is typically most posterior, is often encountered first; meticulous dissection is necessary to identify the common bile duct and hepatic duct deep within the porta hepatis (Pottakkat et al, 2009).

Hepaticojejunostomy

Approach to the Right Hepatic Duct

A plane of dissection between the Glisson capsule along the base of segment IVb and the peritoneal reflection enveloping the porta hepatis is developed, effectively lowering the hilar plate. In this way, the confluence of the right and left hepatic ducts may be exposed (see Fig. 29.4). If the extrahepatic course of the right hepatic duct is too short to be visualized in this way, as is often the case, the intrahepatic right portal pedicle may be exposed through hepatotomies created along the base of the gallbladder fossa and the caudate process (see Chapter 90A; Launois & Jamieson, 1992). The right portal pedicle may be encircled and delivered, and further mobilization can permit delivery of the right anterior and posterior sectional ducts (see Fig. 29.5).

Approach to the Left Hepatic Duct

The ligamentum teres is ligated with a firm tie and divided to permit anterocephalad retraction; this enhances exposure of the undersurface of the left hemiliver (see Fig. 29.3). The left hepatic duct runs with the left portal vein within a peritoneal reflection along the undersurface of the left hemiliver and is best approached by lowering the hilar plate (Fig. 29.6; Blumgart & Kelley, 1984). This dissection is greatly facilitated by placing a curved or malleable retractor to elevate and retract segment IVb in an anterocephalad direction.

Approach to the Segment III Hepatic Duct

On occasion, the presence of bulky, irresectable tumor along the hepatic hilus may make operative exposure in that region impermissible. In this circumstance, access to the left hepatic duct upstream of the point of obstruction may provide a means of adequately draining the obstructed liver. This can be achieved by exposing the left hepatic duct within the umbilical fissure (Bismuth & Corlette, 1975; Voyles et al, 1983). If the left hemiliver has not atrophied from long-standing biliary obstruction, unilateral left-sided biliary drainage will effectively relieve obstructive jaundice and restore adequate hepatic function, even when the biliary drainage of the excluded right hemiliver remains completely obstructed (Baer et al, 1994). As before, the ligated falciform ligament is elevated, and the bridge of hepatic tissue overlying the umbilical fissure (if present) is divided to optimize exposure of the segment III duct. This can be facilitated by dividing the liver tissue along the left of the ligamentum teres, through which the segment III duct may be exposed and opened without fear of injury to the vascular inflow to segment III (Fig. 29.7). On occasion, a wedge resection of a portion of segment III can also be performed to provide exposure of the segment III duct (Fig. 29.8).

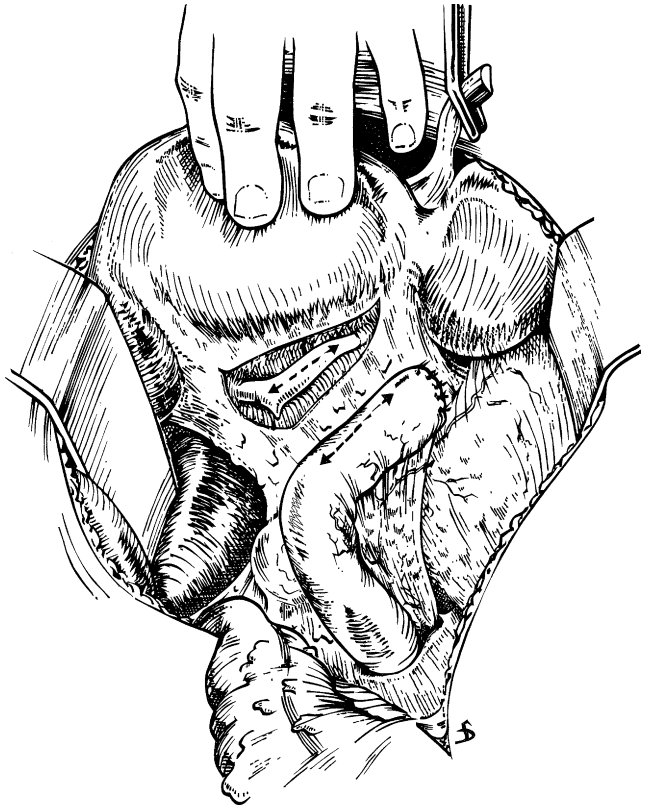


FIGURE 29.6. The hilar plate is lowered, and the left hepatic duct is exposed for dissection. The exposure is carried medially and to the right to expose the confluence and the right hepatic duct.

Anastomotic Technique

We have used a standardized technique for hepaticojejunostomy that can be applied for nearly all circumstances of proximal biliary drainage. This technique is of particular utility for difficult high anastomoses, where duct mobility and size are limited. A 70-cm Roux-en-Y limb of jejunum is prepared and delivered through a transverse mesocolonic defect fashioned to the right of the middle colic vessels. A small jejunotomy, whose diameter is slightly smaller than that of the duct, is cut at the site of planned anastomosis. We do not typically use transanastomotic stents, but if a stent is to be used, it is preferable to pass it through the cut hepatic duct prior to construction of the anastomosis. The stent is affixed against the duct wall with a single 4-0 or 5-0 absorbable catgut suture, which is tied on the outside of the duct wall (Fig. 29.9); this maneuver helps to avoid inadvertent dislodgment of the tube during placement of the anastomotic sutures.

When more than one biliary duct orifice is present, every effort should be made to approximate them with a row of 4-0 or 5-0 absorbable sutures so that they may be treated as a single duct for anastomotic purposes (Fig. 29.10). Anastomotic construction begins with an anterior row of 4-0 or 5-0 absorbable sutures placed along the hepatic duct only, working from left to right. In cases where the duct orifice is small, interrupted sutures should be used. The needles are left on the sutures, which are then retracted in a cephalad direction so as to enhance exposure of the posterior duct wall. A posterior row of full-thickness sutures securing the duct mucosa to the jejunal mucosa is then placed, again working from left to right. Once this row is completed, the sutures are pulled to bring the duct and jejunum into close apposition. The anterior sutures are again retracted to facilitate exposure of the posterior wall of the anastomosis, the posterior sutures are tied, and all but the right and left corner stay sutures are cut. The anterior row of the anastomosis is then completed by suturing the remaining needles to the jejunum, working from right to left. These sutures are left untied so as to maximize exposure of the duct lumen; once this row is completed, the sutures are tied to complete the anastomosis (Fig. 29.11).

In cases where the duct orifice is large, we use a simpler and faster alternative anastomotic technique commonly used for choledochojejunostomy; it is described in detail below.

Choledochojejunostomy

Approach to the Extrahepatic Biliary System

Drainage of the common hepatic duct or common bile duct is typically undertaken after exploration of the extrahepatic biliary system for calculous disease or for biliary decompression in cases of periampullary obstruction. These procedures are only rarely performed in isolation, as they have been largely replaced by endoscopic and percutaneous approaches. An important exception can be found in circumstances where effective biliary decompression must be durable, as might be seen in young patients with benign or indolent etiologies for jaundice. It is quite likely that operative bypass of the extrahepatic biliary system may provide favorable long-term outcomes without the need for repeat stent replacements or revisions that are often eventually required after nonoperative biliary decompressive maneuvers.

Anastomotic Technique

The hepaticojejunostomy or choledochojejunostomy can be performed in an end-to-side or a side-to-side manner. When undertaken in an end-to-side manner, a cholecystectomy is performed, and the common hepatic duct or common bile duct is encircled at the point of planned transection. The duct is sharply transected, the endobiliary stent (if present) is removed, and a specimen of bile may be aspirated for microbiologic analysis. The distal aspect of the duct is oversewn with 3-0 absorbable suture, and a 70-cm Roux-en-Y limb of jejunum is prepared for construction of the biliary-enteric anastomosis to the proximal aspect of the duct. The posterior wall of the duct is sutured against the jejunum with a running row of 3-0 or 4-0 absorbable sutures. A corresponding jejunotomy is fashioned just opposite the duct, and a series of interrupted 3-0 or 4-0 absorbable sutures are used to approximate the exposed mucosa along the posterior wall of the jejunotomy against the posterior wall of the duct. The anterior row of the anastomosis is then completed with the running sutures used to construct the posterior row (Fig. 29.12). We use a single row of sutures; placement of a second layer merely introduces the risk of excessively narrowing the lumen of the anastomosis. Of course, care must be taken to ensure that the sutures are secured tightly and placed at close intervals so as to avoid bile leakage. Placement of a sponge circumferentially around the completed anastomosis provides an intraoperative opportunity to ensure the absence of a significant leak.

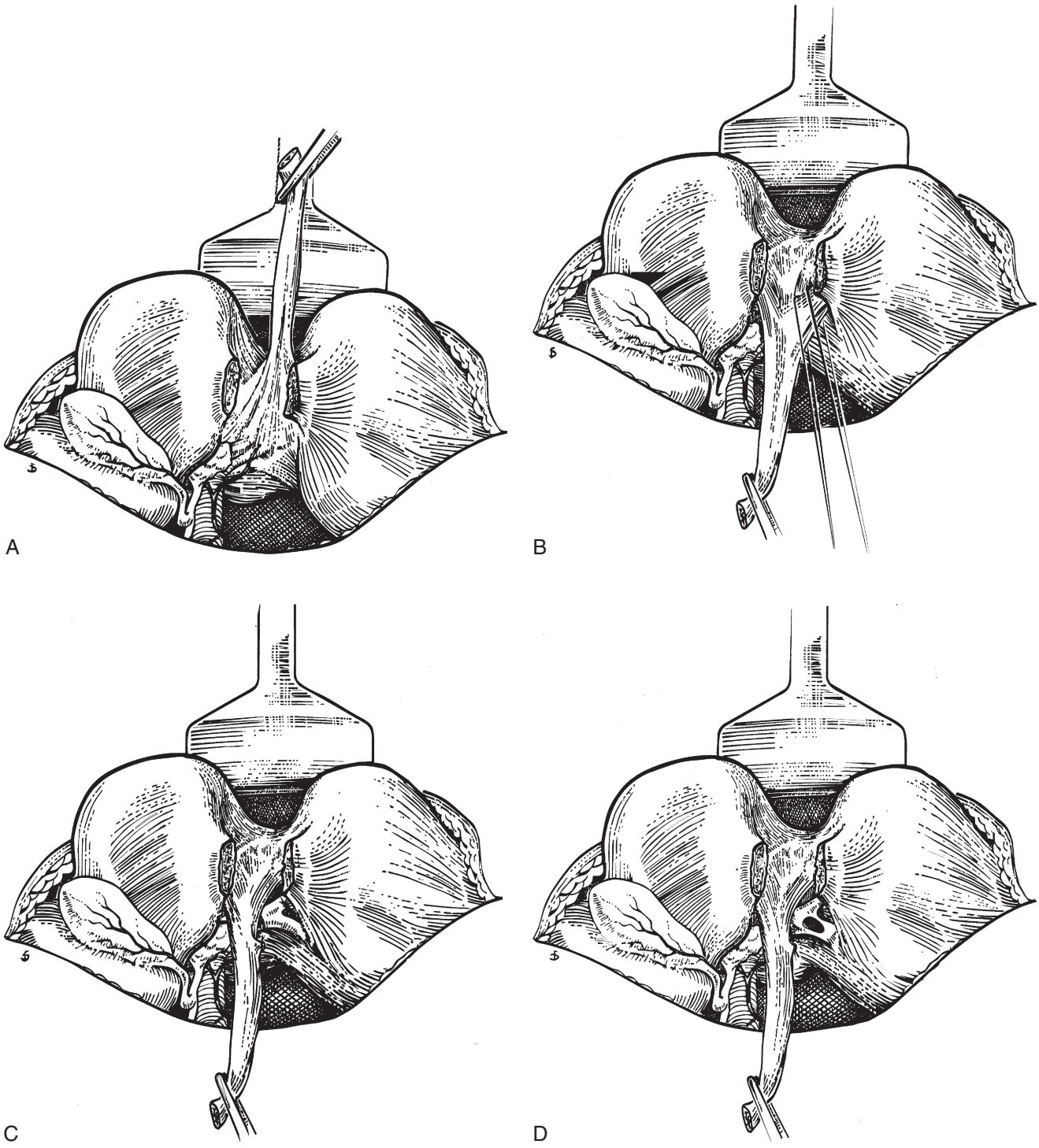


FIGURE 29.7. **A,** The liver is held up so that its inferior surface is seen. The bridge of liver between the quadrate lobe and the left lobe of the liver has been divided. The base of the ligamentum teres is seen. **B,** The ligamentum teres is then pulled downward. The peritoneum of its upper surface on the left side is incised, and the extensions passing into the liver are exposed. The left sides of these extensions are divided between ligatures, which must be passed carefully using aneurysm needles. This part of the dissection is tedious and should be carried out meticulously because hemorrhage within the recess adjacent to the segment III duct can be difficult to control. **C,** The segment III duct is exposed. **D,** The duct is opened longitudinally for anastomosis, which is carried out by the technique illustrated in Fig. 29.13.

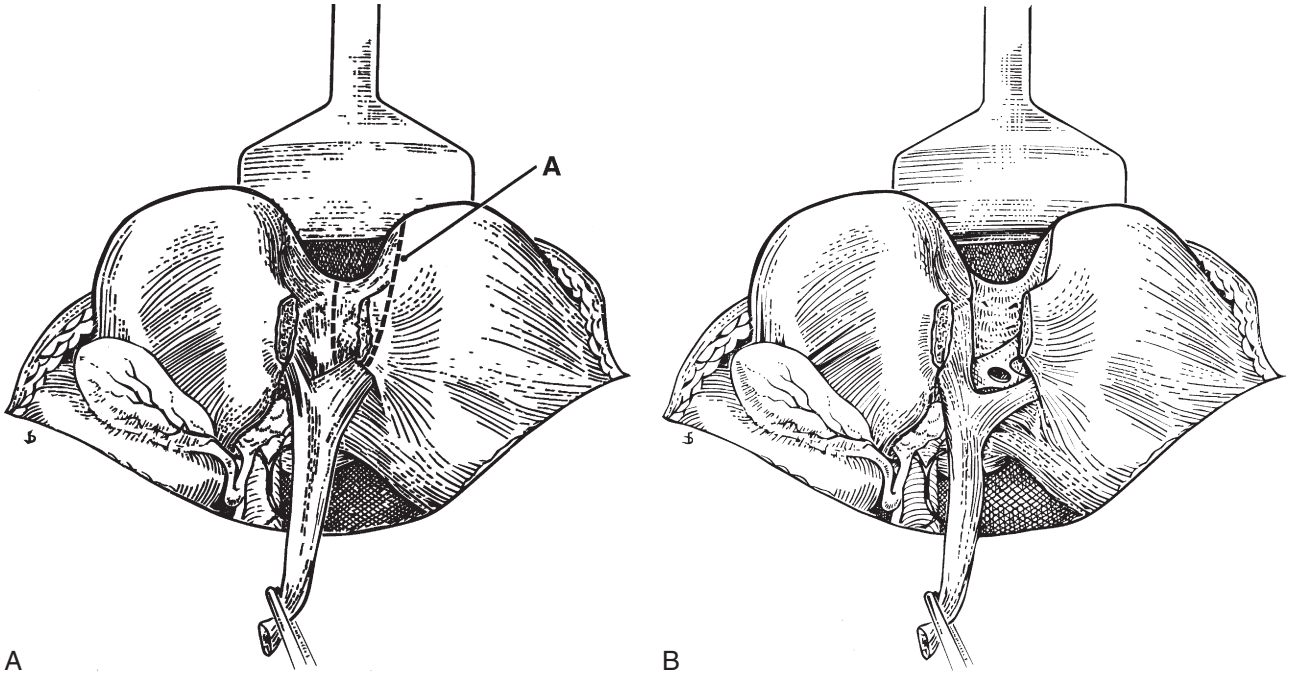


FIGURE 29.8. **A,** The liver is split to the left of the ligamentum teres in the umbilical fissure, and it may be necessary to remove a small wedge of liver tissue. **B,** The segment III duct is exposed at the base of the liver split above and behind its accompanying vein and is ready for anastomosis.

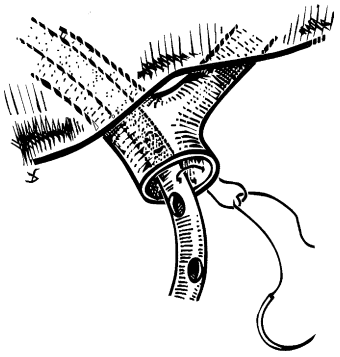


FIGURE 29.9. Manner of fixation of transanastomotic tubes. Note the introduction of the absorbable suture in a mattress fashion across the ductal wall proximal to the future site of anastomosis. This secures the tube conveniently during anastomosis.

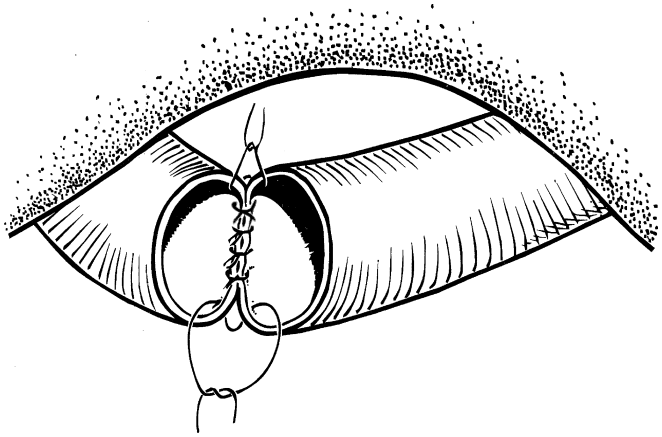


FIGURE 29.10. Adjacent ductal orifices may be approximated before anastomosis.

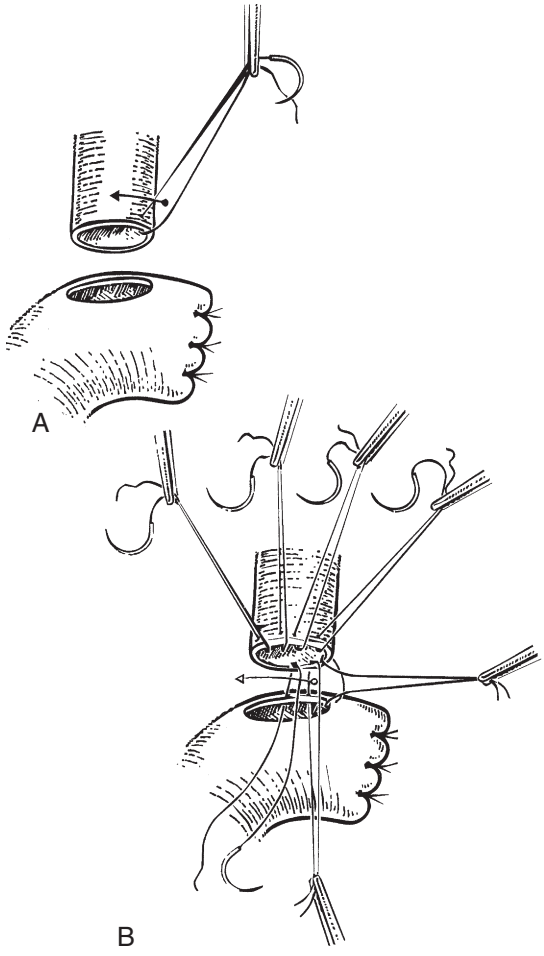


FIGURE 29.11. **A,** The initial step in the creation of hepaticojejunostomy Roux-en-Y. The anterior layer of suture (3-0 Vicryl) on the bile duct is inserted first, and the sutures are passed from the inside out, starting from the patient's left and working toward the right. The needles are retained, and the sutures are kept in order. **B,** The anterior layer of sutures is elevated. This displays the posterior ductal wall, and the posterior row of sutures is now placed, again from left to right.

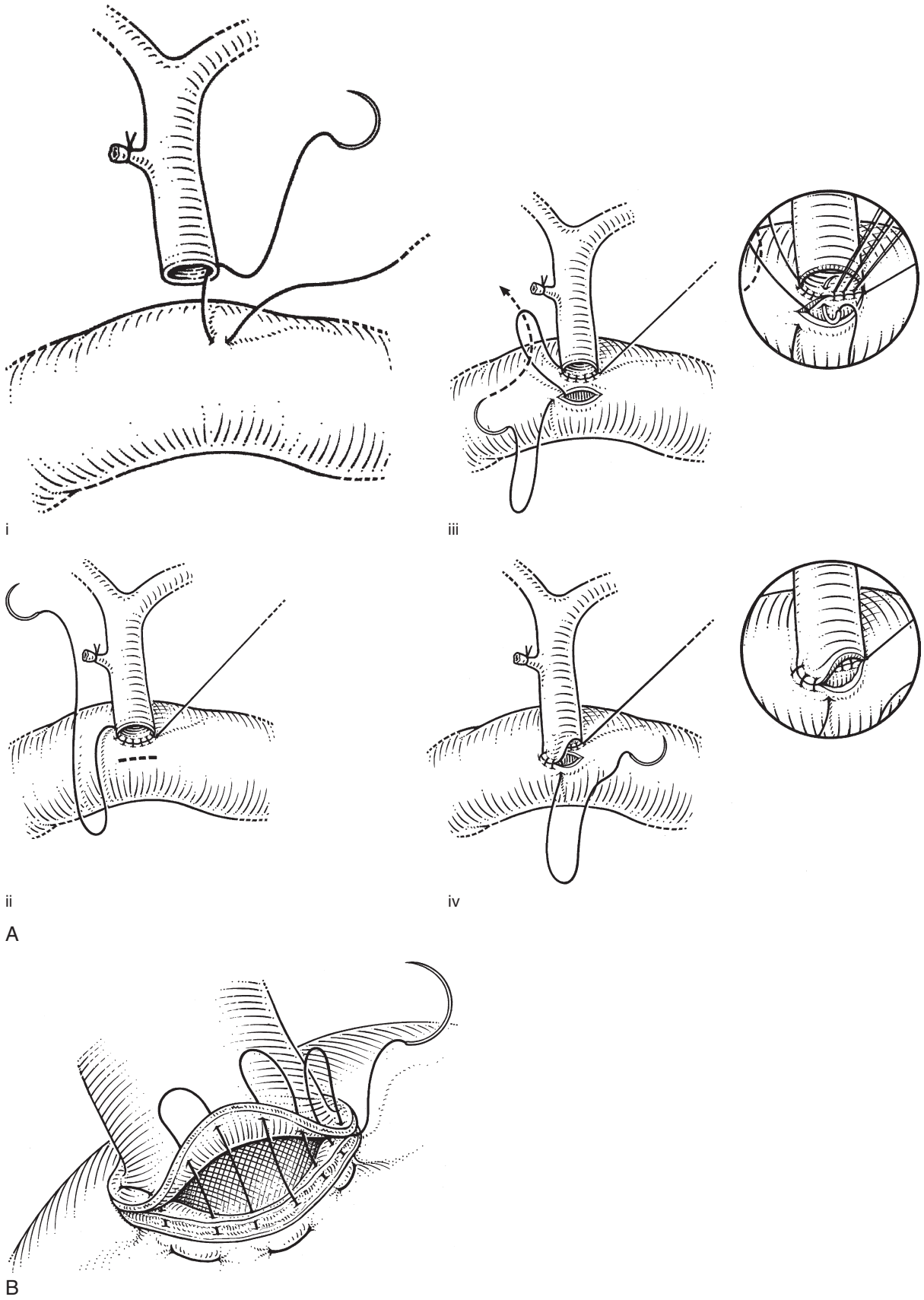


FIGURE 29.12. **A,** Technique for end-to-side anastomosis of the bile duct below the hilus to jejunum. *i,* A 3-0 Vicryl suture is used, and the serosa of the jejunum is sutured to the full thickness of the bile duct. *ii,* This suture is developed as the posterior wall of the bile duct is attached to the jejunal serosa. The *dotted line* marks the point of incision in the jejunum, which is made after the posterior layer is attached. *iii,* The suture is now developed either as a continuous or an interrupted suture on the anterior layer. The posterior layer of the jejunal mucosa is not sutured directly to the bile duct mucosa. Several interrupted sutures may be inserted before completing the anterior layer, however, to approximate the mucosa (*inset*). *iv,* The anastomosis is completed. The *inset* shows the posterior layer with mucosal apposition. **B,** Alternatively, the jejunum may be opened, and a mucosa-to-mucosa anastomosis may be performed with a continuous polydioxanone suture as illustrated.

Alternatively, the side-to-side anastomosis is initiated by placing stay sutures of 4-0 absorbable suture along either side of the planned longitudinal ductotomy, which is fashioned sharply. The biliary-enteric anastomosis is then constructed to a Roux-en-Y jejunal limb using a technique similar to that used for the choledochoduodenostomy (described below). Potential advantages of the side-to-side anastomosis include less devascularization of the untransected duct and the retention of biliary-duodenal continuity, in those circumstances in which future endoscopic retrograde cholangiographic procedures may be desirable (Winslow et al, 2009).

Choledochoduodenostomy

The choledochoduodenostomy can also be a useful operative maneuver when a distal periampullary stricture is present. It is most commonly performed after common bile duct exploration for calculous disease; in this way, a supraduodenal choledochotomy may be anastomosed to a duodenotomy instead of to an external T-tube. In this procedure, a longitudinal choledochotomy is made, through which the extrahepatic biliary system may be explored. For optimal anastomosis, the duct opening should measure at least 2.5 cm in length; this will typically require extension onto the common hepatic duct. A generous Kocher maneuver is performed to permit easy mobility of the duodenum, and a longitudinally oriented duodenotomy is made along the superior aspect of the postbulbar duodenum. Because of the flexibility of the duodenal wall, the duodenotomy may be considerably shorter in length than the ductotomy (Fig. 29.13). Three corner 4-0 or 5-0 absorbable sutures are placed between the ends of the duodenotomy and the midpoints of the ductotomy and between the distal end of the ductotomy and the midpoint of the posterior aspect of the duodenotomy. Retraction of these sutures reorients the distal portion of the ductotomy transversely, which facilitates placement of the posterior row of sutures. The fourth corner suture is then placed between the proximal end of the ductotomy and the midpoint of the anterior aspect of the duodenotomy. Retraction of this suture tents the remaining anterior wall of the anastomosis forward, which facilitates placement of the anterior row of sutures (Fig. 29.14). As with the hepaticojejunostomy and choledochojejunostomy, a single row of sutures is used.

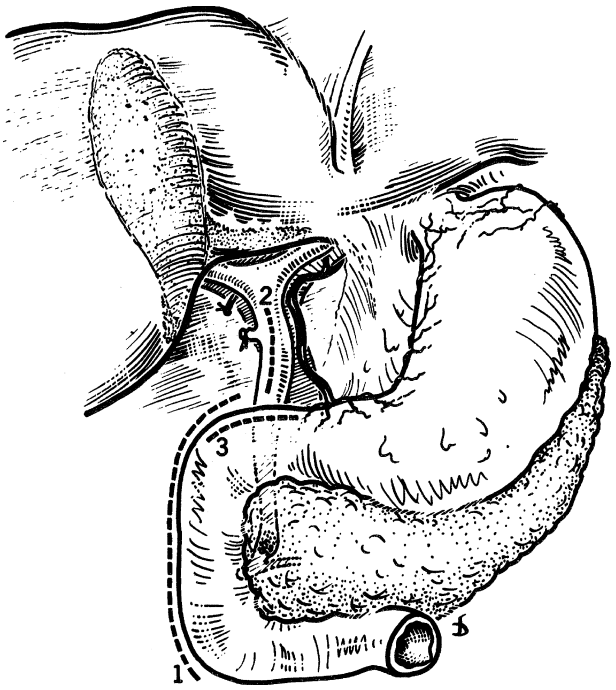


FIGURE 29.13. After the gallbladder is removed, the common bile duct is removed through a conventional longitudinal incision following a Kocher incision *(1)* freeing the lateral duodenum around the common duct. Routine common duct exploration is carried out. If indications for a choledochoduodenostomy exist, the anastomosis is performed. The incision in the common duct *(2)* is extended to 2.5 cm by direct measurement. In almost all instances, the incision in the duct carries into the common hepatic duct. The incision in the postbulbar duodenum *(3)* is slightly smaller because the stoma in the duodenum stretches to approximate the choledochal incision.

Cholecystoduodenostomy and Choledochojejunostomy

An alternative approach to cases of distal biliary obstruction is direct drainage of the gallbladder. High rates of patency failure have been documented, particularly with cholecystoduodenostomy; as a result, we typically do not use this procedure except when advanced malignancy mandates the use of a simple operative intervention (Dayton et al, 1980). Cholecystoenterostomy for palliative biliary decompression is particularly suitable where major tumoral obstruction obscures access to the porta hepatis. Prior to undertaking cholecystoenterostomy, it is imperative to confirm that the extrahepatic biliary obstruction does not extend to the level of the cystic duct insertion. In addition, the presence of significant stone burden within the gallbladder makes this operative strategy less attractive.

The gallbladder is almost invariably distended in patients who are appropriate candidates for cholecystoenterostomy. The gallbladder and cystic duct are carefully evaluated to confirm that the cystic duct does not insert distally into the common bile duct at the level of tumoral obstruction. If cholecystoduodenostomy is undertaken, a generous Kocher maneuver is performed to permit sufficient mobility of the duodenum. If cholecystojejunostomy is planned, a loop of jejunum is utilized; we do not routinely use construction of a Roux-en-Y jejunal limb for this purpose. The gallbladder fundus is secured to the small bowel with a row of 3-0 sutures, a longitudinal cholecystotomy is fashioned, and bile is aspirated. Any stones present in the lumen of the gallbladder are evacuated, and a bile specimen may be sent for microbiologic analysis. Decompression of the common hepatic duct is confirmed, and a corresponding longitudinal enterotomy is fashioned opposite the cholecystotomy. An anterior row of sutures is then placed to complete the anastomosis (Fig. 29.15).

Outcomes after Biliary-Enteric Anastomosis

Longitudinal analyses of outcomes after biliary-enteric anastomosis for benign and malignant diseases confirms the safety and efficacy of the operative approaches outlined in this section (Chapman et al, 1995; Jarnagin et al, 1998; Moraca et al, 2002; Tocchi et al, 1996). Comparative analyses of effectiveness of the various surgical options are limited, but short-term

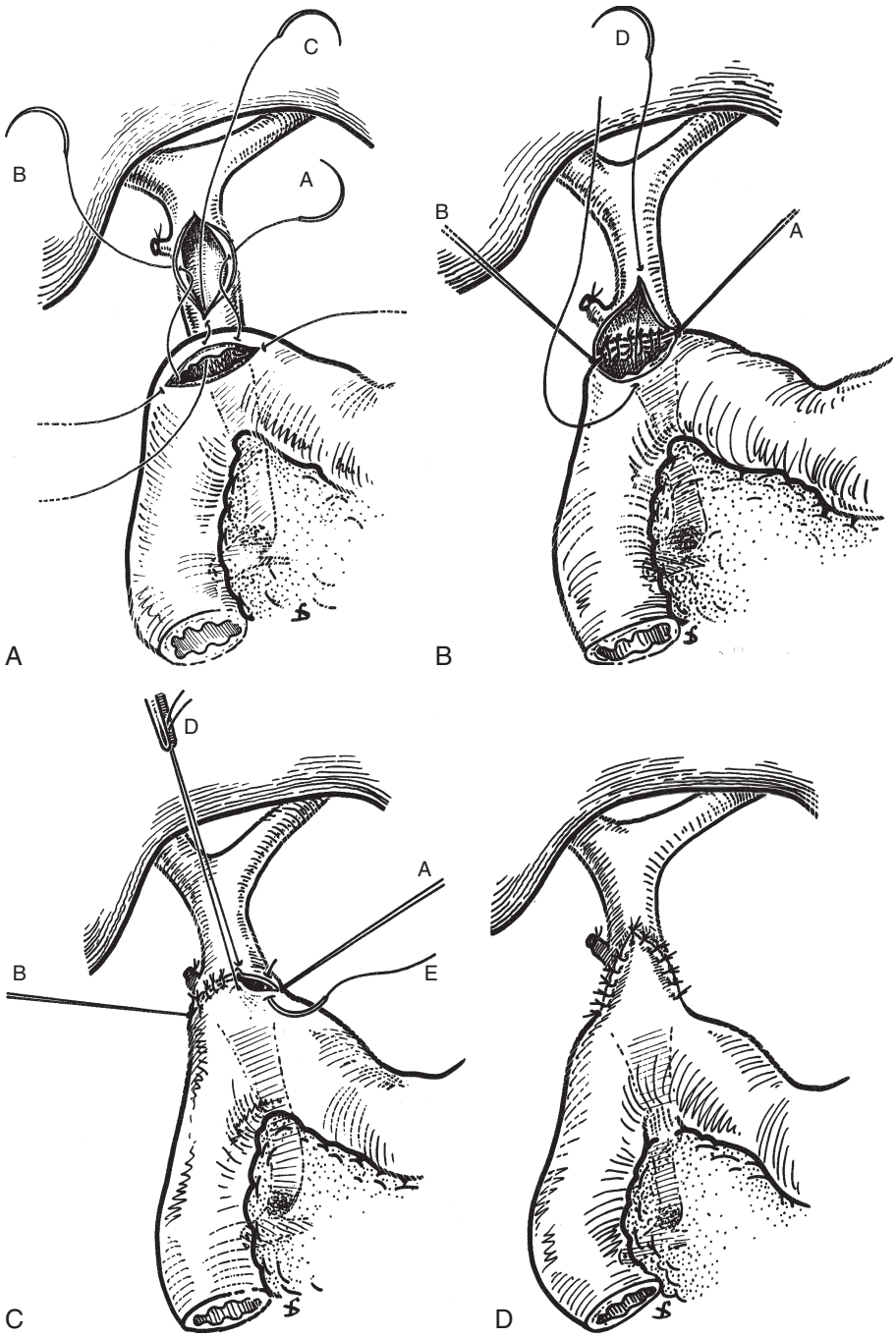


FIGURE 29.14. A, Each side of the choledochoduodenostomy is bisected by suture (*A* and *B*) of absorbable material (chromic catgut or polyglycolic acid) that passes from the end of the duodenal incision through the midpoint of the choledochal incision. Likewise, the duodenal incision is bisected by a suture through the posterior wall of the duodenal incision and the lower apex of the choledochal incision *(C)*. These stitches convert part of the longitudinal choledochotomy incision into a transverse ostium. The lax approximation of the duodenal and choledochal incisions occurs, with the duodenum mobilized, by placing tension on a lateral stay suture (*A* or *B*) and the middle stay suture *(C)*. **B,** Sutures may be placed to complete the posterior suture line approximating the common bile duct to the posterior duodenal incision. After placement of the sutures, they are tied so that the knots are within the lumen. The anterior wall is similarly approximated using a suture bisecting the anterior duodenal incision *(D)* and through the original apex of the bile duct incision. **C,** With this bisecting suture *(D)* tented forward, each of the segments between the tied lateral stay suture and this anterior suture is similarly approximated using interrupted sutures with the knots tied on the outside. The anastomosis is completed by completing the third segment of this triangle with sutures placed between the remaining lateral stay suture and the bisecting, anterior suture *(D)*. It is important in the placement of these last sutures that they do not catch the posterior suture line. The benefit of placing all the sutures in one line of the triangular closure and tying them all after placement is that it allows an internal inspection before the lumen of the choledochoduodenostomy is obscured. A single row of sutures is all that is used. A second row does nothing but decrease the choledochoduodenostomy orifice size and should be avoided. The sutures should be placed close enough for a bile-tight approximation. Digital pressure on the duodenum or the common duct should give no evidence of leakage. **D,** The completed anastomosis allows a thumb-sized defect to be palpated through the duodenal tongue that has been brought on to the common bile duct and common hepatic duct. The anastamosis may be drained or not, according to preference (the leak rate is 1%). The presence of a closed-suction drain (Jackson-Pratt type) obviates the need for a subsequent percutaneous drainage catheter if this uncommon complication occurs.

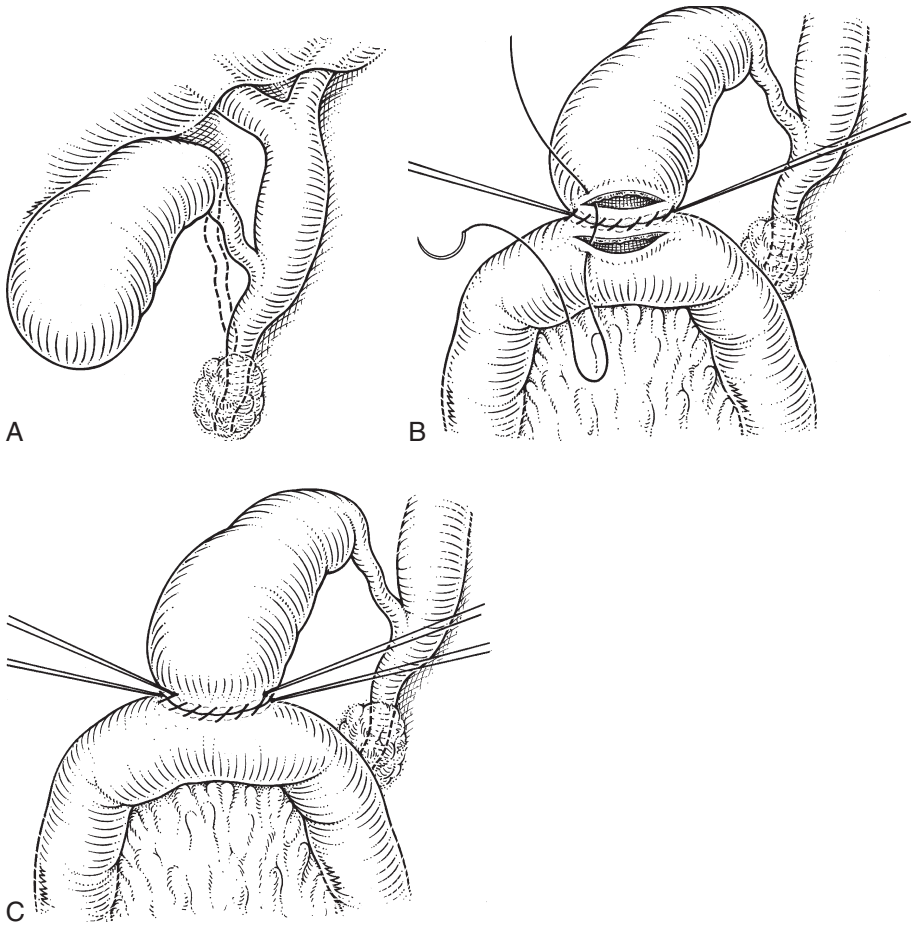


FIGURE 29.15. Technique of cholecystojejunostomy. **A,** The cystic duct should join the common bile duct above the tumor. If it enters at the level of the tumor (*dashed line*), the procedure is contraindicated. **B,** The posterior layer of the anastomosis is performed with a running suture between the openings at the fundus of the gallbladder and the jejunum. **C,** The anterior layer of the side-to-side anastomosis is completed. (We do not use an associated enteroenterostomy.)

perioperative morbidity and long-term patency appear favorable after segment III bypass when compared with bypasses to the right sectoral ducts. Of note is a measurable incidence of cholangiocarcinoma after biliary-enteric anastomosis; long-term follow-up of 1003 patients who underwent biliary bypass for benign disease identified 55 cases (5.5%) of primary bile duct cancer after intervals of 132 to 218 months (Tocchi et al, 2001).

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PART 5: Biliary Tract Disease

SECTION I
Inflammatory, Infective, and Congenital

A. Gallstones and Gallbladder

CHAPTER 30

Natural history of gallstones and asymptomatic gallstones

Pierre F. Saldinger and Andrei Cocieru

HISTORY

Gallstones have been recognized since antiquity and have even been found during autopsies of Egyptian mummies. The Greek physician Trallianus described calculi within radicles of a human liver (Glenn & Grafe, 1966). Vesalius and Fallopius described gallstones in the gallbladders of dissected human bodies (Schwartz, 1981), and in 1882, Langenbuch performed the first successful cholecystectomy, setting the path for therapeutic intervention in cholelithiasis.

EPIDEMIOLOGY

Gallstones represent a sizeable problem for the contemporary health care system in both developed and developing countries alike. In the year 2000, there were 2,624,111 admissions and 778,632 outpatient visits for gallstones in the United States. With 6.3 million affected men and 14.2 million affected women between the ages of 20 and 74 years, and at an annual cost of $6.5 billion, cholelithiasis is the most expensive digestive tract disorder today in the United States (Shaffer, 2006). Incidence of gallstones and gallstone-related operations in developed countries appears to be increasing. With an overall prevalence of 10% to 15% in developed countries, geographic-specific prevalence is from 0% to 10% in Africa and up to 60% to 70% in certain populations, such as Pima Indians; this likely reflects combined differences in environmental, dietary, and genetic factors (Shaffer, 2006). The most common type of gallstones in developed countries are composed primarily of cholesterol, and the highest incidence is in the Native American population; moderate prevalence is seen in Hispanics, and the lowest prevalence is seen in black Americans, East Asians, and sub-Saharan Africans. Increased incidence of brown-pigmented stones are noted in East Asians, reflecting a higher rate of biliary tract infections (Shaffer, 2006; see Chapter 43). More detailed information about geographic disparities in the prevalence of gallstone disease can be found in Table 30.1.

Risk Factors for Gallstones Development

Gallstone disease clearly results from a complex interaction of genetic and environmental factors. This is confirmed by an altered incidence of gallstone detection when people from diverse geographical areas travel and settle in areas with a different dietary regimen, level of physical activity, and hygiene. The common mechanisms of gallstone formation include cholesterol hypersecretion, alteration in intestinal bile salt/cholesterol absorption, and gallbladder hypokinesia, which leads to bile cholesterol supersaturation and nucleation (see Chapter 7). Bacterial infection and an increase in bilirubin load play a role in the development of black and brown gallstones. The following is a quick overview of the most common risk factors for the development of gallstones.

Age

The incidence of gallstones increases with age across all ethnic groups, and it is very low among infants and children (Chen et al, 1998). Some specific populations such as Pima Indians,

Table 30.1

Geographic Prevalence of Gallstones as Assessed by Ultrasound

Study	Geographic Area	Male Population (%)	Female Population (%)
Everhart et al, 1999, 2002	North America	5.3-29.5	13.9-64.1
Miguel et al, 1998; Covarrubias et al, 1995; Moro et al, 2000	South America	8.3-14.5	10.0-49.4
Palasciano et al, 1989; Glambek et al, 1987; Misciagna et al, 1994; Mellström et al, 1988	Europe	0-37	4.8-50.5
Khuroo et al, 1989; Chen et al, 1998; Lu et al, 1990	Asia	0-10.7	4.6-29.1
Walker et al, 1989; Bagi Abdel, 1991	Africa	0-5.6	5.1-10

mentioned previously, have an increased incidence of gallstones (up to 70%) by 30 years of age, implicating hereditary metabolic factors (Sampliner et al, 1970). Pediatric populations with chronic hemolytic conditions, such as sickle cell anemia, also represent another distinct group in whom gallstones develop early.

Gender

Female gender is a risk factor for developing gallstones, surpassing males in the incidence of gallstones and the chance of having surgery by 2:1 or 3:1 in most studies (see Table 30.1). Pregnancy is associated with up to a 30% risk of developing biliary sludge, and low-dose estrogen therapy in postmenopausal women increases the risk of gallstone formation (Maringhini, et al, 1993; Hulley et al, 1998).

Obesity, Diet, Physical Activity, and Weight Loss

Obesity is a well-established major risk factor for the development of gallstones. The association with simple obesity is important in females; in males it is mostly associated with intraabdominal (central) obesity and metabolic syndrome (Maclure et al, 1989; Heaton et al, 1991; De Santis et al, 1997; Tsai et al, 2004).

The frequency of gallstones has almost doubled in the last 60 years, in parallel with the changed composition of stones from pigment to cholesterol. In humans, most cholesterol found in gallstones is from the diet, since de novo hepatic synthesis is only about 20% (Paigen & Carey, 2002). This emphasizes the importance of high caloric and carbohydrate intake as risk factors for the development of gallstones in modern society.

Bariatric patients are at a high risk for the development of cholelithiasis after weight-reduction surgery. Sludge and gallstones form in up to 35% of patients following bariatric procedures, with weight loss more than 1.5 kg/week being a risk factor (Shiffman, et al, 1991; Weinsier et al, 1995).

Patients receiving total parenteral nutrition (TPN) are another group with a high incidence of gallstone and sludge development. After 3 months of TPN therapy, approximately 45% of patients will develop gallstones; 100% of patients will develop sludge within 6 weeks (Shaffer, 2001; Murray et al, 1992). Low levels of physical activity are associated with development of gallstones in large observational and population studies also related to obesity and diet (Leitzmann et al, 1999). Finally, patients receiving long-term somatostatin analogue therapy for various disorders (acromegaly, functional neuroendocrine tumors) are at increased risk for gallstone formation as a result of reduced gallbladder motility and reduced bile flow (Bornschein et al, 2009).

Genetics

Population studies indicate a 30% genetic component in the development of gallstone disease. Hepatic cholesterol hypersecretion, resulting in bile supersaturation and cholesterol stone formation, may be caused by increased hepatic uptake and synthesis of cholesterol, decreased hepatic synthesis of bile salts, decreased hepatic synthesis of cholesterol esters for inclusion in very-low-density lipoprotein (VLDL), and derangements in the intestinal absorption of cholesterol and bile salts. Genes controlling hepatic cholesterol metabolism have been implicated in the pathogenesis of gallstone formation in transgenic/knockout mouse models and in humans (Table 30.2). Excess cholesterol load in smooth muscles of the gallbladder can affect signaling via the cholecystokinin A (CCK-A) receptor and contribute to the development of gallstones by inducing bile stasis. Intestinal cholesterol/bile salt absorption is tightly controlled and genes responsible for cholesterol absorption (*NPC1L1,* Niemann-Pick C1-like protein) or cholesterol efflux (*ABCG5*/*G8*) have been implicated in the development of gallstones in certain populations because of intestinal bile salt loss. Single-gene mutations result in hemolysis and increase the incidence of black stones because of an excess of unconjugated bile acids forming polymerized calcium bilirubinate stones. A summary of genes found to be involved in gallstone pathogenesis can be found in Table 30.2 (Grünhage & Lammert, 2006).

Other Risk Factors

Certain medical conditions and medications can cause gallstones by multiple mechanisms. Cirrhosis can induce decreased bile salt synthesis and bile salt malabsorption together with chronic hemolysis and a hyperestrogenic state. Inflammatory bowel disease (Crohn disease) or ileal resection can also interfere with bile salt absorption, estrogen can increase biliary cholesterol secretion, and progesterone can impair gallbladder motility. In addition to causing gallbladder hypomotility, octreotide increases the amount of reabsorbed deoxycholic acid and results in cholesterol supersaturation. Ceftriaxone is excreted in bile in significant amounts and can cause biliary pseudolithiasis and sludge, which usually disappears after antibiotic therapy is discontinued (Lambou-Gianoukos & Heller, 2008).

NATURAL HISTORY OF GALLSTONES

Gallstones do not cause any symptoms in up to 80% of carriers. Within 5 years, 10% to 20% became symptomatic. The risk of further symptoms is approximately 2% per year with an overall risk of biliary complications (acute pancreatitis and symptomatic choledocholithiasis) in asymptomatic patients of 0.3% per year; the risk of gallbladder cancer is 0.02% per year (Gibney, 1990; Thistle et al, 1984; Attili et al, 1995; Gracie & Ransohoff,

Table 30.2

Genes Involved in Gallstone Pathogenesis

Genes and Encoded Proteins	Mechanism	Significance in Humans
ABCB4, ATP binding cassette transporter B4	Decreased biliary phospholipid secretion	+
ABCB11, ATP binding cassette transporter B11	Decreased bile salts secretion	+
APOB, apolipoprotein B	Decreased hepatic VLDL secretion	+/?
APOE, apolipoprotein E	Increased intestinal cholesterol absorption, decreased bile acid secretion	+/?
CCKAR, cholecystokinin A receptor	Gallbladder hypomotility	?
CETP, cholesteryl ester transfer protein, plasma	Increased HDL metabolism	+
CFTR, cystic fibrosis transmembrane conductance regulator	Increased biliary bilirubin secretion and bile salt excretion in feces, decreased bile pH	+
ANK1, EPB42, SPTA1, SPTB, SLC4A1, associated with hereditary spherocytosis	Increased bilirubin load	+
HBB, hemoglobin-β, associated with sickle cell anemia and thalassemia	Increased bilirubin load	+
AK1, G6PD, GPI, GSR, PGK1, PKLR, associated with erythrocyte enzyme deficiencies	Increased bilirubin load	+
CYP39A1, oxysterol 7-alpha-hydroxylase	Induced hypercholesterolemia	+
UGT1A1, Gilbert syndrome–associated protein	Increased bilirubin load	+
NPC1L1, NPC1 (Niemann-Pick disease, type C1, gene)–like protein 1	Reduced cholesterol intestinal absorption	+
ABCG5/ABCG8, ATP binding cassette G5/G8, cholesterol transporter	Increased cholesterol intestinal efflux	?

ATP, adenosine triphosphate; HDL, high-density lipoprotein; VLDL, very-low-density lipoprotein; +, clear evidence; ?, potentially related but no definitive evidence

1982; Friedman, 1993; McSherry et al, 1985). Half of the patients with symptoms develop a second attack within a year, but in 30% of all cases, there is only one symptomatic attack. The analysis of the natural history of gallstones started with a landmark study by Gracie and Ransohoff (1982), which followed 123 Michigan University faculty members—110 men and 13 women—with asymptomatic gallstones at screening for 15 years. At 5, 10, and 15 years of follow-up, 10%, 15%, and 18% had become symptomatic, respectively. None of the subjects developed complications before the onset of typical symptoms. The approximate rate at which the subjects developed biliary pain was 2% per year for the first 5 years with a subsequent decrease over time. Three patients in this study developed biliary complications, all of which were preceded by biliary pain. The investigators concluded that, based on these results, prophylactic cholecystectomy for asymptomatic gallstones could not be recommended (Gracie & Ransohoff, 1982).

Attili and colleagues (1995) also followed 151 subjects with gallstones over 10 years. Of those subjects, 33 had symptoms, and 118 were asymptomatic at the beginning of the study. The cumulative probability of developing biliary colic was 12% at 2 years, 17% at 4 years, and 26% at 10 years. The cumulative probability of developing complications after 10 years was 3% in the initial asymptomatic group and 7% in the symptomatic group. The authors concluded that the natural history of gallstone disease might not be as benign as previously thought.

The results of several other natural history studies have been reported. In a Japanese study, Wada and Imamura (1993) found one third of 1850 patients with cholelithiasis to be symptomatic. Of the remaining 680 asymptomatic patients, 20% became symptomatic over a median follow-up of 13 years. Patients older than 70 years were more likely to become symptomatic than patients younger than 70 years. McSherry and colleagues (1985) followed 135 asymptomatic men and women with gallstones who were subscribers to the Health Insurance Plan of Greater New York. Of these subjects, 10% developed symptoms, and 7% required cholecystectomy over a median follow-up of 46 months. A placebo group of 193 asymptomatic patients who were part of a chemical dissolution trial were followed for 24 months (Thistle et al, 1984). In this study, 31% of patients eventually developed biliary pain, which is high but perhaps related to the intense surveillance or to the requirement that participants have no symptoms only for the 12 months preceding the trial. Cucchiaro and colleagues (1990) followed 125 asymptomatic patients for 5 years. Fifteen patients developed symptoms during that time, and 2 patients required emergent surgery for gallstone complications; 54 patients died during that period because of malignancies, cardiovascular disease, or renal insufficiency, but none died from gallstone disease. Friedman and coworkers (1989) followed 123 asymptomatic patients for 20 years and found that 6% of patients developed severe gallstone-related symptoms during the first 5 years after diagnosis. Halldestamm and colleagues (2004) followed 120 asymptomatic patients, 14 of whom required treatment for symptoms or gallstone-related complications over a median observation period of 87 months. The authors calculated that the cumulative risk of requiring treatment during the first 5 years after detection of gallstones was 7.6%. A summary of the natural history of gallstones as reported by various authors is shown in Table 30.3.

In a Marcov model, simulation investigators from the Netherlands attempted to predict the effect of cholecystectomy on adverse events during a 10-year period (Venneman et al, 2005). In this particular model, 3.2% of the small gallstone carriers developed acute cholecystitis, 1.8% developed symptomatic

Table 30.3

Natural History of Gallstones

Study	N	No. Years	Biliary Pain (%)	Biliary Complications (%)
Gracie & Ransohoff, 1982	123	15	18	2
Attili et al, 1995	118	10	26	3
Juhasz et al, 1994	110	6	22*	–
Wada & Imamura, 1993	680	10-17	20	–
McSherry et al, 1985	135	4	17	0
Friedman et al, 1989	123	5	–	6
Thistle et al, 1984	193†	2	31	–
Cucchiaro et al, 1990	125	5	12	2
Angelico et al, 1997	426	10	38	–
Halldestamm et al, 2004	120	7	12‡	–

*Patients requiring cholecystectomy
†Asymptomatic for 12 months preceding the study
‡Symptoms or complications

choledocholithiasis, and up to 3.4% developed acute pancreatitis. There was no clear cost benefit and no life-years were gained from prophylactic cholecystectomy, indicating no clear-cut advantages of prophylactic cholecystectomy in asymptomatic cholelithiasis. As a result, in patients with asymptomatic gallstones, expectant management is recommended.

Patients with diabetes may have a higher incidence of gallstones from the indirect effects of the metabolic syndrome, obesity, and a family history of gallstones. No data show worse evolution of asymptomatic cholelithiasis in diabetics, and prophylactic cholecystectomy in asymptomatic gallstones carriers with diabetes is not recommended (Sleisenger & Fordtran, 1993).

The size of gallstones is thought to be linked to a higher risk for the development of gallbladder cancer, but this is controversial (see Chapter 49). Cholecystectomy is possibly indicated in some populations carrying a high risk of gallbladder cancer (Chilean Hispanics, Mapuche Indians, and Maoris from Easter Island), even when associated with asymptomatic cholelithiasis (Randi et al, 2006; Grimaldi et al, 1993). Prophylactic cholecystectomy also could be indicated in patients with active hemolytic anemias, before or during renal transplantation or during bariatric surgery (Bonatsos et al, 2001; Graham et al, 1995; Shiffman et al, 1993).

GALLSTONES, PORCELAIN GALLBLADDER, AND GALLBLADDER CARCINOMA (SEE CHAPTER 49)

Gallstones are closely associated with gallbladder cancer (level V evidence, descriptive studies only), and it is speculated that gallstones larger than 3 cm, family history of gallbladder cancer, and duration of cholelithiasis are all potential risk factors for the development of gallbladder cancer (Miyazaki et al, 2008). Gallstones are present in 60% to 90% of gallbladder cancer cases (Goldin & Roa, 2009), although no direct causal relationship between gallstones and gallbladder cancer has been proven. The presence of large gallstones could simply reflect the duration of cholelithiasis rather than causality, and a significant difference in prevalence of gallbladder cancer worldwide points to the influence of other factors. The risk of developing carcinoma is estimated to be 1% of calculous gallbladders 20 years after the initial diagnosis of gallstones, with the risk increased mainly in men (Maringhini et al, 1987); however, given the high incidence of gallstones and the rarity of gallbladder cancer, this estimate would seem to be high. In some series, no patients with gallstones developed gallbladder cancer over a 10-year period. As a result, cholecystectomy to prevent the development of gallbladder cancer in patients with gallstones is not recommended. Some populations such as Pima Indians, Chileans, and Pakistani women with gallstones have an unusually high incidence of gallbladder cancer (12 to 21 per 100,000; Goldin & Roa, 2009). In these unique populations, prophylactic cholecystectomy to prevent the development of gallbladder cancer is probably justified.

Calcification of the gallbladder is encountered in up to 0.8% of all gallbladder pathology specimens. Porcelain gallbladder or diffuse gallbladder calcification was long considered to be a significant risk factor for the presence of gallbladder cancer, ranging from 12% to 62% (Stephen & Berger, 2001; Towfigh et al, 2001; Cunningham & Alexander, 2007). Recently, two studies from the United States analyzed a large database of cholecystectomy specimens and reported much lower incidence rates of cancer in porcelain gallbladder than in previous studies (Stephen & Berger, 2001; Towfigh et al, 2001). Diffuse calcification appeared to confer little or no increased risk of cancer; by contrast, the incidence of cancer in gallbladders with selective, not diffuse, calcifications was much higher at 7% (Stephen & Berger, 2001). Based on this data, at least in Western populations, the incidence of cancer in porcelain gallbladder should be considered to be increased but not as high as reported previously. Taking into account that older studies from other populations (Japan and South America) are citing a much higher association of porcelain gallbladder with gallbladder cancer, and because gallbladder cancer is a highly lethal disease, careful decision making should be undertaken when assessing individual risk of cancer in patients with a calcified gallbladder.

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CHAPTER 31

Cholecystitis

Kaitlyn Kelly and Sharon Weber

OVERVIEW

Cholecystitis, a common condition usually resulting from complications of cholelithiasis, occurs in two forms, acute and chronic. Acute cholecystitis requires urgent intervention, typically with antibiotics followed by cholecystectomy. In the setting of acute cholecystitis, cholecystectomy is optimally performed soon after the diagnosis is made. If urgent cholecystectomy is not feasible, operation can be delayed until after the acute episode has resolved, and then the operation may be performed electively, provided that the acute process can be controlled, and the symptoms resolve. Chronic cholecystitis is the manifestation of ongoing, intermittent inflammation or so-called biliary colic. Patients with this condition benefit symptomatically from elective cholecystectomy. A less common version of cholecystitis is acute acalculous cholecystitis, which occurs most often in critically ill patients. Although gallstones are, by definition, absent in this condition, cholecystectomy specimens in patients with acute acalculous cholecystitis often reveal biliary sludge.

ACUTE CHOLECYSTITIS

Pathogenesis

The cause of acute cholecystitis is an impacted gallstone in the outlet of the gallbladder, either in the infundibulum or in the cystic duct (Sjodahl et al, 1978). The impacted gallstone results in gallbladder distension and edema with acute inflammation, which eventually can result in venous stasis and obstruction, followed by thrombosis of the cystic artery. Ultimately, ischemia and necrosis of the gallbladder occur. Because the fundus of the gallbladder is the greatest distance from the cystic arterial blood supply, it is more sensitive to ischemia and is the most common location for necrosis of the gallbladder. The acute inflammation of cholecystitis may be complicated by secondary biliary infection. Positive biliary cultures are found in about 20% of patients with acute cholecystitis (den Hoed et al, 1998), the most common of which are gram-negative bacteria of gastrointestinal origin, such as *Klebsiella* spp. and *Escherichia coli.*

Clinical Manifestations

Most patients with acute cholecystitis present with severe, constant, right upper quadrant or epigastric pain, sometimes with radiation to the subscapular area. This pain may be preceded by intermittent, self-limited bouts of abdominal pain from episodes of biliary colic. Acute cholecystitis is frequently associated with fever and leukocytosis, findings that are not present in cases of uncomplicated biliary colic. Patients also may develop a Murphy sign, or inspiratory arrest on palpation of the right upper quadrant. Other presenting symptoms include nausea, vomiting, and anorexia.

Differential Diagnosis

Several disease processes can present similarly to cholecystitis and should be considered in the differential diagnosis. These include peptic ulcer disease, gastritis and gastroenteritis, irritable bowel syndrome, inflammatory bowel disease, right lower lobe pneumonia, and biliary dyskinesia. An initial chest radiograph is generally sufficient to assess for a right lower lobe infiltrate. The other diagnoses should be entertained and worked up appropriately in symptomatic patients without gallstones on ultrasound (US).

Diagnostic Evaluation and Imaging

Abdominal US (see Chapter 13) is useful for assessing patients suspected to have acute cholecystitis. Typical findings include gallstones, gallbladder wall thickening (>4 mm), and pericholecystic fluid (Fig. 31.1). In addition, the sonographer can assess for pain and inspiratory arrest when the gallbladder is directly compressed by the US probe (sonographic Murphy sign). Typically, conventional gray scale imaging is used, which is highly sensitive and specific for diagnosing acute cholecystitis, with an overall accuracy of greater than 90% (Soyer et al, 1998). Other techniques of imaging that assess blood flow, such as color velocity imaging, may improve accuracy in selected cases (Soyer et al, 1998; Uggowitzer et al, 1997).

Hepatobiliary scintigraphy (see Chapter 15) is a useful study in selected patients when the diagnosis is uncertain. This nuclear medicine study is performed with derivatives of aminodiacetic acid (hepatoiminodiacetic acid [HIDA], isopropylacetanilido imidodiacetic acid [PIPIDA], or di-isopropylacetanilido iminodiacetic acid [DISIDA]), which are taken up by hepatocytes and secreted in the bile. When the tracer is labeled with technetium, it is possible to visualize biliary function with scintigraphy. A normal scan delineates the biliary tree, including the gallbladder, and shows prompt emptying of the agent into the duodenum. Nonvisualization of the gallbladder on hepatobiliary scan is consistent with acute cholecystitis (Fig. 31.2).

An added utility of this test is that in addition to gallbadder filling or nonfilling, it also evaluates gallbladder emptying. Abnormal emptying is defined as an ejection fraction (EF) of 35% or less on scintigraphy, a finding suggestive of biliary pathology. Middleton and Williams (2001) reported on 141 patients with normal US and scintigraphy with normal gallbladder filling and an EF of 35% or less who underwent

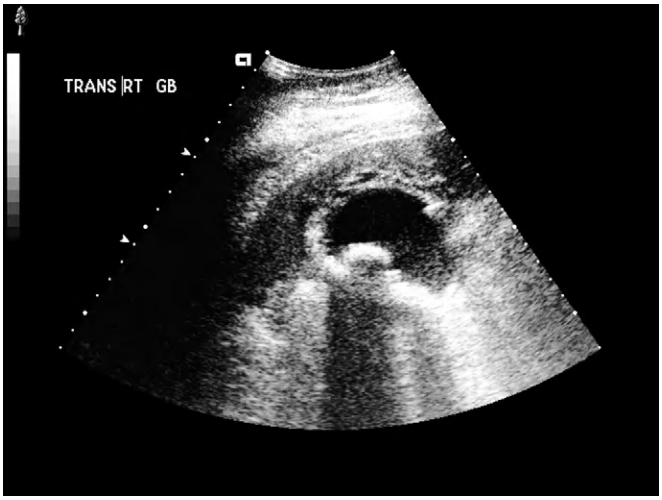


FIGURE 31.1. Transverse view of the gallbladder on ultrasound in a patient with calculous cholecystitis, revealing gallstones and gallbladder wall thickening.

cholecystectomy. Of these patients, 95% had significant improvement or complete resolution of symptoms after surgery, and 41% of these patients had cholecystitis on histologic evaluation of the gallbladder.

Hepatobiliary scintigraphy is not useful in patients with poor hepatic function because it requires hepatic excretion of bile, but it is accurate in about 90% of patients and may be more accurate than US alone. Hepatobiliary scintigraphy is more involved, more expensive, and requires a longer time than US; however, it should be reserved for selected cases (Chatziioannou et al, 2000; Kalimi et al, 2001). Mahid and colleagues (2009) have suggested a diagnostic approach that starts with US for patients with biliary symptoms. If no gallstones are definitively identified, this should be followed by esophagogastroduodenoscopy to exclude alternative causes of symptoms, such as peptic ulcer disease or gastritis. If this test result is negative, hepatobiliary scintigraphy should follow.

Computed tomography (CT; see Chapter 16) can also help diagnose acute cholecystitis and provides more detailed anatomic information than US. CT is particularly useful in patients whose symptoms suggest a complication such as pericholecystic abscess or an alternative diagnosis. The CT findings of acute cholecystitis are the same as those seen on US and include wall thickening, pericholecystic stranding, distension of the gallbladder, high-attenuation bile, pericholecystic fluid, and subserosal edema. CT generally is less sensitive than US for diagnosing acute cholecystitis, particularly early in the course, when the imaging findings may be subtle (Fidler et al, 1996; Harvey & Miller, 1999).

Treatment

Initial treatment with antibiotics active against enteric bacteria should begin as soon as the patient is diagnosed with acute cholecystitis. In addition, oral intake should be restricted, and intravenous resuscitation should be started in preparation for surgery with parenteral analgesics administered as needed.

The definitive treatment for acute cholecystitis is cholecystectomy. From the time this operation was first performed in 1882 by Langenbuch, open cholecystectomy has been the standard of care for patients with acute cholecystitis. With the advent of laparoscopic cholecystectomy in the 1980s, the standard approach has changed such that cholecystectomy is now routinely performed laparoscopically. The benefits of laparoscopic cholecystectomy are discussed in depth elsewhere (see Chapters 33 and 34), but they include a shorter postoperative stay and decreased analgesia requirements (Cox et al, 1993). Although the laparoscopic approach is now standard for most cases, it is interesting to note that two prospective, randomized studies suggested little or no difference in several outcome measures between laparoscopic versus small-incision open cholecystectomy (Majeed et al, 1996; Keus et al, 2008).

Early analysis of the results of laparoscopic cholecystectomy in patients with acute versus chronic cholecystitis showed increased morbidity and mortality rates for patients with simple or complicated acute cholecystitis. Because of the increased

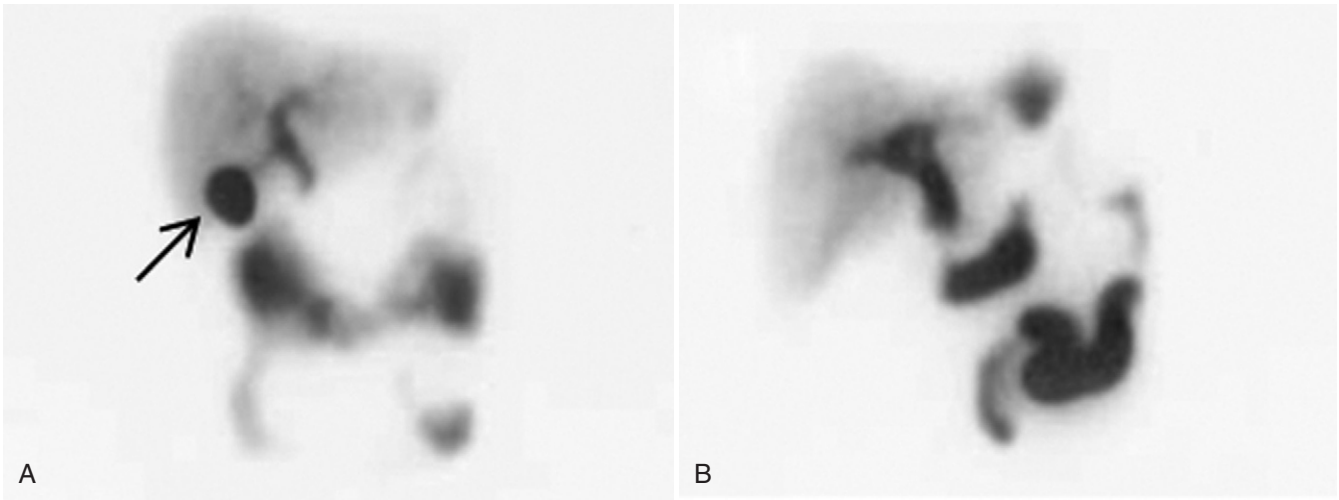


FIGURE 31.2. A, Normal hepatoiminodiacetic acid (HIDA) scan demonstrating contrast-filled gallbladder (*arrow*). **B,** Abnormal HIDA scan demonstrating nonfilling of the gallbladder consistent with cystic duct obstruction. *(Courtesy Dr. Scott Perlman, University of Wisconsin Hospital and Clinics.)*

morbidity and mortality, acute cholecystitis initially was considered a relative contraindication to laparoscopic cholecystectomy (Flowers et al, 1991). Subsequent reports have shown the improved safety of this technique in the acute setting (Chandler et al, 2000; Johansson et al, 2003; Lai et al, 1998; Lo et al, 1998). The conversion rate to an open procedure is higher for patients with acute cholecystitis compared with patients undergoing elective operations for simple biliary colic (Schirmer et al, 1991), but most patients with acute cholecystitis (>80%) can undergo laparoscopic cholecystectomy successfully (Papi et al, 2004). Retrospective series revealed that risk factors for conversion to open cholecystectomy include obesity (Rosen et al, 2002), elevated white blood cell count (Alponat et al, 1997; Kanaan et al, 2002), and male gender (Kanaan et al, 2002).

Other novel surgical techniques have been proposed to treat patients with acute cholecystitis, including so-called minilaparoscopic cholecystectomy (see Chapter 33), which uses 2- to 3-mm ports (Hsieh, 2003), and minicholecystectomy (Assalia et al, 1997), in which a small (mean, 5.5 cm) incision is used to remove the gallbladder. A prospective, randomized trial demonstrated that minilaparoscopic cholecystectomy resulted in decreased postoperative pain and superior cosmesis when compared with conventional laparoscopic cholecystectomy, with no significant difference in operative time, blood loss, or complications (Novitsky et al, 2005).

Laparoscopic subtotal cholecystectomy (LSC) has also been evaluated as a means of decreasing the conversion rate to open procedure in patients with acute cholecystitis (Horiuchi et al, 2008; Singhal et al, 2009). This procedure involves leaving the posterior wall of the gallbladder when it is significantly difficult to dissect from the liver bed, with cauterization of the remnant mucosa and suturing or stapling of the gallbladder neck in cases of severe inflammation of the triangle of Calot. Indeed, in the face of severe inflammatory change, such an approach is safter than risking injury to the common hepatic duct by pursuing dissection within the porta hepatis. Horiuchi and colleagues (2008) demonstrated a significant decrease in conversion rate to open procedure with the use of these techniques with no increase in postoperative complications. All patients undergoing LSC had temporary subhepatic drains placed in this study. This technique, although innovative, does not have wide clinical applicability because of limited availability of instruments, specialist surgeons trained in their use, or both. Laparoscopic cholecystectomy remains the standard therapy for definitive treatment of patients with acute cholecystitis, with conversion to an open procedure if necessary.

In patients with a high perioperative risk from sepsis or other underlying medical comorbidities, initial treatment of acute cholecystitis with percutaneous cholecystostomy tube placement is preferred (see Chapters 28 and 32). These tubes can be placed using either US or CT guidance (Hatzidakis et al, 2002). This procedure effectively decompresses the gallbladder, evacuating the infected bile and relieving the pain associated with gallbladder distension, and it is associated with a low complication rate (Akyürek et al, 2005; Byrne et al, 2003; Spira et al, 2002; Werbel et al, 1989). In addition, most patients (>80%) improve clinically within a short time (Byrne et al, 2003; Hatzidakis et al, 2002; Vauthey et al, 1993). After stabilization of the patient, and if the clinical situation otherwise warrants, delayed cholecystectomy should be performed, which often can be done laparoscopically (Spira et al, 2002). Akyürek and colleagues (2005) demonstrated decreased hospital stay and cost in high-risk patients undergoing percutaneous cholecystostomy followed by early laparoscopic cholecystectomy compared with those treated conservatively with intravenous (IV) antibiotics and bowel rest followed by delayed cholecystectomy. In high-risk patients in whom general anesthesia is contraindicated, percutaneous stone extraction has been used successfully (Gibney et al, 1987; Wong et al, 1999). More recently, single and repeated percutaneous transhepatic gallbladder aspiration has been shown to be successful in high-risk patients with acute cholecystitis who do not respond to conservative therapies (Tsutsui et al, 2007). This treatment modality is not widely practiced, however.

Timing of Surgery

The optimal interval of time between the diagnosis of acute cholecystitis and definitive treatment with cholecystectomy has been the subject of many prospective randomized trials, nine evaluating open cholecystectomy and five evaluating laparoscopic cholecystectomy (Papi et al, 2004; Siddiqui et al, 2008). The concern in operating on patients with early cholecystitis (typically defined as <3 days) is the potential for increased postoperative complications, including common bile duct injury. The risk of performing cholecystectomy late (weeks after the diagnosis of cholecystitis) is that a subset of patients have recurrent symptoms during the period between diagnosis and surgical treatment, which leads to recurrent hospital admissions and urgent surgery (Papi et al, 2004). In multiple randomized prospective trials evaluating the timing of open cholecystectomy, patients undergoing early operation experienced no increased perioperative morbidity or mortality and had a shorter length of hospital stay compared with patients undergoing delayed operation (Norrby et al, 1983; Van der Linden & Edlund, 1981). In addition, a meta-analysis of these trials demonstrated that more than 20% of patients failed medical management while awaiting definitive treatment, and approximately half of these patients required urgent surgical treatment as a result (Papi et al, 2004). In this same analysis, no increase in morbidity was seen in patients undergoing early definitive treatment with laparoscopic (P = .6) or open (P = .2) cholecystectomy compared with delayed treatment, but a clear difference was seen in length of hospital stay, with patients undergoing delayed treatment requiring a more prolonged hospitalization (Papi et al, 2004). Although it is safe to perform cholecystectomy either early or late after an episode of acute cholecystitis, patients benefit when surgery is performed early.

Performing laparoscopic cholecystectomy in patients with acute cholecystitis poses unique challenges to surgeons because of the potential for increased morbidity, including the most feared complication, common bile duct injury. The concern is that the acute inflammation may obscure the anatomy, leading to an increase in postoperative complications. Five prospective randomized trials have evaluated the outcome of patients with acute cholecystitis undergoing early versus late laparoscopic cholecystectomy (Table 31.1). Although a significant increase in operation time was experienced for those undergoing early compared with delayed cholecystecomy (P = .002), the results of these trials uniformly showed no significant difference in postoperative morbidity or mortality, including common bile duct injury, when surgery is performed early (Siddiqui et al, 2008). Additionally, no significant difference was found in the conversion rate to open cholecystectomy, although it was clearly

Table 31.1

Results of Five Prospective, Randomized Trials Comparing Early vs. Delayed Laparoscopic Cholecystectomy for Acute Cholecystitis

Reference	N	Definition	Morbidity Rate	Failure of Conservative Treatment in Delayed Group	Conversion to Open Cholecystectomy
Kolla et al, 2004	40	Early: <4 days	0%	25%	20%
		Late: 6-12 weeks		25%	15%
Johansson et al, 2003	145	Early: <7days	26%	31%	18%
		Late: 6-8 weeks		29%	10%
Chandler et al, 2000	43	Early: <3 days	32%	24%	10%
		Late: after symptom resolution		36%	9%
Lai et al, 1998	104	Early: <24 hours	16%	21%	9%
		Late: 6-8 weeks		24%	8%
Lo et al, 1998	99	Early: <3 days	20%	11%	13%
		Late: 6-8 weeks		23%	29%

higher (20% to 30%) in patients with cholecystitis compared with prior studies evaluating patients undergoing elective laparoscopic cholecystectomy in the nonacute setting. Perhaps the most important finding was that in all but one study, patients randomized to late cholecystectomy failed conservative management in 15% to 30% of cases. Although patients in the early group generally experienced a longer postoperative hospitalization ($P = .004$), most of these trials demonstrated a decrease in overall length of hospital stay in the early group versus the delayed group (cumulative $P < .001$) (Chandler et al, 2000; Johansson et al, 2003; Kolla et al, 2004; Lai et al, 1998; Lo et al, 1998). Early laparoscopic cholecystectomy is therefore the preferred surgical technique for patients with acute cholecystitis. Catena and colleagues (2009) have proposed the use of a harmonic scalpel for improved hemostasis and biliostasis in laparoscopic cholecystectomy, and preliminary data suggest it may decrease the conversion rate to open procedure in patients undergoing laparoscopic cholecystectomy for acute cholecystitis. A prospective, randomized controlled trial is underway to compare the use of harmonic versus monopolar diathermy for laparoscopic cholecystectomy (Catena et al, 2009).

The majority of trials of early versus delayed laparoscopic cholecystectomy define "early" as within 72 hours of symptom onset. A recent nonrandomized, prospective study by Tzovaras and colleagues (2006) assessed 129 patients undergoing laparoscopic cholecystectomy for acute cholecystitis during the index admission. The patients were divided into three groups regarding the timing of their surgery from symptom onset: within 3 days, between 4 and 7 days, and after 7 days. They found no significant difference in conversion rate, morbidity, or postoperative hospital stay among these groups and thus suggest that the benefits of early cholecystectomy are not limited to patients who present within 72 hours of symptom onset.

Another factor to consider is whether early or delayed laparoscopic cholecystectomy for acute cholecystitis is more cost effective. A meta-analysis of randomized and other studies performed by Lau and colleagues (2006) concluded that early surgery was more cost-effective because of reduced overall length of hospital stay and avoidance of readmissions for recurrent cholecystitis or biliary colic.

CHRONIC CHOLECYSTITIS

Pathogenesis and Clinical Manifestations

Chronic cholecystitis may result after one or more episodes of acute cholecystitis, or it may evolve, initially without symptoms, merely from the presence of gallstones. In most cases, patients describe one or more episodes of abdominal pain that is clinically consistent with biliary colic. The term *colic* is a misnomer, because the pain from chronic cholecystitis is usually constant in nature and is similar to that seen initially with acute cholecystitis, although it is self-limited and often less severe. The pain associated with chronic cholecystitis seems to be the result of intermittent obstruction of the gallbladder outflow.

There are numerous well-described risk factors for the development of gallstones and subsequent chronic cholecystitis. Patients at particularly high risk include obese women, in whom pathologic changes of chronic inflammation are found even in the absence of gallstones (Calhoun & Willbanks, 1987; Csendes et al, 2003); this may be due to an increase in the cholesterol saturation of bile in obese patients (St. George & Shaffer, 1993; see Chapter 7). These patients are often asymptomatic.

Diagnostic Imaging

US examination of the gallbladder most often reveals circumferential thickening of the gallbladder wall with cholelithiasis. In advanced cases, a small, shrunken gallbladder with a thickened wall and multiple gallstones are seen. Discomfort may be reproduced with direct pressure on the gallbladder with the US probe. Commonly, particularly in obese patients and in those with mild symptoms, the US examination shows no particular gallbladder wall abnormalities (Calhoun & Willbanks, 1987).

Treatment

Elective cholecystectomy is the treatment of choice for patients with symptoms of chronic cholecystitis. In most (≥90%) cases, cholecystectomy can be accomplished laparoscopically. Patients occasionally are seen with atypical pain (left hypochondrium) or with minimal or no pain but rather intermittent nausea or

bloating. In such cases, evaluation for other possible causes of symptoms should be undertaken, particularly if US shows gallstones, but no sequelae of chronic cholecystitis are seen.

ACUTE ACALCULOUS CHOLECYSTITIS

Pathogenesis

Acalculous cholecystitis usually occurs in patients with coexisting major illnesses, such as generalized sepsis, major trauma, or burns or in those undergoing a prolonged recovery from major operations who are unable to tolerate oral intake (Kalliafas et al, 1998). It has been speculated that in such situations, there is no stimulus of the gallbladder to contract, the bile becomes inspissated, and biliary sludge forms. The exact pathogenesis is unknown but likely involves some combination of ischemia, biliary stasis, and sepsis (Hakala et al, 1997; Warren, 1992), and inspissated bile and sludge seem to play some causative role. Although this condition traditionally has been described in the patient groups mentioned earlier, several reports suggest an increase in the de novo presentation of acalculous cholecystitis in the outpatient population, including patients with atherosclerotic vascular disease, such as seen in hypertension and diabetes (Parithivel et al, 1999; Ryu et al, 2003; Savoca et al, 1990). Overall, acalculous cholecystitis represents approximately 5% to 15% of all cases of acute cholecystitis. A male predominance is seen in cases of acalculous cholecystitis, in contrast to acute calculous cholecystitis, which occurs most often in women (Kalliafas et al, 1998; Ryu et al, 2003; Wang et al, 2003).

A prospective study evaluating trauma patients with serial US examinations found that the incidence of acalculous cholecystitis in severely injured patients (injury severity score ≥12, requiring intensive care for >4 days) was 11% (Pelinka et al, 2003), which is similar to other reports (Imhof et al, 1992). In addition, three factors were correlated with an increased risk of developing acalculous cholecystitis in this high-risk population: 1) high injury severity score, 2) increased heart rate, and 3) transfusion requirement at the time of admission. This study suggests that more acutely injured patients, who are expected to require prolonged ventilatory and nutritional support, are at higher risk for the development of acalculous cholecystitis (Pelinka et al, 2003).

Clinical Manifestations

Part of the difficulty in making the diagnosis of acalculous cholecystitis is that many patients presenting with this condition are critically ill and require ventilatory support and sedation. The symptoms and signs are often masked by the patient's underlying condition or the interventions used to treat it (Kalliafas et al, 1998). In the outpatient population seen with acalculous cholecystitis, the diagnosis is more straightforward, mimicking the signs and symptoms of acute calculous cholecystitis (Ryu et al, 2003).

The most frequent physical and laboratory findings are fever, right upper quadrant pain, leukocytosis, and hyperbilirubinemia. These findings are often nonspecific, however, in the setting of sepsis and critical illness (Kalliafas et al, 1998). Incidence of gangrene and perforation seems to be increased in patients with acalculous cholecystitis compared with acute calculous cholecystitis, likely because of the delay in diagnosis that is common with this disease. Severe gallbladder complications such as gangrene, perforation, and empyema occur more commonly in older patients with an elevated white blood cell count (Ryu et al, 2003; Wang et al, 2003). In many series, the risk of severe gallbladder complications was found to be 50% to 60% (Kalliafas et al, 1998; Swayne, 1986; Wang et al, 2003). This high risk may be the result of the disturbance in capillary microcirculation that has been shown in pathologic studies on gallbladder specimens after cholecystectomy for acalculous cholecystitis (Hakala et al, 1997; Warren, 1992). In addition, partly as a result of the severity of the patient's underlying condition, the mortality rates are high—15% in some series (Wang et al, 2003).

Diagnostic Evaluation and Imaging

Imaging algorithms for patients with suspected acalculous cholecystitis are similar to algorithms for patients with acute cholecystitis. The initial imaging test is usually US, which classically reveals gallbladder distension, a thickened gallbladder wall, and biliary sludge without stones (Fig. 31.3; Wang et al, 2003). The difficulty with interpreting these findings is that many critically ill, parenteral nutrition–dependent patients have these findings. Partly because of this difficulty, the accuracy of US to diagnose acalculous cholecystitis has been highly institution dependent, with some series showing it to be highly sensitive and specific (Pelinka et al, 2003) and others showing it to be less accurate (Kalliafas et al, 1998). US is widely available and easy to use, even in acutely ill patients, because it can be performed at the bedside, and it is inexpensive. US should be performed as the initial imaging modality for suspected acalculous cholecystitis.

Evaluating the natural history of abnormalities visualized on US in acutely injured patients is problematic; a prospective trial assessed 255 severely injured trauma patients with serial US examinations. In this trial, all patients with US findings consistent with acalculous cholecystitis and major clinical symptoms—abdominal pain or distension or both, hemodynamic instability, or organ failure—underwent cholecystectomy, and all had acalculous cholecystitis on final pathology. A few patients had positive US findings, but no major clinical symptoms were observed. In this group, all US findings returned to normal within 3 weeks. In addition, 15% of patients developed hydrops of the

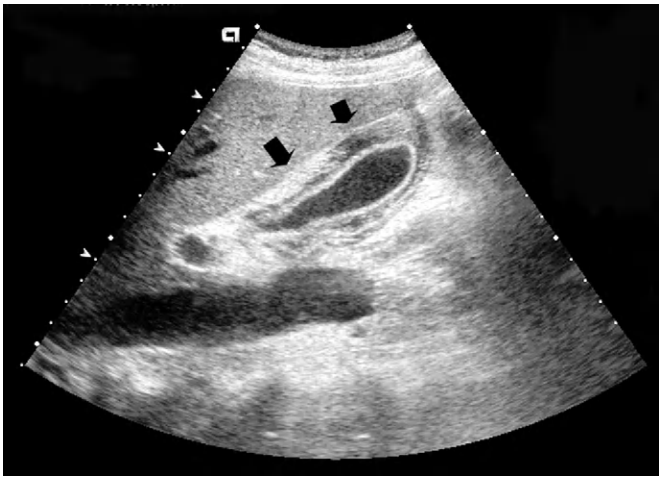


FIGURE 31.3. Ultrasound of a patient with acalculous cholecystitis reveals marked thickening of the gallbladder wall (*arrows*).

gallbladder without clinical symptoms, and subsequent normalization of the US was observed in all (Pelinka et al, 2003). These findings suggest that although many critically ill patients may develop US abnormalities consistent with acalculous cholecystitis, the combination of clinical symptoms and positive imaging findings will identify most patients who require intervention.

Because of the difficulty establishing a diagnosis in these critically ill patients, CT has been used as an additional imaging test. The advantage of CT is that imaging of the entire chest, abdomen, and pelvis can be obtained; this is particularly important in this patient cohort, in whom clinical signs and symptoms may be misleading or whose signs and symptoms may result from other causes. CT may be more sensitive and specific than US (Blankenberg et al, 1991; Mirvis et al, 1986), but it has the disadvantage of requiring transport of the patient outside of the intensive care unit.

When a patient's diagnosis is questionable based on physical findings or US evaluation or both, hepatobiliary scintigraphy may be used. In past reports, a high rate of false-positive results was seen in patients with acalculous cholecystitis (Mirvis et al, 1986), but more recent evaluation of this modality has shown improved accuracy in diagnosing acalculous cholecystitis (Kalliafas et al, 1998; Ryu et al, 2003). In some series, scintigraphy has been found to be more sensitive than CT or US in diagnosing acalculous cholecystitis (Kalliafas et al, 1998; Prevot et al, 1999; Puc et al, 2002; Ryu et al, 2003). The specificity of hepatobiliary scintigraphy can be improved by administering morphine to cause constriction of the sphincter of Oddi and improve gallbladder filling. This maneuver decreases the incidence of false-positive studies and improves specificity, but it does not result in improvements in sensitivity compared with conventional scintigraphy (Cabana et al, 1995; Flancbaum et al, 1989; Kalliafas et al, 1998).

Treatment

The definitive treatment for acalculous cholecystitis is cholecystectomy, which can be performed laparoscopically in most cases. In patients who are critically ill, placement of a percutaneous cholecystostomy tube allows for decompression of the gallbladder and drainage of contained, infected bile; this allows time for the patient to recover from the acute illness before considering proceeding with cholecystectomy (McClain et al, 1997; Akyürek et al, 2005). Percutaneous cholecystostomy may be the definitive treatment for acalculous cholecystitis, because there is no chronic obstruction of the gallbladder outlet as in acute cholecystitis (Davis et al, 1999; Vauthey et al, 1993; see Chapters 28 and 32).

COMPLICATIONS OF CHOLECYSTITIS

Gangrenous Cholecystitis

Gangrenous cholecystitis is a more common finding in diabetic patients with acute cholecystitis who present with a leukocytosis (Fagan et al, 2003). In addition, the risk of gangrenous cholecystitis is higher in patients with acalculous cholecystitis, likely owing to the delay in diagnosis that commonly occurs in this disease (Kalliafas et al, 1998; Swayne, 1986; Wang et al, 2003). As previously mentioned, the most common site for necrosis to occur is in the fundus. Full-thickness necrosis is by definition always present in patients with gangrenous cholecystitis, but this condition may or may not result in free perforation of the gallbladder. In patients with free perforation, bile-stained abdominal fluid is present.

Because these patients are generally ill, imaging with CT scan is often performed. Findings most specific for acute gangrenous cholecystitis on CT scan include air in the wall or lumen, intraluminal membranes, an irregular wall, or pericholecystic abscess. As expected, a contrast-enhanced CT scan may show a lack of mural enhancement in patients with gangrenous cholecystitis (Bennett et al, 2002).

Empyema

In cases of empyema, the gallbladder is filled with purulent bile. This condition usually is associated with acute cholecystitis and occurs in the setting of infected bile and an obstructed cystic duct. Most patients with empyema have calculous cholecystitis, but empyema also can occur in patients with acalculous disease (Tseng et al, 2000). The clinical course can mimic that of an intraabdominal abscess from other causes, and patients are often seen initially with clinical manifestations of sepsis. Patients with gallbladder empyema require urgent cholecystectomy or percutaneous cholecystostomy, depending on the severity of illness at the time of presentation (Tseng et al, 2000). Critically ill patients may be best served by a temporary cholecystostomy tube followed by elective cholecystectomy.

Emphysematous Cholecystitis

Emphysematous cholecystitis is a rare entity that results from the presence of gas-forming bacteria in the bile. Emphysematous cholecystitis may be seen in association with acute or gangrenous cholecystitis, and it is more common in men and diabetic patients (Tellez et al, 1999). The diagnosis occasionally can be made by simple abdominal radiographs, but more often it is diagnosed on US (Fig. 31.4) or CT scan (Fig. 31.5; Bennett & Balthazar, 2003; Gill et al, 1997; Konno et al, 2002). Patients should receive intravenous antibiotics to include coverage for *Clostridium* species, followed by emergent cholecystectomy.

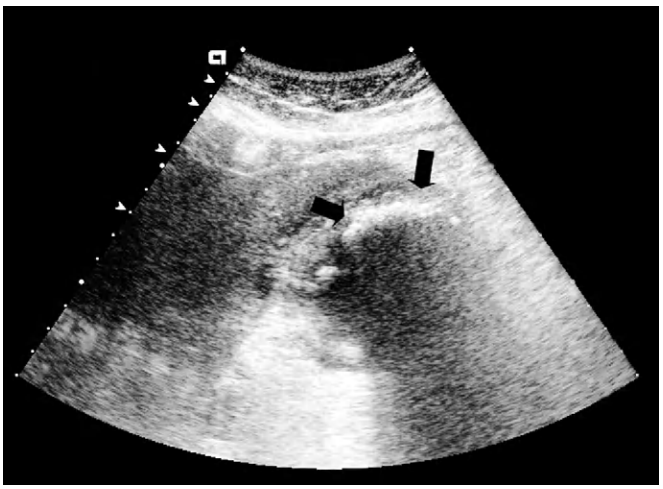


FIGURE 31.4. Ultrasound of the gallbladder revealing air within the gallbladder (*arrows*) consistent with emphysematous cholecystitis.



FIGURE 31.5. CT scan (noncontrast) in a patient with emphysematous cholecystitis showing gallbladder filled with air.

Mirizzi Syndrome

Mirizzi syndrome is defined as biliary obstruction secondary to cholecystitis. It occurs in 0.3% to 3% of patients undergoing cholecystectomy (Lai & Lau, 2006). An impacted stone in the gallbladder infundibulum or cystic duct can compress the bile duct, usually at the level of the common hepatic duct (type I), or a stone can erode from the gallbladder or cystic duct into the common hepatic duct, resulting in a cholecystocholedochal fistula (type II). Patients are seen with symptoms of acute cholecystitis but with the additional finding of hyperbilirubinemia and elevated alkaline phosphatase. A laparoscopic approach to this condition has been shown to result in high conversion and complication rates and is not recommended (Lai & Lau, 2006; Antoniou et al, 2009). Open cholecystectomy is the gold standard for treatment when this condition is identified preoperatively. If inflammation has obliterated the triangle of Calot, a partial cholecystectomy with removal of any stones may be all that is possible and usually resolves the condition. In the acute setting, the biliary obstruction often resolves after cholecystectomy and resolution of the inflammatory process. In some cases, however, the chronic inflammation leads to fistulation from the gallbladder to the bile duct, or a biliary stricture results, both of which will complicate the operative procedure and may require biliary reconstruction (see Chapters 42A and 42B).

Cholecystoenteric Fistula

Cholecystoenteric fistula, or perforation of the gallbladder into an adjacent hollow organ, is a rare complication of acute cholecystitis. The duodenum and the transverse colon are the most common sites of fistulation, which results in decompression of the gallbladder and may result in brief symptomatic improvement. This complication occurs most frequently in women in their sixth to seventh decades and has been shown to be associated with Mirizzi syndrome or an additional hepatobiliary abnormality such as gallbladder cancer (Beltran et al, 2008; Chowbey et al, 2006; Costi et al, 2009). Contamination of the biliary tree by enteric organisms may result, and patients may be seen with cholangitis and pneumobilia. Approximately 10% to 15% of patients with cholecystoenteric fistulae will pass gallstones into the small intestine and be seen with small bowel obstruction, termed *gallstone ileus.* In patients with cholecystocolonic fistula, chronic diarrhea is the most common presenting symptom in nonemergent cases (Costi et al, 2009).

Patients with cholecystoenteric fistula require cholecystectomy with takedown and closure of the fistula. When cholecystoenteric fistula is encountered at the time of surgery, concomitant Mirizzi syndrome should be considered. Patients with gallstone ileus require removal of the obstructing stone via enterotomy (Chowbey et al, 2006), and it is important to perform a thorough examination of the bowel for any other stones. Fistula takedown and cholecystectomy can be performed at the same procedure or at a second, delayed procedure if the patient is too unstable to tolerate a prolonged initial operation, or if the pericholecystic inflammation is so severe as to make initial cholecystectomy unsafe.

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CHAPTER 32

Percutaneous approaches to the treatment of gallbladder disease

Christoph D. Becker and Sylvain Terraz

IMAGE-GUIDED INTERVENTION

Image-guided interventional techniques have been developed to provide minimally invasive treatment of gallbladder disease (see Chapters 28 and 31). Percutaneous, image-guided cholecystostomy is now an accepted method to decompress the acutely inflamed gallbladder if surgery is not indicated. Various methods aiming at elective, nonsurgical removal of gallbladder stones were introduced in the early 1990s, including extracorporeal shock-wave lithotripsy (ESWL), contact dissolution of gallstones with methyl tert-butyl ether (MTBE), and percutaneous mechanical cholecystolithotomy. As a result of the successful introduction of laparoscopic cholecystectomy (see Chapter 34), surgical treatment of cholecystolithiasis has become less invasive, and definitive treatment of cholecystolithiasis may be accomplished with much shorter hospitalization. Because none of the existing nonsurgical techniques of gallstone removal can prevent recurrent gallstone formation, the indication to perform percutaneous gallstone removal without surgery is now very limited. This chapter gives an overview of image-guided treatment methods for gallbladder disease.

PERCUTANEOUS CHOLECYSTOSTOMY FOR ACUTE CHOLECYSTITIS

Surgical cholecystostomy (see Chapters 28 and 31) has long been used to provide external decompression of the acutely inflamed gallbladder in patients who are at high risk for operation or general anesthesia, such as those with sepsis, diabetes, or severe cardiac, pulmonary, hepatic, or renal failure. Percutaneous cholecystostomy was initially developed to provide a minimally invasive method of gallbladder decompression in elderly and very ill patients with acute acalculous or calculous cholecystitis or with gallbladder hydrops secondary to malignant disease (Elyaderani & Gabriele, 1979; Pearse et al, 1984). Percutaneous cholecystostomy also has been used to treat complications of cholecystitis (e.g., gallbladder perforation, empyema, or pericholecystic abscesses) or as an alternative to percutaneous transhepatic drainage of the bile ducts in obstructive jaundice. More recently, percutaneous cholecystostomy has been used to provide access to the gallbladder for elective gallstone treatment with stone dissolution techniques, percutaneous cholecystolithotomy, or other techniques.

The percutaneous access route to the gallbladder usually is determined with ultrasound (US) and is based on the individual anatomic situation. Computed tomography (CT) can be used if US does not provide sufficient information. Most authors favor the transhepatic approach to the gallbladder, because a puncture through the attached portion of the gallbladder should reduce the risk of bile leakage into the peritoneal cavity (Fig. 32.1). The area of attachment cannot be anticipated reliably with imaging techniques, and the direct, transperitoneal route also has been used successfully (Vogelzang & Nemcek, 1988). The acutely inflamed gallbladder is usually distended and immediately adjacent to the anterior abdominal wall, and the direct approach through the gallbladder fundus avoids the trauma to the liver that may be associated with percutaneous gallstone removal at a later date. The use of a removable percutaneous anchor was proposed to prevent the gallbladder wall from moving away from the trocar or from the catheter during exchange over a guidewire (Cope et al, 1990).

The initial gallbladder puncture is performed under local anesthesia, and prophylactic administration of atropine has been recommended to prevent vasovagal reactions (vanSonnenberg et al, 1984). With portable US equipment, the percutaneous cholecystostomy procedure can be performed at the patient's bedside (e.g., in the intensive care unit). If there is doubt regarding a safe access route, however, it may be preferable to combine US or CT with fluoroscopy (Fig. 32.2). Several suitable needle/catheter or needle/guidewire systems are available, and the optimal method of catheter introduction is a matter of personal preference. Repeat punctures with introducer needles should be avoided, because leakage of gallbladder content through the puncture channel may lead to internal decompression of the gallbladder into the peritoneal cavity and prevent further attempts to enter the gallbladder lumen. A catheter size of 6.5 to 7 Fr is usually sufficient to provide effective external gallbladder drainage, but 8 Fr or more may be necessary to drain gallbladder empyema or pericholecystic abscesses (Fig. 32.3; vanSonnenberg et al, 1991). If percutaneous cholecystostomy is done for acute cholecystitis, catheter manipulations should be kept to a minimum to avoid inadvertent perforation of the frail inflamed gallbladder wall or leakage of gallbladder contents alongside the catheter. To prevent inadvertent dislodgment of the catheter on the ward, it is preferable to use a self-retaining catheter. Diagnostic cholangiography through the cholecystostomy catheter may be obtained after a few days to assess the presence of gallstones and patency of the cystic duct. It is advisable to leave the cholecystostomy catheter in place for 7 to 10 days to let a tract develop and to avoid bile leakage into the peritoneal cavity.

Although transient right upper quadrant pain is a relatively common side effect of percutaneous cholecystostomy, serious procedure-related complications are uncommon. In a review of 252 percutaneous cholecystostomies reported in the English language literature, there were 4 cases of bile peritonitis and 1 death (0.3%); other procedure-related complications included vasovagal reaction or hypotension, self-limited hemobilia, and

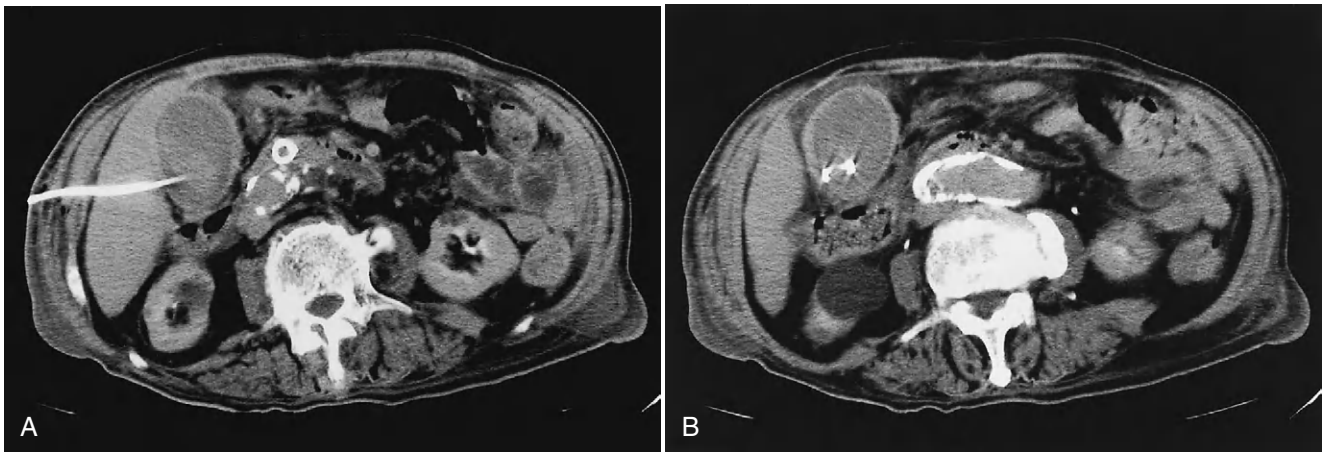
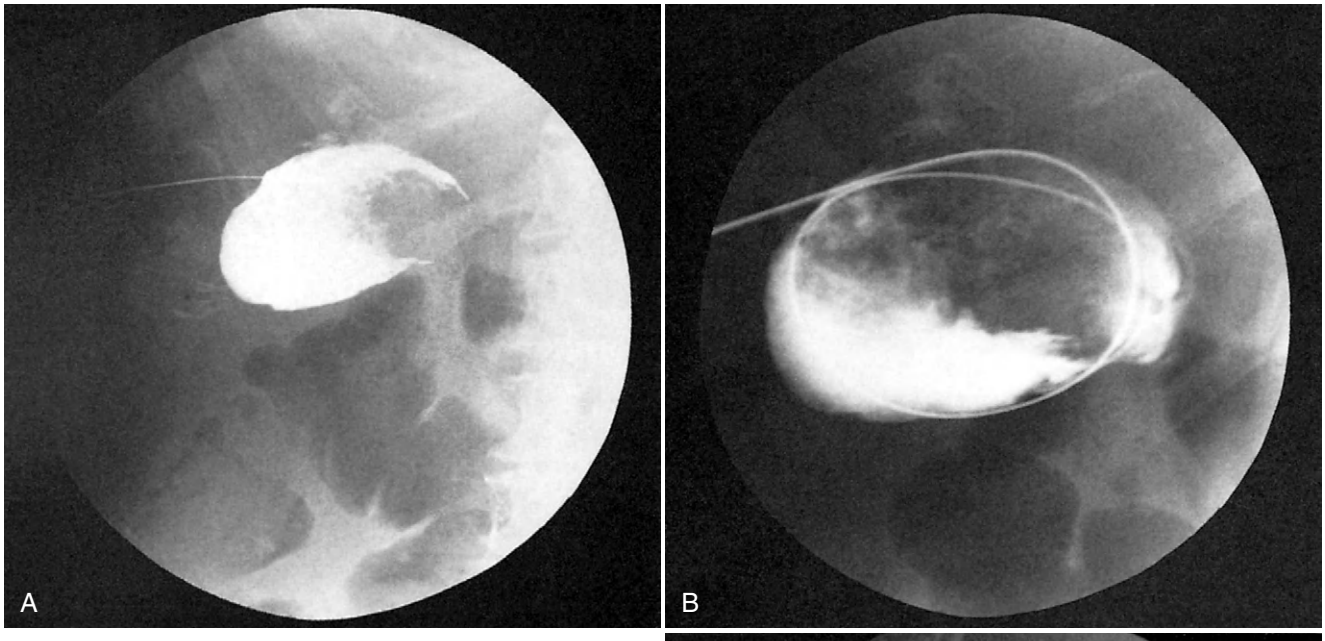


FIGURE 32.1. Percutaneous cholecystostomy for acute acalculous cholecystitis in a 74-year-old patient with recent myocardial infarction. **A,** Contrast-enhanced computed tomography (CT) for planning shows inflammation of the gallbladder wall and hyperdense content. **B,** The puncture of the gallbladder across liver parenchyma is performed with a 20-gauge needle under CT fluoroscopy. **C,** A 6-Fr pigtail drain is placed in the gallbladder using a Seldinger technique. **D,** Ten days later, the drain has been removed, and contrast-enhanced CT shows the gallbladder with decreased inflammation.



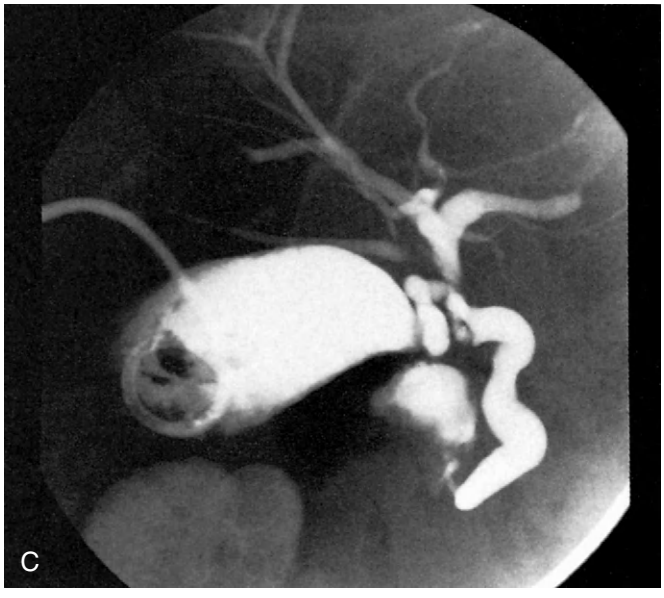


FIGURE 32.2. Percutaneous transhepatic cholecystostomy for acute acalculous hemorrhagic cholecystitis. After an initial gallbladder puncture under ultrasound guidance with a 22-gauge needle, the procedure was continued under fluoroscopic control. **A,** Direct cholecystography showed a large filling defect in the infundibulum of the gallbladder. **B,** The 22-gauge access was converted to a larger caliber, and a guidewire was introduced into the gallbladder. A 6.5-Fr self-retaining pigtail catheter was placed in the gallbladder lumen. There was no opacification of the cystic duct at the time of the initial procedure. **C,** Repeat cholangiography was done 1 week after emergency cholecystostomy. The cystic duct was patent, and there was unimpeded flow of contrast material into the duodenum. Most of the debris within the gallbladder had disappeared. The cholecystostomy catheter was removed 1 week after cholecystostomy; elective cholecystectomy was not required.

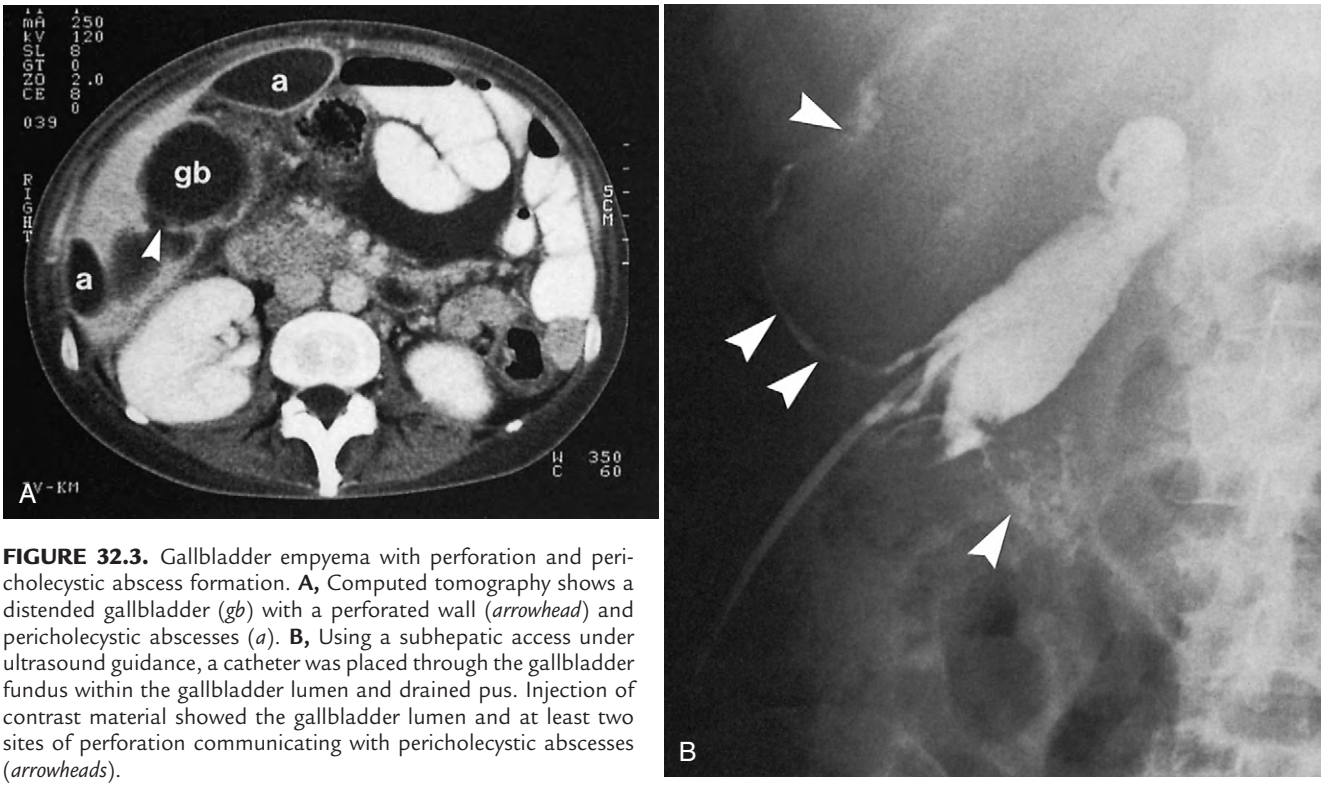


FIGURE 32.3. Gallbladder empyema with perforation and pericholecystic abscess formation. **A,** Computed tomography shows a distended gallbladder (*gb*) with a perforated wall (*arrowhead*) and pericholecystic abscesses (*a*). **B,** Using a subhepatic access under ultrasound guidance, a catheter was placed through the gallbladder fundus within the gallbladder lumen and drained pus. Injection of contrast material showed the gallbladder lumen and at least two sites of perforation communicating with pericholecystic abscesses (*arrowheads*).

acute cholecystitis secondary to an impacted stone in the cystic duct (Teplick, 1989). In a series of 127 patients undergoing gallbladder puncture and cholecystostomy, the reported rate of minor and major complications was 3.9% and 8.7%, respectively. The 30-day mortality rate of that series was 3.1%, but all deaths were due to underlying diseases (vanSonnenberg et al, 1992).

In view of the severely compromised health of most patients undergoing the procedure, percutaneous cholecystostomy is relatively safe. The efficacy of percutaneous cholecystostomy is difficult to determine, because the diagnosis of acute cholecystitis is often unreliable in patients with multiple concomitant medical and surgical problems (McGahan & Lindfors, 1988, 1989). If the indication for percutaneous cholecystostomy is restricted to patients with clinical or imaging findings of acute cholecystitis, a response rate of 90% can be expected (van Overhagen et al, 1996). If patients with unexplained abdominal sepsis are included, the response rate is lower (Boland et al, 1994; Lee et al, 1991; McGahan & Lindfors, 1989). In patients with acute acalculous cholecystitis, interval cholecystectomy may be unnecessary, and percutaneous cholecystostomy may be a definitive therapy (Vauthey et al, 1992). A randomized, controlled trial showed that percutaneous cholecystostomy and drainage is significantly more effective than simple gallbadder aspiration (Ito et al, 2004). Results of retrospective clinical studies on percutaneous cholecystostomy are summarized in Table 32.1. Current experience indicates that percutaneous cholecystostomy is an effective temporizing measure in elderly or critically ill patients with acute cholecystitis and a safe alternative to emergency surgery (Chok et al, 2010). Recently, this has been recognized by a surgical consensus conference (Miura et al, 2007). In clinical situations that warrant, interval cholecystectomy can be performed on an elective basis.

NONSURGICAL TECHNIQUES TO REMOVE GALLBLADDER STONES

Percutaneous Gallstone Removal via Cholecystostomy

Percutaneous Contact Dissolution of Gallbladder Stones with Methyl Tert-Butyl Ether

MTBE is the most potent cholesterol solvent available. Because of its boiling point of 55.2° C, it remains liquid at body temperature and is easier to handle than diethyl ether. Direct instillation of MTBE through a small percutaneous cholecystostomy catheter has been used successfully to dissolve cholesterol stones of the gallbladder within hours (Allen, 1985). Most treatments with MTBE have been done on an elective basis in patients who had an increased risk of surgery or anesthesia because of coexisting medical conditions or who refused to undergo surgery for other reasons (Hellstern et al, 1990; Thistle et al, 1989). The selection criteria for MTBE therapy includes symptomatic uncomplicated gallstone disease, uncalcified gallstones on CT, and normal hepatic laboratory test results.

The use of MTBE requires several precautions. Because of its unpleasant odor, inflammability, and anesthetic effect, MTBE must be used in a well-ventilated room. Catheters, syringes, and stopcocks must be made of special materials, such as Teflon, polyethylene, glass, and metal. After percutaneous cholecystostomy, a 5-Fr pigtail catheter is positioned within the gallbladder under fluoroscopic control so as to provide close contact with the gallstones to be dissolved. The gallbladder overflow volume is assessed by contrast injection into the gallbladder. A similar volume of MTBE is instilled and aspirated in continuous cycles (Fig. 32.4). Depending on the stone volume,

Table 32.1

Retrospective Results of Percutaneous Cholecystostomy in Acute Cholecystitis

Study	No. Patients	Calculous vs. Acalculous	US vs. CT	Technical Success (%)	Clinical Success* (%)	Long-Term Success† (%)	Procedure-Related Mortality (%)	Complications (%)	Comments
Chok KS et al, 2010	23	23/0	23/0	100	87	38	4.2	4.2	1 death from hemoperitoneum
Leveau P et al, 2008	35	23/12	24/11	97	76	65	0	2.9	1 bile duct leakage
Bakkaloglu et al, 2006	27	2/25	27/0	100	89	70	0	3.7	1 hepatic bleeding
Byrne et al, 2003	45	31/14	45/0	100	78	24	0	2.2	1 hemoperitoneum
Spira et al, 2002	55	?	24/31	98	96	?	0	1.8	1 bleeding liver laceration
Patel et al, 2000	53	18/35	?	100	83	15	0	0	—
Borzellino et al, 1999	84	53/31	84/0	96	100	?	0	2.4	1 bile duct leakage, 1 intracholecystic hemorrhage
Sugiyama et al, 1998	38	25/13	38/0	100	95	58	0	2.6	1 catheter self-removal
Hamy et al, 1997	41	29/12	41/0	?	?	63	0	2.4	1 intracholecystic hemorrhage
Melin et al, 1996	22	10/11	?	100	81	64	0	4.5	1 bile peritonitis
Lo et al, 1995	58	28/30	58/0	100	93	43	0	1.7	?

*Clinical improvement
†No symptom, no tube, no surgery
CT, computed tomography; US, ultrasound

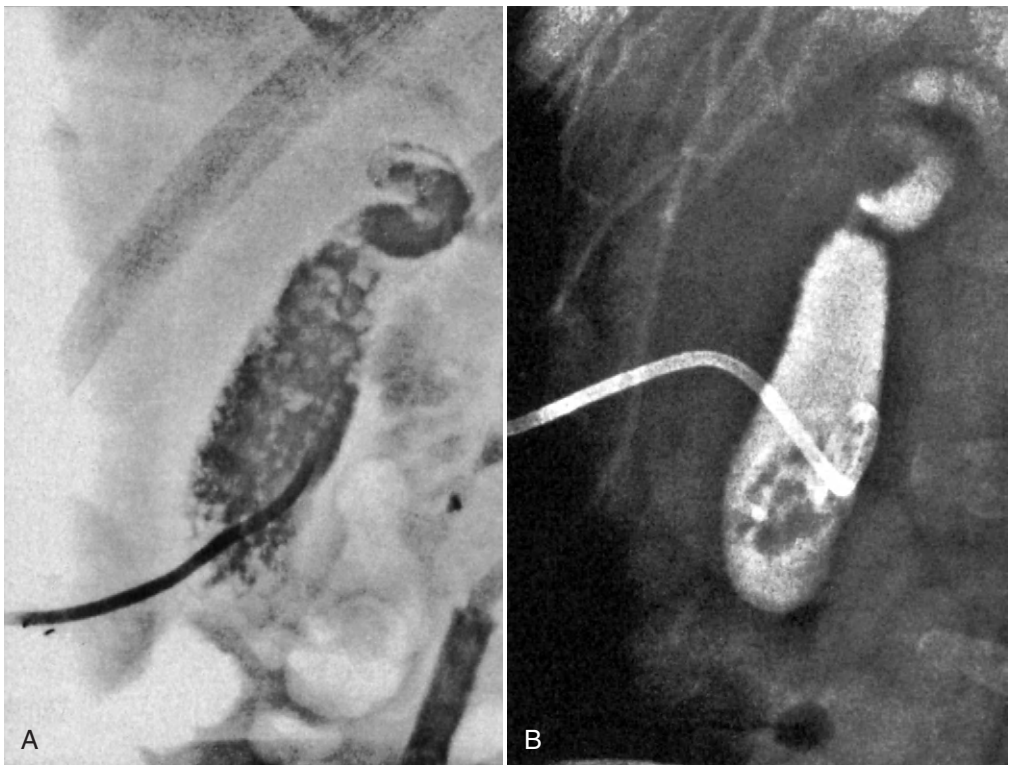


FIGURE 32.4. Percutaneous dissolution of cholesterol gallstones with methyl tert-butyl ether (MTBE). **A,** Direct cholangiography obtained through a cholecystostomy catheter showed multiple small calculi in the gallbladder lumen. **B,** After a few hours of MTBE dissolution treatment, the stone volume had diminished considerably.

complete dissolution is usually accomplished during a hospitalization of 2 to 3 days with several hours of treatment each day.

Minor side effects include nausea, vomiting, or a burning sensation in the right upper abdomen, which may be due to the drug itself, to minor leakage of bile alongside the catheter, or to catheter manipulations within the gallbladder. Serious complications, such as major bile leakage, hemobilia, or stone impaction in the cystic duct or common bile duct, are uncommon. The success rate of MTBE dissolution treatment has been reported to be 96%, although residual debris was still visible on US in many patients at the time of discharge (Hellstern et al, 1990; Thistle, 1991; Thistle et al, 1989). In the era of laparoscopic cholecystectomy, indications for MTBE dissolution treatment of gallbladder calculi are rare (see Chapter 34).

Percutaneous Cholecystolithotomy

The term *percutaneous cholecystolithotomy* is used to describe a variety of techniques to remove gallbladder stones percutaneously. In contrast to MTBE dissolution treatment, percutaneous cholecystolithotomy can be done regardless of the size, number, and composition of the calculi. A small, shrunken, thick-walled gallbladder generally is considered a contraindication to all forms of percutaneous cholecystolithotomy. The common steps of all techniques of percutaneous cholecystolithotomy are 1) percutaneous access to the gallbladder by means of percutaneous cholecystostomy; 2) immediate or sequential dilation of the cholecystostomy tract to a relatively large size, ranging from 10 to 30 Fr; 3) introduction of instruments for gallstone fragmentation and removal; and 4) external drainage of the gallbladder after the procedure (Akiyama et al, 1985; Kerlan et al, 1985).

Regardless of the technique used for tract dilation, the procedure is painful unless performed under intravenous sedation or general anesthesia. The most important risks are hemorrhage if a transhepatic access is used and bile leakage and loss of access if a subhepatic transperitoneal route is chosen. Smaller calculi can be removed with wire baskets (Cope et al, 1990). Fragmentation of larger calculi may be done with electrohydraulic, ultrasonic, or laser-mediated intracorporeal lithotripsy (Bogan et al, 1989; Burhenne, 1975; Gillams et al, 1992; Picus et al, 1989). These techniques require direct contact between the lithotripsy probes and the calculi under endoscopic vision. The *rotary gallstone lithotrite* was specially designed for percutaneous gallstone lithotripsy and enables pulverization of gallbladder calculi in a manner similar to a household blender: the device consists of a six-pronged basket surrounding a 3-mm impeller, which rotates in a 7-Fr catheter at 30,000 rpm, pulling the stones into the basket and crushing the stones into fragments smaller than 2 mm within minutes (Miller et al, 1991a, 1991b, 1991c). This technique can be performed under fluoroscopic vision and requires a percutaneous tract no larger than 10 Fr. Because the device must be able to open freely within the gallbladder, the stone volume should not exceed 75% of the volume of the gallbladder (Fig. 32.5).

The technical success rate of percutaneous cholecystolithotomy is 88% (Gillams et al, 1992). Procedure-related complications occur in 15% and include subhepatic bile collections, cholangitis, gallbladder perforation with pericholecystitis, and wound infections. Although in the early 1990s elective percutaneous cholecystolithotomy was proposed to avoid cholecystectomy in patients with symptomatic but uncomplicated cholecystolithiasis, this indication seems to be obsolete in the

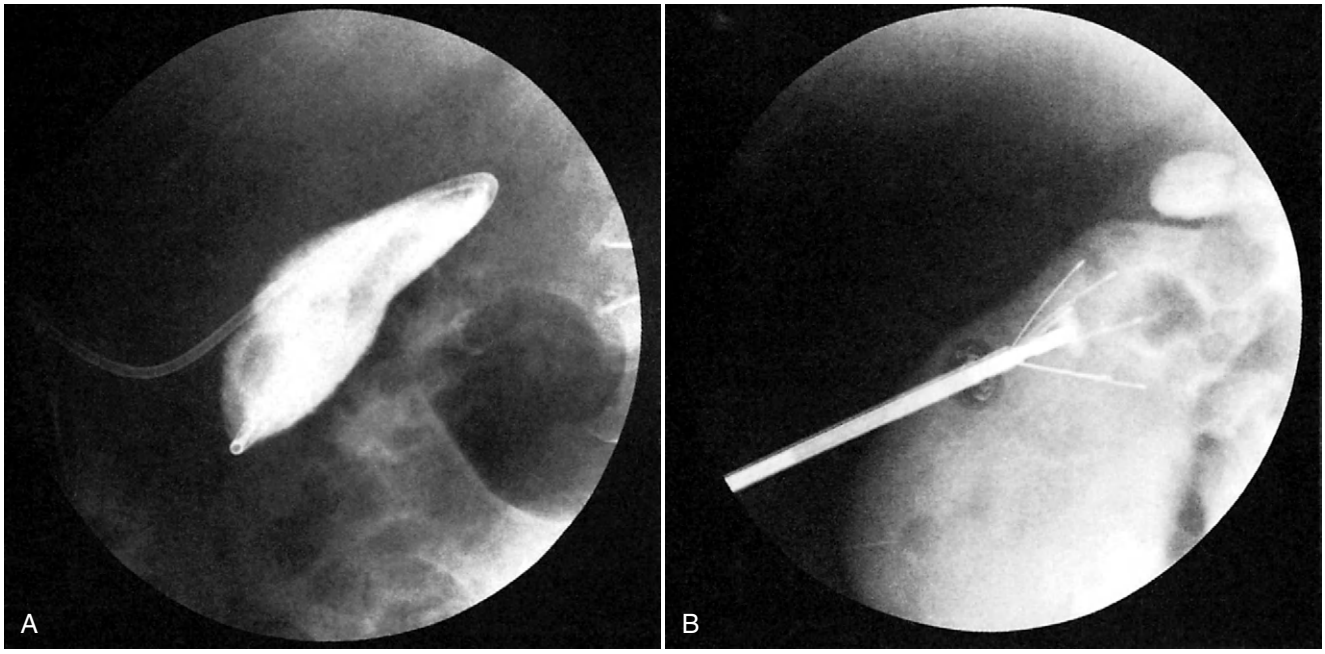


FIGURE 32.5. Percutaneous cholecystolithotomy with the rotational lithotrite. **A,** Access to the gallbladder was established by percutaneous transhepatic cholecystostomy using a right anterolateral entry into the gallbladder. The catheter entered the gallbladder wall in its distal half, and there were multiple filling defects as a result of calculi. **B,** After dilation of the percutaneous tract, the rotational lithotrite with its sheath has been introduced into the gallbladder lumen. The gallbladder was distended with dilute contrast material, and the calculi were well visualized. The struts around the propeller protected the gallbladder wall, whereas the calculi were attracted into the propeller by a vortex created within the gallbladder fluid.

era of laparoscopic cholecystectomy. Now most procedures are done on an elective basis.

Combined Surgical and Radiologic Intervention: Minicholecystostomy

The minicholecystostomy procedure was described by Burhenne and Stoller (1985) and included provision of emergency decompression of the gallbladder and the possibility of percutaneous stone removal 7 to 10 days later without the need for tract dilation. After localization of the gallbladder by US, a small abdominal incision is made over the gallbladder fundus under local anesthesia and intravenous analgesia. A 24-Fr Foley catheter is placed into the gallbladder, and the fundus of the gallbladder is sutured to the combined peritoneum and posterior layer of the rectus sheath, creating a short, wide tract. After 1 week of external gallbladder drainage, the gallstones can be removed under fluoroscopic control, usually without analgesia. Large stones can be fragmented with stone-crushing forceps and removed mechanically with a variety of instruments (Fig. 32.6).

The minicholecystostomy approach avoids the risks of hepatic hemorrhage, bile leakage, and vasovagal reactions associated with dilation of a percutaneous cholecystostomy tract, and it facilitates repeated subhepatic access to the gallbladder. The success rate of stone removal was 97% for gallbladder stones, 86% for cystic duct stones, and 63% for common bile duct stones; no serious complications and no deaths resulted (Burhenne & Stoller, 1985; Gibney et al, 1987). Given the safety and efficacy of laparoscopic cholecystectomy and percutaneous cholecystostomy, this technique is rarely indicated.

Extracorporeal Shock-Wave Lithotripsy

ESWL of gallstones was developed in the 1980s as a noninvasive form of treatment in selected patients with symptomatic, uncomplicated cholecystolithiasis (Burhenne et al, 1989; Sackmann et al, 1991; Sauerbruch et al, 1986). The original investigators and most subsequent investigators used relatively strict selection criteria, including a normal gallbladder on US, opacification of the gallbladder on oral cholecystography, and a limited number (one to three) and size (0.5 to 3 cm) of calculi. Cholestasis, pancreatitis, severe liver disease, hemorrhagic diathesis, abdominal aortic aneurysm, and pregnancy are considered contraindications, and most treatment protocols restrict ESWL treatment to calculi consisting of cholesterol, and they combine ESWL with adjuvant oral bile acid therapy. Usually two competing mechanisms lead to clearance of fragments from the gallbladder after ESWL: spontaneous passage of fragments through the cystic duct and fragment dissolution within the gallbladder by the adjuvant bile acids. ESWL alone also may lead to successful gallbladder clearance, regardless of the composition of the calculi, but a high number of shock waves and multiple treatment sessions are often needed (Fache et al, 1990; Rawat & Burhenne, 1990).

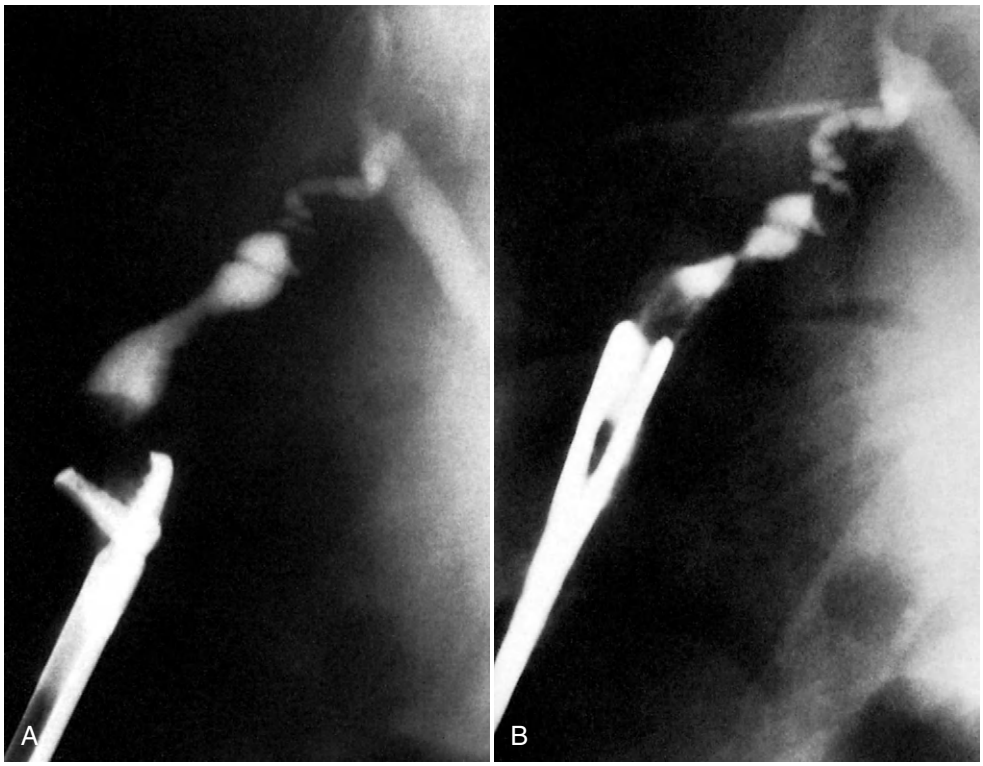


FIGURE 32.6. Mechanical cholecystolithotripsy through a subhepatic surgical minicholecystostomy. **A,** Because the gallbladder fundus had been sutured to the anterior abdominal wall at the time of emergency cholecystostomy, percutaneous tract formation was not necessary, and percutaneous gallstone removal was feasible 1 week later through a short, straight, 24-Fr percutaneous tract. The Storz stone-crushing forceps was introduced into the gallbladder, and a large calculus was fragmented. **B,** The fragments subsequently were extracted with the Mazzariello-Caprini forceps.

Three principal types of shock wave generators are available: 1) spark-gap, 2) piezoelectric, and 3) electromagnetic. The power settings and shock wave numbers may influence the result of ESWL considerably, but all three types of shock wave generators allow effective gallstone fragmentation. All devices of the current generation use water cushions with coupling membranes for transmission of the shock waves. ESWL requires no percutaneous cholecystostomy; targeting is accomplished with real-time US, and treatment can be done successfully in one or two sessions in an outpatient setting. Side effects of the treatment are minor and include cutaneous petechiae and occasional hematuria. Approximately one third of patients develop at least one attack of biliary pain attributable to fragment passage, and mild transient biliary pancreatitis is observed in approximately 2% of patients.

The rate of fragment clearance after ESWL depends on the total stone volume and on the size of the largest remaining fragment. On average, 70% of patients are stone free within 1 year, and 80% are stone free within 1.5 years after successful ESWL and adjuvant bile acid therapy (Becker et al, 1992; Ell et al, 1990; Sackmann et al, 1991). If only patients with solitary gallstones 2 cm in diameter are treated, the stone clearance rate is 80% to 90% within 6 to 18 months (Pauletzki et al, 1994; Sackmann et al, 1991). The problem of gallstone recurrence remains unresolved. Studies have shown that more than two thirds of patients develop recurrence within 6 years, and it is argued that laparoscopic cholecystectomy should be performed in the first place (Barkun et al, 1997; Borch et al, 1996; Cesmeli et al, 1999; Go et al, 1995).

Percutaneous Ablation of the Gallbladder

Despite successful gallstone removal, none of the percutaneous techniques can provide definitive cure of gallstone disease, because the abnormal, lithogenic gallbladder remains in place. It must also be considered that gallbladder-preserving treatment does not eliminate the risk of gallbladder carcinoma (So et al, 1990).

Nonsurgical ablation of the gallbladder may be defined as fibrotic obliteration of the gallbladder lumen. Ideally, the gallbladder mucosa would be eradicated completely, because this not only would eliminate the possibility of gallstone recurrence but also the long-term risk of gallbladder adenocarcinoma. Percutaneous gallbladder ablation was developed and tested experimentally and clinically to prevent gallstone recurrence by eliminating the functioning gallbladder through a cholecystostomy. A two-step approach was developed, including preliminary obliteration of the cystic duct by means of bipolar radiofrequency electrocautery and subsequent sclerotherapy of the gallbladder. Concentrated ethanol and sodium tetradecyl sulfate were used for gallbladder sclerotherapy without toxic side effects. Histologic studies in preliminary animal experiments revealed necrosis of the gallbladder wall within 2 weeks and fibrotic obliteration of the gallbladder within 8 weeks (Becker et al, 1988, 1989). The ablation procedure was tested in a group of 10 patients who, because of multiple medical risk factors, had undergone cholecystostomy instead of cholecystectomy for acute gallbladder disease (Becker et al, 1990). Although follow-up US studies gave no evidence of mucocele formation or stone recurrence, small gallbladder lumina remained visible in all patients, indicating that mucosal ablation was still incomplete. Although occasional attempts at gallbladder ablation have been reported by other investigators (van Overhagen et al, 1996), further technical improvements would be needed before wider clinical application.

SUMMARY

Percutaneous image-guided cholecystostomy offers a minimally invasive treatment of acute cholecystitis in high-risk patients. In acalculous disease, percutaneous cholecystostomy alone may be curative, unless the gallbladder wall already has become necrotic in the course of gangrenous cholecystitis. In calculous disease, interval cholecystectomy usually is required, although percutaneous gallstone removal through the cholecystostomy tract may be preferable in some cases. The indication for elective percutaneous gallstone removal by means of MTBE or percutaneous cholecystolithotomy has virtually disappeared, because the hospitalization required for these procedures is similar to that of laparoscopic cholecystectomy, and a definitive cure cannot be provided. ESWL is a noninvasive outpatient procedure and may be considered as a useful treatment option in the small group of patients who fulfill the selection criteria. Because of the relatively high recurrence rates observed in recent studies, however, laparoscopic cholecystectomy seems to be the more effective treatment.

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CHAPTER 33

Technique of cholecystectomy

Shishir K. Maithel

OVERVIEW

The indications for performing open cholecystectomy have evolved since the advent and widespread use of laparoscopic cholecystectomy (see Chapter 34). Surgeons are now trained in laparoscopy at the initiation and for the duration of their training. In fact, as the pendulum has swung so far toward performing laparoscopic cholecystectomy, it may be argued that surgeons completing their training today are not appropriately versed in the techniques of the open operation, which ironically are most useful and best applied to the difficult gallbladder that is not amenable to laparoscopic excision. Along with discussing important anatomic and clinical considerations, this chapter focuses on three main techniques for performing open cholecystectomy: 1) *retrograde*, 2) *anterograde* (fundus-down), and 3) *partial* (subtotal) cholecystectomy for difficult situations.

LAPAROSCOPIC VERSUS MINILAPAROTOMY CHOLECYSTECTOMY

Any discussion of open cholecystectomy would be incomplete without briefly reviewing the major comparative studies that have addressed the different approaches mentioned above for removing the gallbladder. A small incision, or *minilaparotomy,* has been defined by most authors as an incision less than 8 cm in length. Many prospective randomized trials have compared the two techniques. Two such early studies were published in *The Lancet* in 1992 and 1994, and both reported advantages of the laparoscopic approach over a minilaparotomy, including shorter postoperative hospital stay and a decreased postoperative convalescence (Barkun et al, 1992; McMahon et al, 1994). However, a different conclusion was reported by Majeed and colleagues in 1996; they found no difference in hospital stay or time to return to work and full activity among patients who underwent cholecystectomy by the two techniques. Subsequent comparative analysis of the costs of laparoscopic versus small-incision cholecystectomy, based on the same population included in the Majeed study, suggested that small-incision cholecystectomy was less expensive than laparoscopic cholecystectomy (Calvert et al, 2000). This pattern of conflicting results has persisted in recent studies as well, as some trials report a benefit to the laparoscopic approach, but others report no difference, depending on the outcomes measured (Ros et al, 2001; Keus et al, 2008). Nevertheless, a market demand of sorts has popularized laparoscopic cholecystectomy as the technique of choice today.

INDICATIONS FOR OPEN CHOLECYSTECTOMY

The introduction of laparoscopic cholecystectomy has significantly influenced the treatment of patients with gallstones, as evidenced by an increase of 20% to 30% in the total number of cholecystectomies performed (Schwesinger & Diehl, 1996). This increase was predominantly in patients with uncomplicated cholelithiasis and in those undergoing elective surgery (Shea et al, 1998). Although it is likely that considerations such as reduced postoperative discomfort and smaller scars have made the procedure more acceptable to patients with minor symptoms, it is worth raising caution that the indications for cholecystectomy should not be extended simply because a minimally invasive approach is available.

Cholecystectomy usually is performed for symptomatic cholelithiasis and for its related complications, such as obstructive jaundice or biliary pancreatitis. Cholecystectomy for acalculous cholecystitis, gallbladder adenoma, or suspected gallbladder carcinoma is less frequent, with the open technique more appropriate for suspected carcinoma. Asymptomatic cholelithiasis has been suggested as an indication for cholecystectomy in diabetic or immunocompromised patients, but this indication remains controversial (Schwesinger & Diehl, 1996). Postcholecystectomy pain, which has been observed in as many as 30% of cases, may be the consequence of an operation performed for symptoms unrelated to the presence of gallstones (Bodvall & Overgaard, 1967).

In a multivariate comparison of complications after laparoscopic and open cholecystectomy, the overall complication rate was found to be distinctly lower after the laparoscopic approach (Jatzko et al, 1995). This finding was confirmed, and a lower mortality rate was observed, in a population-based cohort study comparing both surgical approaches (Zacks et al, 2002). However, in the laparoscopic era, it is exceedingly important to consider patient selection and preoperative factors when comparing the two techniques in a retrospective fashion. Wolf and colleagues (2009) recently reported on a single surgeon's experience with open cholecystectomy over a 9-year period from 1997 to 2006. In this study, more than half (56%) of patients who underwent an open cholecystectomy were American Society of Anesthesiologists class III or IV compared with only 10% of those who underwent a laparoscopic procedure. Furthermore, nearly 10% of patients in the open cholecystectomy group had prior upper abdominal surgery, compared with only 1% of those in the laparoscopic group. These factors clearly

predispose to the reported increase in morbidity and mortality rates associated with open cholecystectomy today.

Open cholecystectomy increasingly is performed only in cases in which laparoscopic techniques do not allow for a safe procedure or as part of a larger procedure, such as pancreaticoduodenectomy or partial hepatectomy. The presence of severe inflammation, such as in xanthogranulomatous cholecystitis (Guzman-Valdivia, 2005), or a concern for excessive bleeding in patients with cirrhotic portal hypertension are two examples of situations in which surgeons are much more likely to use the open technique. Although two prospective studies from centers where surgeons have considerable experience performing cholecystectomy in patients with cirrhotic portal hypertension have reported the feasibility and superiority of the laparoscopic approach in these patients (Ji et al, 2005; El-Awadi et al, 2009), it is the author's opinion that most surgeons still opt for an open procedure. These difficult cases may be recognized preoperatively or during laparoscopy. It has been suggested, however, that attempts at performing a laparoscopic operation prior to converting to an open technique might increase the incidence of major complications (Wolf et al, 2009). Finally, as mentioned above, a gallbladder mass that is concerning for malignancy is usually better suited to an open procedure. Concern over intraoperative gallbladder perforation (Z'Graggen et al, 1998; Weiland et al, 2002), inadequate staging, and an incomplete resection with a laparoscopic procedure are some of the reasons to choose an open technique when carcinoma is suspected.

PREOPERATIVE ASSESSMENT

Some clinical features should alert the surgeon to possible operative difficulties. A history of repeated and prolonged attacks of right upper quadrant pain might be associated with chronic inflammation and dense adhesions or fibrous obliteration of the triangle of Calot. Liver function tests should be performed routinely before cholecystectomy. Any abnormality (i.e., elevation) of the serum bilirubin or alkaline phosphatase requires serious attention, because it may not be caused by the presence of stones in the bile duct but may be a sign of other extrahepatic biliary tract disease. Possibilities of such alternate diagnoses include Mirizzi syndrome (Chapters 35 and 42A); tumors of the gallbladder (Chapter 49), bile duct (Chapter 50B), or pancreas (Chapter 58); a choledochal cyst (Chapter 46); and sclerosing cholangitis (Chapter 41). Although patients who are submitted to cholecystectomy usually will have undergone ultrasonography, more detailed investigations should be performed if any doubt exists as to the integrity of the bile duct. Computed tomography (CT; see Chapter 16) and magnetic resonance imaging cholangiography (see Chapter 17) are the initial studies of choice. Should further diagnostic evaluation be necessary, endoscopic retrograde cholangiography (see Chapter 18) usually helps identify stones or other ductal abnormalities. Attention should be directed to any anatomic variants in the biliary system or extrahepatic vasculature that may be visualized on the above imaging modalities. A mild elevation of the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) may also signify considerable pericholecystic inflammation causing localized hepatocellular necrosis. This scenario is particularly relevant in the elderly population, in diabetic patients, and in patients who are relatively immunocompromised with a history and physical exam that is not indicative of the underlying severe inflammation.

Preoperative assessment may orient the operation toward either a laparoscopic or open technique. The results of these studies should not be used to condemn laparoscopic cholecystectomy for appropriate indications, but rather to argue for more critical preoperative evaluation of imaging studies that may alter the operative approach.

OPERATION

Two operative approaches are used to perform open cholecystectomy: 1) the *retrograde* technique, which entails initial dissection of the hilar structures of the gallbladder in the triangle of Calot, and 2) the *anterograde* or *fundus-down* technique, in which the gallbladder is first separated from the liver along the cystic plate, before the cystic duct and artery are ligated and divided. The retrograde approach was traditionally used in most cases, until the advent of laparoscopic cholecystectomy greatly altered the patient population undergoing open cholecystectomy. Now, given that open cholecystectomy is more frequently reserved for surgically difficult situations, the anterograde approach has gained popularity to avoid initial dissection in a hostile triangle of Calot. In addition, the anterograde technique has facilitated the use of small incisions.

Anatomy

A commanding knowledge of the anatomy of the bile ducts and of the possible variations is necessary to perform safe cholecystectomy, whether by a laparoscopic or open technique. Unidentified anatomic anomalies during operation may result in iatrogenic injuries to the biliary tree, so precise intraoperative identification of the anatomy is necessary before ligating or dividing any structure.

The triangle of Calot, first described in 1891, forms the basis of the anatomic dissection for performing safe cholecystectomy. As originally described, this triangle is formed by the cystic duct, common hepatic duct, and the cystic artery. A common misperception is that the superior border of this triangle is the inferior border of the liver. This, rather, is termed the *triangle of cholecystectomy,* and it has for its upper limit not the cystic artery but the inferior surface of the liver (Fig. 33.1; Rocko & Di Gioia, 1981). Routine meticulous dissection of this area will minimize iatrogenic injury and allow for safe cholecystectomy.

The normal location of the gallbladder neck and cystic duct junction is between the peritoneal surfaces within the right superior portion of the hepatoduodenal ligament. A variety of abnormalities can alter the standard anatomy or appearance of the gallbladder. A bilobar gallbladder or presence of septa usually is not relevant, as the gallbladder most often retains its normal location with respect to the liver and vital portal structures. Duplication of the gallbladder is rare and might be associated with one or two cystic ducts. Complete gallbladder agenesis is extremely rare, and the perceived absence of a gallbladder is most often associated with an intrahepatic location. In such cases, the gallbladder infundibulum is usually visualized extrahepatically. The gallbladder may be lying on the left side of a right-sided round ligament, still attached to the right side of the liver. In even rarer instances, the gallbladder has been observed attached to the left lobe of the liver, situated to the left of the round ligament (Fig. 33.2) (Fujita et al, 1998).

Variations in the junction between the cystic duct and common bile duct should be considered the rule rather than the

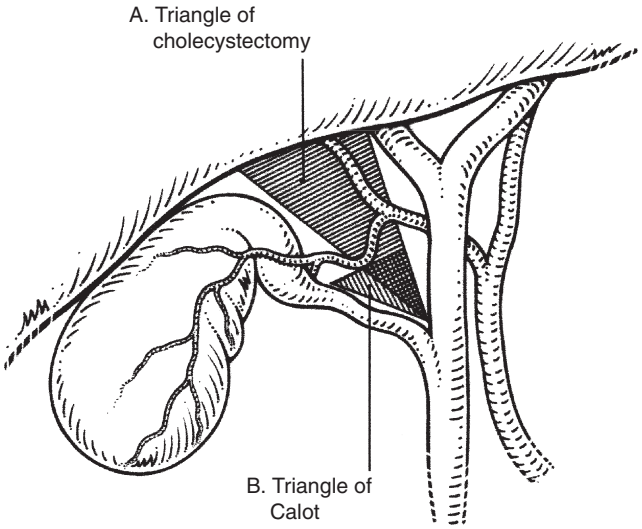


FIGURE 33.1. **A,** Triangle of cholecystectomy limited by the common hepatic duct, right hepatic duct, cystic duct, and inferior liver edge. **B,** The triangle of Calot limited by the common hepatic duct, cystic duct, and cystic artery.

exception in order to maintain a healthy respect for the anatomy and minimize iatrogenic injury during cholecystectomy (Figs. 33.3 and 33.4). The cystic duct may join the right side of the common bile duct after a long parallel course, or it may be very short and almost nonexistent. For the latter, it is imperative not to mistake the common bile duct for the cystic duct, which can lead to inadvertent ligation and division of the common bile duct. On the contrary, a perceived short cystic duct might actually be a long structure that is fused and running parallel to the common hepatic duct, or it may be draining directly into the right hepatic duct. The cystic duct also may empty into the left side of the hepatic duct, having crossed it anteriorly or posteriorly. The cystic duct occasionally may be contracted as a result of a chronic inflammatory process.

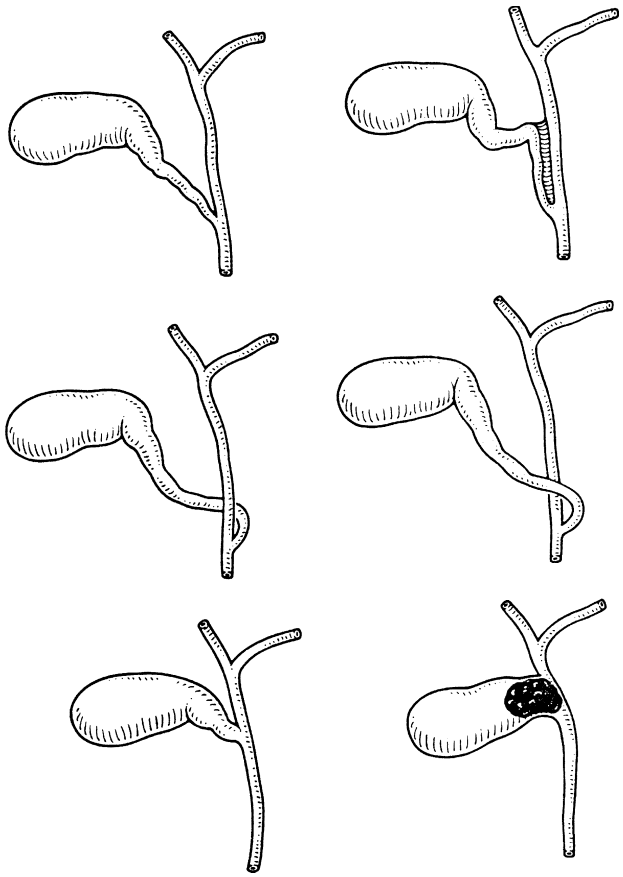


FIGURE 33.3. Variations in the confluence of the cystic duct and common hepatic duct.



FIGURE 33.2. Gallbladder located on the left side of the umbilical fissure and the ligamentum teres, attached to segment III of the liver.

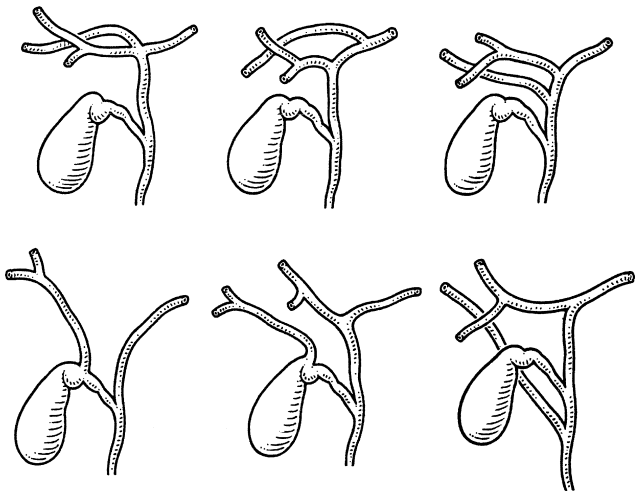


FIGURE 33.4. Variations in the confluence of the extrahepatic bile ducts and cystic duct.

An unrecognized abnormal confluence of the hepatic ducts probably represents the most important source of error leading to damage to the biliary tract during cholecystectomy (see Chapter 42A). A common anomaly that is worth noting is an early takeoff of the right posterior sectoral bile duct from the common duct either just above or below the cystic duct insertion. This sectoral duct may be confused for the cystic duct as it travels just inferior to or through the triangle of Calot. Alternatively, the cystic duct may actually arise from the right posterior sectoral duct. An abnormal confluence of the hepatic ducts has been reported in 43% of cases, and a low-lying right posterior sectoral duct has been reported in up to 20% of cases (Couinaud, 1957; Puente & Bannura, 1983; Champetier et al, 1989; see Fig. 33.4).

Although the necessity to systematically perform intraoperative cholangiography has been controversial for decades (Talamini, 2003), some surgeons have advocated the routine use of this procedure for many years. Besides showing unidentified stones or pathology in the intrahepatic or extrahepatic bile ducts, intraoperative cholangiography provides a precise view of the anatomy of the biliary ductal system. This view may help to avoid errors that result in severe biliary injury, or at least may facilitate early intraoperative detection of an injury (see Chapter 42A). In a review of 78 postcholecystectomy biliary strictures, intraoperative cholangiography was performed in only 29% (Kelley & Blumgart, 1985). Although some investigators advocate routinely performing intraoperative cholangiography in an effort to lower the incidence of iatrogenic bile duct injuries (Flum et al, 2003), its selective application still remains justified (Livingston et al, 2007).

Unrecognized abnormalities of the arterial anatomy may result in inadvertent ligation and division of the right branch of the hepatic artery. The cystic artery normally runs transversely toward the gallbladder as it branches off the right hepatic artery. The right hepatic artery travels posterior to the common hepatic duct in 80% of cases, thus an anterior location may be unexpected and predisposes it to injury, as it may be confused for the cystic artery. An accessory or replaced right hepatic artery that originates from the superior mesenteric artery is located posterolateral to the common bile duct and behind the cystic duct, where it also may be vulnerable to injury if unrecognized. Under normal circumstances, the cystic artery is a small vessel; if it appears to be unusually large, dissection must be continued to delineate the anatomy prior to dividing any structures to avoid injury to the right hepatic artery.

Technique

The retrograde technique, which involves initial dissection of the hilar structures of the gallbladder and of the cholecystectomy triangle, can be chosen when there is clear visualization of its anatomic limits. Whenever the features in this region are not clear because of acute or chronic inflammation, the anterograde or fundus-down technique is generally considered safer, because initial dissection of the gallbladder from the fundus allows progressive demonstration of the anatomy down to the infundibulocystic junction. The cystic duct may be safely ligated only when its relation with the gallbladder has been clearly delineated. Obtaining the "critical view" prior to cystic duct division as advocated by Strasberg (2002) for laparoscopic cholecystectomy is not only applicable but necessary for open cholecystectomy and to minimize iatrogenic biliary injury. The basic tenet of dissecting close to the gallbladder and clearly demonstrating every structure prior to ligation and transection should be adhered to for every procedure.

Incision

The operating surgeon usually stands to the right of the patient and has a choice of various types of incisions to gain access to the gallbladder. Three common incisions used include 1) an upper midline incision, 2) a right subcostal incision, and 3) an upper midline with right lateral extension. Depending on the clinical situation and the patient's body habitus, one incision may be preferred over the others; a right subcostal incision is most commonly performed, as it provides good, direct access to the gallbladder.

The increased emphasis on minimally invasive surgery across all surgical disciplines has resulted in a trend toward making shorter incisions. The safety of the procedure should not be compromised because of lack of exposure, especially because most open cholecystectomies are now performed for technically difficult situations. Ultrasound and axial images (computed tomography or magnetic resonance imaging) obtained preoperatively may help to localize the gallbladder and select the best incision. The minilaparotomy incisions have been described as the "minimum necessary" and "tailored to the individual patient," and their length may range from 2.5 to 10 cm (Majeed et al, 1996). When utilizing small incisions, it is important to maintain adequate exposure of the triangle of Calot in the right paramedian region, at the level of the twelfth thoracic vertebra. Exposure of the fundus of the gallbladder is less important, as it can be mobilized by traction into the operative field. To reduce abdominal wall trauma and minimize postoperative pain, small incisions should be optimized by using muscle-splitting techniques.

The *minimal-stress triangle* is located in the subxiphoid area and has for its base a horizontal line, joining the bilateral eighth costochondral cartilages, and for its vertex, the xiphoid process; the *triangle of Calot* lies within the boundaries of the minimal-stress triangle. Because the abdominal wall is less subject to tension and movement at this level during ventilatory and other movements, an incision in the minimal-stress triangle is reported to result in less operative pain (Tyagi et al, 1994).

The technique of microceliotomy described by Tyagi and colleagues (1994) uses a 3-cm transverse skin incision to the right of midline at the level of the base of the minimal stress triangle with a corresponding vertical incision of the anterior and posterior rectus sheath 1 cm lateral to the linea alba for approximately 5 cm in length extending inferiorly from the xiphoid process. This incision involves a muscle-splitting technique with lateral retraction of the rectus muscle and incision of the peritoneum through the falciform ligament. Clezy (1996) described a transverse incision situated 8 cm below the xiphoid process and to the right of midline followed by an incision of the anterior rectus sheath, medial retraction of the rectus muscle, and incision of the posterior sheath to allow access to the triangle of Calot.

The advantages of performing a cholecystectomy through a minimal incision versus a conventional one are controversial. Some prospective randomized studies have not demonstrated a clear advantage of small-incision cholecystectomy over conventional cholecystectomy after elective operations (Schmitz et al, 1997), but others have found the small incision to be associated with less postoperative pain, a shorter hospital stay, and an

earlier return to full activities after emergency cholecystectomy (Assalia et al, 1997).

Initial Assessment

Adhesions to the gallbladder may be present, especially in cases of severe cholecystitis. Such adhesions may be dense, vascular, and inflammatory, thus obscuring the anatomy. Dissection should be performed close to the gallbladder, keeping in mind that a cholecystocolic or cholecystoduodenal fistula might be present. In this case, the fistula must be divided in order to expose the gallbladder, with the opening in the colon or duodenum subsequently sutured closed or attended to in the most appropriate manner. If the gallbladder cannot be identified, one should suspect that it is scarred and contracted or that it is located within the liver parenchyma. In this instance, an intraoperative ultrasound examination may be useful. It may be feasible and safe to try to identify first the distal bile duct and trace it superiorly toward the infundibulum of the gallbladder and cystic duct junction, but this maneuver is not routinely recommended.

An abdominal exploration and manual palpation of other organs should be performed whenever possible, with special emphasis on the liver, hepatoduodenal ligament, and pancreas. The gallbladder must be palpated gently and not emptied by compression to prevent distal migration of small stones into the common bile duct.

Placement of Retractors and Optimizing Exposure

A self-retaining retractor that is fixed to the operating table is best used to provide adequate and constant body-wall retraction and spare the hand of the assistant. A fixed retractor should be placed in the right upper quadrant to provide upward and lateral retraction on the costal margin, regardless of which incision is used. For minilaparotomy incisions, however, retraction may need to be frequently altered and thus may be best suited for manual retraction. If feasible, upward retraction on segment VI and the left lateral segments of the liver facilitates exposure of the triangle of cholecystectomy (see Fig. 33.1). Care must always be taken not to compromise blood flow in the left portal pedicle with excessive or improperly placed retraction and not to tear the liver capsule. Moist laparotomy pads help to expose and isolate the operative field; pads placed behind and posterior to the right hepatic lobe serve to push the gallbladder into the wound. Perhaps the most crucial maneuver to optimize exposure is caudal retraction of the duodenum, gastric antrum, and colon. This is best accomplished with the assistant's hand or a hand-held, wide, malleable retractor or carefully applied fixed retraction to provide gentle traction on the hepatoduodenal ligament.

Emptying the Gallbladder

The dissection usually is facilitated by slight distension of the gallbladder, and thus routine aspiration of the gallbladder contents should not be performed; however, gross distension may obscure adequate exposure and inhibit the surgeon's ability to handle the gallbladder. In this circumstance, one may choose to puncture the fundus and aspirate bile, and bile culture is indicated for cholecystitis or cholangitis. Opening the gallbladder or spillage of bile should be avoided at all costs when there is a suspicion of gallbladder cancer. Spilled bile from a gallbladder containing malignant cells can result in peritoneal cavity seeding and tumor implantation, thus converting a potentially curable situation into an incurable disease.

Retrograde Cholecystectomy

A large Kelly clamp or similar instrument is placed to grasp the fundus of the gallbladder in the region of the Hartmann pouch (Fig. 33.5A), and dissection of the cholecystectomy triangle is started. The peritoneum covering the hepatoduodenal ligament is incised anteriorly across the region of the Hartmann pouch; this incision is continued posteriorly in the same way, giving complete access to the infundibulum of the gallbladder. It is important to keep the dissection close to the gallbladder and to delineate the junction between the gallbladder and the cystic duct. The lower limit of the triangle is the cystic duct, and a suture ligature is passed around it but is not tied; the slight tension produced by a clamp hanging on this ligature helps prevent migration of stones from the gallbladder into the cystic duct. The cystic artery is normally found just above the cystic duct, although a posterior location is also possible. It is important to dissect the artery toward the gallbladder to see its final distribution into the gallbladder wall (Fig. 33.5B) to prevent inadvertent ligature of an aberrant or anterior right hepatic artery. At this stage, the junction of the gallbladder infundibulum with the cystic duct and the distribution of the cystic artery into the gallbladder wall should be clearly visible. The cystic duct is palpated to detect stones, which if present should be "milked" back into the gallbladder (Fig. 33.6), and the cystic artery is ligated and transected (Fig. 33.7).

At this juncture, if a cholangiogram will be performed, a ligature or a clip is placed at the junction of the gallbladder and the cystic duct, and the cystic duct is partially opened through a small transverse incision approximately 2 to 3 mm distal. A 5-Fr catheter for cholangiography is inserted gently into the cystic duct, taking care not to tear the duct (Fig. 33.8). If easy passage is inhibited, and if the presence of a stone has been excluded by palpation, a valve or tortuous cystic duct may be the cause. It is helpful in this event to insert the end of a fine clamp into the cystic duct to dilate it gently; this often facilitates passage of the catheter. The tip of the catheter should remain in the cystic duct.

The catheter is fixed by tying the previously passed ligature around the cystic duct or by the loose application of a clip. Some catheters are equipped with an inflatable balloon that prevents the catheter from dislodging. Prior to performing cholangiography, the biliary system should be flushed with 10 to 20 mL of saline. This often allows for passage of small stones measuring less than 4 mm in diameter. All instruments and retractors are removed, and the patient is slightly rotated (20 degrees) to the right before contrast medium is injected. It is important to initially inject a small quantity (1 to 2 mL) of the contrast agent to be able to identify small stones in the bile duct. The ductal system of the biliary tract should be fully displayed, including intrahepatic ducts and free passage into the duodenum on the fluoroscopic images. Intravenous administration of 1 to 2 mg of glucagon may help to relax the sphincter of Oddi to faciliate passage of small stones. Once the biliary system is clear, the cholangiogram catheter is removed, and the cystic duct is ligated with a resorbable suture ligature; it is my preference to use a 3-0 vicryl suture (Fig. 33.9) and to place a clip to ensure biliary stasis from the cystic duct stump.

The gallbladder is dissected from its fossa with diathermy, gentle traction, or occasionally suction dissection. The dissection

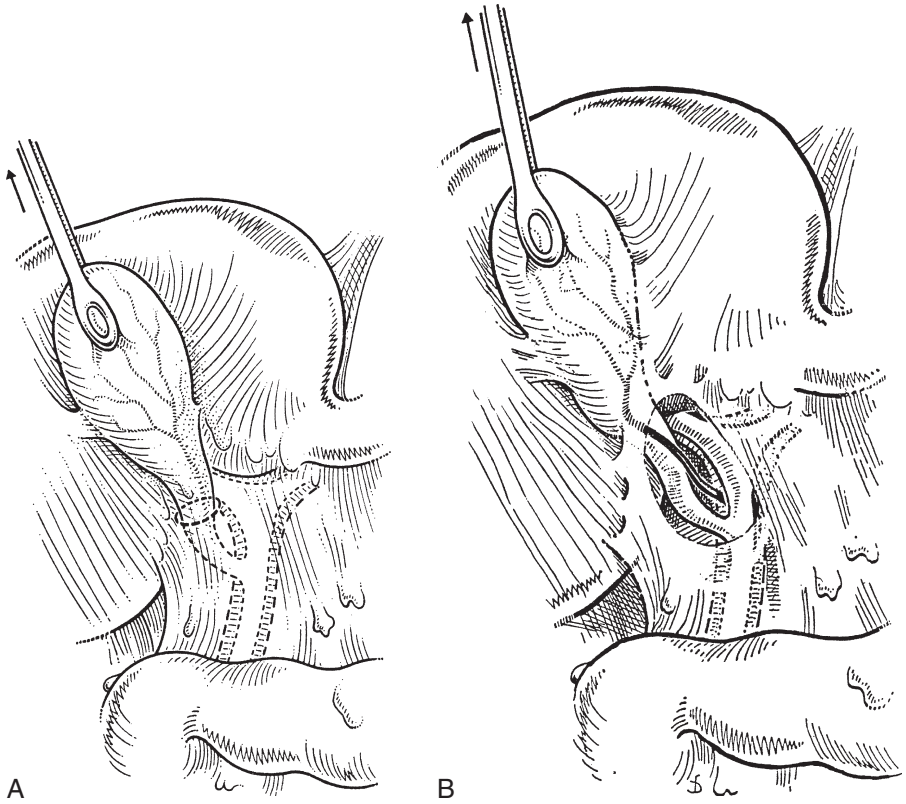


FIGURE 33.5. **A,** The gallbladder is grasped with a clamp, and dissection of the cholecystectomy triangle is started. **B,** The cystic artery is in its normal position, above the cystic duct.

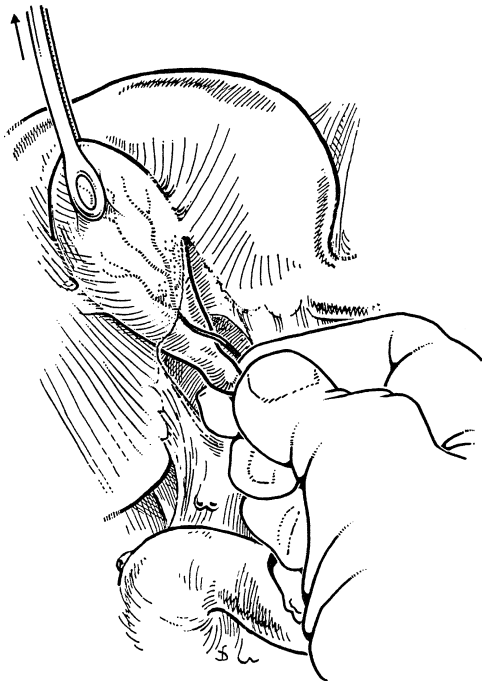


FIGURE 33.6. Palpation reveals a stone in the cystic duct, which may be "milked" back into the gallbladder.

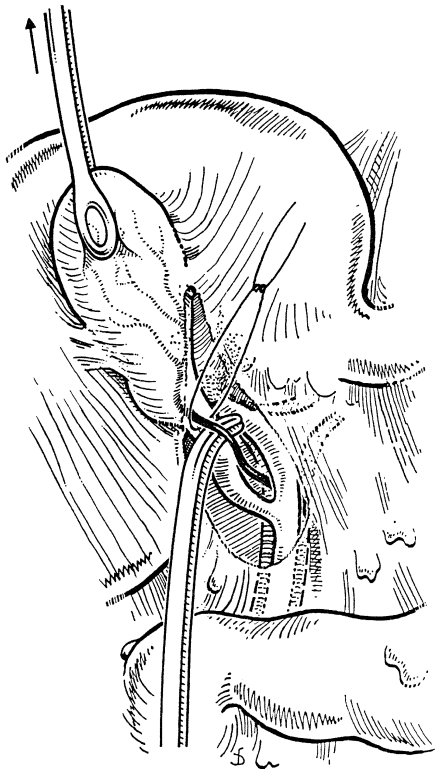


FIGURE 33.7. The cystic artery is ligated close to the gallbladder wall.

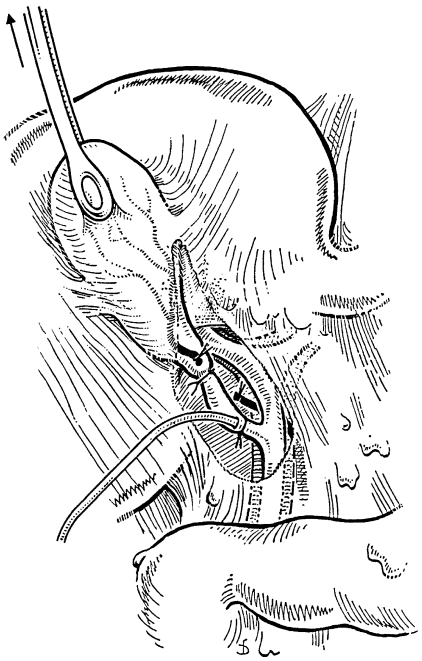


FIGURE 33.8. The cystic duct is ligated at its junction with the gallbladder, and a catheter has been inserted for intraoperative cholangiography.

should be kept close to the gallbladder and within the cystic plate to avoid damage to the liver parenchyma, which nevertheless may occur in the presence of severe inflammation. In cases of acute cholecystitis with considerable edema, this plane may be best found by sharp dissection.

Occasionally, small bile ducts may connect the gallbladder to the intrahepatic bile ducts. Transection of these so-called *ducts of Luschka* is usually without consequence, when the biliary tree

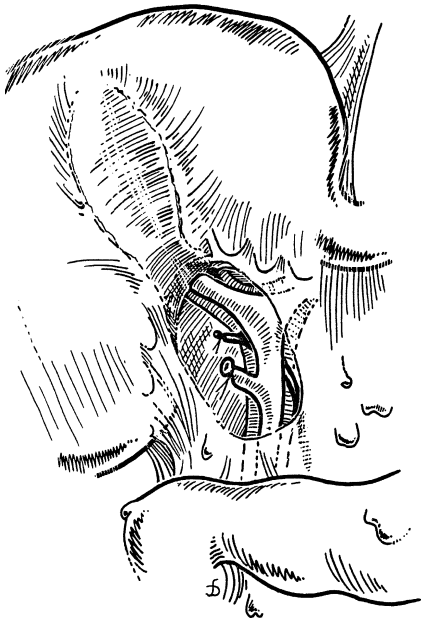


FIGURE 33.9. The catheter is removed, and the cystic duct is suture ligated.

is not obstructed distally. Hemostasis of the gallbladder fossa is obtained and, if available, the argon beam coagulator may be valuable here. If the liver parenchyma has been lacerated, however, a gauze pack should be placed in the gallbladder bed and held in place with constant pressure for at least 5 to 10 minutes. If the hemorrhage is not controlled with simple pressure, deep hemostatic sutures can be placed. Care should be taken to ensure that such sutures do not entrap major branches of the right portal pedicle, which can lie in close proximity. Formal closure of the gallbladder bed is not necessary and may even predispose to formation of a postoperative local fluid collection.

Once removed, the gallbladder should be routinely opened and assessed for the presence of tumors. The insertion of a drain before closing the abdominal wall is controversial and in most cases unnecessary. If a small bile leak is suspected or identified, insertion of a drain positioned close to the gallbladder bed usually prevents collection of bile. A small leak is without consequence and closes spontaneously within a few days if the distal bile duct is not obstructed. If only serosanguinous fluid drains during the first 48 hours, the drain can be safely removed; however, the drain should be retained if excessive oozing or leakage of bile occurs.

Anterograde, or Fundus-Down, Cholecystectomy

A large Kelly clamp or similar instrument is placed to grasp the fundus of the gallbladder, and an Adson (tonsil) clamp is used to grasp the peritoneum at the interface of the gallbladder and liver edge. An incision of the gallbladder serosa is performed 0.5 cm from the liver edge using diathermy, and a plane is developed between the serosa and the gallbladder wall to allow entry to the cystic plate. This plane is developed medially and laterally to dissect the gallbladder away from the liver. It is important to complete this dissection posterolaterally to facilitate lateral retraction of the gallbladder to best expose the cystic duct and artery. The gallbladder is still vascularized via the cystic artery (Fig. 33.10), and this structure is encountered as the medial dissection is continued toward the triangle of Calot. In the region of the infundibulum, the cystic artery is seen to enter the gallbladder wall (Fig. 33.11). After ligature and division of the cystic artery close to the gallbladder wall, thus protecting the right hepatic artery, the infundibulum is dissected free down toward its junction with the cystic duct. This technique may cause migration of stones from the gallbladder into the cystic duct, but careful palpation should identify these stones after the cystic duct has been isolated. If detected, the stones should be milked back into the gallbladder. Not more than 0.5 to 1 cm of cystic duct should be dissected to prevent injury to the common bile duct. Cholangiography and cystic duct ligature are performed in the same way as described for the retrograde technique.

Cholecystectomy Through Small Incisions

There is no fundamental difference between small-incision cholecystectomy and the techniques described above. Some authors prefer operating from the left side of the patient when a small incision is used; smaller retractors are adequate, and an additional light source (head lamp, light retractor, light suction) may be useful. The anterograde technique is the preferred approach through small incisions. The use of clips for controlling the

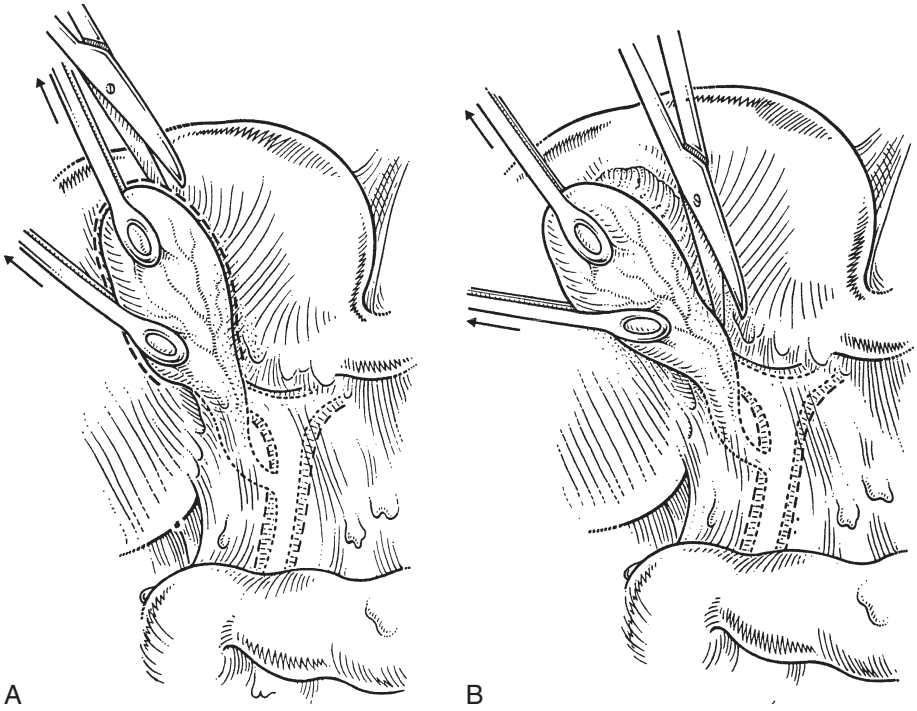


FIGURE 33.10. A, Anterograde, or fundus-down, cholecystectomy; the serosa of the gallbladder is incised 5 mm from the liver edge around the fundus. **B,** A plane is developed between the serosa of the gallbladder and the gallbladder wall, then between the liver and the gallbladder within the cystic plate.

cystic artery and the cystic duct may be safer than awkwardly tying through a small incision.

Partial Cholecystectomy

Cholecystectomy may be hazardous when only the fundus of the gallbladder can be recognized, and when the region of the infundibulum cannot be delineated because of fibrosis and inflammation obscuring the triangle of Calot (Fig. 33.12). In this case, it is often judicious to open the fundus and introduce a finger into the gallbladder to guide the dissection (Fig. 33.13A). Once the gallbladder is open, if no bile appears, the cystic duct is probably occluded by fibrosis and inflammation. If visualized, impacted stones should be removed, and care should be taken not to push any stones further into the cystic duct. If a gush of bile appears when a big impacted stone is

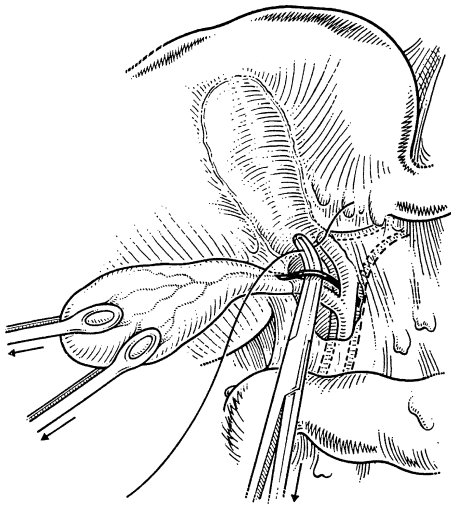


FIGURE 33.11. As the anterograde dissection progresses toward the gallbladder neck medially, the cystic artery is identified, ligated, and divided.

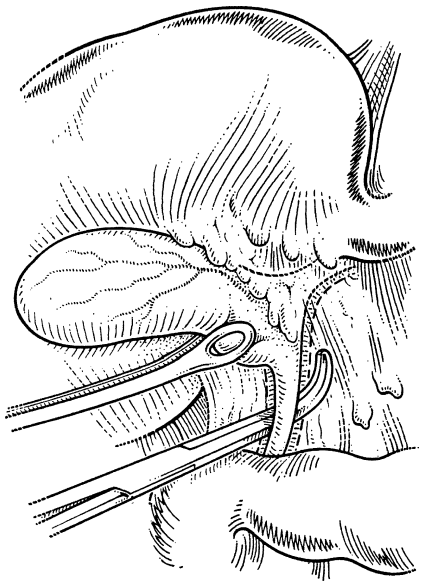


FIGURE 33.12. The common hepatic duct can be mistaken for the cystic duct when the region of the infundibulum cannot be delineated because of fibrosis and inflammation.

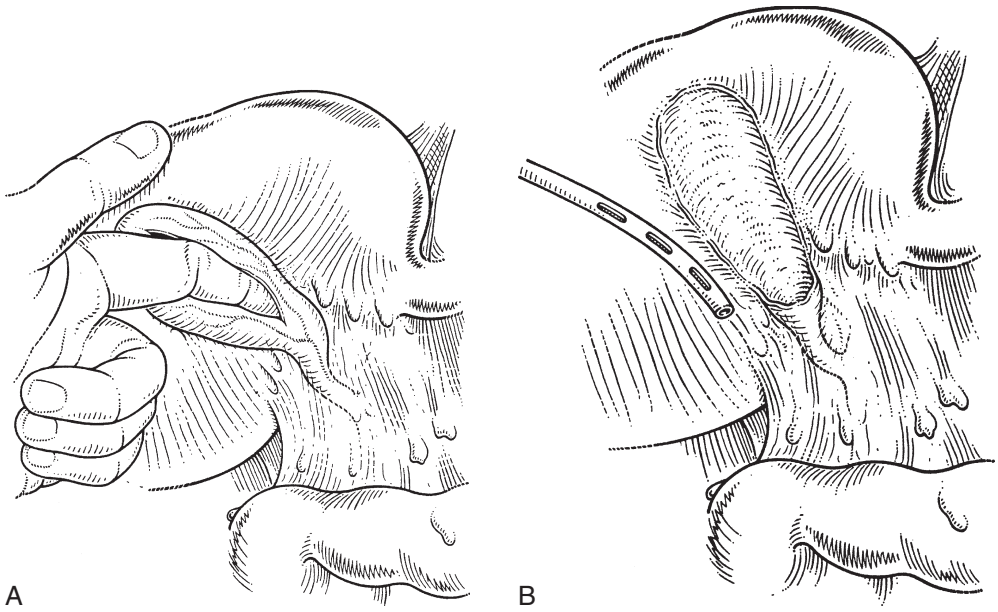


FIGURE 33.13. A, The fundus of the gallbladder has been opened, and a finger is introduced into the gallbladder for palpation. **B,** Partial cholecystectomy. The superficial part of the fundus and body of the gallbladder has been excised, leaving in place its attachment to the liver. The remaining mucosa is removed by curettage and/or fulgurated with electrocoagulation, and a closed-suction drain is placed near the infundibulum.

removed from the infundibulum, a cholecystocholedochal fistula may be present (Mirizzi syndrome type II; see Chapter 42A). In this circumstance, continued dissection to identify the cystic duct–bile duct junction risks significant biliary injury.

In cases of severe inflammation, a partial cholecystectomy may be the safest procedure (Di Carlo et al, 2009; Sharp et al, 2009). The anterior visible wall of the gallbladder is excised, but the posterior wall that contacts the liver is left in place down to the region of the infundibulum. The posterior wall mucosa may be removed by curettage, or it may be fulgurated with electrocoagulation or argon beam coagulation, although this last step is not mandatory. A closed-suction drain is placed in the region of the infundibulum (Fig. 33.13B). When the regional anatomy is severely altered by inflammation, any attempt at ligating the cystic duct may predispose to injury and can usually be safely avoided, particularly when no bile leakage is visualized. Should the anatomy favor an attempt at cystic duct closure, or when bile leakage is observed, the orifice of the cystic duct is best closed from within the gallbladder, using a purse-string or oversew technique. When a cholecystocholedochal fistula is suspected, it is advisable to keep a rim of gallbladder wall intact to allow for a subsequent cholecystoduodenostomy or a cholecystojejunostomy (see Chapters 29 and 42A). Adequate biliary drainage with closed-suction drains obviates the need for immediate definitive repair and/or reconstruction; it can be delayed, possibly even avoided, with postoperative endoscopic stenting procedures. Attempts at immediate, direct repair of the fistula are unnecessary, difficult, and potentially hazardous (Baer et al, 1990).

Partial cholecystectomy has also been advocated for patients with severe portal hypertension to prevent significant hemorrhage during dissection of the triangle of Calot (Bornman & Terblanche, 1985; Cottier et al, 1991). Bleeding from the transected wall of the remaining gallbladder is controlled with a running absorbable suture.

INTRAOPERATIVE PROBLEMS

Intraoperative problems have been related to three main causes: 1) dangerous surgical technique, 2) dangerous anatomy, and 3) dangerous pathology (Johnston, 1986; see Chapter 42A). Insufficient preoperative assessment of a complicated situation is another avoidable reason for intraoperative difficulties.

Dangerous technique arises from inadequate or imprecise application of the principles of cholecystectomy, insufficient experience, inadequate incision and exposure, or inadequate assistance (Andren-Sandberg et al, 1985). Some of the anatomic variations that have been mentioned previously are particularly dangerous, especially a narrow common bile duct, which can be mistaken for the cystic duct (see Chapter 42A).

Dangerous pathology includes chronic or acute inflammation that results in obscured anatomy and increased vascularity in the region of the cholecystectomy triangle (see Fig. 33.12). Portal hypertension is associated with increased venous collateralization, which makes the dissection hemorrhagic and dangerous. Partial cholecystectomy has been advocated in both situations (Bornman & Terblanche, 1985; Cottier et al, 1991).

Hemorrhage in the cholecystectomy triangle represents a potential danger, because attempts at hemostasis by placing clamps with obstructed and insufficient view may result in inadvertent clamping of the right or common hepatic artery or of the bile duct (Fig. 33.14). In this situation, the surgeon should first attempt to control the hemorrhage by digital compression or by clamping the hepatoduodenal ligament (Fig. 33.15) to localize its precise origin. Grasping the bleeding vessel should be done with precision so as to limit the risk of including another structure in the ligature. Cholangiography, even if already performed, may be repeated and analyzed carefully after hemostasis is achieved, because it may reveal an iatrogenic

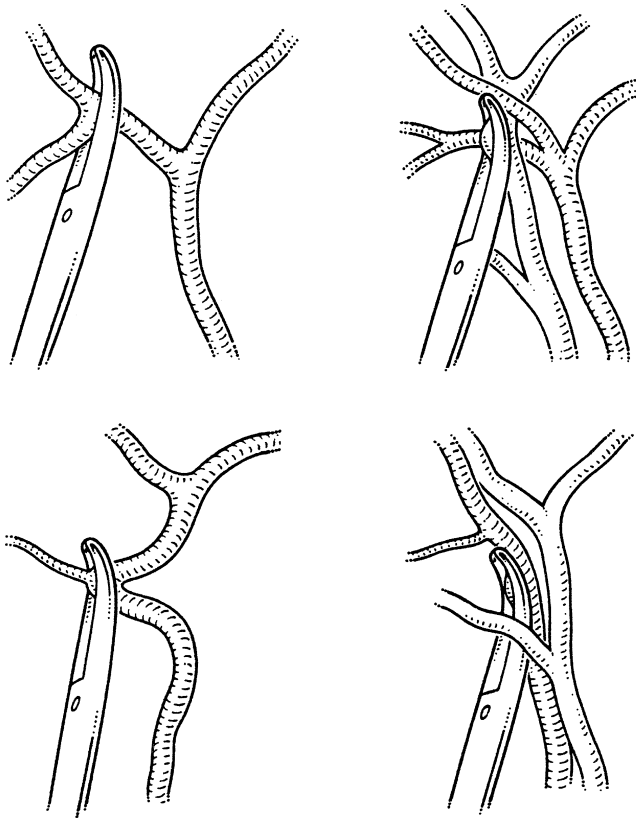


FIGURE 33.14. Blind placement of clamps for hemostasis can result in injury to the hepatic artery or bile duct.

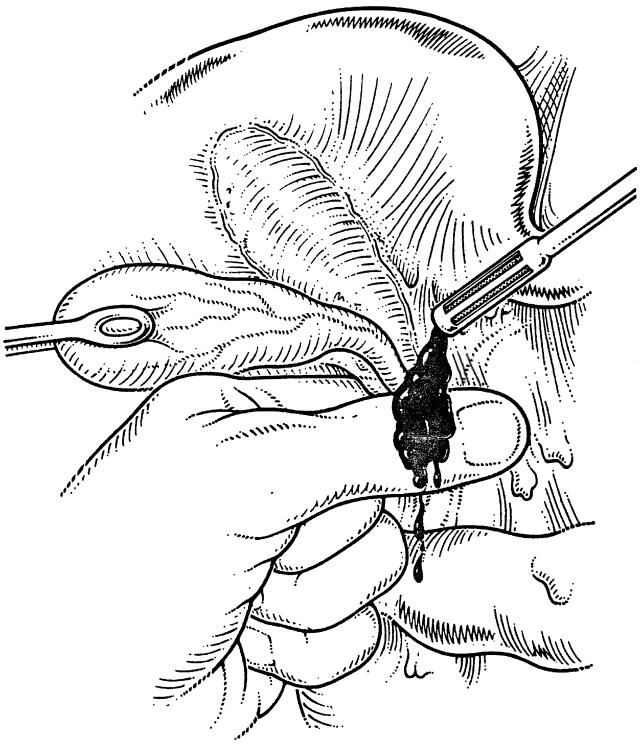


FIGURE 33.15. Hemorrhage should be controlled first by manual clamping of the hepatoduodenal ligament until exposure is optimized, thus facilitating precise hemostasis.

injury to the bile duct, such as a leak or an incomplete or complete occlusion. Methods to deal with intraoperative recognition of an iatrogenic injury of the bile duct are discussed in Chapter 42A.

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CHAPTER 34

Laparoscopic cholecystectomy and choledocholithotomy

Alexander Nagle and Nathaniel J. Soper

OVERVIEW

Gallstones are an extremely common condition, occurring in approximately 10% to 20% of the adult population. It has long been recognized that the treatment for symptomatic gallstones is cholecystectomy, one of the most commonly performed abdominal surgical procedures. In developed countries, most cholecystectomies are performed laparoscopically. To give an example, 90% of cholecystectomies in the United States are performed laparoscopically (Csikesz et al, 2009). Laparoscopic cholecystectomy is considered the gold standard for the surgical treatment of gallstone disease, because it results in less postoperative pain, better cosmesis, shorter hospital stays, and less disability when compared with open cholecystectomy (Soper et al, 1992c). The early experience with laparoscopic cholecystectomy was associated with an increased risk for common bile duct (CBD) injuries. However, through advances in education and training, this risk has been decreased. In the hands of properly trained surgeons, laparoscopic cholecystectomy can be safely performed in the majority of patients.

Over the past several years, much investigation has been done on techniques to improve outcomes from laparoscopic cholecystectomy. One approach has been to use smaller diameter ports and instruments to perform the operation (Gurusamy et al, 2010); however, the limited variety of 2 mm diameter instruments and their lack of robustness have hindered this approach. More recently, there has been an upsurge in interest in the performance of laparoscopic cholecystectomy using a single incision at the umbilicus or via natural orifice translumenal endoscopic surgery (NOTES). Up to this time, no study has definitely proven the advantage of either smaller incisions or fewer incisions compared with standard multiport laparoscopic cholecystectomy, other than the potential for improved cosmesis. This chapter discusses the history and current status of laparoscopic cholecystectomy and the laparoscopic management of CBD stones.

HISTORY

Gallbladder disease has plagued humanity since antiquity, and gallstones have been found in Egyptian mummies dating from more than 2000 years ago (Beal, 1984). Some have even conjectured that the death of Alexander the Great was caused by acute cholecystitis. Although the presence of the gallbladder was acknowledged by anatomists beginning in the fifth century, the gallbladder's true function was not elucidated until relatively recently. The potential for elective surgical treatment of gallstones was limited by the crude diagnostic techniques available, but the first successful cholecystolithotomy likely occurred in 1676, when Joenisius apparently extracted gallstones from a biliary fistula of the abdominal wall (Beal, 1984). By the eighteenth century, physicians increasingly realized that cholelithiasis could cause abdominal pain and jaundice. As surgical treatment was not considered to be feasible, numerous treatments were described, including purgatives, therapeutic bleeding, and emetics. It was not until 1867 that John S. Bobbs of Indianapolis performed an elective cholecystotomy for hydrops of the gallbladder under chloroform anesthesia (Cutter, 1928). Various other surgeons then described techniques for performing cholecystolithotomy in this era, as Listerian principles were being adopted around the world.

Carl Langenbuch of Berlin performed the first elective cholecystectomy in 1882 on a patient who had been suffering from symptomatic cholelithiasis for more than 10 years. Although the patient was found "smoking a cigar" the following day, he was not discharged from the hospital for two months. Dr. Langenbuch stated, "My opinion is that a cholecystectomy is suitable for those cases in which both the patient and physician have reached the end of their patience" (Langenbuch, 1882). The first cholecystectomy was not performed in the United States until 1886, by Justus Ohage of Minnesota. For the next 30 years, considerable debate followed at surgical meetings as to whether a cholecystolithotomy or cholecystectomy would be preferable for gallstone disease. By the 1920s it was generally accepted that cholecystectomy was most suitable, except in the face of severe inflammation, rendering the dissection hazardous to the patient.

Over the ensuing 6 decades, open cholecystectomy was the procedure of choice for patients with symptomatic cholelithiasis. Great strides were made in developing diagnostic methods for demonstrating the presence of gallstones, using either cholecystography or ultrasound (US). Throughout much of this time, many of the operations were done by family physicians not well trained in surgical techniques, and thus bile duct injuries were seen relatively frequently. In Christopher's *Textbook of Surgery* from 1936 it states, "Frank hemorrhage from the cystic artery and injury to the CBD are the two great dangers in performing cholecystectomy. Cholecystectomy will not only be easier but safer if it is begun at the cystic duct, since the circulation will be controlled at the outset." Later, other surgeons suggested that a top-down or fundus-first technique for performing cholecystectomy would be less likely to result in CBD injury. Various surgical debates included whether to perform intraoperative cholangiography on a routine or selective basis and the appropriate timing for performing cholecystectomy in the face of acute cholecystitis. Some surgeons advocated performing cholecystectomy via a small incision (minicholecystectomy) to minimize the discomfort and disability brought

about by larger incisions during gallbladder removal (Basu et al, 2006).

By the 1980s, the rates of morbidity and mortality for open cholecystectomy were quite acceptable. In published reports of large series taken from population-based studies or from single institutions, mortality rates ranged from 0.1% to 0.6%, and overall morbidity was 10% to 15% with bile duct injuries occurring in 0.1% to 0.2% of patients. It was also shown clearly that complications occurring with open cholecystectomy were directly related to the condition of both the patient and the gallbladder at the time of operation. Postoperative hospital length of stay for open cholecystectomy varies widely, but most elective cases are discharged within 4 days of operation (Hall, 1987).

Medical Therapy for Gallstone Disease

The prevailing public perception of open cholecystectomy as a procedure that results in pain, disability, and a disfiguring scar engendered many attempts in the 1980s and 1990s at nonoperative treatment of gallstones (Schoenfield & Lachin, 1981; Schoenfield et al, 1990). In addition, an understanding of the chemistry of gallstones led to numerous attempts to develop agents that could dissolve cholesterol gallstones. By the mid-1980s, ursodeoxycholic acid was made commercially available for oral administration, and its use was described in several clinical studies. Unfortunately, the indications for this agent were limited, and the 40% rate of complete gallstone dissolution in this highly selected group was disappointing (Roda et al, 1982). In the late 1980s gastroenterologists and interventional radiologists tried to increase this dissolution rate by attempting direct contact dissolution of gallstones. The biliary tree was accessed percutaneously, and methyl tert-butyl ether (MTBE) was instilled in the gallbladder. This therapy was invasive and had significant side effects, thus it was rapidly abandoned (Thistle et al, 1989).

In the early 1980s, extracorporeal shock wave lithotripsy (ESWL) was shown to be efficacious therapy for kidney stones. Others extrapolated that shock wave therapy might also break gallstones into smaller fragments that could then be more effectively dissolved. A brief flurry of interest and activity in the use of ESWL for gallstones followed, but the selection criteria limited this to fewer than 20% of gallstone patients. Despite strict selection criteria, the efficacy of treatment at 6 months was only 22%, and the gallstone recurrence rate of 10% per year for the first 5 years left much to be desired (Sackmann et al, 1990).

These disappointing results with therapies that dissolve or fragment gallstones while leaving the gallbladder in situ reinforced the concept that cholecystectomy was the only therapy that cured symptomatic cholelithiasis immediately and permanently. At the same time that the poor results of ESWL were being disseminated, a revolutionary new means of gallbladder removal was being developed.

Laparoscopic Cholecystectomy

The technique of laparoscopy (*lapara,* the flank; *skopein,* to examine) was initially developed near the outset of the twentieth century. However, until the 1960s, its use was strictly limited to diagnostic procedures within the peritoneal cavity. Gynecologists first used laparoscopic techniques to perform tubal ligation. By that time, the laparoscopic optics, light sources, and carbon dioxide insufflators had been markedly improved, but the eyes of the surgeon were wedded to the eyepiece of the laparoscope during performance of the operation. Despite this limitation, Dr. Kurt Semm of Kiehl, Germany, the father of "pelviscopy," performed the first laparoscopic appendectomy in 1980 (Semm, 1982). By 1983, Semm stated that "laparoscopic cholecystectomy and the bowel anastomosis under laparoscopic vision had moved into the domain of the possible" (Manegold, 1985). Two years later, a German surgeon named Eric Muhe working in Böblingen, West Germany, performed the first laparoscopic cholecystectomy (Litynski, 1996). He used a modified operating laparoscope placed at the umbilicus after establishing pneumoperitoneum. Muhe later changed his technique to perform cholecystectomies through a small, open tube placed in the right upper quadrant without pneumoperitoneum. Despite presenting his initial work at the congress of the German Surgical Society in 1986, Muhe's approach was rejected by German surgeons and largely forgotten. In 1987 a French surgeon, Phillipe Mouret of Lyon, France, performed laparoscopy on a woman with both gallstones and a gynecologic disorder. He performed the first video laparoscopic cholecystectomy by using a camera attached to the laparoscope, thereby allowing the entire operating team to view the operative field. As he was in private practice, few other surgeons learned of his work initially, but word spread within France. The following year both François DuBois in Paris and Jacques Perissat in Bordeaux, working in academic centers, performed laparoscopic cholecystectomy. Relatively soon thereafter, two groups of general surgeons in the southern United States performed laparoscopic cholecystectomy. They used a laser to dissect the gallbladder away from the liver bed, as it was thought that monopolar electrocautery used within the closed abdomen was potentially a hazard for combustion. The first publication of the "laparoscopic laser cholecystectomy" was published in the industry publication "Laser Practice Report" by Reddick in December 1988, whereas DuBois and colleagues published their first 36 cases (in English) in 1990.

All of these early pioneers in laparoscopic cholecystectomy used a four-port technique with the laparoscope placed at the umbilicus, albeit the French surgeons stood between the patient's legs, and the Americans worked from the patient's left side. Word of this new laparoscopic operation spread relatively rapidly after its introduction at the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) meeting in Louisville in April 1989, and the subsequent American College of Surgeons meeting in Atlanta in October 1989. Given that cholecystectomy makes up nearly a third of the work in many general surgeons' practices, surgeons in the United States feverishly attempted to learn this technique for a competitive advantage. Numerous courses sprang up across the United States and Europe. Many of these courses were sponsored by industry and provided little hands-on experience for surgeons who generally were poorly trained in basic laparoscopic techniques. It must be remembered that laparoscopy differs significantly from traditional open surgery in several important ways: 1) a satisfactory pneumoperitoneum of carbon dioxide gas must be established in the abdominal cavity; 2) the laparoscopic image of the operative field is controlled by someone other than the surgeon, and this image is highly magnified and two-dimensional; 3) the surgeon views a video screen, rather than the operative field itself; and 4) the laparoscopic ports act as a fulcrum, so the tips of the instruments move in the direction opposite the surgeon's

hands. Given these and other differences, it is not surprising that a learning curve effect was quickly recognized, whereby the incidence of bile duct injuries was much higher in a surgeon's early cases compared with later in his or her experience (Meyers & Southern Surgeons Club, 1991).

Despite the increased incidence of bile duct injury, which was not initially acknowledged, the visible evidence of diminished incision length and anecdotal reports of less postoperative pain rapidly caught the eye of the lay public. Articles appeared in newspapers and news magazines touting the advantages of "minimally invasive surgery," "minimal access surgery," and other monikers such as "belly button surgery," "laser surgery," and so on, with the result that those who required cholecystectomy demanded that the operation be performed laparoscopically.

Going from an unheard of procedure in 1988 to one that had become the subject of numerous published case series by 1992, the adoption rate of this technology in the United States was unprecedented. In 1992, the National Institutes of Health (NIH) organized a consensus development conference titled "Gallstones and Laparoscopic Cholecystectomy," which was sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases and the NIH office of Medical Applications of Research. At the conclusion of the conference, it was determined that laparoscopic cholecystectomy "provides a safe and effective treatment for patients with symptomatic cholelithiasis" and "provides distinct advantages over open cholecystectomy" but that "the outcome of laparoscopic cholecystectomy is influenced greatly by the training, experience, skill, and judgment of the surgeon performing the procedure" (Gollen et al, 1993).

It was also in 1992 that the first of several small prospective randomized trials comparing laparoscopic to open cholecystectomy was published. Each of these showed that the laparoscopic approach was associated with less pain, shorter hospitalization, and a more rapid return to full activity (Barkun et al, 1992). Coincidentally, 1992 was also the year in which a publication of a large series of laparoscopic cholecystectomies first suggested that this technique may become the new gold standard for performance of the operation (Soper et al, 1992b). By contrast, a relatively large randomized trial comparing laparoscopic with open cholecystectomy using a minilaparotomy showed no difference in many standard outcome measures (Majeed et al, 1996).

Over the ensuing years, a number of trials confirmed what had previously been shown in the open cholecystectomy literature. The aphorism "get it while it's hot" could be used to describe the preferred approach to laparoscopic cholecystectomy for acute cholecystitis: prospective randomized trials showed that early cholecystectomy resulted in fewer complications and shorter hospitalization than interval cholecystectomy (Lo et al, 1998). Intraoperative cholangiography was performed on a selective basis by the majority of practicing surgeons, despite several population-based studies showing decreased rates of bile duct injury when performed by surgeons using cholangiography routinely during laparoscopic cholecystectomy (Flumm & Massarweh, 2007). Numerous reports were published concerning the causes of bile duct injury during laparoscopic cholecystectomy and the means by which these injuries could be minimized, including dissecting "the critical view of safety" before clipping or dividing the cystic structures (Strasberg et al, 1995).

Table 34.1

Indications for Laparoscopic Cholecystectomy

Symptomatic cholelithiasis
Biliary colic
Acute cholecystitis
Asymptomatic cholelithiasis
Sickle cell disease
Total parenteral nutrition
Chronic immunosuppression
No immediate access to health care facilities (e.g., missionaries, military personnel, Peace Corps workers, relief workers)
Incidental cholecystectomy for patients undergoing laparoscopic procedure for other indications
Acalculous cholecystitis (biliary dyskinesia)
Gallstone pancreatitis
Gallbladder polyps greater than 1 cm in diameter
Porcelain gallbladder

INDICATIONS

An increase in the number of cholecystectomies performed has been documented since the introduction of laparoscopic cholecystectomy (Escarce et al, 1995; Legorreta et al, 1993; Nenner et al, 1994; Steiner et al, 1994). It is unclear whether patients are more willing to undergo a laparoscopic procedure, rather than to endure biliary colic, or whether the indications for cholecystectomy have become more liberal with the advent of laparoscopic cholecystectomy.

The indications for laparoscopic cholecystectomy are, and should be, the same as the indications for open cholecystectomy (Table 34.1). Patients generally have documented cholelithiasis and symptoms attributable to a diseased gallbladder (see Chapter 30). Biliary colic is typically a severe and episodic right upper abdominal or epigastric pain that often radiates to the back. Attacks frequently occur postprandially, or they awaken the patient from sleep. Patients with asymptomatic gallstones have less than a 20% chance of ever developing symptoms, and the risks associated with prophylactic operation outweigh the potential benefit of surgery in most patients (Fendrick et al, 1993; Ransohoff & Gracie, 1993; Ransohoff et al, 1983). Prophylactic laparoscopic cholecystectomy for asymptomatic cholelithiasis may be justified for certain patients, however, such as those with sickle cell disease, those who require long-term total parenteral nutrition, and those who are therapeutically immunosuppressed after solid organ transplantation. Patients with sickle cell disease often have hepatic or vasoocclusive crises, which can be difficult to differentiate from acute cholecystitis (Tagge et al, 1994). In transplant patients, there is concern that immunosuppression would mask the signs and symptoms of inflammation until overwhelming infection had occurred (Hull et al, 1994). Recommendations in the literature range from mandatory screening and treatment of biliary disease before transplantation (Girardet et al, 1989) to prophylactic cholecystectomy 6 months after transplantation (Boline et al, 1991) to expectant management of all asymptomatic patients (Fendrick et al, 1993; Steck et al, 1991). Other possible indications for prophylactic laparoscopic cholecystectomy include known gallstones in patients who may not have access to modern health care facilities for an extended period, such as missionaries and military personnel, and patients who already are undergoing laparoscopic abdominal surgery for other indications (incidental laparoscopic

Table 34.2

Contraindications to Laparoscopic Cholecystectomy

Absolute

Unable to tolerate general anesthesia
Refractory coagulopathy
Suspicion of carcinoma

Relative

Previous upper abdominal surgery
Cholangitis
Diffuse peritonitis
Cirrhosis or portal hypertension
Chronic obstructive pulmonary disease
Cholecystenteric fistula
Morbid obesity
Pregnancy

cholecystectomy). Less commonly, individuals without gallstones but with typical biliary symptoms (i.e., acalculous cholecystitis or biliary dyskinesia) may be considered for the procedure (Soper, 1991). Other indications for laparoscopic cholecystectomy include gallstone pancreatitis and gallbladder polyps greater than 1 cm in size (see Chapter 49).

CONTRAINDICATIONS

Absolute and relative contraindications to performing laparoscopic cholecystectomy (Table 34.2) have decreased since the 1990s, as minimally invasive surgical equipment and skills have improved. Absolute contraindications include the inability to tolerate general anesthesia or laparotomy, refractory coagulopathy, diffuse peritonitis with hemodynamic compromise, cholangitis, and potentially curable gallbladder cancer. Diffuse peritonitis with hemodyInamic compromise represents a surgical emergency in which attempted laparoscopic cholecystectomy is not prudent, because the cause of the peritonitis is unclear or uncertain. Standard open laparotomy allows rapid determination of the cause and more expeditious management of the disorder, and pneumoperitoneum may exacerbate hypotension by diminishing venous return. Suspicion of gallbladder malignancy generally mandates that standard open resection be undertaken; this is because of persistent concerns with adequacy of resection and reports of port-site metastases associated with the use of minimally invasive surgical techniques for the treatment of intraabdominal malignancies (see Chapter 49). Relative contraindications are dictated primarily by the surgeon's philosophy and experience. These include previous upper abdominal surgery with extensive adhesions, cirrhosis, portal hypertension, severe cardiopulmonary disease, morbid obesity, and pregnancy.

Previous Abdominal Surgery

Intraabdominal adhesions secondary to previous abdominal surgery can tether underlying viscera and consequently increase the risk of hollow organ injury during placement of laparoscopic trocars (Wolfe et al, 1991). Previous lower abdominal operations typically add little difficulty in performing cholecystectomy, but patients with previous *upper* abdominal operations, especially in the right upper quadrant, present much more difficulty in gaining access to the area around the gallbladder. To diminish the risk of intraperitoneal injury, we routinely use the open Hasson technique for placement of the initial trocar. Other surgeons advocate the use of the Veress needle and percutaneous insertion of the initial trocar at a site remote from the abdominal wall scars. Once the initial trocar is placed, additional trocars are placed under direct laparoscopic visualization in an area free of adhesions. Some degree of laparoscopic adhesiolysis may be necessary to allow optimal port placement. Although early series demonstrated that previous abdominal surgery with the accompanying risk of adhesions was a predictor of conversion, it is clear that laparoscopic cholecystectomy may be performed safely on most of these patients.

Cirrhosis

Cirrhosis (see Chapter 70B) results in a brittle, friable, heavy liver that may be difficult to retract in the cephalad direction, limiting exposure of the porta hepatis and gallbladder. Cirrhosis also may be accompanied by decreased synthetic function of the liver, resulting in coagulopathy and portal hypertension. Coagulopathies should be reversed before performance of laparoscopic cholecystectomy.

The ability to achieve effective hemostasis laparoscopically is significantly compromised compared with that of open exposure. Portal hypertension and aberrant portosystemic venous collateralization may lead to exsanguinating hemorrhage from small veins in the liver bed and porta hepatis or from large veins in the abdominal wall (e.g., a recanalized umbilical vein) at risk for laceration during trocar puncture. Laparoscopic cholecystectomy may be attempted with care in these patients by experienced surgeons. Various hemostatic agents and energy sources need to be available in case bleeding develops; the argon cautery device can be quite useful. Prompt conversion to an open procedure is recommended in the face of unusual bleeding, regardless of the stage of the operation (Soper, 1993). Additionally, particular care should be taken in making watertight closures for all incisions to minimize postoperative ascitic leak (Poggio et al, 2000).

Cardiopulmonary Disease

Preexisting cardiac conditions mandate vigilant intraoperative observation for significant arrhythmias known to be associated with establishment of a carbon dioxide pneumoperitoneum, including bradycardia and ventricular ectopy. In patients with cardiac pacemakers, alternative energy sources, such as bipolar electrosurgery or ultrasonic coagulation, should be used because of known interference problems caused by monopolar electrosurgical devices.

Most patients undergoing laparoscopic cholecystectomy exhibit mildly elevated P_{CO_2} (Liu et al, 1991). Chronic obstructive pulmonary disease may predispose patients to carbon dioxide retention disproportionate to the measured end-tidal value during laparoscopic cholecystectomy (Wittgen et al, 1991). Prudent measures in these patients include obtaining preoperative pulmonary function tests, making arterial blood gas determinations, and maximizing pulmonary function by smoking cessation and bronchodilator therapy. An intraoperative arterial catheter also should be placed to allow frequent measurement of P_{CO_2} and pH. Hypercarbia may manifest as hypertension, tachycardia, or ventricular arrhythmias; these should be addressed by immediate evacuation of the

pneumoperitoneum and stabilization. Gradual reestablishment of the pneumoperitoneum with a low pressure limit may be attempted, but the procedure should be terminated or converted to open if the hypercarbia recurs and is refractory to continued pneumoperitoneum.

Morbid Obesity

Morbid obesity was initially a relative contraindication to laparoscopic cholecystectomy primarily because of thickness of the abdominal panniculus relative to the length of early trocar and sheath designs, making institution and maintenance of a pneumoperitoneum problematic if not impossible. Various instrument manufacturers have since developed longer trocars to obviate this problem. The extra thickness of the wall inhibits the mobility of the trocars; therefore the trocars should be placed at the angle most likely to be used during the cholecystectomy. Longer trocars are also needed to traverse the abdominal wall to avoid trocar displacement and subsequent insufflation within the abdominal wall and subcutaneous emphysema. Longer instruments may be required to reach the gallbladder, and the initial umbilical trocar may need to be placed at a supraumbilical position.

Other challenging factors associated with morbid obesity include the presence of an enlarged, friable, fatty liver and an increased amount of adipose tissue around the gallbladder and in the area of the triangle of Calot. The surgeon should not hesitate to place additional trocars if needed (Schirmer et al, 1992). Retrospective and prospective studies have shown modestly increased operative times with performance of minimally invasive procedures in obese patient groups (Schirmer et al, 1992; Underwood et al, 1998). Today, laparoscopic cholecystectomy is commonly performed in morbidly obese patients and seems to offer the same advantages as in nonobese patients; it may also offer advantages more specific to obese patients, such as a decrease in wound infections, incisional hernias, and thrombotic complications (Miles et al, 1992; Talamini & Gadacz, 1992). Rather than being contraindicated in morbidly obese patients, laparoscopic cholecystectomy may become the preferred mode of therapy for these patients.

Pregnancy

Pregnancy is a controversial relative contraindication to laparoscopic cholecystectomy because of the unknown effects of prolonged carbon dioxide pneumoperitoneum on the fetus. It is generally accepted that elective laparoscopic cholecystectomy for biliary colic should be deferred until after pregnancy if possible. If necessary, laparoscopic cholecystectomy should be restricted to the second trimester, after organogenesis is complete and before the size and height of the uterine fundus cause it to encroach on the operative field. In the right upper quadrant, an open insertion of the initial port or alternative location of the initial port should be used to avoid injury to the gravid uterus, and the insufflation pressure should be limited to less than 12 mm Hg to avoid respiratory embarrassment and decreased vena caval return. The patient should be positioned in the left lateral decumbent position to minimize compression of the vena cava, and maternal hyperventilation with close monitoring of end-tidal carbon dioxide should be undertaken to prevent fetal acidosis. When visualization of the biliary tree is required, laparoscopic ultrasound (LUS) is used in place of cholangiography to avoid fetal radiation exposure. Finally, perioperative consultation with an experienced obstetrician is advisable, as is perioperative monitoring of the fetal heart.

Studies have shown that laparoscopic cholecystectomy can be performed safely during pregnancy, but only with great care (Soper et al, 1992a); A retrospective cross-sectional analysis of hospital discharge data from the Healthcare Cost and Utilization Project Nationwide Inpatient Sample database was conducted to study outcomes after cholecystectomy during pregnancy (Kuy et al, 2009). In this study, 9714 pregnant women who underwent cholecystectomy experienced significantly higher surgical, maternal, and fetal complication rates, lengths of stay, and costs with open cholecystectomy compared with laparoscopic surgery (Kuy et al, 2009). This may reflect the reasons for choosing an open cholecystectomy—such as prior surgery, gangrenous gallbladder, or trimester of pregnancy—rather than a true difference in complication rates between the procedures. High-volume surgeons, defined as those providers above the 75th percentile based on the annual number of cholecystectomies performed, had significantly lower rates of surgical complications.

PREOPERATIVE EVALUATION AND PREPARATION

Laboratory Test and Imaging Studies

Patients undergoing elective laparoscopic cholecystectomy for biliary colic should have preoperative liver function tests (LFTs). Elevations in these tests suggest the presence or recent passage of CBD stones. In patients with cholecystitis, LFTs are not typically elevated, because the obstruction is limited to the gallbladder; if present, elevated LFTs should raise concerns about complicating conditions such as cholangitis, choledocholithiasis, or Mirizzi syndrome (a gallstone impacted in the distal cystic duct causing extrinsic compression of the CBD; see Chapter 35).

In a patient with typical biliary colic, the only diagnostic study necessary before laparoscopic cholecystectomy is an abdominal US revealing gallstones. US shows the size and number of stones, the thickness of the gallbladder wall, the presence or absence of pericholecystic fluid, and the diameter of the CBD and other components of the biliary ductal system (see Chapter 13). Other nonbiliary disorders, such as hepatic lesions or steatosis, masses in the pancreas, or renal tumors, also may be diagnosed. When US results are negative despite typical biliary symptoms, cholecystokinin-stimulated biliary scintigraphy showing a low gallbladder ejection fraction with or without pain reproduction suggests acalculous cholecystitis or gallbladder dyskinesia (Soper, 1993).

If a patient with gallstones has atypical symptoms, however, a more extensive workup that includes upper gastrointestinal contrast radiography or endoscopy, computed tomography (CT), or cardiac and pulmonary evaluation may be appropriate to rule out significant nonbiliary disease processes. Magnetic resonance cholangiopancreatography (MRCP) may be useful to evaluate the common duct in patients with mild elevations of their transaminases or mild CBD dilatation on US (see Chapter 17). Additionally, if a patient has a dilated CBD, CBD stones, or jaundice, consideration should be given to a preoperative endoscopic retrograde cholangiopancreatography (ERCP) with

clearing of the stones followed by laparoscopic cholecystectomy (see Chapter 18).

Antibiotics

Routine preoperative antibiotic administration for elective laparoscopic cholecystectomy is controversial, with strong opinions on both sides. A recent meta-analysis of randomized controlled trials concluded that prophylactic antibiotics do not prevent infections in low-risk patients undergoing laparoscopic cholecystectomy; the usefulness of prophylaxis in high-risk patients—those older than 60 years and those with diabetes, acute colic within 30 days of operation, jaundice, acute cholecystitis, or cholangitis—remains uncertain (Choudhary et al, 2008). The most recent randomized, prospective study included in the above-mentioned meta-analysis showed no difference in the postoperative wound infection rate, although the control group had a 1.5% infection rate, and the antibiotic group had a 0.7% infection rate; however, because there was a total of 277 patients in the study, a type II error might have been made (Chang et al, 2006). Among papers that suggest a benefit of antibiotic prophylaxis is a recent randomized study that found fewer wound infections with ampicillin-sulbactam versus cefuroxime, particularly for infection caused by *Enterococcus* in the setting of high-risk patients undergoing elective cholecystectomy (Dervisoglou et al, 2006).

Accordingly, the routine use of antibiotic prophylaxis remains controversial. However, patients at high risk for having bacterial contamination of the bile should be given prophylactic antibiotics. These patients include those with acute cholecystitis, prior biliary tree instrumentation, choledocholithiasis, or those who are older than 70 years. Patients who are immunosuppressed and those with prosthetic devices also should receive preoperative antibiotics. Prophylactic antibiotics should be given within 1 hour of the skin incision, and the patient should be redosed if the procedure lasts more than 4 hours. The recommended antibiotics are cefazolin (1 to 2 g intravenously) or, in patients allergic to penicillins and cephalosporins, clindamycin plus one of either ciprofloxacin, levofloxacin, gentamicin, or aztreonam.

Deep Venous Thromboembolism Prophylaxis

The increased intraabdominal pressure as a result of pneumoperitoneum, reverse Trendelenburg position, and systemic vasodilation associated with general anesthesia in laparoscopic cholecystectomy may confer theoretical increased risk of deep venous thromboembolism (DVT). Despite scientific studies that demonstrate diminished venous outflow in femoral veins of patients undergoing laparoscopic procedures, implying venous stasis, no study to date has demonstrated a decrease in DVT with pharmacologic prophylaxis (unfractionated or low-molecular-weight heparin). Given the low rate of DVT in this patient population, an appropriately powered study designed to show a benefit of prophylaxis would require a vast number of patients. In the absence of convincing evidence in the literature, we recommend DVT prophylaxis with calf-length pneumatic compression devices in all patients undergoing laparoscopic cholecystectomy. In patients with additional risk factors—previous DVT, cancer, obesity, exogenous estrogens, projected operating time longer than 2 hours, age over 40 years—we recommend the addition of pharmacologic prophylaxis.

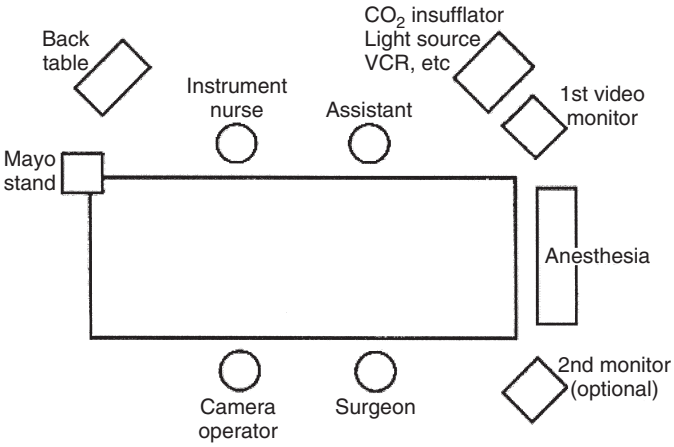


FIGURE 34.1. Room setup for laparoscopic cholecystectomy.

OPERATIVE TECHNIQUE

Operating Room Setup

Using the "American" technique, the surgeon stands to the left of the patient, the first assistant stands to the patient's right, and the laparoscopic video camera operator stands to the left of the surgeon (Fig. 34.1). In the "French" technique, the patient's legs are abducted, and the surgeon stands between them. The camera operator always must maintain the proper orientation of the camera and keep the operating instruments in the center of the video image. Following all instruments as they enter or exit the operative field is a matter of surgeon preference. Sharp instruments should never be moved intracorporeally unless they are under direct videoscopic vision.

Pneumoperitoneum

A working space, generally provided by a pneumoperitoneum, is essential for the surgeon to both view and operate within the abdominal cavity. Carbon dioxide has the advantage of being noncombustible and rapidly absorbed from the peritoneal cavity; however, it may lead to hypercarbia in patients with significant cardiopulmonary disease (Fitzgerald et al, 1992). Pneumoperitoneum can be established by either a closed or an open technique. In the closed technique, carbon dioxide is insufflated into the peritoneal cavity through a Veress needle placed blindly into the abdominal cavity; the needle is subsequently replaced with a laparoscopic port. In the open technique, a laparoscopic port is inserted under direct vision into the peritoneal cavity via a small incision; pneumoperitoneum is established only after ensuring definitive and safe peritoneal entry. Both techniques have advantages and disadvantages, and surgeons performing laparoscopic cholecystectomy should learn both techniques and use them selectively.

For the closed technique, the surgeon should perform various tests to ensure the safety of the needle insertion before insufflation. A syringe containing 5 mL of normal saline solution is attached to the end of the needle to aspirate and show the absence of blood, urine, or enteric contents. If any one of the aforementioned fluids is recovered, the needle should be removed and its position changed. If no fluid is aspirated, an assessment is made of the ease with which saline solution flows by gravity into the zero-pressure abdominal cavity, or the "drop

test." This test is done either by instilling a few drops of saline solution into the hub of the needle or by removing the barrel of the syringe. Manually elevating the abdominal wall near the needle site decreases intraabdominal pressure and enhances free flow; the fluid flows much more slowly, or not at all, if the needle is in an extraperitoneal position.

Insufflator tubing is connected to the Veress needle, and carbon dioxide is insufflated at a low flow rate of approximately 1 L/min. The initial pressure of the abdomen is usually 2 to 6 mm Hg and should not increase appreciably during the early phase of insufflation. Asymmetric distension, a rapid increase in pressure with low insufflated volume, or an initial pressure greater than 10 mm Hg suggests that the needle is not in the proper position. The abdomen should be serially percussed to confirm symmetric tympany associated with insufflation. The abdomen is fully insufflated with the upper pressure limit set at 12 to 15 mm Hg; this usually requires 3 to 6 L of carbon dioxide, depending on the size of the abdominal cavity and degree of muscle relaxation. If intraabdominal pressures exceed 20 mm Hg, central venous pressures and blood pressures decrease because of decreased venous return and diminished cardiac output (Chui et al, 1993; Sharma et al, 1997). Studies also have shown direct negative effects on urine output relative to increased intraabdominal pressures (McDougall et al, 1996, 1997).

During the initial period of insufflation, the patient must be monitored closely for signs of gas embolism (hypotension, decreased oxygen saturation, decreased end-tidal carbon dioxide, "mill-wheel" heart murmur), vagal reaction (hypotension, bradycardia), ventricular arrhythmias, and hypercarbia with acidosis. Most of these complications require immediate treatment by desufflation followed by gradual reestablishment of the pneumoperitoneum after the patient's condition has stabilized. Gas embolism results in an "air lock" right ventricular outflow obstruction with a dramatic decrease in end-tidal carbon dioxide concentration. When suspected, this problem should be treated by placing the patient in a steep Trendelenburg and left lateral decubitus position followed by insertion of a central venous catheter to aspirate the carbon dioxide from the apex of the right ventricle (Chui et al, 1993; Hanney et al, 1995; Lantz & Smith, 1994; Sharma et al, 1997).

After the pneumoperitoneum is established, the Veress needle is replaced with a trocar/port through a periumbilical incision into which the laparoscope may be inserted. This port is inserted carefully while manually elevating the abdominal wall to avoid iatrogenic injury to intraabdominal viscera or retroperitoneal structures.

Using the open technique, the pneumoperitoneum is established similarly to an open diagnostic peritoneal lavage. A 1.5-cm skin incision is made in the infraumbilical or supraumbilical skin fold. Dissection of the subcutaneous tissue is performed at the base of the umbilical raphe to reach the fascia rapidly, even in obese patients, because this is the thinnest part of the abdominal wall. Kocher clamps are applied to both sides of the linea alba, and a small vertical incision is made to gain access to the peritoneal cavity. A finger is placed into the wound to ensure that the free peritoneal cavity has been entered and to sweep away any adhesions that may be present. If a Hasson trocar (Weck & Co, Research Triangle Park, NC) is available, two sutures are placed on both sides of the fascial incision and are tied to the wings of the wedge-tipped sheath after it is inserted into the peritoneal cavity under direct vision

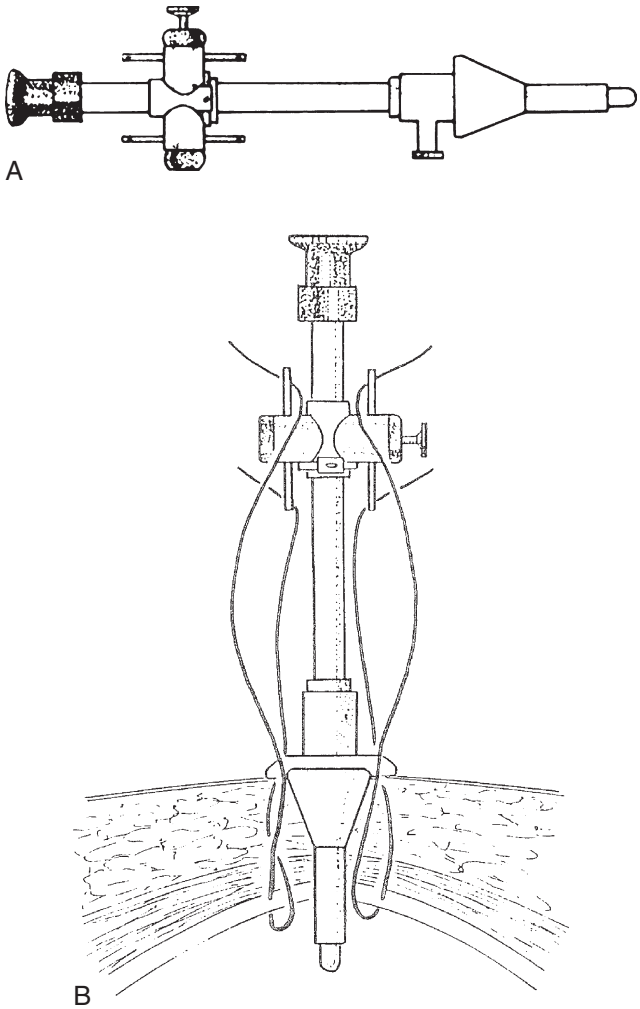


FIGURE 34.2. A, Reusable Hasson trocar/cannula. **B,** Securing the Hasson cannula to the abdominal fascia. The fascial stay sutures are wound around the wings of the cannula to secure it in place and seal the fasciotomy and peritoneotomy. *(Courtesy Quality Medical Publishing, St Louis, MO.)*

(Fig. 34.2). Alternatively, standard laparoscopic sheaths can be used after placing two concentric polypropylene purse-string stitches around the fascial incision. After removing the sheath at the conclusion of the procedure, the outer purse-string suture is removed, and the inner one is tied. Open insertion of the initial port takes a few minutes longer than its closed counterpart. Extraction of the gallbladder at the conclusion of the operation is easier, however, which equalizes the time differential of the two access techniques.

Port Placement and Exposure

Depending on the surgeon's preference, a 5- or 10-mm laparoscope is inserted into the abdomen through the umbilical port. The area immediately posterior to the umbilicus is viewed initially to ensure that there is no injury as a result of trocar insertion. Thorough intraabdominal visual exploration is performed; the pelvic viscera are examined for pathologic abnormalities before evaluating the upper abdomen, and the anterior surface of the intestines, the omentum, and the stomach also

are examined for disease. The patient is placed in a reverse Trendelenburg position of 30 degrees while rotating the table to the left by 15 degrees. This maneuver allows the colon and duodenum to fall away from the liver edge. The falciform ligament and both lobes of the liver are examined carefully for abnormalities. The gallbladder usually can be seen protruding beyond the edge of the liver.

Two small accessory subcostal ports are placed under direct vision. The first 5-mm trocar is placed along the right anterior axillary line between the twelfth rib and the iliac crest. A second 5-mm port is inserted in the right subcostal area in the midclavicular line. Grasping forceps are placed through these two ports to secure the gallbladder. The assistant manipulates the lateral grasping forceps, which are used to elevate the liver and expose the fundus of the gallbladder. The surgeon uses dissecting forceps to raise a serosal fold in the most dependent portion of the fundus. The assistant's heavy grasping forceps are locked onto this fold using either a spring or a ratchet device. With these axillary grasping forceps, the fundus of the gallbladder is pushed in a lateral and cephalad direction, rolling the entire right lobe of the liver cranially; this maneuver is complicated in patients with a fixed, cirrhotic liver or a heavy, friable liver resulting from fatty infiltration.

In patients with few adhesions to the gallbladder, pushing the fundus cephalad exposes the entire gallbladder, cystic duct, and porta hepatis. Most patients have adhesions between the gallbladder and the omentum, hepatic flexure, or duodenum; these are generally avascular and may be lysed bluntly by grasping them with dissecting forceps at their site of attachment to the gallbladder wall and gently stripping them down toward the infundibulum. After exposing the infundibulum, blunt grasping forceps placed through the midclavicular trocar are used to grasp and place traction on the neck of the gallbladder. The operative field is established, and the final working port is inserted.

A final operating trocar/port is placed through an incision in the midline of the epigastrium. This trocar usually is inserted approximately 5 cm below the xiphoid process, but the precise position and angle depend on the location of the gallbladder and the size of the medial segment of the left lobe of the liver. When the appropriate position for this trocar is hard to determine, a Veress needle may be placed first at the proposed site to ascertain whether its location and angle of insertion seen through the laparoscope are optimal. The trocar is inserted in a controlled fashion, angling its tip just to the right of the falciform ligament, aiming toward the gallbladder. Dissecting forceps are inserted and directed toward the gallbladder neck. The orientation of the laparoscope is generally parallel to that of the cystic duct when the fundus is elevated, whereas the instruments placed through the other three ports enter the abdomen at right angles to this plane (Figs. 34.3 and 34.4).

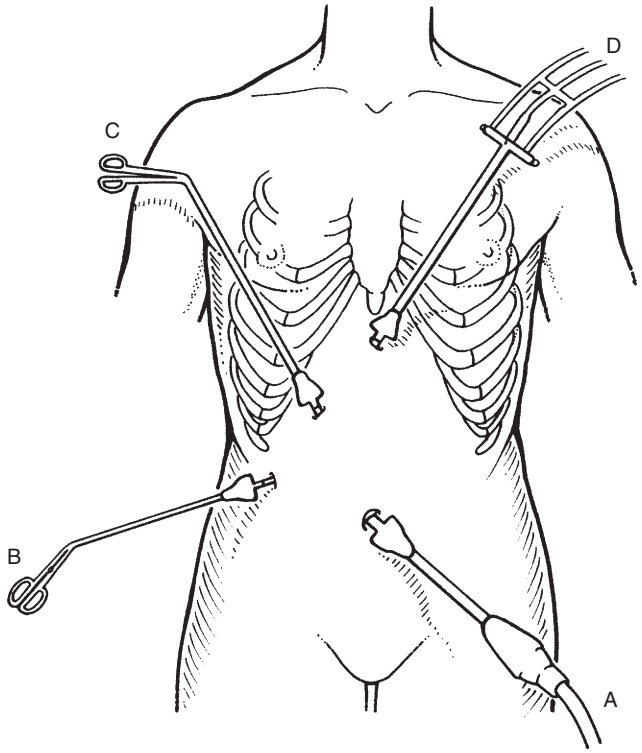


FIGURE 34.3. Positions for insertion of the initial (*A*) and accessory sheaths (*B* through *D*).

Dissection

A grasping instrument on the infundibulum exerts traction on the gallbladder away from the CBD in a superior and lateral direction. Fine-tipped dissecting forceps are used to dissect away the overlying fibroareolar structures from the infundibulum of the gallbladder. This is done with a blunt stripping action, always starting on the gallbladder and stripping the tissue toward the porta hepatis (Fig. 34.5). The dissection should begin on a known structure (e.g., the gallbladder), rather than in an unknown area, to avoid damage to the underlying structures, such as the bile duct or the hepatic artery.

It is important to identify clearly the structures forming the sides of the triangle of Calot (i.e., cystic duct, cystic artery, and common hepatic duct), the standard ventral aspect, and its reverse (dorsal) aspect (Fig. 34.6). Distinction is made here with the hepatocystic triangle proper, which is the ventral aspect of the area bounded by the gallbladder wall and cystic duct, the liver edge, and the common hepatic duct; the cystic artery and the triangle of Calot lie within this space. The hepatocystic triangle is maximally opened and converted into a trapezoid shape

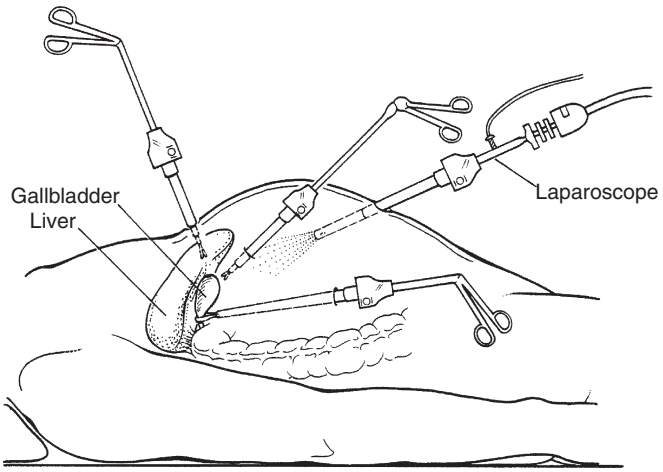


FIGURE 34.4. Diagram of the abdomen after the creation of a pneumoperitoneum and the insertion of laparoscopic instruments.

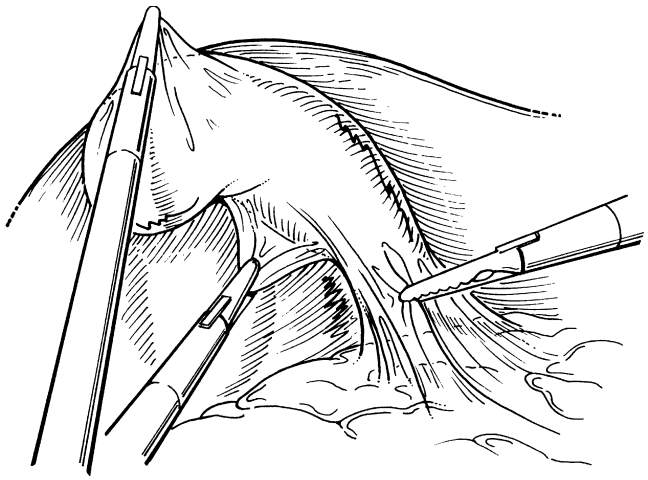


FIGURE 34.5. The omentum and adhesions are bluntly divided by carefully pulling them away with atraumatic grasping forceps.

by retracting the infundibulum of the gallbladder inferiorly and laterally, while maintaining the fundus under traction in a superior and medial direction. A lymph node usually lies adjacent to the cystic artery, and occasionally it is necessary to use a brief application of electrosurgical coagulation to obtain hemostasis as the lymph node is bluntly swept away. To expose the reverse of Calot's triangle, the infundibulum of the gallbladder is pulled in a superior and medial direction (see Fig. 34.6).

After clearing the structures from the apex of the triangle, the junction between the infundibulum and the origin of the proximal cystic duct can be identified clearly. The strands of peritoneal, lymphatic, and neurovascular tissue are stripped away from the cystic duct to clear a segment from the surrounding tissue. Curved dissecting forceps are helpful in creating a window around the posterior aspect of the cystic duct to skeletonize the duct itself. Alternatively, the tip of the hook cautery can be used to encircle and expose the duct. It is generally unnecessary and potentially harmful to dissect the cystic duct down to its junction with the CBD.

Next, the cystic artery is separated from the surrounding tissue by similar blunt dissection. If the cystic artery crosses anterior to the duct, the artery may require dissection and division before approaching the cystic duct. The neck of the gallbladder is dissected away from its liver bed, leaving only two structures entering the gallbladder: the cystic duct and artery. No structure should be divided until the cystic duct and cystic artery are unequivocally identified. This is the "critical view" of safety (Fig. 34.7) essential to prevent bile duct injury during laparoscopic cholecystectomy (Strasberg et al, 1995).

Intraoperative Evaluation for Choledocholithiasis

After initially dissecting the proximal cystic duct, the CBD should be imaged if there is any concern for choledocholithiasis or any question regarding the biliary anatomy. This can be achieved by radiographic intraoperative cholangiography (IOC) or intracorporeal LUS (see Chapter 21). Before either procedure, a clip is applied high on the cystic duct at its junction with the gallbladder to prevent stones from migrating down the duct. To perform IOC, the anterolateral wall of the cystic duct is

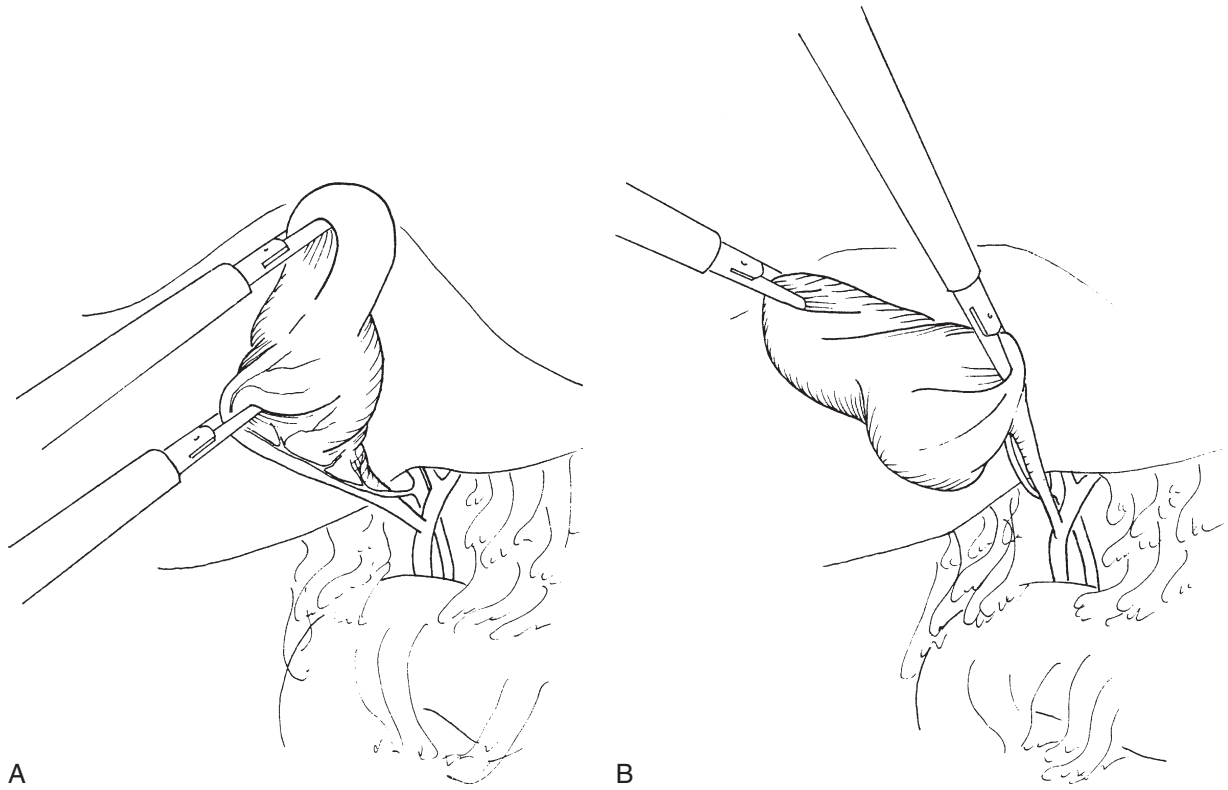


FIGURE 34.6. Proper gallbladder retraction for exposure of Calot's triangle (**A**) and reverse Calot's triangle (**B**). *(Courtesy Quality Medical Publishing, St Louis, MO.)*

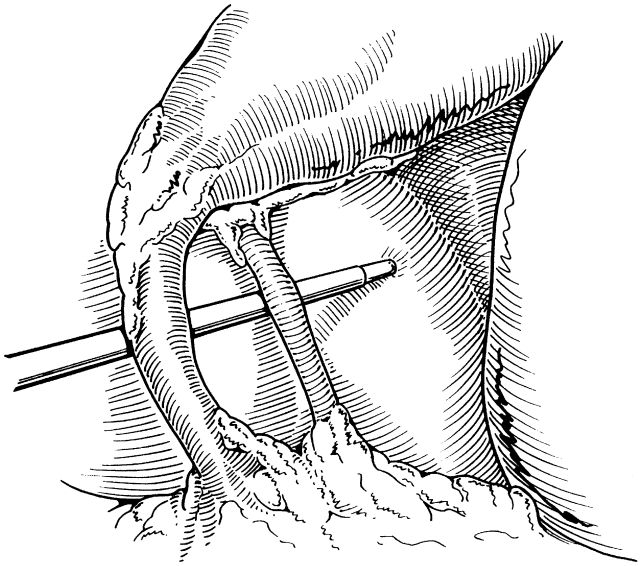


FIGURE 34.7. Critical view. Hepatocystic triangle is dissected free of all tissue except for the cystic duct and artery, and the base of the liver bed is exposed. When this view is achieved, the two structures entering the gallbladder can only be the cystic duct and artery.

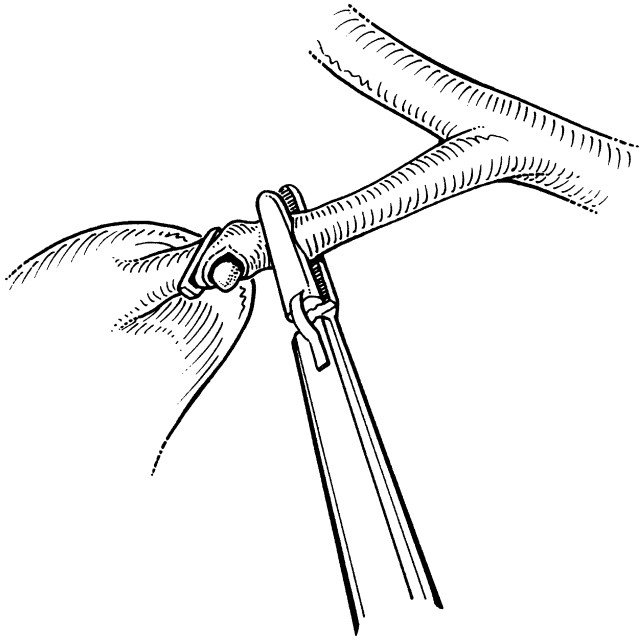


FIGURE 34.9. A cystic duct stone is "milked" out of the ductotomy.

incised, and dissecting forceps are used to compress the cystic duct gently and systematically back toward the gallbladder, "milking" stones away from the CBD and out the ductotomy (Figs. 34.8 and 34.9). A 4- to 5-Fr catheter is inserted into the duct through a hollow, 5-mm metal tube that has an appropriate gasket to prevent carbon dioxide leakage around the catheter itself. The cholangiography catheter is inserted into the cystic duct, and a clip is applied loosely to secure the catheter in place (Fig. 34.10). If the introducer has grasping jaws, it can be used to secure the catheter into the duct (Fig. 34.11). Alternatively, catheters equipped with balloons proximal to the tip may be used for fixation.

Cholangiography can be performed by either real-time fluoroscopy (dynamic IOC) or by obtaining two standard radiographs (static IOC) after injecting 5 mL and 10 mL of water-soluble contrast medium (Figs. 34.12 and 34.13). The films should be inspected for the following: 1) the length of cystic duct and location of its junction with the CBD, 2) the size of the CBD, 3) the presence of intraluminal filling defects, 4) free flow of contrast material into the duodenum, and 5) anatomy of the extrahepatic and intrahepatic biliary tree. After the cholangiocatheter is removed, the cystic duct is doubly

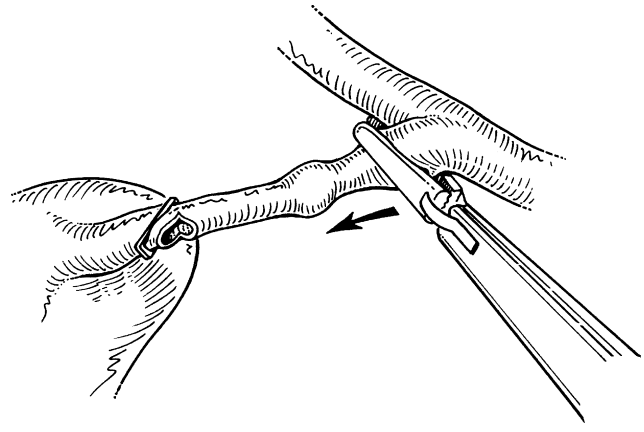


FIGURE 34.8. After a clip is placed across the junction of the gallbladder with the cystic duct, and a cystic ductotomy is made on the anterior side, the cystic duct is gently "milked" back toward the ductotomy.

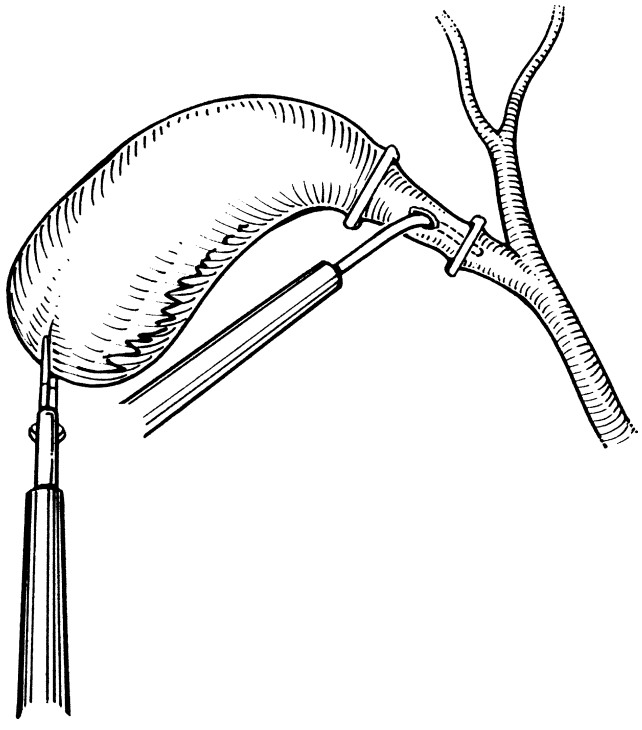


FIGURE 34.10. Cystic duct cholangiography can be performed with a catheter clipped into place.

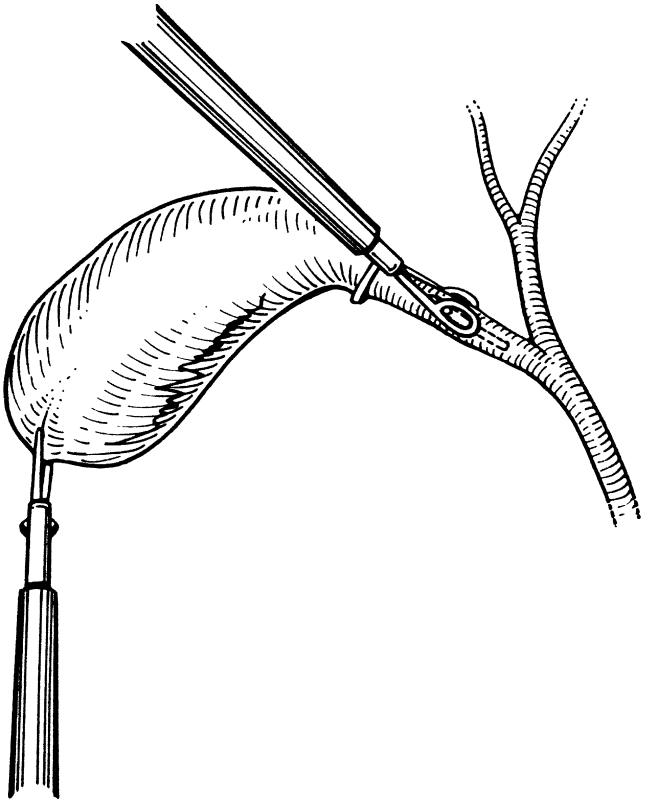


FIGURE 34.11. Alternatively, a cholangiogram catheter can be held in place with a clamp.



FIGURE 34.12. Intraoperative cholangiogram showing absence of a bile duct calculus with free flow of contrast medium into the duodenum. *(From Blumgart LH, Fong Y [eds], 1997: Surgery of the Liver and Biliary Tract CD-ROM. Philadelphia, Churchill Livingstone.)*



FIGURE 34.13. Intraoperative cholangiogram showing a filling defect of the distal common bile duct. The defect has a characteristic "meniscus" appearance, and there is no flow of contrast medium into the duodenum. *(From Blumgart LH, Fong Y [eds], 1997: Surgery of the Liver and Biliary Tract CD-ROM. Philadelphia, Churchill Livingstone.)*

clipped below the ductotomy, with care taken to avoid the wall of the CBD, and divided. The posterior jaw of the clip applier must be visualized before applying each clip to avoid injury to the surrounding structures. Great care should be taken so that the CBD is not "tented up" into the clip. If the cystic duct is particularly large or friable, it may be preferable to replace one of the clips with a hand-tied or preformed suture.

Evaluation of the CBD by LUS is an alternative to cholangiography. Several studies performed at open cholecystectomy reported LUS to be more accurate than IOC in assessing the CBD for stones (97% to 99% vs. 89% to 94%; Machi et al 1993a, 1993b; Orda et al, 1994a, 1994b). Although few surgeons have adopted US for this purpose, LUS has been used in several centers during laparoscopic cholecystectomy and is gaining popularity (Jakimowicz, 1993; John et al, 1994; McIntyre et al, 1994; Orda et al, 1994a, 1994b; Steigmann et al, 1994). With LUS, the transducer has a higher frequency with improved resolution compared with that used with transabdominal US. In experienced hands, LUS seems to be as accurate as cholangiography for showing choledocholithiasis, but it can be performed more rapidly (Steigmann et al, 1995). In a prospective multicenter trial with 209 laparoscopic cholecystectomy patients, the time to perform LUS (7 ± 3 min) was significantly less than that of IOC (13 ± 6 min; Steigmann et al, 1995). The study showed that LUS was more sensitive for detecting stones but that IOC was better in delineating intrahepatic anatomy and defining anatomic anomalies of the ductal system. The authors concluded that the two methods of ductal imaging were complementary. Despite these promising data,

more clinical experience is needed to establish the appropriate role of LUS for the detection of choledocholithiasis during laparoscopic cholecystectomy (Soper, 1997; Wu et al, 1998a).

Completion of Cholecystectomy

After clip ligation and division of the cystic duct, the cystic artery is dissected from the surrounding tissue for an adequate distance to permit placement of three clips. The surgeon must ascertain that the structure is the cystic artery and not the right hepatic artery, looping up onto the neck of the gallbladder, or an accessory or replaced right hepatic artery (see Chapter 1B). After an appropriate length of cystic artery has been dissected free, it is clipped proximally and distally before its transection. Electrocautery should not be used for this division, because the current may be transmitted to the proximal clips and lead to subsequent necrosis and hemorrhage. A common error is to dissect and divide the anterior branch of the cystic artery, mistaking it for the main cystic artery; this may result in hemorrhage from the posterior branch during dissection of the gallbladder fossa.

The ligated stumps of the cystic duct and the artery are examined to ensure that there is no leakage of either bile or blood and that the clips are placed securely; they should compress the entire lumen without impinging on adjacent tissues. A suction-irrigation catheter is used to remove any debris or blood that has accumulated during the dissection. Separation of the gallbladder from its hepatic bed is initiated using an electrosurgical probe to coagulate small vessels and lymphatics. While maintaining cephalad traction on the fundus of the gallbladder with the axillary forceps, the midclavicular forceps pulls the neck of the gallbladder anterosuperiorly and then alternatively medially and laterally to expose and place the tissue connecting the gallbladder to the fossa under tension (Fig. 34.14). An electrocautery spatula or hook is used in a gentle sweeping motion with low power (25 to 30 W) to coagulate and divide the tissue. Intermittent blunt dissection facilitates exposure of the proper plane.

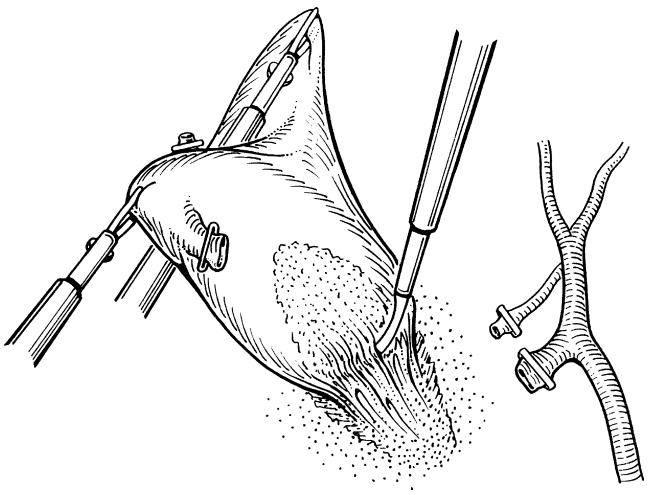


FIGURE 34.14. Separation of the gallbladder from its bed by dissection with a blunt-tipped thermal energy probe. The neck of the gallbladder is placed on traction in a superior direction, then twisted to the left and right to place tension on the junction between the gallbladder and the hepatic fossa.

Dissection of the gallbladder fossa continues from the infundibulum to the fundus, progressively moving the midclavicular grasping forceps cephalad to allow maximal countertraction. The dissection proceeds until the gallbladder is attached by only a thin bridge of tissue. At this point, before completely detaching the gallbladder, the hepatic fossa and porta hepatis are inspected again for hemostasis and bile leakage. Small bleeding points are coagulated, and the right upper quadrant is liberally irrigated and aspirated dry while checking for any residual bleeding or bile leakage. The final attachments of the gallbladder are divided, and the liver edge is examined again for hemostasis.

After the cholecystectomy has been performed, the gallbladder must be removed from the abdominal cavity. If the stone burden is small, the gallbladder can be extracted at the subxiphoid port site. Usually, the gallbladder is most easily removed at the umbilical port site, where there are no muscle layers anterior to the fascial plane. Also, if the fascial opening needs to be enlarged because of large or numerous stones, extension of the umbilical incision causes less postoperative pain and has better cosmesis than does enlarging the subxiphoid incision. The laparoscope is removed from the umbilical port and placed through the epigastric port. Large, claw-like grasping forceps are introduced through the umbilical port to grasp the infundibulum of the gallbladder. The forceps, trocar, and gallbladder neck are retracted as a unit through the umbilical incision, and the neck of the gallbladder is exteriorized through the anterior abdominal wall with the fundus remaining within the abdominal cavity.

If the gallbladder is not distended with bile or stones, it can be withdrawn with gentle traction. In most cases, a suction catheter introduced through an incision in the gallbladder neck is used to aspirate bile and small stones. Stone forceps also can be placed into the gallbladder to extract or crush calculi if necessary (Fig. 34.15). Occasionally, the fascial incision must be extended to extract larger stones or thick-walled gallbladders. After the gallbladder is extracted, the operator's finger is used to occlude the port entry site. If any question concerning hemostasis or contamination of the right upper quadrant remains, the umbilical port can be replaced under direct vision, and the upper part of the abdomen can be copiously irrigated and aspirated again. If not, all laparoscopic ports are removed after allowing escape of the carbon dioxide.

Each incision is infiltrated with bupivacaine for postoperative analgesia, and the fascia of the umbilical incision is closed with one or two large, absorbable sutures. Closure of the subxiphoid fascia is optional, because visceral herniation is unlikely to occur owing to the oblique entry angle of the trocar into the abdominal cavity and its location anterior to the falciform ligament. The skin of the subxiphoid and umbilical incisions is closed with subcuticular absorbable sutures. The skin incisions at both 5-mm port sites can be closed with adhesive strips or skin closure adhesives. The orogastric tube is removed in the operating room, and the patient is transferred to the postanesthesia care unit.

Intraoperative Treatment of Common Bile Duct Stones

The reported incidence of CBD stones found during laparoscopic cholecystectomy ranges from 3% to 10% (see Chapters 30 and 34 through 37) (Barkun et al, 1993; Frazee et al, 1993). It is unclear whether uncomplicated and asymptomatic

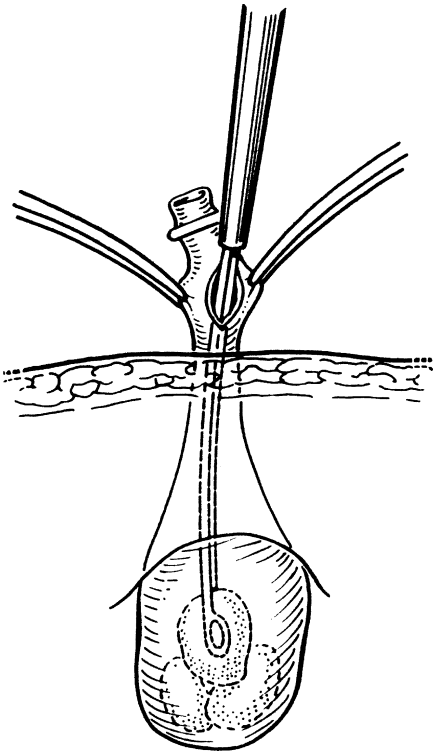


FIGURE 34.15. Gallstones contained within the fundus may be crushed or removed after delivering the neck of the gallbladder through the umbilical incision.

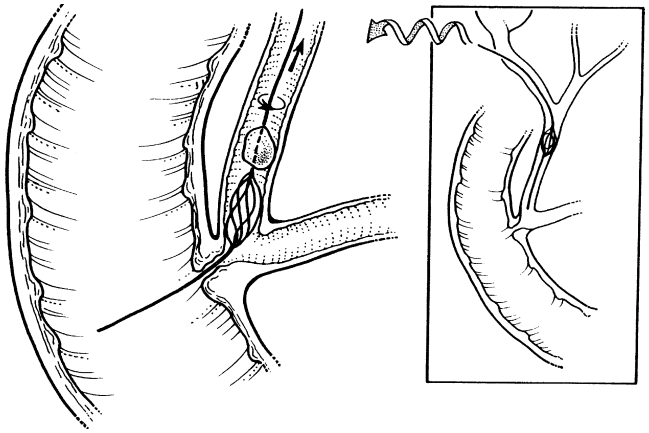


FIGURE 34.16. Transcystic retrieval of common bile duct stones using a helical basket under fluoroscopy.

choledocholithiasis requires treatment. Autopsy series have shown that many patients with silent gallbladder stones also harbor silent CBD stones (Crump, 1931). Smaller stones are known to pass through the ampulla of Vater, as shown by stool analysis in patients with acute pancreatitis (see Chapter 53) or acute biliary colic (Acosta & Ledesma, 1974; Kelly, 1980). In one study, the rate of symptoms or complications in patients with retained CBD stones after cholecystectomy was 94%, with a mortality rate of 3% over 5 years (Hicken & McAllister, 1964). It is unclear what stone size precludes passage or which indicators predict complications of cholangitis (see Chapter 43) or pancreatitis if the stones are left in situ.

It is generally recommended to treat choledocholithiasis when it is discovered intraoperatively; options include laparoscopic CBD management, open CBD exploration, and postoperative endoscopic or percutaneous transhepatic stone extraction. In the current state of evolving techniques, and in the absence of definitive prospective randomized trials guiding the management of patients with choledocholithiasis, the technical expertise of the local physicians is a major determining factor in CBD stone management.

Laparoscopic CBD exploration can take the form of accessing the CBD through the cystic duct (transcystic technique) or directly incising and opening the CBD with stone retrieval (laparoscopic choledochotomy). In the transcystic duct approach, stones smaller than 4 mm often can be flushed through the ampulla into the duodenum, a technique that is facilitated by pharmacologic relaxation of the sphincter of Oddi using sublingual nitroglycerin or intravenous glucagon. When these simple methods fail, a helical stone basket can be passed over a guidewire through the cystic duct and into the CBD to extract stones under fluoroscopic guidance (Fig. 34.16) (Hunter, 1992).

If attempts at transcystic basket extraction fail, the next step is to insert a 7- to 8-Fr choledochoscope to remove the stones under direct vision. If the CBD stone is larger than the lumen of the cystic duct, the duct should be balloon dilated first to a maximum of 8 mm in diameter, but never larger than the internal diameter of the CBD (Hunter & Soper, 1992). The choledochoscope is passed into the peritoneal cavity through the midaxillary port, using a sheath to prevent damage to the scope by the port's valve. The choledochoscope is inserted through the cystic duct into the CBD under direct vision. The lumen of the duct is optimally visualized by continuously infusing saline through the biopsy channel. Under visual guidance, the tip of a Segura-type stone basket is advanced beyond the stone and opened. As the basket is pulled backward and rotated, the stone is ensnared (Fig. 34.17; Jones & Soper, 1996).

A completion cholangiogram should always be performed to ascertain clearance of the duct. Because of tissue edema secondary to ductal dilation and manipulation, the cystic duct stump is ligated, rather than clipped, for added security. Successful extraction has been reported in 67% to 96% of patients treated in most series (Table 34.3; Bagnato, 1993; DePaula et al, 1994; Dion et al, 1994; Ferzli et al, 1994; Franklin et al, 1994; Hunter, 1992; Petelin, 1993; Phillips et al, 1994). Complications such as infection and pancreatitis have been reported in 5% to 10% of patients, with a mortality rate of 1% to 2%. The duration of hospitalization after an uncomplicated transcystic duct stone extraction is the same as that for laparoscopic cholecystectomy alone, averaging 1 to 2 days. The main advantage of the transcystic approach is that it avoids the need to incise the CBD, with subsequent suture closure and placement of a T-tube. Poor candidates for transcystic extraction techniques are patients with large or multiple CBD stones, patients with stones in the proximal ductal system, and patients with small or tortuous cystic ducts.

If the transcystic approach fails, we recommend direct incision of the CBD laparoscopically. Indications for laparoscopic choledochotomy are stones that are multiple, large, or positioned within the proximal bile ducts in patients with a CBD diameter larger than 8 to 10 mm (Dion et al, 1994; Phillips

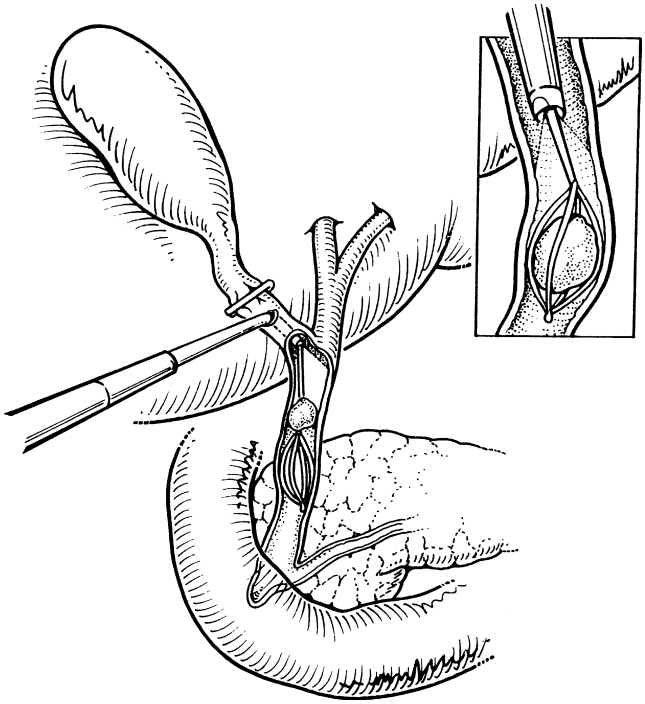


FIGURE 34.17. Transcystic choledochoscopy. The flexible choledochoscope is passed into the common bile duct through the cystic duct. Under direct vision, the basket is advanced distal to the stone and opened. *Inset,* As the basket is withdrawn through the working channel of the choledochoscope, the stone is ensnared. The basket, stone, and choledochoscope are removed as a unit.

et al, 1994). Stay sutures usually are placed on either side of the midline of the CBD wall to allow anterior traction on the duct. A longitudinal choledochotomy is made on the distal CBD, with adequate length to allow easy placement of a choledochoscope and removal of the largest stone. Stones are removed under endoscopic visualization, and an appropriate-size T-tube is placed in the duct. The ductotomy is closed with fine absorbable sutures using intracorporeal suturing techniques, and the T-tube is exteriorized through the lateral port site. The patient generally is discharged 2 to 4 days postoperatively and returns for a final T-tube cholangiogram and removal of the T-tube at 14 to 21 days postoperatively. Retained stones shown by T-tube cholangiography may be effectively removed percutaneously after allowing maturation of the T-tube tract. Percutaneous extraction is successful in more than 95% of patients with retained stones (Burhenne, 1980).

Overall, laparoscopic choledochotomy is successful in more than 90% of patients, with a minor morbidity rate of 5% to 10% and a mortality rate of 1% to 2% (see Table 34.3). Complications of this technique include laceration of the CBD, bile leakage, sewn-in T-tubes, and postoperative CBD strictures (Dion et al, 1994). Many surgeons have not mastered laparoscopic suturing to the point that they feel comfortable closing the choledochotomy, for fear of a resultant stricture. Nevertheless, advantages of the direct laparoscopic approach are that every portion of the ductal system can be accessed, and stone size is unimportant. The alternative approach of open operation with exploration of the CBD with or without choledochoduodenostomy should always be considered in difficult cases (see Chapters 29 and 35).

The possibility of finding CBD stones and the means by which they can be treated must be discussed with the patient before operation to formulate a plan of therapy. Many surgeons routinely leave CBD stones in place during laparoscopic cholecystectomy for planned postoperative endoscopic removal (see Chapter 27). Factors favoring postoperative endoscopic therapy include the presence of small, nonobstructing duct stones; a patient with significant comorbidities, making a prolonged operation risky; and a small CBD prone to postoperative stricture. In resorting to postoperative endoscopic retrograde cholangiography and sphincterotomy, the goals of minimally invasive surgery are maintained with a rapid return to full activity. Relying on postoperative endoscopic sphincterotomy (ES) subjects the patient to an additional procedure, with its associated morbidity and possibly a second operation if endoscopic stone extraction fails. In experienced hands, ES has an overall failure rate for stone clearance of 5% to 10% (Cotton, 1993).

Leaving a transcystic catheter in the CBD at the time of laparoscopic cholecystectomy may decrease the likelihood of failure by allowing a guidewire to be passed into the duodenum to facilitate cannulation of the CBD (Deslandres et al, 1993). It is reasonable to submit a patient to postoperative endoscopic stone extraction when the endoscopic expertise is high, whereas an open CBD exploration should be strongly considered when only an inexperienced endoscopist is available in the local setting. The expertise of the laparoscopist and the endoscopist are critical determinants of the means by which CBD stones are managed (Cotton, 1993).

Table 34.3

Techniques for Treatment of Choledocholithiasis

Method	Success Rate (%)	Length of Stay (Days)	Return to Work (Days)
Transcystic duct extraction	67-96	1-2	7-10
Laparoscopic CBDE	85-100	4-7	14-30
Open CBDE	90-100	5-10	20-42
ERC/ES	85-95	2-3	7-14

CBDE, common bile duct exploration; ERC, endoscopic retrograde cholangiography; ES, endoscopic sphincterotomy

POSTOPERATIVE MANAGEMENT

Patients may be observed in the hospital overnight or discharged later the same day. The patient is allowed clear liquids in the immediate postoperative period and is advanced to a regular diet as tolerated. Postoperative referred shoulder and neck pain may occur transiently as a result of diaphragmatic irritation. No activity restrictions are placed on the patient; functional status depends entirely on the degree of abdominal tenderness, which usually subsides by postoperative day 2 or 3. The patient may return to work as soon as the abdominal discomfort is tolerable, often within the first week.

Although laparoscopic cholecystectomy was initially thought of as a procedure that could reduce a typical 5-day hospital stay for an open cholecystectomy to 1 to 2 days, third-party payers in the United States have begun to push for discharge of the

patient on the same day of surgery; the principal advantage is reduction of hospital costs. Nevertheless, not all patients are candidates for outpatient laparoscopic cholecystectomy. In a prospective analysis of 506 consecutive laparoscopic cholecystectomy cases, Saunders and colleagues (1995) argued that most complications, including life-threatening complications, were not apparent by 8 hours postoperatively and were clinically detected only 39% of the time at 24 hours after the procedure. These investigators recommended great caution in selecting patients for outpatient laparoscopic cholecystectomy. Patients who may benefit from an overnight stay include elderly patients, those with significant comorbid illnesses, those requiring substantial analgesia postoperatively, and patients with complications. For same-day discharge, patients should be healthy, reliable, and sensible; have undergone an uncomplicated operation; and have good home support. Written instructions are given to the patient and the family, with detailed advice concerning signs of potential problems. Routine postoperative follow-up at 2 to 4 weeks is advised for all patients.

SPECIAL CONSIDERATIONS

Acute Cholecystitis

Numerous reports indicate that laparoscopic cholecystectomy can be done safely for patients with acute cholecystitis (Prakash et al, 2002; Suter & Meyer, 2001). There is a higher rate of conversion in the setting of acute cholecystitis; in particular, after 72 hours, the rate of conversion increases significantly (Madan et al, 2002).

The timing of laparoscopic cholecystectomy for acute cholecystitis has been a long-standing matter of debate. Based on several prospective studies, early surgical intervention has economic, social, and medical benefits and is the preferred approach for experienced laparoscopic surgeons in the management of acute cholecystitis (Feldman et al, 2002). Our practice is to proceed with laparoscopic cholecystectomy immediately after the diagnosis of acute cholecystitis has been made. In a patient who is seen after 72 hours of symptoms, a laparoscopic cholecystectomy is attempted only if the patient has no preexisting medical conditions that preclude an open cholecystectomy. If the patient does have significant comorbid illnesses, we continue with antibiotic therapy and possibly a percutaneous cholecystostomy tube (see Chapter 32) and subsequent elective laparoscopic cholecystectomy 6 to 8 weeks later.

Intervention during the early phase reveals an inflamed, thick-walled, tensely distended organ. To gain adequate traction on the gallbladder with the grasping forceps, it may be necessary to decompress the gallbladder by aspirating its contents with a large-gauge needle. As long as the inflammation is limited to the gallbladder, laparoscopic cholecystectomy is usually technically feasible. If inflammation extends to the porta hepatis, however, great care must be taken in proceeding with the operation. The normally thin, minimally adherent tissue that invests the cystic duct and artery is markedly thickened and edematous and may not separate readily from these structures with the usual blunt dissection techniques. The duct wall also may be edematous, making its external diameter similar to the gallbladder neck and CBD. If the anatomy is unclear, cholangiography must be performed before clipping or dividing tissue.

When acute inflammation has been present for several days or weeks before operation, the pericholecystic tissue planes may be obliterated by thick, "woody" tissue that is difficult to dissect bluntly. In these cases, some authors recommend attempting a fundus-first technique and possibly even a subtotal cholecystectomy (Beldi & Glattli, 2003; Mahmud et al, 2002). Subtotal cholecystectomy involves transecting the infundibulum as close to the cystic duct as possible and extracting all stones. The gallbladder neck is then sutured closed if possible, and a drain is placed in the gallbladder bed. This transection of an edematous, friable wall may be facilitated by using the ultrasonic shears. The surgeon must be comfortable in his or her ability to safely perform the procedure laparoscopically; however, the decision to convert to an open procedure should not be considered a complication but rather good surgical judgment based on the existing anatomy, local conditions, and the surgeon's experience and confidence in his or her ability to complete the procedure using minimal-access techniques.

In a gallbladder densely adherent to the liver, where the plane between the two is obliterated, or in the presence of portal hypertension, it may be preferable to leave the back wall of the gallbladder intact and fully cauterize its mucosa (Beldi & Glattli, 2003). An active suction drain should be left beneath the liver if the integrity of the cystic duct closure is in question or with any suspicion of bile leakage from the gallbladder bed. We do not place a drain to monitor for bleeding.

Several authors have reported performing laparoscopic cholecystectomy in the face of acute inflammation with success, but with a higher conversion rate than for elective laparoscopic cholecystectomy (Cooperman, 1990; Hermann, 1990; Rattner et al, 1993; Reddick et al, 1991; Unger et al, 1991). Lo and colleagues (1996) reported in their prospective study that despite longer operative times and postoperative stays for early laparoscopic cholecystectomy in patients with acute cholecystitis (treatment within 5 days) versus delayed laparoscopic cholecystectomy (initial conservative treatment followed by laparoscopic cholecystectomy 3 to 4 months later), the advantage of early laparoscopic cholecystectomy was the reduction in the total hospital stay, from 15 to 7 days.

Rattner and associates (1993) retrospectively reviewed 20 patients who underwent attempted laparoscopic cholecystectomy for acute cholecystitis and examined factors that were predictive of a successful procedure. Seven of the 20 patients (35%) required conversion to open cholecystectomy. The interval from admission to cholecystectomy in the successful cases was 0.6 days versus 5 days in the cases requiring conversion to open cholecystectomy. Converted cases also had a significantly higher white blood cell count, alkaline phosphatase levels, and Acute Physiology and Chronic Health Evaluation (APACHE II) scores compared with cases involving successful laparoscopic cholecystectomy. US findings, such as gallbladder distension, wall thickness, and pericholecystic fluid, did not correlate with the success of laparoscopic cholecystectomy.

In a prospective study of 105 patients randomized to early laparoscopic cholecystectomy (within 24 hours of diagnosis of acute cholecystitis) versus delayed laparoscopic cholecystectomy (6 to 8 weeks later), no significant difference was found in conversion rate (early 21% vs. delayed 24%), postoperative analgesic requirement, or number of postoperative complications. The early group did have a longer operative time (123 minutes vs. 107 minutes, $P = .04$), but total hospitalization was shorter (8 days vs. 12 days, $P = .001$) (Lai et al, 1998). Laparoscopic cholecystectomy should be performed immediately after the diagnosis of acute cholecystitis. Delaying surgery

Table 34.4

Complications of Laparoscopic Cholecystectomy

Hemorrhage
Bile duct injury
Bile leak
Retained stones
Pancreatitis
Wound infection
Incisional hernia

Pneumoperitoneum-Related Complications

Carbon dioxide embolism
Vasovagal reflex
Cardiac arrhythmias
Hypercarbic acidosis

Trocar-Related Injury

Abdominal wall bleeding, hematoma
Visceral injury
Vascular injury

Table 34.5

When to Convert from Laparoscopic to Open Cholecystectomy

Injury to major blood vessels, viscus, or bile duct
Anatomy unclear
Failure to progress in a timely fashion
Pathology not amenable to minimal access surgical techniques
Choledocholithiasis untreatable by minimal-access surgical techniques or postoperative endoscopic techniques

allows inflammation to become more intense and neovascularized, increasing the technical difficulty of laparoscopic cholecystectomy.

COMPLICATIONS

Many complications related to laparoscopic removal of the gallbladder are similar to the complications that occur during traditional open cholecystectomy (Table 34.4) and include hemorrhage, bile duct injuries, bile leaks, retained stones, pancreatitis, wound infections, and incisional hernias (see Chapter 33). Other potential complications are pneumoperitoneum related (gas embolism, vagal reaction, ventricular arrhythmias, or hypercarbia with acidosis) and trocar related (injuries to the abdominal wall, intraabdominal organs, or major blood vessels). Most complications occur early in the surgeon's experience. In a multivariate regression analysis of 8839 laparoscopic cholecystectomies, in which 15 bile duct injuries occurred, the only significant factor associated with an adverse outcome was the surgeon's experience with the procedure (Moore & Bennett, 1995). The regression model predicted that a surgeon had a 1.7% chance of a bile duct injury occurring in the first case and 0.17% chance of a bile duct injury in the fiftieth case.

Conversion to Open Operation

Surgeons performing laparoscopic cholecystectomy should not think of conversion to open operation as a failure but rather as mature judgment. A surgeon should not hesitate to convert to a traditional open cholecystectomy if the anatomy is unclear, complications arise, or reasonable progress cannot be made in a timely manner (Table 34.5). It is better to open one too many than to open one too few, even if it means a longer hospital stay for the patient. Some complications requiring laparotomy are obvious, such as massive hemorrhage, bowel perforation, or major injury to the bile duct. Open laparotomy allows the additional tool of manual palpation and tactile sensation and should be performed when the anatomy cannot be delineated because of inflammation, adhesions, or anomalies. Fistulae between the biliary system and bowel are rare but may require laparotomy for optimal management. The demonstration of potentially resectable gallbladder carcinoma (see Chapter 49) also dictates an open exploration. Finally, when CBD stones cannot be removed laparoscopically and are unlikely to be extracted endoscopically owing to Billroth II anastomosis, previously failed ERCP, or an inexperienced endoscopist, the procedure should be converted to open operation without hesitation.

Anatomic Variations

One of the most frequent anomalies is a right hepatic artery that loops up onto the infundibulum of the gallbladder (see Chapter 1B). This anomaly may be misidentified as the cystic artery, leading to injury to the hepatic artery (Berci & Sackier, 1994). The surgeon also occasionally notices only a small cystic artery on the medial aspect of the gallbladder; when this occurs, the surgeon should be alert for a posterior branch leading onto the dorsal aspect of the gallbladder. If great care is not taken, brisk hemorrhage may occur.

A short cystic duct is seen frequently and may be draining into the right hepatic duct or a low-entry right sectoral hepatic duct (2%) or common hepatic duct (1%), or it may connect the infundibulum with the CBD by a duct of only a few millimeters in length in 5% to 6% of cases (Berci, 1992; Reid et al, 1986). During open cholecystectomy, this is relatively easy to recognize, especially if the cholecystectomy is performed in a fundus-first fashion. During laparoscopic cholecystectomy, these ducts are in danger of being mistaken for a normal cystic duct and divided (Fig. 34.18; Meyers et al, 1996). The most dangerous variant is when the cystic duct joins a low-lying aberrant right sectoral duct. These injuries are underreported, because occlusion of an aberrant duct may be asymptomatic and even unrecognized. In addition to anomalous biliary ducts, accessory ducts may drain into the cystic duct or from the liver directly into the gallbladder (ducts of Luschka). Since the widespread use of laparoscopic cholecystectomy, there has been an increased occurrence of bile leaks from the so-called ducts of Luschka. It is likely that many of these bile leaks are due to dissection into the liver substance with injury to a normal, albeit superficial, intrahepatic biliary radicle.

Intraoperative Gallbladder Perforation

Perforation of the gallbladder with bile or stone leakage can be a nuisance, but it should not ordinarily require conversion to open cholecystectomy. Perforation may occur secondary to traction applied by the grasping forceps or electrosurgical thermal injury during removal of the gallbladder from its bed. In our experience, almost one third of the patients have had

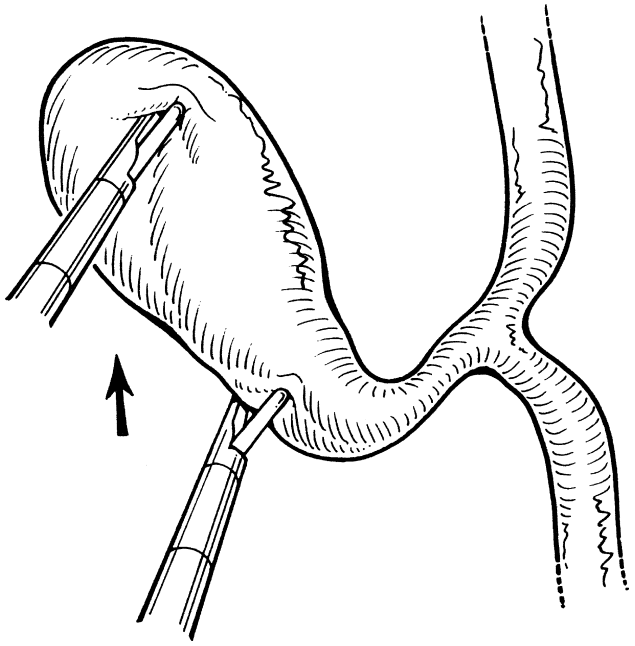


FIGURE 34.18. With a short cystic duct at the junction of the common hepatic duct and the common bile duct, pulling the infundibulum can result in tenting of the common bile duct. This can mimic the appearance of the cystic duct.

intraoperative spillage of bile or stones (Jones et al, 1995). Patients with a bile leak have not experienced an increased incidence of infection, prolongation of hospitalization or postoperative disability, or adverse long-term complications (mean follow-up of 41 months in 250 consecutive laparoscopic cholecystectomy patients). The only difference between patients with and without bile leakage was that the operating time for patients with a gallbladder perforation was approximately 10 minutes longer, presumably owing to the time spent cleaning up the operative field. When perforation does occur, the bile should be aspirated completely, and irrigation should be used liberally. The hole in the gallbladder is best secured with a grasping instrument and sutured or tied with an endoloop, and the stones should be retrieved and removed. Gallbladder spillage, when treated in this manner, results in no adverse short-term or long-term complications.

Escaped stones composed primarily of cholesterol pose little threat of infection. Pigment stones frequently harbor viable bacteria, however, and may lead to subsequent infectious complications if allowed to remain in the peritoneal cavity (Deziel et al, 1993). The long-term complications of retained stones, either intraabdominally with resultant abscess formation or intramurally with resultant port-site abscess, have not been prospectively studied, but case reports and case series in the surgical literature document a clear potential for long-term infectious complications (Carlin et al, 1995; Horton & Florence, 1998; Parra-Davila et al, 1998; Shocket, 1995; Zamir et al, 1999). The relative infrequency of these complications probably does not justify conversion to open operation in the face of spilled stones, but vigilance in avoidance of perforation, a careful search for escaped stones, and liberal use of a plastic retrieval bag for large and friable gallbladders are recommended (Zamir et al, 1999).

Biliary Injury

Of all the potential complications, biliary injuries have received the most attention; these are discussed at length elsewhere in this text (see Chapter 42A). Most series quote major bile duct injury rates of 0.30% or less during open cholecystectomy, whereas the incidence of bile duct injuries during laparoscopic cholecystectomy is 0.40% or higher (Strasberg et al, 1995). These injuries can cause major morbidity, prolonged hospitalization (Cates et al, 1993), high costs, and litigation (Asbun et al, 1993). In addition to aberrant anatomy and the surgeon's inexperience, many reports mention acute or chronic inflammation with dense scarring, operative bleeding obscuring the field, or fat in the portal area contributing to biliary injuries (Adams et al, 1993; Davidoff et al, 1992; Moosa et al, 1992; Soper et al, 1993). The classic biliary injury occurs, however, when the CBD or a right hepatic duct is mistaken for the cystic duct and is divided between clips. Many surgeons attribute this misidentification to the direction of traction of the gallbladder (i.e., pulling the CBD and the cystic duct into alignment, making them appear to be one). Other contributing factors to misidentification are a short cystic duct; a large stone in the Hartmann pouch, making retraction and display of the cystic duct difficult; or tethering of the infundibulum to the CBD by acute or chronic inflammation (Figs. 34.19 and 34.20). Constant awareness of these potential misidentifications and technical causes of biliary injuries is the best method of prevention. If a bile duct injury occurs, an immediate repair should be

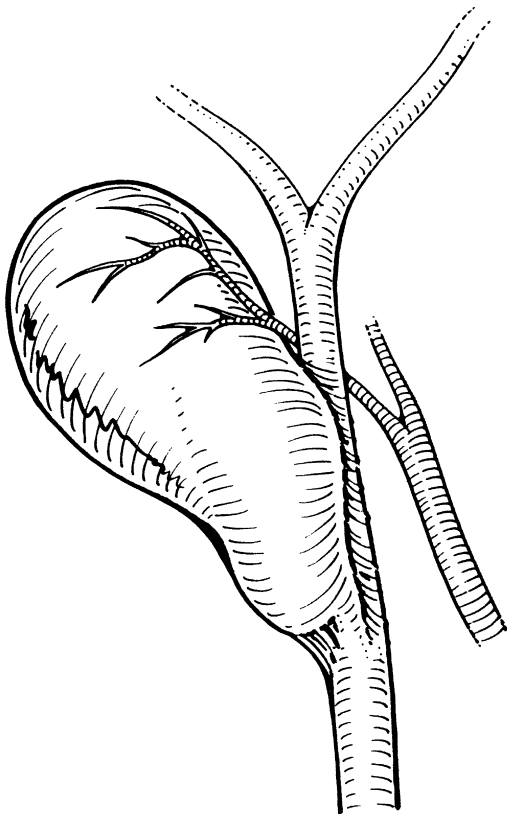


FIGURE 34.19. Severe acute cholecystitis or long-standing chronic cholecystitis may result in the cystic duct and infundibulum of the gallbladder becoming partially adherent or difficult to separate from the common bile duct itself.

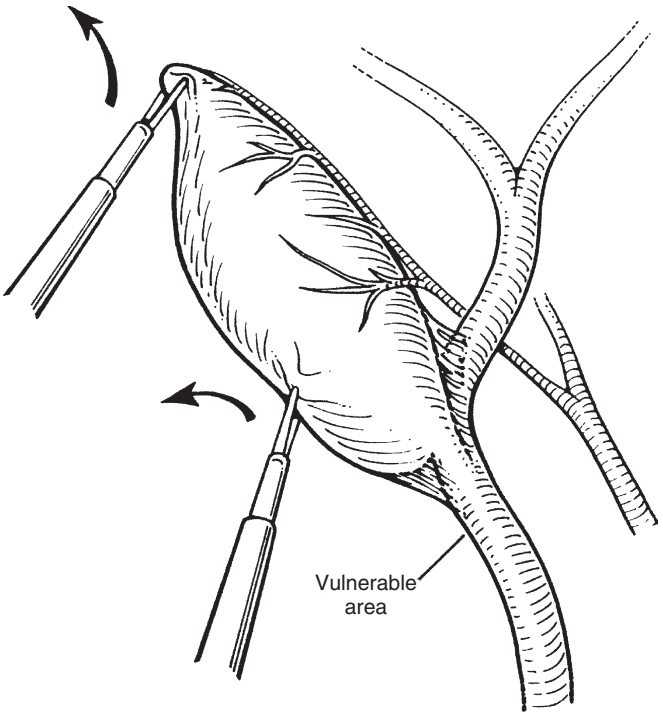


FIGURE 34.20. With excessive traction on the neck of the gallbladder, the common bile duct (CBD) becomes tented and appears to be entering the gallbladder directly. The marked portion of the CBD is most vulnerable to injury during laparoscopic cholecystectomy.

performed with no hesitation in asking for the help of a surgeon experienced in biliary repair.

A bile injury may also be unrecognized at the time of surgery but evident in the postoperative period. A postoperative bile leak occurs in less than 1% of cholecystectomies. Symptoms usually occur 4 to 10 days after surgery and consist of abdominal pain, fever, and abdominal distension. In this setting, it is mandatory to evaluate for biliary injury. Many postoperative bile leaks are considered minor biliary injuries, such as a cystic duct stump leak or an unclipped duct of Luschka. When a bile duct injury is discovered in the postoperative period, a coordinated effort by radiologists, endoscopists, and surgeons is necessary to optimize management (Strasberg et al, 1995). The initial diagnostic study should be US or CT of the abdomen. Fluid will typically be seen in the gallbladder fossa, hepatorenal recess, right gutter, and right subdiaphragmatic spaces. The biloma can be drained percutaneously, and the biliary anatomy should be evaluated with ERCP, which is preferred because it is both diagnostic and potentially theurapeutic. For example, a cystic duct stump leak can be treated successfully in the majority of cases with a temporary transsphincteric biliary stent.

Bleeding

The incidence of uncontrollable bleeding from laparoscopic cholecystectomy is 0.1% to 1.9% and can occur from three distinct sites: 1) the liver, 2) arterial sources, and 3) port insertion sites. Significant bleeding from the liver bed is fairly common and is now appreciated to be from the often close proximity of the middle hepatic vein and its radicals to the gallbladder fossa in up to 10% to 15% of patients. Bleeding usually occurs during the final aspects of the removal of the gallbladder from the hepatic fossa and generally requires immediate conversion to open surgery to control profuse hemorrhage through stitch ligation, if initial attempts at laparoscopic hemostatic control fail. Arterial control issues involving the cystic artery can be identified immediately and controlled with clips, but only if anatomical landmarks can be safely ensured because of a high association with right hepatic arterial injury; such issues may also first be evident postoperatively as an acute hemodynamic decline requiring resuscitation, transfusions, and often reoperation—the culprit is usually a dislodged clip in this scenario. Finally, incision or trocar sites can bleed.

When a trocar injury to a major blood vessel is suspected, the patient must be opened immediately without removing the trocar, and the involved blood vessel must be isolated. In contrast, if the small-bore Veress needle enters a viscus or blood vessel, the operation generally can be completed, and the patient is monitored closely for signs of complications in the postoperative period. Additionally, bleeding may occur if a trocar lacerates a blood vessel within the abdominal wall, such as the epigastric artery or one of its branches. Before removal, each trocar should be visualized from the peritoneal aspect using the laparoscope. If significant hemorrhage is seen, it generally can be controlled with cautery or a through-and-through suture on each side of the trocar insertion site.

Bowel Injury

Inadvertent bowel injury has been described in approximately one to four patients in 1000 laparoscopic procedures. The injury typically occurs during insertion of the initial trocar, and it may occur with either the Veress or open technique. After the initial trocar is inserted, a brief inspection should be performed to evaluate for bowel injury. All other additional trocars should be placed under direct laparoscopic visualization and only in an area free of adhesions. The "protective" shield on disposable trocars is not a guarantee against perforation of intestine or major vessels, especially after previous abdominal operations. Trocar insertion should never be aimed toward the spine or the great vessels, and a hand should be used as a "brake" to prevent inadvertently introducing the trocar too far. Management of this complication is dictated by the clinical scenario. If the injury is identified at the time of surgery, conversion to an open procedure for repair is indicated, if it cannot be repaired through the laparoscope.

One of the most dreaded complications after any laparoscopic surgery is a missed enterotomy. Patients may present with trocar site pain, abdominal distension, diarrhea, leukopenia, and cardiovascular collapse from sepsis, typically within 96 hours of the procedure. If the patient is septic or has free air, an emergent laparotomy is indicated. When the presentation is more indolent and controlled, standard enterocutaneous fistula management with nutritional support and adequate drainage and wound care may be appropriate.

Postcholecystectomy Syndrome

The term *postcholecystectomy syndrome* (PCS; see Chapter 38) describes the presence of symptoms after cholecystectomy. These symptoms can represent either the continuation of symptoms thought to be caused by the gallbladder or the development of new symptoms normally attributed to the gallbladder. PCS also includes the development of symptoms

caused by removal of the gallbladder and is caused by alterations in bile flow resulting from loss of the reservoir function of the gallbladder. Two types of problems may arise: The first is continuously increased bile flow into the upper gastrointestinal (GI) tract, which may contribute to esophagitis and gastritis. The second is related to the lower GI tract, where diarrhea and colicky lower abdominal pain may result. PCS affects about 10% to 15% of patients; however, it is usually a temporary diagnosis, and an organic or functional diagnosis is established in most patients after a complete workup (Jaunoo et al, 2010). Postoperative symptoms may occasionally be caused by retained CBD stones or stones in the cystic duct remnant. Initial workup includes LFTs and US. MRCP or ERCP may be indicated if a retained CBD stone is suspected. A thorough preoperative evaluation is essential to minimize PCS, and patients should be warned of the possibility of postoperative symptoms. Although attempts to preoperatively identify patients at increased risk for PCS have largely been unsuccessful, the consensus opinion holds that the more secure the preoperative diagnosis, the lower the risk of PCS.

RESULTS OF LAPAROSCOPIC CHOLECYSTECTOMY SERIES

Several prospective, randomized trials have compared open cholecystectomy with laparoscopic cholecystectomy, and results have been mixed in showing advantages of laparoscopic cholecystectomy over an open approach in treating elective symptomatic cholelithiasis (Table 34.6). The largest study prospectively randomized 310 patients to laparoscopic cholecystectomy versus minilaparotomy open cholecystectomy with 155 patients in each group. Conversion to large-incision cholecystectomy was significantly more common with laparoscopic cholecystectomy (13% vs. 4%), and complications were significantly more frequent with laparoscopic cholecystectomy (9% vs. 3%). When laparoscopic cholecystectomy was successful, hospital stay was significantly shorter than for open cholecystectomy (2 days vs. 3 days), but overall the hospital stay was not significantly different. Postoperative analgesia requirements were reduced, and return to normal activities and to work was faster after laparoscopic cholecystectomy, but no significant cost difference was reported between the two procedures (McGinn et al, 1995).

Similarly, another study prospectively randomized 200 patients in a single-blinded fashion (identical wound dressings were applied in both groups so that caregivers would be blinded to the type of operation) to laparoscopic cholecystectomy versus minilaparotomy open cholecystectomy. Laparoscopic cholecystectomy took significantly longer than small-incision cholecystectomy (median, 65 min vs. 40 min; $P < .001$). No significant difference was reported in length of stay (median, 3 days for laparoscopic cholecystectomy vs. 3 days for small-incision open cholecystectomy; $P = .74$), return to work (median, 5 weeks vs. 4 weeks; $P = .39$), and time to full activity (median, 3 weeks vs. 3 weeks; $P = .15$) (Majeed et al, 1996).

A follow-up to this study prospectively randomized 200 additional patients to laparoscopic cholecystectomy or minilaparotomy open cholecystectomy. Postoperative pain, analgesic and antiemetic consumption, perceived health, and metabolic and respiratory responses were compared. Pain scores in both groups were low, but laparoscopic cholecystectomy was associated with lower postoperative pain scores and analgesic requirements compared with small-incision open cholecystectomy, however, the antiemetic requirements were greater after laparoscopic cholecystectomy. The duration of hospital stay and the perceived

Table 34.6

Prospective Randomized Trials of Open vs. Laparoscopic Cholecystectomy

Study, Procedure	*N*	Operating Time (min)	Complications (%)	Length of Stay (Days)	Return to Work (Days)
Barkun et al, 1992					
OC (minilap)	25	73	8	4*	20*
LC	37	86	2.7	3	12
Trondsen et al, 1993					
OC	35	50*	20	4*	34*
LC	35	100	17	3	11
Berggren et al, 1994					
OC	12	69*	—	3*	24*
LC	15	87	—	2	12
McMahon et al, 1994					
OC (minilap)	148	57*	20	4*	—
LC	151	71	17	2	—
Majeed et al, 1996					
OC (minilap)	100	40*	Not reported	3	35
LC	100	65	Not reported	3	28
Kiviluoto et al, 1998					
OC	31	*	23*	6*	—
LC	32	—	3	4	—

*$P < .05$

LC, laparoscopic cholecystectomy; minilap, minilaparotomy; OC, open cholecystectomy

Table 34.7

Results of Large Series of Laparoscopic Cholecystectomy

Study	No. Patients	Conversion (%)	Mortality Rate (%)	Complications* (%)	Bile Duct Injuries (%)
Deziel et al, 1993	77,604	–	0.04	2	0.6
Scott et al, 1992	12,397	4.3	0.08	4	0.4
Deveney, 1993	9597	–	0.04	2.5	0.3
Croce et al, 1994	6865	3.1	0.06	2.5	0.3
Orlando et al, 1993	4640	6.9	0.13	8.6	0.3
Schlumpf et al, 1994	3722	7	0.08	4.8	0.6
Collet et al, 1993	2955	4.8	0.20	3.4	0.6
Airan et al, 1992	2671	4.6	0.15	–	0.2
Kane et al, 1995	2490	7.8	–	–	–
Litwin et al, 1992	2201	4.3	0	–	0.1
Kimura et al, 1993	1989	2.7	0	1.8	0.6
Larson et al, 1992	1983	4.5	0.10	2.1	0.3
Fullarton et al, 1994	1683	17	0.50	5.9	0.7
Newman et al, 1995	1525	2.2	0.26	4.1	0
Meyers & Southern Surgeons Club, 1991	1518	4.7	0.07	1.5	0.5
Cuschieri et al, 1991	1236	3.6	0	1.6	0.3
Brune et al, 1994	800	1.2	0	2.8	0.2
Perissat et al, 1992	777	5.5	0.10	3.3	0.4
Jatzko et al, 1995	740	5.4	0.14	1.9	–
Wu et al, 1998b	1200	2.1	0.10	2.7	0.2

*Includes intraoperative and postoperative complications

health after operation were the same, and both procedures were associated with a similar reduction of respiratory function. Twenty-four hours after operation, the inflammatory (C-reactive protein) response to laparoscopic cholecystectomy (22 ± 20 mg/L) was significantly lower than after small-incision open cholecystectomy (68 ± 30 mg/L), but the neuroendocrine (cortisol) response was similar (laparoscopic cholecystectomy, 475 ± 335 nmol/L compared with small-incision open cholecystectomy, 710 ± 410 nmol/L; Squirrell et al, 1998).

Numerous clinical series of laparoscopic cholecystectomy, accrued prospectively or retrospectively, also have been reported (Table 34.7). Among our personal series of more than 1,500 laparoscopic cholecystectomies performed in a teaching institution, the conversion rate was 2.1% with one perioperative death (<0.1%) owing to myocardial infarction at 1 week postoperatively. Significant postoperative complications occurred in 2.7%, including three minor duct injuries (0.2%). The mean operative time decreased from more than 100 minutes in the first 100 patients to 85 minutes in the most recent 100 patients. The postoperative course in most patients was uneventful, with more than 90% of patients discharged from the hospital within 24 hours of surgery; only 10% required parenteral narcotics after leaving the recovery room. Similarly, the duration of disability was minimal, with the average postoperative interval to return to full activity being 10 days. These results compared favorably with the results of traditional open cholecystectomy, in which the morbidity and mortality rates were similar, but hospitalization for 3 to 5 days and return to work at 1 month after surgery were standard (Wu et al, 1998b).

Our data mirror those from most series of laparoscopic cholecystectomy reported to date. Morbidity rates range from 1.5% to 8.6%, and bile duct injuries range from 0.2% to 0.7%. Death is rare after this procedure and usually is attributed to unrelated events. The conversion rates from laparoscopic to open operation in most series range from 1.8% to 7.8% and generally are greater early in the surgeon's experience with the procedure. A nationwide study reported a conversion rate to open procedure of 5% to 10% (Livingston & Rege, 2004). In addition, studies have shown that advanced age, longer duration of procedure, and acute cholecystitis significantly increase postoperative morbidity and the length of stay (Lyass et al, 2000; Perraux et al, 2000).

As would be predicted for this excisional procedure, laparoscopic cholecystectomy effectively treats gallstone disease. Postcholecystectomy problems (see Chapter 38) occur in some patients, however. Kane and colleagues (1995) noted 89% of patients undergoing laparoscopic cholecystectomy had preoperative biliary-type pain, and only 10.6% of the patients had similar pain postoperatively. Similarly, Ure and colleagues (1995) found that the percentage of patients with biliary colic was reduced from 83% before laparoscopic cholecystectomy to 6.4% after laparoscopic cholecystectomy. Fenster and associates (1995) examined symptom relief in 225 patients who underwent laparoscopic cholecystectomy, followed postoperatively for 3 weeks to 3 months. They differentiated symptomatic gallstones from acalculous cholecystitis and discovered that 82% of patients with biliary colic and gallstones had complete relief of upper abdominal pain after the operation compared with only 52% of patients with acalculous cholecystitis (Fenster et al, 1995). These data are comparable to the data for open cholecystectomy, which showed that biliary-type pain persisted at follow-up (<1 year) in 9% to 34% of patients with

symptomatic gallstones (Bates et al, 1991; Gilliland & Traverso, 1990; Scriven et al, 1993). In terms of cost-effectiveness, several studies have shown that laparoscopic cholecystectomy is less expensive than an open procedure (Bass et al, 1993; Fullarton & Bell, 1994), whereas others have shown the opposite (McMahon et al, 1994).

EMERGING TECHNIQUES

Natural Orifice Translumenal Endoscopic Surgery Cholecystectomy

Over the past few years, many technical innovations have attempted to further minimize the field of laparoscopy. In 2004, peritoneoscopy was performed in an animal model by passing a flexible endoscope through the wall of the stomach and into the peritoneal cavity (Kalloo et al, 2004). This resulted in the concept of natural orifice translumenal endoscopic surgery (NOTES), with its general goal of minimizing trauma by eliminating incisions through the abdominal wall and utilizing natural orifices. Although a number of potential natural orifices can theoretically be used to access the abdominal cavity, clinical cases have thus far only used transgastric (TG) and transvaginal (TV) approaches. Human applications currently have been limited and have relied on laparoscopic-assisted or so-called hybrid techniques.

TG and TV cholecystectomy were both first described in humans in the United States in 2007. Compared with TG cholecystectomy, TV cholecystectomy is technically easier to perform because of the direct vision-guided access and a straight route to the upper abdomen. In addition, the TV route obviates the risk of gastric content leakage via an imperfectly closed gastrotomy access site. As a consequence, many more NOTES cholecystectomies have been performed in humans via a TV approach as opposed to a TG approach. All reports of NOTES cholecystectomy have highlighted the limits imposed by the inadequacy of current instrumentation, resulting in lack of exposure, fine dissection, and safe cystic duct ligation, therefore requiring a hybrid technique to perform the operation safely. In general, TV procedures take up to twice as long as standard laparoscopic operations, whereas TG operations triple the operating time. Few complications have been reported to date. Currently, NOTES remains investigational and is only performed at a few centers worldwide. Many of the limitations remain centered on instrument development, very few data exist to quantify postoperative pain and disability, and no prospective randomized trials comparing NOTES cholecystectomy to laparoscopic cholecystectomy have been done. Again, given the high bar that has been set for the results of laparoscopic cholecystectomy, it may be difficult to show a meaningful clinical advantage of NOTES cholecystectomy. However, the concept of NOTES has challenged surgeons to further advance surgery, and it continues to drive the development of new technology and techniques.

Single-Incision Laparoscopic Surgery Cholecystectomy

Single-incision laparoscopic surgery (SILS) cholecystectomy was first described in the Italian literature in the mid-1990s. Navarra and colleagues (1997) published the first case series of 30 patients who underwent what they described as "one-wound laparoscopic surgery." Their method used three extracorporeal stay sutures and two 11-mm working ports in the umbilicus, and the incisions were connected at the end of the case to facilitate the removal of the gallbladder. The mean operative time was 123 minutes, and the mean postoperative stay was 1.8 days. These initial reports did not receive much attention, but recently a resurgence of interest in SILS has been seen with a concurrent rapid development of instrumentation.

SILS emphasizes the concept of surgery through one small transabdominal incision, rather than the standard multiple trocar sites, with theoretic benefits of less pain and better cosmesis. The allure of SILS is that the surgeon can use relatively standard laparoscopic instruments and skills without the technical difficulties associated with NOTES. As a result, SILS can be more readily implemented and is likely to have a higher degree of acceptance. Several small series have demonstrated the feasibility and safety of SILS cholecystectomy. However, because it is relatively new and in evolution, many techniques have been described, and no widely accepted standard exists.

Although SILS cholecystectomy provides an apparent cosmetic advantage by hiding the surgical scar in the umbilicus, other proposed benefits are yet to be determined. Concerns revolve around the surgeon's limited ability to triangulate and to exercise traction and countertraction on tissue dissecting planes. In addition, the view is often in line with the camera, which may compromise depth perception and visualization. It is of paramount importance to maintain the same surgical principles and not to compromise visualization of the anatomic landmarks to avoid unnecessary complications, such as bile duct injuries. Supplemental stab incisions or extracorporeal stay sutures in the right upper quadrant are often needed to provide adequate retraction of the gallbladder and proper visualization of the triangle of Calot. Specialized instrumentation, such as reticulating instruments and multichannel ports, have been also developed to help overcome some of these limitations. Standard four-port laparoscopic cholecystectomy remains the gold standard treatment for benign gallbladder disease, but SILS cholecystectomy will continue to develop and may have a role in select groups of patients. Well-designed clinical trials powered adequately are needed to better understand the risk-benefit profile of SILS cholecystectomy.

CONCLUSION

The vast majority of cholecystectomies in the developed world are performed laparoscopically with excellent results. Many patients now can undergo this operation in an ambulatory setting. Most CBD stones can be removed at the time of laparoscopic cholecystectomy, extracted through the cystic duct or by direct choledochotomy. Attempts at improving outcomes from laparoscopic cholecystectomy are valuable and will drive the development of novel surgical instrumentation. The newer approaches to cholecystectomy, including single-incision laparoscopy and NOTES procedures, should be pursued but must also be compared honestly and openly to the current gold standard of laparoscopic cholecystectomy.

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CHAPTER 35

Stones in the bile duct: clinical features and open surgical approaches and techniques

Katia Papalezova and Bryan Clary

OVERVIEW

Although the era of intervention for choledocholithiasis can be traced to over a century ago, with the first successful common bile duct (CBD) exploration by Thornton in 1889 and with the introduction of catheter-based biliary decompression by Courvoisier and Kehr, significant advances and refinements did not occur until recent decades. For many years, open cholecystectomy and exploration of the CBD remained the standard treatment for patients with choledocholithiasis, and it was a procedure carried out on a regular basis by most general surgeons. During that era, the morbidity and mortality rates of CBD exploration were very low, the percentage of retained stones was only 1% to 3%, and in long-term follow-up, revisional surgery was necessary in only about 10% of the patients (Gonzalez et al, 1997; Hammarström et al, 1995; Neoptolemos et al, 1987; Targarona et al, 1996).

The past 3 decades, however, have seen major changes in the management of choledocholithiasis, prompted by the introduction of high-quality noninvasive imaging, the more widespread availability of percutaneous and endoscopic approaches to duct clearance (see Chapters 27 and 28), and the introduction of minimally invasive surgical approaches in the performance of choleycstectomy and CBD exploration (see Chapter 34). Although the overwhelming majority of cholecystectomies are now performed laparoscopically, laparoscopic exploration of the common bile duct (LCBDE) is infrequently performed, given the advanced skills typically required and the availability of endoscopic retrograde cholangiopancreatography (ERCP; see Chapter 18). In a recent survey of general surgeons practicing in a rural area of the United States, the preferred approach to choledocholithiasis was ERCP (75%), followed by laparoscopic (21%) and open (4%) exploration. Time constraints and lack of equipment were the main factors preventing the application of the laparoscopic technique for treating choledocholithiasis (Bingener & Schwesinger, 2006).

Despite these considerations, there remain indications for operative choledochotomy and, more specifically, for open exploration. This chapter presents a review of the clinical features of choledocholithiasis with an emphasis on the technical aspects of open CBD exploration.

ORIGIN OF CHOLEDOCHOLITHIASIS

Most CBD stones are secondary in nature, having migrated from the gallbladder. This is in contrast to primary CBD stones that originate within the CBD. The existence of such primary stones is suggested by their occurrence in patients with congenital absence of the gallbladder and in those whose CBD had been previously cleared at the time of prior cholecystectomy. The practice of routine cholangiography during the era of open cholecystectomy was common and demonstrated an incidence of choledocholithiasis approaching 10% in patients without clinically evident common duct involvement (McSherry & Glenn, 1980; Hampson et al, 1981; Doyle et al, 1982; Lygidakis, 1983; Coelho et al, 1984; Ganey et al, 1986; DenBesten & Berci, 1986; Girard, 2000). Some 10% to 15% of gallstone patients concomitantly suffer from bile duct stones. In the United States and other Western countries, CBD stones are predominantly secondary, although primary stones are more common in Asia. This is associated with the high incidence of intrahepatic bile duct stones seen primarily in Southeast Asian countries, Taiwan, Hong Kong, and Singapore (Kim et al, 1995; see Chapter 39). The relative prevalence of intrahepatic bile duct stones in all gallstone cases in Taiwan is extremely high (>50%), and coexisting intrahepatic and extrahepatic bile duct stones are found in approximately 70% of these. Furthermore, the gallbladder stones are primarily cholesterol or black-pigment stones, whereas most bile duct stones are brown-pigment (calcium bilirubin stones).

CLINICAL FEATURES

The natural history of CBD stones is unpredictable, with many small stones passing spontaneously. In the era of open cholecystectomy, a healthy debate surrounded the need for routine intraoperative cholangiography in patients without clinical signs of choledocholithiasis. Detractors noted that although 10% to 15% of patients had cholangiographic findings of CBD stones when routine cholangiography was used, a much lower percentage of patients developed clinical sequelae of CBD stones in series that utilized a more selective approach to cholangiography.

More recent series of laparoscopic cholecystectomy with a selective approach toward cholangiography appear to confirm this same experience (Fogli et al, 2009). In one of the more notable recent experiences, Collins and colleagues (2004) identified filling defects consistent with stones in 4.6% of patients. In these patients, access was maintained for the performance of postoperative cholangiograms. At 48 hours, 26% of patients had a normal cholangiogram, and an additional 26% had evidence for passage of the stones by 6 weeks. Twenty-two patients (2.2% of total population) had persistent CBD stones at 6 weeks after laparoscopic cholecystectomy and underwent ERCP for retrieval (Collins et al, 2004).

Symptomatic presentations include biliary colic, jaundice, cholangitis, pancreatitis, or combinations of these. Infection in

the setting of CBD obstruction gives rise to the classic triad of fever with chills, jaundice, and pain; in some patients this can be associated with clinical signs of sepsis (see Chapter 43). In the absence of infection, jaundice may occur in an often fluctuating manner, as the stone intermittingly obstructs passage of bile. Over long periods, this process can lead to secondary biliary cirrhosis. After biliary colic, pancreatitis is the second most frequent symptomatic presentation of CBD stones (see Chapter 53). Depending on the timing of cholangiography, CBD stones can be identified in up to 50% of patients. Patients who have symptomatic bile duct stones are at risk of experiencing further symptoms or complications if left untreated. More than one half of patients who had retained bile duct stones experienced recurrent symptoms during a follow-up period of 6 months to 13 years (Johnson & Hosking, 1987), and 25% developed serious complications (Caddy & Tham, 2006). Given the potentially serious nature of CBD stones, it is critical that an approach be adopted to identify patients with CBD stones and ensure their clearance.

PREOPERATIVE DIAGNOSIS

The identification of patients with choledocholithiais in the absence of clinical signs requires a careful history and physical examination in conjunction with attention to routine blood work and abdominal ultrasound. Clinical, ultrasonographic, and serum chemistry data are sensitive in 96% to 98% and specific in 40% to 75% for identification of patients with choledocholithiasis (Alponat et al, 1997; Koo & Traverso, 1996; Trondsen et al, 1998). Liu and colleagues (2001) triaged patients before laparoscopic cholecystectomy using guidelines incorporating patient information obtained from clinical evaluation, serum chemistry analysis, and abdominal US and assigned them into four groups based on the level of suspicion for choledocholithiasis (group 1, extremely high; group 2, high; group 3, moderate; group 4, low). The occurrence of choledocholithiasis was 92.6%, 32.4%, 3.8%, and 0.9% for groups 1, 2, 3, and 4, respectively. Patient triage resulted in the identification of CBD stones during preoperative ERCP in 92.3% of the patients who were subsequently referred for endoscopic clearance. Many other groups have also demonstrated the value of liver function tests (LFTs) in predicting the presence of CBD stones (Peng et al, 2005; Sgourakis et al, 2005). Although the trends of bilirubin and alkaline phosphatase are more typically used, a raised gamma-glutamyltransferase level has been suggested to be the most sensitive and specific indicator of CBD stones. A value greater than 90 U/L has been proposed to indicate a high risk of choledocholithiasis, with sensitivity and specificity of 86% and 74.5%, respectively (Peng et al, 2005).

In patients identified to be at risk by clinical history and/or abnormalities in serum chemistries, if imaging and therapy are necessary, an efficient and thoughtful approach is required. Transabdominal ultrasound (TUS) is the most commonly used initial diagnostic tool for suspected biliary stones (see Chapter 13). It has the advantage of being noninvasive, widely available, and inexpensive; however, US is highly operator dependent. TUS has low sensitivity, 25% to 60%, for detection of bile duct stones, but it has a very high specificity, 95% to 100% (Sugiyama & Atomi, 1997; Amouyal et al, 1994). Indirect evidence, such as the presence of gallstones or biliary ductal dilation with a CBD diameter greater than 6 mm in the appropriate clinical setting, is predictive of bile duct stones.

Computed tomography (CT) scanning has a similarly low sensitivity in the detection of bile duct stones and is used primarily to document biliary dilation or to exclude other causes of biliary obstruction (e.g., a mass lesion; see Chapter 16). The role of helical CT cholangiography is still in evolution, particularly in the United States. Intravenously administered contrast agents combined with high-resolution helical scans and three-dimensional reconstructions can be very useful in diagnosing choledocholithiasis (Cabada Giadàs et al, 2002; Maniatis et al, 2003). The sensitivity of this technique can be as high as 97%, and the specificity is 85% to 96% (Polkowski et al, 1999; Cabada Giadas et al, 2002; Maniatis et al, 2003; Gibson et al, 2005; Kim et al, 2007). Although this accuracy is comparable to magnetic resonance cholangiopancreatography (MRCP), helical CT cholangiography is limited by 1) possible allergic reactions to the contrast agents, as high as 15% in one series using intravenous iotroxate (Gibson et al, 2005); 2) suboptimal ductal contrast opacification in the presence of significant jaundice, evidenced by bilirubin more than two or three times the upper limits of normal (Polkowski et al, 1999; Soto et al, 1999); and 3) limited visualization of intrahepatic duct branches, particularly when using oral contrast agents (Gibson et al, 2005; Chopra et al, 2000).

Since its introduction in 1991 (Wallner et al, 1991), MRCP has emerged as an accurate, noninvasive diagnostic modality for investigating the biliary and pancreatic ducts (Hallal et al, 2005) and has been recommended in some circles as the preoperative procedure of choice for the detection of CBD stones (Hallal et al, 2005; Taylor et al, 2002; Topal et al, 2003; see Chapter 17). MRCP provides excellent anatomic detail of the biliary tract and has a sensitivity of 81% to 100% and a specificity of 92% to 100% in detecting choledocholithiasis (Hallal et al, 2005). The accuracy of MRCP in diagnosing CBD stones is comparable with that of ERCP (see Chapter 18) and intraoperative cholangiogram (Hallal et al, 2005; Vargghese et al, 2000; see Chapter 21). It thus avoids the need for an invasive procedure in about 50% of patients (Demartines et al, 2000), allowing selective use of ERCP or surgical CBD exploration in those patients who require a therapeutic intervention. These results have led some practitioners to consider MRCP the new gold standard for biliary imaging (Hallal et al, 2005; Shanmugam et al, 2005), although MRCP may miss stones smaller than 5 mm in diameter. It can also underestimate the number of stones detected (Vargghese et al, 2000). MRCP is an expensive option that requires significant expertise for interpretation, and it may not always be readily available.

For years, the gold standard for preoperative visualization of the bile duct has been ERCP (see Chapter 18); however, the nonselective use of ERCP in all patients with suspected choledocholithiasis detects CBD stones in less than 50% (Behrns et al, 2008; Petrov et al, 2008) and results in over half of patients undergoing an unnecessary procedure, exposed to its associated morbidity and mortality. The first publications on the usefulness of the alternative, noninvasive modality, endoscopic ultrasonography (EUS), in diagnosing CBD stones appeared around 1990 (Amouyal et al, 1989; Edmundowicz et al, 1992; see Chapter 14). Since then, more than 25 prospective studies, incorporating more than 2500 patients with suspected choledocholithiasis, have shown excellent accuracy with EUS, as well as safety.

The overall diagnostic performance of EUS has been evaluated in two recent metanalyses (Garrow et al, 2007; Tse et al, 2008); the pooled sensitivity and specificity of EUS were 89% to 94% and 94% to 95%, respectively. A review of all randomized controlled trials of EUS-guided ERCP versus ERCP alone in patients with suspected choledocholithiasis demonstrated that by performing EUS first, ERCP may be safely avoided in two thirds of patients, and the use of EUS significantly reduced the risk of overall complications and post-ERCP acute pancreatitis (Petrov & Savides, 2009). The data suggest that the ERCP should be reserved solely for patients with a high probability of CBD stones.

Before the advent of laparoscopy, preoperative clearance of CBD stones with ERCP before open exploration was uncommon. Several well-performed studies did not demonstrate any improvement in morbidity or mortality with preoperative endoscopic sphincterotomy (Heinerman et al, 1989; Neoptolemos et al, 1988; Stain et al, 1991). One study showed an increase in morbidity when preoperative ERCP with sphincterotomy was added to open cholecystectomy compared with cholecystectomy and open CBD exploration (Stain et al, 1991). A Cochrane systematic review by Martin and colleagues (2006) showed that open surgery results in a lower primary treatment failure, fewer additional procedures, fewer average number of procedures required per patient, and less mortality. Largely based on these studies, preoperative ERCP with sphincterotomy was uncommon in the era of open cholecystectomy, and it did not become more widespread until laparoscopic approaches to cholecystectomy appeared.

When laparoscopic cholecystectomy was introduced, preoperative ERCP was frequently used for patients suspected of having choledocholithiasis, as evidenced by jaundice, elevated liver function tests, a history of pancreatitis, and a dilated biliary system. Even with these criteria, however, it is difficult to predict which patients will have choledocholithiasis, and a negative ERCP was performed in 40% to 70% of patients, because most of these abnormalities were caused by transient biliary obstruction secondary to stones that subsequently passed into the duodenum (Stain et al, 1991; Ponsky, 1992; Delorio et al, 1995; Cotton, 1993; Cuschieri et al, 1996).

Two prospective randomized controlled trials have compared preoperative ERCP with sphincterotomy followed by laparoscopic cholecystectomy during the same hospital admission with single-stage laparoscopic management (Cuschieri et al, 1999; Sgourakis et al, 2005). The results demonstrate equivalent success rates of duct clearance and patient morbidity for the two management options, but a significantly shorter hospital stay was reported with the single-stage laparoscopic treatment. Cuschieri and colleagues (1999) concluded that in fit patients (ASA I and II), single-stage laparoscopic treatment is the better option, and preoperative endoscopic sphincterotomy (ES) should be confined to poor-risk patients, such as those with cholangitis or severe pancreatitis.

Performing ERCP has clinical and financial costs that must be weighed against the likelihood of successful extraction of stones that otherwise would result in significant disease manifestation. Complications that include postprocedural pancreatitis, bleeding, infections, and perforations are not uncommon. ERCP has an overall complication rate of 10% and a mortality rate less than 0.5% (Ponsky, 1992; Delorio et al, 1995; Cotton, 1993; Davis et al, 1997). A recent systematic analysis of prospective studies has shown that complications continue to occur at a relatively consistent rate and that the majority of events are of mild to moderate severity (Andriulli et al, 2007).

Certain clinical situations mandate preoperative ERCP. Preoperative endoscopic drainage should be used in acute cholangitis for decompression and amelioration of sepsis (Cuschieri et al, 1999; Leung, 2003) and in patients with severe gallstone pancreatitis and evidence of persistent choledocholithiasis. Patients with other major comorbidities or limited life expectancy represent another indication for ERCP with endoscopic sphincterotomy (ES) and decompression (Cuschieri et al, 1999), often as the definitive management without cholecystectomy.

COMMON BILE DUCT EXPLORATION AT CHOLECYSTECTOMY

In the early 1970s, ES was introduced as a treatment modality for CBD stones. During the following decades, it gained wide acceptance as a less invasive, highly effective alternative for the treatment of biliary obstruction as a result of gallstones (see Chapters 18 and 27). However, in patients with residual stones in the gallbladder, subsequent cholecystectomy was considered necessary. In a prospective randomized trial, it was demonstrated that ES before open cholecystectomy did not lead to earlier recovery or less postoperative morbidity compared with primary open cholecystectomy combined with CBD exploration. In a prospective randomized trial published in 1995 by Hammarström and colleagues, an expectant policy after ES was compared with open cholecystectomy combined with CBD exploration. It appeared that 20% of the patients after ES alone needed cholecystectomy during follow-up.

Similar results were reported in 1996 by Targarona and colleagues. In this prospective randomized trial of high-risk patients, the policy of ES and subsequent open cholecystectomy was compared to ES alone. In their experience, patients who underwent elective open cholecystectomy had significantly fewer recurrent biliary symptoms (6% vs. 21%) and needed fewer readmissions (4% vs. 23%) than patients who did not undergo surgery after ES. (Targarona et al, 1996). Given the recognition that cholecystectomy is necessary in most patients with CBD stones, even in the presence of a papillotomy, the appropriate timing and method of CBD clearance must be considered.

In less developed health care environments, where endoscopic or percutaneous approaches to biliary decompression and stone clearance are limited, open cholecystectomy with bile duct exploration is indicated in patients with a strong clinical suspicion for common duct stones, such as those with abnormal LFTs or cholangitis, as well as when palpable stones are present in the CBD, or when stones are visualized on an intraoperative cholangiogram.

In more developed health care settings with access to endoscopic, radiologic, or laparoscopic expertise, there will still be some patients in whom an open approach to CBD exploration is required. These include 1) patients with large or impacted CBD stones, in whom biliary enteric drainage is indicated; 2) those with anatomic considerations that preclude endoscopic treatment, such as prior gastric resection, duodenal diverticulae, and so on; and 3) patients who require an open approach for cholecystectomy, including those with Mirizzi syndrome, biliary-enteric fistula, a high index of suspicion for cancer, and those with CBD stones demonstrated by palpation or cholangiogram.

Postcholecystectomy Choledocholithiasis

Incidence

Although most initial operations for gallstone disease with or without demonstrated choledocholithiasis are curative, a few patients are found later to have additional stones in the CBD. Approximately 1% to 2% of all patients who undergo cholecystectomy have stones left in the CBD that require further intervention (Roslyn, 1993). Although retained or overlooked calculi after open cholecystectomy without CBD exploration are rare (Bergdahl & Holmlund, 1976), their incidence after open cholecystectomy with concomitant CBD exploration has been reported to be less than 5% (Dayton et al, 1984; Kappes et al, 1982; Roslyn, 1993), with a higher frequency after positive than after negative CBD exploration. After a second operation on the biliary tract, a recurrence rate of approximately 20% has been reported (Saharia et al, 1977; Way, 1973), with even higher rates after subsequent reoperation (Allen et al, 1981).

Treatment

The choice of management is determined by the clinical presentation, condition of the patient, availability of equipment, availability of clinical expertise, and presence or absence of a T-tube. Currently, operative management of retained and recurrent CBD stones is resorted to only if nonoperative procedures have failed.

RETAINED STONES IN THE PRESENCE OF A T-TUBE

With the advent of laparoscopic biliary surgery, the use of the T-tube has become less common, eliminating methods for accessing the biliary tree postoperatively without an invasive procedure. If a patient with a retained CBD stone is in the immediate postoperative period and still has a T-tube in place, the management options are observation, mechanical extraction, or ES.

In the absence of biliary obstruction or infection, no treatment is necessary for 4 to 6 weeks. During this time, 10% to 25% of retained stones found on postoperative cholangiography can be expected to pass spontaneously into the duodenum, and no further treatment is required. If after 4 to 6 weeks the stone persists, the choice of treatment is between a radiologic approach through the T-tube tract (see Chapter 28) or endoscopic retrograde sphincterotomy (see Chapter 27). Because of its high success rate and low morbidity and mortality, nonoperative mechanical extraction through the T-tube tract is an attractive treatment choice. A success rate of 95% has been reported with a morbidity rate of only 4% (Mazzariello, 1978). Burhenne (1980) reported no deaths in 661 patients. When complications do occur, they can be treated medically in most instances, and only 0.2% of cases have required surgery (Mazzariello, 1978).

ES also has been shown to be effective in the management of retained stones in the early postoperative period after exploration of the CBD with a T-tube still in place (Hammarström et al, 1996; O'Doherty et al, 1986). Although ES has the considerable advantage that it can be carried out as soon as retained stones are discovered, treatment may be unnecessary in some patients, because stones may pass spontaneously. The results of mechanical stone extraction through the T-tube tract are better than any reported for ES (Lambert et al, 1988), which may be best used when the patient is clinically unstable, the T-tube is inappropriate in size and position, or mechanical extraction through the T-tube has failed. If these techniques fail, operative management can be resorted to with the expectation of a high success rate and rates for morbidity and mortality comparable to those for endoscopic retrograde sphincterotomy (Cameron, 1989; Girard & Legros, 1981).

RETAINED OR RECURRENT STONES IN THE ABSENCE OF A T-TUBE

For a patient without a T-tube in place, ES is the procedure of choice and should be attempted first (Cameron, 1989; Sivak, 1989). Most reports of ES indicate a success rate in achieving overall clearance of stones from the CBD of more than 85% (Cotton, 1984; Lambert et al, 1991). Although early complication rates for ES are 5% to 10%, with emergency surgery being required in 1% to 2% of cases, most complications can be managed conservatively (Cotton, 1984; Escourrou et al, 1984). Hemorrhage, pancreatitis, cholangitis, and perforation are the most frequent complications, and mortality usually is reported at 0.5% to 2% (Lambert et al, 1991; Sivak, 1989). Long-term complication rates, mainly from stenosis or new stones or both, are low (<10%), and most complications can be managed endoscopically (Cotton, 1984; Escourrou et al, 1984; Hammarström et al, 1996; Sivak, 1989).

If for any reason ES is contraindicated, or if it fails, operative management is a reasonable alternative (Cameron, 1989). Reoperation for retained or recurrent stones can be performed with negligible operative mortality and morbidity (Girard & Legros, 1981). This report, which included many series, showed that reoperation on the CBD for retained or recurrent stones is possible, with a mortality rate of less than 2%. Miller and colleagues (1988) reported 237 patients with CBD stones treated by CBD exploration or ES. Success was higher and mortality was lower for the operatively managed group. The complication rate was similar, but the complications tended to be more serious and more apt to require surgery in the ES group. These studies show that the success, morbidity, and mortality rates of surgery are comparable to those of endoscopic approaches and suggest that operation should not be forgotten in the treatment of retained or recurrent bile duct stones.

When performing reoperation for retained CBD stones, if the stones can be adequately and completely removed, the most appropriate surgical procedure is choledocholithotomy, choledochoscopy, placement of a T-tube, and completion cholangiography. This procedure is adequate for most patients, and the overall failure rate is only 3% (Girard & Legros, 1981). Others have reported failure rates of 18% and 30% (Allen et al, 1981; Saharia et al, 1977). Allen and colleagues (1981) and Lygidakis (1982) recommended a biliary-enteric drainage procedure in all patients with previous choledocholithotomy (see Chapter 29). Tompkins and Pitt (1982) and Cameron (1989) emphasized, however, that concomitant biliary drainage should not be done as a mandatory procedure in all patients with retained or recurrent stones. In general, biliary-enteric drainage at reoperation should be carried out if any of the following occur: 1) stricture or stenosis of the distal bile duct or sphincter of Oddi, 2) marked dilation of the duct of 2 cm or more, 3) multiple or primary bile duct stones, 4) inability to remove all stones from the duct, 5) a third operation.

Transduodenal sphincteroplasty (see further on), choledochoduodenostomy, or choledochojejunostomy is effective (Braasch et al, 1980; Johnson & Harding Rains, 1978; Jones, 1978). Sphincteroplasty is rarely necessary, because ES suffices in many cases. ES is of no value, however, in the presence of a

long stricture of the distal duct. Sphincteroplasty is the preferred operative approach in patients with a duct smaller than 1.5 cm in diameter to avoid possible stricture formation at the anastomosis, but it carries a greater risk of postoperative pancreatitis. Side-to-side or end-to-end choledochoduodenostomy and end-to-side Roux-en-Y choledochojejunostomy are suitable for CBDs larger than 1.5 cm and offer better decompression of an extremely large duct. The mortality rate of choledochoduodenostomy is lower than that attending transduodenal sphincteroplasty, and it has been shown to be a safe and simple operation with low morbidity and mortality, especially in elderly patients (Lygidakis, 1982; Schein & Gliedman, 1981). Occasionally, recurrent or primary stones are seen in patients with dilated ducts and a widely patent sphincter. In such cases, which also have been reported after endoscopic papillotomy, side-to-side choledochoduodenostomy or end-to-side Roux-en-Y choledochojejunostomy is necessary.

Table 35.1

Mortality Rates of Biliary Reoperation for Retained or Recurrent Bile Duct Stones

Reference	No. Operations	No. Deaths (%)
Saharia et al, 1977	30	0
Jones, 1978	22	0
McSherry & Glenn, 1980	341	7 (2%)
Allen et al, 1981	47	1 (2%)
De Almeida et al, 1984	24	1 (4%)
DenBesten & Berci, 1986	86	2 (2.3%)
Girard, 2000	88	0
TOTAL	920	15 (1.6%)

Results of Clinical Experience with Reoperation

The courses of all patients who had a reoperation for retained or recurrent choledocholithiasis at the Maisonneuve-Rosemont Hospital between 1969 and 1990 were reviewed (Girard, 2000). Eighty-five patients underwent a total of 88 operations, 43 of which were performed in patients older than age 60. Of the 88 operations, 85 were second operations, and 3 patients needed a third operation; CBD stones were confirmed in all patients before reoperation.

Three three types of bile duct reoperation were performed: choledocholithotomy with T-tube drainage (64 patients), choledocholithotomy with side-to-side choledochoduodenostomy (15 patients), and choledocholithotomy with transduodenal sphincteroplasty (6 patients). Choledocholithotomy with T-tube drainage in 1 patient and choledocholithotomy with side-to-side choledochoduodenostomy in 2 patients were performed at a third operation.

The average hospital stay was 9.3 days. No patient died despite the presence of associated risk factors in 44 patients. There were only six minor complications, and none of them necessitated urgent surgery. Two patients (3%) of the 64 who had choledocholithotomy with T-tube drainage developed recurrent bile duct stones 4 and 5 years after a second operation, and side-to-side choledochoduodenostomy was performed.

Taking Girard's (2000) experience with that of other reported series, there have been 15 deaths among 920 patients submitted for reoperation for recurrent bile duct stones (Table 35.1). In one of these series (McSherry & Glenn, 1980), choledocholithotomy was done for retained or recurrent stones in 341 patients; seven patients died after the procedure, resulting in a mortality of 2%. If three patients who underwent operation for cholangitis or pancreatitis were excluded, however, and only the elective procedures were considered, only four patients died (1%) after repeat choledocholithotomy. These results show that the overall mortality rate for retained or recurrent stones is less than 2%, with most deaths occurring in elderly patients. This mortality rate is comparable to that of ES.

Comments

Retained or recurrent bile duct stones can be managed safely with reoperation, which is associated with little or no mortality, low morbidity, and a high success rate. Reoperation is effective and safe and should not be forgotten. In a patient with a retained stone with a T-tube in place, extraction through the T-tube tract or ES should be attempted first; if a T-tube is not in place, ES should be attempted first. If ES is contraindicated, or if it fails, operative management is a reasonable alternative, with the expectation of a high success rate and comparable mortality and morbidity rates to sphincterotomy. Most patients do not require a biliary-enteric drainage procedure; however, a drainage procedure is required to prevent further problems in selected patients.

Many options are now available for the management of CBD stones. Gastroenterologists, radiologists, and surgeons working in close cooperation should assess patients. The traditional surgical management of patients with CBD stones has reached a high level of efficacy and safety, even in elderly patients. The choice between open surgery, laparoscopic surgery, and ES should take into account not only reported information and expertise but also the local availability and efficacy of the different methods. The goal of open CBD exploration for calculous disease is to explore patients with choledocholithiasis, detect and remove all stones within the bile ducts safely, and prevent retained and recurrent stones.

Before operation, the surgeon must make an accurate diagnosis, which should be confirmed by intraoperative cholangiography. The only reliable methods to confirm complete clearance of stones from the biliary tree at operation are postexploratory choledochoscopy and cholangiography (see Chapter 21). Biliary enteric drainage procedures should be used selectively when indicated. Patients with residual or recurrent CBD stones generally should be managed by ES, but other approaches may be used, depending on the general condition of the patient, the available expertise, and the presence or absence of a T-tube.

SURGICAL TECHNIQUES FOR EXPLORATION OF THE COMMON BILE DUCT

Routine exploration of the CBD (see Chapter 29) should be through a supraduodenal choledochotomy, and the transduodenal route should be reserved for patients in whom stones cannot be removed readily from above. Although impacted stones at the ampulla may be broken down and removed by a

supraduodenal approach, they probably should be removed by means of a transduodenal sphincteroplasty, because it is less traumatic in such circumstances (see Chapter 29).

The only reliable methods to confirm complete clearance of stones from the biliary tree are postexploratory choledochoscopy and cholangiography (see Chapters 21 and 28). The value of choledochoscopy has been confirmed by many authors (Dayton et al, 1984; Kappes et al, 1982; Nora et al, 1977). Postexploratory cholangiography also must be used and should be obtained before closure of the abdomen, not only because it can locate occasional missed stones, but also because it may reveal unsuspected disruption of the biliary ductal system. Although often regarded as unreliable because of the failure of contrast material to enter the duodenum and the difficulty of eliminating air bubbles, postexploratory cholangiography can be done reliably with attention to detail. Myatt and colleagues (1973) described a reliable technique that does not involve suture of the choledochotomy before postexploratory films are obtained. After exploration, a T-tube (at least 14 Fr) is left within the CBD to permit postoperative cholangiography and percutaneous extraction of retained stones if necessary. The techniques for exploration of the CBD are detailed in this section (see also Chapter 29).

The selective use of biliary-enteric drainage procedures is another method to decrease the incidence of subsequently symptomatic retained stones. Although we do not recommend routine biliary-enteric decompression at initial operation, it should be considered carefully in patients with multiple duct stones, particularly in dilated ducts in elderly patients and in those with a large stone, or stones, within a dilated duct. If these conditions pertain in an elderly or poor-risk patient, choledochoduodenostomy may obviate reexploration. Other indications include 1) the presence of irretrievable intrahepatic stones, 2) proven ampullary stenosis, or 3) an impacted ampullary stone.

Supraduodenal Choledochotomy and Exploration of the Common Bile Duct

Exposure

The liver is retracted superiorly with a broad-bladed, slightly curved retractor. This retractor should be deep enough to displace the liver but not so curved as to traumatize it. The curved, broad-based Hartmann ("sweetheart") retractor often serves this purpose well. A pack should be put over the hepatic flexure of the colon down to the hepatorenal pouch and the medial part of the duodenum. This pack is retracted by a similar, broad-bladed retractor to prevent the colon or duodenum from obscuring vision (Fig. 35.1). The lesser omentum and stomach are retracted to the left after placement of another pack. The gallbladder usually is removed before exploration of the CBD, because it may obstruct vision, although in some cases it can be a useful aid to retraction. Palpation of the CBD and handling of its lower part during exploration and subsequent choledochoscopy cannot be done properly without having performed a classic Kocher maneuver (Fig. 35.2).

Choledochotomy

The site of the choledochotomy depends on several factors. Choledochoduodenostomy may become necessary (see Chapter 29), so the opening must be in the lowest part of the supraduodenal CBD that is consistent with an easy subsequent anastomosis (Figs. 35.3 and 35.4). A distal choledochotomy is recommended so that as much as possible of the CBD is left proximally, in case the duct is needed for some further procedure (e.g., repair of a stricture) in this part of the duct. Another reason why the choledochotomy should be placed distal and close to the duodenum is that the usual distance from this point to the papilla measures 7 cm or more. This is the exact length of the rigid choledochoscope used to do CBD exploration, and a clear view of the papilla of Vater is obtained. The anatomy of the cystic duct is so variable that care must be exercised to open the correct duct (see Chapter 1B). A cystic duct lying anterior or closely applied to the CBD can be easily opened in error (Fig. 35.5). Bile is aspirated by gentle suction, and a specimen should be sent for culture.

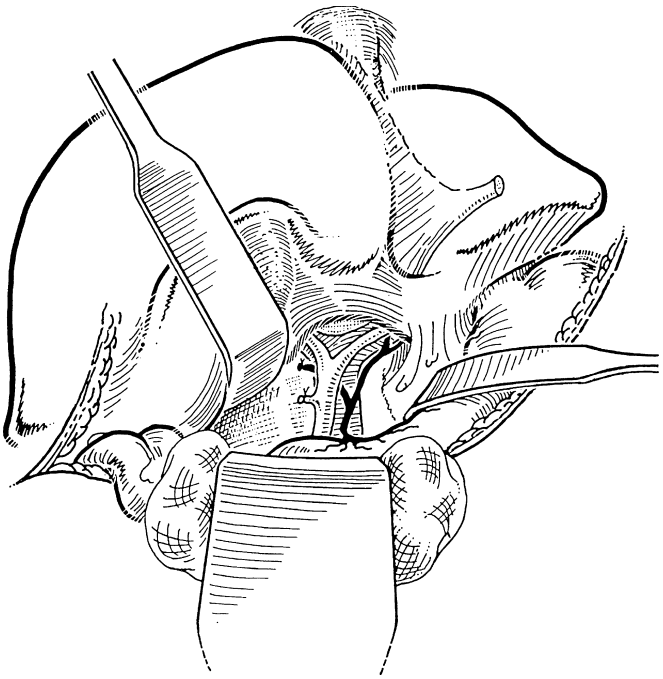
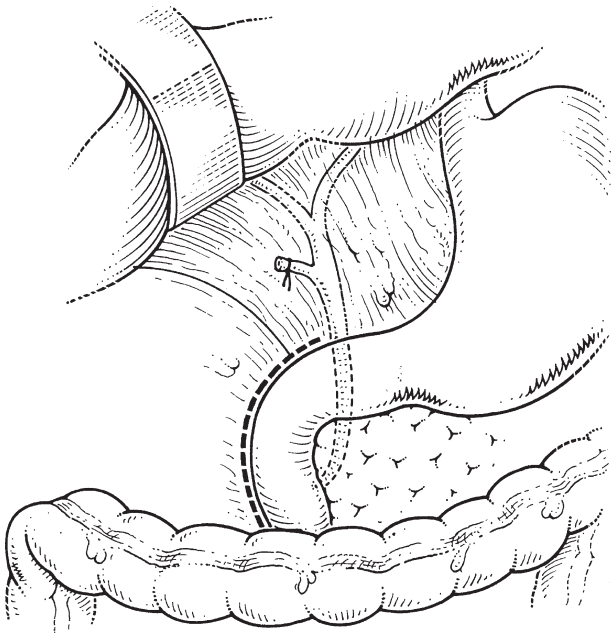


FIGURE 35.1. Exposure of the common bile duct by packs and retractors.

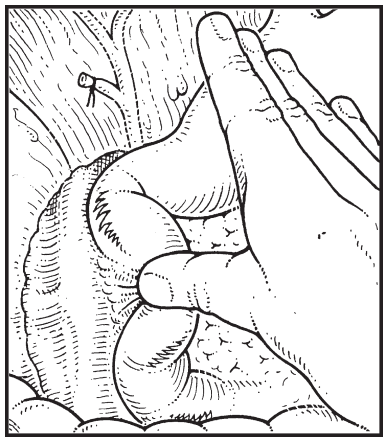
Exploration of the Duct (See Chapter 29)

Exploration should be as atraumatic as possible, and the use of rigid instruments should be avoided (Gunn, 1983; Orloff, 1978). Grasping forceps of any type may catch the wall of the duct and cause damage and possible late stricture formation. Bougies traditionally have been used, but metal instruments can create a false passage into the duodenum or the pancreas. The Fogarty balloon catheter has been found to be suitable for CBD exploration (Fogarty et al, 1968; Fox & Gunn, 1984).

The Fogarty probe is held in long forceps and introduced into the CBD. The forceps is held in the surgeon's dominant hand (Fig. 35.6), and the catheter is passed into the duodenum. The balloon is inflated, and the catheter is withdrawn until it impinges against the papilla (Fig. 35.7). As already mentioned, the duct is normally about 7 cm from the point of choledochotomy to the duodenum. The second part of the duodenum is palpated, and the balloon is identified to determine the site of the papilla in case duodenotomy is necessary. Any stone usually can be felt against the shaft of the catheter. The balloon is



A



B

FIGURE 35.2. A, The gallbladder has been removed. The *dotted line* indicates the incision in the retroperitoneum to allow mobilization of the duodenum by the Kocher maneuver (**B**).

deflated and gently withdrawn through the papilla, and this can be detected by a sudden easing of the pull on the catheter; the balloon is reinflated immediately. The catheter is held by the syringe in the surgeon's nondominant hand, and the degree of inflation is controlled by the thumb and the plunger. With gentle traction superiorly from long forceps held in the surgeon's dominant hand, the catheter is gradually pulled up to the choledochotomy site (Fig. 35.8), with care being taken to prevent any stone slipping into the proximal biliary tree. If the traction is anterior rather than superior, there is the risk of lacerating the opening into the duct (Fig. 35.9), and the risk is increased when the opening in the duct is longitudinal. The procedure is repeated until the distal duct is considered to be clear.

The catheter is withdrawn and reinserted upward into each of the main hepatic ducts, and the procedure is repeated again.

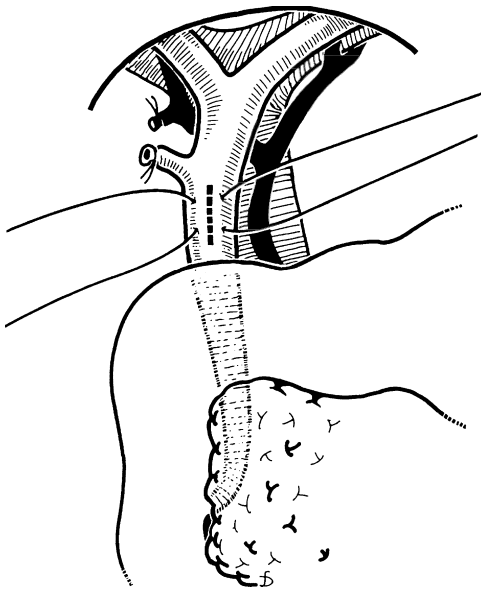


FIGURE 35.3. The common bile duct is opened just above the duodenum to leave room for a choledochoduodenostomy if necessary.

The balloon inflation needs to be correct: overinflation could damage the ducts, and underinflation could result in missing any stone that is present. Correct inflation can be achieved by inflating the balloon until the tension of the syringe plunger can be felt in the fingers. This tension is maintained as the catheter is withdrawn into the gradually widening duct.

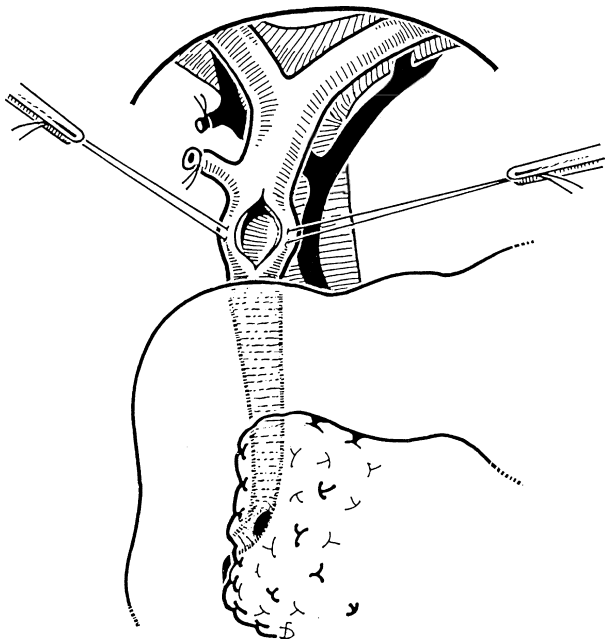


FIGURE 35.4. Two fine stay sutures of 3-0 polydioxanone suture or 3-0 polyglactin 910 (Vicryl) are used to lift and render the common bile duct (CBD) tense for an incision about 1 to 2 cm long, depending on the size of the duct and the size of the stones. If the CBD is not made tense, damage can be done to the posterior wall, or an irregular incision can be made.

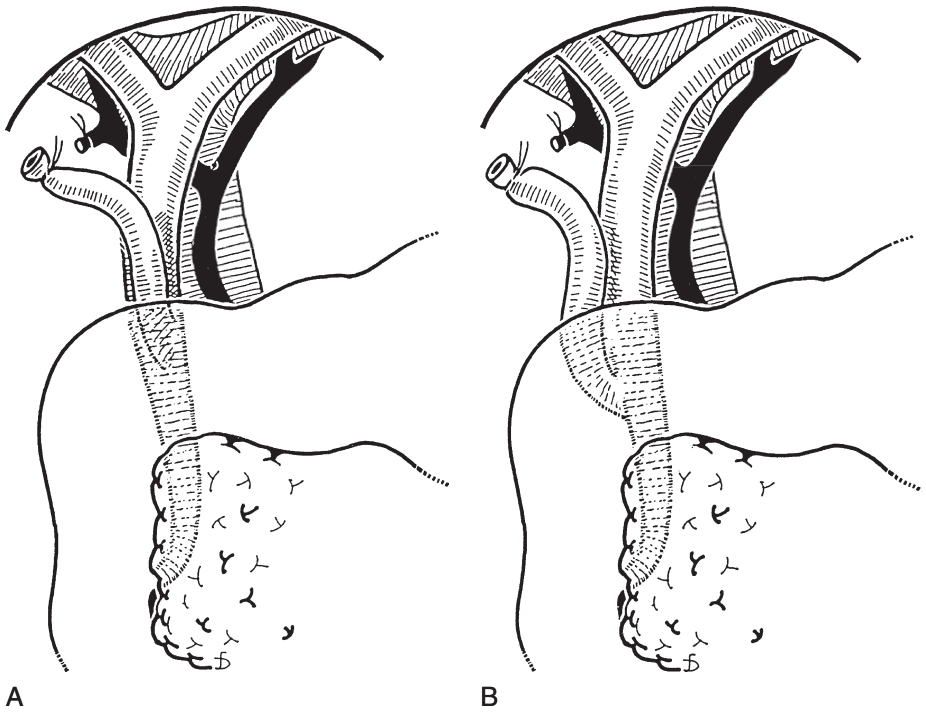


FIGURE 35.5. **A,** The cystic duct may lie anterior to the common bile duct (CBD) and may be opened in error. **B,** The cystic duct may run parallel to the CBD with a low entrance, mimicking a dilated duct.

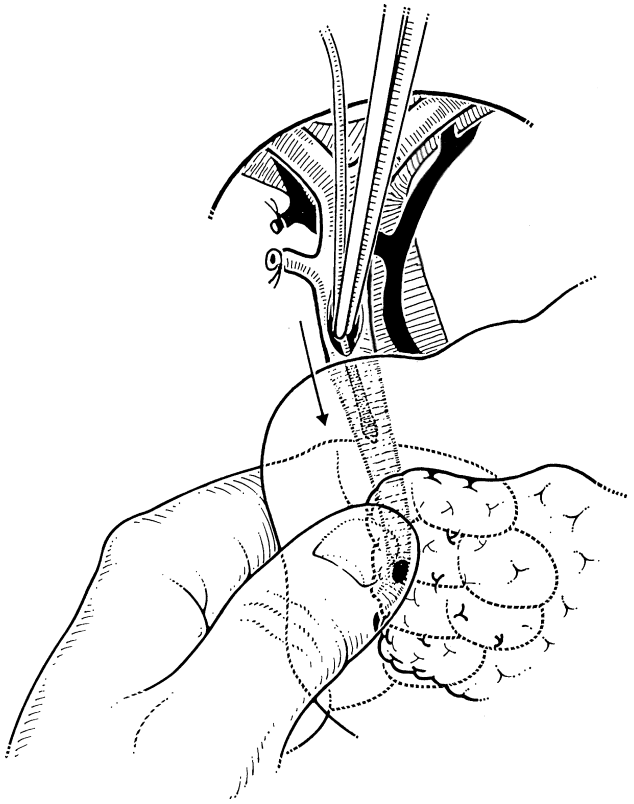


FIGURE 35.6. A Fogarty catheter is fed into the duct with forceps using the dominant hand. The operator's nondominant hand is used to grasp the mobilized duodenum, which allows palpation of the passage of the catheter and of any stones within the intrapancreatic portion of the common bile duct.

It is important to remove the stone when it appears at the choledochotomy opening and to avoid letting it fall into another part of the duct. The second step in CBD exploration is to irrigate the duct with saline. Small stones, sludge, and debris can be flushed into the duodenum or back into the choledochotomy opening by irrigating the ductal system. The last step in this technique is to pass the Fogarty catheter again into the duodenum, inflate the balloon, and retract it against the papilla. While the catheter is held in the surgeon's dominant hand, the index and middle fingers of the other hand are placed posterior to the duodenum with the thumb anterior; this allows palpation of the duct against the wall of the catheter for any residual stones.

Postexploratory Investigations

Following exploration, the surgeon must make every effort to ensure that the duct system is normal.

Choledochoscopy (See Chapter 21)

Choledochoscopy is the established method to ensure that the duct system is normal. Modern instruments are small enough to allow visualization of the major right and left hepatic ducts and intermediate hepatic ducts and to allow visualization of the orifices of the smaller biliary radicles. Some surgeons experienced in choledochoscopy recommend exploration of the CBD and removal of stones under direct vision using the choledochoscope (Berci, 2000).

T-Tube Cholangiography

After insertion of a T-tube and closure of the choledochotomy, T-tube cholangiography is another option for postexploratory investigation. With proper technique and use of fluoroscopy,

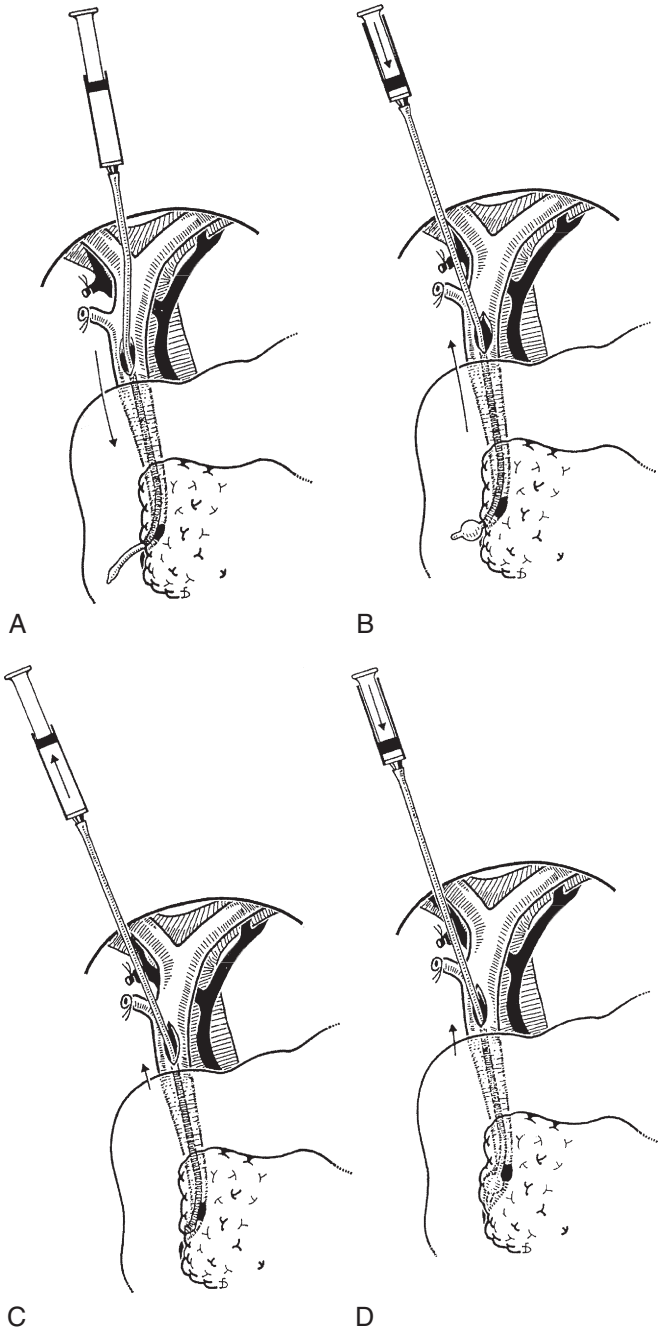


FIGURE 35.7. A, The Fogarty catheter is attached to a syringe, and the balloon is inflated in the duodenum. **B,** The Fogarty catheter is retracted with the balloon against the papilla. **C** and **D,** The balloon is deflated and gently withdrawn until it slips through the papilla; the balloon is then reinflated.

T-tube cholangiography is an excellent tool for detecting residual stones after CBD exploration (Fig. 35.10). The cystic duct stump, a possible location of residual stones, can be delineated, and incorrect placement of the T-tube can be detected to prevent complications after the operation. In case of residual stones, the T-tube has to be removed, and the duct needs to be explored again; this necessitates a second suture of the CBD, which is a major disadvantage of T-tube cholangiography. The technique described by Myatt and colleagues (1973), whereby the cholangiogram is done before closure of the duct, can be valuable in this regard.

T-TUBE DRAINAGE. The standard practice is to use a T-tube to allow spasm or edema of the sphincter to settle after the trauma of the exploration. Failure to drain the duct might result in a buildup of pressure in the extrahepatic ductal system and cause leakage at the disruption of the closure of the duct, along with biliary peritonitis. Another important reason for the use of a T-tube is for the detection and subsequent treatment of retained stones. In the event of a retained stone, the T-tube can be useful later for interventional radiologic techniques through the tract created by the tube (Fig. 35.11).

The use of a T-tube creates a fistula between the skin and the lumen of the duct, and both are potentially contaminated surfaces; the tract of the fistula crosses the peritoneal surface. The size of the T-tube should be adapted to the diameter of the CBD; 14 Fr is the smallest size that should be used, if a satisfactory tract is to be left for subsequent interventional radiology. A significant proportion of patients who have choledochoscopy and cholangiography have a greatly reduced number of residual stones, but a wise surgeon should accept that stones occasionally are left.

T-TUBE PLACEMENT. First, the limbs of the T-tube must be shortened (Fig. 35.12A). T-tubes can become obstructed, particularly if they are tight fitting, and they can be difficult to extract. This situation can be avoided by cutting off a strip of the wall (Fig. 35.12B). The practice of dividing the back wall of the T-tube makes subsequent interventional radiology more difficult, because the guidewire lodges in the posterior defect. In the main, this problem can be avoided by making the length of the T-tube appropriate or by limiting the division of the T-tube. The modified T-tube is held in Desjardin forceps, which conveniently grasps the T-junction of the tube, allowing it to be slipped into the choledochotomy (Fig. 35.13). The long limb of the tube is placed at the lower end of the opening, and repair is begun just above the upper apex of the incision using continuous or interrupted resorbable material. The final stitch should close the opening against the T-tube (Fig. 35.14).

AVOIDING PROBLEMS IN THE CLOSURE OF THE CHOLEDOCHOTOMY. Care must be taken that the wall of the T-tube is not caught in one of the sutures, and the end of the suture should not be tied around the tube. Either of these faults may result in the tearing of the duct when the tube is withdrawn. The proximal limb of the T-tube should not enter one of the hepatic ducts because this can produce obstruction (Fig. 35.15), and the distal end must not enter the duodenum, because this can act as a siphon. In addition, a tube through the papillary orifice may incite pancreatitis. The correct position of the T-tube is with the long limb emerging under the costal margin laterally (Fig. 35.16). This position facilitates radiologic techniques for later postoperative removal of stones should this be necessary. A suction drain is placed on the right, within the abdomen as high as possible in the hepatorenal pouch.

POSTOPERATIVE MANAGEMENT. Initially, bile is allowed to drain freely into a bile bag to allow any spasm or edema of the sphincter to settle before testing the suture line of the

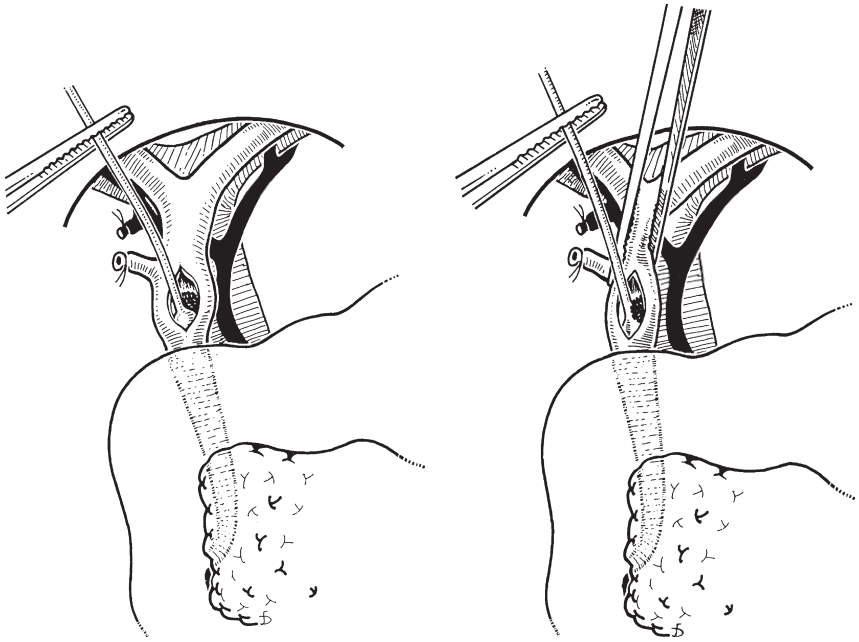


FIGURE 35.8. **A,** The balloon is withdrawn gently, revealing the stone. **B,** Long forceps can be used to obstruct the common hepatic duct to prevent the stone from slipping upward.

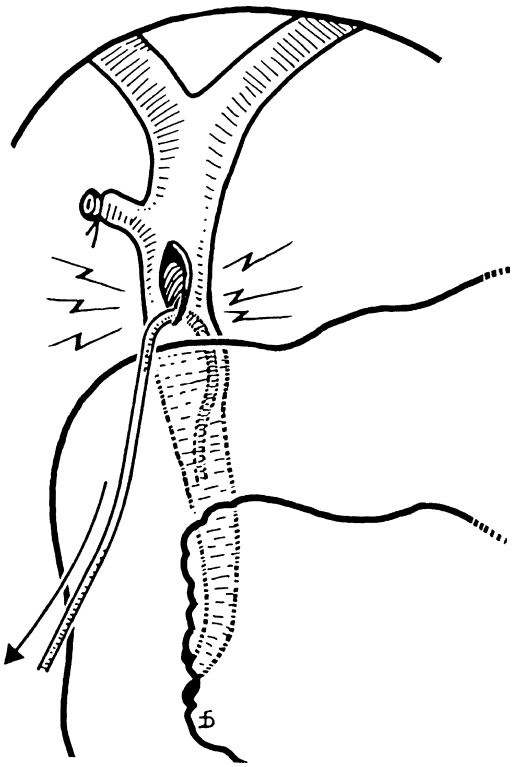


FIGURE 35.9. Angled traction on the Fogarty catheter results in tearing of the lower end of the choledochotomy.



FIGURE 35.10. A postexploration T-tube cholangiogram identifies a residual stone in the intrahepatic bile ducts that was missed during operative exploration of the bile duct.

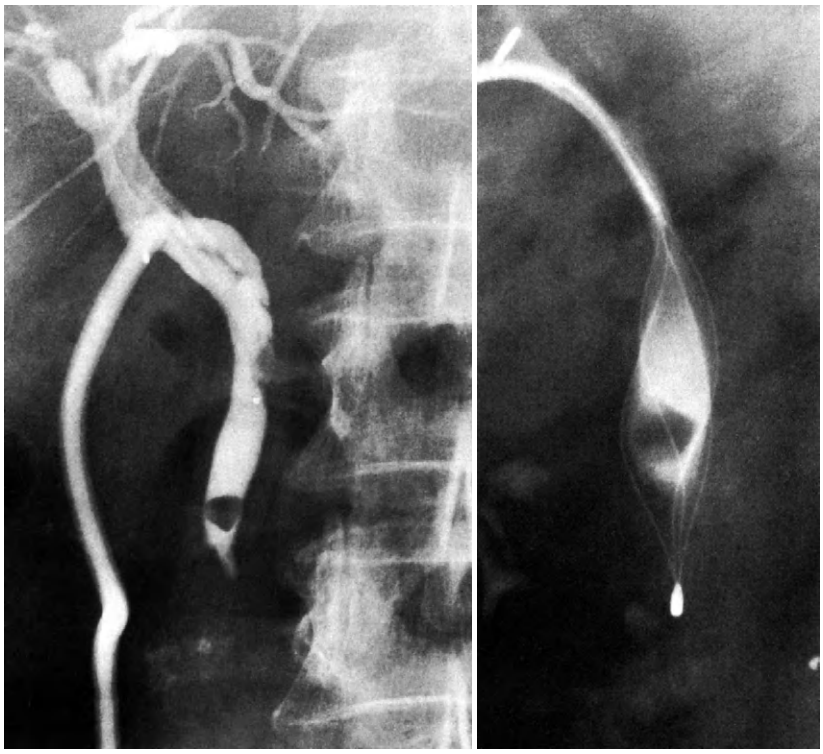


FIGURE 35.11. A, Faceted retained distal common bile duct (CBD) stone on T-tube cholangiography 1 week after operation. The T-tube is inserted in the common hepatic duct above the confluence of the cystic duct. **B,** The retained CBD stone is ensnared in the wire basket before extraction. This stone measured 5 mm in diameter and was extracted intact through the sinus tract of a 14-Fr T-tube.

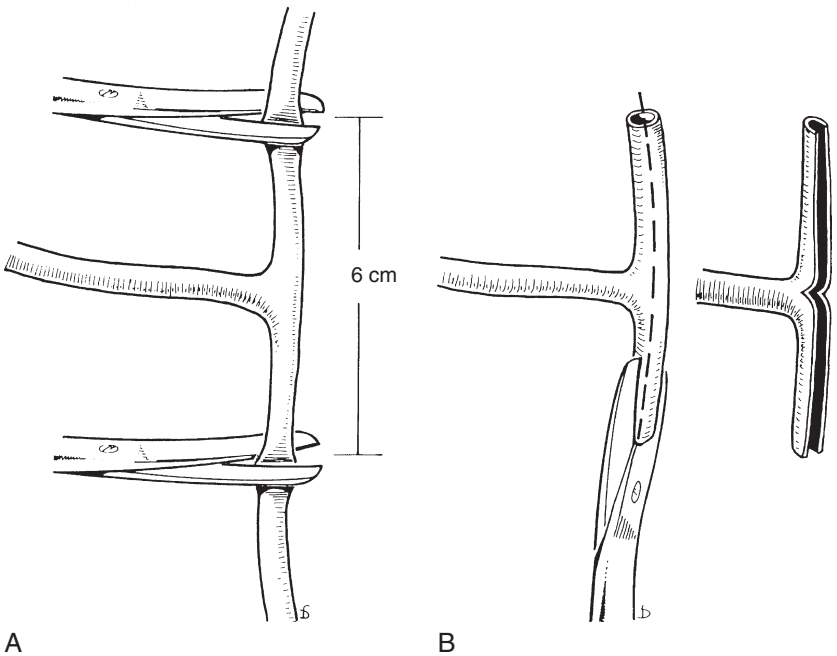


FIGURE 35.12. A, The T-tube is modified by shortening the limbs to prevent proximal obstruction and distal entry into the duodenum. **B,** A T-tube is modified by removing half the diameter to prevent obstruction and enable easy removal.

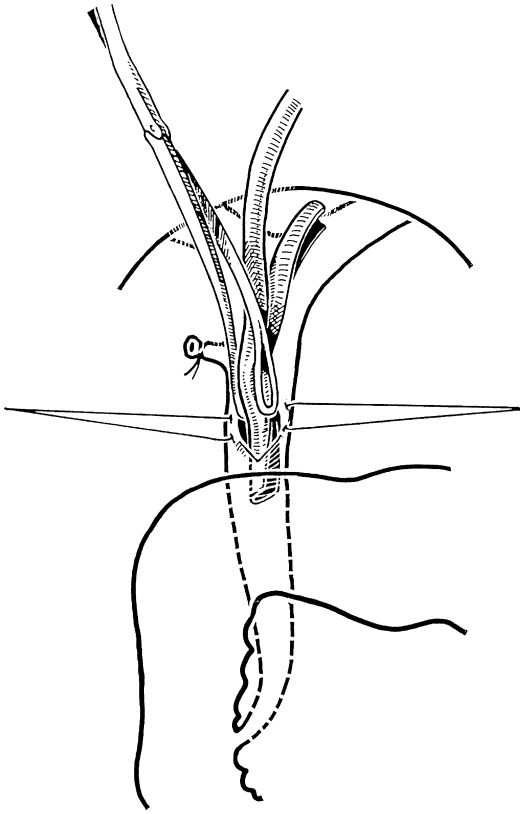


FIGURE 35.13. The T-tube is introduced by Desjardin forceps.

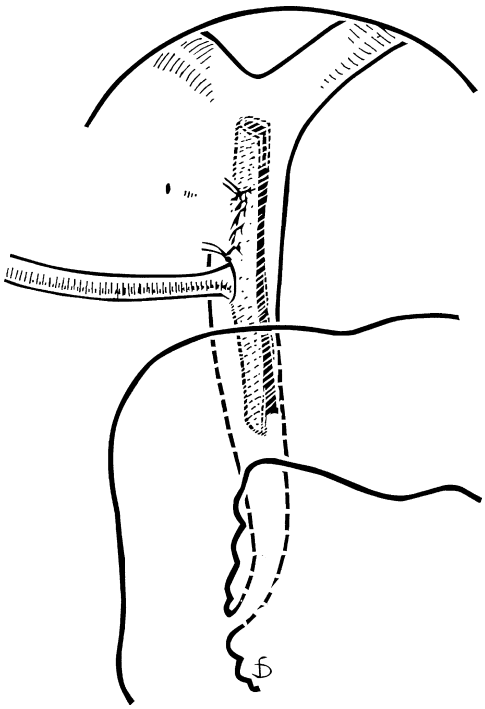


FIGURE 35.14. The choledochotomy closure is begun above with the T-tube emerging at the lower end of the repair.

choledochotomy. The volume drained varies, with the amount decreasing as flow increases through the sphincter. If the volume drained remains high or increases, the reason should be established. This increased volume may be due to continuing distal obstruction or to the distal limb lying within the duodenum. Similarly, there is a problem if there is no drainage of the bile, or if bile drains around the T-tube; the tube may have become blocked or dislodged from the duct.

The answer to all these problems is revealed by T-tube cholangiography. Provided that there have been no problems, subsequent management is aimed at waiting for the bile to flow easily through the papilla into the duodenum, and the bile bag should not be lifted or clamped. A T-tube cholangiogram is taken about 5 to 7 days after the operation. If it appears normal, the tube is removed on day 7 or 8 by gentle traction.

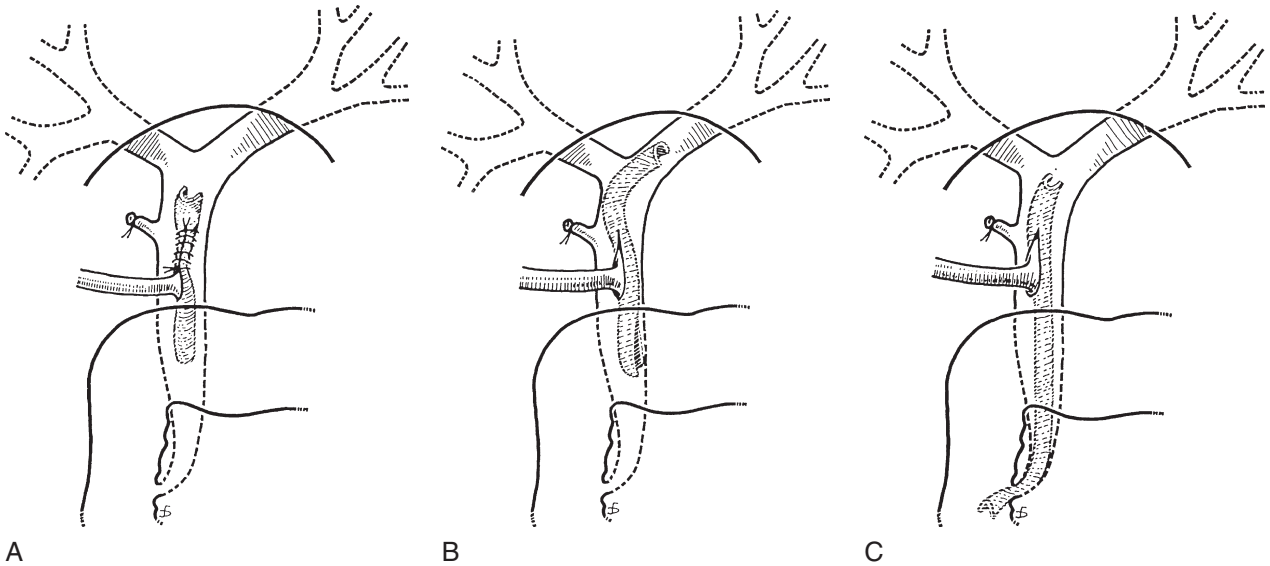


FIGURE 35.15. A, The suture must not catch the tube as shown here. **B,** The T-tube limb should not enter the hepatic duct, as shown here. **C,** The distal end of the T-tube should not enter the duodenum, as shown here.

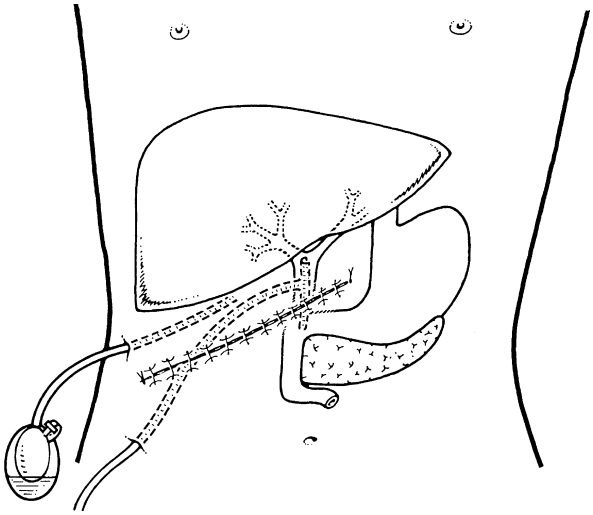


FIGURE 35.16. The T-tube should be brought out lateral to the wound, and a closed-suction drain should be placed in the hepatorenal space beneath the liver.

If there are residual stones or unclear findings on T-tube cholangiography, it is a good practice to repeat the procedure several days later. If a stone is still seen, it is managed initially by sending the patient home with a sealed drainage system and instructions to open the drain and connect it to a bag in the event of any problems. After about 5 weeks, further cholangiography is carried out. If the stone is still present, it is extracted via interventional radiology or endoscopic papillotomy (Fig. 35.17).

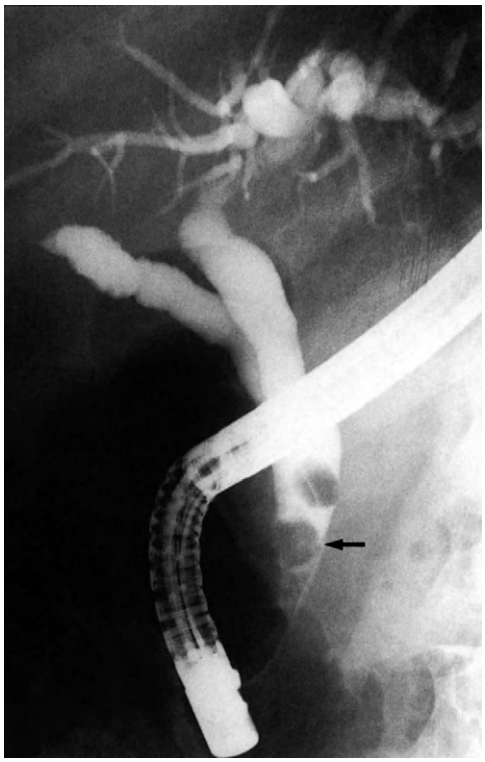


FIGURE 35.17. Balloon extraction of a single stone (*arrow*).

Transduodenal Sphincteroplasty

Transduodenal sphincteroplasty (see Chapter 29) has a place in the management of CBD stones, particularly if a stone is impacted at the ampulla or with failure of ES, in patients with Billroth II gastrectomy, and in patients with pancreatitis when a drainage procedure of the duct of Wirsung is indicated (Lehman & Sherman, 1998). Similarly, hydatid cyst remnants and membranes can be readily extracted from the CBD. Exploration may extend to the left and right hepatic ducts, and angled Randall forceps are useful for this purpose.

Sphincteroplasty consists of suturing the outer edge or both edges of a surgical sphincterotomy to avoid possible future stenosis of the incision. The stitches achieve hemostasis of the incision margins and help to avoid possible leakage of the duodenal contents should the excision extend beyond the common portion of the sphincter, incurring the risk of retroduodenal perforation. Transduodenal sphincteroplasty is contraindicated in the presence of a large CBD (>2 cm) or where there is a long suprasphincteric stricture. It also should not be attempted in the presence of a duodenal diverticulum or where there is severe periampullary inflammation.

Indications

The most common indications for transduodenal sphincteroplasty relate to bile duct stones and cholangitis.

STONES IMPACTED IN THE DISTAL AMPULLARY REGION. An impacted stone is often readily palpable, and the incision may be made safely using the stone as a guide. In such cases, extraction through a supraduodenal choledochotomy is often impossible without undue risk of creating a false passage and without significant risk of postoperative pancreatitis.

MULTIPLE AND RECURRENT COMMON BILE DUCT STONES. In cases of multiple and recurrent CBD stones, sphincteroplasty should provide long-term biliary drainage. When 20 or more stones are removed from the CBD, it is probable that one or more stones are still present (Stain et al, 1991). In this situation, choledochoduodenostomy or sphincteroplasty yields excellent results.

PAPILLARY STENOSIS. Papillary stenosis is encountered less frequently than in the past. When it is found at operation, transduodenal sphincteroplasty ensures good biliary drainage and prevents restenosis (Ramirez et al, 1994). ES is technically successful in only 60% to 80% of cases, and mortality rate exceeds 1% (Seifert et al, 1982). In addition, sphincterotomy for papillary stenosis is five times more likely to lead to restenosis than if the same procedure is performed for calculi (Tzovaras & Rowlands, 1998).

PYOGENIC CHOLANGITIS (SEE CHAPTER 43). If papillary stenosis or CBD stones or both exist together with cholangitis, transduodenal sphincteroplasty can be an excellent procedure for definitive biliary drainage.

CHRONIC PANCREATITIS AND ACUTE GALLSTONE PANCREATITIS (SEE CHAPTERS 53, 54, AND 55). In chronic pancreatitis, some authors report good long-term results with transduodenal sphincteroplasty alone (Hacaim et al, 1994) or in addition to transpapillary septectomy (Moody et al, 1983) or

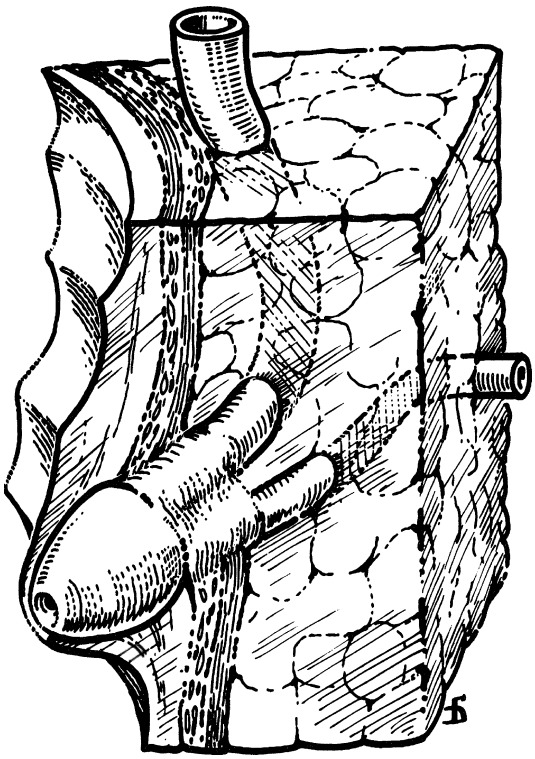


FIGURE 35.18. A section of the sphincter of Oddi. Note the distinction between the papilla, the common portion of the sphincter, and the sphincters of the common bile duct and duct of Wirsung.

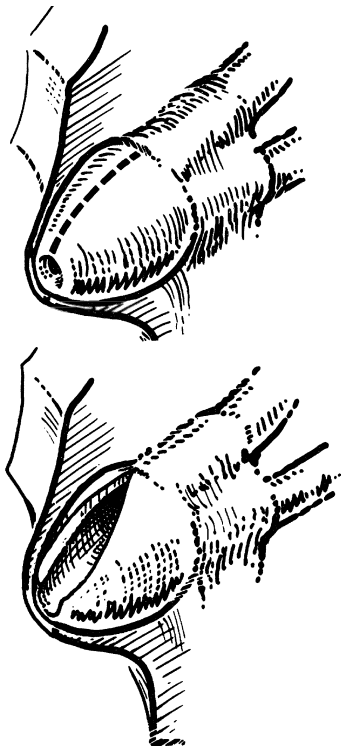


FIGURE 35.19. Subtotal lower sphincteroplasty involves only the papilla, whereas the common bile duct and the duct of Wirsung are preserved.

with other drainage procedures of the duct of Wirsung (Kestens et al, 1996). The presence of a stone at the lower end of the CBD or pancreatic duct may cause biliary pancreatitis, and transduodenal sphincteroplasty with clearance of the CBD is a treatment option.

Technique

Sphincteroplasty consists of the incision of the common portion of the sphincter of Oddi (Fig. 35.18) with partial suture of the incision margin. By this procedure, the sphincters of the CBD and the duct of Wirsung are not involved, and their functions are not impaired. The procedure also can be called a *subtotal lower sphincteroplasty* (Fig. 35.19; Stefanini et al, 1977). The approach to the sphincter of Oddi is through a minimal duodenotomy in the second part of the duodenum.

Preparation, Position of the Patient, and Incision

Preoperative preparation is routine. A nasogastric tube is introduced before operation and is maintained until postoperative day 3 or 4. The patient is placed in a supine position on a radiotransparent operating table. A transverse incision below the right costal margin is preferred (Vogt & Hermann, 1981). This incision allows optimal light and excellent access, it is particularly suitable in obese patients, and the incidence of postoperative incisional hernia is probably lower than with vertical and oblique incisions. The incision of the abdominal wall follows a transverse line, from the midaxillary to the median line at the level of the eleventh and twelfth ribs (Fig. 35.20).

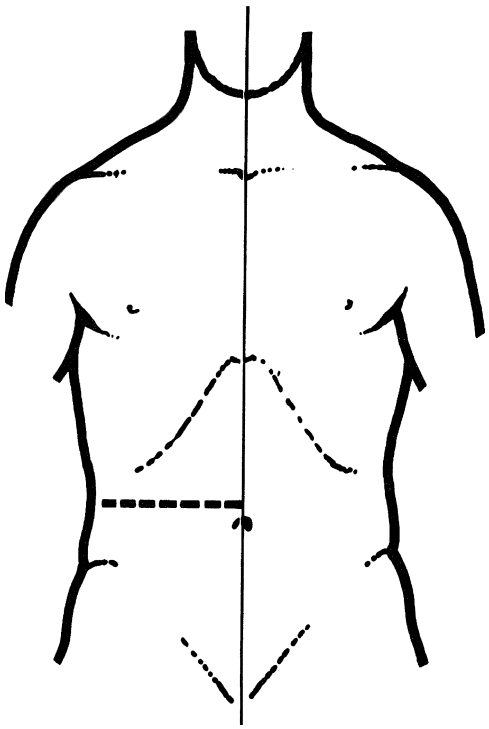


FIGURE 35.20. Transverse subcostal incision offers excellent exposure with a low incidence of postoperative incisional hernia.



FIGURE 35.21. It is important to expose and mobilize the third portion of the duodenum to easily identify and operate on the papilla and allow facile closure of the duodenotomy.

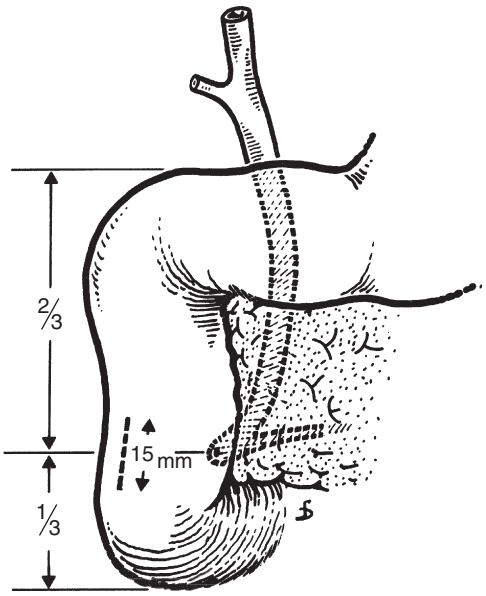


FIGURE 35.22. The duodenotomy is performed above the junction of the second and third portions of the duodenum; the surgeon takes into account that the papilla usually is located at the junction of the upper two thirds and lower third of the second part of the duodenum.

Preparation of the Operative Field and Exposure

The abdomen is opened, and a large retractor is positioned at the upper margin of the wound. The right flexure of the colon is displaced inferiorly, and the stomach is displaced to the left by means of two surgical pads. Viscera are maintained in this position with two large, curved Deaver retractors. For the performance of the sphincteroplasty, extended mobilization of the duodenum and pancreas (Kocher maneuver) is mandatory (Moody et al, 1983). The assistant surgeon displaces the second portion medially and forward, and the peritoneum is incised posteriorly along the curved lateral margin of the duodenum. The mesocolon of the right colic flexure is cleared inferiorly. At this point, the assistant surgeon also should displace the duodenum superiorly (see Fig. 35.2). Access is provided to the avascular space between the posterior aspect of the head of the pancreas anteriorly and the perinephric fat and inferior vena cava posteriorly; elevation of the structures should reach the left margin of the inferior vena cava. It is important to expose and mobilize the third portion of the duodenum to allow easy access to the papilla and for closure of the duodenotomy without tension (Fig. 35.21).

Duodenotomy

Duodenotomy is performed in the lateral duodenal wall by surgical diathermy. The cut is 10 to 15 mm long immediately above the inferior knee of the duodenum, with the surgeon taking account of the fact that the papilla usually is located at the junction of the lower third with the upper two thirds of the second portion of the duodenum (Fig. 35.22). The duodenal incision may be longitudinal or transverse; both types are suitable, provided that the suture of such incisions is always transverse. We prefer a longitudinal incision, because if the retractor on the duodenum widens the duodenotomy, this occurs longitudinally. In the case of a transverse duodenotomy, any inadvertent extension would cause a transverse enlargement of the wound.

Identification of the Papilla

After the duodenal incision, the papilla is readily shown on the medial duodenal wall in 15% to 20% of patients. It appears as a roundish elevation with a central orifice. When the papilla is not readily visible, it should be detected by displacement and flattening of the mucosal folds. This should be done with great care to avoid tearing of the mucosa, which would hinder good exposure. Identification of the papilla under direct vision is possible in 80% of patients. If this is not the case, digital palpation can be used running the forefinger, introduced through the duodenotomy, across the medial duodenal wall. The papilla is identified as a small elevation (Fig. 35.23). If digital palpation fails, a small (5 to 6 Fr) Nélaton catheter can be introduced via the cystic duct stump and advanced downward to emerge at the papilla. This maneuver should never be performed with rigid catheters, because this may result in the formation of false passages.

Sometimes a very small papilla is detected, and its catheterization is difficult or impossible. In such cases, the orifice is probably that of the duct of Santorini. The major papilla should be searched for in a lower position.

Sphincteroplasty

After the papilla has been identified, it is exposed by gentle extraction with an Allis or similar clamp. This clamp is applied laterally, never medially, to avoid trauma to the duct of Wirsung

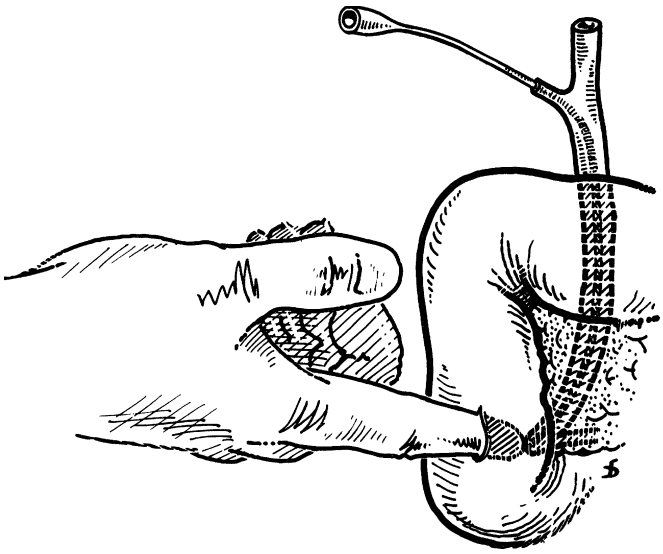


FIGURE 35.23. If the papilla is not easily seen, a small Nélaton catheter is introduced through the cystic duct stump until it is seen to protrude from the papillary orifice. The forefinger, introduced through the duodenotomy, detects the papilla as a small, thick elevation.

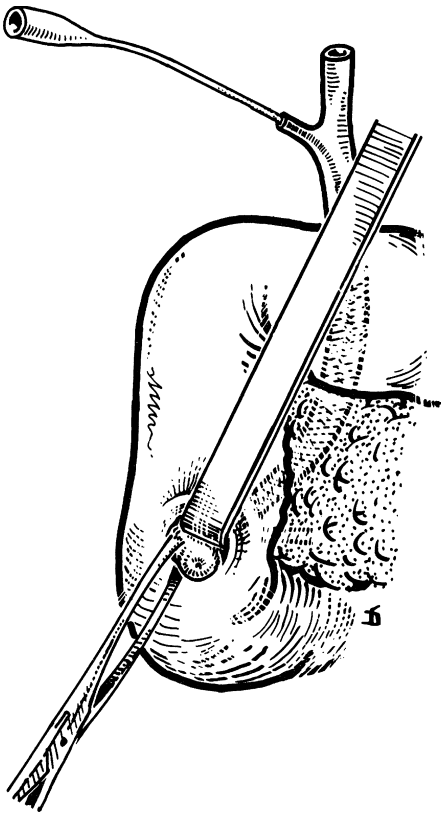


FIGURE 35.24. The duodenotomy is kept open by a suitable retractor placed in the upper margin of the duodenal incision. The papilla is exposed by gentle traction with an Allis clamp placed laterally, never medially, to avoid trauma to the duct of Wirsung.

(Fig. 35.24; Partington, 1977). A Nélaton catheter (4 to 5 Fr) is introduced from the outside or via the cystic duct. Following the line of the catheter—and avoiding plastic catheters, which melt when surgical diathermy is applied—the surgeon makes a cut using surgical diathermy. This cut is made superiorly (at the 11 o'clock position) for 4 to 5 mm (Fig. 35.25). We prefer surgical diathermy, because the instrument ensures good hemostasis. When a sample for biopsy is required, it should be obtained with a scalpel and be taken only from the outer margin of the incision. Possible bleeding from the cut, usually modest, can be arrested with a stitch. After sphincterotomy, two or three stitches are placed between the duodenal mucosa and the wall of the CBD on the outer margin using an atraumatic needle and 3-0 silk. Traction is applied to these sutures, and incision of the sphincter is extended for another 6 to 7 mm with sutures placed every 2 to 3 mm, all laterally, until the entire common tract of the sphincter of Oddi has been incised (Fig. 35.26). The incision is complete when it is 10 to 12 mm long and an appropriate forceps can be easily introduced (Fig. 35.27). Its entry into the CBD allows an abundant flow of bile owing to distension of its sphincter. Sutures should be placed only on the outer margin of the sphincterotomy to prevent the risk of damage to the duct of Wirsung. The opening of the duct of Wirsung usually is identified as a small orifice from which clear, colorless pancreatic juice flows.

Instrumental Exploration of the Common Bile Duct

After sphincteroplasty, instrumental exploration of the CBD and extraction of stones is performed (Speranza et al, 1982). An angled Randall forceps is introduced into the CBD, and the left and right hepatic ducts are carefully explored. The maneuver should be repeated several times to extract all stones. The next step is to rinse with saline solution, introduced under slight pressure with a Nélaton catheter (8 to 9 Fr) and abruptly withdrawn so that small fragments flow downstream with the siphoning (Fig. 35.28). Other means to extract stones from the CBD are with a Fogarty catheter and Dormia basket. The problem of residual stones is best prevented with choledochoscopy; the endoscope is introduced via the sphincteroplasty.

Duodenal Closure

As already emphasized, initial longitudinal duodenotomy always should be closed transversely to avoid stenosis of the duodenum. First, the superior and inferior margins of the incisions are approximated, and the resulting gaps are sutured with two extramucosal, nonabsorbable purse-string sutures. Three or four nonabsorbable seromuscular sutures are added (Fig. 35.29). The suture should not be under tension, and for this reason preliminary extended mobilization of the duodenum and pancreas is mandatory. The operation is now complete, and the wound is closed without abdominal drains.

Comment

It is not necessary to perform transduodenal sphincteroplasty combined with supraduodenal choledochotomy, which has a higher associated mortality rate (Scheridan et al, 1987). The cystic duct remnant may be used to introduce a Nélaton catheter to assist recognition of the papilla. There is no need to insert a T-tube, which lengthens the hospital stay and may predispose the patient to stenosis and infection of the CBD (Ratych et al, 1991; Scheridan et al, 1987). Patients with no drainage tubes or complications may be discharged on postoperative day 5 or 6.

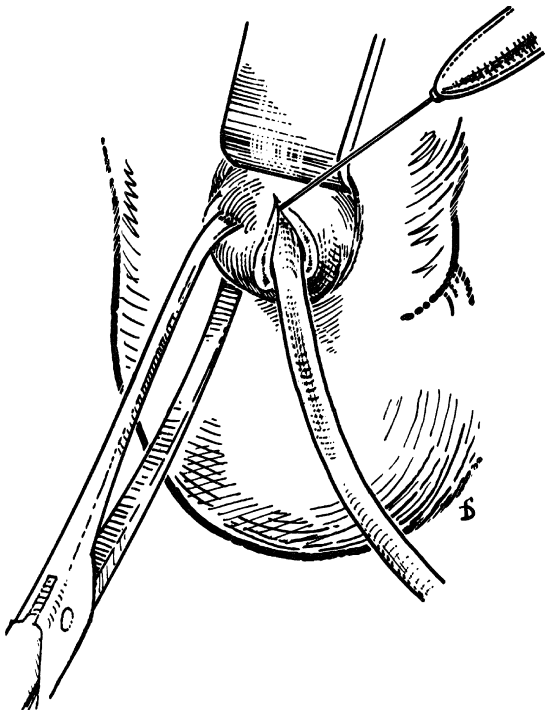


FIGURE 35.25. With a Nélaton catheter as a guide, a cut is made using surgical diathermy on the medial wall of the duodenum extending superiorly and slightly externally (11 o'clock position). With diathermy, good hemostasis is achieved.

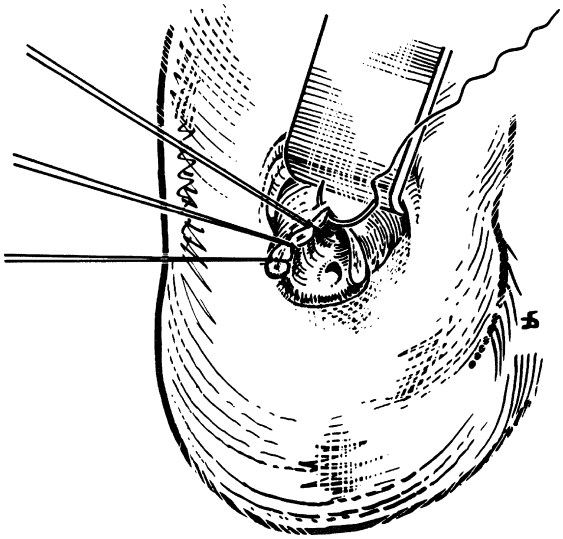


FIGURE 35.26. After sphincterectomy is performed, several stitches are placed between the duodenal mucosa and the wall of the common bile duct (CBD) using an atraumatic needle and 3-0 suture. Sutures should be placed only on the outer margin of the sphincterotomy to avoid the risk of damaging the duct of Wirsung, which in its distal portion runs inferiorly and medially along the length of the CBD.

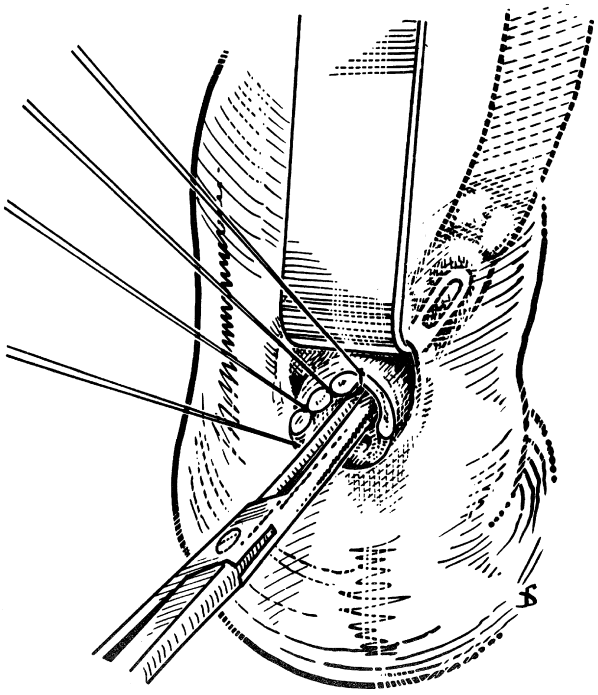


FIGURE 35.27. Sphincteroplasty is completed when the incision is 10 to 21 mm long, and a Randall forceps can be introduced easily into the common bile duct to extract stones or other foreign bodies.

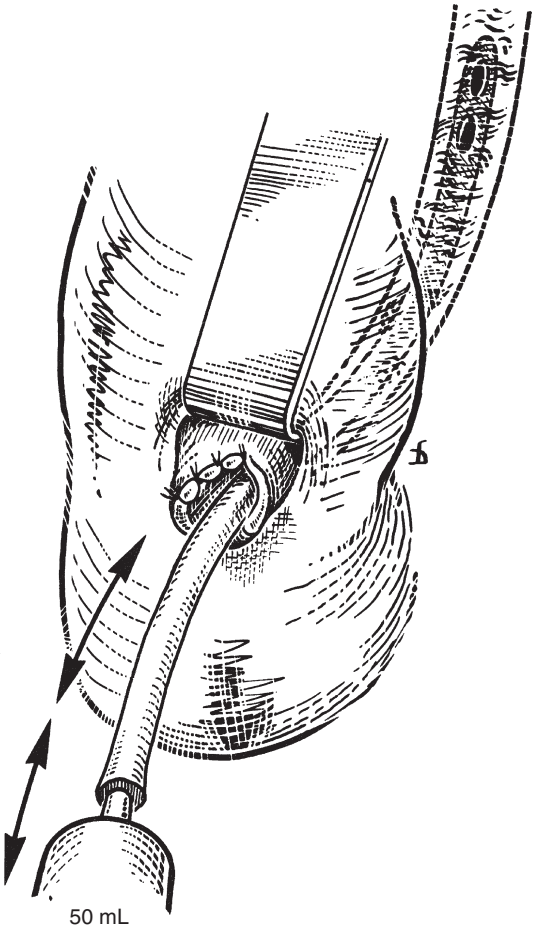


FIGURE 35.28. After the extraction of stones, the common bile duct is rinsed with saline solution introduced under slight pressure with a Nélaton catheter and with subsequent siphoning so that small fragments can run downstream.

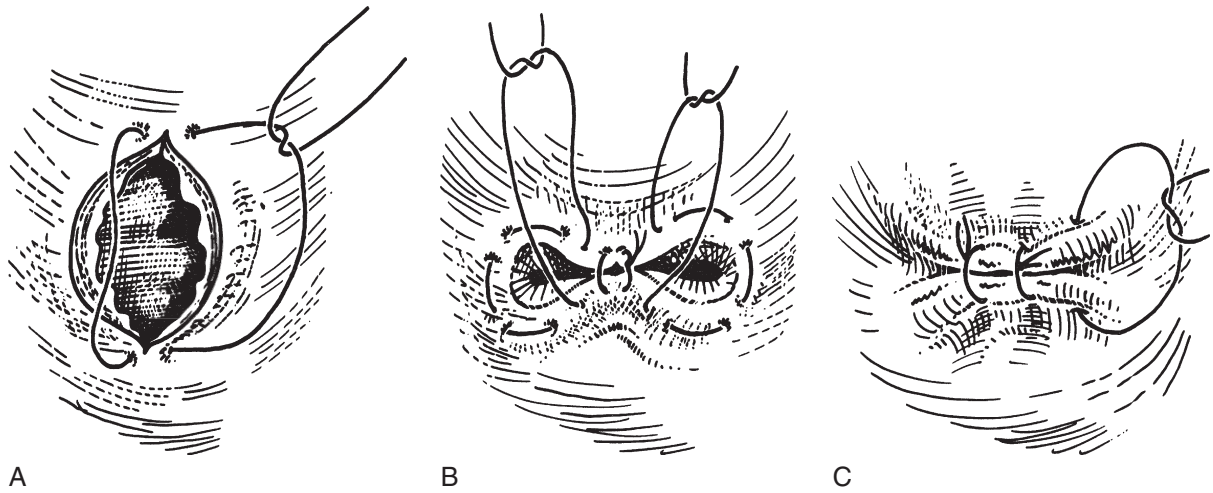


FIGURE 35.29. The duodenotomy always should be closed transversely to avoid stenosis of the duodenum. **A,** The superior and inferior angles are approximated. **B,** The resulting lateral gaps are sutured with two extramucosal nonabsorbable purse-string sutures. **C,** Three to four nonabsorbable seromuscular stitches are added as a second layer. The sutures should not be under tension.

Review of Reported Results

In a retrospective analysis of 25,541 transduodenal sphincteroplasties done by 130 surgeons in different countries, early transduodenal sphincteroplasty–related complications were bleeding (0.65%), acute pancreatitis (0.60%), dehiscence of the duodenal closure (0.55%), and cholangitis (0.50%), for an overall morbidity rate of 2.3% and a mortality rate of 0.8% (Negro et al, 1984). A retrospective study (Sellner et al, 1988) found that the factors affecting mortality in 2.1% of 333 patients (but only in 0.9% for sphincterectomy-related complications) were age older than 70 years and a bilirubin level greater than 85 mmol/L, diabetes, renal failure, and coagulopathy. The mortality rate increased when supraduodenal choledochotomy was combined with transduodenal sphincteroplasty and when a T-tube was used (Sellner et al, 1988). Transduodenal sphincteroplasty alone (Hacaim et al, 1994) or associated with transampullary septectomy (Kelly & Rowlands, 1996) has led to good long-term results in patients with chronic and acute recurrent pancreatitis, even in cases with pancreas divisum and in selected patients with abdominal pain of hepatobiliary origin.

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CHAPTER 36

Stones in the bile duct: endoscopic and percutaneous approaches

Srinivas R. Puli and David L. Carr-Locke

HISTORICAL OVERVIEW

In the 1970s and 1980s, endoscopic retrograde cholangiopancreatography (ERCP) transformed the diagnostic approach to suspected biliary disease and jaundice (see Chapters 18 and 27). Similarly, in the years since it was first performed in humans (Classen & Demling, 1974; Kawai et al, 1974), endoscopic sphincterotomy (ES) has had a dramatic impact on the management of biliary disease, specifically in the treatment of common bile duct (CBD) stones. Approximately 150,000 endoscopic biliary sphincterotomies are performed annually in the United States, and the availability of this procedure undoubtedly influences surgical decision making, when CBD stones are diagnosed on imaging or suspected, and when ERCP and ES are readily available. The surgical community initially resisted the introduction of ERCP and ES into CBD stone management, until their roles became established when they were shown to reduce the mortality rate significantly in a range of situations (Carr-Locke & Cotton, 1985; Cotton, 1984). Interest in ERCP and endoscopic sphincterotomy as definitive therapy for CBD stones grew in the 1990s after the introduction of laparoscopic cholecystectomy. Patient-related factors, clinical judgment, availability of expertise, and current evidence from clinical trials must be combined to decide on an endoscopic, percutaneous, or surgical approach. Although ERCP as a diagnostic modality has been replaced by noninvasive imaging modalities such as magnetic resonance cholangiopancreatography (MRCP; see Chapter 17), it remains the major nonoperative tool to manage biliary diseases such as CBD stones and obstructive jaundice.

INDICATIONS FOR ENDOSCOPIC THERAPY

Patients with CBD stones may be seen initially with asymptomatic stones on noninvasive imaging or direct cholangiography or with a variety of clinical problems alone or in combination, such as cholestasis, pain, cholangitis, and pancreatitis (see Chapter 30). In the early days of ES—at a time when few endoscopy centers could offer the technique, and criticisms by surgical experts were common—it was considered justifiable only in elderly postcholecystectomy patients with recurrent or retained bile duct stones who were at high risk of serious complications from open surgical CBD exploration or reexploration (Blumgart & Wood, 1978). The impressive successes of ES in this group combined with expanded availability, a low rate of complications, and strong patient preference led many centers to widen their indications for the procedure to include younger and fitter postcholecystectomy patients and those with a gallbladder in situ. This change initially occurred in the absence of comparative trial data, and there was such enthusiasm for ES that the establishment of randomized trials was difficult, although nevertheless essential to clarify relative morbidity and mortality risks, as different groups of patients were likely to be treated empirically by endoscopic or surgical means and were not comparable (Cotton, 1984).

The endoscopist now must consider several clearly defined conditions for which endoscopic management may be indicated in patients with confirmed or suspected bile duct stones:

1. Acute cholangitis regardless of gallbladder status
2. Acute gallstone pancreatitis regardless of gallbladder status
3. Obstructive jaundice
4. Postcholecystectomy, stone shown on intraoperative cholangiogram
5. Postcholecystectomy, retained stone, early presentation
6. Postcholecystectomy, late presentation
7. Gallbladder in situ, variable risk factors for surgery, possible need for subsequent cholecystectomy

Many studies now show endoscopic therapy to be optimal in many of these settings, or they suggest it has a defined role in the treatment algorithm.

ENDOSCOPIC TECHNIQUES (SEE CHAPTER 27)

An endoscopy service to treat CBD stones must have access to an appropriate endoscopy facility, high-quality fluoroscopy, and either rapid film processing of permanent radiographs or digital storage that allows immediate review of stored images. The endoscopy team must be fully cognizant of all the basic procedures, less frequently used techniques, and potential complications and their management. It is essential to explain the nature of the procedure to the patient and to outline the purpose, benefits, advantages, alternatives, and potential hazards.

ES is usually the first therapeutic step and immediately follows diagnostic ERCP, which delineates the problem to be treated and allows accurate placement of instruments within the CBD. Standard pull-type sphincterotomes allow a vertical incision to be made from the papillary orifice in a cephalad direction along the intramural course of the CBD for a variable length (average, 10 to 15 mm) depending on local anatomy, the degree of CBD dilation, and the size of stone to be removed (Fig. 36.1). The incision is produced by the controlled application of monopolar electrocautery delivered by a generator specifically designed for endoscopic use, which does not exceed 150 W output. It is fundamental to good ES technique that complete control of wire tension and electrocautery be

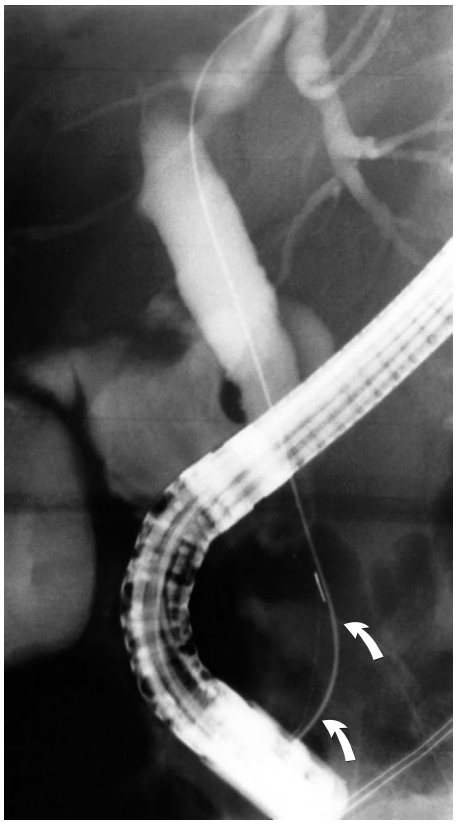


FIGURE 36.1. Endoscopic retrograde cholangiopancreatography showing cholangiography with dilated bile duct, a single duct stone just below the endoscope, a guidewire, and a sphincterotome in position during sphincterotomy (*arrows*).

maintained at all times, whether the ES incision is made as a single continuous movement or in incremental steps. "Smart" generators incorporate a pulsed generator (Erbe, Tubingen, Germany; ConMed Endoscopic Technologies, Billerica, MA) with feedback-controlled power output, and there is potential for increased safety in avoiding a "zipper effect" and reducing pancreatitis and bleeding.

Radiographic confirmation of correct sphincterotome placement within the CBD is mandatory to avoid pancreatic trauma. Occasionally, a *precut papillotomy,* more appropriately called an *access papillotomy,* is needed to initiate ES when the standard instrument cannot be inserted deeply. This incision is often needed when cannulation has been prevented by an impacted stone. The needle-knife is more useful in this situation, because the intramural CBD is usually grossly distended and easily incised, starting from the papilla and extending cephalad. Needle-knife fistulotomy is a variant of this technique; the incision is begun above the papilla to form a choledochoduodenal fistulotomy. This technique is similar in efficacy to needle-knife papillotomy, but more often it requires mechanical lithotripsy, although it may have a lower rate of pancreatitis (Mavrogiannis et al, 1999). Patients with Billroth II partial gastrectomy (Fig. 36.2) and Roux-en-Y bypass operations present special problems to the endoscopist, and numerous methods have been described to obtain successful cannulation (Lin et al, 1999; Wright et al, 2002) and removal of CBD stones (Bergman et al, 2001).

It is standard practice to attempt stone extraction from the CBD immediately after ES. The two accessory instruments

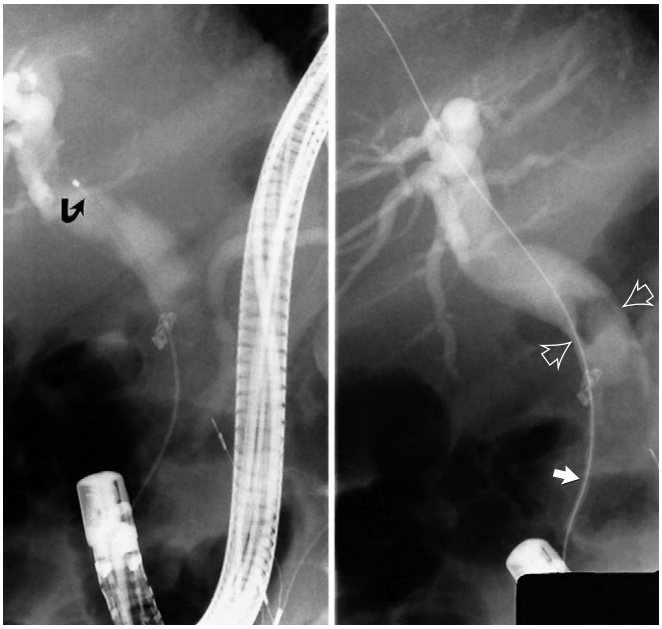


FIGURE 36.2. Endoscopic retrograde cholangiopancreatography in a patient with Billroth II partial gastrectomy showing insertion of a catheter (*curved arrow*) and placement of a guidewire and short biliary endoprosthesis (*solid arrow*) immediately before needle-knife sphincterotomy and demonstration of common bile duct stones (*open arrows*).

used most commonly for this are the Dormia basket (Fig. 36.3) and the Fogarty balloon (Fig. 36.4), which are greater than 90% successful in clearing the CBD. It also is possible to extract stones without a preliminary ES using a balloon dilator (Fig. 36.5) (Bergman et al, 1997). Randomized trials of balloon dilation of the papilla compared with ES have shown similar outcomes for successful stone removal but an increased need for lithotripsy, and although the overall complication rates were similar, there was a higher rate of post-ERCP pancreatitis after balloon dilation if sphincterotomy was not performed beforehand (Baron & Harewood, 2004; Bergman et al, 1997; Disario et al, 2004). Large-diameter balloon dilation after sphincterectomy has become a popular and safe technique (Attasaranya et al, 2008).

Difficult Stones

The most difficult circumstances encountered during endoscopic stone removal result from technical difficulties with achieving deep biliary cannulation or in performing ES. These difficulties are sometimes because of an inaccessible papilla related to aberrant anatomy or unfavorable duodenal or papillary structures, such as a periampullary diverticulum, or prior surgery, such as Billroth II or Roux-en-Y reconstruction. Techniques have been described for the unique challenge of selective bile duct cannulation in a patient with a Billroth II partial gastrectomy (Lin et al, 1999). The performance of ES is also a challenge, because the visualized anatomy is inverted. In especially difficult cases, needle-knife sphincterotomy with a stent, nasobiliary drain, or guidewire used as a guide for cutting may be an option, or specially designed reverse-direction accessories. The literature on techniques of cannulation and sphincterotomy in Roux-en-Y reconstructions is limited (Wright et al, 2002), but some success has been reported with balloon enterosocopy or



FIGURE 36.3. Endoscopic retrograde cholangiopancreatography showing large stone in the proximal bile duct (*arrows*) and basket extraction of a distal bile duct stone (*chevrons*) after endoscopic sphincterotomy.

overtube-assisted ERCP (Koornstra et al, 2008, Kikuyama et al, 2009).

When ES has been successfully performed, extraction may be hindered by a variety of stone factors—including size, number, consistency, shape, and location of stones—ductal factors such as contour and diameter at the level of and distal to the stones, and the presence of coexisting pathology (e.g., stricture or tumor). Stones that are likely to be more difficult to extract and may require adjuvant techniques to remove them

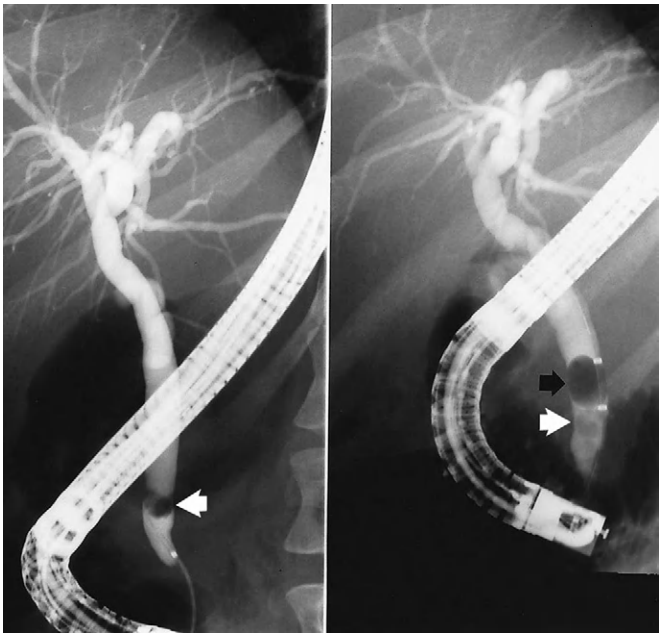


FIGURE 36.4. Endoscopic retrograde cholangiopancreatography showing a nondilated bile duct containing a single distal stone (*white arrow*) and extraction balloon (*black arrow, right*) placed above the stone immediately before its removal after endoscopic sphincterotomy.

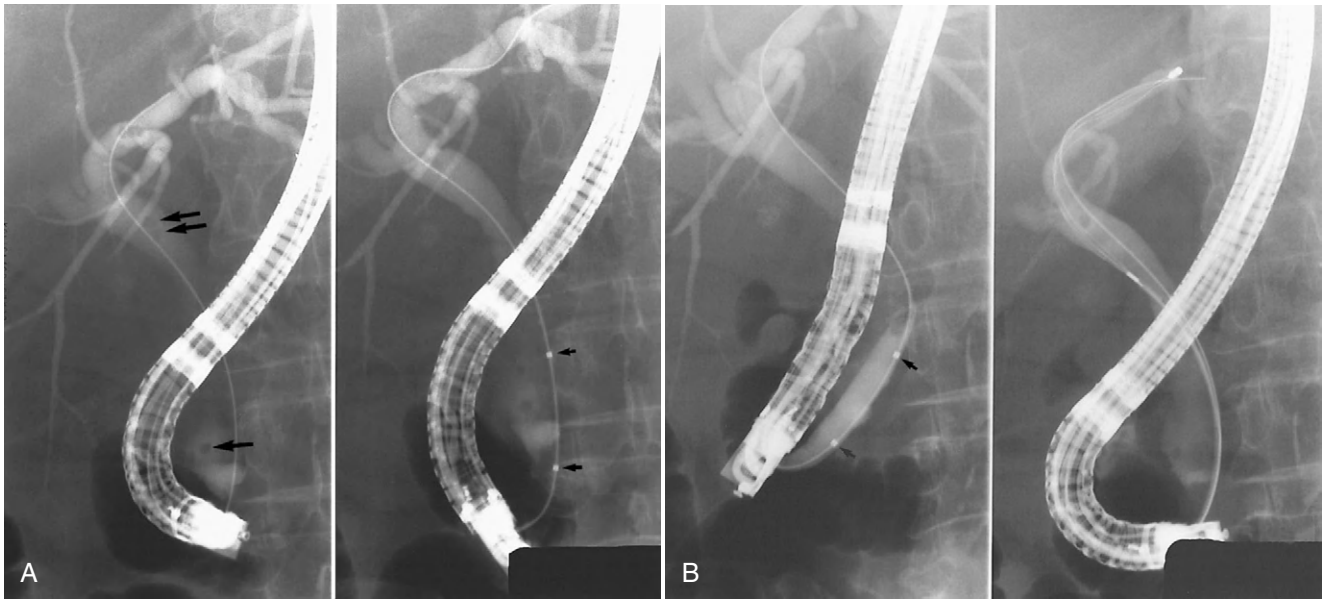


FIGURE 36.5. Endoscopic retrograde cholangiopancreatography series showing technique of balloon dilation of the papilla for extraction of small stones. **A,** Initial cholangiography with demonstration of three small stones (*long arrows, left*) and placement of a guidewire and insertion of an 8-mm dilating balloon located between two radiopaque markers (*small arrows, right*). **B,** Inflation of the dilating balloon (*left*) followed by insertion of an extraction basket for stone removal (*right*).

are those that appear larger than the endoscope on radiographic imaging (usually >15 mm); stones that are numerous or hard in consistency; stones that are square, piston shaped, or faceted that tightly fit the bile duct or that are packed against each other; intrahepatic stones; or stones located proximal to a stricture or narrowed distal bile duct or in a sigmoid-shaped duct. Techniques that have been developed to reduce stone size and facilitate endoscopic removal include mechanical lithotripsy, extracorporeal shock-wave lithotripsy (ESWL), intracorporeal lithotripsy with laser or electrohydraulic probes, and chemical contact dissolution therapy. Treatment options must be discussed jointly by the endoscopist, surgeon, and interventional radiologist when difficulties are encountered (Fig. 36.6; see Chapter 27).

Mechanical Lithotripsy

Removal of large CBD stones is a challenge for the most skilled endoscopist. Mechanical lithotripsy (see Chapter 27; Leung & Tu, 2004; Leung et al, 2001) remains the best initial option for stones that cannot be removed by conventional techniques, because it can be applied safely and effectively during the initial endoscopic procedure. Standard retrieval baskets contained within a polytef (Teflon) sheath may fail to crush large stones, because most exceed the breaking strength of the catheter. Standard-type, lithotripsy-compatible, and lithotripsy-convertible baskets are commercially available. Mechanical lithotripters are modifications of standard Dormia baskets and possess great tensile strength (Fig. 36.7). The reinforced basket is opened in the CBD, and the stone is entrapped within the braided wires. This procedure can be performed through the endoscope instrumentation channel, or it can be done after the endoscope has been removed from the patient and a metal sheath has been extended over the inner Teflon catheter. The end of the metal sheath is attached to a winding mechanism, which retracts the basket when cranked and impales the stone against the rigid distal end of the metal sheath leading to stone fracturing. The stone fragments can be removed with the same basket or a standard retrieval basket or balloon. In experienced centers, this technique allows removal of more than 90% of difficult bile stones that are refractory to standard extraction techniques (Chang et al, 2005; Shaw et al, 1993; Van Dam & Sivak, 1993).



FIGURE 36.6. Endoscopic retrograde cholangiopancreatography showing a dilated bile duct containing multiple faceted stones in a postcholecystectomy patient positioned such that standard extraction techniques might be difficult.

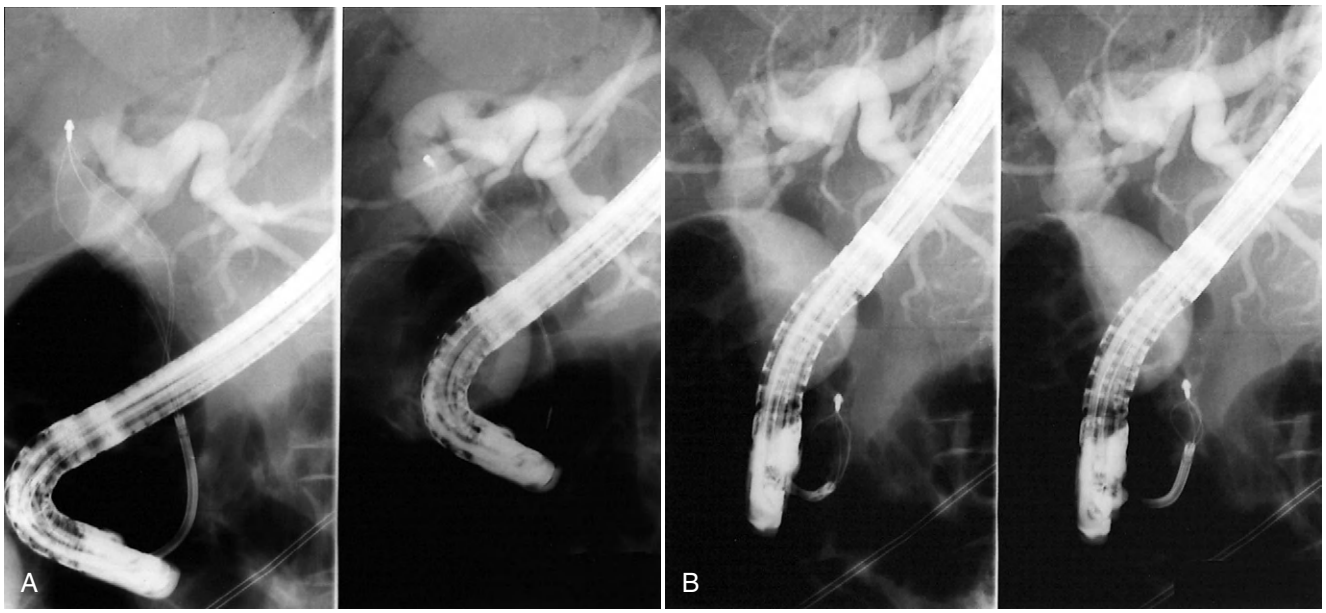


FIGURE 36.7. Endoscopic retrograde cholangiopancreatography sequence showing use of transendoscopic mechanical lithotripsy. **A,** Positioning of the mechanical lithotripsy basket with its metallic sheath in the proximal bile duct (*left*) and its slow withdrawal toward the distally placed stone to entrap it (*right*). **B,** Process of lithotripsy after stone entrapment within the basket (*left*) as the basket wires cut through the stone (*right*) to produce stone fragmentation.

Other Lithotripsy Modalities

For the 5% of patients with biliary stones resistant to ES and mechanical lithotripsy, other methods are available, including intracorporeal techniques (laser or electrohydraulic probes) and ESWL (Adamek et al, 1996). The choice between these methods or surgery depends largely on availability and local expertise.

Laser Lithotripsy

The first-generation laser systems using continuous wave energy neodymium:yttrium-aluminum-garnet (Nd:YAG) devices were ineffective at stone fragmentation and carried a high risk of thermal bile duct injury (Ell et al, 1988). Second-generation devices that have gained acceptance are based on high-energy, flashlamp, pulsed-dye laser technology. The application of the laser pulse leads to rapid expansion and collapse of a plasma on the stone surface, resulting in a mechanical shock wave. Initially, the only means to ensure laser-stone apposition was through the use of "mother and baby" dual endoscope systems (Cotton et al, 1990; Neuhaus et al, 1992a; Ponchon et al, 1991), but more recently, laser lithotripsy has been possible under fluoroscopic guidance with the use of devices that recognize the difference between stone and tissue. Two randomized trials comparing the xenon flashlamp pulsed rhodamine 6G laser with an integrated stone-tissue detection system with ESWL showed similar or improved efficacy in stone clearance, requiring fewer fragmentation and endoscopic sessions with use of the laser (Jakobs et al, 1997; Neuhaus et al, 1998).

Electrohydraulic Lithotripsy

Since its development during the 1950s in the former Soviet Union as a method to fragment rocks during mining, electrohydraulic lithotripsy has been adapted for medical use in the treatment of nephrolithiasis and, more recently, biliary tract calculi. The electrohydraulic probe consists of two coaxially isolated electrodes at the tip of a flexible catheter, which is capable of delivering electric sparks in short, rapid pulses leading to sudden expansion of the surrounding liquid environment and generating pressure waves that result in stone fragmentation (Picus, 1990). Stone contact with the electrode is achieved through the use of basket or balloon catheter systems (Siegel et al, 1990; Arya et al, 2004) or under direct visual targeting (Fig. 36.8) through the working channel of a daughter endoscope (Hixson et al, 1992), minimizing the risk of CBD injury and perforation. Reports document complete stone clearance after multiple sessions in 86% of patients (Adamek et al, 1996; Hixson et al, 1992; Siegel et al, 1990; Arya et al, 2004), and in a prospective nonrandomized trial, electrohydraulic lithotripsy was comparable to ESWL in stone clearance (Adamek et al, 1996). Its main advantages over laser lithotripsy are its lower cost and increased portability.

Extracorporeal Shock-Wave Lithotripsy

ESWL with a variety of lithotripsy machines is now an accepted alternative to endoscopic fragmentation of difficult bile duct stones. In contrast to intracorporeal techniques, direct contact with the stone is unnecessary. Most centers localize stones with fluoroscopic focusing during contrast perfusion of the bile duct through an endoscopically placed nasobiliary catheter or percutaneous drain (Gordon et al, 1991; White et al, 1998). Ponchon and colleagues (1990) reported ESWL success with an ultrasound localization system, although it was less effective when multiple stones were present. Several large series (Bland et al, 1989; Gilchrist et al, 1997; Sackman et al, 2001; Sauerbruch & Stern, 1989) indicated success rates for ESWL stone fragmentation of 53% to 91% and duct clearance in 58% to 90%. Minor complications are common and include hematuria, biliary pain, hemobilia, transient liver function test elevations, and cutaneous petechiae. Overall, with the use of endoscopic techniques such as mechanical lithotripsy, electrohydraulic lithotripsy, laser lithotripsy, and ESWL, one report showed successful stone removal in 98% of 217 patients, with only five patients requiring surgery (Schumacher et al, 1998).

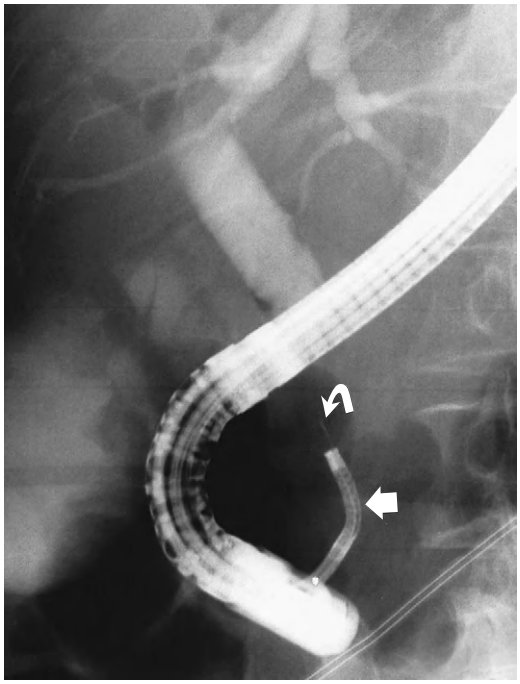


FIGURE 36.8. Use of carrier duodenoscope and direct cholangioscope (*arrow*) inserted within the bile duct with protruding electrohydraulic lithotripsy probe (*curved arrow*) in close proximity to the stone to be fragmented (not visible).

Dissolution Therapy

Contact chemical dissolution of stones (see Chapter 28) has been attempted by perfusing the CBD with solvents administered via an indwelling nasobiliary tube, percutaneous transhepatic catheter, cholecystostomy tube, or an existing T-tube. The initial results with these agents were disappointing because of incomplete stone dissolution and complications. A semisynthetic vegetable oil, monooctanoin, composed of 70% glycerol-1-monooctanoate and 30% glycerol-1,2-dioctanoate, was used experimentally for the dissolution of CBD stones beginning in 1977. Results collected from 222 clinicians treating 343 patients with CBD stones between 1977 and 1983 reported a success rate for complete stone dissolution of only 25.6% and an additional partial success rate of 28% (Palmer & Hoffmann, 1986). Serious adverse effects leading to discontinuation of treatment occurred in 5% of patients, including hemorrhage from duodenal ulceration, acute pancreatitis, jaundice, pulmonary edema, acidosis, anaphylaxis, septicemia, and leukopenia, but no deaths were reported. The use of organic solvents, such as the aliphatic

ether methyl tert-butyl ether (MTBE) (Allen et al, 1985), also has been disappointing, with complete stone dissolution achieved in only 30% to 45% and an unacceptable complication rate related to systemic absorption from spillover of solvent into the duodenum and intrahepatic bile ducts (Brandon et al, 1988; Diaz et al, 1992; Kaye et al, 1990; Murray et al, 1988; Neoptolemos et al, 1990). Sophisticated computer-controlled two-way pump systems may reduce complications and improve efficacy, but total success for large CBD stones using cholesterol solvents is unlikely, because these stones are composed primarily of bile pigments with small concentrations of cholesterol. Expectations of developing a solvent-chelating agent (ethylenediaminetetraacetic acid) for pigment stones have not been realized. As a result of its low efficacy and morbidity, contact dissolution therapy has not assumed an important role in patients with refractory CBD stones, and newer agents with better methods for instillation are awaited.

Endoprosthesis Placement

In the few situations in which stone extraction is incomplete or impossible because of stone size, local anatomy, bleeding, or technical difficulty leading to incomplete ES, a nasobiliary tube (Fig. 36.9) or endoprosthesis (Fig. 36.10) must be inserted to provide biliary decompression and prevent stone impaction in the distal CBD. This is a temporizing therapy to allow the patient's clinical condition to improve, until complete stone clearance is achieved via additional endoscopic maneuvers or surgery. In patients with uncertain duct clearance, a follow-up cholangiogram can be obtained via a nasobiliary tube without the need for repeat ERCP.

Nasobiliary tubes are rarely tolerated beyond a few days. The primary problem with tube placement has been accidental dislodgment, and this has led to the alternative therapy of temporary biliary endoprosthesis placement (Kiil et al, 1989; Rustgi & Schapiro, 1991). In a poor-risk surgical patient, ES and long-term placement of a biliary endoprosthesis has been proposed as a nonsurgical alternative (Cotton et al, 1987; Foutch et al, 1989; Nordback, 1989; Soomers et al, 1990). Stent patency is not of major clinical importance in this situation, because the sphincterotomy typically provides an adequate conduit for bile flow around the prosthesis, which then serves principally to prevent stone impaction. The use of oral ursodeoxycholic acid in these patients has resulted in CBD stone disappearance, but additional studies are necessary to determine the true efficacy in this setting (Johnson et al, 1991). Of 84 patients intentionally treated with permanent stents for endoscopically irretrievable stones and followed for a mean of 3 years, 49 (58%) developed biliary complications, and nine died as a result of complications. Most of the patients had a long, symptom-free interval, however, before complications developed, supporting stenting as effective short-term treatment (Bergman et al, 1995; Maxton et al, 1995). In a randomized study with a shorter mean follow-up (1.5 years) that compared placement of a plastic biliary stent with ES as definitive therapy with stone clearance by means of the basket, balloon, or mechanical lithotripter, the patients with stents had a significantly greater rate of cholangitis (36%) than the patients managed by a conventional endoscopic duct clearance approach (14%). The high risk of long-term complications does not support the concept of permanent stent therapy except for patients with severe comorbidity and a short life expectancy.

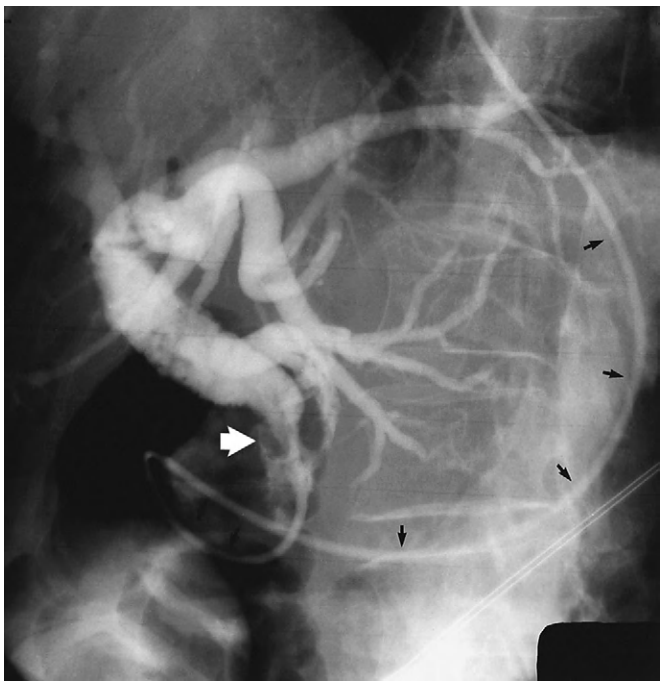


FIGURE 36.9. Radiograph showing placement of a nasobiliary drainage tube (*small arrows*) for the initial treatment of severe cholangitis caused by a single bile duct stone (*large arrow*).



FIGURE 36.10. Endoscopic retrograde cholangiopancreatography showing placement of a 10-Fr diameter endoprosthesis for the temporary management of cholangitis caused by several bile duct stones.

RESULTS OF ENDOSCOPIC THERAPY

Successful endoscopic treatment of CBD stones requires an adequate ES, which is now achieved in greater than 90% of attempts in most reported series, with noticeable improvement

as experience increases (Blumgart & Wood, 1978; Cotton, 1984; Cotton & Vallon, 1981; Geenen et al, 1981; Leese et al, 1985a; Schumacher et al, 1998; Seifert et al, 1982; Siegel, 1981). Although success rates for achieving ES are fairly uniform, rates for complete clearance of the CBD vary because not all endoscopists use extraction methods routinely, and follow-up ERCP may be incomplete. Most experts now would expect to extract stones in at least 90% of successful sphincterotomies. Failure to extract or pass stones may be due to the size or number of stones within the duct or unfavorable duct diameter, usually in its retropancreatic segment. Stones 10 mm in diameter do not give rise to many problems, but in general, with size greater than 15 to 20 mm, the chance of retention increases. Interpretation of success rates necessitates care, because centers with greater expertise are more likely to be referred difficult cases that may be failures from attempts elsewhere, and this would bias some results. Patient groups also vary considerably from unit to unit and country to country, reflecting different referral patterns, selection of patients, and attitudes toward endoscopic therapy. Results from centers around the world (Cotton, 1984; Cotton & Vallon, 1981; Freeman et al, 1996; Geenen et al, 1981; Leese et al, 1985a; Nakajima et al, 1979; Reiter et al, 1978; Safrany, 1978; Schumacher et al, 1998; Seifert et al, 1982; Sherman et al, 1991; Siegel, 1981; Vaira et al, 1989) with individual and collected series of 430 to 9041 patients range from 75% to 96% for duct clearance with a median value of 91%.

Complications of Endoscopic Therapy

Early complications of ES have been well documented, and despite the disparate indications and selection of patients among centers, the incidence seems to be remarkably consistent at 5% to 10% (Cotton, 1984; Cotton & Vallon, 1981; Freeman et al, 1996; Geenen et al, 1981; Leese et al, 1985a; Masci et al, 2001; Seifert et al, 1982; Siegel, 1981; Vandervoort et al, 1996). The expected higher complication rate during early experience with ES is reflected in a single-center series comparing the results of the first 394 procedures (Leese et al, 1985a), which carried an overall morbidity rate of 10.4%, with a subsequent consecutive group of 300 sphincterotomies, in which this rate decreased to less than 6%. However, the respective proportions of individual complications remain similar in most reports: acute hemorrhage from the sphincterotomy site, 2% to 2.9%; acute pancreatitis, 1.5% to 5.4%; cholangitis, 1% to 2.7%; and retroperitoneal perforation, 0.3% to 1%, with small numbers of other problems, such as impacted basket, gallstone ileus, and acute cholecystitis overall accounting for 1.1%. Emergency surgery was required in 1% to 2.5% of cases for bleeding, cholangitis, perforation, and pancreatitis in descending order of frequency. Complication rates must be interpreted with caution, because definitions of hemorrhage, acute pancreatitis, cholangitis, and perforation often differ and are not always given.

A consensus conference provided a set of standards for defining complications and their severity (Cotton et al, 1991a). We have always included any episode of overt bleeding (hematemesis or melena) and a decrease in hemoglobin of 2 g/dL or more after ES as significant hemorrhage, although some authors have included only episodes requiring transfusion. Use of aspirin or related drugs in the usual doses does not seem to increase the incidence of hemorrhage (Freeman et al, 1996). The diagnosis of pancreatitis and cholangitis must depend on the presence of clinically recognizable syndromes rather than asymptomatic hyperamylasemia or transient elevation of temperature alone. There does not seem to be a significant influence on the rate or type of complication based on the initial presentation of the CBD stone (pain alone, jaundice alone, pancreatitis, a combination of these), except that cholangitis and cholecystitis are more likely after ES if cholangitis is preexisting. Present evidence does not suggest that complications are more likely in older patients or after previous biliary surgery (Clarke et al, 2001).

Statistically significant risk factors for complications include difficulty in cannulation, access (precut) papillotomy, suspected sphincter of Oddi dysfunction, more than two pancreatic cannulations, acinarization of the pancreas, failed biliary access or drainage, and technical skill of the endoscopist; the age and general medical condition of the patient were not statistically significant (Freeman et al, 1996; Neoptolemos et al, 1989; Vandervoort et al, 2002). Duodenal diverticula, although sometimes rendering ERCP and ES technically more difficult, do not seem to add any further risk. Many series do not include nonendoscopic complications occurring after ES, such as cardiovascular, cerebrovascular, or respiratory events. In addition, although surgery for the treatment of complications is usually documented, surgery for failed endoscopic therapy is often not documented. These factors are important if comparative data from the surgical literature are to be interpreted correctly.

Management of Complications

The management of complications by centers performing ES is well standardized, but many patients are referred from other hospitals to which they are returned after the procedure, where experience in managing complications may be limited. Of all complications, hemorrhage usually requires surgical intervention, but this occurs only in a few cases. In the rare major arterial hemorrhage, endoscopic view of the papillary area is often obscured completely by blood, and further endoscopic therapy may be impossible. The sphincterotomy usually is converted to a formal surgical sphincteroplasty, which includes the likely bleeding artery. Immediate methods for hemostasis include balloon tamponade, direct bipolar electrocautery, injecting or washing the area with 1:10,000 epinephrine solution, application of hemostatic clips, laser coagulation, superselective arterial catheterization and embolization, and infiltration with sclerosant (Grimm & Soehendra, 1983; Leung et al, 1995; Wilcox et al, 2004).

Acute pancreatitis is managed in the standard fashion (see Chapters 53 and 54), and although many attacks are mild and self-limited, clinicians should not be complacent, because some attacks are more severe and should be graded and treated appropriately. Wire-guided cannulation decreases the risk of post-ERCP pancreatitis when compared to the contrast-injection method (Cennamo et al, 2009). There is no evidence that pre-ES or post-ES administration of aprotinin (Trasylol) or glucagon influences the incidence or severity of pancreatitis. In contrast to hemorrhage, the onset of pancreatitis may be delayed for several hours or, rarely, for 1 or 2 days. Gabexate, a synthetic protease inhibitor, and somatostatin have been shown in randomized, double-blind controlled trials to reduce the extent of enzyme elevations and the incidence of pancreatitis after ERCP (Cavallini et al, 1996; Masci et al, 2001; Poon et al, 2003). Gabexate was infused for 30 to 90 minutes before and for 6.5 to 12 hours after ERCP, whereas somatostatin was administered



FIGURE 36.11. Computed tomographic scan of the stomach with oral contrast administration showing extensive retroperitoneal, intraperitoneal, and subcutaneous air caused by a perforation from endoscopic sphincterotomy. The patient made an uneventful recovery on conservative treatment.

either as a bolus infusion or in a manner similar to gabexate (Bordas et al, 1998; Poon et al, 1999, 2003). A trial suggested diclofenac administered as a rectal suppository after ERCP reduced the incidence of post-ERCP pancreatitis (Murray et al, 2003). Trials using secretin are in progress.

Cholangitis is confined almost completely to patients in whom CBD clearance has not been achieved, and measures should be directed at providing adequate bile drainage (e.g., by nasobiliary catheter or endoprosthesis) and administering parenteral antibiotics (see Chapter 43). Emergency surgery for cholangitis carries high risk but is indicated in patients who do not improve within 24 hours.

Perforation may be asymptomatic and noticed only as retroperitoneal gas (Fig. 36.11) or extravasation of radiographic contrast material, but even in a symptomatic patient, conservative treatment is often effective, with spontaneous resolution and avoidance of potentially difficult surgery. Occasionally, this complication presents late after ES with a retroperitoneal collection of bile or pus in the flank or inguinal region (Neoptolemos et al, 1984a; Leese et al, 1985a) and requires percutaneous or surgical drainage.

Gallstone ileus is a rare complication, but its recognition needs to be emphasized, because symptoms may be obscure in elderly patients, and they occur many days after ES and stone release; treatment is along standard surgical lines.

The impaction of an extraction basket occurs rarely in experienced hands, because many endoscopic maneuvers have been learned to prevent or salvage this situation. These maneuvers include 1) avoiding basket closure during initial attempts to extract a large stone to prevent impaling the basket wires in the stone surface; 2) converting the standard basket into a crushing type by replacing the handle with a mechanical lithotripter; and 3) extending the ES incision by removing the duodenoscope over the impacted basket catheter and reintroducing it alongside the catheter, introducing a second duodenoscope, or passing a sphincterotome along the same instrument channel as the impacted basket catheter when using large channel (3.7 mm or 4.2 mm) endoscopes.

Mortality

Death after ES has not been reported in a standardized way. Deaths directly attributable to the procedure are fairly constant at 0.8% to 1.5% (Cotton, 1984; Cotton & Vallon, 1981; Geenen et al, 1981; Leese et al, 1985a; Nakajima et al, 1979; Reiter et al, 1978; Safrany, 1978; Seifert et al, 1982; Siegel, 1981; Sivak, 1989), with almost equal distribution of causes between hemorrhage, pancreatitis, cholangitis, and perforation. Most of the deaths are postprocedural. Mortality rate as a proportion of complications ranges from 7% to 17%, which presumably reflects the comprehensive reporting of all complications by some authors, but reporting of only more severe complications by others. Using the accepted method of reporting 30-day surgical mortality, mortality within 1 month of ES was 3.3% compared with 0.8% immediate postprocedural mortality (Leese et al, 1985a). The additional deaths were due to a variety of vascular, respiratory, renal, infectious, and malignant conditions in a group whose mean age was 79 years. Another group of 59 elderly patients considered unfit for surgery by surgeons underwent ES (Neoptolemos et al, 1984b) with only one death (1.7%).

Long-Term Morbidity

Long-term follow-up of 1 to 15 years after ES in postcholecystectomy patients (Cotton, 1984; Escourrou et al, 1984; Hawes et al, 1990; Ikeda et al, 1988; Rosch et al, 1981; Seifert et al, 1982; Sivak, 1989) shows more than 90% of patients to be well on symptomatic review and 7% to 11% have significant symptoms secondary to recurrent stones (5%), with or without stenosis of the ES site (1.5% to 3%) and cholangitis (2%). One study with long-term follow-up of 15 years after ES found an early complication rate of 15% with a high incidence of late complications, including recurrent stones and pancreatitis in 24% (Bergman et al, 1996); however, this study included only procedures performed between 1976 and 1980. A higher rate of asymptomatic stones and stenosis might result from the use of plain abdominal radiography for detecting pneumobilia, barium studies for detecting duodenobiliary reflux, radionuclide scanning, and repeat ERCP, which do not seem justified outside clinical trials. Most of these long-term complications are amenable to further endoscopic treatment.

Percutaneous Approach

In the 5% to 10% of patients for whom the endoscopic approach is unsuccessful at clearing the CBD of stones, two nonsurgical approaches are available: a *rendezvous procedure* and a *complete percutaneous procedure* (see Chapters 27 and 28). If the papillary region can be reached endoscopically, the rendezvous procedure may be used. This involves a two-stage procedure with the introduction of a percutaneous guidewire through the bile ducts and papilla into the duodenum in the first stage followed by an ERCP (Dowsett et al, 1989; Martin, 1994; Verstandig et al, 1993). In one report of rendezvous procedures for choledocholithiasis, 0.9% (15 of 1753) of ERCPs were unsuccessful at biliary cannulation, usually owing to duodenal diverticula or Billroth II anatomy (Calvo et al, 2001). Three patients

underwent surgery, and 93% of the remaining patients underwent a successful rendezvous procedure. There was one complication with a retroperitoneal perforation that required surgical management, and during follow-up, only one patient developed recurrent choledocholithiasis requiring a repeat rendezvous procedure. In the multicenter prospective trial of endoscopic biliary sphincterotomy complications (Freeman et al, 1996), the combined endoscopic-percutaneous approach was a risk factor for the development of complications, with a high rate of complications at 22.6% with 6.5% classified as severe.

The complete percutaneous approach is labor intensive and typically requires multiple sessions. It has been established as treatment for hepatolithiasis (Yeh et al, 1995; see Chapters 39 and 44), but it may be used for choledocholithiasis. The procedure involves initial establishment of a transhepatic fistula, followed by stone extraction under fluoroscopy or cholangioscopy 7 to 8 days after the fistula forms. In a series of 31 patients with failed endoscopic procedures, percutaneous biliary access was achieved in all patients, and stone clearance was complete in 87% after a mean of 5.6 sessions (Van der Velden et al, 2000). All patients underwent balloon dilation of the papilla, and most patients required additional means of stone fragmentation, including mechanical lithotripsy, electrohydraulic lithotripsy, and ESWL. Complications including pancreatitis and bacteremia occurred in 9.7% and did not require surgical intervention. The four patients who did not respond to percutaneous management underwent surgery. Bile duct access by endoscopic ultrasonography has largely removed the need for percutaneous approaches (see Chapter 14).

COMPLICATIONS, MORTALITY RATES, AND LONG-TERM RESULTS OF BILE DUCT SURGERY

Open Bile Duct Exploration (See Chapters 29 and 35)

Morbidity and mortality after open bile duct exploration have been well documented (Allen et al, 1981; Blamey et al, 1983; Dixon et al, 1983; Doyle et al, 1982; Girard & Legros, 1981; Glenn, 1974, 1975; Kune, 1972; McSherry & Glenn, 1980; Pitt et al, 1981; Vellacott & Powell, 1979; Way et al, 1972), with examination of specific risk factors (Blamey et al, 1983; Dixon et al, 1983; Pitt et al, 1981) that allow some prediction of the likelihood of complications and perhaps predict the need for preoperative biliary drainage. Direct comparison with the endoscopic data is not valid, because extremely diverse groups of patients are being treated by these modalities. This situation highlights the concept of "apples and oranges" succinctly stated by Cotton (1984), but mention must be made of published surgical figures to enable some clinical judgments to be made in the absence of randomized trials. It is immediately apparent that, in contrast to endoscopic therapy, surgical morbidity and mortality are determined by patient age, comorbidities (Glenn, 1975; McSherry & Glenn, 1980; Vellacott & Powell, 1979), hemotologic and biochemical factors (Blamey et al, 1983; Dixon et al, 1983; Pitt et al, 1981), and whether the operation is elective (Houghton & Donaldson, 1983; Sullivan et al, 1982) or emergent (Boey & Way, 1980; Thompson et al, 1982). Mortality rates range from 1% in relatively fit younger patients to 28% in unfit and elderly patients and 12% to 14% in younger patients undergoing emergency surgery for cholangitis. These figures nearly all refer to primary bile duct operations and should be compared only with results of ES when the gallbladder is in situ. Equivalent results for secondary bile duct explorations are less well recorded, but mortality rates of 2% are possible for elective surgery (Girard & Legros, 1981; McSherry & Glenn, 1980). Consideration also must be given to biliary drainage operations, which avoid problems of stone retention, although this may be at the expense of an increased postoperative morbidity and mortality. Average mortality rates are 1% to 5% for choledochoduodenostomy and transduodenal sphincteroplasty (Capper, 1961; Jones, 1978; Lygidakis, 1981; Madden et al, 1970; Speranza et al, 1982; Stuart & Hoerr, 1972). A review of 246 such operations (Baker et al, 1985) in which one of these drainage procedures was used revealed a mortality rate of 5.4% for each of the two types of operations and major morbidity rates of 12% for choledochoduodenostomy and 21% for transduodenal sphincteroplasty. The results stated here should be read in conjunction with those reported in Chapters 29 and 35.

Long-Term Follow-up of Surgically Explored and Reexplored Bile Ducts

Long-term follow-up data after open bile duct exploration are lacking. The wide variation in reported recurrent stone rates has been mentioned, but morbidity and the need for further surgery have been found in 5% after 5 years (Larson et al, 1966), 10% after 12 years (Peel et al, 1975), and 21% after 6 to 11 years (Lygidakis, 1983) when exploration without biliary drainage has been performed. After choledochoduodenostomy (see Chapter 29), there was no morbidity in a 6- to 11-year follow-up (Lygidakis, 1983) with similar results for transduodenal sphincteroplasty (Degenshein, 1964; Stuart & Hoerr, 1972). Follow-up of 90% of the survivors of one series of 246 patients 1 to 12 years postoperatively (mean, 4.4 years) revealed that complications had been treated in 3% of the choledochoduodenostomy group (mainly sump syndrome) and 6% of the transduodenal sphincteroplasty group (mainly cholangitis), with additional symptoms discovered on interview in 8% of the choledochoduodenostomy and 5% of the transduodenal sphincteroplasty groups.

Laparoscopic Common Bile Duct Exploration

Laparoscopic CBD exploration (see Chapter 34) was first performed in the early 1990s and is now used increasingly in experienced tertiary referral centers (Khoo et al, 1996; Martin et al, 1998; Rhodes et al, 1995). Ductal exploration may be accomplished through the cystic duct or directly through a choledochotomy. The transcystic route is the least invasive and generally does not require any ductal manipulation or drainage procedure, whereas choledochotomy requires either closure of the duct over a T-tube or primary closure of the choledochotomy with or without a biliary stent placed in an antegrade fashion without need for a T-tube (Huang et al, 1996; Rhodes et al, 1995). Bile duct clearance rates average 90%, with a median rate of conversion to open operation of 4% (Tranter & Thompson, 2002). Complication rate is 2.5%, with a median mortality rate of 1% (Strasberg et al, 1995).

In a randomized trial of laparoscopic CBD exploration versus postoperative ERCP for CBD stones (Rhodes et al, 1998), the clearance rates at the first intervention were the same

(75%). With subsequent treatment, predominantly in the form of repeated ERCP, duct clearance rates approached 100% in both groups. In a similar study sponsored by the European Association of Endoscopic Surgeons (Cuschieri et al, 1996), patients were randomized to preoperative ERCP followed by laparoscopic cholecystectomy or laparoscopic cholecystectomy with laparoscopic CBD exploration. Duct clearance was similar in the two groups, but there was a higher rate of conversion to open surgery and decreased length of stay with single-stage surgical treatment. Our group has shown that therapeutic ERCP can be performed safely as an outpatient procedure without need for hospitalization (Tham et al, 1997). To minimize hospital stay, the outpatient ERCP would need to be coupled with laparoscopic cholecystectomy, which requires good coordination between the surgeon and the endoscopist.

SPECIFIC CLINICAL PROBLEMS

Postcholecystectomy with T-Tube In Situ (See Chapter 29)

CBD stones of less than 10 mm in diameter detected in the early postoperative period on T-tube cholangiography may pass spontaneously or with hydrostatic pressure from flushing or perfusing the T-tube. Most of these stones require additional mechanical manipulation, however. Increased morbidity, mortality, and retained stone rate after secondary bile duct explorations stimulated the development of alternative techniques, including hydraulic T-tube irrigation with or without pharmacologic relaxation of the sphincter of Oddi with glucagon or nitrates (Tritapepe et al, 1988), T-tube infusion of cholesterol solvents (Tritapepe et al, 1988), T-tube tract choledochoscopy and lithotripsy (Josephs & Birkett, 1992), and percutaneous extraction of stones through a mature T-tube tract. Success rates with the last technique have ranged from 77% to 96%, but multiple sessions are often required and the technique may be complicated by sepsis, biliary trauma, and biliary leakage in 4% to 8% of patients (Burhenne, 1980; Caprini, 1988; Cotton, 1990; Mason, 1980; Nussinson et al, 1991; Tritapepe et al, 1988). Delays of 4 to 6 weeks are required before manipulation to allow maturation of the T-tube tract.

Alternatively, early ES can be applied safely and effectively after stone detection without the need for T-tube maturation, allowing timely discharge from hospital. The results from eight endoscopic series totaling 337 patients indicate an overall endoscopic success rate of 90% with a morbidity rate of 7% and mortality rate of 0.6% (Bickerstaff et al, 1988; Danilewitz, 1989; Lambert et al, 1988; Nussinson et al, 1991; O'Doherty et al, 1986; Simpson et al, 1985; Soehendra et al, 1981; Tandon et al, 1990). The choice between these two techniques depends on local expertise, because direct comparisons have not been made in controlled trials.

Postcholecystectomy Without T-Tube

The incidence of retained CBD stones is approximately 2% to 5% after conventional and laparoscopic cholecystectomy and 5% to 15% after CBD exploration. ES remains the treatment of choice for elderly patients seen days to years after cholecystectomy (Danilewitz, 1989), because these patients are at higher risk from further abdominal surgery (Cranley & Logan, 1980; Sheridan et al, 1987). ES also is recommended for choledocholithiasis in young, fit postcholecystectomy patients, even those with normal diameter ducts (Cotton et al, 1998).

Pregnancy

Symptomatic choledocholithiasis during pregnancy poses a diagnostic and therapeutic challenge. The frequency of choledocholithiasis in pregnancy requiring intervention may be 1 in 1200. Traditionally, intervention in these patients has been surgical. Although surgery has an overall low morbidity and mortality for the expectant mother, it carries a 4- to 6-week recovery period with a possible increased risk of fetal loss.

Endoscopic treatment can be performed safely with a complication rate comparable to that in nonpregnant patients (Jamidar et al, 1995; Kahaleh et al, 2004; Tham et al, 2003, Simmons et al, 2004). We reviewed our experience with 15 pregnant patients who underwent ERCP (Tham et al, 2003). Precautions were taken to minimize fetal exposure to radiation, which included covering the pelvis of all patients with an abdominal lead apron and minimizing fluoroscopy. No adverse outcomes occurred to the mother or the fetus, and the average fetal radiation dose was 310 mrad, which is below the 5- to 10-rad level considered teratogenic. These patients should undergo cholecystectomy on completion of pregnancy to prevent recurrence.

Patients with Gallbladder In Situ

In elderly patients or in patients with significant comorbidity, a deliberate decision often is made to leave the gallbladder in situ after ES and CBD stone removal. The short-term and long-term results and complications of ES in patients with gallbladders do not differ from those in postcholecystectomy patients (Kaw et al, 2002). One randomized study of high-risk surgical patients reported a higher rate of recurrent biliary symptoms in the ES group compared with patients who underwent open cholecystectomy with operative cholangiography (Targarona et al, 1996); however, details of the endoscopic procedure were not reported in the article, and the failure rate for ES was high at 20%. In view of their shorter life expectancy, high-risk patients can be managed expectantly, unless symptoms dictate otherwise. Careful follow-up for 5 to 10 years in patients with intact gallbladders indicates that approximately 10% develop gallbladder symptoms or complications sufficient to warrant cholecystectomy, and most occur in the first year (Davidson et al, 1988; Escourrou et al, 1984; Hill et al, 1991; Rosseland & Solhaug, 1984; Siegel et al, 1988; Tanaka et al, 1987). The risk for developing gallbladder symptoms is similar to that of patients with asymptomatic cholelithiasis (Gracie & Ransohoff, 1982). Most patients requiring cholecystectomy can be treated electively.

The risk of developing biliary symptoms seems to depend on the continuing presence of stones in the gallbladder. In two reports (Siegel et al, 1988; Tanaka et al, 1987), none of the patients with acalculous gallbladders at initial ES developed symptoms or complications that subsequently required cholecystectomy. In patients with gallstones, there were no reliable predictors to identify patients with cholelithiasis who were likely to develop gallbladder complications after ES. Nonfilling of the gallbladder with radiographic contrast material at ERCP (Worthley & Toouli, 1988) or with radiotracer by nuclear

scintigraphy (Holbrook et al, 1991) may confer a higher likelihood of developing symptoms, although results from other series do not concur (Davidson et al, 1988; Hill et al, 1991). These results suggest that the low risk of subsequent gallbladder complications after ES and bile duct clearance, when patients are kept under supervision, outweighs the known higher mortality rate of cholecystectomy in high-risk patients and mitigates against routine cholecystectomy in this group. Few physicians would recommend this approach in a fit patient, in whom the expectation for long-term survival and development of symptoms necessitating cholecystectomy are greater. The risk of elective cholecystectomy is probably smaller than the risk of subsequently developing gallbladder symptoms in this group, so elective cholecystectomy would seem most appropriate. This idea was confirmed by a study of 120 patients with known gallstones who underwent successful ES with bile duct clearance; the study excluded patients who were not surgical candidates, and patients were randomized to laparoscopic cholecystectomy within 6 weeks after ES or a wait-and-see policy with median 2.5-year follow-up. Nearly half the patients in the wait-and-see group developed biliary-related problems, including biliary pain and cholecystitis, which led to cholecystectomy or repeat ERCP or both, whereas none of the patients in the cholecystectomy group experienced biliary-related problems. The wait-and-see group also had a higher rate of conversion to an open procedure at the time of surgery (Boerma et al, 2002).

The place of preoperative ES in young, low-risk surgical patients with suspected choledocholithiasis has been examined to determine whether preoperative ES confers an advantage in terms of morbidity, mortality, and length of hospital stay compared with a conventional approach of open cholecystectomy, operative cholangiography, and CBD exploration. Two prospective, randomized controlled trials (Neoptolemos et al, 1987; Stiegmann et al, 1992) have addressed this question with the conclusion that no advantage is conferred by initial endoscopic bile duct clearance before cholecystectomy. High-risk surgical patients were excluded from these studies, and both studies were conducted in the era of open cholecystectomy, before the use of high-quality MRCP.

Laparoscopic Cholecystectomy and Endoscopic Retrograde Cholangiopancreatography

Laparoscopic cholecystectomy (see Chapter 34) has replaced open cholecystectomy as the procedure of choice for gallbladder removal in most patients with symptomatic cholelithiasis. Optimal management of patients with suspected or documented CBD stones varies according to the expertise available in a particular institution. Laparoscopic transcystic CBD exploration (Hunter, 1992) or direct choledochotomy (Jacobs et al, 1991) can be performed at the time of laparoscopic cholecystectomy, but these procedures require special expertise and equipment. Laparoscopic transcystic choledochoscopy is hindered by the small size and tortuosity of the cystic duct, making instrument passage and stone lithotripsy and removal potentially difficult.

In patients with suspected CBD stones, MRCP has replaced ERCP as the diagnostic modality of choice to identify the presence or absence of CBD stones (see Chapter 17). A need for endoscopic management has evolved, with ERCP playing a central role in preoperative and postoperative CBD stone removal. Initially, we and others (Cotton et al, 1991b) found it useful to stratify patients preoperatively into low, intermediate, and high likelihood for CBD stones (Table 36.1) based on established clinical and biochemical indicators, including elevated liver function tests, a dilated CBD (>8 mm on ultrasound), and a history of jaundice or pancreatitis (Del Santo et al, 1985; Hauer-Jensen et al, 1985; Lacaine et al, 1980). In the absence of clinical or biochemical indicators, CBD stones are present in only 2% to 3% of individuals (Neuhaus et al, 1992b). Small asymptomatic stones may be of minor clinical relevance, because their natural history is unknown, and conceivably many if not most of these calculi would pass spontaneously without ever coming to clinical attention. We have favored selective evaluation of the CBD only for patients with risk factors for choledocholithiasis.

Table 36.1

Cholangiography Stratification for Risk of Choledocholithiasis

High Likelihood (Preoperative ERCP)
Bilirubin >2 mg/dL
Alkaline phosphatase >150 U/L
Present/recent history of jaundice/pancreatitis
Dilated CBD/stone on sonography
Intermediate Likelihood (IOC)
Bilirubin 1.5-2 mg/dL
Alkaline phosphatase 110-150 U/L
Transaminases >2× normal
Remote jaundice/pancreatitis
Low Likelihood (No ERCP/IOC)
Normal liver function tests
No ductal dilation
No jaundice/pancreatitis

ERCP, endoscopic retrograde cholangiopancreatography; CBD, common bile duct; IOC, intraoperative cholangiography

We have proposed three general strategies to manage patients with suspected or documented CBD stones (Tham et al, 1998). Algorithm 1 offers the advantage of complete surgical management at a single procedure without the need for additional postoperative stone extraction. The major disadvantage is the high rate of conversion to an open procedure, which is not in keeping with the desire to maintain a minimally invasive approach to therapy, but it is required in some patients (Cuschieri et al, 1999; Huang et al, 1996). This strategy has not gained widespread acceptance, but it would be a reasonable approach in centers incapable of providing adequate endoscopic therapy, or when techniques are achieved for performing laparoscopic CBD exploration. Algorithm 2 focuses on endoscopic cholangiography and stone clearance before performance of laparoscopic cholecystectomy. This approach seems justified in a patient with a high likelihood of a CBD stone; it would avoid prolonging the operative procedure with intraoperative cholangiography while maintaining the minimally invasive approach and reducing the need for conversion to an open CBD exploration for laparoscopic failures (Tham et al, 1998; Wright et al, 2002). It is often possible to remove small stones (3 mm in diameter) during ERCP through the intact papilla, sparing the patient the potential short-term and long-term risks of ES (Cotton, 1993; Ibuki et al, 1992; Staritz et al, 1985). Algorithm

Table 36.2

Endoscopic Retrograde Cholangiopancreatography in 1847 Laparoscopic Cholecystectomies at Brigham & Women's Hospital (1990–1992)

Preoperative ERCP	135 (7.3%)
Normal	83 (62%)
Stones	43 (32%)
Mirizzi syndrome	1 (0.7%)
Aberrant anatomy	2 (1.5%)
Failed ERCP	2 (1.5%)
Intraoperative cholangiography	87 (5%)
Successful	39 (45%)
Stones	2 (2%)
Not attempted	1625/1847 (88%)

ERCP, endscopic retrograde cholangiopancreatography

3 uses laparoscopic transcystic cholangiography to detect CBD stones and postoperative ERCP to remove stones in patients with positive cholangiograms. This strategy relies heavily on ERCP expertise, because failed stone removal necessitates referral to a more experienced endoscopist or a second open operative procedure. The choice between these strategies should be strongly influenced by the surgical and endoscopic expertise available. It should be stressed that noninvasive imaging of the CBD with MRCP has replaced ERCP as the diagnostic modality of choice for patients with suspected CBD stones.

At our institution, in a prospective series of 1847 consecutive laparoscopic cholecystectomies (Table 36.2), preoperative ERCP (algorithm 2) was performed in 135 (7.3%) patients considered highly likely to have CBD stones based on a total bilirubin greater than 2 mg/dL, alkaline phosphatase greater than 150 U/L, a dilated CBD on ultrasound, or a recent history of jaundice or pancreatitis. ERCP was successful in 133 (98.5%) patients, and 43 (32%) were found to have CBD stones. All stones were removed after sphincterotomy, with nine complications: six cases of pancreatitis (three mild, three moderate), two of hemorrhage (one mild, one moderate), and one fever with negative blood cultures. Aberrant ductal anatomy was present in two ERCPs, Mirizzi syndrome (see Chapter 42) was present in one, and 83 were normal. Using stricter criteria for preoperative ERCP selection, we increased the preoperative detection rate of CBD stones from 32% to 56% predicted.

We suggest performance of precholecystectomy ERCP 24 to 48 hours before the planned surgery whenever logistically feasible to avoid the infrequent occurrence of stone migration from the gallbladder into the CBD during the ERCP-laparoscopy interval, resulting in the possibility of a retained CBD stone. This sequence of events occurred early in our series in one patient who passed a stone from the gallbladder into the CBD during a 3-week interval between the preoperative ERCP and laparoscopy, but it has not recurred with subsequent performance of preoperative ERCP at the recommended 24- to 48-hour interval. Selective intraoperative cholangiography (algorithm 3) was performed in 87 patients (5%) believed to be at intermediate risk for CBD stones based on preoperative indicators that included a total bilirubin elevation of 1.5 to 2 mg/dL, alkaline phosphatase of 110 to 150 U/L, transaminases greater than twice normal, or a remote history of jaundice or pancreatitis. Only two (2%) of these studies were positive. Patients without preoperative indicators (1625 patients) and considered low risk did not undergo cholangiography, and 21 (1.3%) were subsequently found to have retained stones, all managed successfully by ERCP and ES.

Acute Cholangitis

Acute cholangitis (see Chapter 43) resulting from CBD stones traditionally was managed by supportive measures and parenteral antibiotics, followed by early surgery if improvement was slow or absent. The mortality from emergency surgery ranges from 12% to 16% with higher rates for elderly patients (Boey & Way, 1980; Cotton, 1984; Thompson et al, 1982). In the 1980s, we analyzed the treatment outcomes of 82 patients with severe acute cholangitis and CBD stones admitted over a 7-year period during which ES was available (Leese et al, 1985b). Mean age was 71 years (range, 19 to 88 years), with 87% older than 60 years and 23% older than 80 years. Overall 30-day mortality rate was 14.6% but varied considerably with different modes of therapy. Eleven patients received conservative treatment only; of these, seven responded to antibiotics alone, but four (36.4%) were moribund and died before any treatment could be instituted. Seventy-one patients underwent early biliary decompression either surgically (n = 28) or endoscopically (n = 43). Of the 11 postcholecystectomy patients, four had early surgery with biliary-digestive bypass, with two deaths within 30 days (50%), and seven had early ES with no deaths. Of the 60 patients with gallbladders, 24 were treated surgically (mean age, 62 years) with a mortality rate of 16.7%; 13 had an ES followed by elective cholecystectomy (mean age, 64 years) with no deaths; and 23 had an ES with gallbladders in situ. Of these, six died from unrelated causes, and two required surgery for empyema of the gallbladder—at 19 days after ES in one and after recurrence of cholangitis at 5 months in the other. Complications after ES occurred in 10 patients: five hemorrhages, three exacerbations of cholangitis, one mild acute pancreatitis, and one gallstone ileus requiring surgical intervention. Bile duct clearance was achieved in 40 (93%) of 43 patients. Of the three failures, one patient died without further therapy, one underwent surgery 4 weeks later, and one remained asymptomatic, having declined further treatment. The 30-day mortality rate for patients treated by early surgery was 21.4% (six of 28), and 30-day mortality rate for patients treated by early ES, regardless of subsequent treatment, was 4.7% (two of 43). We concluded that patients not responding to standard initial therapy within 24 hours should be offered endoscopic biliary decompression and bile duct clearance if this is locally available. The only randomized trial of emergency endoscopic versus surgical management of severe calculous cholangitis (Lai et al, 1992) showed a threefold difference in mortality rate (10% vs. 32%; $P < .03$) in favor of ERCP.

Gallstone Pancreatitis

Acute pancreatitis (see Chapters 53 and 54) resulting from impaction of gallstones in the ampulla of Vater was first reported by Opie in 1901. From his observations in this study, an "obstructive theory" was derived to explain the mechanism responsible for gallstone pancreatitis. Stone impaction in the common channel of the pancreatic duct and CBD is postulated to result in obstruction of the two systems with resultant reflux of bile into the pancreatic duct (Moody et al, 1993). In support of the obstructive theory, gallstones can be recovered from the

feces of 85% to 95% of patients (Acosta & Ledesma, 1974; Kelly, 1980a, 1980b), and the incidence of CBD stones is 80% in patients undergoing urgent operative or endoscopic intervention compared with a 5% to 30% incidence when the procedure is delayed (Acosta et al, 1978; Kelly, 1980a, 1980b; Ranson, 1979; Stone et al, 1981).

The Ranson, Imrie, Glasgow, and Acute Physiology, Age, and Chronic Health Evaluation (APACHE II) assessments provide well-established criteria for assessing the severity of pancreatitis and predicting local adverse events—such as necrosis, hemorrhage, infection, and pseudocyst formation—and systemic complications of acute respiratory distress syndrome, disseminated intravascular coagulation, distant fat necrosis, and renal failure (see Chapters 52 to 54; Banks, 1991). Stratifying patients by severity based on these criteria has been helpful in directing appropriate management. Most patients experience mild pancreatitis resulting from transient impaction of a stone in the ampulla followed by spontaneous migration into the duodenum. These patients do well with conservative therapy alone and are unlikely to benefit from urgent intervention. In contrast, it has been proposed that more severe cases of pancreatitis result from persistent stone impaction or choledocholithiasis with infected bile, suggesting the possibility that early stone extraction by surgical or endoscopic techniques would halt progression of the acute event and prevent the development of future attacks in the short term.

Early surgical therapy in cases of acute gallstone pancreatitis has been challenged owing to the high operative morbidity and mortality. Results and conclusions from numerous series comparing early and late surgical therapy in gallstone pancreatitis are difficult to interpret. The mortality rates range from 2% to 67%, studies are retrospective with frequent comparisons to historical controls, and stratification for severity of illness has not been used (Acosta et al, 1978; Kim & Bosner, 1988; Osborne et al, 1981; Ranson, 1979). In one series, Kelly and Wagner (1988) prospectively randomized 165 patients with gallstone pancreatitis to early or delayed surgery. In the group with severe pancreatitis, mortality was 48% after urgent operative intervention compared with 11% mortality rate in patients in whom surgery for gallstones was delayed for more than 48 hours. In contrast, patients with mild pancreatitis had mortality rates of 3.3% and 0%, respectively. Another study of moderate to severe gallstone pancreatitis with peripancreatic fluid collections confirmed these results, with complications in 44% of patients in the early surgery group compared with 6% in the delayed surgery group (Nealon et al, 2004). These results would favor avoidance of early operative intervention in the acute phase of biliary pancreatitis, unless local complications from necrotizing disease dictate otherwise.

An endoscopic approach to gallstone pancreatitis offers the theoretical advantage of immediate relief of ampullary obstruction and ductal clearance without the risks of general anesthesia or surgery. There was initial reluctance to perform ERCP in patients with acute pancreatitis because of concerns that the procedure would exacerbate the illness and lead to death. The Leicester investigators (Neoptolemos et al, 1986) were the first to perform a controlled study to evaluate the efficacy of ERCP in biliary pancreatitis. A group of 121 patients with suspected gallstone pancreatitis was randomized to urgent (within 72 hours of hospitalization) ERCP or conventional nonendoscopic management. ES was performed if bile duct stones were present on ERCP. CBD stones were found in 63% of the patients in the predicted severe group and in only 26% of patients with predicted mild attacks. Patients with mild pancreatitis had favorable outcomes regardless of treatment strategy, with a similar incidence of complications and no deaths. In the group of patients with severe pancreatitis defined by modified Glasgow criteria, urgent ES significantly reduced the morbidity (local and systemic complications) from 61% to 24% and reduced the length of hospitalization from 17 days to 9.5 days compared with conservatively managed patients. Mortality was lower in the ERCP group (4% vs. 18%), but the difference did not reach statistical significance.

A second study published by the Hong Kong group (Fan et al, 1993) prospectively randomized 195 consecutive patients with pancreatitis of any cause to urgent (within 24 hours of hospital admission) ERCP with papillotomy or initial conservative treatment with selective ERCP only if the clinical condition deteriorated. In this region of the world, where biliary lithiasis is frequently responsible for acute pancreatitis, emergency ERCP resulted in a reduction of biliary sepsis from 12% in the conservatively treated patients to 0% in patients undergoing endoscopic papillotomy and stone extraction. Overall, no significant differences were found in the incidences of either local (10.3% vs. 12.2%) or systemic (10.3% vs. 14.3%) complications. In the subset of patients with severe pancreatitis and CBD stones, urgent ES resulted in a decrease in the combined incidence of local and systemic complications to 21% and mortality rate to 5.3% compared with the conservatively managed group, in which the rates were 68.8% and 25%, respectively.

A third randomized trial (Nowak et al, 1998) had a different design from the two preceding studies. All 280 patients with acute gallstone pancreatitis in the study underwent urgent duodenoscopy within 24 hours of onset of their disease; nearly 25% were found to have impacted stones at the papilla, which were treated by immediate sphincterotomy. The remaining 205 patients were randomized to conventional treatment or sphincterotomy regardless of the cholangiographic findings. Compared with conventional treatment, the authors showed a significant advantage for patients treated endoscopically with respect to morbidity (17% vs. 36%; $P < .001$) and mortality (2% vs. 13%; $P < .001$). Both rates also were more strikingly reduced the earlier the endoscopic intervention was undertaken. Because all patients seem to benefit regardless of severity, the conclusion was that emergency ERCP and sphincterotomy were indicated in all patients with acute gallstone pancreatitis, but further analysis of the data is required when the full report is available.

A much criticized fourth randomized multicenter study in Germany (Folsch et al, 1997) showed that endoscopic intervention in gallstone pancreatitis in the absence or low likelihood of bile duct obstruction or cholangitis did not show benefit, but increased morbidity and mortality rates were reported in the ERCP group that were not previously found in other trials. The study has been criticized because it randomized significantly fewer patients with severe pancreatitis, and 19 of 22 centers contributed fewer than two patients per year to the study.

These studies show that ERCP and endoscopic stone extraction can be performed safely in the setting of acute biliary pancreatitis. Urgent ERCP and ES can be performed with good rationale in patients with severe or progressive pancreatitis, owing to the resultant reduction in major local peripancreatic complications and the increasingly recognized coexistence of acute cholangitis, potentially translating to reduced mortality. Subsequent elective cholecystectomy should be considered,

although in a high-risk patient the gallbladder may be left in situ. In a patient with mild pancreatitis, no immediate intervention is advised. If a patient later is proved to have gallstones or microlithiasis (Lee et al, 1992; Targarona et al, 1995), elective laparoscopic cholecystectomy with preoperative ERCP or intraoperative cholangiography should be performed. In a postcholecystectomy patient, endoscopic therapy is definitive. The role of ES in lieu of cholecystectomy for a high-risk patient with an intact gallbladder and gallstone pancreatitis in the absence of choledocholithiasis requires further evaluation (May & Shaffer, 1991).

CONCLUSIONS

Endoscopic management of choledocholithiasis is widely accepted as a highly effective therapy for choledocholithiasis. Endoscopic techniques are well established, and accessories have been developed to enhance success and safety. ES is the standard of care in the management of elderly high-risk and fit patients with CBD stones in most clinical situations, regardless of the presence or absence of the gallbladder and in all patients presenting with CBD stones late after previous biliary surgery, when the only alternative is further surgical intervention. The endoscopic removal of retained stones in the early postoperative period has been shown to be effective, it carries a small risk of complications, and it allows early discharge from the hospital. In addition, patients of all ages with acute cholangitis not responding to conventional therapy should be considered for endoscopic management before emergency surgery if this is logistically feasible. The case for ERCP and ES in the treatment of patients with severe gallstone-associated pancreatitis has been made in controlled trials. Integrated endoscopic therapy for biliary disease is well established in centers where surgical and endoscopic clinicians work closely together and provide each other with a suitable forum for critical evaluation of alternative therapeutic techniques. This has become increasingly manifest with the establishment of laparoscopic cholecystectomy with more complex laparoscopic manipulations of the bile ducts. As arguments and clinical practice come full circle, it is tempting to suggest that the enthusiastic speculations of the early 1970s—that in stone disease, the surgeon should treat the gallbladder, and the endoscopist should treat the bile duct—has come to pass 3 decades later.

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CHAPTER 37

Cholecystolithiasis and stones in the common bile duct: which approach and when?

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CHOLECYSTOLITHIASIS

Indications for Cholecystectomy

Asymptomatic Gallstones

Surprisingly, most patients with gallstones, about 65% to 80%, are asymptomatic (see Chapter 30). Studies of the natural history of *silent gallstones* have shown that symptoms develop in 1% to 2% of patients per year. Among patients with asymptomatic gallstones, about 10% develop symptoms in 5 years, and about 20% develop symptoms by 20 years. Additionally, most patients experience symptoms for some time before they develop a complication (National Institutes of Health [NIH] Consensus Statement Online, 1992; Stewart et al, 1989; Festi et al, 2010; McSherry et al, 1985). So, the majority of patients with asymptomatic gallstones can be observed, and surgical intervention (laparoscopic cholecystectomy) can be offered if symptoms develop.

Surgical treatment of asymptomatic gallstones is indicated in a number of patient populations for whom prophylactic cholecystectomy was once recommended. These populations comprise transplant patients and those with diabetes mellitus, chronic liver disease, sickle cell anemia or other chronic hemolytic anemia, patients undergoing bariatric or other gastrointestinal operations, and those with a potentially increased risk of gallbladder carcinoma (Table 37.1).

Prophylactic cholecystectomy for asymptomatic cholelithiasis was previously recommended for patients with diabetes mellitus. Studies in the late 1960s reported a higher mortality following emergency cholecystectomy in diabetic patients. Subsequent meta-analysis revealed that diabetes was not an independent variable; instead, cardiovascular, peripheral vascular, cerebrovascular, or prerenal azotemia were associated with more severe acute cholecystitis (Stewart et al, 1989; Hickman et al, 1988). More recent series have shown similar complication rates for acute cholecystectomy among diabetic and nondiabetic patients. Diabetic patients with asymptomatic gallstones today are managed expectantly.

The incidence of gallstones is twice as high in patients with chronic liver disease. Most of these patients remain asymptomatic. Operative morbidity and mortality rates for patients with chronic liver disease are also significantly higher. Meta-analyses report no increase in mortality in asymptomatic patients with an expectant management approach (Stewart et al, 1989; NIH Consensus Statement Online, 1992).

Patients undergoing bariatric surgery have a higher incidence of cholelithiasis, because obesity is associated with cholelithiasis, and gallstones may form during rapid weight loss. Studies report a cholelithiasis incidence of 27% to 35% before bariatric operations and a 28% to 71% increase in gallstone formation following bariatric surgery (Wudel et al, 2002). Many surgeons utilize bile salt medications during periods of rapid weight to help prevent cholesterol gallstones. But even if gallstones form, most are asymptomatic, and elective cholecystectomy is safe for symptomatic disease (NIH Consensus Statement Online, 1992).

Several factors must be considered for potential transplant patients with asymptomatic cholelithiasis: cholelithiasis is common, immunosuppression may increase infectious morbidity, and morbidity and mortality may be increased with emergency surgery. This problem was examined with a recent decision analysis, using probabilities and outcomes derived from a pooled analysis of published studies (Kao et al, 2005). The authors recommended prophylactic posttransplantation cholecystectomy for cardiac transplant recipients with asymptomatic cholelithiasis. For pancreas and kidney transplant patients with asymptomatic cholelithiasis, however, expectant management was recommended.

Asymptomatic gallstones found at another gastrointestinal operation should generally be removed if exposure is adequate, if the cholecystectomy can be done safely. Studies of expectant management for patients with asymptomatic gallstones undergoing laparotomy for other conditions have shown a high (up to 70%) incidence of symptoms and/or complications from the biliary system, and a significant percentage (up to 40%) of patients require a cholecystectomy within 1 year of the initial operation. Further, no increase in morbidity is associated with concomitant cholecystectomy (Stewart et al, 1989; Klaus et al, 2002).

The management of patients with asymptomatic gallstones undergoing abdominal aortic aneurysm (AAA) repair has recently evolved, especially with the advent of endovascular aortic procedures. In the past, when AAA repair and cholecystectomy were open operations, concomitant cholecystectomy was recommended to prevent the higher morbidity associated with the development of acute cholecystitis in the postoperative period. Studies reported no increase in graft infection or morbidity when cholecystectomy was done following closure of the retroperitoneum; however, more recent data show similar mortality rates with or without concomitant cholecystectomy. Today, laparoscopic cholecystectomy is typically performed after endovascular AAA repair, without increased morbidity (Cadot et al, 2002).

Children with asymptomatic gallstones comprise two main etiologic groups: those with hemolytic anemia (sickle cell

Table 37.1

Management of Asymptomatic Gallstones

Patient Population	Management
Healthy adults	Expectant
Children (without hemoglobinopathy or hemolytic anemia)	
Diabetes mellitus	
Chronic liver disease	
Previous bariatric procedure	
Abdominal aortic aneurysm repair	
Transplant	
Kidney or pancreas	Expectant
Cardiac	Cholecystectomy posttransplant
Undergoing gastrointestinal operation	Incidental cholecystectomy
Hemoglobinopathy/chronic hemolytic anemia (sickle cell disease, spherocytosis, elliptocytosis, β-thalassemia)	Elective cholecystectomy
High-risk group for gallbladder carcinoma (>3 cm gallstones, calcified gallbladder, Native American race)	

disease, β-thalassemia, hemoglobinopathies) and those whose cholelithiasis stems from some other cause (total parenteral nutrition, short bowel syndrome, cardiac surgery, leukemia, lymphoma). Expectant management for children with hemolytic anemia is associated with a significant increase in morbidity and postoperative hospital stay, so elective cholecystectomy is recommended (Curro et al, 2007). For patients with sickle cell disease and asymptomatic gallstones, elective cholecystectomy is advised, because expectant management yields more than a twofold increase in morbidity. Further, the diagnosis of acute cholecystitis can be difficult to differentiate from acute vasoocclusive sickle cell crisis (Curro et al, 2007). In contrast, children with asymptomatic gallstones caused by other etiologies can be safely managed expectantly. These gallstones even regress in 17% to 34% of cases.

Finally, gallstones have a proven association with gallbladder carcinoma (Tewari, 2006; see Chapter 49). In a review of 200 consecutive calculous cholecystitis specimens, Albores-Saavedra and colleagues (1980) reported that 83% exhibited epithelial hyperplasia, 13.5% atypical hyperplasia, and 3.5% carcinoma in situ. The risk of gallbladder carcinoma increases with larger gallstones: the relative risk rises from 2.4 for stones 2 to 2.9 cm in diameter to 10 for gallstones larger than 3 cm. Native Americans and patients with gallbladder calcification also have a higher incidence of gallbladder cancer. Elective cholecystectomy has been recommended in patients with gallstones greater than 3 cm in diameter, but no proof is available to support that such an approach is warranted from an oncologic standpoint.

Symptomatic Gallstones

Approximately 30% of patients with gallstones develop symptoms. Cholecystectomy is indicated to relieve suffering and to prevent complications of gallstones. The spectrum of severity characterizing symptomatic gallstones ranges from episodic pain to life-threatening infection and shock.

BILIARY COLIC. Biliary colic is the most typical clinical presentation of symptomatic gallstones. It usually occurs a few hours after a meal, especially one of high fat or spice content, as a slowly progressive and constant pain that occurs in the epigastrium and right upper quadrant (RUQ) of the abdomen and often radiates posteriorly to the scapula and right shoulder. This visceral pain likely reflects the gallbladder contracting against a cystic duct blocked by an impacted gallstone. If it persists and escalates, it heralds a worse complication of gallstones, such as cholecystitis, cholangitis, or pancreatitis. Typically, it remits after several hours, rendering a false sense of security in some patients that it can be overlooked. More than 60% of patients will suffer recurrent pain within 2 years after their initial attack. Several studies have indicated that gallstone-associated complications occur more frequently in patients suffering biliary colic. For these reasons, biliary colic is the most common indication for cholecystectomy.

CHOLECYSTITIS. Acute cholecystitis occurs in about 20% of patients with symptomatic gallstones (see Chapter 31). The pathogenesis is prolonged calculous obstruction of the cystic duct with resulting inflammation. The inflamed gallbladder becomes dilated and edematous, manifested by wall thickening, and an exudate of pericholecystic fluid can develop. If the gallstones are sterile, the inflammation is initially sterile, which can occur in patients with cholesterol gallstones. In other cases, however, gallstone formation occurs as a result of bacterial colonization of the biliary tree, rendering pigmented gallstones containing bacterial microcolonies (Stewart et al, 2002). In these cases, obstruction of the cystic duct results in a contained infection of the gallbladder. Research on the pathogenesis of gallstone-associated infections has shown that patients with bacteria-laden gallstones have more severe biliary infections. In addition, acute cholecystitis can coexist with choledocholithiasis, cholangitis, or gallstone pancreatitis. In the general population, 5% of patients presenting with cholecystitis have coexisting common bile duct stones. In the elderly, however, this figure rises to 10% to 20% (Siegel & Kasmin, 1997).

The initial treatment for patients with acute cholecystitis is intravenous hydration, antibiotics, and bowel rest. Many patients should be offered early cholecystectomy, but others will benefit from delayed intervention, either following conservative therapy or percutaneous gallbladder drainage. Several factors govern the approach to patients with acute cholecystitis. One consideration is patient comorbidity; emergency cholecystectomy in patients with significant comorbidities can be associated with high morbidity (20% to 30%) and mortality (6% to 30%) rates. Guidelines for the management of acute cholecystitis and acute cholangitis were described at an international consensus meeting held in Tokyo in 2006 (Takada et al, 2007). The Tokyo Guidelines define three levels of severity for acute cholecystitis and serve as a useful tool in the management of acute cholecystitis (Table 37.2).

Grade I Acute Cholecystitis. Patients presenting with mild grade I acute cholecystitis should be offered early cholecystectomy, performed laparoscopically if possible; numerous studies document a high success rate for laparoscopic cholecystectomy when the procedure is performed within 48 to 96 hours of onset

Table 37.2

Tokyo Guidelines for Acute Cholecystitis

Grade	Criteria
I Mild	Acute cholecystitis that does not meet the criteria for a more severe grade Mild gallbladder inflammation, no organ dysfunction
II Moderate	The presence of one or more of the following: 1. Elevated while blood cell count (>18,000/mm^3) 2. Palpable tender mass in the right upper abdominal quadrant 3. Duration of complaints >72 h 4. Marked local inflammation (biliary peritonitis, pericholecystic abscess, hepatic abscess, gangrenous cholecystitis, emphysematous cholecystitis)
III Severe	The presence of one or more of the following: 1. Cardiovascular system: hypotension requiring dopamine >5 μg/kg/min or any dose of dobutamine 2. Nervous system: decreased level of consciousness 3. Respiratory system: Pao_2/Fio_2 ratio <300 4. Renal system: serum creatinine >2.0 mg/dL 5. Liver: PT-INR >1.5 6. Hematologic system: platelet count <100,000/mm^3

PT-INR, prothrombin time/international normalized ratio

of acute cholecystitis (Hadad et al, 2007). Further, a Cochrane review of five randomized trials showed a shorter hospital stay for early cholecystectomy patients and no significant difference in complication rates or conversion rates between early laparoscopic cholecystectomy (within 7 days) versus delayed laparoscopic cholecystectomy (6 to 12 weeks; Gurusamy & Samraj, 2006). Conversion rates, however, were 45% among patients randomized to the delayed group, those who required a cholecystectomy between 1 and 6 weeks. For patients with significant medical problems, cholecystectomy may need to be delayed to maximize medical therapy. Most patients with acute cholecystitis can be safely managed with antibiotics and bowel rest with resolution of their acute illness; they can then undergo an elective cholecystectomy once their medical problems have been addressed.

Grade II Acute Cholecystitis. Patients presenting with grade II acute cholecystitis are a more diverse group. Many will be well managed with early cholecystectomy; this is particularly true for cases with delayed presentation as their only grade II finding. In these cases, laparoscopic cholecystectomy should be performed if possible within 7 days of the acute illness. In cases with severe local inflammation, early gallbladder drainage (percutaneous or surgical) is recommended as the initial treatment of choice, followed by elective cholecystectomy once the acute inflammation resolves. The key is to identify which patients have such an inflammatory process. Several studies have correlated such findings as age older than 50 years, male sex, presence of diabetes, elevated bilirubin level (>1.5 mg/dL), and leukocytosis (while blood cell count >15,000 mm^3) in the setting of gangrenous cholecystitis (Nguyen et al, 2004). These findings are also frequently associated with a severe inflammatory process. Other factors suggestive of an inflammatory process include symptoms of gastric outlet obstruction. Patients with such symptoms should have cross-sectional imaging, with either computed tomography (CT) or magnetic resonance imaging (MRI), to determine whether a severe inflammatory process is present (Fig. 37.1), followed by percutaneous cholecystostomy if such is found (Takada et al, 2007).

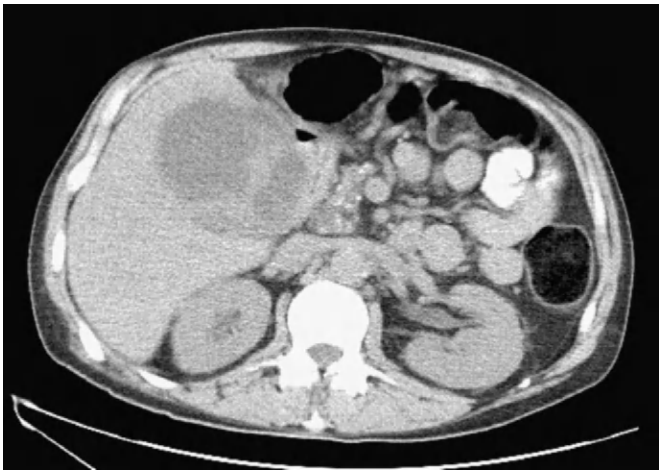


FIGURE 37.1. Computed tomographic scan demonstrating a severe inflammatory process in the setting of acute cholecystitis. This patient was treated with percutaneous cholecystostomy followed by elective laparoscopic cholecystectomy once the inflammatory process had resolved.

Grade III Acute Cholecystitis. Patients presenting with grade III acute cholecystitis have associated organ dysfunction, and they require intensive organ support and medical treatment. Because the source of their inflammatory (septic) response and organ dysfunction is the severe cholecystitis, percutaneous cholecystostomy is necessary to treat the severe infection as well as the associated organ dysfunction. Numerous studies have documented the success of percutaneous cholecystostomy in achieving control of the underlying infection within 24 to 48 hours (Howard et al, 2009). In rare cases, urgent cholecystectomy may be required, such as cases with biliary peritonitis as a result of perforation of the gallbladder; but in general, cholecystectomy in the acute phase of grade III acute cholecystitis should be avoided (Takada et al, 2007).

Cholecystectomy Technique

Choosing Laparoscopic Versus Open Techniques

For typical uncomplicated gallstone disease, laparoscopic cholecystectomy is the preferred method of removing the gallbladder (Keus et al, 2006). Since its debut, cholecystectomy rates have increased worldwide, reflecting patient acceptance of the laparoscopic technique. Because the technical aspects of this operation are covered in other chapters (see Chapters 33 and 34), this section will focus on concepts of feasibility and safety that relate to disease severity and the choice between laparoscopic and open cholecystectomy (Callery, 2006).

Laparoscopic cholecystectomy should be performed only by surgeons properly trained and proctored, and experience should be correlated to how difficult the operation may be based on disease severity. Laparoscopic cholecystectomy for severe acute and chronic inflammation is considerably more difficult and is an advanced operation. Less experienced surgeons must recognize this and seek the help they need during the operation, and conversion to open cholecystectomy may be necessary in some patients (Ishizaki et al, 2006). Biliary injuries are more likely to occur during difficult laparoscopic operations, no different than

with open operations, but at a higher incidence (see Chapter 42). When laparoscopic cholecystectomy is performed for acute cholecystitis, biliary injuries occur three times more often than during elective laparoscopic cases and twice as often compared with open cholecystectomy for acute cholecystitis.

Today, the selection of open cholecystectomy may be difficult for some. Over the past 20 years, open cholecystectomy has been far less frequently performed. Trainees during this period presumably have received valid instruction and proctoring for laparoscopic cholecystectomy but have less experience with difficult open cases (Schulman et al, 2007). The experience needed to command the laparoscopic operation potentially reduces the level of comfort with the open technique. Finally, there is the pressure related to patient expectation for rapid recovery.

Behind these two very different techniques are scenarios that might subtly account in part for static biliary injury rates (Khan et al, 2007). Because of inexperience, the surgeon ignores or resists the sensible default option to convert to the open technique, does not, and causes injury. In other instances, the surgeon overextends laparoscopic experience when disease severity warrants conversion. What can help prevent this? First, during informed consent, patients need to be made fully aware that open cholecystectomy is always a possibility. If faced with acute or chronic cholecystitis at operation, the surgeon should seek help rather than persist on marginal laparoscopic or open cholecystectomy experience. Conversion from laparoscopic to open cholecystectomy is not a defeat but rather is reflective of caution and good judgment (Jenkins et al, 2007; Wolf, 2009).

Ideally, a surgeon would suspect the likelihood of conversion on clinical grounds. The anesthesia and operative teams should be so notified and prepared. Open-case instruments need to be readily available, and trocar stab incisions should be placed along a predrawn right subcostal incision line. Unless there is need to control bleeding, the surgeon enters the RUQ deliberately and is not stressed by the decision to convert. Everyone should be ready for what lies ahead, and it should be clear to all that it will be a difficult operation.

The difficult open cholecystectomy demands adequate exposure, retraction, and identification of anatomy by dissection in the anterior and posterior aspects of the triangle of Calot, followed by dissection of the gallbladder off the liver bed. The surgeon achieves conclusive identification of the cystic structures as the only two structures entering the gallbladder, eliminating the possibility of misidentification (Callery, 2006). As with the laparoscopic technique, once the critical view is attained, the cystic structures can be occluded with ligatures and divided. Failure to achieve this critical view should prompt cholangiography to define ductal anatomy. Avoidance of ductal injury in the liver bed depends upon a combination of patience and staying in the correct plane of dissection, with meticulous technique and experience. In some cases of acute cholecystitis, the gallbladder "shells out" relatively easily from its edematous hepatic bed. In other cases, and especially in chronic cholecystitis, the dissection of the gallbladder out of the liver bed can be tedious, frustrating, and bloody. Hemostasis can take time but must be achieved, with argon beam, cautery, packing, and topical hemostatics if necessary. Subtotal cholecystectomy is always a valid option, especially in patients with cirrhosis or in those with severe inflammation that obscures the anatomy within the porta hepatis. Surgeons should indicate in operative notes for open and laparoscopic cholecystectomy precisely how they identified the cystic structures for division. For conversions, they should specify the circumstances, stressing safety and surgical judgment.

Percutaneous Cholecystostomy (See Chapter 32)

The indications for percutaneous cholecystostomy include grade II acute cholecystitis with a severe inflammatory process, grade III acute cholecystitis with associated organ dysfunction, or acute cholecystitis in patients with severe medical morbidity that limits the surgical options (Takada et al, 2007; Hirota et al, 2007; Yamashita et al, 2007; Howard et al, 2009). The technical success rate of percutaneous radiologically guided cholecystostomy is 98% to 100% with few procedure-related complications (mortality and major complications, 0% to 6.5%; minor complications, 0% to 20%) (Howard et al, 2009; Sugiyama et al, 1998).

Timing of Subsequent Operation for Cholecystitis

Once the inflammatory process has resolved, elective cholecystectomy can be performed early (within 1 to 7 days) or delayed (6 to 8 weeks) with excellent success and conversion rates as low as 3% (Akyurek, 2005). Some have reported using percutaneous cholecystostomy as definitive treatment for acute cholecystitis in high-risk, elderly, and debilitated patients. In patients who do not have subsequent cholecystectomy, recurrent biliary symptoms occur in 9% to 33% (Griniatsos et al, 2008; Sugiyama et al, 1998).

CHOLEDOCHOLITHIASIS (SEE CHAPTER 35)

The clinical clues of common bile duct (CBD) stones were recognized during the Roman Empire by Soranus of Ephesus, who described jaundice, itching, dark urine, and acholic stools. Not all common bile duct stones render such a classic clinical scenario, but they still carry risk if left unidentified and untreated. More than 85% of CBD stones originate in the gallbladder and secondarily migrate into the CBD. For patients undergoing cholecystectomy for symptomatic gallstones, the prevalence of choledocholithiasis ranges from 10% to 15%. Primary CBD stones are far less common and are typically associated with conditions of biliary infection and stasis: benign biliary strictures, sclerosing cholangitis, and choledochal cysts. Primary CBD stones are more prevalent in Asians and can relate to parasitic infections (Kaufman et al, 1989).

Silent Common Bile Duct Stones

Published reports using routine intraoperative cholangiography have found that at least 12% of CBD stones are clinically silent (Murison et al, 1993), and approximately 6% do not exhibit abnormalities in liver function tests (LFTs) or in the diameter of the CBD (Majeed et al, 1999). When prospectively followed, data suggest that more than one third of asymptomatic stones will pass spontaneously after the first 6 weeks after cholecystectomy (Collins et al, 2004).

Diagnostic Considerations

More often than not, the presence of CBD stones is uncertain. Clinicians use predictive models based on risk factors that include clinical features, abnormal LFTs, jaundice, and CBD dilation. These are very sensitive (96% to 98%) but not very

specific (0% to 70%) (Koo & Traverso, 1996). The American Society of Gastrointestinal Endoscopy (ASGE) provides a practical strategy that assigns low (<10%), intermediate (10% to 50%), or high (>50%) risk of CBD stones using relevant risk factors (ASGE Standards of Practice Committee et al, 2010).

Imaging Modalities: Why and When

Transabdominal Ultrasound

Transabdominal ultrasound (US) is an appropriate initial modality in the evaluation of CBD stones (Williams et al, 2008). US can identify bile duct dilation owing to stone obstruction, and it can visualize the actual stone (sensitivity 0.3, specificity 1.0; see Chapter 13). If the extrahepatic bile duct diameter is less than 5 mm, CBD stones are exceedingly rare, whereas a diameter greater than 10 mm with jaundice predicts CBD stones in more than 90% of cases (Abboud et al, 1996). Axial CT scans have better sensitivity (84%) for choledocholithiasis than US (see Chapter 16). Helical CT scans outperform conventional nonhelical CT, with 88% sensitivity and 73% to 97% specificity (Tseng et al, 2008). In terms of availability, cost, and radiation exposure, US prevails as the first-line diagnostic.

Magnetic resonance cholangiopancreatography (MRCP) is the most accurate noninvasive modality available (see Chapter 17). Regardless, its sensitivity decreases for small CBD stones (29% if <5 mm) (Sugiyama et al, 1998). MRCP is the standard investigation for CBD stones for patients with intermediate probability or for those who need to be investigated to exclude other differential diagnoses. MRCP is especially helpful when anatomical considerations preclude endoscopic retrograde cholangiopancreatography (ERCP; status post–Billroth II gastrectomy, Roux-en-Y biliary bypass, duodenal stenoses).

Endoscopic Retrograde Cholangiopancreatography

ERCP is still considered the gold standard diagnostic modality (see Chapter 18), although it is invasive, requires radiation, and has significant complications (Andriulli et al, 2007). Routine ERCP prior to all laparoscopic cholecystectomies is impractical and unnecessary. When overused, most cholangiograms are normal, and costs and complication rates are prohibitive. Even in patients at high risk—those with jaundice, cholestatic LFTs, CBD dilation, and a history of pancreatitis—half will not have CBD stones at the time of ERCP (Daradkeh et al, 2000), therefore ERCP is now reserved more for its therapeutic than diagnostic strength.

Endoscopic Ultrasound

Endoscopic US (EUS) is very sensitive for choledocholithiasis (see Chapter 14; Garrow et al, 2007), and a meta-analysis reveals that EUS can reduce unnecessary diagnostic ERCP (Tse et al, 2008). A systematic review reveals that patients who undergo EUS can avoid ERCP in 67% of cases, with fewer complications and less pancreatitis compared with those undergoing ERCP initially (Petrov & Savides, 2009). The diagnostic efficacy of EUS and MRCP compared with ERCP have revealed the tests to be quite comparable (Verma et al, 2006).

Real-Time Fluoroscopic Intraoperative Cholangiography

Real-time fluoroscopic intraoperative cholangiography (IOC) during cholecystectomy can accurately diagnose CBD stones and both minimize and maximize the need for ERCP (see Chapter 21). The technique can be performed safely in both open and laparoscopic approaches. Surgeons can interact with the findings, flushing the duct to clear stones or debris. Open and laparoscopic IOC can successfully be completed in about 95% of patients (see Chapter 34), with sensitivity for detecting CBD stones between 80% and 92% and specificity of 93% to 97% (Machi et al, 1999). Regardless, an ongoing debate remains whether IOC should be performed routinely or selectively during cholecystectomy. When used routinely, it has high sensitivity and specificity both for suspected CBD stones and for the 3% to 4% of stones that are not clinically suspected but may become symptomatic postoperatively. Other suggested benefits specifically relate to the prevention of bile duct injuries (Fletcher et al, 1999). No large prospective randomized trials that answer the question definitively, so most practicing surgeons perform IOC selectively.

Symptomatic Common Bile Duct Stones

The symptoms of CBD stones relate to partial or complete biliary obstruction with and without inflammatory complications such as cholangitis, hepatic abscesses, or pancreatitis. In chronic scenarios, and depending on the extent and duration of biliary obstruction (>5 years), choledocholithiasis may also lead to secondary biliary cirrhosis and portal hypertension (see Chapter 35). Because of the uncertain clinical behavior and potential harmful complications, it is currently accepted that in the great majority of situations, CBD stones should be removed, even if they are asymptomatic (Williams et al, 2008).

Definitive Treatment Approaches: Biliary Obstruction

Catheter-Based Approaches (See Chapters 27, 28, and 36)

ERCP. Before the laparoscopic era, ERCP was not commonly used, because open surgical bile duct clearance was superior to ERCP in terms of success and morbidity (see Chapters 29 and 35; Martin et al, 2006). This changed as laparoscopic cholecystectomy emerged and outpaced the abilities of most surgeons to perform laparoscopic CBD stone removal. Indeed, ERCP captured and has held its role as the first-line approach to CBD stones, being successful in more than 90% of patients (Rieger & Wayand, 1995). Although well tolerated in most, a 10% rate of complications remains constant for ERCP (Andriulli et al, 2007), with a serious morbidity rate of 1.5% and an overall mortality rate of 0.2% to 0.5% (Freeman et al, 1996). When surgical and endoscopic teams are inexperienced with CBD stones, the perceived need for preoperative ERCP increases. In this setting, ERCP allows laparoscopic cholecystectomy to be performed quickly and with confidence that CBD stones are already managed. If ERCP fails, the surgical plan will need to consider intraoperative management of choledocholithiasis. Conversely, in centers where successful sphincterotomy and stone extraction is almost assured, the rate of preoperative ERCP will be lower. If the surgeon finds a stone at operation, ERCP becomes a reliable postoperative option. Current consensus accepts the use of ERCP prior to laparoscopic cholecystectomy for patients with a high probability of choledocholithiasis. It is recommended that patients with a low or intermediate index of suspicion for choledocholithiasis undergo additional imaging techniques (MRCP, EUS, IOC) to avoid unnecessary biliary instrumentations (Tse et al, 2004; Williams et al, 2008; ASGE Standards of Practice Committee, 2010).

PERCUTANEOUS TRANSHEPATIC CHOLANGIOGRAPHY (SEE CHAPTER 28). Compared with ERCP, percutaneous transhepatic cholangiography (PTC) is time consuming, more involved, and likely more stressful for a patient. It is usually reserved for patients in whom anatomical considerations preclude safe ERCP, such as in the case of an impossible ampullary cannulation. Experienced PTC groups have reported successful stone removal rates in more than 90% of cases, with complication rates around 5% (Garcia-Vila et al, 2004), although these are hardly the norms. PTC stone removal takes time, involving insertions of catheters that are upsized over time, before stones are actually retrieved with stone baskets. Consequently, there are many reports of attempts to make it easier. Gil and colleagues (2000) have reported the safety and utility of balloon dilation of the papilla in the clearing of CBD stones using occlusion balloon pushing. This is also gaining popularity for the laparoscopic surgeon during IOC.

Surgical Approaches: Open and Laparoscopic Techniques (See Chapters 29 and 35)

The same issues discussed in choosing open versus laparoscopic cholecystectomy are accentuated when common bile duct exploration (CBDE) is considered. Today, many trainees will graduate residency having never performed an open CBDE. Their ability to succeed with laparoscopic CBDE is quite variable, as many train with a default dependence on ERCP.

CHOLECYSTECTOMY WITH INTRAOPERATIVE CHOLANGIOGRAPHY (SEE CHAPTERS 21 AND 34). Open and laparoscopic IOC can successfully be completed in the majority of patients by the majority of surgeons (Machi et al, 1999). IOC can be performed through the direct insertion of contrast medium into the gallbladder or more often by intubating the cystic duct. Plain radiographs have largely been replaced by digital fluoroscopic imaging. IOC is common, and most surgeons receive sufficient training. Laparoscopic ultrasound cholangiography is also efficacious (Stiegmann et al, 1995) but not broadly used.

Since the introduction of laparoscopic cholecystectomy, the debate over routine versus selective IOC has been rekindled because of the increased incidence of CBD injuries and the inability to palpate the CBD during laparoscopy. IOC accurately defines the biliary anatomy and may protect against intraoperative bile duct injuries (Fletcher et al, 1999), or at least it reduces their severity (Woods et al, 1995). Opponents claim that routine IOC may lead to bile duct injury and unnecessary CBD explorations because of false positives and that it may add time and costs unnecessarily.

Selective IOC pivots upon predicting the probability of choledocholithiasis. In general, patients with a low probability (normal LFTs, normal CBD diameter) may undergo cholecystectomy with no further preoperative investigation and selective IOC. Patients with intermediate risk (isolated abnormal LFTs or CBD dilatation) may undergo further preoperative imaging (MRCP) and routine IOC at an absolute minimum. Patients with high risk (jaundice, cholangitis) warrant confirmatory/therapeutic ERCP (ASGE Standards of Practice Committee, 2010) at most centers. In fact, today many patients are triaged for this purpose, but in years past, many would undergo open CBDE. Ultimately, the choice of modality depends on local availability and expertise in minimally invasive treatments coupled with considerations of cost and convenience.

CBDE: TRANSCYSTIC VERSUS CHOLEDOCHOTOMY ACCESS (SEE CHAPTERS 29, 34, AND 35). When IOC reveals CBD stones, they can readily be removed during cholecystectomy. The open choledochotomy to allow cholangioscopy, flushing, forceps and balloon clearance, and T-tube placement is rarely performed or taught today. Instead, laparoscopic common bile duct exploration (LCBDE) has evolved as an efficient, well-accepted, and broadly utilized technique as described in other chapters. Several studies have shown LCBDE to be as efficient as preoperative or postoperative ERCP in terms of stone clearance, morbidity, mortality, and short hospital stay (Martin et al, 2006; Clayton et al, 2006) and is thus recommended for surgeons with appropiate skills and facilities. Further, for capable surgeons, LCBDE is as safe and efficient as ERCP, thus avoiding the discomfort, costs, and potential complications of an extra procedure (Martin et al, 2006).

LCBDE can be safely performed through either transcystic or choledochotomy approaches. Many prefer the transcystic approach. It is feasible in most cases, saves time, does not violate the CBD, and shows no higher morbidity than standard laparoscopic cholecystectomy alone (Hanif et al, 2010; Tinoco et al, 2008). The most consistent risk factor for failing transcystic stone clearance is the size of the stone. Once stones exceed 5 mm, the likelihood of transcystic extraction falls considerably (Stromberg et al, 2008), and laparoscopic choledochotomy becomes necessary. However, many surgeons do not have the laparoscopic dissection and suturing expertise to perform this procedure; they rely instead on ERCP, or they convert to an open operation. Experienced surgeons can remove larger or multiple CBD stones with reported success rates of up to 90% (Lien et al, 2005). A 2007 Cochrane review was not able to conclude significant differences in outcomes for primary closure of the CBD versus the routine use of T-tube drainage after open CBD exploration (Gurusamy, 2009). Similar outcomes have been reported from a recent randomized clinical trial for LCBDE through choledochotomy (Zhang et al, 2009).

Gallstone Pancreatitis

Acute gallstone pancreatitis is the most frequent form of acute pancreatitis in Western countries (see Chapter 53). The two most commonly accepted mechanisms for the pathogenesis of gallstone pancreatitis are reflux of bile into the pancreatic duct and transient ampullary obstruction caused by temporary impaction of a stone in the ampulla. The disease is mild in approximately 80% of patients, but 20% experience a more severe clinical course that includes complications such as pancreatic necrosis, multisystem organ failure, and even death (see Chapter 54; Acosta et al, 1997; Alexakis et al, 2007; NIH, 2002).

In many patients, the biliary obstruction has spontaneously resolved at the time of presentation, so biliary decompression is not needed. These patients should undergo elective cholecystectomy once the pancreatitis has resolved. At the other end of the spectrum are patients with gallstone pancreatitis and associated acute cholangitis (see Chapter 43). Clear evidence shows that endoscopic biliary drainage is beneficial in patients with acute cholangitis, thus these patients should have early biliary decompression.

A secondary question is whether patients with gallstone pancreatitis, without cholangitis, benefit from biliary decompression. Clinical and experimental studies suggest that impacted ampullary stones and persistent biliopancreatic

obstruction are associated with a more severe clinical course. In theory, early endoscopic removal of obstructing ampullary gallstones should improve outcomes (Acosta et al, 1997; Alexakis et al, 2007). Between the late 1970s and mid-1980s, urgent surgery with biliary decompression was studied as a treatment of choice for patients with acute gallstone pancreatitis, but this approach was associated with an increased mortality rate among patients with severe pancreatitis. As such, surgical treatment during the acute phase of the gallstone pancreatitis is not recommended.

The role of nonsurgical intervention, prior to definitive surgical therapy, has been examined in several prospective randomized studies in which patients with cholangitis were excluded. Integral to any interpretation of treatment approach is the severity of the gallstone pancreatitis. These studies defined *severe pancreatitis* utilizing a number of systems that included the Ranson criteria (>3), Glasgow criteria (>3), or the Acute Physiology and Chronic Health Evaluation (APACHE) II score (>8). The Ranson and Glasgow criteria have the advantage of ease of use and considerable areas of overlap (Table 37.3). A recent meta-analysis analyzed five prospective randomized studies that examined the use of early biliary decompression in cases of gallstone pancreatitis without cholangitis (Moretti et al, 2008). This study reported a significant reduction in pancreatitis-related complications in patients with predicted severe pancreatitis (rate difference of 38.5%; 95% confidence interval, –53% to –23.9%); $P < .0001$); but no advantage was seen in cases with mild pancreatitis, and no difference in mortality rate was noted.

Table 37.3

Ranson and Glasgow Criteria for Severity of Acute Pancreatitis

Criterion*	Action
Ranson	
Age >55 years	Admission
WBC count >16,000/mm^3	Admission
Glucose >200 mg/dL	Admission
AST >250 IU/L	Admission
LDH >350 IU/L	Admission
Increased BUN >8 mg/dL	48 hr
Pa_{O_2} <60 mm Hg	48 hr
Calcium <8.0 mg/dL	48 hr
Base deficit <4 mEq/L	48 hr
Fluid sequestration ≥6 L	48 hr
Glasgow	
Age >55 years	Admission
WBC count >15,000/mm^3	Admission
Glucose >200 mg/dL	Admission
AST/ALT >96 IU/L	48 hr
LDH >219 IU/L	48 hr
BUN >45 mg/dL	Admission
PaO_2 <76 mm Hg	Admission
Calcium <8.0 mg/dL	48 hr
Albumin <3.4 g/dL	48 hr

*Mortality rates: 0 to 2 = 2%, 3 to 4 = 15%, 5 to 6 = 40%, >7 = 100%
WBC, white blood cell count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; BUN, blood urea nitrogen

The severity of the patient's illness guides the timing of intervention. Patients whose biliary obstruction has spontaneously resolved at the time of presentation and those who have mild predicted pancreatitis should have early elective cholecystectomy once their pancreatitis has resolved. Patients with severe predicted pancreatitis and those with associated cholangitis should undergo early biliary decompression (ERCP or PTC). Among cases of escalating pancreatitis, biliary decompression should be performed within 24 to 72 hours of admission (Moretti et al, 2008). For cases with associated cholangitis, biliary decompression should occur within 24 hours of presentation. Elective cholecystectomy can then be performed once the severe illness has resolved.

Cholangitis (See Chapter 43)

Clinical findings associated with acute cholangitis include RUQ abdominal pain, jaundice, fever, and chills—also known as *Charcot's triad* (1877). Not all patients with cholangitis manifest all findings: 90% develop fever, but only about 50% to 70% of patients develop all three symptoms. *Reynolds' pentad* (1959)—Charcot's triad plus shock and altered mental status—represents a form of severe (grade III) cholangitis, which can also manifest with multiorgan dysfunction. Severe cholangitis is present in about 30% of patients with acute cholangitis (Gouma, 2003).

Cholangitis is a localized infection of the biliary tree, and an understanding of the pathophysiology of cholangitis guides treatment decisions. Research in this disease has shown that bacteria-laden gallstones are the source of infection. These bacteria exist in a bacterial microcolony (biofilm) within the pigmented matrix of gallstones (Fig. 37.2; Stewart et al, 2002). The bacteria must detach from the biofilm to cause a localized infection, and it must reflux into the cholangiovenous circulation to cause a more severe illness, including bacteremia and organ dysfunction (Raper et al, 1989; Stewart et al, 2003). Cholangiovenous reflux occurs with biliary pressures greater than 20 cm H_2O, and even at this pressure, bacterial characteristics (slime production) influence cholangiovenous reflux (see Chapter 7). In addition, bacterial breakdown by complement releases endotoxin, and this influences the induction of inflammatory cytokines that drive the septic manifestations.

The 2006 Tokyo International Consensus Meeting described three grades of acute cholangitis (Table 37.4): *grade I* is mild and responds to initial medical treatment; grade II is moderate and does not respond to initial medical treatment, but it is not associated with organ dysfunction; and grade III is severe and is associated with organ dysfunction (Miura et al, 2007). All patients with suspected cholangitis should be treated with intravenous hydration and antibiotics that cover the most common biliary organisms: *Escherichia coli*, *Klebsiella* spp., *Enterococcus*, *Enterobacter cloacae*, *Pseudomonas* spp., and anaerobic pathogens. Patients with severe grade III cholangitis also require organ support and stabilization of organ dysfunction.

The critical component of the treatment of cholangitis is biliary decompression. Because elevated biliary pressure drives cholangiovenous reflux, decompression of the biliary tree with ERCP is crucial; PTC may be used if ERCP is not available. Not only does biliary drainage prevent bacterial cholangiovenous reflux, it has also been shown to be associated with a marked decreased in bile and serum endotoxin levels. In a prospective randomized trial, Lai and colleagues (1992)

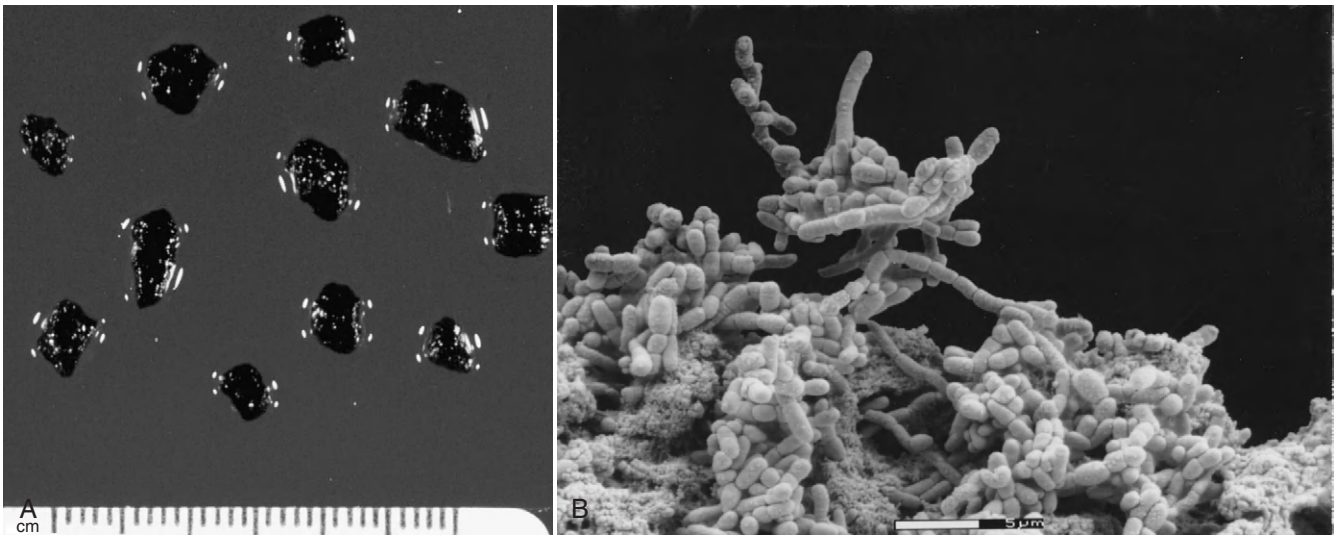


FIGURE 37.2. A, Black pigment gallstones. **B,** Scanning electron micrograph of the black pigment stones demonstrating bacterial microcolonies. Note the bacterial bridges and three-dimensional nature of the biofilm. *(From Stewart L, et al, 2002: The pathogenesis of pigment gallstones in Western societies: the central role of bacteria. J Gastrointest Surg 6:891-904.)*

demonstrated decreased mortality associated with endoscopic drainage compared with urgent surgical intervention, 10% versus 32%, respectively. A nonrandomized study by Leese and others (1986) showed similar findings. These and other studies emphasize the need for nonsurgical decompression in the setting of severe acute cholangitis.

The Tokyo Guidelines provide a useful tool for the management of acute cholangitis (see Table 37.4). Patients with grade I cholangitis who respond to medical therapy can be treated with ERCP (within 24 hours) followed by definitive surgical treatment (laparoscopic cholecystectomy), or the surgeon can proceed to laparoscopic cholecystectomy with intraoperative LCBDE after medical stabilization (Takada et al, 2007; Miura et al, 2007). Factors guiding these choices include the patient's clinical findings and the surgeon's experience with LCBDE.

By definition, patients with grade II cholangitis do not respond to medical therapy, so they require urgent biliary decompression. Patients with severe (grade III) cholangitis require urgent endoscopic or percutaneous transhepatic biliary drainage following stabilization of organ dysfunction. For patients with grade II or III cholangitis, the initial therapy should emphasize biliary decompression rather than definitive removal of all common duct stones. Prolonged procedures with excessive manipulation in an attempt to remove large stones should be avoided in patients with active infectious manifestations. Once the acute illness has resolved, early cholecystectomy can be performed within 6 weeks of biliarydecompression with no increase in postoperative complications (Li et al, 2010).

Table 37.4

Tokyo Guidelines for Acute Cholangitis

Grade	Criteria
I Mild	Responds to initial medical treatment
II Moderate	Does not respond to the initial medical treatment but is not associated with organ dysfunction
III Severe	Associated dysfunction at least in one of the following organ systems: 1. Cardiovascular system: hypotension requiring dopamine >5 μg/kg/min or any dose of dobutamine 2. Nervous system: decreased level of consciousness 3. Respiratory system: Pao_2/Fio_2 ratio <300 4. Renal system: serum creatinine >2.0 mg/dL 5. Liver: PT-INR >1.5 6. Hematologic system: platelet count <100,000/mm^3

PT-INR, prothrombin time/international normalized ratio

Need for Cholecystectomy After ERCP/Sphincterotomy

There has been considerable debate over whether cholecystectomy is required after ERCP/sphincterotomy for patients who initially present with choledocholithiasis. Retrospective studies have reported a low incidence of cholecystectomy among patients with a gallbladder in situ following ERCP/sphincterotomy managed by watchful waiting (10% to 15% over 5 to 14 years) (Schreurs et al, 2004; Sugiyama et al, 1998). Many of these studies involved older patient populations and patients with multiple medical illnesses. More recently, however, a Cochrane review of prospective randomized studies reported that elective cholecystectomy is recommended (McAlister et al, 2007). For five randomized trials with 662 participants, an increased mortality in the expectant group compared with the cholecystectomy group was noted, and patients in the observation group had higher rates of recurrent biliary pain, jaundice, or cholangitis and more need for repeat ERCP or cholangiography (McAlister et al, 2007).

CONCLUSION

In 1970, who could have predicted that the common ailments of cholecystolithiasis and choledocholithiasis would soon face historical advances in technology? Patients now benefit from improved imaging and minimally invasive endoscopic and laparoscopic techniques, especially when combined. Indeed, our treatment approaches today only occasionally resemble those of a recent but bygone era in biliary surgery.

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CHAPTER 38

Postcholecystectomy problems

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OVERVIEW

Cholecystectomy for gallbladder diseases has become the most common abdominal operation in Westernized countries. Since it was first performed in 1987, laparoscopic cholecystectomy (LC) has surpassed the open approach as the gold standard operation, largely because of significant decreases in operative time, patient pain, hospital stay, and costs (Begos & Modlin, 1994; see Chapter 34). At present, approximately 750,000 LCs are performed annually in the United States, accounting for roughly 90% of all cholecystectomies (Khan et al, 2007). This minimally invasive approach has revolutionized the treatment of patients with gallbladder disease and improved outcome, and it has permitted a liberalization of indications. Patients who would have otherwise been turned away from open cholecystectomy (OC) are now undergoing LC, and the open operation is now reserved for the most complicated scenarios (Khan et al, 2007).

Although LC has some advantages for both patients and surgeons, a new set of complications has arisen. The popularity of LC, combined with its innovative technology and the decreased threshold to whom it is offered, has resulted in novel postoperative problems, such as dropped stones, port-site hernias, and unique forms of common bile duct (CBD) injuries (see Chapter 42). More disturbing is that despite the widespread acceptance of LC and increasing experience with the procedure, it has a higher *serious* complication rate than that of the open approach. Furthermore, just as with open cholecystectomy, patients with abdominal pain that masquerades as gallbladder disease may undergo LC yet continue to be persistently symptomatic after the operation. This chapter addresses the causes of postcholecystectomy problems, both biliary and nonbiliary, along with optimal diagnostic and treatment strategies. Henceforth, we will refer to *postcholecystectomy problems* (PCPs) as persistent symptoms after surgical removal of the gallbladder regardless of etiology.

INDICATIONS FOR CHOLECYSTECTOMY (SEE CHAPTERS 30 AND 31)

Gallstones that cause symptoms of epigastric and/or right upper quadrant (RUQ) pain, usually occurring after fatty meals and associated with dyspepsia and sometimes excessive flatulence, are most commonly treated with cholecystectomy. LC is successful in eliminating pain in 85% of patients with this constellation of presurgical symptoms (Tantia et al, 2008). Furthermore, patients with acute cholecystitis manifested by fevers, RUQ pain, elevated white blood count (WBC), and nausea and vomiting are also treated with LC.

A more contentious indication for cholecystectomy falls into the category of functional biliary disorders. Patients with persistent episodes of prolonged RUQ pain who lack a defined organic etiology should be evaluated for a functional biliary disorder. This condition, commonly referred to as *biliary dyskinesia*, affects approximately 2.4% of patients with biliary pain in the absence of cholelithiasis and results from the impaired physiologic contraction of the gallbladder, leading to insufficient emptying and pain (Barbara et al, 1987). Various studies suggest that patients with motility disorders of the gallbladder may benefit from LC (Westlake et al, 1990; Chen et al, 2001). However, if the physiologic derangement is downstream of the cystic duct, pain may persist even after removal of the gallbladder. This nebulous condition is termed *sphincter of Oddi dysfunction,* and it will be discussed in more detail later in this chapter. Finally, carcinoma of the gallbladder is an uncommon problem—only 9250 new cases of gallbladder cancer occurred in the United States in 2008—that is optimally treated with cholecystectomy and en bloc partial hepatectomy; but it is associated with a poor prognosis, with 5-year survival rates between 5% and 10% and an overall median survival of 3 to 6 months from diagnosis (Hueman et al, 2009). An in-depth discussion of these indications for cholecystectomy is found in Chapters 30, 31, and 49.

COMPLICATIONS OF CHOLECYSTECTOMY

Postsurgical complications may be classified by biliary and nonbiliary causes. Furthermore, biliary complications may be subdivided into *early*, *late*, and *mechanical* (Table 38.1). Despite the advantages in care offered by the laparoscopic approach, cholecystectomy should still be recognized and referred to as a *major* operation. This is emphasized by the fact that mortality rates after cholecystectomy exceed many elective operations felt to be far more significant in scope, such as cardiac bypass, colonic resection, and even pancreatectomy. In a multivariate comparison of postcholecystectomy complications studied by Jatzko and colleagues (1995), open cholecystectomy was associated with higher morbidity (7.7% vs. 1.9%) and mortality rates (5% vs. 1%) than those of LC. The incidence of pathology seen in patients who are symptomatic after having a cholecystectomy is summarized in Table 38.2.

Early Complications

The most common early biliary complications are related to intraoperative difficulties or technical considerations. By far, the most relevant of these are bile duct injuries, hemorrhage, and abscess formation.

Table 38.1

Classification of Causes of Postcholecystectomy Symptoms

Biliary	Nonbiliary
Early	Pancreatic disease
Biliary leak: minor and major	Pneumonia
Hematoma	Liver disease
Abscess	Flatulent dyspepsia syndrome
Dropped stones	Peptic ulcer
Insufficient cholecystectomy	Gastroesophageal reflux
Late	Irritable bowel syndrome
Persistent postoperative pain/ neuroma	Diverticular disease
Hernia: port site/incisional	Renal disease
Chronic inflammation	Postsurgical adhesions
Mechanical	Psychosomatic disorders
Stricture: malignant or benign	Others
Fistula	
Retained stones	
Papillary disorders	



FIGURE 38.1. Depiction of a common bile duct "tent" injury.

Biliary Injury

Despite the advantages of LC over OC, common bile duct injuries are seen more frequently in the laparoscopic approach (0.2% to 0.7%) than in OC (0.1% to 0.04%) (Konsten et al, 1993; Nuzzo et al, 2005; Soderlund et al, 2005; Ali et al, 2007; Karvonen et al, 2007). Retrospective analyses of CBD injuries reveal that the two most common factors associated with injury are acute cholecystitis, wherein the normal gallbladder and biliary anatomy is obscured or distorted because of indurated and/or edematous tissues, and misperceptions or inexperience on the part of the surgeon. A learning curve is also implicated. In a series of 350 LCs reviewed by Huang and colleagues, CBD injuries occurred more often in the first 10 to 15 operations performed by a surgeon (Huang et al, 1993). In addition to the classic direct CBD injuries caused by misidentification of the cystic and common bile ducts, clipping of the "tented" CBD may occur in cases specific to LC when applying the first clip on the cystic duct by excessive traction of the CBD into the clip itself (Fig. 38.1). These injuries can lead to stricture and obstruction of the CBD and may be avoided by placing the first clip with visualized distance from the cysticocholedochal junction (Duca et al, 2003). In a retrospective review of 10,000 patients undergoing LC in a single center by four separate surgeons with no documented CBD injuries, it was found that surgical experience, preoperative imaging, precise operative

Table 38.2

Incidence of Pathology in Symptomatic Patients after Cholecystectomy

					BILIARY DISEASE			
	No. of Patients	Organic Disease (%)	Nonbiliary Disease (%)	Pancreatic Disease (%)	Total (%)	Stone (%)	Stricture (%)	Periampullary Problems (%)*
Burnett & Shields, 1958	20	90	80	–	10	5	0	0
Schofield & MacLeod, 1966	74	45	37	0	8	8	0	0
Bodvall & Overgaard, 1967	764	–	–	–	9	8	–	–
Christiansen & Schmidt, 1971	77	66	53	8	13	–	–	–
Stefanini et al, 1974	249	–	–	0	14	9	0	6
Brandstatter et al, 1976	47	66	23	–	43	–	–	–
Hess, 1977	199	58	54	–	4	–	–	–
Ruddell et al, 1980	102	51	24	21	27	23	4	0
Hamilton et al, 1982	109	–	–	–	36	33	3	–
Hunt & Blumgart, 1982	157	81	18	10	63	25	9	22
Sugawa et al, 1983	164	73	22	17	34	28	5	17
McCloy & Kirwan, 1983	21	76	5	0	71	67	0	19
McCloy et al, 1984	70	96	16	4	80	35	35	19
Ros & Zambon, 1987	93	47	48	18	2	2	–	–
Bates et al, 1991	292	82	68	–	–	–	–	–
Muhe, 1992	59	12	37	–	8	8	0	–
Singh et al, 1996	239	–	–	5	78	37	22	5

*Periampullary diseases include papillary stenosis, choledochoduodenal fistulae, and ampullary tumors.

procedures, and conversion from LC to OC when needed are necessary prophylactic measures to prevent CBD injuries (Ou et al, 2009). In addition, regular reliance on the "critical view" technique, along with abandonment of the infundibular dissection approach, can optimize a safer dissection (Strasberg et al, 2000; Strasberg, 2002).

Minor biliary leaks from the bed of the gallbladder, so-called *Luschka leaks,* may also be troublesome intraoperatively. Often, such leaks occur as a result of errant dissection into a deep plane of hepatic parenchyma. Accessory bile ducts found in the gallbladder bed may be controlled by ligation when transection and spillage is identified, but if these leaks are not identified in the operating room, postoperative bilomas and even bilious ascites may ensue. If the drainage of these "minor" leaks exceeds 500 mL over a 24-hour period, endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy and transampullary stenting is useful in decompressing the biliary system and preventing reoperation (Pinkas & Brady, 2008; Pawa & Al-Kawas, 2009).

Hemorrhage

In a retrospective analysis of 9542 consecutive LCs by Duca and colleagues (2003), intraoperative hemorrhage occurred in 224 patients for an incidence of 2.3%. Bleeding was most commonly from the gallbladder bed and was treated with a fibrin-collagen patch. Conversion to an open procedure with suturing of the gallbladder peritoneum was required in five patients, however. It was noted that such hemorrhage from the gallbladder bed was encountered most commonly in patients with acute cholecystitis or cirrhosis. Tangential lesions of the cystic artery or, less commonly, total sectioning of the cystic artery occurred in 95 cases. In the majority of cases, the intraoperative bleeding was controlled laparoscopically with hemostatic clips, but conversion to an open procedure occurred in one patient. Damage to the hepatic artery occurred in one patient and required immediate open conversion. Finally, bleeding from the greater omentum was seen in 18 patients and was controlled laparoscopically in 16 patients.

Another source of massive intraoperative blood loss is from inadvertent incursion into a deep plane of hepatic parenchyma, where distal tributaries of the middle hepatic vein may be encountered. In fact, 10% of patients harbor large branches of the middle hepatic vein directly adjacent to the gallbladder fossa, which may lead to significant hemorrhage in instances of even minimal parenchymal dissection (Ball et al, 2006). Furthermore, postoperative hemorrhage may occur from trocar placement, or the bleeding may be from the cystic artery itself, albeit less than 1% of the time (Marakis et al, 2007). Finally, it should be recognized that management of profuse bleeding during LC, particularly when unexpected, can be fraught with significant ramifications that include major vascular ligation (hepatic artery, portal vein) and/or bile duct injury. This occurs from haphazard clip application or aggressive use of cautery in a poorly visualized field, thus conversion to open laparotomy is often the more prudent approach.

Dropped Stones

In 6% to 40% of LC procedures perforation of the gallbladder with subsequent spillage of gallstones occurs (Helme et al, 2009). These stones are usually retrieved under direct visualization, and the Morison pouch can be copiously irrigated; however, in 13% to 32% of patients these stones may be "lost" (Helme et al, 2009). This scenario contributes to postoperative morbidity 0.1% to 6% of the time, and the effects may vary in presentation and timing (Hand et al, 2006). Although such complications are infrequent, the patient may have symptoms such as fever, chronic abdominal pain, and/or intestinal obstruction. Furthermore, a meta-analysis by Zehetner and colleagues (2007) revealed that complications from "dropped stones" may present months to years after LC, most commonly as subcutaneous or intraabdominal abscesses or fistulas to less frequent manifestations such as liver abscesses or bacteremia. Additionally, stones have also been reported to erode into the chest cavity, causing empyema and broncholithiasis with expectoration (Zehetner et al, 2007). Perforation of the gallbladder during LC often occurs as the organ is dissected off of the liver by excessive retraction, direct puncture, or during omental adhesiolysis, but it may also occur as the gallbladder is being removed through trocar sites. Regular use of a retrieval bag may decrease complications from removal through trocar sites. Iatrogenic perforation of the gallbladder occurs more frequently in LC compared with OC; furthermore, spilled stones are arguably better visualized and more readily retrieved during open operations.

In a large retrospective review of more than 10,000 LCs, Schafer and colleagues reported a 6% incidence of gallbladder perforation with complications from dropped stones in 0.08% (Schafer et al, 1998). Furthermore, a 3-year prospective study by Rice and colleagues (1997) of 1059 patients who underwent LC at the Mayo Clinic revealed a perforation rate of 29% with an 11% dropped-stone rate. In this study, 2% of patients with perforated gallbladders developed subhepatic abscesses, and patients with intact gallbladders extracted had abscesses (Rice et al, 1997). In experimental studies using rabbit, rat, and dog models, the intraperitoneal introduction of gallstones resulted in a predominantly benign course without long-term complications (Welch et al, 1991; Sax & Adams, 1993; Cline et al, 1994; Cohen et al, 1994; Johnston et al, 1994; Zisman et al, 1995; Tzardis et al, 1996). Therefore, when gallbladder perforation and dropped stones are encountered, efforts should be made to retrieve stones with suctioning or forceps, and the subhepatic fossa should be copiously irrigated. Conversion to an open procedure is not necessary owing to a low rate of complications; however, it is a good policy to document the event and to inform the patient that stone spillage occurred.

Insufficient Cholecystectomy

In patients with severe acute inflamed cholecystitis, visualization of the cystic duct can be difficult, and historically this was treated with subtotal cholecystectomy. This approach has been proven to be effective and safe in open procedures. Recent reports suggest that when a critical view is impossible to obtain, laparoscopic subtotal cholecystectomy is also relatively safe (Hobbs et al, 2006; Ji et al, 2006; Sharp et al, 2009). When the triangle of Calot cannot be safely dissected, transection and oversewing of the gallbladder neck with resection of the anterior wall of the gallbladder, leaving a small strip of posterior gallbladder wall, can be an option.

Although this is a viable albeit rare approach, PCPs requiring an invasive reintervention still occur (Pernice & Andreoli, 2009). In a study from the United Kingdom of 26 cases of laparoscopic subtotal cholecystectomy over a 3-year period, five patients underwent postoperative ERCP for persistent biliary

leak (n = 4) or retained common bile duct stones (n = 1). One patient developed a subphrenic abscess and underwent reoperative laparotomy, and another patient who was critically ill before surgery died postoperatively. A completion LC was required for one patient with a gallstone in a retained pouch, and two patients developed port-site hernias (Philips et al, 2008). In cases mandating laparoscopic subtotal cholecystectomy, the procedure must be performed by experienced surgeons, a drain should be left at the level of transection, and if a posterior wall is retained, it should be coagulated. A late manifestation of "partial" cholecystectomy is a remnant gallbladder pouch with potential for retained stones or cholecystitis.

Infections

Postoperative infection after cholecystectomy is a rare event. In a 7-year study conducted by the Centers for Disease Control and Prevention, out of 54,504 patients, the rate of surgical site infections (SSIs) was significantly lower in the laparoscopic approach when compared with open surgery (0.62% vs 1.82%, $P = .001$); however, the pathogens that caused SSIs were similar in both groups (Richards et al, 2003). The pathogens identified included *Enterobacter* species, *Escherichia coli,* and *Staphylococcus aureus.* The majority of infections in the open approach were seen in superficial spaces; in the laparoscopic approach, the majority of infections were intraabdominal. As expected, the SSI rates were higher in patients taken to the operating room emergently or with an ASA of 3 or higher (Richards et al, 2003). That said, prophylactic antibiotics given preoperatively to any low-risk patient undergoing elective LC are not indicated as evidenced by several reported studies (Chang et al, 2006; Tocchi et al, 2000; Uludag et al, 2009).

Late Postoperative Complications

Months to years after undergoing a cholecystectomy, patients may be seen with abdominal pain that differs from the symptoms felt before surgery. The incidence of pain from abdominal incisions is higher in OC (9%) versus LC (5%) over a 6-month period as reported by Vander Velpen and colleagues (1993). Bile duct neuromas have also been reported as a cause of pain up to 45 years after cholecystectomy (Paquette et al, 2009). A randomized controlled study performed by Halm and colleagues with 1-year follow-up in the prelaparoscopic era demonstrated that incisional hernias complicated 2% (1 of 60) of patients undergoing OC with a transverse incision compared with 14% (9 of 63) with a midline incision (Halm et al, 2009). Muhe (1992) reported that 12% of patients developed incisional hernias or pain after OC compared with 2% after LC.

Mechanical Causes of Postcholecystectomy Problems

Common causes of mechanical obstruction of the biliary tree after cholecystectomy include benign or malignant strictures, retained stones in the common or cystic ducts, or downstream ampullary sphincter dysfunction.

Strictures (See Chapter 42)

Benign stenosis of the CBD is more common after LC, and 95% of the time, it is related to iatrogenic injury in the form of partial or total sectioning, clipping, or ligation (Kassab et al, 2006). The incidence of patients developing strictures after LC varies from 0% to 2.7% compared with 0.2% to 0.5% after OC (Deziel et al, 1993; Strasberg et al, 1996). Postsurgical benign strictures may also result from delayed thermal injury or intraoperative ischemic devascularization (Genest et al, 1986; Deziel et al, 1993). Additionally, choledochoduodenal fistula formation tends to manifest more commonly after such stricture formation. In the postoperative period, the problems caused by strictures may result in abdominal pain, fever, and jaundice. Cholestasis may lead to choledocholithiasis and recurrent cholangitis (Kassab et al, 2006). Malignant strictures after cholecystectomy should also be considered, as rare cases have been reported (Sharma et al, 2008). This indicates a misdiagnosis prior to the cholecystectomy.

Biliary strictures have historically been treated by surgical reconstruction via hepaticojejunostomy, although many studies have recently reported the safety and efficacy of endoscopic balloon dilation and/or stenting as a noninvasive method to treat such problems (Kassab et al, 2006; Gouma, 2007). Surgery is therefore reserved for major bile duct injuries or failure of endoscopic therapy. A more detailed discussion of both benign and malignant strictures can be found in Chapters 42 and 50.

Retained Stones

The remnant of the cystic duct or gallbladder (in subtotal cholecystectomy) has historically been implicated as the source of pain, nausea, and vomiting in postcholecystectomy patients (Bodvall, 1973). Several theories as to the etiology of such symptoms, characterized as the *cystic duct stump syndrome,* have been hypothesized (Garlock & Hurwitt, 1951). An increase in choledochal pressure resulting in cystic stump distension, inflammation or stone obstruction within the remnant of the cystic duct or gallbladder, and an increase in the sphincter of Oddi pressure have all served as causes of postcholecystectomy problems (Bodvall, 1973). However, various studies have confirmed that symptomatic improvement only occurs when a stone is present in the CBD or cystic duct and is subsequently removed endoscopically or via operative reintervention (Hopkins et al, 1979; Mergener et al, 1999; Tantia et al, 2008). In general, persistent symptoms following a cholecystectomy in which no cholangiogram was performed warrants analysis of the liver function profile and/or noninvasive imaging with either ultrasound or MRCP to assess for retained stones. If CBD stones are present, therapeutic ERCP is suggested (Fig. 38.2). The comprehensive management of common bile duct stones is discussed in Chapters 35 through 37.

Papillary Disorders

The apparatus responsible for directing the flow of biliary and pancreatic secretions is the sphincter of Oddi, which consists of three segments of smooth muscle: 1) the CBD segment, which is about 10 mm in length; 2) the pancreatic segment, which is roughly 6 mm in length; and 3) the segment of the confluence of both the bile duct and pancreatic duct, which is intraduodenal and close to 6 mm in length (Bistritz & Bain, 2006). When constricted, this sphincter impairs forward flow of both bile and pancreatic juices.

Sphincter of Oddi dysfunction (SOD) continues to be a diagnostic dilemma, and its management is controversial. Many entities have been reported describing this phenomenon, including papillary stenosis, sclerosing papillitis, and biliary spasm. The pathogenesis of this disorder is incompletely understood but is thought to result from an increase in basal sphincter pressure resulting in an increase in CBD pressure and stasis from obstructed biliary and pancreatic flow (Funch-Jensen et al,

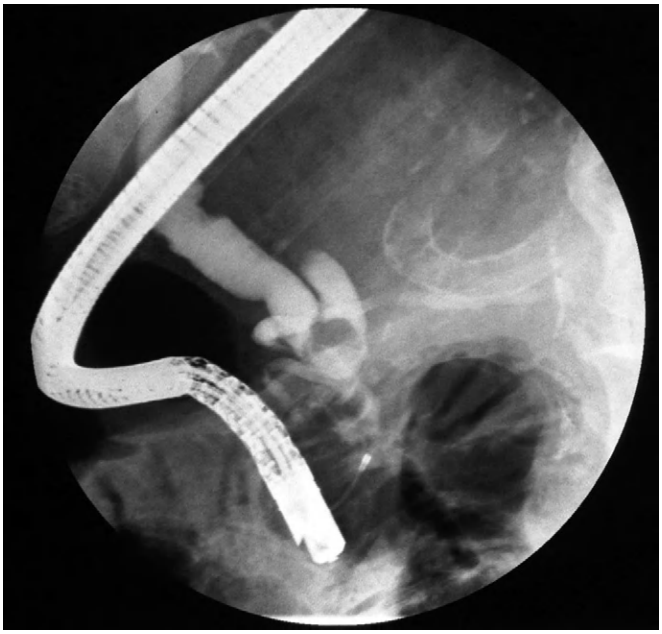


FIGURE 38.2. Depiction of a stone retained in the cystic duct stump.

2006). Microlithiasis causing transient obstruction has also been implicated as a result of stasis in the CBD from sphincter dysfunction, but this has been shown in several studies to be of little consequence in postcholecystectomy pain (Quallich et al, 2002; Rashdan et al, 2003; Bistritz & Bain, 2006). Uncoordinated spasm of the sphincter of Oddi has also been shown to produce the classic symptoms of RUQ colic with elevated liver function tests (LFTs) and has been characterized as biliary dyskinesia (Chuttani & Carr-Locke, 1993), therefore SOD may be described as two separate mechanisms: stenosis and dyskinesia.

Sphincter of Oddi Stenosis

Sphincter of Oddi *stenosis* refers to a fixed constriction or narrowing of part or all of the anatomic structures of the sphincter of Oddi. The stenosis may result from the trauma of recurrent passing gallstones, repeated attacks of pancreatitis, the effects of iatrogenic instrumentation, or other nonspecific causes. These insults result in fibrotic changes that cause a noncompliant orifice and elevated resting pressures, correlating to symptoms that fall into the category of type I biliary SOD (Bistritz & Bain, 2006). Ampullary biopsies of 43% of patients with SOD show evidence of fibrosis and inflammation (Ponchon et al, 1995). In the postcholecystectomy patient, the resulting backpressure of "papillary stenosis" is compounded by the lack of a gallbladder, which could normally serve as a reservoir for increased pressure in the CBD (Bistritz & Bain, 2006).

Sphincter of Oddi Dyskinesia

Uncoordinated contraction and relaxation of the sphincter of Oddi results in transient obstruction of biliary and/or pancreatic secretions. This leads to an elevation of intraluminal pressure with a concurrent elevation of LFTs. An increase in frequency of phasic contractions and a paradoxical response to the administration of cholecystokinin (failure of relaxation) may also occur in patients with dyskinesia (Tanaka, 2002). Interestingly, there is a significant overlap in patients with biliary dyskinesia and other intestinal motility disorders such as irritable bowel syndrome or hypertensive lower esophageal sphincter disorder (Evans et al, 1995, 1997; Chan et al, 1997).

Clinically, SOD presents in 1% of patients after cholecystectomy and in 14% to 23% of patients presenting with the postcholecystectomy syndrome (Bar-Meir et al, 1984; Meshkinpour & Mollot, 1992; Drossman et al, 1993). SOD can also manifest as recurrent pancreatitis or with recurrent acalculous RUQ pain in patients with an intact gallbladder. Patients with SOD may be classified into three types based on presentation, laboratory results, and ERCP findings. Specifically, two classification systems, shown in Tables 38.3 and 38.4, stratify patients into three clinical groups for both biliary and pancreatic symptoms and predict the outcomes of endoscopic versus surgical treatment (Hogan & Geenen, 1988; Sherman et al, 1991). Patients with type I disease have biliary pain, elevated LFTs, an increase in the diameter of the CBD (>12 mm) with a delay in contrast drainage of more than 45 minutes. Patients with type II disease present with biliary pain and one or two of the remaining criteria delineated above. Patients with type III disease are seen initially with the sole criteria of biliary-type pain (Hogan & Geenen, 1988).

When patients present with the constellation of symptoms that fall under SOD, including pain that lasts at least 30 minutes, other organic causes of RUQ pain must be ruled out with laboratory tests that include complete blood counts and LFTs with amylase and lipase measurements. Transabdominal or endoscopic ultrasonography along with nuclear hepatobiliary scans and cholangiopancreatography may aid in narrowing the diagnostic differential. Often evidence of a dilated common bile duct is seen in the setting of type I SOD and is most amenable to treatment with sphincterotomy (Rolny et al, 1993; Sugawa et al, 2001). Although no specific test is available to assess for SOD, ampullary manometry may be utilized to define

Table 38.3

Milwaukee Biliary Group Classification

Group	Biliary-Type Pain	Abnormal LFTs*	Dilated CBD†	Delayed Drainage‡
I	+	+	+	+
II	+	One or two of the above		
III	+	None of the above		

*Alanine aminotransferase and aspartate aminotransferase more than two times normal value on at least two occasions
†Dilated CBD: >12 mm on ultrasound scan or 10 mm on ERCP
‡Delayed drainage: >45 minutes on ERCP, supine position
LFTs, Liver function tests; CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography

Data from Hogan WJ, Geenen JE, 1988: Biliary dyskinesia. Endoscopy 20:179-183.

Table 38.4

Pancreatic-Type Pain Classification

Group	Recurrent Pancreatitis and/or Typical Pain	Abnormal Enzymes*	Dilated Pancreatic Diameter†	Delayed Drainage‡
I	+	+	+	+
II	+	One or two of the above		
III	+	None of the above		

*>1.5 to 2 times the upper normal limit
†>6 mm in the head, >5 mm in the body on endoscopic retrograde cholangiopancreatography
‡>9 minutes

Data from Sherman S, et al, 1991: Frequency of abnormal sphincter of Oddi manometry compared with the clinical suspicion of sphincter of Oddi dysfunction. Am J Gastroenterol 86:586-590.

hypertensive sphincters (>40 mm Hg) or to detect an increase in the frequency of phasic contractions as well as a paradoxical response to cholecystokinin (Geenen et al, 1989; Thune et al, 1991; Smithline et al, 1993). A further discussion of the diagnostic tools and management strategies used for SOD ensues later in this chapter.

NONBILIARY CAUSES OF POSTCHOLECYSTECTOMY PROBLEMS

In 70% to 80% of patients seen with postcholecystectomy pain, the etiology is attributed to nonbiliary gastrointestinal causes including gastroesophageal reflux, peptic ulcer disease, gastritis, irritable bowel syndrome, or diverticular disease (Burnett & Shields, 1958; Bates et al, 1991). These may have been the original source of symptoms in poorly chosen patients for cholecystectomy. Discomfort in the epigastrum and RUQ is often reproduced in patients with gastric, esophageal, pancreatic, hepatic, duodenal, and even pulmonary sources and therefore must be investigated in patients with postcholecystectomy symptoms. In addition, patients with flatulent dyspepsia prior to surgery often continue to have persistent symptoms after removal of the gallbladder. Patients with RUQ pain and gallstones are often immediately offered a cholecystectomy, although other gastrointestinal sources of pain or discomfort may exist and persist subsequent to surgery, presenting as a PCP.

Postcholecystectomy diarrhea (PCD), defined as three or more loose stools per day, can occur long term in up to 12% of patients after cholecystectomy (O'Donnell, 1999). At least 5% to 8% of patients report a change in their bowel habits after cholecystectomy (O'Donnell, 1999). The etiology of PCD is incompletely understood but may relate to the malabsorption of bile acids (Merrick et al, 1985). Three categories of bile acid malabsorption have been defined. In type I malabsorption, patients have previously undergone a terminal ileal (TI) resection, as bile acids are normally reabsorbed by the TI, or they may have an ileal mucosal abnormality. Type II malabsorption is considered idiopathic, and patients with type III bile acid malabsorption have either undergone a vagotomy or cholecystectomy (Fromm & Malavolti, 1986). The pathogenesis of bile acid–induced diarrhea in patients after cholecystectomy revolves around the premise that the storage depot of bile, the gallbladder, is absent, and bile acids have the ability to flow with more ease into the colon, which allows for osmotic and electrolyte shifts as well as increased transit time. The use of diagnostic studies including a synthetic radiolabeled bile acid 23-selena-25 homocholytaurine (SeHCAT) assay may be useful in narrowing the etiology of diarrhea in patients after cholecystectomy; the retention of SeHCAT at 7 days after oral administration demonstrates normal absorption of bile acids (Ford et al, 1992). The diagnostic accuracy of SeHCAT is not convincing because of studies that reveal normal levels of fecal bile acids in patients with PCD (Fromm et al, 1987). The use of bile acid binding agents such as cholestyramine have varied effects as reported in the literature (Sciarretta et al, 1986; Arlow et al, 1987; Fromm et al, 1987), however, traditional antidiarrheals may also be used in the treatment of PCD.

Postcholecystectomy pancreatic disease may be another cause of PCPs and is often concurrent and undiagnosed, with patient complaints having led to the cholecystectomy. Some studies show, however, that cholelithiasis itself may cause pancreatic changes as seen on patients undergoing ERCP (Axon et al, 1979). Whether these concurrent pancreatic changes are the cause of pain is uncertain, as not all patients with pancreatic disease after cholecystectomy underwent ERCP at the time of cholecystectomy. Furthermore, reports of patients with pancreatic disease at the time of cholecystectomy who do not manifest postoperative problems also exist (Schofield & Macleod, 1966).

Finally, after all other organic causes of PCPs are ruled out, the diagnosis of psychosomatic pain must be entertained. Various studies have revealed a higher incidence of anxiety, depression, psychosomatic disorders, and use of psychotropic drugs in patients presenting with abdominal complaints after cholecystectomy (Hansky & Dreiling, 1963; Christiansen & Schmidt, 1971; Kakizaki et al, 1976; Talley et al, 1986; Haug et al, 1995; McMahon et al, 1995). In particular, patients with type III SOD (biliary pain only) have been shown to exhibit increased rates of depression, anxiety, and obsessive-compulsive traits (Desautels et al, 1999). However, care should be taken to thoroughly evaluate patients for biliary or other abdominal causes of pain before the diagnoses of psychosomatic disorders are entertained.

Diagnostic Studies in the Evaluation of Postcholecystectomy Problems

The evaluation of patients presenting with PCPs should be undertaken in a systematic fashion, and knowledge of the diagnostic tools available is essential. Before radiologic assessment is pursued, a full history and physical with identification of laboratory derangements, including a complete blood count and chemistry panel, and a review of any intraoperative reports and imaging must be analyzed. Thereafter, the use of ultrasonography and cholangiopancreatography can be very helpful in narrowing the differential diagnosis.

Ultrasonography (See Chapter 13)

The first imaging modality used to evaluate patients with RUQ pain is often ultrasonography, because it is inexpensive, quick, and noninvasive; however, it is highly operator dependent. With experienced technicians, ultrasonography can be used to assess for retained stones and CBD diameter and, less commonly, for sphincter of Oddi dysfunction (Funch-Jensen et al, 2006). In the early postoperative period, transabdominal ultrasonography (TUS) is particularly useful in identifying fluid collections such as bilomas, abscesses, or hemorrhage. If fluid collections are large, ultrasound-guided aspiration and culture should be performed; if the character of the collection is bilious or purulent, drainage catheters are left in place. Bile duct imaging with TUS is difficult, and the sensitivity of ultrasonography to detect stones in the distal CBD is low (Dewbury & Smith, 1983; Filip et al, 2009). Visualizing the pancreatic duct is also difficult with ultrasonography because of overlying gas from the stomach or intestines, which often obscures the acoustic windows.

The use of TUS in the detection of SOD has also been investigated. Measurements of the CBD (upper limits of normal <8 to 10 mm) can be taken after the infusion of cholecystokinin or 45 minutes after the ingestion of a fatty meal, which in the face of distal obstructive physiology, such as that of SOD, will demonstrate dilation of the diameter of the CBD over baseline (Rosenblatt et al, 2001). These diagnostic tools have not gained popularity in the assessment of SOD because of low sensitivity rates and low reproducibility (Simeone et al, 1982; Darweesh et al, 1988; Rosenblatt et al, 2001).

Endoscopic ultrasonography (EUS) is another alternative to more accurately assess the presence of CBD stones and has the ability to better visualize the stomach, duodenum, and pancreas to rule out other organic causes of postcholecystectomy syndrome (see Chapter 14). EUS is also useful in the diagnosis of chronic pancreatitis and in the detection and staging of pancreatic, ampullary, and bile duct carcinoma. In patients with suspected choledocholithiasis, EUS may also be used prior to more invasive testing, such as ERCP. In EUS the ampulla itself is not cannulated, and although not therapeutic, this method has lower complication and failure rates. Additionally, the initial use of EUS may obviate the need for ERCP in one half to two thirds of patients (Filip et al, 2009; Petrov & Savides, 2009). Limitations of EUS include the need for sedation and limited availability, and it may not be conclusive in the presence of duodenal stenosis and previous sphincterotomy and/or biliary stenting in which pneumobilia may obscure a clear view (Stewart et al, 2001). Therefore patients with an elevated serum bilirubin, with or without an elevation of alkaline phosphatase, and a CBD measurement greater than 8 to 10 mm on TUS may be candidates for EUS which, if results are negative for stones or other pathology, may obviate the need for further invasive testing such as with ERCP, thereby decreasing the risk of radiation exposure, postprocedural pancreatitis, and postsphincterotomy bleeding or perforation.

Cholangiopancreatography (See Chapter 18)

Cholangiopancreatography provides direct visualization of the biliary tree, papilla, and pancreatic duct and is highly sensitive and specific in diagnosing the causes of PCPs. The use of magnetic resonance cholangiopancreatography (MRCP; see Chapter 17) provides a noninvasive method to evaluate various biliary and pancreatic disease processes including obstructive stones. Although there is no therapeutic value to MRCP, patients with abnormal LFTs and dilated CBDs (>10 mm) after cholecystectomy with no evidence of stones or other pathology on TUS may be candidates for MRCP (Terhaar et al, 2005). MRCP has been reported to be 95% to 100% sensitive and 88% to 97% specific in detecting biliary obstructions, although it is less sensitive in detecting stones less than 6 mm in size (Terhaar et al, 2005; Tse et al, 2006).

MRCP with secretin (MRCP-S) allows for functional testing of the pancreatic duct (Mariani et al, 2003). Long-term results of MRCP-S reveal diagnostic accuracy comparable to that of ERCP and with excellent positive predictive value; however, when the test showed abnormalities, radiologists were unable to distinguish between the biliary and the pancreatic segment dysfunction of the sphincter of Oddi. Additionally, the negative predictive value of MRCP-S was poor at 64% (Testoni et al, 2008). MRCP and EUS are diagnostic tools that may be used in patients with abnormal but inconclusive first-line testing (laboratory values and TUS) to obviate the need for further invasive options. The gold standard diagnostic and therapeutic procedure in patients with biliary obstruction is ERCP. It carries a sensitivity and specificity of more than 95% in the detection of obstruction and, where pathology is seen, it may also be therapeutic, allowing for sphincterotomy, stent placement, and tissue collection (Snady et al, 1992; Palazzo et al, 1995; Prat et al, 1996; Buscarini et al, 2003). However, ERCP carries a significant risk of complications. Acute pancreatitis is the most common complication and occurs in 5% to 40% of patients. Additionally, pancreatic necrosis, duodenal or biliary tree perforation, multiorgan failure, and death may occur, albeit less than 1% of the time (Dancygier & Nattermann, 1994; Masci et al, 2001; Barthet et al, 2002; Lieb & Draganov, 2007).

In patients with postcholecystectomy pain where SOD is suspected, ERCP can also allow for concurrent sphincter of Oddi manometry (SOM), which is considered the gold standard for detection of SOD (Khashab et al, 2009). A triple-lumen catheter connected to external transducers is positioned in the sphincter of Oddi segment of both the CBD and pancreatic duct separately, and baseline pressure and phasic wave amplitude, duration, and frequencies are measured with video recording for subsequent analysis (Csendes et al, 1979; Geenen et al, 1980). SOD is a dynamic process, and a single, normal endoscopic evaluation may not be sufficient in patients with persistent symptoms (Varadarajulu et al, 2003; Khashab et al, 2009). In a study of 5352 patients who underwent SOM over a 13-year period, 1037 had SOM readings within normal limits (Table 38.5). Of these patients, 30 had repeat ERCP for persistent symptoms, and 60% of these were given the diagnosis of SOD (Khashab et al, 2009).

The most common cause of abdominal pain occurring after cholecystectomy is residual or recurrent choledocholithiasis (see Chapter 35), seen in 42% of patients undergoing ERCP in one study of more than 1000 patients with PCPs (Tondelli &

Table 38.5

Normal Sphincter of Oddi Manometric Readings

Baseline Pressure	Phasic Wave Amplitude	Wave Duration	Wave Frequency
5-15 mm Hg	100-140 mm Hg	4-6 sec	3-6 waves/min

Data from Funch-Jensen P, et al, 2006: Evaluation of the biliary tract in patients with functional biliary symptoms. World J Gastroenterol 12(18):2839-2845.

Gyr, 1983; Zhou et al, 2003). ERCP findings of biliary or pancreatic strictures are second to stones in frequency in patients with PCPs (Goenka et al, 1996; Singh et al, 1996). Furthermore, in various studies in which ERCP was performed on patients with severe PCPs manifesting as pain and/or jaundice, the diagnosis was made in over half of the patients; CBD stones comprised the majority (Ruddell et al, 1980; Hamilton et al, 1982; Carlson et al, 1992).

As noted above, bile leak from CBD injury or inadequate cystic duct stump ligation are serious complications of cholecystectomy. In this scenario, intervention via ERCP with the use of endoprosthetic stents with or without sphincterotomy is an important diagnostic and therapeutic tool (Katsinelos et al, 2006). In some cases, endoscopic access to the biliary tree is limited, such as in patients who have had diverting gastric bypass surgery, and percutaneous transhepatic cholangiography (PTC) is an alternative approach. However, a majority of patients with biliary injuries following cholecystectomy may be successfully managed initially with ultrasound or computed tomography (CT) guided percutaneous drainage of biliary collections. Patients with persistent leaks or those who present with jaundice should be considered for ERCP as a first-line diagnostic and therapeutic option (Zerem & Omerovic, 2009).

Hepatobiliary Scintigraphy (See Chapter 15)

In patients who have undergone cholecystectomy, nuclear scanning reveals rapid flow of intravenously administered ^{99m}Tc-n-(2,6,dimethylphenylcarbamoylmethyl) iminodiacetic acid (^{99m}Tc-HIDA) from the hepatocytes to the biliary canaliculi then to the CBD and ultimately to the duodenum via the sphincter of Oddi. In patients with SOD a marked delay in transpapillary transit times is seen with stasis in the intrahepatic and extrahepatic biliary system. This sort of quantitative cholescintigraphy may aid in the diagnosis of patients suspected to have SOD following cholecystectomy (Shaffer et al, 1986; Corazziari et al, 1994; Madacsy et al, 1999; Corazziari et al, 2003). It is also useful in confirming the presence of a biliary leak after cholecystectomy, although discrimination of the precise location is often not possible.

Axial Imaging

If the aforementioned techniques do not reveal the cause of PCPs, CT or magnetic resonance imaging (MRI) can be employed to rule out other sources of pain not suspected preoperatively (e.g. tumors, rib fractures, pneumonia). Postoperative complications, such as dropped stones, abscesses, hematomas, or hernias can also be detected. A scan that is inconclusive is often reassuring to the surgeon, as it can at least define that postoperative complaints are not obviously organic in nature, which can lead the workup of symptoms in other directions.

Treatment Strategies in Patients with Postcholecystectomy Problems

Early Postcholecystectomy Problems

Once the appropriate diagnostic workup is performed, various treatment strategies exist to address common PCPs. In the early days to weeks after operation, the finding of a gallbladder fossa hematoma (relatively common) should be managed with serial hematocrit values and correction of any coagulopathy. Most hematomas are asymptomatic and self-limited; however, if a patient's anemia worsens and impacts their clinical status, operative reexploration must be pursued. If an abscess is identified on diagnostic ultrasound or CT scan, percutaneous drainage is the preferred treatment, if the abscess is large enough, and if the procedure is technically feasible. Smaller or inconveniently placed collections may be successfully managed with antibiotics alone, and operative drainage is rarely necessary.

In the scenario of a biliary leak presenting as a biloma, the initial management should be aimed at percutaneous drainage to control local sepsis; however, endoscopic management may ultimately be necessary. In minor injuries, ERCP and sphincterotomy will eliminate the transpapillary pressure gradient, allowing for uninhibited flow across the papilla, thereby diminishing the extent of the leak, until it eventually ceases (De Palma et al, 2002). The endobiliary stent may also seal off the flow of bile through a physical apposition against the defect in the biliary tree, although this is less likely. External drainage of bile usually dissipates immediately, within a few days; the stent may be removed a month later, if the cholangiogram shows resolution of the leak. If external drainage does not resolve, or if it recurs in the early period, the next approach would be the serial placement of multiple endobiliary stents in a "bunched" fashion, or even deployment of a temporary covered metal stent. Should these maneuvers fail, operative repair is required and usually calls for a bilioenteric bypass. Major damage to the biliary tree can usually be salvaged by stents, but massive bile ascites causing generalized peritonitis may require an operative washout and drainage; this can sometimes be achieved laparoscopically, realizing that an open approach may ultimately be required to definitively address the damage.

Late Postcholecystectomy Problems

When patients come to the hospital months to years after having a cholecystectomy with symptoms of PCPs, a complete laboratory and diagnostic workup will guide the surgeon's management decisions. In the case of abnormal LFTs, with or without leukocytosis, and abnormal TUS findings, the patient should proceed directly to ERCP. If, however, a postcholecystectomy patient's LFTs are abnormal, but the TUS is equivocal or normal, it is reasonable to proceed with EUS or MRCP prior to ERCP. The various endoscopic management strategies regarding choledocholithiasis, strictures, and fistulae are discussed elsewhere in this textbook (see Chapters 35 and 42).

A diagnostic workup that points toward the diagnosis of SOD will alter the physician's management strategy. The goal for treatment in patients with SOD is free flow of biliary and pancreatic fluid into the duodenum. This objective may be achieved medically, endoscopically, or surgically.

Medical treatment of SOD is often attempted as a first-line management option, but results are usually poor. The utility of calcium channel blockers and oral nitrates have been plagued with poor outcomes secondary to tachyphylaxis and side effects of the medications (Staritz et al, 1985; Fullarton et al, 1992; Khuroo et al, 1992; Sand et al, 1993; Craig & Toouli, 2002; Wu et al, 2005b; Bistritz & Bain, 2006). Although controversial and underexamined, some studies reveal a decrease in sphincter of Oddi basal pressures with the use of intravenous somatostatin and its analogues (Fazel et al, 2002; Wu et al, 2005a).

Endoscopic treatment of SOD utilizes the ability to decrease transpapillary pressures with sphincterotomy. Patients with a functional obstruction resulting in SOD, as seen in type I disease in particular, benefit from sphincterotomy even when

manometry may not reveal hypertension. Symptomatic relief has been achieved at more than 2-year follow-up in patients with type I SOD with or without manometric findings of hypertension (Rolny et al, 1993; Sugawa et al, 2001). Based on these and other findings that corroborate these results, sphincterotomy without manometry is advised in all patients with type I SOD. In contrast, patients with type II SOD only benefit from sphincterotomy when basal sphincter pressures are elevated. Therefore, manometry should precede endoscopy in this patient population (Geenen et al, 1989; Toouli & Craig, 1999). In patients without objective evidence of biliary obstruction (type III), the response to sphincterotomy does not correlate well with manometric findings, thus it has been suggested that patients who carry a diagnosis of type III SOD should undergo hepatobiliary scintigraphy to gather additional objective data prior to invasive manometry or sphincterotomy (Wehrmann et al, 1996). In this patient population, botulinum toxin may also be used to avoid sphincterotomy and its resultant complications such as bleeding, pancreatitis, and perforated viscera (Wehrmann et al, 1998). Recent studies suggest that phosphodiesterase type 5 inhibitors such as vardenafil (Levitra) infused into the duodenum with endoscopy may reduce basal sphincter of Oddi pressures without significant adverse events (Cheon et al, 2009). These and other agents are under active investigation as alternatives to the more invasive approach of sphincterotomy.

Endoscopic stenting for SOD in patients without an elevated basal sphincter pressure has been attempted with poor response and a high associated risk of stent-induced pancreatitis (Goff, 1995). Additionally, stent placement has also been advocated to predict which patients would respond to sphincterotomy; although in some studies, these trials were able to detect a population of patients who would respond, this method did not gain popularity because of the risks involved and the lack of compelling evidence (Bistritz & Bain, 2006). Therefore the use of biliary stenting in the setting of SOD is not advisable.

Surgical intervention for SOD was developed before the advent of ERCP (Madura et al, 2005). Transduodenal sphincteroplasty with transampullary septectomy (TDS-TAS) was the procedure of choice at that time (Fig. 38.3). Prior to the advent of ERCP, no objective studies could accurately diagnose patients with SOD; subjective intraoperative methods, such as palpation of the sphincter through the wall of the duodenum, were used to select patients for TDS-TAS. As time progressed, various studies were developed to improve patient selection, such as the morphine–neostigmine evocative test (Nardi & Acosta, 1966). Expertise in endoscopy also continued to progress, until endoscopic sphincterotomies were standardized by the mid-1970s (Kawai et al, 1974). Advantages of the surgical approach include accurate apposition of the duodenal and ductal mucosa, as well as access to the transampullary septum, which cannot always be accomplished with ERCP (Madura et al, 2005). Endoscopic transampullary septotomy is rare, and drainage of the pancreatic duct is inadequate (Fuji et al, 1989; Rolny et al, 1989). In a series of 17 patients, pain from an unsuccessful sphincteroplasty was relieved by excision of the septum in 12 patients (Moody et al, 1990). These studies and others demonstrate the importance of a septotomy; however, both surgical and endoscopic results are not optimal owing to the vague nature of this disease (Tables 38.6 and 38.7). Patients with a suspected diagnosis of SOD should be treated by experienced surgeons and endoscopists working in concert. A treatment algorithm for patients presenting with PCP is illustrated in Figure 38.4.

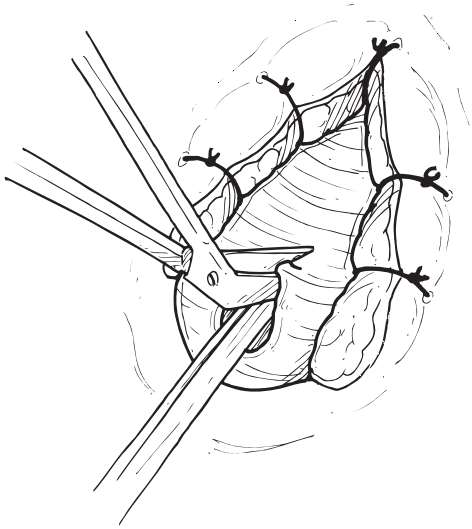


FIGURE 38.3. Transduodenal sphincteroplasty. Depiction of transampullary septectomy.

Table 38.6

Results of Surgical Treatment for Sphincter of Oddi Disorder

Reference	*N*	Follow-up	Result (%)	Morbidity (%)
Moody et al, 1983	83	1-10 yr	Good, 43; fair, 33; poor, 24	21
Nardi et al, 1983	89*	5-20 yr	Pain free, 50	—
Anderson et al, 1985	28	67.5 mo (mean)	Good, 79; poor, 21	—
Stephens & Burdick, 1986	81	6 mo	Pain free, 68; fair, 25; poor, 7	7
Hastbacka et al, 1986	22	—	Good, 59; moderate, 23; poor, 18	18
Williamson, 1988	20	6-100 mo	Pain free, 60; improved, 25; poor, 5	20
Nussbaum et al, 1989	29	22 mo (mean)	Excellent/good, 62; fair, 14; poor, 4	38
Kelly & Rowlands, 1996	20	9-80 mo	Pain free, 55; good, 10; poor, 35	10
Toouli, 1996	26*	9-105 mo	Pain free, 58; mild, 30; poor, 12	8
Tzovaras & Rowlands, 2002	36	54 mo	Good, 56; moderate, 28; poor, 16	11

*For recurrent acute pancreatitis exclusively

Table 38.7

Results of Endoscopic Treatment for Sphincter of Oddi Disorder

Reference	*N*	Follow-up	Result (%)	Morbidity (%)
Reimann et al, 1983	25	2-9 yr	Pain free, 48; improved, 32; poor, 20	–
Roberts-Thomson & Toouli, 1985	46	25 mo (mean)	Pain free, 13; improved, 48; poor, 39	5
Thatcher et al, 1987	46	15.9 mo (mean)	Pain free, 67	16
Neoptolemos et al, 1988	30	46 mo (median)	Good, 63.3; poor, 36.7	25
Seifert, 1988	127	–	Pain free, 55.1; improved, 32.3; poor, 12.6	–
Geenen et al, 1989	47	1 yr	Good, 43; fair, 35; poor, 22	–
Bozkurt et al, 1996*	23	19 mo (mean)	Pain free, 57; improved, 26; poor, 17	22
Wehrmann et al, 1996*	33	2.5 yr (median)	Improvement (II), 60; improvement (III), 8	–
Toouli et al, 2000	81	2 yr	Improvement, 62; no change, 38	10

*Prospective trial, type II and type III Milwaukee classification, manometric criteria for sphincterotomy

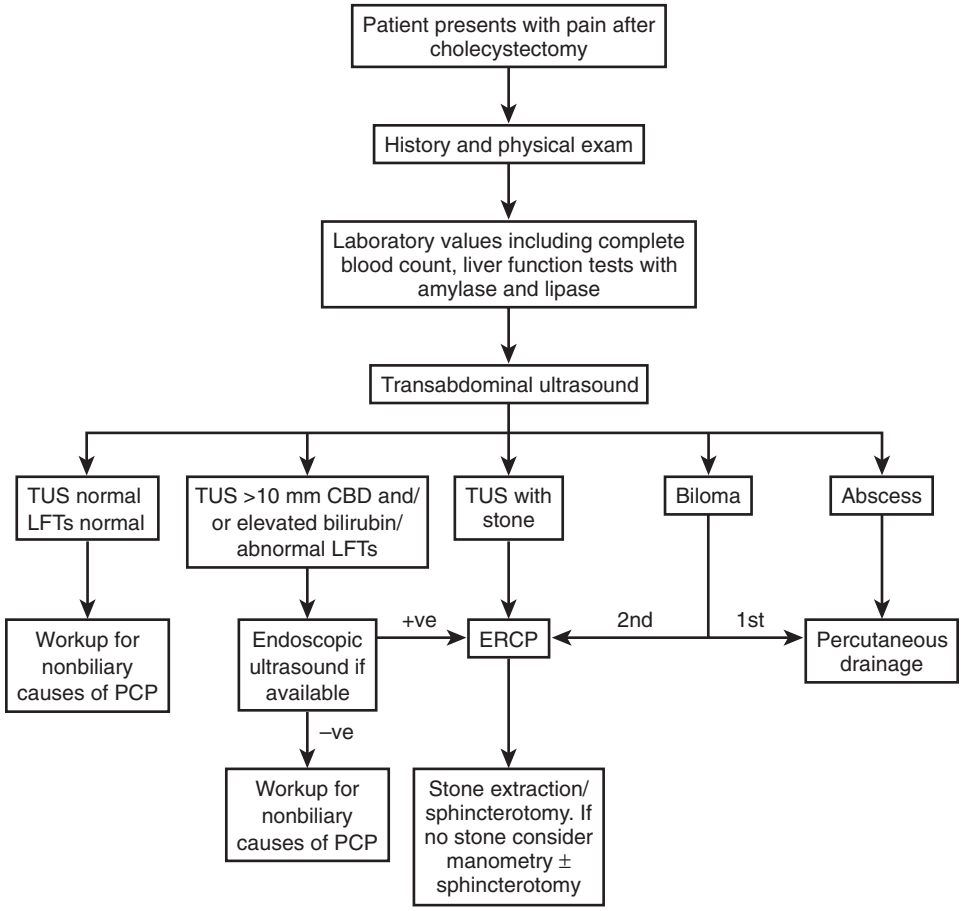


FIGURE 38.4. Treatment algorithm for patients with postcholecystectomy problems.

POTENTIAL PITFALLS IN MODERN APPROACHES TO CHOLECYSTECTOMY

The field of hepatobiliary surgery has progressed in various ways over the years, but one of the most fascinating leaps in modern surgery is the pace at which minimally invasive methods are supplanting open operative interventions. From single incision laparoscopic surgery (SILS) to natural orifice translumenal endoscopic surgery (NOTES), the approach to cholecystectomy appears poised for further changes. To date, scant data are available regarding the outcomes of such novel approaches, but there is no doubt that these innovative methods will introduce a

host of new PCPs. In fact, an early outcomes report of 39 patients undergoing NOTES cholecystectomy, both transvaginal and transgastric, revealed NOTES-related complications such as gastric hematomas and esophageal and colonic perforations (Salinas et al, 2009). Because of safety concerns, NOTES procedures still have to be further refined prior to widespread dissemination, although SILS techniques seem to be embraced with more enthusiasm because of the ability to use existing instrumentation and the improved clinical outcomes. Clearly, additional studies are essential for the further evolution of these contemporary techniques (Kuon Lee et al, 2009).

CONCLUSIONS

Symptoms resembling those encountered prior to cholecystectomy may recur in 10% to 40% of patients undergoing either laparoscopic or traditional open cholecystectomy (Pernice & Andreoli, 2009). This occurrence is disappointing and sometimes vexing for both the patient and surgeon, therefore it is imperative that the surgeon caring for these patients rule out the most serious complications first, namely, bile duct injury, bleeding, and retained choledocholithiasis. The use of diagnostic tools and therapeutic options and the systematic approach outlined in this chapter should provide the caregiver with enough data to accurately diagnose and treat the etiology of a patient's PCPs. The vast majority of the time, these problems will be organic in nature and therefore treatable. However, we have described the diagnostic dilemma that SOD presents, and it is imperative that a stepwise, logical methodology also be applied to these patients whose outcomes are less gratifying.

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CHAPTER 39

Intrahepatic stones

Yuji Nimura and Yuichi Kitagawa

OVERVIEW

Although hepatolithiasis is a rare disease prevalent only in East Asia—including China, Hong Kong, Korea, and Japan—it has increasingly been encountered in Western countries (Herman et al, 2005; Vetrone et al, 2006; Catena et al, 2006; Nuzzo et al, 2008; Al-Sukhni et al, 2008). Patients with intrahepatic stones follow a specific clinical course characterized by recurrent cholangitis with recurrent stones or liver abscess, which may cause pyogenic sepsis or liver dysfunction and result in biliary cirrhosis. Advances in hepatobiliary diagnostic modalities have allowed more precise delineation of the biliary anatomy and extent of disease, and the application of modern treatment modalities has resulted in a longer stone-free period over the past 2 decades. Intrahepatic stones include brown pigment stones (calcium bilirubinate stones), cholesterol stones, and other rare types. The majority of intrahepatic stones are brown pigment stones. Some centers, not only in Asia but also in Western countries, have reported increasing numbers of patients with primary cholesterol stones originating in the liver.

DEFINITION AND SURGICAL ANATOMY

Intrahepatic stones are defined as concretions existing in the intrahepatic bile ducts. Although the confluence of the hepatic ducts is situated outside of the parenchyma of the liver, for convenience an *intrahepatic bile duct* is defined as any bile duct proximal to the confluence of the right and left hepatic ducts. Established by the Japanese Ministry of Health, Labor, and Welfare, the Japan Research Group for the Study of Hepatolithiasis proposed a classification of patients with hepatolithiasis into two groups: *type I* patients have stones only in the intrahepatic bile duct, and *type IE* patients have stones in the intrahepatic and extrahepatic bile ducts. Patients are classified further by location of stones within the liver: right side (*type R*), left side (*type L*), right and left sides (*type LR*), and caudate lobe (*type C*) (Nimura et al, 2005).

In Japan, the proportion of type I intrahepatic stones was 20.6% from 1975 through 1979, increasing to 45.5% from 1989 through 1992 (Tanimura et al, 1994). In Hong Kong, type I constituted 51% of intrahepatic stones from 1991 to 1996 (Liu et al, 1998). In Kaohsiung, Taiwan, the percentage of type I stones was 18.3% from 1980 through 1986 (Yuan et al, 1990). In addition to the findings in East Asian countries, type I intrahepatic stones were diagnosed in 77.3% of patients between 1986 and 2003 in Bologna, Italy (Vetrone et al, 2006).

Many patients with intrahepatic stones are reported to have no stones in the gallbladder. Yuan and colleagues (1990) reported that only 62 (30.7%) of 202 patients with intrahepatic stones had stones in the gallbladder. Regarding distribution of stones in the liver, type L is reported to be dominant. In Japan, the rate was 45.5% for type L, 26.1% for type R, and 26.3% for type LR for 1989 through 1992. The distribution was 52.1% (type L), 11.5% (type R), and 31.3% (type LR) in Hong Kong and 55% (type L), 18.3% (type R), and 26.7% (type LR) for 1989 through 1992 and 71.5% (type L), 16.2% (type R), and 12.2% (type LR) from 2000 through 2005 in Taiwan (Lee et al, 2007). Similarly, it was 59.0% (type L), 18.3% (type R), and 22.7% (type LR) for 1986 through 2003 in Italy (Vetrone et al, 2006). The incidence of stones in the caudate lobe (type C) was reported to be 6.6% (Nimura et al, 1998).

Hepatobiliary radiologists, endoscopists, and surgeons should have a thorough knowledge of the segmental and subsegmental anatomy of the intrahepatic bile ducts for preoperative diagnosis of intrahepatic stones, for an understanding of the variations of the intrahepatic biliary tree, and for decision making about therapeutic approaches to difficult biliary stenosis (see Chapter 1). The subsegmental anatomy of the intrahepatic bile ducts (Fig. 39.1) was established on the basis of clinical cholangiograms (Nimura, 1997). This cholangiographic anatomy is related to the radiologic study of the intrahepatic portal branches (Takayasu et al, 1985). The left lateral segmental ducts (B2, lateral posterior branch; B3, lateral anterior branch) join just behind the umbilical portion of the left portal vein. The left medial segmental duct (B4) enters this common trunk on the right of the umbilical portion of the left portal vein and forms the left hepatic duct. Segmental ducts B3 and B4 may make a common trunk that B2 joins to form the left hepatic duct. The right *anterior* segmental branches are superimposed over the right *posterior* segmental branches and are difficult to distinguish from each other on clinical cholangiograms taken with the patient in a supine position; they are divided clearly by the right hepatic vein on cholangiograms taken with the patient in the right lateral position, the right anterior in the left cranial area, and the right posterior in the right caudal area. The right posterior segmental duct joins the left hepatic duct in 12.6% of Taiwanese patients and 16.8% of Japanese patients with intrahepatic stones. This is an important anatomic variation when considering the distribution of intrahepatic stones (Kitagawa et al, 2003).

PATHOLOGY

Intrahepatic calcium bilirubinate stones are composed mainly of bilirubin, cholesterol, fatty acids, and calcium. They are dark brown, soft, and friable. On a cut surface, a lamellar structure can be seen (Fig. 39.2). Stones are frequently located in the large bile ducts, such as the common, right, or left hepatic ducts.

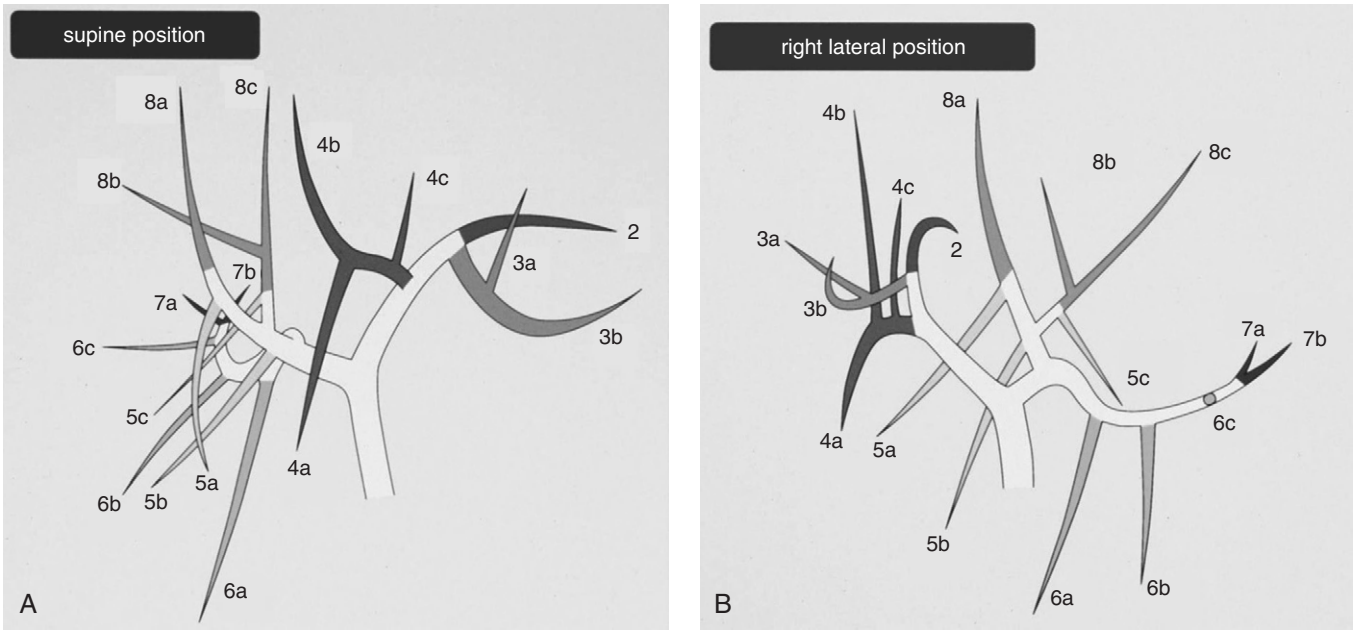


FIGURE 39.1. Cholangiographic anatomy of the intrahepatic segmental ducts according to the patient's position. Numerals refer to Couinaud's segments. *3a*, Superior branch; *3b*, inferior branch; *4a*, inferior branch; *4b*, superior branch; *4c*, dorsal branch; *5a*, ventral branch; *5b*, dorsal branch; *5c*, lateral branch; *6a*, ventral branch; *6b*, dorsal branch; *6c*, lateral branch; *7a*, ventral branch; *7b*, dorsal branch; *8a*, ventral branch; *8b*, lateral branch; *8c*, dorsal branch (Nimura et al, 1997).

Diffuse dilation of the biliary tree, chiefly of the stone-containing ducts and their merging peripheral branches, and stenosis-like ductal lesions distal to the stones are commonly noted.

The histologic changes of the bile ducts with calcium bilirubinate stones are classified as either 1) chronic proliferative cholangitis, 2) suppurative cholangitis, or 3) chronic granulomatous cholangitis (Nakanuma et al, 1981). *Chronic proliferative cholangitis* consists of extensive proliferation of fibrous connective tissue in the ductal wall, moderate to severe infiltration of the inflammatory cells (primarily lymphocytes), and proliferation of mucin-producing glandular elements in the ductal wall. *Suppurative cholangitis* is characterized by ulceration and suppurative inflammation of the ductal wall. Chronic granulomatous cholangitis is characterized histologically by prominent granulomatous changes in the ductal wall and periductal tissues.

In chronic proliferative cholangitis, histologic observation shows that most proliferative glands in the ducts have mucin-producing activity. These glands are observed to secrete a large amount of sialylated and sulfated acid mucins into the lumen (Maki et al, 1971; Sasaki et al, 1996). The affected part of the liver frequently shows atrophic changes. When the whole liver is involved, patients with intrahepatic stones may develop biliary cirrhosis and portal hypertension.

Intrahepatic cholesterol stones are composed mainly of cholesterol. They are yellow, small, and hard (Fig. 39.3). On a cut surface, a radial or crystalloid structure can been seen. Bile ducts containing cholesterol stones generally show a milder degree of fibrosis and glandular hyperplasia than ducts with calcium bilirubinate stones. Foamy cell aggregates and multinucleated giant cells are characteristic findings in patients with intrahepatic cholesterol stones.



FIGURE 39.2. Cut surface of a resected liver specimen shows dilated intrahepatic ducts filled with calcium bilirubinate stones. On the cut surface, a lamellar-like structure is seen.

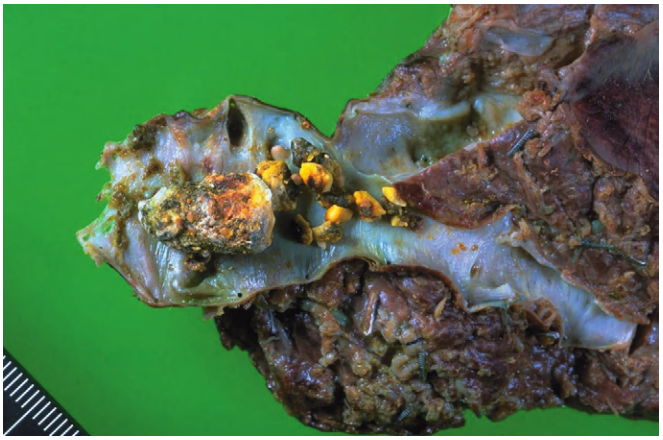


FIGURE 39.3. Resected liver specimen shows dilated bile duct with cholesterol stones.

Long-standing chronic cholangitis with biliary epithelial regeneration may be causally related to its malignant transformation, and several studies have demonstrated cholangiocarcinogenesis related to hepatolithiasis. Intraductal papillary growth of neoplastic epithelia in the liver (IPNL) is associated with hepatolithiasis and often displays variable gastroenteric metaplasia and significant intraductal spread. A continuous histologic spectrum may be observed, from papillary growths with low-grade and high-grade dysplasia to carcinoma in situ and finally to invasive carcinoma, particularly mucinous carcinoma (Chen et al, 2001). Mucin-secreting tumors of the intrahepatic biliary tract show frequent expression of *MUC2* and nuclear *CDX2*. *MUC2* expression in intestinal differentiation is closely related to the expression of *CDX2* in IPNL, and mucinous intrahepatic cholangiocarcinoma (ICC) is associated with hepatolithiasis in the same manner as intestinal metaplasia in gastric mucosa and Barrett esophagus. This suggests that a common pathway of carcinogenesis may be involved in ICC with hepatolithiasis, gastric carcinoma, and adenocarcinoma in Barrett esophagus, in which *CDX2*-dependent intestinal metaplasia develops (Ishikawa et al, 2004). Further studies revealed that two types of neoplastic lesions preceding invasive ICC were identified: a flat-type neoplastic lesion called *biliary intraepithelial neoplasia* (BilIN) and *intraductal papillary neoplasm of the bile duct* (IPNB) or IPNL. Multistep carcinogenesis has been suggested in both lesions, and immunophenotypes of *MUCs* and cytokeratins might characterize three cholangiocarcinogenetic pathways in hepatolithiasis. IPNB and increased expression of *MUC1* in BilIN are associated with tubular adenocarcinoma, and colloid carcinoma in IPNB is characterized by *MUC1*-negativity and less advanced pathologic stages (Zen et al, 2006).

Further immunohistochemical studies reveal that decreased membranous expression of β-catenin and E-cadherin is an early event in the tumorigenesis of both BilIN and IPNB lineages. However, different expression of cancer-related molecules was suggested in the progression of the BilIN and IPNB lineages in cholangiocarcinogenesis related to hepatolithiasis. The expression of matrix metalloproteinase (MMP) 7 and membrane type (MT) 1 MMT was closely associated with invasive growth of the BilIN lineage, and the *Wnt* signaling pathway may play an important role in the tumorigenesis of the IPNB lineage (Itatsu et al, 2007). The reported incidence of ICC detected at operation varies from 1.4% to 13% in Asian countries (Jeng et al, 1996; Liu et al, 1998), and it was 8.6% (three of 35 cases) in an Italian hospital (Nuzzo et al, 2008). A report from Hong Kong that assessed the long-term efficacy of hepatic resection for stone clearance in 103 patients noted cholangiocarcinoma in 10 patients (four known preoperatively) at the time of operation and in another three patients during follow-up (Chen et al, 2004). A similar report from Taiwan showed that three (2.4%) of 123 patients with intrahepatic stones had associated cholangiocarcinoma at the time of hepatectomy, and two (1.6%) had cholangiocarcinoma develop during a median follow-up of 40 months (range, 5 to 58 months) (Lee et al, 2007). Patients with retained stones or recurrent hepatolithiasis after percutaneous transhepatic cholangioscopic lithotomy have a high incidence of cholangiocarcinoma; four (17%) of 23 cases during a median follow-up of 11 years (range, 1 to 23 years; Chen et al, 2005). Intrahepatic stones associated with ICC are calcium bilirubinate stones in 89.1% of reported cases (57 of 64 cases; Sato et al, 1998). An autopsy case of intrahepatic cholesterol stones with peripheral ICC was reported, in which the causal relationship between the stones and the carcinoma remained speculative (Terada et al, 1989).

ETIOLOGY

Most intrahepatic stones appear as brown pigment (calcium bilirubinate) stones on macroscopic inspection and infrared analysis. The chemical composition of intrahepatic calcium bilirubinate stones is not identical to that of brown pigment stones in the extrahepatic bile ducts; the former contain more cholesterol and less bilirubin and bile acid and include lesser amounts of bile acids modified by bacterial metabolism (Shoda et al, 1991, 2003; Yamashita et al, 1988). The high incidence of bactibilia in patients with intrahepatic calcium bilirubinate stones suggests a relationship between bacteria and formation of stones (Maki, 1966). Among the bacteria in bile, *Escherichia coli*, *Clostridium* spp., and *Bacteroides* spp. show β-glucuronidase activity and are thought to be responsible for the hydrolysis of bilirubin glucuronide, the water-soluble form of bilirubin in bile, to free unconjugated bilirubin, which is water insoluble and combines with ionized calcium in bile to form calcium bilirubinate; this leads to stone formation. Bacterial infection alone cannot explain why intrahepatic brown pigment stones contain a higher amount of cholesterol than stones in the extrahepatic ducts. Upregulated cholesterogenesis and downregulated bile acid synthesis in the liver may be one of the causative factors responsible for the formation of hepatic bile substantially supersaturated with cholesterol, which leads to subsequent formation of cholesterol-rich stones (Shoda et al, 1995, 2003).

It is suggested that the risk factors of intrahepatic stone formation after surgery for choledochal cyst are anastomotic stricture, residual debris in the intrahepatic ducts, and dilated intrahepatic bile ducts. A Japanese surgical study reported secondary hepatolithiasis that developed after choledochal cyst excision with hepaticoenterostomy (CEHE). Although no stone formation was seen in the 145 children who had CEHE at the age of 5 years or younger, three (5.5%) of 55 children older than 5 years who underwent CEHE had intrahepatic stones develop. On the other hand, intrahepatic stones developed in five (12.5%) of the 40 adult patients with CEHE. Two of the five developed anastomotic stricture of the end-to-side hepaticojejunostomy distally to the stone at the porta hepatis with or without left intrahepatic duct dilation. The incidence of post-CEHE hepatolithiasis in children aged 5 years or younger was significantly lower than in other children and adults. In addition to the hepatolithiasis, one adult developed ICC at age 54 years, 6 years after CEHE converted from cholecystectomy performed 16 years previously (Yamataka et al, 1997). On the other hand, intrahepatic stones developed in patients with biliary atresia who had undergone hepatic portoenterostomy, and almost 100% calcium bilirubinate stones were found in bile lake in the resected liver (Tainaka et al, 2006).

A study from Taiwan investigated the possible association between biliary helminthic infestation (ascariasis or clonorchiasis) and hepatolithiasis (Huang et al, 2005). By using immunologic techniques, the authors showed a higher prevalence of ascariasis and clonorchiasis in patients with intrahepatic stones than in control subjects (33.6% vs. 17.4%; $P = .005$). However, analysis of patients with hepatolithiasis with and without evidence of helminthic infestation showed no differences in the rates of biliary stricture formation, stone recurrence, secondary biliary cirrhosis, or cholangiocarcinoma. An epidemiologic

study suggested that lower socioeconomic and hygienic status may be involved in stone formation in Taiwan (Momiyama et al, 2008). In the Kami-Goto Islands of Japan, where incidence of this disease is high, there were similar hygienic and social problems from the 1960s to the 1980s. However, there has been no new case of hepatolithiasis in the generation born after the 1970s, after improvements in the environment and economic status (Yasaka, 2008).

The most important factors for the formation of intrahepatic calcium bilirubinate stones are biliary stasis, bacterial infection, and biliary mucin produced from the covering and proliferated mucous gland epithelium of the intrahepatic bile ducts. Calcium bilirubinate and fatty acid–calcium soap occur through hydrolysis of bilirubin conjugates and lecithin by bacterial β-glucuronidase and phospholipase in bile. These salts can precipitate and form microcalculi, particularly if a nidus is present, such as desquamated epithelium or biliary mucin (Forstner & Forstner, 1975). These microcalculi coalesce to form large stones. Chronic proliferative inflammation seems to precede bile duct damage: the development of intrahepatic stones leads to biliary strictures, which promote further propagation of stones through alterations of bile flow (Nakanuma et al, 1988).

A study on the biliary dynamics of patients with intrahepatic stones revealed that the time-activity curves of technetium-99m-ethylenediaminetetraacetic acid (EDTA) were prolonged significantly in affected and apparently unaffected intrahepatic bile ducts compared with the curves in normal subjects (Takahashi et al, 1986). This result suggests a global impairment of bile flow, even when only one side of the liver is affected by stones. The curves in the intrahepatic bile ducts of the left lobe were more prolonged than those of the right lobe, even in normal liver; this prolongation could explain why involvement of the left lobe is more common.

Sphincter of Oddi motility has been analyzed in patients with intrahepatic and common bile duct (CBD) stones by percutaneous transhepatic manometry (Yuasa et al, 1994). This study disclosed no significant manometric differences among three groups—an intrahepatic stone group, a cholecystectomy group with CBD stones, and a noncholecystectomy group with CBD stones—with the exception of the higher frequencies and greater duration of burst contractions during duodenal phase III of the migrating motor complex in the cholecystectomy group with CBD stones, although this abnormality probably plays little role in the etiology of intrahepatic stones.

Indirect evidence suggests that metabolic factors play a more important etiologic role in intrahepatic cholesterol stones. Cholesterol supersaturation and microscopic cholesterol crystallization, which represent major stages in the formation of cholesterol gallbladder stones, have been observed in the hepatic bile of patients with intrahepatic cholesterol stones (Schillio et al, 1992: Strichartz et al, 1991). Activity of apolipoprotein A1, which is one of the inhibiting factors of cholesterol nucleation in bile, is reported to be decreased in the hepatic segments containing cholesterol stones (Ohta et al, 1993).

SIGNS AND SYMPTOMS

Abdominal pain, either in the right upper quadrant or in the upper abdomen, is the most frequent initial symptom observed in 70% of hepatolithiasis patients (Tanimura et al, 1994). Jaundice and fever follow and are present in 10% to 30% of cases. Other abdominal complaints, including abdominal discomfort and vomiting, are also observed. These symptoms are not pathognomonic for intrahepatic stone disease. Asymptomatic cases have increased in number to 16.1% because of advances in diagnostic imaging modalities and more frequent medical checkups. Previous biliary operations for calculous disease had been performed in 42.1% of patients with intrahepatic stones, and 22.2% had had two or more operations, indicating an intractable course of disease.

DIAGNOSIS

With the introduction of various new imaging modalities, intrahepatic stones are now diagnosed more accurately before surgery. Ultrasonography (US) is a noninvasive, reliable, and inexpensive procedure. It may reveal features of biliary obstruction, stones in the biliary system, pneumobilia, or liver abscesses. The major findings of stones on US examination are hyperechoic lesions with acoustic shadows or ductal dilation (Choen et al, 1991; Itai et al, 1980; Lim et al, 1990). Interpretation may be difficult, however, owing to the presence of pneumobilia as a result of a previous papillotomy or biliary-enteric anastomosis. In addition, intrahepatic stones that do not cast a sonic shadow may not be well visualized on US.

Computed tomography (CT) provides information regarding the location and composition of stones and generally offers more anatomic detail, which is necessary for decisions regarding definitive treatment. Round or oval high-density shadows in the dilated ducts are a sign of intrahepatic calcium bilirubinate stones (Fig. 39.4); the false-positive rate is quite low (Itai et al, 1980; Menu et al, 1985). Cholesterol stones or pigmented stones containing less calcium are hard to detect, so it is important to examine noncontrast films first (Fig. 39.5), because intrahepatic stones may be less conspicuous after parenchymal enhancement. Pneumobilia does not hinder the CT evaluation of the biliary system. In addition, CT determines the degree of atrophy of the affected part of the liver and detects the segmental or subsegmental duct involvement when cholangiography fails to visualize these ducts; CT also provides an accurate localization of liver abscesess, raises the suspicion of cholangiocarcinoma, and detects the presence of portal hypertension as a result of biliary cirrhosis. Accurate diagnosis of cholangiocarcinoma is difficult, however, because small tumors often appear as abscesses or escape detection altogether, even on high-quality helical CT scans. Park and colleagues (2006) reported several factors that were significantly associated with cholangiocarcinoma in patients with hepatolithiasis: 1) presence of periductal soft-tissue density, 2) higher enhancement of the duct than adjacent bile duct on portal venous phase images, 3) ductal thickening, 4) portal vein obliteration, and 5) lymph node enlargement.

Magnetic resonance imaging (MRI), especially MR cholangiopancreatography (MRCP), is useful for the defining stone location, obstructed intrahepatic segmental ducts, and bile duct anatomy (Kim et al, 2002; Park et al, 2004). In some cases, the bile duct diameter can be calculated for evaluation of bile duct dilation and stricture (Nimura et al, 2005).

If these modalities show intrahepatic stones only in the left lobe, no more imaging investigations for deciding the surgical intervention may be necessary. If stones are located in the right liver or are bilateral, however, percutaneous transhepatic biliary drainage (PTBD) followed by percutaneous transhepatic cholangioscopy (PTCS) should be done to determine the optimal treatment (Nimura et al, 1981, 1988). US, CT, and MRCP

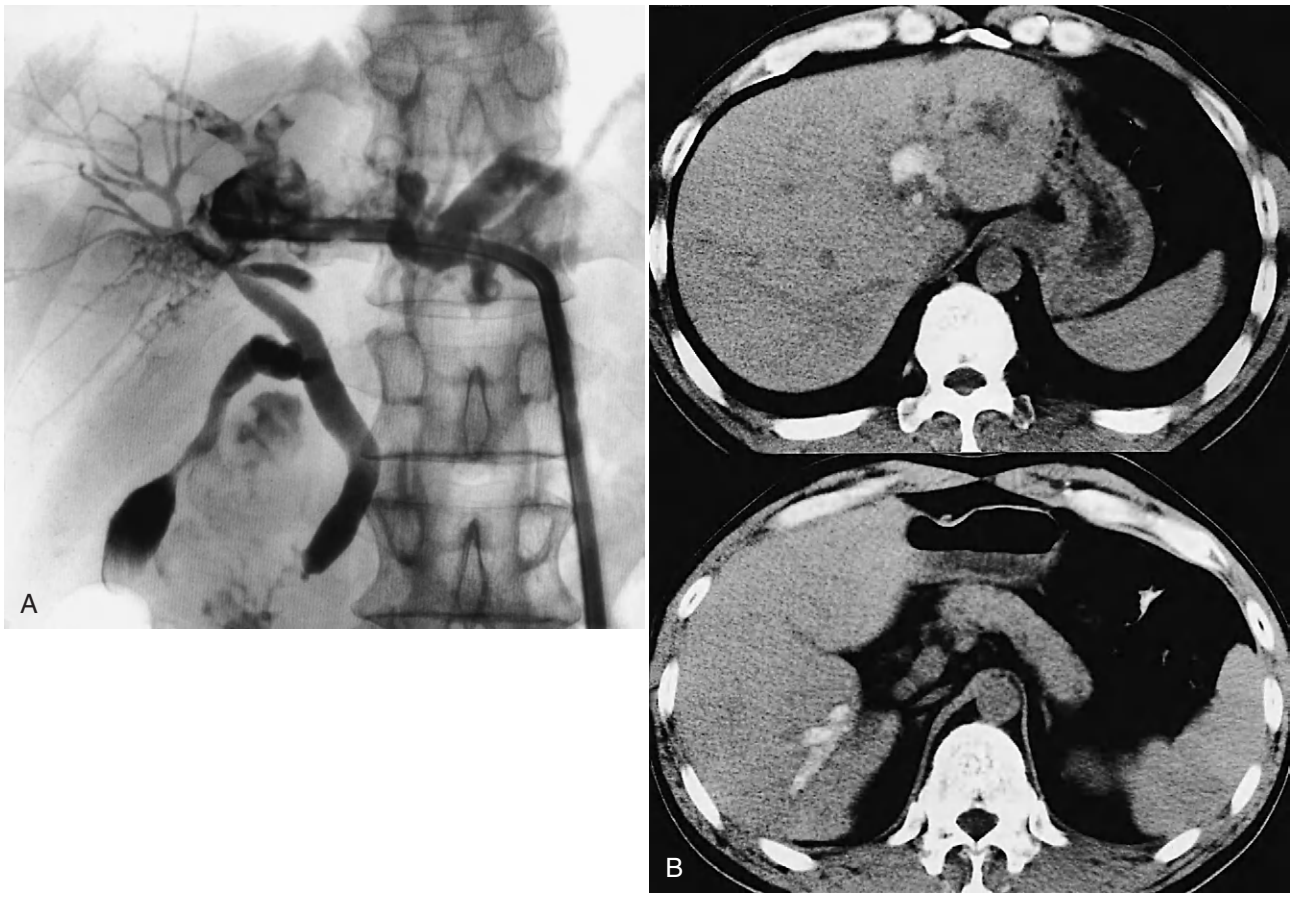


FIGURE 39.4. Intrahepatic calcium bilirubinate stones. **A,** Cholangiography through a percutaneous transhepatic biliary drainage catheter shows multiple filling defects in the dilated intrahepatic bile ducts. **B,** Precontrast computed tomography shows high-density shadows in the left lobe and right posterior sector.

provide less precise information about segmental and subsegmental anatomy of the intrahepatic bile ducts and strictures than percutaneous transhepatic cholangiography (PTC), tube cholangiograms via PTBD, or selective cholangiography by PTCS. Endoscopic retrograde cholangiopancreatography (ERCP) frequently misdiagnoses intrahepatic stones, because intrahepatic bile ducts peripheral to stones and strictures are often poorly visualized. ERCP has the other associated disadvantage of potentially causing cholangitis in patients with multiple intrahepatic stones.

With the aid of US, dilatated intrahepatic radicles can be accurately punctured and visualized by PTC, although this

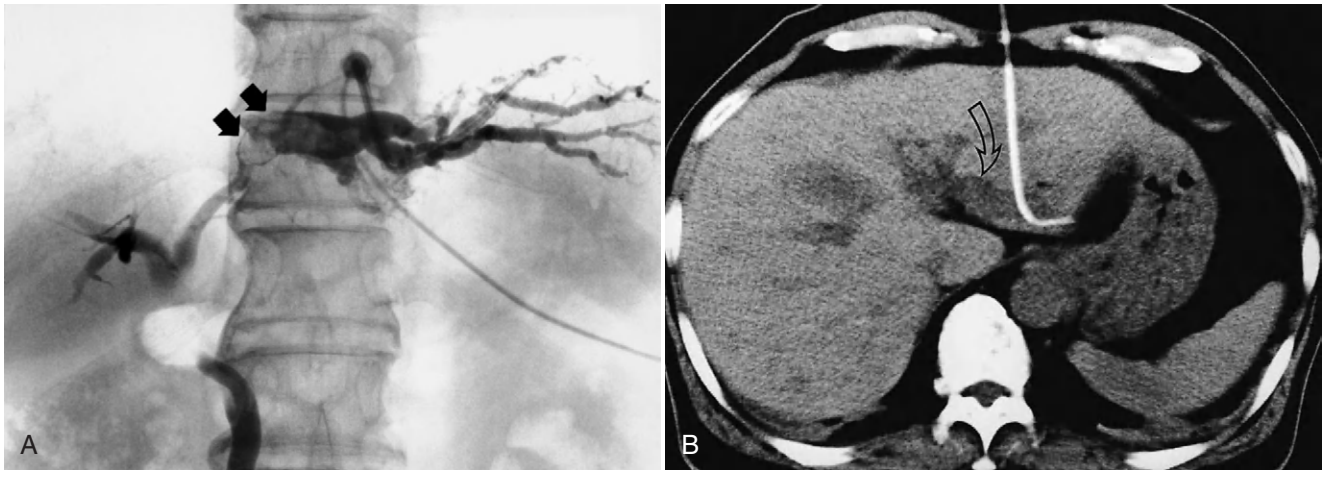


FIGURE 39.5. Intrahepatic cholesterol stones. **A,** Cholangiography through a percutaneous transhepatic biliary drainage catheter shows filling defects (*arrows*) in the dilated intrahepatic bile ducts of the left lateral posterior segment (S2). **B,** Precontrast computed tomography shows low-density shadows (*arrow*) in S2.

does not always provide sufficient biliary information, owing to impacted stones, mud, or mucin in the intrahepatic ducts. Tube cholangiography via PTBD and selective cholangiography by PTCS are more informative than PTC, because the images are obtained after biliary drainage, which decompresses the biliary tree and decreases mud or mucin around the stones thereby improving visualization. Because cholangiograms can be taken from various projections, such as right/left anterior oblique or right/left lateral positions, for defining the segmental anatomy of the intrahepatic biliary tree, PTCS makes it possible to obtain clear, selective cholangiograms before and after removal of impacted stones.

Patients with calcium bilirubinate stones seem to have more frequent biliary strictures with proximal biliary dilation on cholangiogram than patients with other types of stones, although some are false findings that disappear on cholangiograms after cholangioscopic lithotomy. A thin flow of contrast medium through the narrow space between stones and the bile duct wall may appear as a false stricture on cholangiography, but a true biliary stricture should be definitely diagnosed as a localized and unchanging diminution of the bile duct caliber. Whether biliary strictures with proximal biliary dilation cause stone formation or result from stones and repeated infections is an open question.

Making the diagnosis of associated cholangiocarcinoma is difficult, because intrahepatic stones and strictures hinder clear visualization of the intrahepatic ducts in their entirety on cholangiography. As diagnostic clues, the importance of persistent filling defects and obliteration of the involved intrahepatic ducts on cholangiography, mucobilia and mucosal changes on cholangioscopy, and gross appearance are emphasized (Chen et al, 1993).

TREATMENT

For patients with acute obstructive suppurative cholangitis, emergency PTBD is indicated and is preferable to operative and endoscopic transpapillary approaches, and local anesthesia for PTBD can alleviate much of the risk to such critically ill patients. Emergency exploration does not allow a definitive treatment and may not provide adequate biliary decompression (Cheung et al, 2005). An endoscopic transpapillary approach is an effective and safer treatment for distal bile duct stones (Cotton et al, 1998), but further studies are required to clarify the therapeutic benefit of this approach.

With the refinement of fiberoptic cholangioscopes and the development of percutaneous transhepatic approaches to the bile ducts, PTCS has allowed nonsurgical removal of intrahepatic stones (Nimura et al, 1981, 1988). The size of extractable stones is limited, however, by the caliber of the PTBD sinus tract. The presence of a biliary stricture in association with intrahepatic stones often makes stone extraction more difficult. To overcome this, laser cholangioscopy has been applied for intrahepatic stones with some success (Hayakawa et al, 1981), and electrohydraulic lithotripsy during cholangioscopy has facilitated extraction of larger stones (Matsumoto et al, 1987). Electrohydraulic lithotripsy is a unique method to disintegrate stones by means of shock waves generated by an electric discharge in a liquid medium. Under cholangioscopic control, the lithotriptor probe can be kept in contact with stones during application of discharge sparks to avoid any damage to the bile duct wall.

Hepatic resection may remove not only the stones and the strictures that led to their formation but also the consequences of repeated injury, such as cholangiocarcinoma. In general, hepatectomy is indicated when a sector or a lobe of the liver is grossly atrophic (Fan et al, 1993; Otani et al, 1999). In addition to atrophic liver, indications for hepatectomy include multiple intrahepatic strictures and cystic dilation of the peripheral intrahepatic bile duct that cannot be managed by endoscopic or radiologic intervention, particularly if the left lobe or the left liver is involved. The surgical mortality rate associated with hepatic resection in this setting is low, but morbidity rates are substantial. When PTCS shows biliary strictures involving the right or left hepatic duct or the biliary confluence, and the liver parenchyma is relatively normal, an end-to-side hepaticojejunostomy (Roux-en-Y) is performed based on the location and level of stricture. Hepatic resection with hepaticojejunostomy may be indicated when PTCS reveals a biliary stricture at the hepatic confluence in a patient with bilateral intrahepatic stones. If the function of the sphincter of Oddi deteriorates, hepaticojejunostomy is mandated.

With advances in interventional radiologic management of residual or recurrent intrahepatic stones with biliary strictures, percutaneous dilation therapy has become the initial treatment of choice for difficult biliary strictures. A wide array of devices, including balloon catheters and metallic stents, are available for possible use in dilation therapy. The clinical value of percutaneous transhepatic placement of metallic stents for benign biliary strictures must be critically evaluated, because clogging, recurrence of intrahepatic stones, and local effect of the material on the bile duct wall often greatly complicate subsequent treatment.

For patients with difficult bilateral intrahepatic stones with bilateral biliary strictures, a stepwise approach is advocated (Nimura, 1984):

1. PTBD through B3 or the left hepatic duct is performed via a direct anterior approach, which has several advantages in the management of right intrahepatic stones. The most advantageous point is easy accessibility of a cholangioscope to the right intrahepatic ducts, especially to the right posterior sectoral ducts, which are much more difficult to access via intraoperative cholangioscopy or postoperative cholangioscopy through a T-tube sinus tract or jejunal loop.
2. The PTBD sinus tract is dilated step by step. One week after the PTBD, the 6-Fr drainage catheter is replaced by a 10- or 11-Fr (PTCS) catheter (Fig. 39.6). The tract is dilated by exchanging the catheter for a larger one a few times a week, until a 16-Fr catheter can be introduced approximately 2 weeks after the initial PTBD. During this period, CT and US reveal pathologic changes of the liver. A hepatectomy is indicated in cases of unilateral atrophy of the liver as discussed earlier.
3. Cholangioscopic lithotomy is performed mainly in the hepatic sectors or lobes that will be preserved. If intrahepatic bile duct stenosis hinders the cholangioscopic lithotomy, the ducts should be dilated by introducing a 12- or 15-Fr PTCS catheter. Advances in lithotripsy technology make it possible to remove impacted stones without difficulty, and lithotripsy is warranted if the affected sectors or lobes are not atrophic. PTCS allows definition of biliary stenosis before surgical treatment. In the case of biliary stenosis at the hepatic hilus,

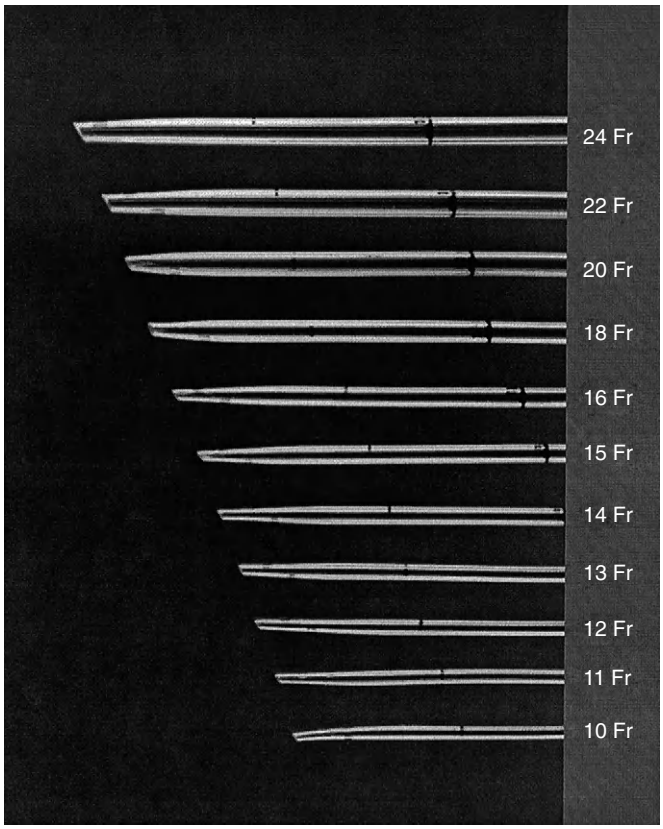


FIGURE 39.6. Percutaneous transhepatic cholangioscopy catheters. Drainage catheters in 11 sizes (10 to 24 Fr) with a tapered tip and two side holes.

hilar bile duct resection with hepaticojejunostomy is indicated (Fig. 39.7).

4. If neither atrophy nor strictures are seen after cholangioscopic lithotomy, surgery is not recommended. Cholecystectomy may be indicated in patients with documented cholelithiasis. In cases of hepatic sectoral or lobar atrophy without biliary stricture at the hepatic hilus, cholecystectomy, hepatectomy, choledochotomy, intraoperative cholangioscopy, and T-tube placement without biliary-enteric anastomosis are recommended (Fig. 39.8). For a patient with some element of atrophy and a stricture at the hepatic duct confluence, hilar bile duct resection with hepaticojejunostomy should be performed in addition to cholecystectomy, hepatectomy, and intraoperative cholangioscopy. If a biliary stricture is defined only at the hepatic duct confluence after endoscopic lithotomy by PTCS, cholecystectomy, hilar bile duct resection, intraoperative cholangioscopy, and hepaticojejunostomy are indicated.
5. In patients subjected to surgical intervention, postoperative cholangioscopy should be performed to assess for and possibly treat residual stones and to evaluate the postoperative changes of the intrahepatic biliary strictures. If the treatment effect is insufficient, biliary stenting with a silicone catheter should be applied.

Regarding treatment of intrahepatic cholesterol stones, it is recommended to select a nonsurgical approach as the first treatment of choice (Fig. 39.9; Kondo et al, 1995). On the contrary, a high incidence (16 of 35 cases) of intrahepatic cholesterol stones was reported from a European institution, and

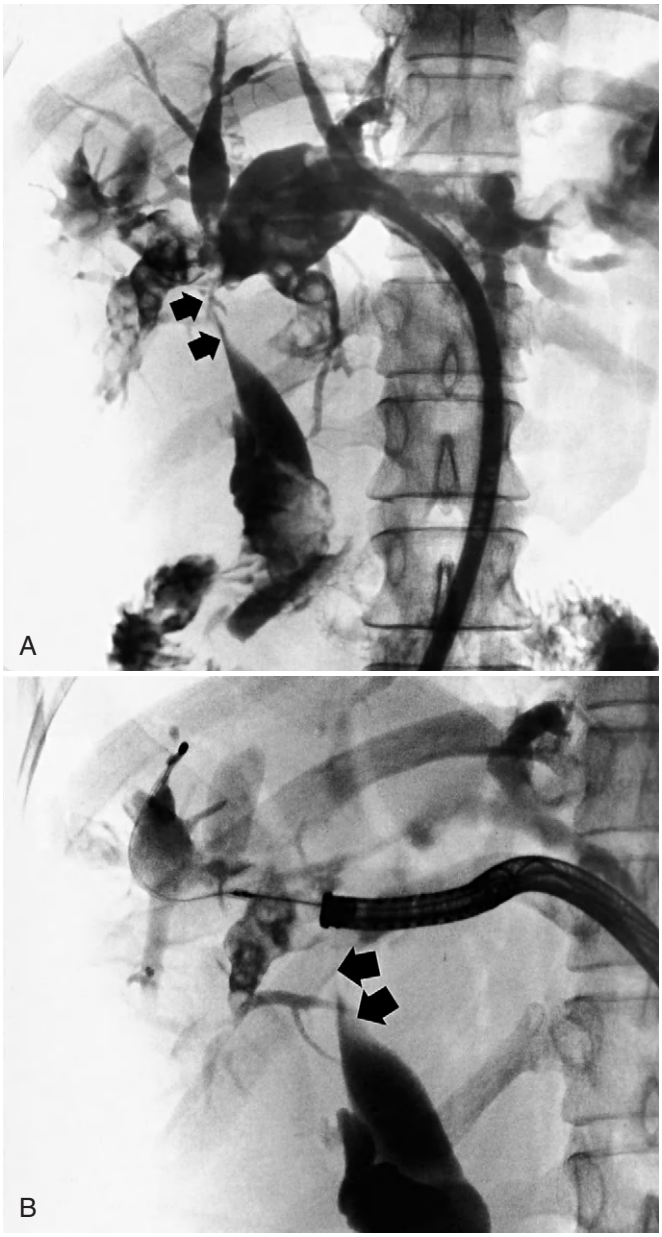
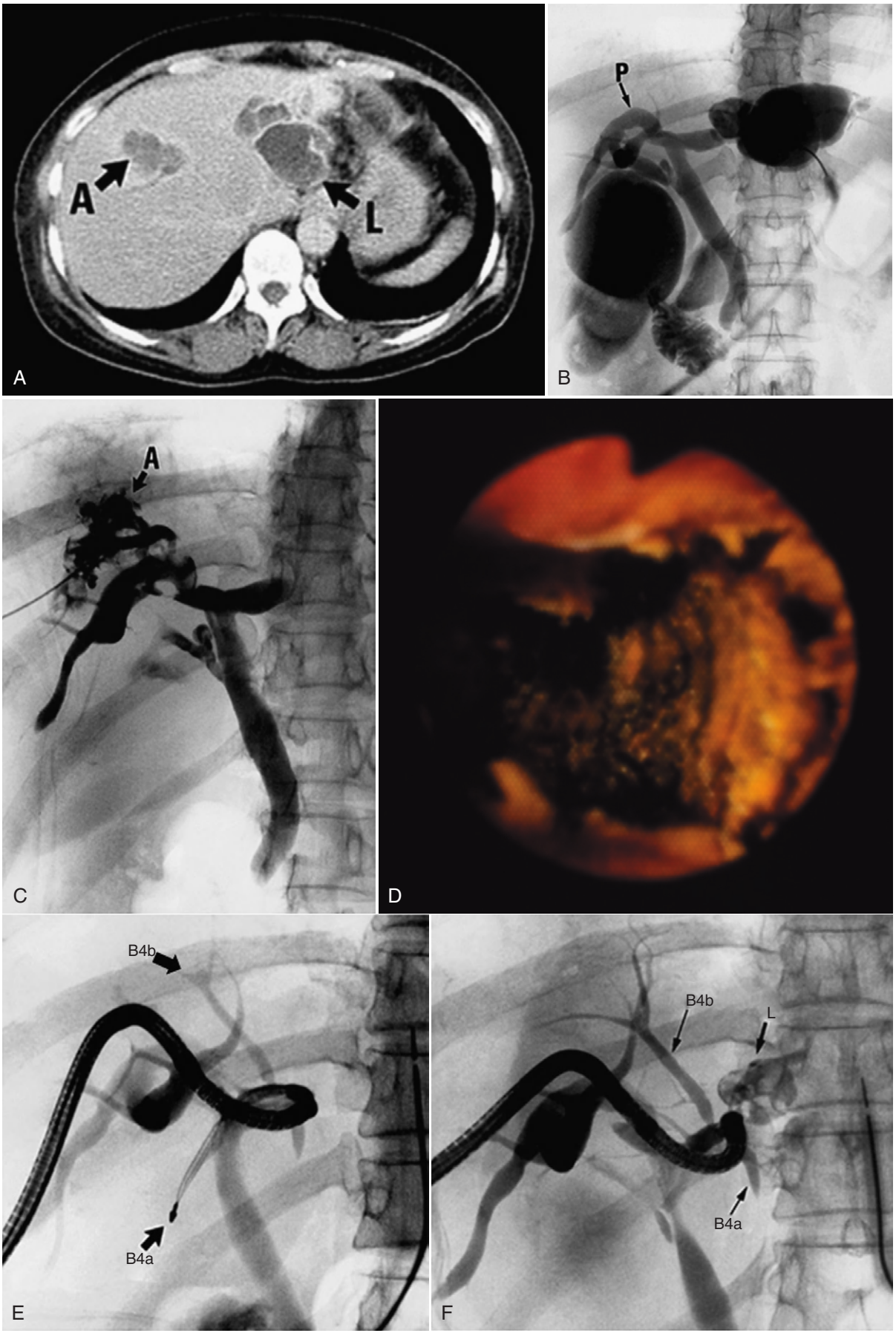


FIGURE 39.7. Bilateral intrahepatic stones with biliary stenosis at the hepatic hilus. **A,** Cholangiogram through a percutaneous transhepatic cholangioscopy (PTCS) catheter revealed severe biliary stenosis at the hepatic hilus (*arrows*). The patient had undergone biliary operations twice without any clinical improvement: first, a choledochoduodenostomy, then a choledochotomy with T-tube drainage. **B,** Cholangiogram during PTCS lithotomy showed marked proximal bile duct stenosis (*arrows*) aremaining after removing most stones in the liver, an indication for hilar bile duct resection with hepaticojejunostomy.

partial hepatectomy is recommended as a safe and effective procedure (Nuzzo et al, 2008). An ERCP approach does not seem feasible because of the generally inaccessible location of the intrahepatic stones. Extracorporeal shock-wave lithotripsy may be effective, especially in combination with dissolution therapy (Okugawa et al, 2002; Staritz et al, 1990). Improvement in bile composition has been reported after oral dissolution therapy in patients with intrahepatic cholesterol stones,


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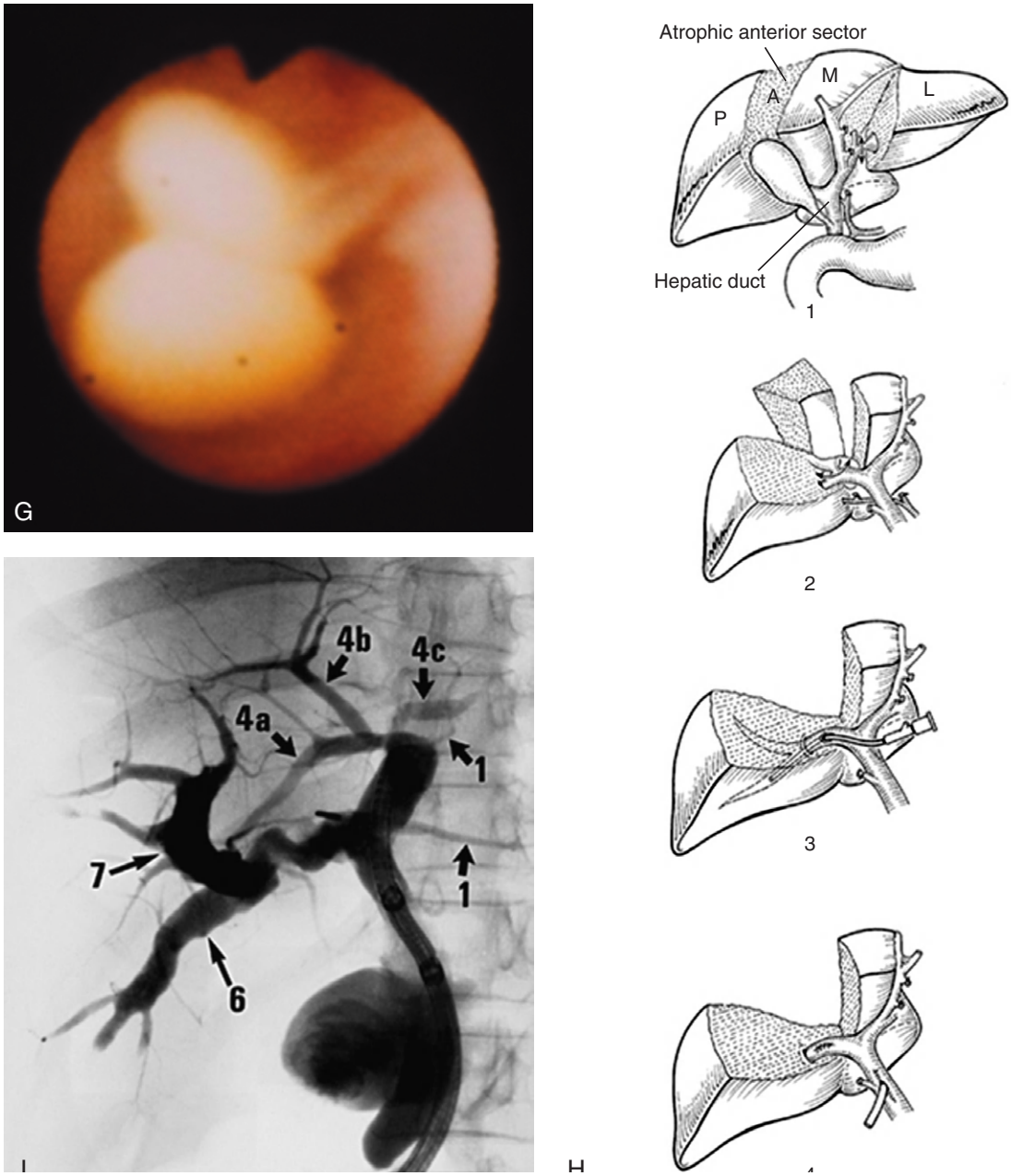


FIGURE 39.8. A case of bilateral intrahepatic stones. **A,** Computed tomography showed two low-density lesions in the left lobe (*L*) and the right anterior sector (*A*) where ultrasound (US) had revealed stones. These two parts of the liver seemed to be atrophic. **B,** US-guided percutaneous transhepatic cholangiography (PTC) revealed the dilated intrahepatic bile ducts of the left lobe. The right posterior sectoral duct (*P*) is shown, but the right anterior sectoral duct is not visualized. **C,** Selective PTC of the right anterior sectoral duct (*A*) was done under US guidance. The right anterior sectoral duct was irregularly dilated and filled with many stones, which made it difficult to make a definite diagnosis of the pathology of the right anterior sectoral duct. Post hoc, percutaneous transhepatic biliary drainage was performed into the right anterior sectoral duct to allow a precise diagnosis. **D,** Cholangioscopic lithotomy was carried out, and an impacted calcium bilirubinate stone was found at the confluence of the right anterior and posterior sectoral ducts and removed. **E,** A cholangioscope was introduced into the left hepatic duct through the right anterior sectoral duct, and selective cholangiograms of the left medial segment (*4a, 4b*) were obtained; that segment was free of hepatolithiasis. After cholangioscopic lithotomy, it became possible to introduce the cholangioscope into the right and left hepatic ducts. **F,** Selective cholangiography of the left lateral segmental ducts (*L*) showed a severe stricture and round shadow defects in the dilated left lateral segmental ducts. **G,** Cholangioscopy revealed whitish cholesterol stones in the dilated left lateral segmental duct. **H,** Scheme of the operation. *1*, A left lobectomy. The dilated left lateral segmental duct is resected proximal to the confluence of the left medial segmental (quadrate) duct. *P,* Right posterior sector; *M,* left medial segment (quadrate); *A*, right anterior sector; *L*, left lobe; *C*, caudate lobe. *2*, A right anterior sectorectomy. The dilated right anterior sectoral ducts are resected at the confluence of the right posterior sectoral duct. *3*, Intraoperative cholangioscopy was performed through the opening of the right posterior sectoral duct. *4*, A T-tube was placed through a choledochotomy. **I,** Postoperative cholangioscopic cholangiography showed no residual stones. The subsegmental bile ducts of the left medial segment (*4a, 4b, 4c*), the right posterior segments (*6, 7*), and the caudate lobe (*I*) were preserved as proposed preoperatively.

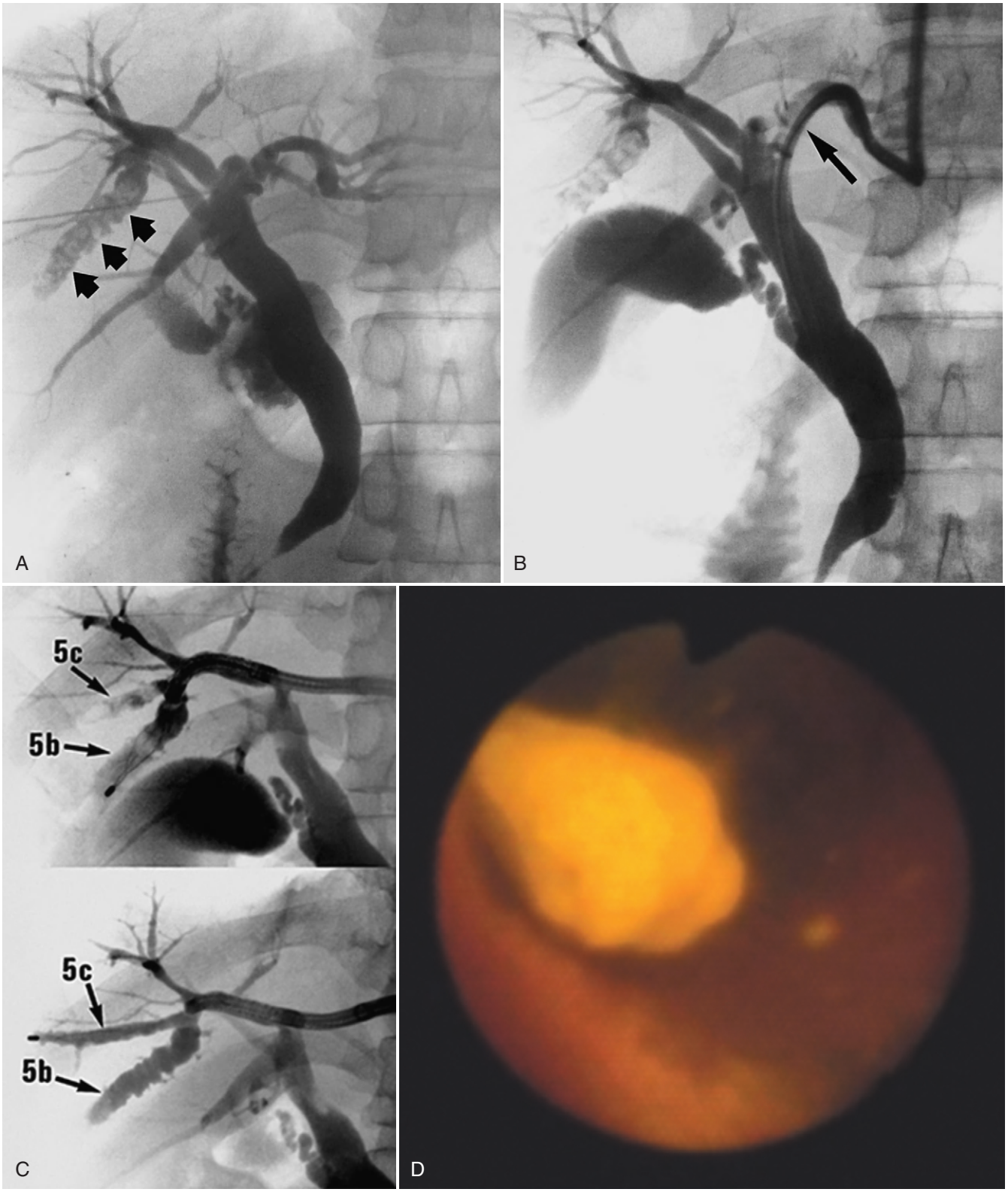


FIGURE 39.9. Intrahepatic cholesterol stones. **A,** Percutaneous transhepatic cholangiography disclosed stones (*arrows*) in the bile duct of segment 5. Note the cylindrical dilation of the stone-bearing duct. **B,** Percutaneous transhepatic biliary drainage of the left hepatic duct (*arrow*) was performed using a direct anterior approach. **C,** Percutaneous transhepatic cholangioscopy (PTCS) revealed intrahepatic stones to be cholesterol stones located only in the subsegmental ducts (5b, 5c) of segment 5. Cholangioscopic lithotomy was done easily with a basket catheter in the absence of biliary stenosis. **D,** Cholangioscopic view of a cholesterol stone.

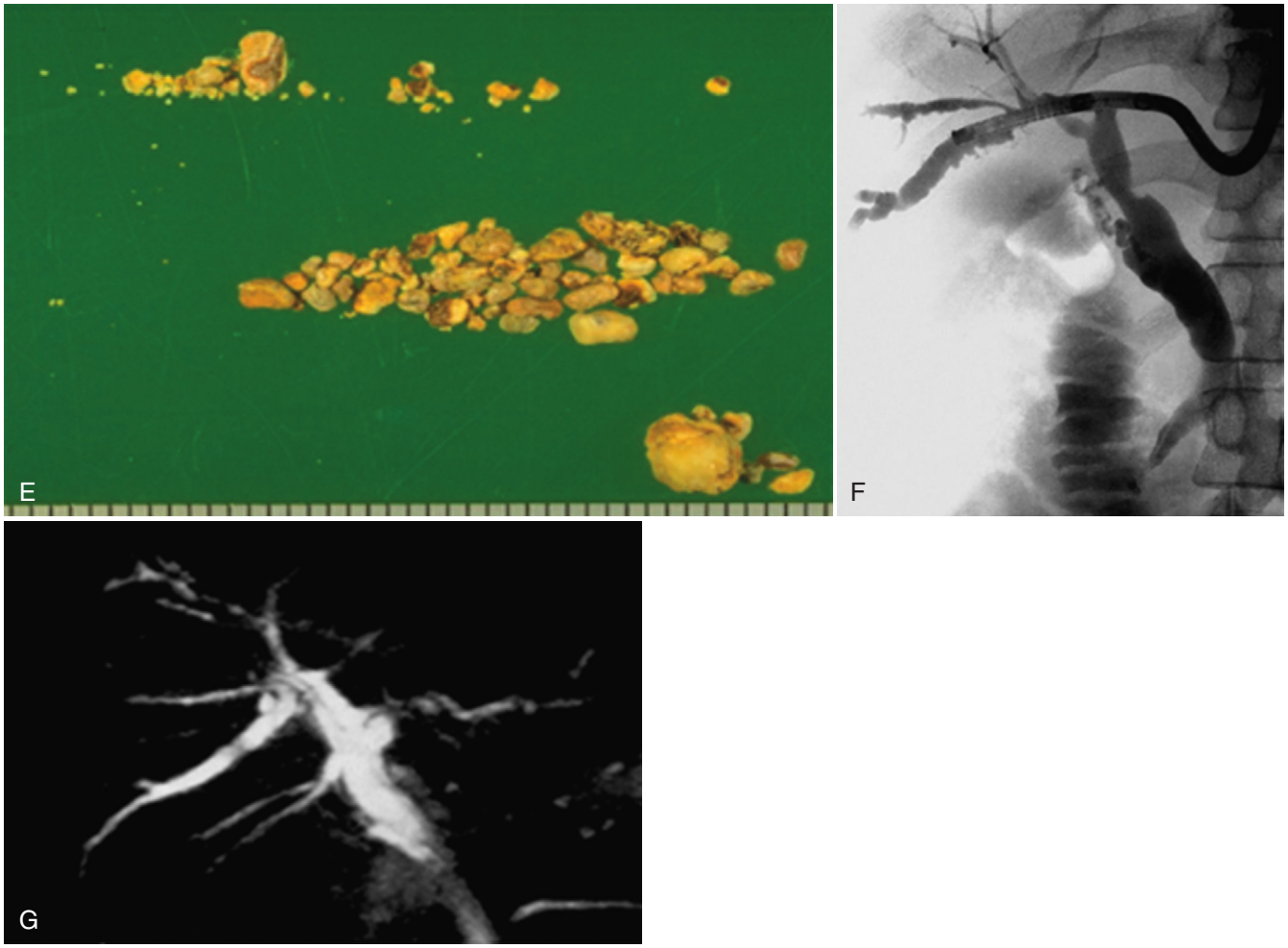


FIGURE 39.9, cont'd. **E,** All stones were removed from bile ducts of 5b and 5c in three sessions of PTCS. **F,** Selective cholangiography shows no residual stones in the subsegmental ducts of segment 5. After cholangioscopic lithotomy, the patient underwent cholecystectomy, which disclosed no stones in the gallbladder with mild cholesterosis. **G,** Magnetic resonance cholangiopancreatography (MRCP) done 17 years after the treatment showed no recurrent intrahepatic stones.

suggesting that this therapy is probably useful as a preventive adjunct (Schillio et al, 1992; Strichartz et al, 1991).

The indications for intervention in asymptomatic patients with intrahepatic stones are controversial. In a patient who has mostly cholesterol stones, treatment may not be indicated. On the contrary, if associated ICC is suspected, further evaluation and consideration for hepatectomy are mandatory. In Kami-Goto Islands of western Japan, a screening survey for intrahepatic stones was performed by US because of the high incidence of ICC in this population. This survey identified 122 asymptomatic patients with intrahepatic stones who had been followed for an average of 10 years (Furukawa et al, 1998). In this group, only 14 (11.5%) of the 122 patients had symptoms develop, and 13 of these (92.9%) had liver atrophy, whereas the incidence of liver atrophy was significantly lower (13%) in patients with no symptoms. Based on these data and other cancer-related investigations (Mori, 2008b; Tsuyuguchi, 2008), no treatment is necessary or recommended for asymptomatic patients without sectoral or lobar atrophy.

PROGNOSIS

Intrahepatic stone disease carries a high rate of recurrence. Of all cases treated in Japan in the years 1989 through 1992, the overall recurrence rate was 6.6% (119 of 1815 cases; Tanimura et al, 1994). The recurrence rate according to treatment was as follows: 5.3% (38 of 719) for hepatic resection, 8.3% (21 of 254) for choledochojejunostomy, 6.4% (40 of 624) for choledochotomy followed by cholangioscopic lithotomy, and 9.6% (20 of 208) for PTCS. The lowest reported recurrence rate is 3.1% (3 of 96) at a mean follow-up period of 26 months in patients treated in Hong Kong (Liu et al, 1998). The highest reported recurrence rate is 32.6% (43 of 132) in patients undergoing lithotomy by PTCS for a mean follow-up period of 5 years in a report from Taiwan (Yeh et al, 1995). In 2008, a nationwide survey was performed in Japan. Despite recent progress in diagnosis and treatment for hepatolithiasis, the recurrence rate was still 18.6%, and cholangiocarcinoma with hepatolithiasis was found in 5.9% of the cases (Mori, 2008a). Another report from Korea showed that 11 (5%) of 225 patients

with intrahepatic stones developed cholangiocarcinoma at 10.7 years (range, 6.6 to 19.7 years) after initial treatment of stones. The 11 cholangiocarcinoma patients consisted of six (4%) of 159 patients with complete stone removal and five (8%) of 66 patients with residual stones after treatment (Cheon et al, 2009).

The survival rate after resection of ICC associated with hepatolithiasis is quite low, primarily because most patients have advanced disease at the time of diagnosis and operation, and postoperative survival rates in 55 Taiwanese patients at 1, 2, and 4 years were 30%, 12.7%, and 3.6%, respectively (Chen et al, 1993). In Japan, 48% of patients with cholangiocarcinoma associated with hepatolithiasis died within one year of operation (Tanimura et al, 1994).

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CHAPTER 40

Biliary atresia

Mark Davenport

OVERVIEW

Biliary atresia (BA) remains a somewhat elusive disease, with our understanding confined as it is to its infancy but yet with the origin of BA essentially unknown. BA is potentially fatal, certainly if left to run its natural course (Hartley et al, 2009), but it can be treated effectively with expeditious surgery in a high proportion of patients. For the remainder, liver transplantation is an option, and indeed BA remains the single most common indication for liver transplant in the pediatric population.

BA is an *occlusive panductular cholangiopathy* affecting both intrahepatic and extrahepatic bile ducts. The most common classification divides BA into three types based on the most proximal level of occlusion of the extrahepatic biliary tree (Fig. 40.1). In types 1 and 2, in which there is a degree of preservation of structure of the intrahepatic bile ducts, blunting, irregularity, and pruning occurs, and dilation may be absent, even when the duct is obstructed. In the most common type of BA, type 3, the intrahepatic bile ducts are grossly abnormal with myriad small ductules coalescing at the porta hepatis. When retrograde cholangiography is possible, this is seen as a "cloud." In approximately 5% of cases, extrahepatic formation of cysts containing clear mucus or bile can occur in the otherwise occluded biliary tree. Such cystic biliary atresia (Caponcelli et al, 2008) is distinguishable clinically and histologically from simple obstruction in a cystic choledochal malformation, where there is preservation of an epithelial lining and retention of a normal and often dilated intrahepatic biliary tree.

ETIOLOGIC HETEROGENEITY

BA is not one disease, certainly not one with a single cause. In all probability it is a phenotype resulting from a number of different etiologies. Three groups can be defined clinically: 1) biliary atresia splenic malformation (BASM) syndrome (Davenport et al, 1993, 2008), 2) cystic BA (Caponcelli et al, 2008), and 3) isolated BA (Table 40.1).

Other related entities are fewer in number, but there seems to be a relationship with other gastrointestinal anomalies, such as esophageal atresia and jejunal atresia, in a small proportion (<1% of large series); occasional cases show a defined chromosomal abnormality, such as "cat-eye" syndrome and chromosome 22 aneuploidy (Allotey et al, 2008).

Developmental biliary atresia is a term we use that includes BASM and cystic BA, for which the onset is almost certainly prenatal and is evident by the time of birth (Livesey et al, 2009). The onset of occlusion in isolated BA is much more contentious, and some authorities hold that the bile duct can be normal and patent at the time of birth and can then become occluded secondarily by virally mediated damage.

Biliary Atresia Splenic Malformation Syndrome

Although the association of BA with polysplenia had been recognized for some time, clarification of what constitutes BASM (Table 40.2) is only relatively recent (Davenport et al, 1993). The constellation of other anomalies is peculiar, and the reasons for this are still obscure. The common embryologic insult may simply be timing (30 to 35 days) rather than a specific genetic defect. Key genes are important in both bile duct development (*JAG1, HNF-6* [*ONECUT1*]; Kohsaka et al, 2002) and visceral and somatic symmetry (*INVS, CFC1;* Bamford et al, 2000; Shimadera et al, 2007), although correlation with the human condition is patchy. A possible genetic link has recently been reported by a French group, who found an increased frequency of mutations in the *CFC1* gene (on chromosome 2) compared with controls (Davit-Spraul et al, 2008).

A maternal diabetic milieu seems to predispose to BASM in the same way that it can cause transposition of the great vessels and sacral agenesis, although these are not part of the usual spectrum of defects. The macroscopic appearance of the biliary tree and liver is also somewhat different from that of isolated BA, with frequent absence of the common bile duct and a miniscule gallbladder and small proximal remnant. The liver is also usually symmetric, whatever the abdominal situs.

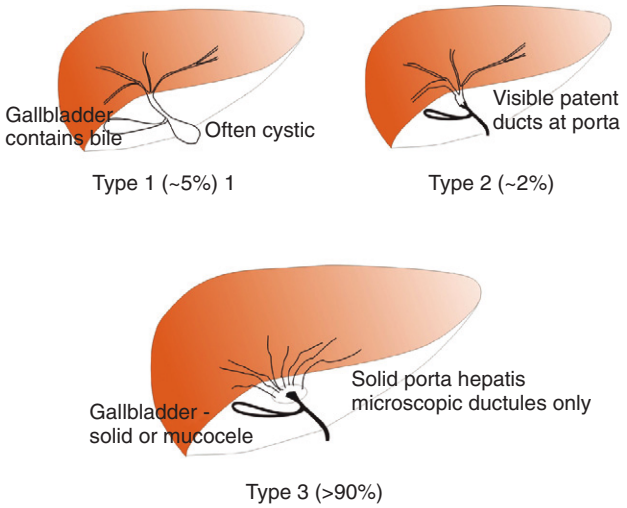


FIGURE 40.1. Classification of extrahepatic morphology in biliary atresia.

Epidemiology

A clear difference in incidence is seen across the globe. The highest is reported in Taiwan, at one in 5000 live births (Hsiao et al, 2008). In Japan, the incidence is one in 10,000 (Nio et al, 2003), with national studies from the United Kingdom and France reporting an incidence of one in 17,000 and 19,000, respectively (Chardot et al, 1999; Livesey et al, 2009; Serinet et al, 2006). Although there are no national studies in North America, smaller regional studies suggest an incidence closer to that of Europe (Yoon et al, 1997) but with some interracial variation (The et al, 2007). Significant regional differences within the United Kingdom have also been observed, again ascribed to variations in racial origin and the nature of the BA. For example, developmental BA is more common in white infants than in those of Asian origin (Livesey et al, 2009).

A distinct female predominance in seen in those with developmental BA that is not seen in the isolated BA group for unknown reasons (Davenport et al, 1993, 2006; Livesey et al, 2009). A seasonal variation in incidence has also been observed in some regionally based studies (Yoon et al, 1997; The et al, 2007), although this has not been confirmed in the larger, national studies (Chardot et al, 1999; Livesey et al, 2009).

Table 40.1

Etiologic Heterogeneity in Biliary Atresia

1. Biliary atresia splenic malformation syndrome
   - **a.** First-trimester onset
   - **b.** Other anomalies, including polysplenia, asplenia, situs inversus, preduodenal portal vein, and others
2. Cystic biliary atresia
   - **a.** First- or second-trimester onset
   - **b.** May be detected on antenatal ultrasound
   - **c.** Usually isolated
3. Isolated biliary atresia
   - **a.** Onset unclear (no clinical evidence) but possibly perinatal
   - **b.** *May* have underlying viral etiology
     - **i.** Direct, such as cytomegalovirus
     - **ii.** Indirect, such as an alloimmune attack following a viral "trigger"

Table 40.2

Spectrum of Anomalies in Biliary Atresia Splenic Malformation Syndrome

Organ System	Malformation	Notes
Splenic	Polysplenia, double spleen (95%); asplenia (5%)	No evidence of immune hypofunction
Situs determination	Inversus (50%)	
Venous	Preduodenal portal vein (40%), portosystemic shunt (<2%); vena cava absence (50%)	
Intestinal development	Malrotation (60%)	
Cardiac	Atrial septal defect, ventricular septal defect, tetralogy of Fallot, etc. (~40%)	± Dextrocardia
Liver	Mirror image, normal, or symmetrical	Position dictated by abdominal situs
Biliary appearance	Atrophic or absent gallbladder	Often noninflammatory remnants with absence of common bile duct and obvious segmental appearance
Pancreas	Annular (<5%)	
Miscellaneous	Immotile cilia syndrome, sacral agenesis	

Pathophysiology

The macroscopic appearance of the extrahepatic biliary tree ranges from being inflamed and hypertrophic yet intact to being an atrophic negligible remnant with absent parts. The histologic appearance within the liver appears more consistent with early portal tract inflammation, a mononuclear cell infiltrate, bile duct plugging, and proliferation and fibrosis giving way to overt biliary cirrhosis from about 3 months on.

The nature of the mononuclear infiltrate has assumed a degree of importance, and many authors suggest this is the specific primary destructive element of BA (Davenport et al, 2001; Mack et al, 2007). Although not necessarily uniformly applied across the spectrum of BA, the infiltrate is largely composed of CD4+ T lymphocytes, specifically Th1 (Mack et al, 2004) and CD56+ natural killer (NK) cells (Davenport et al, 2001; Shivakumar et al, 2009), which exhibit markers for proliferation (CD71+) and activation (particularly LFA-1+ but also CD25+). Infiltrating CD8+ cells appear to lack markers of activation—such as perforin, granzyme B, and Fas ligand (Ahmed et al, 2001)—in contrast to other diseases such as primary biliary cirrhosis (see Chapter 9).

Expression of cell adhesion molecules, proteins involved in cell-cell binding, is an important precursor to an immune-active cell infiltrate. Both interstitial cell adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 are important in binding circulating leukocytes by interaction with cell-surface

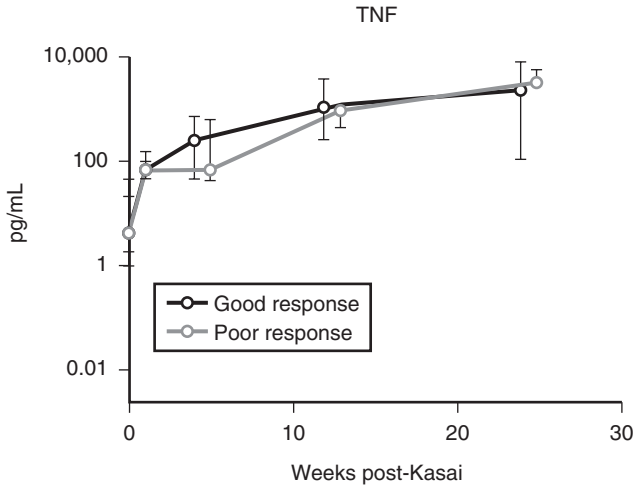


FIGURE 40.2. Postoperative plasma tumor necrosis factor (*TNF*)-α levels in biliary atresia (n = 21), showing progressive increase whether clearance of jaundice was achieved (good, n = 11) or not (poor, n = 10). *(Modified from Narayanaswamy B, et al, 2007: Serial circulating markers of inflammation in biliary atresia: evolution of the post-operative inflammatory process. Hepatology 46:180-187.)*

integrins, and they are expressed on sinusoidal and biliary epithelium of infants with BA (Dillon et al, 1997; Davenport et al, 2001).

Expression of soluble(s) ICAM-1 and sVCAM-1 in the circulation is also increased (Minnick et al, 1998; Davenport et al, 2005), as is seen in other immunologically mediated liver diseases such as primary biliary cirrhosis and sclerosing cholangitis; levels of sVCAM-1 at the time of presentation have been shown to be prognostic (Davenport et al, 2005). Increasing levels of various other cytokines (interleukin [IL]-2, tumor necrosis factor [TNF]-α, IL-18) can also be shown postoperatively (Fig. 40.2), but most discriminate poorly between patients who would clear their jaundice and those who would not; conversely, some cytokines (IL-2, interferon [IFN]-γ, IL-4, IL-10, TNF-α, and sICAM-1) were better predictors of subsequent need for early transplantation (Narayanaswamy et al, 2007).

Resident (Kupffer cells) or systemic/recruited macrophages and monocytes seem to play a dual role in BA, as both the presenters of antigenic material in the first place and as the initiating driver for fibrosis in the development of chronic liver disease. Tracy and colleagues (1996) first showed increases in resident macrophages (CD68+) with marked expression of the lipopolysaccharide receptor CD14+. Increased levels of both CD68+ cells and circulating markers of CD68+, TNF-α, and IL-18, have been shown to predict outcome post-Kasai (Kobayashi et al, 1997; Narayanaswamy et al, 2007).

Viral Hypothesis of Biliary Atresia

One suggested cause of BA is infection with hepatotropic viruses, such as rotavirus, reovirus, and cytomegalovirus, either as an indirect trigger of an abnormal immune-mediated reaction or as an actual pathologic agent. The evidence is largely based on animal models in which intraperitoneal innoculation on the first day of life is able to mimic postnatal biliary inflammation (Riepenhoff-Talty et al, 1993; Petersen et al, 1998). Subsequent translation into humans has been more problematic. Serologic evidence of viremia is contradictory (Morecki et al, 1982; Tarr et al, 1996), and isolation of both viral RNA and DNA have (Riepenhoff-Talty et al, 1996; Tyler et al, 1998; Fischler et al, 1999) and have not (Brown et al, 1988; Steele et al, 1995; Bobo et al, 1997; Jevon & Dimmick, 1999) been identified by PCR techniques.

The most recent study is one from Hannover, Germany, in which liver biopsies from 74 infants obtained at the time of portoenterostomy were tested for a panel of DNA and RNA hepatotropic viruses (Rauschenfels et al, 2009). One or more viruses was detected in about one third of infants, and the rate of detection increased with infant age, which suggested that observed viral infection was more likely to be a secondary finding rather than a specific cause.

One problem with the viral hypothesis is the lack of an explanation as to why such ubiquitous organisms only damage the biliary tree in such a small fraction of infants and children. It may be that such infants are in some way susceptible to cholangiocyte damage and require a (viral) trigger to set off an immune-mediated destructive process (Mack, 2007).

RNA gene expression studies in rotavirus-induced murine models have shown upregulation of many proinflammatory genes, among them the IFN-γ inducers *IRF7* and *IRF9* (Carvalho et al, 2005). Similar gene-expression profiling in human BA samples has also shown overexpression of immune regulatory genes and differences between isolated and syndromic forms (Bezerra et al, 2002; Zhang et al, 2004).

A number of studies have shown different but specific elements of genetic variation between patients with isolated BA and unaffected control subjects. Thus, susceptibility may be imparted by polymorphisms in a number of relevant genes. Examples of this include vascular endothelial growth factor (*VEGFA*; Lee et al, 2010), macrophage migration inhibitory factor (*MIF*, Arikan et al, 2006), and intercellular adhesion molecules (*ICAM*s; Arikan et al, 2008).

Most recently, maternal microchimerism, a novel mechanism of immune damage, has been suggested based on the observation that male infants with BA have a threefold increase in cells of maternal origin in their livers (Hayashida et al, 2007). These were later shown to be maternal-origin chimeric CD8+T cells and CD45 NK cells capable of initiating immune cholangiolar damage (Muraji et al, 2008).

CLINICAL FEATURES

The cardinal features of BA are conjugated jaundice persisting beyond 14 days of age, pale and unpigmented stools, and dark urine in an otherwise healthy, term neonate. Liver fibrosis and cirrhosis are later developments, even in infants with intrauterine BA evident at birth (Makin et al, 2009); therefore ascites and marked hepatosplenomegaly are rarely seen before 3 months. Fat malabsorption occurs by stealth, and these infants will fall behind in their growth (Livesey et al, 2009). Fat malabsorption can also cause fat-soluble vitamin K deficiency, and some infants (<3%) will be seen with a possibly catastrophic bleeding tendency and a raised international normalized ratio (INR).

A proportion of infants (approximately 5%) will be seen initially with an abnormal antenatal ultrasound (US) scan (Caponcelli et al, 2008). These will be shown to have cystic BA, with the "cyst" evident from at least 20 weeks' gestation. This has no untoward effects during pregnancy but clearly needs thorough investigation postnatally. The differential diagnosis for these

infants, if the cyst is actually recognized as of hepatobiliary origin, is that of a cystic choledochal malformation, better known as a choledochal cyst (Hinds et al, 2004).

Diagnostic Workup

Liver biochemistry will show a conjugated hyperbilirubinemia that is variable but rarely above 250 μmol/L (more than 15 mg/dL), modestly raised transaminases (aspartate aminotransferase, alanine aminotransferase), significantly raised γ-glutamyl transpeptidase (GGT), and usually normal protein and albumin levels. Hemoglobin and white cell counts are normal, although the platelet count may be raised.

The differential diagnosis of medical conditions that cause conjugated jaundice is long, and all can mimic the occluded bile duct of BA. Exclusion of TORCH infections—*Toxoplasma*, cytomegalovirus, hepatitis, and so on—α1-antitrypsin deficiency, Alagille syndrome, and cystic fibrosis should run in parallel with efforts to establish a diagnosis of BA.

US examination is a key part of the workup in order to exclude other possible surgical diagnoses (choledochal malformation, inspissated bile syndrome), and evidence of at least intrahepatic bile duct dilation should be visible (Davenport et al, 2003). Although suggestive and supportive, US is uncommonly diagnostic of BA and typically shows a shrunken, atrophic gallbladder with no evidence of filling between feeds. Some US signs do appear more reliable, such as the "triangular cord sign" (Park et al, 1997). This suggests a sonographic appearance of the proximal solid biliary remnant in front of the bifurcation of the portal vein, and advocates quote accuracy rates of greater than 80% (Humphrey & Stringer, 2007).

Radioisotope hepatobiliary imaging with technetium-labeled iminodiacetic acid derivatives has a role in some centers in showing the need for laparotomy. In BA there will be severe cholestasis and no bile excretion, but this can be seen in many cases of neonatal hepatitis and other medical conditions, depending on the severity of cholestasis. Placement of a nasoduodenal tube and aspiration over 24 hours has been used in many centers, chiefly Asian, as a simple, low-cost diagnostic measure, although this has rarely found favor in Western centers. Percutaneous liver biopsy to assess for histologic features of large-duct obstruction versus those of neonatal hepatitis is safe and well-tolerated but needs an experienced pathologist to interpret.

Direct cholangiography is becoming more prevalent in larger centers with direct access to endoscopic retrograde cholangiopancreatography (ERCP) (Shanmugam et al, 2009; Petersen et al, 2009). It requires a sufficiently small endoscope and a level of familiarity with the procedure, as failure to cannulate the bile duct are features of both BA and an inexperienced operator. Laparoscopy with or without liver biopsy offers an alternative to ERCP, and it may be the prelude to the definitive procedure. Direct puncture of the gallbladder is relatively straightforward to show presence or absence of bile and as an access point for a cholangiogram. This can be coupled with liver biopsy.

SURGERY: KASAI PORTOENTEROSTOMY

Preoperative preparation for a Kasai portoenterostomy includes normalizing the coagulopathy and possibly providing a bowel preparation regimen.* An intravenous perioperative antibiotic regimen active against aerobic and anaerobic bowel flora is standard.

Cholangiogram

The diagnosis is always confirmed initially through a limited right-upper quadrant muscle-cutting incision, allowing access to the gallbladder (does it contain bile?) and a cholangiogram if needed. It should be obvious that a cholangiogram is not always possible, simply because the gallbladder may not have a lumen. Nonetheless, this is in itself presumptive of the diagnosis. To exclude BA, the cholangiogram should demonstrate proximal intrahepatic ducts. This can be difficult, as contrast preferentially fills the distal duct and duodenum. A small, distal vascular or "bulldog" clamp should aid reflux into the more proximal biliary tree if patent.

Mobilization

The liver should be fully mobilized by dividing the falciform, coronary, and triangular ligaments such that the organ can then be everted outside of the abdominal cavity (Fig. 40.3). This allows full exposure of the porta hepatis and facilitates dissection; it also reduces venous return, and an increase in intravenous volume support is always needed, together with close communication between surgeon and anesthesiologist.

Portal Dissection

Initially the gallbladder is mobilized and the distal CBD divided (Fig. 40.4A), with the dissection consisting of elevation of the proximal pyramidal remnant from the right hepatic artery and bifurcation of portal vein (Fig. 40.4B). Small veins to the porta hepatis need division and facilitate downward traction of the portal vein and exposure of the posterior part of the portal plate and caudate lobe. On the left side, the recessus of Rex, where the umbilical vein joins the left portal vein, should be exposed; an isthmus of liver parenchyma from segment III to IV may need division by coagulation diathermy to achieve this. On the right side, remnant biliary tissue can be identified almost circumferentially around the right vascular pedicle. The division into right anterior and posterior pedicles should be visualized, and the posterior pedicle's biliary elements should also

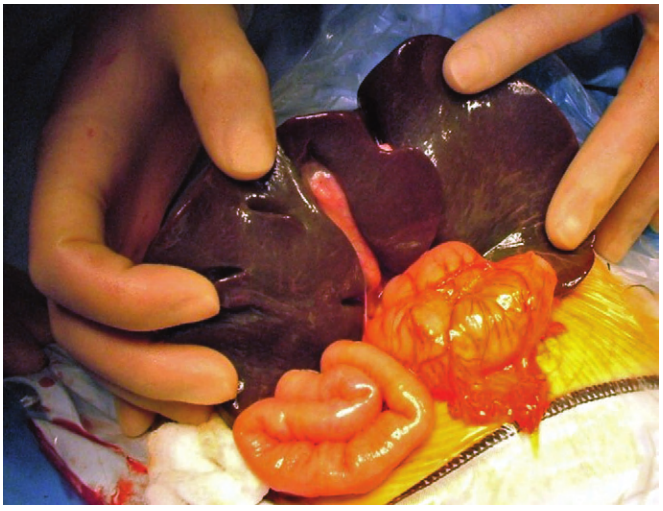


FIGURE 40.3. Operative appearance of liver in biliary atresia. The liver is relatively soft, and the gallbladder is collapsed and contains no bile, which is consistent with a type 3 biliary atresia.

*Morio Kasai (1922-2008), pediatric surgeon from Sendai, Japan, who pioneered radical excision of biliary remnants and subsequent portoenterostomy.

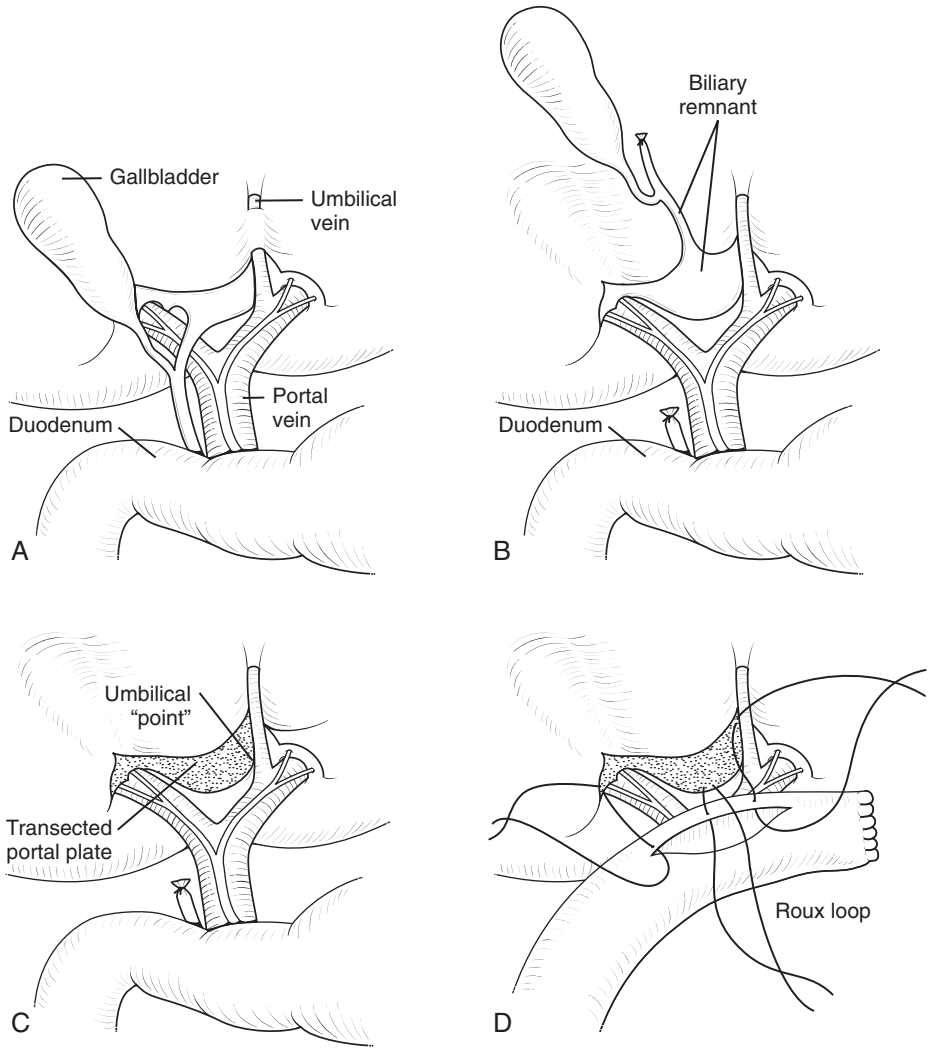


FIGURE 40.4. Schematic illustration of Kasai portoenterostomy. **A,** Mobilization of gallbladder and division of distal common bile duct. **B,** Elevation of biliary remnants and separation from vascular structures at level of porta hepatis (portal vein confluence, right hepatic arterties, and, to a lesser extent, left hepatic arteries). **C,** Transection of portal plate from umbilical "point" to around the division of right-sided (anterior and posterior) portal pedicles. **D,** Portoenterostomy with 40- to 45-cm retrocolic Roux loop.

be incorporated into the subsequent Roux loop. Excision of remnants flush with the liver capsule is accomplished by developing a plane between solid white biliary remnant and the underlying liver (Fig. 40.4C); excising liver parenchyma itself does not seem to improve bile drainage. All the denuded area of the porta hepatis needs to be incorporated into the Roux loop as the portoenterostomy. Some authors (Gittes & Koybayashi, 2007) have suggested a role for frozen section of the portal plate to determine that the observed ductules are large enough. My view is that there should be nothing left to resect from the initial dissection. Burrowing into liver parenchyma itself seems pointless, possibly because subsequent scarring obliterates any exposed ductules.

Roux Loop and Portoenterostomy

A standard retrocolic Roux loop measuring 40 to 45 cm should be constructed (Fig. 40.4D). The jejunojejunostomy should lie about 10 cm from the ligament of Treitz and can be stapled or sutured. The proximal anastomosis must be wide (approximately 2 cm), and as such, an end-to-side tension-free arrangement is preferred. Fine, precise sutures (e.g., 6-0 PDS) at the edge of the portal plate are satisfactory. Remnant ductules are concentrated in the right and left recesses, and it is important that all parts of the transected plate are incorporated.

Aftercare

Nasogastric drainage and intravenous fluids are required for 2 to 4 days postoperatively. Antibiotics, intravenous at first and then oral, are given in our institution for 1 month. All these infants, even those clearing their jaundice, have subnormal quantities of intestinal bile and to ameliorate the effects of fat malabsorption, they should have a formula rich in medium-chain triglycerides. Vitamin supplementation is standard, both enteral and parenteral, and choleretic agents, such as ursodeoxycholic acid, may have some value but only in those patients who have reestablished bile flow. The value of steroids is discussed later.

Table 40.3

International Outcome Statistics in Biliary Atresia (1989–2009)

Study	Country	N	Period	Clearance of Jaundice*	NATIVE LIVER SURVIVAL (%)		OVERALL SURVIVAL (%)	
					4/5 Years	10 Years	4/5 Years	10 Years
Nio et al, 2003	Japan	108	1989	NA	62	53	69	66
		129	1994	NA	53	—	78	—
Davenport et al, 2004a	England and Wales	148	1999-2002	57%	51	—	89	—
Serinet et al, 2006	France	472	1986-1996	NA	40	29	70	68
		271	1997-2002	40%	42	—	87	—
Schneider et al, 2006	United States†	104	1997-2000	~40%	56 at 2 years	—	86 at 2 years	—
Schreiber et al, 2007	Canada	349	1985-1995	NA	35	—	74	—
			1996-2002	NA	39	—	82	—
Wildhaber et al, 2008	Switzerland	48	1994-2004	NA	37	—	92	—
Davenport et al, 2011	England and Wales	424	1999-2009	55%	46	40	90	89

*Defined as achieving a level of <20 mmol/L (1.5 mg/dL)
†Biliary Atresia Research Consortium (nine centers)

POSTOPERATIVE COMPLICATIONS AND OUTCOME

The aims of portoenterostomy are to restore bile flow and reduce bilirubin levels to normal. This is achievable in isolated BA in about 50% to 60% of infants (Davenport et al, 2004a, 2008); and should halt the progression of liver fibrosis. Table 40.3 illustrates current outcome statistics derived from national studies. Our own studies have shown that in a centralized system with experienced surgeons, the clearance of jaundice can be achieved after Kasai portoenterostomy in about 50% to 55% of patients, with translation into a 5- and 10-year native liver survival of approximately 50% and 45%, respectively. Overall survival depends heavily on the access to efficient liver transplant programs and can be approximately 90% at both 5 and 10 years (Davenport et al, 1997, 2004a, 2009). If success is achieved after either portoenterostomy or transplantation, children can grow and develop normally to adulthood with minimal medical support.

The most common complication is that the portoenterostomy does not work, and therefore it will have no effect on restoration of bile flow, and jaundice will worsen and lead to end-stage liver disease. For these infants, transplantation will be required for survival, typically within the first 2 years of life (Schneider et al, 2006; see Chapters 71 and 97A). Such infants have increasingly evident portal hypertension with splenomegaly, ascites, and variceal formation. They fail to thrive and have reduced synthetic liver function with falling levels of serum albumin and increasing evidence of a vitamin K–independent coagulopathy (DeRusso et al, 2007). This is a crucial period within which most deaths occur as a result of biliary atresia, and unfortunately most are already on a transplant waiting list.

Cholangitis

Cholangitis is presumed to occur by bacterial ascent from the Roux loop via patent biliary ductules (see Chapter 43). It is therefore uncommon in those who have no effect from Kasai surgery. Nonetheless, it may occur in 30% to 50% and is most frequent within a year of surgery (Ecoffey et al, 1987). Clinically, cholangitis is characterized by worsening jaundice, fever, and acholic stools. The diagnosis may be confirmed by blood culture or by percutaneous liver biopsy, but it is important to treat suspected cases early with broad-spectrum antibiotics effective against gram-negative organisms (e.g., ceftazidime, amoxycillin, piperacillin). Sometimes recurrent cholangitis may be problematic, which can be associated with intrahepatic cyst formation (Bu et al, 2002), presumably acting as a bacterial nidus. Most patients respond to prolonged antibiotic prophylaxis, either with intravenous broad-spectrum antibiotics via an indwelling vascular access device or with oral nonabsorbable antibiotics (e.g., neomycin). If cholangitis still recurs despite these measures, liver transplantation should be considered.

Sometimes cholangitis occurs some years after the portoenterostomy in children with otherwise good liver function. It is important in these cases to exclude a mechanical Roux loop obstruction, typically at the level of the mesocolon, because corrective surgery for obstruction is relatively simple (Houben et al, 2006). Percutaneous transhepatic cholangiography and radionuclide hepatic imaging may be useful for diagnosis.

Portal Hypertension

Elevated portal venous pressure can be shown in virtually all infants at the time of the Kasai operation (Duché et al, 2006). However, whether it persists or regresses depends on the degree of established fibrosis and, most importantly, the response to surgery (Kang et al, 1993). About 60% of children who survive to 2 years will have endoscopic evidence of esophageal varices, although only approximately half of these will ever bleed. The severity and degree of the varices themselves are not necessarily related to the original degree of liver fibrosis or to the number of episodes of cholangitis (Kang et al, 1993). Endoscopic surveillance of the upper gastrointestinal tract in children with treated biliary atresia has been suggested from about the age of 2 years because of this unpredictability of variceal formation (see Chapter 71).

The age at first hemorrhage is typically approximately 2 to 3 years, and it manifests as sudden hematemesis and melena from rupture of an esophageal varix. Ectopic intestinal variceal bleeding may also occur, usually in an older child with relatively normal liver function. The initial treatment of bleeding varices is supportive, with restoration of blood volume and correction of platelet deficiency and any coagulopathy. Drugs such as octreotide, or more recently terlipressin, may be used be used to reduce portal venous pressure. Banding has become the most efficacious technique to control varices, although it may be limited by patient size (Hall et al, 1988). For infants and small children, endoscopic sclerotherapy is still effective (Stringer et al, 1989), using sclerosants such as ethanolamine or sodium tetradecyl sulfate. Even with various pharmacologic and endoscopic alternatives, sometimes the only means of variceal control is a Sengstaken or equivalent pattern tube. Transjugular intrahepatic portosystemic shunt (TIPS) as a method of acutely reducing portal hypertension is also possible in children with BA, but it should be regarded only as a "bridge" to transplantation (Johnson et al, 1996; Cao et al, 1997), and it is not widely available.

Hepatopulmonary Syndrome and Portopulmonary Hypertension

Hepatopulmonary syndrome (HPS) is characterized by cyanosis, hypoxia, and clubbing and is due to shunting across the pulmonary vascular bed, likely caused by failure to deactivate vasoactive substances, possibly endothelin-1, by the damaged liver (Iqbal et al, 2008). Patients with HPS have higher levels of exhaled nitric oxide, presumably the final link in this chain. It is more commonly seen in those with BASM, suggesting a congenital element (Davenport et al, 2004a), and it can occur even in those who are anicteric. The diagnosis is made by arterial blood gas estimation showing significant hypoxia with no improvements seen on increasing ambient oxygen. Radionuclide lung scans with macroaggregated tagged albumin can be used to quantify the degree of shunting and can range from 4% to 50% (Al-Hussaini et al, 2010).

Portopulmonary hypertension is much less common and may share the same underlying vascular mechanism as HPS. Although it is often silent and perhaps only detected because of cardiomegaly on a chest radiograph, it can be a cause of sudden death and is associated with systolic pulmonary arterial pressures greater than 40 mm Hg. Although no real therapy is available for the pulmonary vascular anomaly, it is a definite indication for liver transplantation and is usually reversible, albeit with an increased risk of complications (Iqbal et al, 2008).

Liver Malignancy

The cirrhotic liver of treated BA is potentially premalignant, and there are several reports (Kohno et al, 1995; Iida et al, 2009; Hol et al, 2008) and a single series of three cases (Tatekawa et al, 2001). This of course may be due simply to the relatively small numbers of long-term survivors, but perhaps it implies only a modest risk. Malignant change may include hepatocellular carcinoma (Hol et al, 2008; Iida et al, 2009; see Chapter 80) or cholangiocarcinoma (Kulkarni & Beatty, 1977; see Chapter 50), but more benign changes, such as focal nodular hyperplasia (Okugawa et al, 2008), may also occur. Although the youngest reported case was diagnosed in a patient 10 months old, but most are seen during later childhood or adolescence as a nodule or mass on routine US screening of the liver. Because of the risk for malignant change, serum α-fetoprotein levels should probably be part of the routine follow-up for such children, although clearly in some, these levels will still be normal.

AREAS OF DEBATE AND CONTROVERSY IN BILIARY ATRESIA

Laparoscopy

The open technique described above requires precision, maximal exposure of the portal plate, and delicate suturing. This can be *approximated* by laparoscopic or robotic means, and small series have been reported (Esteves et al, 2002; Lee et al, 2004; Dutta et al, 2007; Ayuso et al, 2008). However, now that the first wave of enthusiasm has perhaps abated, it appears that the results are not comparable to the open technique (Wong et al, 2008). The only outcomes that matter are clearance of jaundice and preservation of the native liver; other outcomes, such as early feeding and better cosmesis, are irrelevant. In many centers, there is currently a self-imposed moratorium, until the reasons for failure become clearer or techniques improve.

Adjuvant Steroids

The inflammatory nature of BA has been emphasized above, and postoperative steroids seem a logical approach to this. In addition, most steroids have a chloretic action, although actual evidence of effect is scant. A number of small, uncontrolled studies from the United States and Japan suggesting benefit have been published (Meyers et al, 2004; Kobayashi et al, 2005). Our large, randomized, double-blind, placebo-controlled trial starting with 2 mg/kg/day showed a significant early effect at 1 month after operation with a lower bilirubin (Davenport et al, 2007), but this did not translate to a diminished need for transplantation or to a significant difference in the proportion with complete clearance of jaundice. Further studies from Germany using a higher starting dose (10 mg/kg/day) showed no difference, although their overall clearance rates were poor (27% were jaundice free at 2 years; Petersen et al, 2008).

Effect of Age at Surgery

It is axiomatic that once cirrhosis is established, the outcome will be worse. And because cirrhosis takes time to develop, it is logical to think that the earlier the surgery, the better the outcome. However, given that we do not know when biliary obliteration starts in isolated BA, trying to identify a relationship with postnatal age may be difficult. Large, multicenter series with multiple surgeons have been unable to show a statistically significant relationship (Davenport et al, 2004a).

Figure 40.5 illustrates this for isolated BA derived from a single center with only two surgeons, and it uses clearance of jaundice (<20 Umol/L) as a measure of outcome. This shows that there is no discernable difference up to 100 days, and certainly no evidence of any "cutoff." By contrast, Figure 40.6 shows the same analysis for one of the developmental forms, cystic BA, and here a relationship is obvious, with an impaired

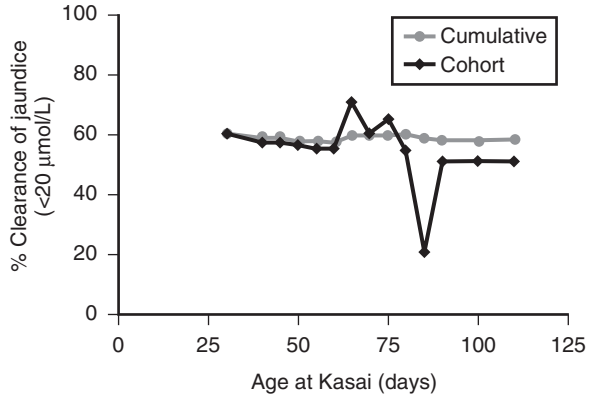


FIGURE 40.5. Relationship of age at surgery to clearance of jaundice in infants with isolated biliary atresia (n = 177). *(Modified from Davenport et al, 2008: Surgical outcome in biliary atresia: etiology affects the influence of age at surgery. Ann Surg 247:694-698.)*

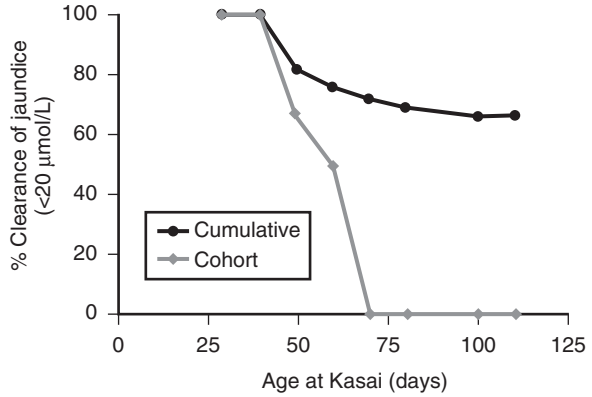


FIGURE 40.6. Relationship of age at surgery to clearance of jaundice in infants with cystic biliary atresia (n = 23). *(Modified from Davenport et al, 2008: Surgical outcome in biliary atresia: etiology affects the influence of age at surgery. Ann Surg 247:694-698.)*

outcome the older the infant is at surgery (Davenport et al, 2008).

Is there any benefit of surgery in those infants who come to surgery after 100 days? By now, this should be relatively infrequent in developed countries, but it still occurs. Such infants are much more likely to have established cirrhosis, and the prognosis is, without doubt, worse. Nevertheless, a Kasai portoenterostomy as the first step may be reasonable and has been associated with long-term jaundice-free survival in our series (Davenport et al, 2004b). The alternative is a primary liver transplant.

Kasai Variations

Although most surgeons operating today follow the original principles set out by Kasai and Suzuki (1959), most likely use a much wider portal dissection to try and incorporate as much as possible of the transected portal plate. There have been published variations in the construction of the Roux loop. Typically these were developed to reduce the postoperative incidence of cholangitis, and it included bringing the Roux loop out as a stoma and creating an antireflux valve (Tanaka et al, 1991; Nakajo et al, 1990). Hindsight suggests these have no real value and serve to impair the later transplant procedure, should it become necessary (Ogasawara et al, 2003). Use of the appendix as a conduit to the duodenum has also been described (Crombleholme et al, 1989), but again, later reports suggest no value (Lee et al, 2007; Tsao et al, 2003).

Biliary Atresia Variations

Types 1 and 2 BA may be found in up to 5% to 10% of all cases and were formerly described as "correctable," because some form of lesser procedure, such as a hepaticojejunostomy, could be done. Nonetheless, care must be taken, and a radical resection of remnant tissue back to the portal plate is now usually considered a better option with an encompassing portoenterostomy.

LIVER TRANSPLANTATION

The first ever attempt at human transplantation occurred in Denver, Colo., by Thomas Starzl on March 1, 1963 (Starzl et al, 1963; see Chapter 97). The patient was a ventilator-bound child born with BA who, because of complications related to severe bleeding, did not survive the operation; nonetheless, a milestone had been passed. Still, very few similar operations were carried out over the next 20 years, until the advent and increasing availability of cyclosporine during the 1980s made effective immunosuppression possible and transplantation a realistic option.

Currently, indications for transplantation include end-stage liver disease (usually following a Kasai portoenterostomy but less commonly as a primary procedure), recalcitrant cholangitis (despite prolonged intravenous antibiotics), severe portal hypertension, hepatopulmonary syndrome, evidence of malignant change, and failure to thrive despite maximal medical intervention.

It is still a surgically challenging procedure with reported early survival rates (1 to 3 years) from 85% to 94% and later (5 to 10 years) survival from 78% to 87% (Diem et al, 2003; Barshes et al, 2005; Fouquet et al, 2005; Cowles et al, 2008). There is, of course, the expectation of life-long immunosuppression; but in return, transplant offers the prospect of an excellent quality of life with normal liver function, and beyond the immediate postoperative period, expectation of long-term survival.

Various transplant programs have evolved in most developed countries with variation depending on cultural background. Nonetheless, all programs still have problems related to waiting-list death, lack of organ donors, and issues of size matching recipient to donor. Active living-donor programs, non–heart-beating donors, and technical advances such as organ reduction and split livers are all being pursued to try and negate these issues.

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CHAPTER 41

Primary sclerosing cholangitis

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OVERVIEW

Primary sclerosing cholangitis (PSC) is a chronic, cholestatic liver disease of unknown etiology characterized by diffuse inflammatory destruction of intrahepatic and/or extrahepatic bile ducts that results in bile stasis, hepatic fibrosis, cirrhosis, and end-stage liver disease. Despite the increased awareness of PSC, the exact etiology and an effective medical therapy have yet to be identified. The disease is associated with specific human leukocyte antigen (HLA) haplotypes and has a close association with inflammatory bowel disease (IBD), which suggests that PSC is an immune-mediated disorder; but unlike other typical autoimmune diseases, there is a 2:1 male predominance. Life expectancy is reduced in PSC patients, because disease progression often results in complications of liver failure and cholangiocarcinoma (see Chapters 50A, 50B, and 50C). Among eligible candidates, surgical therapy has moved largely to orthotopic liver transplantation (OLT), as it remains the only effective, life-extending treatment for advanced-stage PSC (see Chapter 97A).

EPIDEMIOLOGY AND DEMOGRAPHICS

PSC mainly affects males during the fourth decade of life (Angulo & Lindor, 1999; Chapman, 2003). In the United States, population-based studies reported an age-adjusted incidence for PSC of 1.25 per 100,000 men and 0.54 per 100,000 women per year (Bambha et al, 2003). In the same study, the calculated prevalence of PSC was 20.9 and 6.3 per 100,000 men and women, respectively (Bambha et al, 2003). The worldwide prevalence and geographic distribution of PSC are undefined, as most epidemiologic data come from Northern Europe and the upper Midwest in the United States. Of interest is the strong association of PSC with IBD. Approximately 75% to 80% of Northern European patients with PSC suffer from IBD, with chronic ulcerative colitis (CUC) being most common, seen in about 90% (Chapman et al, 1980; Olsson et al, 1991; Wiesner et al, 1989). Conversely, only approximately 5.5% of patients with CUC have PSC (Olsson et al, 1991).

Smoking is the only environmental factor known to influence PSC susceptibility, and it is associated with a reduced risk of PSC. In a study from The Netherlands, the incidence of current smoking was 19% in patients with PSC compared with 38% in control subjects (Van Erpecum et al, 1996). Similarly, a U.S. study showed that 4.9% of patients with PSC were reported to smoke compared with 26.1% of a control population matched for age and gender. This reported difference was not attributable to the prevention of CUC (Loftus et al, 1996b). Nevertheless, smoking and alcohol consumption should be discouraged in PSC patients, because both are associated with the development of cholangiocarcinoma in this population (Bergquist et al, 1998; Chalasani et al, 2000).

Adenocarcinoma of the bile ducts appears in 8% to 15% of patients with PSC, rendering it a premalignant condition (Chalasani et al, 2000; De Groen et al, 1999; Foutch et al, 1990; see Chapters 50A, 50B, and 50C). In a recent study, 161 PSC patients without evidence of cholangiocarcinoma upon entry were followed over a median of 11.5 years. During that period, 59 patients (36.6%) died, 50 patients (31.1%) underwent liver transplantation, and 11 patients (6.8%) had cholangiocarcinoma develop (Burak et al, 2004). No association was found between the duration of PSC and the incidence of cholangiocarcinoma, and multivariate analysis revealed that variceal bleeding was the only significant risk factor for the diagnosis of cancer (risk ratio, 24.2; 95% confidence interval, 3.3% to 67%) (Burak et al, 2004).

CLINICAL PRESENTATION

PSC can affect any age group, but it is more common among men in their fourth decade of life (Wiesner & LaRusso, 1980; MacCarty et al, 1983). PSC can also occur in childhood, and children with PSC frequently have liver disease with features similar to autoimmune hepatitis (AIH) (El-Shabrawi et al, 1987; Wilschanski et al, 1995). In fact, the overlap between PSC and AIH in children can be as high as 35% (Feldstein et al, 2003). In contrast, overlap of PSC and AIH affects only about 5% of adults (Kaya et al, 2000; Van Buuren et al, 2000).

The clinical presentation of PSC varies depending on the disease stage at the time of diagnosis. PSC can be diagnosed in asymptomatic individuals who come to medical attention because of abnormal liver function tests. Approximately 15% to 40% of patients are asymptomatic at the time of diagnosis (Talwalkar & Lindor, 2005). There are no pathognomonic signs or symptoms when the disease becomes clinically apparent. The symptomatic patient may be seen initially with signs, symptoms, and complications of cholestatic liver disease or hepatic failure. In a recent study, the most common first symptoms were abdominal pain (20%), pruritus (10%), diarrhea (8%), jaundice (6%), fatigue (6%), and fever (4%) (Kaplan et al, 2007). Symptoms of bacterial cholangitis are uncommon, unless dominant biliary strictures or biliary stones are present.

Physical examination may reveal jaundice, hepatomegaly, splenomegaly, and excoriations. Ascites and peripheral edema are observed with the development of biliary cirrhosis and portal hypertension (see Chapter 70A). These findings are less common today, because PSC patients are usually evaluated before the development of end-stage liver disease. A commonly

encountered clinical scenario is a patient with CUC who presents with a cholestatic pattern of liver enzymes. Further medical evaluation results in the concurrent diagnosis of PSC. As with other chronic liver diseases, health-related quality of life is significantly impaired among PSC patients compared with healthy individuals (Younossi et al, 2001).

DIAGNOSTIC CRITERIA

The diagnosis of PSC is made based on clinical presentation, biochemical profile, and characteristic cholangiographic appearance of the bile ducts. Before the 1960s, PSC was a diagnosis of exclusion following abdominal exploration and biopsy of a suspected bile duct neoplasm (Schwartz & Dale, 1958). In the 1960s, diagnosing PSC became more frequent, when its association with IBD was recognized (Thorpe et al, 1967). With the advent of endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC) in the 1970s, the characteristic "beaded" or "pruned tree" cholangiographic appearance obviated the need for exploratory surgery to diagnose PSC and resulted in its increased recognition (Wiesner & LaRusso, 1980; see Chapter 18).

The first formal diagnostic criteria included 1) absence of previous operative trauma to the biliary system; 2) sclerosis and stenosis involving all or most of the extrahepatic bile ducts; 3) exclusion of malignant disease involving the biliary tree, such as cholangiocarcinoma; and 4) absence of calculi in the gallbladder and common bile duct (Holubitsky & McKenzie, 1964). Following the introduction of ERCP, the criteria were expanded to include a subset of PSC cases recognized to have intrahepatic bile duct involvement alone (MacCarty et al, 1983). In addition, serial ERCP examinations of PSC patients demonstrated the subsequent development of cholangiocarcinoma (Chapman et al, 1980). As such, malignancy arising in the setting of sclerosing cholangitis was eliminated as an exclusionary criterion. Imaging techniques (i.e., ERCP) have also shown biliary tract calculi in many patients with established PSC, suggesting the removal of calculi as an exclusionary criterion (Kaw et al, 1995).

The diagnosis of PSC currently relies on 1) characteristic cholangiographic abnormalities of the biliary tree; 2) compatible clinical and biochemical findings, typically of ductal cholestasis with elevated serum alkaline phosphatase level for at least 6 months duration; and 3) exclusion of other causes of secondary sclerosing cholangitis (SSC). The clinical and cholangiographic features of SSC can mimic PSC, but SSC originates from known pathologic processes. Several well-described causes of SSC are listed in Table 41.1 (Abdalian & Heathcote, 2006). Currently, the most common presentation is an asymptomatic patient with persistently elevated levels of alkaline phosphatase first noted on routine serum biochemical screening. In the proper clinical context, a characteristic cholangiographic appearance of the bile ducts is sufficient for making the diagnosis.

Liver biopsy is not always necessary for diagnosing PSC, nor does it contribute new information that affects the clinical management of patients. In a study of 79 patients with PSC who had an already established diagnosis by cholangiography, liver biopsy did not affect management (Burak et al, 2003). Thus the role of liver biopsy in PSC is to 1) exclude other causes of liver disease, 2) diagnose small-duct PSC (discussed later), and 3) define the disease stage for determining prognosis and assessing efficacy of treatment prior to entering in therapeutic trials. Small-duct PSC comprises approximately 5% of histologically confirmed PSC cases (Angulo et al, 2002) and has significantly better long-term prognosis compared with classic PSC. However, some patients with small-duct disease can progress to classic PSC (Angulo et al, 2002). Patients with small-duct PSC usually have IBD and are seen intially with a cholestatic pattern of liver enzymes but normal cholangiography. Nevertheless, liver biopsy reveals classic histologic features of PSC. In the majority of patients, the history, serum biochemical profile, and cholangiography distinguish PSC from other causes of chronic cholestatic liver disease. The differential diagnosis of PSC is presented in Table 41.2.

Table 41.1

Causes of Secondary Sclerosing Cholangitis

AIDS-associated cholangiopathy
Amyloidosis
Bile duct neoplasm (in the absence of primary sclerosing cholangitis)
Chemicals/drugs (e.g., 5-fluorouracil)
Choledocholithiasis
Congenital bile duct abnormalities (Caroli disease)
Iatrogenic biliary strictures/trauma
Recurrent pyogenic cholangitis
Autoimmune pancreatitis
Intraarterial chemotherapy
Abdominal trauma, surgical or blunt
Eosinophilic or mast cell cholangitis

AIDS, acquired immunodeficiency syndrome

Table 41.2

Differential Diagnosis of Primary Sclerosing Cholangitis

Primary biliary cirrhosis
Drug-induced cholestasis
Congenital abnormality of the biliary tract
Idiopathic adult ductopenia
Cholestasis associated with autoimmune hepatitis or alcoholic liver disease
Bile duct carcinoma (cholangiocarcinoma)
Extrahepatic obstruction
Secondary sclerosing cholangitis

BIOCHEMICAL AND SEROLOGIC ABNORMALITIES

Biochemical cholestasis of at least 6 months' duration gives reason to suspect PSC. Alkaline phosphatase remains the most commonly elevated liver enzyme, often showing a threefold to fourfold increase. Nevertheless, a normal alkaline phosphatase level does not exclude the diagnosis of PSC, because normal levels have been reported in patients with cholangiographically proven disease (Balasubramanian et al, 1988). Therefore a normal alkaline phosphatase level should not dissuade further investigation if the clinical history (e.g., presence of IBD) and other evidence suggest liver disease.

Aminotransferase levels are often modestly elevated in patients with PSC, except in children, in whom these levels can be markedly increased. On average, adults with PSC have aminotransferase levels less than three times the upper limit of normal (Lee & Kaplan, 1995). PSC patients with highly elevated aminotransferases may show concomitant serologic evidence and histologic features of AIH (Czaja, 1998).

Serum bilirubin levels are normal in 60% of patients at diagnosis (Talwalkar & Lindor, 2005), but bilirubin levels will markedly rise as PSC progresses. An abrupt, sustained rise of bilirubin may herald a dominant biliary stricture, a bile duct stone, or the development of cholangiocarcinoma; therefore it should prompt additional investigation. Serum copper and ceruloplasmin levels and hepatic and urinary copper values are often abnormal. Hepatic copper levels can be elevated to the degree seen in Wilson disease and primary biliary cholangitis (PBC) (LaRusso et al, 1984); the copper increase is a reflection of prolonged cholestasis.

No autoantibody is pathognomonic for diagnosing PSC. The prevalence of antineutrophil cytoplasmic antibodies (ANCAs), anticardiolipin antibodies, and antinuclear antibodies (ANAs) in patients with PSC is 84%, 66%, and 53%, respectively (Angulo et al, 2000). Antimitochondrial antibodies (AMAs) and anti–smooth muscle antibodies are rare in patients with PSC. Approximately 25% of patients have hypergammaglobulinemia, and immunoglobulin M (IgM) levels are the most commonly elevated component (Wiesner & LaRusso, 1980). Autoantibody testing is helpful to identify those PSC patients with concurrent AIH, but antibody titers are not important in following PSC activity.

IMAGING STUDIES

Visualization of the biliary tree is essential for establishing the diagnosis of PSC, and ERCP is the gold standard imaging technique (see Chapter 18). Typical cholangiographic findings of PSC include multifocal stricturing and beading throughout the biliary tree characteristic of alternating fibrosis and ectasia of the bile ducts (Fig. 41.1). Strictures of the bile ducts are the hallmark of the disease. They are often diffusely distributed and annular with intervening segments of dilated ducts. The classic cholangiographic findings involve both the intrahepatic and extrahepatic biliary tree. Strictures can vary in length and confluency, ranging from a bandlike appearance 1 to 2 mm in length to dense, annular strictures several centimeters in length. Approximately 25% of patients have biliary outpouchings that resemble diverticula. Similarly, 30% to 40% of patients may have mural irregularities that produce a shaggy appearance, varying from a fine brush border to frank nodularity (MacCarty et al, 1983).

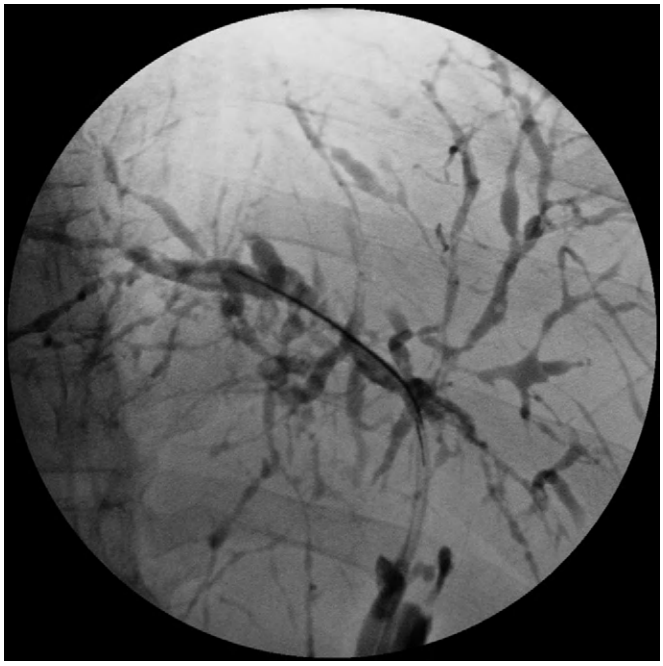


FIGURE 41.1. Endoscopic retrograde cholangiopancreatography showing the typical cholangiographic findings of primary sclerosing cholangitis: multifocal structuring and beading involves the intrahepatic bile ducts.

In a study of 86 patients with PSC, cholangiographic findings revealed involvement of the intrahepatic and extrahepatic ducts in 80 and 85 patients, respectively, when there was adequate visualization of the intrahepatic biliary tree. Involvement of only the intrahepatic and proximal extrahepatic ducts was seen in 20% of patients, and a very small number of patients had only small-duct PSC with a normal cholangiogram (MacCarty et al, 1983). Gallbladder and cystic duct involvement is less severe but is present in as many as 15% of patients (Brandt et al, 1988). ERCP should be considered in all patients suspected of having PSC. In addition to establishing the diagnosis, ERCP defines the extent and distribution of disease, identifies benign dominant strictures for endoscopic dilation or stenting, and allows brushings for cytology studies to screen for cholangiocarcinoma.

As many as 10% of cholangiocarcinomas have radiologic features that mimic PSC. Cholangiographic features that may suggest malignant degeneration of established PSC are markedly dilated biliary ducts or ductal segments, presence of a polypoid mass of 1 cm or greater in diameter, and progressive stricture formation. Nevertheless, these cholangiographic features are not specific for cholangiocarcinoma and can be seen in the absence of malignancy (MacCarty et al, 1985).

Despite the high diagnostic and therapeutic capabilities of ERCP, the procedure is invasive and is associated with clinical complications. The Mayo Clinic experience has shown that among PSC patients undergoing ERCP, the estimated rate of procedural complications requiring hospitalization is more than 10%. PSC patients undergoing ERCP are expected to have longer procedural time and a higher incidence of cholangitis compared with non-PSC patients (see Chapter 43), but the risk of pancreatitis, perforation, and bleeding are similar (Bangarulingam et al, 2009).

Magnetic resonance cholangiography (MRC) is a noninvasive substitute for ERCP (Fig. 41.2; see Chapter 17). Recent studies have estimated the sensitivity and specificity of MRC for diagnosing PSC to be between 80% to 82% and 87% to 98%, respectively (Talwalkar et al, 2004; Berstad et al, 2006). These studies concluded that MRC has diagnostic accuracy comparable to ERCP and results in cost savings when used as the initial diagnostic strategy. In another study, MRC was shown to be better than ERCP in identifying peripheral intrahepatic bile duct strictures (Vitellas et al, 2002).

In a retrospective, nonblinded study of PSC patients with known biliary tract carcinoma, MRC findings of a well-defined mass exhibiting abnormal signal intensity were classified as definite cholangiocarcinoma in six or seven patients (Vitellas et al, 2002). MRC will likely replace diagnostic ERCP, but at present it is less sensitive and does not allow for biliary biopsy and cytology or therapeutic intervention.

PTC is useful when access to the biliary tree by ERCP is not technically feasible. Abdominal ultrasonography (US) and

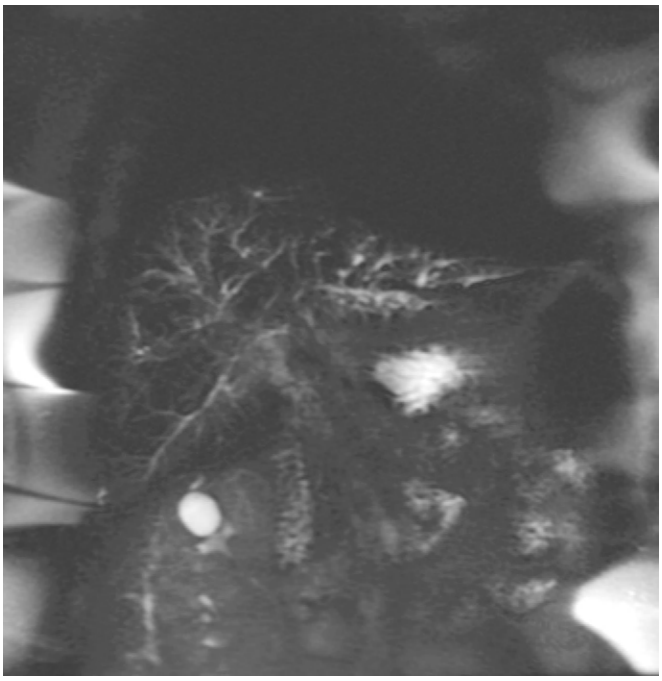


FIGURE 41.2. Magnetic resonance cholangiography images demonstrate mild dilation of numerous intrahepatic bile ducts in a segmental fashion. The findings are consistent with primary sclerosing cholangitis.

computed tomography (CT) are valuable in affirming ductal dilation and evaluating complications of PSC such as biliary stones, cirrhosis, and bile duct malignancy (see Chapters 13 and 16). US is often able to show large duct dilation and mural thickening of the common bile duct in patients with confirmed abnormalities on ERCP. It can further be used to detect gallstones or biliary tract calculi, which are important in the evaluation of bacterial cholangitis, worsening cholestasis, or jaundice.

Morphologic features of ductal abnormalities and cirrhosis can be seen on CT. Atrophy of the left lateral segment and hypertrophy of the caudate lobe may differentiate cirrhosis associated with PSC from that seen in other types of cirrhosis (Caldwell et al, 2001). CT can also complement cholangiography in the evaluation of malignancy with its ability to detect peripheral intrahepatic cholangiocarcinoma and metastatic spread within the liver parenchyma and the abdomen (Campbell et al, 1998, 2001). However, perihilar lymphadenopathy is very common in PSC with or without cholangiocarcinoma, and this finding cannot be taken as direct evidence of malignancy or metastasis.

PATHOLOGY

PSC can affect the entire biliary system. On rare occasions, it may be limited to the small intrahepatic ducts and be detectable only on histology. Small-duct PSC is thought to account for 5% of histologically confirmed PSC cases, although its true prevalence remains unknown (Angulo et al, 2002).

Liver biopsy findings alone are rarely sufficient to establish the diagnosis of PSC, which is characterized by damage to, atrophy of, and ultimately loss of bile ducts, thus sharing histologic features with other hepatobiliary diseases (Scheuer, 1998).

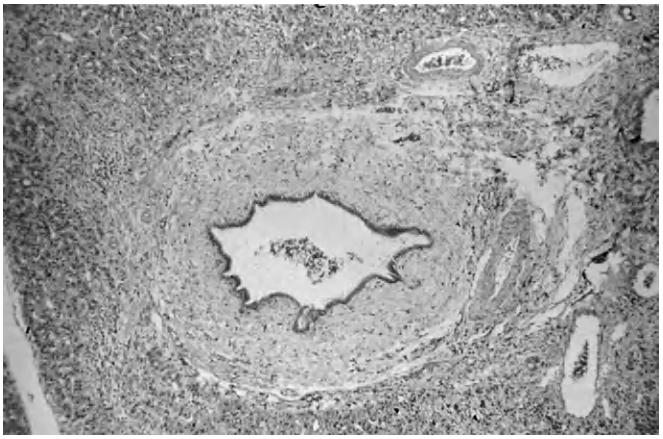


FIGURE 41.3. Histologic findings of early-stage primary sclerosing cholangitis, demonstrating prominent cholangiectasis and fibrosing cholangitis of an interlobular bile duct (hematoxylin/eosin stain ×100).

Liver biopsy specimens from patients show portal tract inflammation and sclerosis (Fig. 41.3). Afflicted bile ducts are surrounded by a cuff of lightly inflamed sheets of fibrous tissue and edema, causing the fibrotic layers to separate and form the characteristic onion skin appearance. This classic histologic finding is nearly pathognomonic, but it is seen in fewer than 10% of PSC patients (Ludwig et al, 1981). Affected bile ducts will eventually atrophy and be replaced by rounded scars.

On occasion, similar fibroobliterative cholangitis can be seen in 1) PBC, 2) mechanical obstruction of larger bile ducts, 3) ductopenic rejection following liver transplantation, and 4) after intraarterial infusion of 5-fluorouracil. Involvement of the large intrahepatic and extrahepatic ducts distinguishes PSC from PBC. Inflammation in early-stage PSC is generally milder than that of PBC, but this distinction is difficult to make (Scheuer, 1998). Granulomas, thought to be classically associated with PBC, may be seen in about 4% of biopsies from PSC patients, making the distinction between PSC and PBC even more challenging (Ludwig et al, 1995).

Distinguishing between PSC-related histopathologic features and changes as a result of simple obstruction of distal bile ducts makes the liver biopsy interpretation difficult. Canalicular cholestasis is nonspecific and can occur as a result of any cause of biliary obstruction. As PSC progresses, however, the histopathologic changes of chronic cholestasis spill into the hepatic parenchyma. The most commonly used liver histology grading system proposed by Ludwig is based on these parenchymal changes. Disease was designated as *stage 1,* portal; *stage 2,* periportal; *stage 3,* septal; and *stage 4,* cirrhotic (Table 41.3; Ludwig et al, 1986). Histologic changes in the same liver can be markedly varied from segment to segment at any given point in time. Whereas histologic staging was formerly used as an independent predictor of the disease's natural history, the revised PSC survival model does not take into account the histologic stage (Kim et al, 2000).

ETIOPATHOGENESIS

To date, the pathogenesis of PSC remains unknown. Current theories regarding the etiology of PSC encompass both genetic elements and environmental exposures. It is believed that the

Table 41.3

Staging of Primary Sclerosing Cholangitis

Portal stage (stage I)	Portal edema, inflammation, ductal proliferation; abnormalities do not extend beyond the limiting plate
Periportal stage (stage II)	Periportal fibrosis and inflammation with or without ductal proliferation; piecemeal necrosis may be present
Septal stage (stage III)	Septal fibrosis or bridging necrosis can be identified
Cirrhotic stage (stage IV)	Biliary cirrhosis evident

host–environment interaction plays an integral role in the development of PSC. Moreover, it is now known that cholangiocytes, the epithelial cells that line the bile ducts, are the target of injury in PSC.

The strong association of PSC with IBD has drawn much attention to the potential role of the inflamed colon. The hypothesis suggests that inflammation of the colon may increase permeability to various intraluminal products—toxins, bacteria, inflammatory mediators—that ultimately lead to liver disease. Bacteria or their toxic metabolic products have been considered but have not been conclusively shown to have a pathogenetic role in PSC development (Eade & Brooke, 1969; Palmer et al, 1980). However, investigators have shown that the absence of low-grade, chronic portal vein bacteremia in patients with CUC could potentially elicit the immune response that is responsible for PSC (Warren et al, 1966). Similarly, histologic evidence of bacteremia manifested as portal phlebitis is mild or absent in most PSC patients (Ludwig et al, 1981). Additional information showed that colonic bacteria might metabolize primary bile acids into toxic bile salts that are then absorbed through the ulcerated colon into the portal circulation, but no evidence of bile acid metabolism abnormalities in patients with PSC or CUC has been found (Siegel et al, 1977).

Animal models of PSC have reported that bacterial chemotactic peptides can lead to portal inflammation and histologic changes of PSC (Hobson et al, 1988: Lichtman et al, 1990). Suppression of the inflammatory response was reported in an animal model following inhibition of tumor necrosis factor (TNF). Nevertheless, in a clinical trial of PSC patients with pentoxifylline, a TNF inhibitor, no beneficial effect on symptoms or liver tests was seen (Bharucha et al, 2000). Clinical observations also cast doubt upon the role of the inflamed colonic mucosa in the development of PSC. First, PSC develops in approximately 25% of patients without evidence of IBD. Invasive screening of asymptomatic patients with PSC reveals that many have no endoscopic or histologic evidence of IBD. Second, lack of association between the severity of colonic disease and the likelihood of development and severity of PSC strengthens the skepticism that CUC may not directly cause PSC. Third, failure of proctocolectomy to modify the natural history of PSC argues against a direct causative role of CUC in PSC (Cangemi et al, 1989; Steckman et al, 1984). Thus, the putative contribution of increased colonic permeability in CUC resulting in inflammation of bile ducts remains unclear.

Genetic factors seem to play a role in the development of PSC. First, there have been reports of familial PSC among siblings (Quigley et al, 1983; Jorge et al, 1987). Second, various HLA associations with PSC have been reported, and HLA B8, DR3, DR2, and haplotype A1, B8, and DR3 have been found more frequently in patients with PSC compared with controls (Chapman et al, 1983; Donaldson et al, 1991; Schrumpf et al, 1982; Wiencke et al, 2007). PSC associated with DR4 is a more aggressive disease, although this correlation has not been universally found (Mehal et al, 1994; Olerup et al, 1995). Additional associations with DRB3*0101, DRB1*0301, DQA1*0501, DQB1*0201 and DRB1*1301, and DQA1*0103 and DQB1*0603 have been reported (Donaldson & Norris, 2002). Polymorphisms in the TNF-α receptor have been described as a possible genetic link to PSC. G to A substitution at position –308 in the TNF-α gene has been associated with susceptibility to PSC (Mitchell et al, 2001). A functional variant of stromelysin, matrix metalloproteinase 3, may also influence PSC susceptibility and disease progression (Satsangi et al, 2001). Moreover, variations in the *MICA* gene (major histocompatibility complex class I–related *MIC* gene family) have a role in PSC predisposition. Independent of other HLA haplotypes, the *MICA* 002 allele appears to significantly reduce the risk of PSC, and the *MICA* 008 allele increases the risk of developing PSC (Norris et al, 2001). Finally, the *CCR5-δ32* mutation, characterized by a 32-base pair deletion in the *CCR5* gene of T cells, has been associated with susceptibility to PSC development and severity (Eri et al, 2004).

Immune-mediated damage to cholangiocytes seems to be the most likely mechanism leading to PSC. Theoretically, certain HLA molecules and haplotypes may contribute by eliciting an immune response against antigenic epitopes present on biliary epithelia. Enhanced expression of MHC class II antigens (i.e., HLA DR) on cholangiocytes in early-stage PSC has drawn suspicion regarding its role in altered immunity in disease pathogenesis. Aberrant expression of HLA DR is also apparent in PBC and extrahepatic biliary obstruction, suggesting that expression of this antigen is an epiphenomenon rather than an implicit cause of PSC (Broome et al, 1990; Chapman et al, 1988; Van Milligen De Wit et al, 1995).

Decreased hepatic clearance of circulating immune complexes, generalized complement activation, and sharing of a specific epitope between human colonic and biliary epithelial cells have also been reported (Bodenheimer et al, 1983; Minuk et al, 1985; Das et al, 1990; Mandal et al, 1994), yet none of these observations have proven pathogenic associations with PSC. Enhanced interactions of intracellular adhesion molecule 1 (*ICAM1*) present on cholangiocytes with its cognate ligand on T lymphocytes, leukocyte function–associated antigen 1 (ITGAL), may play a role in PSC development. Genetic polymorphisms of *ICAM1* have been implicated in susceptibility to PSC. Homozygote status of the E469E allele for *ICAM1* has been associated with protection against PSC (Yang et al, 2004). Both enhanced expression on proliferating cholangiocytes and increased serum levels of ICAM1 have been reported in PSC patients (Van Milligen De Wit et al, 1995; Adams et al, 1991; Bloom et al, 1995).

ASSOCIATED DISEASES

PSC is strongly associated with IBD, most commonly CUC. PSC patients may also have biochemical, serologic, and histologic features of AIH, and a variety of other diseases have been reported to associate with PSC. Given the lack of large studies, it is unclear whether these weak associations are true or simply

Table 41.4

Diseases Associated with Primary Sclerosing Cholangitis

Chronic ulcerative colitis
Crohn disease
Chronic pancreatitis
Sicca syndrome
Hypereosinophilia
Reidel thyroiditis
Celiac disease
Autoimmune hemolytic anemia
Sarcoidosis
Glomerulonephritis

coincidental. An abridged list of associated diseases is presented in Table 41.4.

Inflammatory Bowel Diseases

The close association of PSC with IBD, particularly CUC, is widely recognized. IBD is seen in approximately 70% to 80% of patients with PSC, and CUC accounts for 85% to 90% of those patients; Crohn disease is responsible for the rest (Fausa et al, 1991; Loftus et al, 1997). Patients with PSC and Crohn disease may have milder liver disease than patients with PSC and CUC, and PSC has not been seen in Crohn disease involving only the small intestine (Rasmussen et al, 1997). Typically, the diagnosis of IBD is established 8 to 10 years before the liver disease is evident, although there is no clear temporal association, and cases of IBD occurring years after diagnosis of PSC have also been reported (Chapman et al, 1980; Loftus et al, 1996a, 1998). No direct correlation has been found between the severity of bowel disease and the severity of liver disease. Furthermore, therapy of the IBD does not alter the course of the liver disease. For instance, proctocolectomy, the most aggressive treatment for CUC, has no effect on PSC natural history (Cangemi et al, 1989). Colitis is usually milder in patients with both CUC and PSC in comparison to patients with CUC alone.

PSC may play a role in the development of colorectal dysplasia in the setting of CUC, as patients with CUC and PSC show a higher risk of colonic dysplasia compared with patients who have only CUC (Broome et al, 1995a, 1995b). In a study from Sweden, the absolute cumulative risk of developing colorectal dysplasia/carcinoma in patients with PSC and CUC was 9%, 31%, and 50% after 10, 20, and 25 years of disease duration, respectively. In patients with CUC alone, the parallel risk was 2%, 5%, and 10%, respectively (Broome et al, 1995b). Subsequent studies also confirmed the observation of Broom and others, where predicted risk of colorectal carcinoma with PSC and concomitant IBD after 10 years of disease duration was up to 25% (Kornfeld et al, 1997; Claessen et al, 2009). Other investigators have reported that patients with both PSC and CUC were five times more likely to develop colonic dysplasia, based on mucosal biopsy, compared with patients with CUC alone (Brentnall et al, 1996). Whether this finding reflects the fact that PSC patients have milder pancolonic disease that remained undetected for a longer period of time is uncertain. Interestingly, a retrospective case-control study found a similar prevalence of PSC in patients with both CUC and colorectal carcinoma compared with those who had CUC but no neoplasia, that is, no carcinoma or dysplasia (Nuako et al, 1998).

Colonic dysplasia has also been reported in PSC patients without IBD (Broome et al, 1995a, 1995b). However, the risk of colorectal carcinoma in patients with PSC at 10 and 20 years of disease duration was much lower (2% and 2%) than in patients with PSC and concomitant IBD (14% and 31%). PSC patients with CUC continue to have increased risk of colorectal dysplasia and neoplasia, even after liver transplantation (Bleday et al, 1993). The increased neoplastic potential is especially critical in PSC patients following liver transplant, because of the life-long immunosuppression. Annual colonoscopy with surveillance biopsies is recommended in patients with PSC and CUC, because screening and early detection improves survival (Narumi et al, 1995; Loftus et al, 1998). Annual colonoscopy is also suggested for PSC patients without IBD.

Autoimmune Hepatitis

An overlap syndrome between PSC and AIH has been described (Gohlke et al, 1996; Luketic et al, 1997). These patients typically fulfill definite criteria for both, having elevated serum alkaline phosphatase and aminotransferases and increased IgG and antinuclear and/or anti–smooth muscle antibody titers. Liver biopsy reveals moderate to severe interface hepatitis with or without biliary damage, and aminotransferase levels are elevated beyond what would be expected for classic PSC, typically less than three times normal. IBD may also be present in patients with concurrent PSC and AIH but at a lower frequency than in PSC alone. In patients with overlap syndrome, AIH may respond to immunosuppressive therapy. Patients who are seen with AIH but do not respond entirely to immunosuppressant therapy and subsequently develop a cholestatic biochemical profile should be suspected of having concomitant PSC.

NATURAL HISTORY

PSC is an insidious and progressive disease that frequently leads to end-stage liver disease and liver failure. Patients with early-stage PSC are generally asymptomatic. Advanced-stage PSC is marked by complications of chronic cholestasis and end-stage liver disease. Prior appendectomy may delay the onset of PSC but does not affect the prevalence or severity of the disease (Florin et al, 2004). In the absence of liver transplantation, the median survival from the time of diagnosis is about 12 years. Even asymptomatic patients have decreased survival compared to age-matched controls (Wiesner et al, 1989). In a study of 45 PSC patients who were asymptomatic at the time of diagnosis, 76% had progression of PSC, and 31% had liver failure develop with a mean follow-up of 6.25 years (Porayko et al, 1990). Early diagnosis of PSC is associated with longer survival because of presumed lead-time bias (Broome et al, 1996; Okolicsanyi et al, 1996).

The progressive pattern and severe complications of PSC warrant close medical management and intervening treatment. Prognostic models for PSC have been developed to predict survival and identify the ideal timing for liver transplantation. Cox multivariable regression analysis has been widely used to define the variables for these models. The revised Mayo PSC natural history model uses six independent, reproducible parameters to estimate the survival of PSC patients. These variables include age, bilirubin, albumin, aspartate aminotransferase, and history of variceal bleeding (Kim et al, 2000). Recently the Model for End-Stage Liver Disease (MELD) has been widely used

to ensure organ allocation priority to end-stage liver disease patients with the highest mortality risk (Kamath et al, 2001).

Small-duct PSC, although rare, has a favorable long-term prognosis. In a multiinstitutional and multinational study, the 83 small-duct PSC patients were matched by age, gender, year of diagnosis, and institution to two patients with large-duct PSC. Approximately 23% patients with small-duct PSC progressed to large-duct PSC over a median of 7.4 years. Patients with small-duct PSC did not develop cholangiocarcinoma, unless the disease progressed to large-duct PSC. The same study showed patients with small-duct PSC had a statistically longer transplantation-free survival: 13 years compared with 10 years. Two patients with small-duct PSC who underwent liver transplantation did have a recurrence of small-duct PSC in the graft after 9 years (Bjornsson et al, 2008). In children with PSC who have progressive disease, the median survival despite medical therapy, and in the absence of liver transplantation, was reported to be 12.7 years (Feldstein et al, 2003).

COMPLICATIONS

Specific PSC complications include cholelithiasis, choledocholithiasis, dominant biliary strictures with or without recurrent bacterial cholangitis, cholangiocarcinoma, and peristomal varices in patients who have undergone proctocolectomy and ileostomy for CUC. Nonspecific PSC complications are related to chronic cholestasis—pruritus, steatorrhea, fat-soluble vitamin deficiency, hepatic osteodystrophy—and to complications associated with end-stage liver disease such as cirrhosis and portal hypertension.

SPECIFIC COMPLICATIONS

Cholelithiasis and Choledocholithiasis (See Chapters 30 and 35)

Although PSC is a disease affecting mainly young men, it is surprising that 25% to 30% will have calculi either in the gallbladder or biliary tree. In a study of 121 patients with PSC, 26% had gallstones, half of which were pigment stones, although the spectrum of pathology in the gallbladder is not limited to stones (Brandt et al, 1988). The same study showed that PSC directly involved the gallbladder in 15% of patients. The gallbladder can also suffer an unusual form of acalculous cholecystitis characterized by a diffuse lymphoplasmacytic infiltrate (Jessurun et al, 1998). Finally, in patients with PSC, gallbladder polyps require special attention. In a study of 102 patients with PSC, 14 patients (13.7%) had an intraluminal gallbladder mass, and eight of these lesions (57%) were adenocarcinomas (see Chapter 49). Recent case series showed that adenocarcinomas of the gallbladder can occur in polyps less than 1 cm (Karlsen et al, 2008), thus in PSC patients with gallbladder polyps, cholecystectomy is recommended (Buckels et al, 2002).

Radiologic studies have shown that intrahepatic calculi are present in approximately 8% of PSC patients (Dodd et al, 1997). Biliary calculi can serve as a nidus for the development of bacterial cholangitis in PSC patients, although this is uncommon in the absence of dominant biliary strictures or prior bile duct surgery. Evidence of bacterial cholangitis requires endoscopic evaluation to remove possible bile duct calculi and/or to dilate biliary strictures. Bacterial cholangitis commonly occurs in patients with PSC following ERCP, thus prophylactic coverage with antibiotics prior to (i.e., a single intravenous dose) and following ERCP (i.e., oral ciprofloxacin for 10 days) is recommended for PSC patients.

Dominant Biliary Strictures

Dominant strictures occur in 20% to 45% of PSC patients and present with progression of jaundice, pruritus, bacterial cholangitis, and right upper quadrant pain. ERCP is necessary to evaluate the bile ducts and allow therapeutic dilation with or without biliary stenting. In a prospective study, 12 symptomatic PSC patients with major ductal strictures were treated with repeated balloon dilation. Eight patients showed sustained improvement following an average of three treatment sessions to obtain satisfactory dilation of the affected bile ducts (Wagner et al, 1996). A retrospective study of 25 PSC patients with symptomatic dominant strictures showed that endoscopic stenting was technically successful in 21 patients (84%) and was associated with significant improvement of serum liver tests. Moreover, 12 (57%) of 21 patients with PSC remained asymptomatic with stable liver biochemistries, and four patients (19%) had clinical and biochemical relapse over a median follow-up of 29 months. All four patients with relapse responded favorably to additional endoscopic therapy (Van Milligen De Wit et al, 1996). The same investigators reported that in 16 patients with symptomatic PSC, short-term biliary stent placement (median, 9 days) was effective, with 13 patients (81%) remaining symptom free and without biochemical evidence of cholestasis after a median follow-up of 19 months (Van Milligen De Wit et al, 1997).

Despite these findings, it is unclear whether dominant biliary strictures are directly responsible for the cholestasis of PSC patients. In a retrospective study of 125 patients with PSC, 56 (45%) had dominant strictures, defined by stenosis of the common bile duct less than 1.5 mm in diameter and/or stenosis of the right or left hepatic duct less than 1.0 mm. Of interest, in PSC patients with (n = 56) or without (n = 69) dominant strictures up to 12 months after cholangiography, alkaline phosphatase and bilirubin levels were not significantly different (Bjornsson et al, 2004).

Cholangiocarcinoma

The most ominous complication of PSC is the development of cholangiocarcinoma (see Chapters 50A, 50B, and 50C), which is estimated to occur in 8% to 15% of patients during the course of the disease (Chapman, 2003; Claessen et al, 2009). In a study of 161 patients with PSC, approximately 7% had cholangiocarcinoma develop over a mean follow-up of 11.5 years (Burak et al, 2004). Among PSC patients, the estimated annual incidence of cholangiocarcinoma is approximately 1.5% (Gores, 2003). The cumulative risk of biliary tract malignancy is approximately 11.2% at 10 years from diagnosis of PSC (Kornfeld et al, 1997). Moreover, at the time of liver transplantation, approximately 10% of explanted livers have histopathologic evidence of unsuspected cholangiocarcinoma.

Patients with PSC and cholangiocarcinoma have poor survival. In a retrospective study of 30 patients with PSC, median survival was 5 months from the time of cholangiocarcinoma diagnosis. Also at the time of diagnosis, 63% had metastatic disease, and 47% considered to have localized tumors had

abdominal metastasis at surgical exploration. Also, metastasis or local extension of disease precluded curative tumor resection in all but one patient, who was cholangiocarcinoma free more than 2 years later. Unfortunately, in PSC patients who develop cholangiocarcinoma, palliative resection, chemotherapy, and radiotherapy do not prolong survival.

Cholangiocarcinoma is usually diagnosed at an advanced stage because of its insidious nature. Many of the signs and symptoms associated with cholangiocarcinoma are typical of PSC itself, making early detection of cholangiocarcinoma difficult. Suspicion for cholangiocarcinoma should be raised when a patient with PSC is seen with rapidly progressive jaundice, weight loss, or abdominal discomfort. In a study comparing PSC patients who developed cholangiocarcinoma with those who did not, the investigators found no clinical or biochemical features that could herald the onset of biliary malignancy in the year prior to diagnosis (Bergquist et al, 1998). In patients with PSC, risk factors for developing cholangiocarcinoma include age, liver histologic stage, concurrent CUC (Rosen & Nagorney, 1991), smoking (Bergquist et al, 1998), and history of variceal bleeding (Burak et al, 2004).

In PSC patients, dysplasia of the biliary epithelium is likely the greatest predisposing factor of cholangiocarcinoma. In a study from the United Kingdom, biliary dysplasia was detected in approximately 20% of liver biopsies from 26 patients with PSC and cholangiocarcinoma, but not in a single case of 60 PSC patients who were free of biliary malignancy for a follow-up period of 2 years (Fleming et al, 2001). Moreover, recognition of biliary dysplasia by three independent pathologists showed moderate reproducibility, further suggesting dysplasia as a feasible indicator of present or developing biliary malignancy (Fleming et al, 2001). Likewise, colonic dysplasia seems to be a risk factor for cholangiocarcinoma, with risk increased significantly in patients with PSC and CUC (Broome et al, 1995b); therefore detection of dysplasia in either the biliary tree or colon requires vigilant surveillance for cholangiocarcinoma and may warrant consideration for liver transplantation under certain circumstances.

Early detection of cholangiocarcinoma, and thus promise for cure, has been hampered by the low sensitivity and specificity of standard diagnostic approaches and techniques. Cholangiocarcinoma of the large bile ducts is not easily detectable by cross-sectional imaging. In this case, ERCP is perhaps the best approach to evaluate for bile duct cancer. To this end, cholangiographic features suggestive of cholangiocarcinoma have been described, but the accurate distinction between benign and malignant biliary disease is often impossible. In fact, about 10% of malignant-appearing biliary strictures are benign (Hadjis et al, 1985). Biliary brush cytology specimens and fine-needle biopsies obtained at ERCP are at best 30% to 40% sensitive for securing the diagnosis of cholangiocarcinoma. A novel test for early detection of cholangiocarcinoma is *fluorescence in situ hybridization* (FISH) on bile duct cytology specimens. In a study on detection of malignant biliary strictures, the sensitivity of FISH (34%) was better than that of standard cytology (15%, $P < .01$), but the specificity of FISH and cytology was similar, at 91% and 98%, respectively ($P = .06$) (Kipp et al, 2004). A recent study of 498 patients undergoing ERCP for pancreatobiliary stricture demonstrated that polysomy of FISH had a significantly higher sensitivity (42.9%) than routine cytology (20.1%) with identical specificity (99.6%) (Fritcher et al, 2009).

Carbohydrate antigen 19-9 (CA19-9) has been used with questionable accuracy to aid the diagnosis of cholangiocarcinoma. In patients with PSC, a cutoff serum level of 129 U/mL is estimated to have a diagnostic sensitivity of 89% and specificity of 98% for diagnosing cholangiocarcinoma (Levy et al, 2005). Similar elevations of CA19-9 can be seen in patients with pancreatic malignancies, bacterial cholangitis, and in active smokers. In PSC patients, periodic CA19-9 testing is recommended, and a sustained rise should raise suspicion for possible development of cholangiocarcinoma. Others have shown that a carcinoembryonic antigen (CEA) level greater than 5 ng/mL was 100% specific but only 38% sensitive for detection of cholangiocarcinoma (Nichols et al, 1993). Another study using an index of CA19-9 and CEA showed an 86% diagnostic accuracy for detecting cholangiocarcinoma. Although most of these patients had radiologically occult disease, and several went on to liver transplantation, the great majority still died from cholangiocarcinoma (Ramage et al, 1995). At present, we have no reliable means to detect cholangiocarcinoma early, at a curable stage, although work is underway to find dependable molecular markers for early cholangiocarcinoma detection.

Endoscopic ultrasound (EUS; see Chapter 14) is better than CT and magnetic resonance imaging (MRI) to evaluate regional lymph nodes for possible cholangiocarcinoma metastasis, including the option to obtain a biopsy of questionable lesions (Gores, 2000). Positron emission tomography (PET) is a promising tool for detection of cholangiocarcinoma in PSC (see Chapter 15), and it can detect small cholangiocarcinomas arising in the setting of PSC with 100% accuracy compared with control groups (Keiding et al, 1998). A blinded study in Sweden examined 24 pretransplant PSC patients without evidence of malignancy on CT, MRI, and US, and PET correctly identified three of three patients with explanted liver pathology showing cholangiocarcinoma. But PET failed to detect a high-grade hilar ductal dysplasia and was falsely positive in a patient with benign epithelioid granulomas (Prytz et al, 2006), therefore, further investigations are necessary to define the role of PET in the diagnosis and routine surveillance of cholangiocarcinoma.

NONSPECIFIC PRIMARY SCLEROSING CHOLANGITIS COMPLICATIONS

Many patients with PSC complain of fatigue and pruritus. The etiology of fatigue is unclear in chronic cholestatic liver diseases, including PSC, and this can affect patients' quality of life. In PSC patients, the pruritus can be debilitating; although its mechanism is not well defined, endogenous opioids and retention of other unknown factors usually excreted in the bile may play some role in its development (Bergasa & Jones, 1995; Spivey et al, 1994; Jones & Bergasa, 1990).

Patients with PSC may also suffer from steatorrhea and subsequent deficiencies of fat-soluble vitamins. In a pretransplant group of PSC patients, deficiencies of vitamins A, D, and E were present in 82%, 57%, and 43% of patients, respectively (Jorgensen et al, 1995). These deficiencies can be treated with simple vitamin supplementation. In patients with PSC and steatorrhea, consideration should be given to exclude celiac sprue or chronic pancreatitis, because either entity can coexist with PSC, and both conditions are treatable causes of fat malabsorption (Hay et al, 1988). Metabolic bone disease is also very common in PSC. Osteopenic bone disease can be severe in

advanced-stage PSC, with 50% of patients having a bone mineral density below the fracture threshold (Hay et al, 1991). Although the majority of PSC patients are males, bone biopsies revealed findings consistent with osteoporosis rather than osteomalacia.

Patients with PSC have complications of portal hypertension, just as patients with other causes of liver cirrhosis do (see Chapters 70, 74, and 75). In a study of 283 patients with PSC, 102 patients (36%) had esophageal varices, including 57 (56%) of moderate to large size. A recent study of PSC patients reported that platelet count, albumin level, and advanced histologic disease were independent predictors of esophageal varices (Zein et al, 2004), which are usually managed with endoscopic banding. If these measures are ineffective, a shunting procedure (TIPS) can be performed as a bridge to liver transplantation. Patients with advanced-stage PSC develop ascites, spontaneous bacterial peritonitis, and encephalopathy. Treatment of such complications is similar to that of other causes of end-stage liver disease, with liver transplantation considered the optimal management (see Chapters 70, 74, 75, and 97A).

TREATMENT

Medical Therapy

To date, there is no specific medical therapy for PSC. Management should focus on the treatment of specific and nonspecific complications. Clinical trials on treating the underlying hepatobiliary disease are underway.

Therapy of Specific Primary Sclerosing Cholangitis Complications

Cholelithiasis and Choledocholithiasis

Symptomatic gallbladder disease in early-stage PSC patients should be treated with cholecystectomy. In an asymptomatic patient with PSC, presence of an intraluminal gallbladder mass requires cholecystectomy. In a study of PSC patients who underwent cholecystectomy, 13.7% of patients were found to have a gallbladder mass, and 57% were adenocarcinomas (Buckels et al, 2002). Cholecystectomy is not normally advocated for polyps less than 1 cm, but it may be justified in PSC patients; adenocarcinomas have been reported in recent case series of polyps less than 1 cm (Karlsen et al, 2008).

Following the diagnosis of choledocholithiasis, the therapeutic intervention of choice is ERCP (see Chapter 27). During this procedure, endoscopic sphincterectomy is performed with removal of biliary stones and dilation of possible strictures. Temporary biliary stent placement is typically recommended but depends on the clinical circumstances.

Dominant Biliary Stricture and Recurrent Bacterial Cholangitis

Dominant biliary stricture should be evaluated by ERCP or percutaneous transhepatic cholangiography (PTC) to ensure comprehensive imaging of the biliary tree and to permit biliary brushings and biopsies of affected areas to exclude cholangiocarcinoma. The main concern is to scrutinize whether the observed biliary stricture represents cholangiocarcinoma or a benign lesion. *Dominant stricture* is defined as a common duct diameter less than 1.5 mm and a hepatic duct less than 1 mm (Stiehl et al, 2002).

The therapeutic management of dominant bile duct stricture includes a combination of biliary dilation and stenting interventions. The preferred approach, ERCP versus PTC, depends on local experience and biliary stricture characteristics, such as region and length. The majority of bile duct strictures are amenable to endoscopic cholangioplasty followed by biliary stenting. PTC is useful for cholangioplasty of biliary strictures that affect intrahepatic ducts and for cases of unsuccessful ERCP. PSC patients with frequent episodes of bacterial cholangitis should have cholangiography to evaluate patency of bile ducts. Recurrent bacterial cholangitis is not always the result of dominant biliary strictures. Edema, inflammatory exudation, and intraluminal debris can result in temporary stenosis of bile ducts and lead to obliteration and subsequent recurrent bacterial cholangitis. To this end, temporary intranasal biliary tubes and biliary lavage have been used to flush out potential irritants and keep the ducts patent. In patients with relapsing episodes of bacterial cholangitis, antibiotics can be used as prophylaxis to prevent these recurrent events, although well-designed studies to address this complication are lacking.

Therapy of Nonspecific Complications

Pruritus

Patients with advanced-stage PSC frequently complain of intense pruritus. This distressing symptom can improve using various medical therapies (Angulo & Lindor, 1999). Cholestyramine is a nonabsorbable bile acid–binding resin that decreases the intestinal absorption of bile acids and alleviates pruritus. Phenobarbital has been used in conjunction with cholestyramine to treat PSC patients with nocturnal pruritus. Ursodeoxycholic acid (ursodiol)—a hydrophilic bile acid that likely replaces hydrophobic, toxic bile acids from the bile pool—may also improve pruritus. Antihistamines, such as hydroxyzine and diphenhydramine, can be used as supplements to cholestyramine or ursodeoxycholic acid, particularly for nocturnal pruritus, because of their sedative properties. Rifampin may also improve pruritus, although its potential side effects, specifically drug-induced hepatitis, make it a second-line agent. Opiate antagonists like naloxone, nalmefene, and naltrexone are also used to alleviate pruritus (Bergasa, 2004).

Steatorrhea, Fat-Soluble Vitamin Deficiency, and Hepatic Osteodystrophy

Prolonged cholestasis causes decreased intestinal bile acid concentration. Therefore, patients with advanced-stage PSC may develop fat malabsorption and steatorrhea, although PSC patients who develop steatorrhea should first be evaluated for other coexisting causes of steatorrhea, including celiac sprue and pancreatic insufficiency (Hay et al, 1988). Because of intraluminal bile acid deficiency, steatorrhea may improve from dietary changes, such as lowering daily fat intake and substituting medium-chain triglycerides for long-chain ones.

Deficiencies of fat-soluble vitamins A, D, E, and K are treated by simple oral replacement. Special consideration must be given in advanced-stage PSC patients who have moderate to severe osteopenia. Calcium supplements, replenishment with vitamin D, and use of estrogens all have shown therapeutic value. PSC patients deficient in vitamin K have prolonged prothrombin time that usually improves with oral vitamin K supplementation.

Decompensated Cirrhosis and Portal Hypertension

Complications of decompensated cirrhosis and portal hypertension should be managed expectantly as in other end-stage liver diseases. As PSC progresses, the complications of end-stage liver disease become intractable, and liver transplantation becomes the only effective therapy.

Therapy of Hepatobiliary Disease

Over the past 2 decades, multiple medical therapies have been evaluated for the treatment of PSC. Cupruretics (D-penicillamine), immunosuppressive agents (cyclosporine, azathioprine, budesonide, silymarin), antifibrogenic drugs (pentoxifylline, colchicine), and choleretic compounds (ursodeoxycholic acid) have been used, but none so far has been shown to be effective.

A double-blind, randomized, controlled study involving 105 PSC patients and standard dose UDCA (13 to 15 mg/kg body weight/day) failed to demonstrate clinical benefit in the treatment group compared with controls over a median follow-up of 2.2 years. Subsequently, pilot studies demonstrated promise with high-dose UDCA in PSC. A small, double-blind, placebo-controlled study from the United Kingdom reported that PSC patients (n = 13) who received high-dose (20 mg/kg body weight/day) UDCA had significant improvement in liver biochemistries, cholangiographic appearance, and reduction of liver fibrosis compared with patients taking placebo (n = 13) (Mitchell et al, 2001). In a similar U.S. study, 30 PSC patients were treated with high-dose (25 to 30 mg/kg body weight/day) UDCA, with reported improvement of the Mayo PSC risk score at the end of therapy (Harnois et al, 2001). Unfortunately, two separate large, randomized, double-blind, placebo-controlled trials indexing a total of 219 and 150 patients, respectively, with extended follow-up over 5 years, showed that long-term, high-dose UDCA (17 to 30 mg/kg body weight/day) improved liver tests but did not decrease clinical end points of cirrhosis, varices, cholangiocarcinoma, liver transplantation, or death (Olsson et al, 2005; Lindor et al, 2009). In fact, Lindor and others demonstrated that adverse events were more likely to occur in the high-dose UDCA group than in the placebo group.

Although UDCA plays a limited role in slowing the progression of liver disease, it has been shown to affect the frequency of colonic neoplasia or cancer in patients with PSC and CUC. In a cross-sectional study of 59 patients with both PSC and CUC who were undergoing colonoscopic surveillance, UDCA use was associated with decreased prevalence of colonic dysplasia (Tung et al, 2001). In another randomized, placebo-controlled trial of 52 patients with concurrent PSC and CUC, use of UDCA resulted in a relative risk of 0.26 for developing colorectal dysplasia or cancer (Pardi et al, 2003). Additional, prospective, randomized controlled studies are needed to verify the proposed chemopreventive effect of UDCA in patients with PSC and CUC.

Surgical Therapy

The surgical approach to PSC has evolved tremendously in the past 3 decades. Choledochotomy with operative cholangiography and biopsy were once required for the diagnosis of PSC, but the need for these procedures has been obviated by the advent of endoscopic and percutaneous cholangiography. Similarly, palliative biliary reconstruction has largely been replaced by liver transplantation.

Reconstructive Biliary Surgery

In 1988, Cameron and colleagues reported the Johns Hopkins experience of reconstructive biliary surgery in 31 PSC patients who underwent this procedure for persistent jaundice or recurrent bacterial cholangitis (Cameron et al, 1988). This surgical approach included excision of the hepatic duct bifurcation and extrahepatic biliary tree, dilation of the intrahepatic ducts, insertion of Silastic transhepatic biliary stents, and bilateral hepaticojejunostomies. Five of 31 patients had cirrhosis. Of the 26 patients without cirrhosis, the 1-, 3-, and 5-year survival rates were 92%, 87%, and 71%, respectively. The mean bilirubin in the noncirrhotic group improved from 9.9 mg/dL to 4.3 mg/dL after 5 years. In contrast, two of the five patients with cirrhosis died after surgery, and only one survived the after the first postoperative year. The authors concluded that primary biliary reconstruction should be considered in noncirrhotic patients with severe stricturing at or near the hepatic duct bifurcation or in the distal biliary tree. Patients with cirrhosis should be referred for liver transplantation.

Over the past decade, biliary reconstructive surgery for PSC has become less common, because endoscopic techniques for bile duct dilation (see Chapter 27) and stenting, as well as outcomes with liver transplantation, have improved (see Chapter 97A). In addition, hesitation arose after several centers reported increased difficulty performing liver transplantation in patients who had previous biliary surgery. Despite this, biliary-enteric anastomosis may still be indicated in noncirrhotic patients with primarily extrahepatic disease. To compare efficacy of these different modes of therapy, Ahrendt and colleagues (1998) retrospectively reviewed 146 patients with PSC seen at the Johns Hopkins Hospital from 1980 to 1994. Of these, 50 patients underwent resection of the extrahepatic bile ducts and long-term transhepatic stenting (replaced every 2.2 months on average), 54 patients were managed nonoperatively with endoscopic balloon dilation with or without percutaneous stenting, 28 patients were treated medically, and 21 patients received liver transplantation (Ahrendt et al, 1998). Of the 50 patients managed with resection of the extrahepatic biliary tree, three patients (6%) died prior to hospital discharge, two of whom had cirrhosis. Of 21 patients, four (19%) died after liver transplant; there were no postprocedural deaths in the endoscopically managed group. In noncirrhotic patients managed with resection, bilirubin levels fell significantly from 8.2 mg/dL preoperatively to just over 3 mg/dL after 5 years. By comparison, those patients managed nonoperatively with endoscopic or percutaneous procedures had a slight lowering of their serum bilirubin levels at 1 and 3 years but returned to pretreatment levels by 5 years. Most significant, however, was the improvement in 5-year and transplant-free survival in patients managed with resection (85% and 78%, respectively) versus those managed with endoscopic dilation and/or percutaneous stenting (59% and 46%, respectively). Part of the difference in survival was due to the development of cholangiocarcinoma in three of the endoscopically managed patients. As the majority of cholangiocarcinomas occur in the perihilar region, this may explain why none of the patients who underwent resection died from this complication.

Myburgh (1994) reported on 24 patients with biliary enteric bypass without the need for transanastomotic stenting. With the Hepp-Couinaud technique, a side-to-side anastomosis 2.5 to

3.5 cm wide was performed between a Roux-en-Y loop of jejunum and the right and left hepatic ducts at their confluence. Without applying stents, the need of stent replacement, and thus the increased risk for bacterial cholangitis, was eliminated. Among the 16 noncirrhotic patients who underwent bypass, survival was 100%, and 11 remained free of jaundice with a median follow-up of 6.5 years; however, patients with cirrhosis derived minimal benefit (Myburgh, 1994).

It appears that biliary reconstructive surgery may be an effective palliative measure for selected noncirrhotic patients with primarily extrahepatic PSC. However, the association of biliary-enteric drainage surgical procedures with development of cholangiocarcinoma is a significant concern (Tocchi et al, 2001). In our practice, we refer PSC patients with dominant biliary strictures for endoscopic dilation, given the high degree of success attained by this procedure and its relative ease and low morbidity/mortality compared with biliary surgery. We recommend biliary reconstructive surgery for those few PSC patients who have persistent cholestasis but no cirrhosis; the biliary obstruction is not amenable to endoscopic treatment, and they are not candidates for liver transplantation.

Orthotopic Liver Transplantation

Orthotopic liver transplantation (OLT; see Chapter 97A) remains the most effective treatment for PSC. At the Mayo Clinic, the 1- and 5-year patient survival rates for PSC are 92% and 86%, respectively. These rates compare favorably with results of OLT for other chronic liver diseases. Wiesner and colleagues (1996) reported outcomes for patients who underwent OLT for PSC and identified risk factors that adversely affected outcome. These factors can be divided into those that influence OLT outcome and those that are specific for PSC. The former include residence in the intensive care unit or being on life support prior to transplantation, age greater than 65 years, poor nutritional status, Child-Pugh class C, and renal failure requiring dialysis prior to or after transplantation. These factors are also predictive of increased blood loss, prolonged ICU stay, and major postoperative complications. Risk factors specific for PSC are disease severity, previous biliary or shunt surgery, concurrent bile duct cancer, and presence of IBD.

Controversy surrounds the impact of prior biliary surgery on subsequent OLT for PSC. There is little doubt that prior biliary surgery increases the technical difficulty of OLT, but it is unknown whether this event affects survival. In a series of 26 patients, Farges and colleagues (1995) reported increased operative time, increased blood loss, and severe complications—including death—in 12 OLT patients who had undergone previous right upper quadrant abdominal operations. In a combined series of 216 patients from the University of Pittsburgh and Mayo Clinic, prior biliary tract and/or portal hypertensive surgery was associated with increased mortality the first 5 years after OLT, but this did not reach statistical significance (Abu-Elmagd et al, 1993). At the University of California at San Francisco, increased operative time and blood loss were reported, but not increased mortality, in PSC patients with history of prior colectomy or biliary surgery other than simple cholecystectomy (Narumi et al, 1995). Ahrendt and others (1998) reported the Johns Hopkins experience with 21 PSC patients who had undergone OLT; they found significantly increased operative time and blood loss in patients with previous biliary tract operations, as well as increased operative mortality, but this finding did not reach statistical significance. These reports suggest that prior biliary tract surgery increases the technical difficulty of OLT for PSC with a trend toward increased mortality.

After OLT, complications occur that are unique to PSC patients. Increased rates of biliary strictures have been noted in patients transplanted for PSC. This increase may not represent disease recurrence, as other factors may also cause biliary stricturing, such as ischemia related to chronic rejection or possible chronic low-grade bacterial cholangitis resulting from the Roux-en-Y anastomosis, which is performed much more frequently in patients with PSC. However, a University of Pittsburgh study found a significantly greater incidence of biliary strictures in allografts of patients transplanted for PSC versus patients who had OLT and choledochojejunostomy anastomosis for other end-stage liver disease (Sheng et al, 1993). Because cholangiographic and other clinical and biochemical criteria for recurrent disease have not been widely accepted, there is no consensus regarding incidence of recurrent PSC in liver allografts. Careful analysis at our institution concluded that 20% of patients transplanted for PSC developed recurrent disease based on characteristic cholangiographic and histologic features (Graziadei et al, 1999). PSC may recur earlier at a higher ratio after living-donor liver transplantation, particularly when the graft is from a biologically related living donor (Tamura et al, 2007). Proposed risk factors for recurrent PSC include IBD, prolonged ischemia time, number of cellular rejection episodes, prior biliary surgery, cytomegalovirus infection, and lymphotoxic cross match (Gautam et al, 2006).

Acute and chronic ductopenic rejection can be severe and steroid resistant, often resulting in graft loss. In a study of 100 consecutive PSC patients transplanted at Baylor University, it was reported that chronic rejection and disease recurrence occurred in 13% and 16%, respectively. These events adversely affected both graft and patient survival, markedly so in those patients with chronic rejection (Jeyarajah et al, 1998). Five-year graft survival rates were 33% and 65%, respectively, for patients with chronic rejection and disease recurrence compared with 76% for patients free of chronic rejection or recurrence. The authors suggested that chronic rejection and disease recurrence after transplantation for PSC are distinct entities, as evidenced by the difference in outcome, and that they should be managed accordingly.

Because many patients with PSC have CUC, concern has arisen over the possibility that OLT and attendant lifelong immunosuppression may increase the risk of colorectal carcinoma. In a study of 108 patients with PSC and concomitant IBD who underwent OLT, Loftus and others reported a fourfold, but not statistically significant, increase in colon carcinoma in the group that did not have a prior colectomy compared with the expected colon cancer in a group with comparable (pre-OLT) duration of IBD. This finding, however, did not affect patient survival (Loftus et al, 1998). Goss and colleagues (1997) also reported no difference in PSC patient survival in groups with or without a prior colectomy. Given the lack of impact on survival, we do not recommend prophylactic proctocolectomy in PSC patients with IBD who undergo OLT. Nonetheless, the risk of colonic neoplasia in these transplanted PSC patients warrants annual surveillance colonoscopy with biopsies and colectomy, even when only low-grade dysplasia is detected.

PSC patients with cholangiocarcinoma undergoing OLT merit additional discussion (see Chapter 97E). Survival after

OLT for patients with PSC and cholangiocarcinoma is dependent upon how and when the cancer is detected. Generally speaking, in PSC patients in whom cholangiocarcinoma was known preoperatively, OLT has been ineffective; indeed, recurrence of cholangiocarcinoma occurred almost uniformly. However, *incidental cholangiocarcinomas,* defined as tumors less than 1 cm in diameter discovered only at the time of pathologic sectioning of the explanted liver, portend a better prognosis. In a UCLA study, 8% of patients transplanted for PSC had an incidental cholangiocarcinoma with 5-year survival of 83%, which is not significantly different from the survival of patients undergoing OLT without incidental cholangiocarcinoma (Goss et al, 1997).

Resection of Cholangiocarcinoma

In the absence of PSC, surgical resection has been the most effective and only potentially curative treatment for cholangiocarcinoma. In patients with PSC and cholangiocarcinoma, resection is discouraged: cholangiocarcinoma is often multifocal, underlying parenchymal disease may preclude resection, and reported recurrent disease with death occurs in more than 90% of patients. This is because PSC is considered a premalignant disease. Historically, cholangiocarcinoma has been regarded as a contraindication for liver transplantation given high tumor recurrence in the transplanted organ, and disease-free and overall survival are no different from those of resection. However, selected liver transplant centers using radiation therapy, chemotherapy, and abdominal exploration prior to transplantation have shown promising outcomes for patients with hilar cholangiocarcinoma, with 5-year survival of 80% (Heimbach, 2008).

Proctocolectomy

The presence of PSC in patients with CUC affects the management of CUC. Much has already been said regarding the increased risk of dysplasia and colon carcinoma in patients with PSC. We currently recommend removal of the colon only for indications pertinent to IBD. However, the decision to perform a Brooke ileostomy or an ileal pouch–anal anastomosis (IPAA) is greatly influenced by the presence of PSC. In a retrospective analysis of patients with PSC and CUC treated with either Brooke ileostomy or IPAA, 8 (26%) of 31 patients with the ileostomy developed peristomal varices and subsequent bleeding, but none of the 40 patients who underwent IPAA developed perianastomotic varices or perineal bleeding (Kartheuser et al, 1996). The cumulative risk of pouchitis at 10 years after IPAA was 61% in patients with PSC compared with 36% in patients with CUC alone (Penna et al, 1996). Therefore in PSC patients who need proctocolectomy, we recommend IPAA and not Brooke ileostomy, because treating pouchitis is simpler than managing bleeding peristomal varices.

CONCLUSION

PSC is a cholestatic liver disease of unknown etiology that primarily affects young men and is strongly associated with IBD. The disease is characterized by a progressive, fibrous obliteration of the biliary tree leading to cirrhosis, portal hypertension, and subsequent liver failure. During the course of PSC, patients develop disease-specific and nonspecific complications. Management is challenging and requires a team approach by experts from multiple subspecialties, although to date effective medical therapy is lacking. Currently, OLT is the only curative treatment. More studies are needed to understand the pathogenesis of PSC before we can develop more effective novel therapies.

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CHAPTER 42A

Benign biliary strictures

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OVERVIEW

Benign biliary strictures pose difficult management problems. In contrast to malignant biliary obstruction, in which short-term palliation is often the goal of therapy, benign strictures require durable repair because most patients are in otherwise good health and are expected to live for years. Many of these strictures result from iatrogenic injuries, often in young patients in the most productive years of life. Improper management has disastrous complications, such as biliary cirrhosis, portal hypertension, or recurrent cholangitis. Repeated intervention greatly reduces the likelihood of a successful outcome. It is imperative that any attempt at repair be carried out in a precise and expert manner in the setting of a specialist center. The best results are achieved through early diagnosis, mature clinical judgment, and technical expertise at the first attempt at repair.

Benign biliary strictures may affect the intrahepatic or extrahepatic bile ducts or both and may be solitary or multiple. Several causes of benign biliary strictures have been described (Table 42A.1). Iatrogenic injuries after cholecystectomy are the most commonly reported and best characterized causes, and they are emphasized in this chapter to illustrate the principles of diagnosis and management. Strictures and other injuries also may occur after common bile duct (CBD) exploration or biliary reconstruction. Other procedures in the upper abdomen may endanger the biliary tract, especially procedures involving the liver, pancreas, and stomach/duodenum. The true incidence of biliary injury after these procedures is difficult to assess, but it seems to be substantially lower than after cholecystectomy.

BILE DUCT INJURY AT CHOLECYSTECTOMY

Incidence

Because of the great frequency with which the operation is performed, cholecystectomy remains the greatest source of postoperative biliary injuries. Open cholecystectomy has long been associated with a modest incidence of biliary injuries. In a review of more than 42,000 open cholecystectomies performed in the United States in 1989, Roslyn and others (1993) documented a 0.2% incidence of biliary injuries. Strasberg and colleagues (1995) reported a 0.3% incidence of injuries in a literature review of more than 25,000 open cholecystectomies since 1980. The advent of laparoscopic cholecystectomy (see Chapter 34) has refocused attention on this issue, however, because of the significant increase in the number of injuries.

Early studies worldwide documented a marked increase in the frequency of bile duct injuries associated with the laparoscopic approach, ranging from 0.4% to 1.3% (Deziel et al, 1993; Richardson et al, 1996; Wherry et al, 1996; Adamsen et al, 1997; MacFadyen et al, 1998; Fletcher et al, 1999). In a review of nearly 125,000 laparoscopic cholecystectomies reported in the literature in the years 1991 through 1993, Strasberg and colleagues (1995) reported an overall incidence of biliary injuries of 0.85% and incidence of major injuries of 0.52%. Recent studies evaluating biliary injury rates more than a decade since the widespread introduction of the laparoscopic technique confirm a stable yet high indicence of iatrogenic injury, with the incidence ranging between 0.3% and 0.6% in larger studies (Nuzzo et al, 2005; Kaman et al, 2006; Waage & Nilsson, 2006; Tantia et al, 2008). Given the inherent difficulties in collecting data on postcholecystectomy biliary injuries, the true incidence at any one time may never be known precisely; however, the figures reported for laparoscopic cholecystectomy represent a substantial increase over historical controls reported for open cholecystectomy.

The bile duct is at increased risk of injury during laparoscopic cholecystectomy compared with open cholecystectomy for several reasons that will be discussed later. It has long been argued that surgeon inexperience is a major factor, and that with increased familiarity with the procedure, the number of injuries would decrease—the so-called *learning curve effect* (Southern Surgeons Club, 1991). Considerable evidence supports this view. Several authors have shown an inverse relationship between the incidence of bile duct injuries and the number of cases performed (Deziel et al, 1993; Gigot et al, 1997; Woods et al, 1994) and a decreased bile duct injury rate when performed by specialized hepatobiliary surgeons (Boddy et al, 2007). Also, large population-based reviews have documented a decline in injuries over time (Richardson et al, 1996; Russell et al, 1996). However, these trends have not been observed by all investigators. A recent report spanning more than 12 years showed that an initial decline in injuries was not sustained at the end of the study (Waage & Nilsson, 2006). Several other reports have suggested no change in the incidence of bile duct injuries over time (Adamsen et al, 1997; Fletcher et al, 1999; Wherry et al, 1996), and the number and complexity of cases referred for repair have remained static at some specialist units (Walsh et al, 1998). Reports of major bile duct injuries inflicted by surgeons with considerable experience continue to appear (Carroll et al, 1996; Gigot et al, 1997). Moreover, the role of hospital volume does not seem to affect the incidence of injuries (Waage & Nilsson, 2006; Csikesz et al, 2009). The data suggest that laparoscopic postcholecystectomy bile duct injuries will remain a significant problem for the foreseeable future.

Pathogenesis

Several factors are associated with an increased risk of bile duct injury at cholecystectomy, some of which are general and some

Table 42A.1

Causes of Benign Biliary Strictures

- **I.** Congenital strictures
  - **A.** Biliary atresia (see Chapter 40)
- **II.** Bile duct injuries
  - **A.** Postoperative strictures
    - **1.** Cholecystectomy or common bile duct exploration
    - **2.** Biliary-enteric anastomosis
    - **3.** Hepatic resection
    - **4.** Portocaval shunt
    - **5.** Pancreatic surgery
    - **6.** Gastrectomy
    - **7.** Liver transplantation (see Chapter 100)
  - **B.** Strictures after blunt or penetrating trauma (see Chapters 102 and 103)
  - **C.** Strictures after endoscopic or percutaneous biliary intubation
- **III.** Inflammatory strictures
  - **A.** Cholelithiasis or choledocholithiasis
  - **B.** Chronic pancreatitis
  - **C.** Chronic duodenal ulceration
  - **D.** Abscess or inflammation of liver or subhepatic space
  - **E.** Parasitic infection (see Chapters 67 and 68)
  - **F.** Recurrent pyogenic cholangitis (see Chapter 44)
- **IV.** Primary sclerosing cholangitis (see Chapter 41)
- **V.** Radiation-induced stricture
- **VI.** Papillary stenosis

Table 42A.2

Classification of Causes of Laparoscopic Biliary Injuries

Misidentification of the bile ducts as the cystic duct
Misidentification of the common bile duct as the cystic duct
Misidentification of an aberrant right sectoral hepatic duct as the cystic duct
Technical causes
Improper techniques of ductal exploration
Failure to occlude the cystic duct securely
Plane of dissection away from gallbladder wall into the liver bed
Excessive traction on cystic duct with tenting upward of common hepatic duct
Injudicious use of electrocautery for dissection or bleeding control
Injudicious use of clips to control bleeding

Modified from Strasberg SM, et al, 1995: An analysis of the problem of biliary injury during laparoscopic cholecystectomy. J Am Coll Surg 180:101–125.

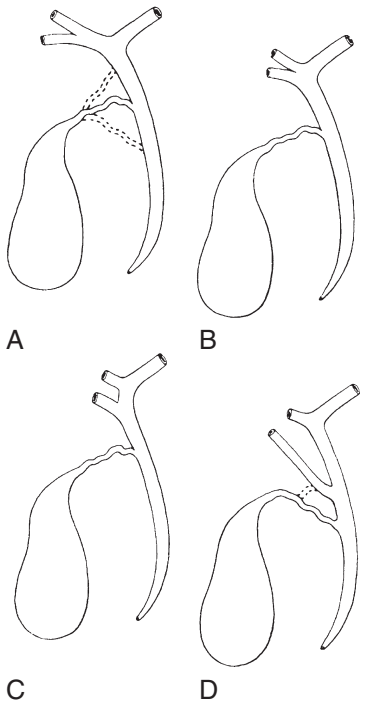


FIGURE 42A.1. Schematic representations of various junctions of the cystic duct with the main extrahepatic biliary channel. **A,** The cystic duct may join the main bile duct very high, almost at the confluence of the hepatic ducts, or it may run parallel to the common hepatic duct before entering almost at the level of the ampulla of Vater. In this illustration, the right anterior and posterior sectoral hepatic ducts join to form a main right hepatic duct. **B,** The right anterior and posterior sectoral hepatic ducts may join the left hepatic duct at a common confluence. **C,** The right anterior and posterior sectoral hepatic ducts may join the left hepatic duct independently. **D,** The right anterior or posterior sectoral hepatic duct may join the common hepatic duct at a much lower level. The cystic duct may drain into such a duct. Another variation, not shown and probably not relevant for postcholecystectomy injuries, is entry of the right anterior or posterior sectoral hepatic duct into the left hepatic duct.

unique to the laparoscopic approach. Ultimately, the final common pathway of most injuries is either a technical error or misinterpretation of the anatomy (Table 42A.2; Strasberg et al, 1995; Olsen, 1997). Many authors classify biliary injuries as major, such as transection of the CBD, or minor, such as biliary leak; but the line separating the two is often blurred. In general, major injuries are more serious and usually require reoperation to repair. Minor injuries are not always trivial, however, and they may require operative intervention. The classification of biliary injuries is discussed later.

Anatomic Variations

Any surgeon operating on the biliary tree must be familiar with the wide range of anatomic variations that may be encountered (see Chapter 1B). Anomalies of the cystic duct insertion into the common hepatic duct are most commonly seen (Fig. 42A.1). The cystic duct may join the common hepatic duct quite high, almost at the biliary confluence, or it may run parallel to the common hepatic duct for a long distance before joining it very low, occasionally at the level of the ampulla. In many patients, perhaps 25%, the right hepatic duct *per se* is absent, and the right anterior and posterior sectoral hepatic ducts join the left hepatic duct independently. In some cases, one of the right sectoral hepatic ducts, usually the anterior, may follow a prolonged extrahepatic course and enter the common hepatic duct quite low, and it may receive drainage from the cystic duct (see Fig. 42A.1D). Such unrecognized, low-entry right sectoral hepatic ducts (Bismuth type 5) are at particular risk of injury during laparoscopic cholecystectomy (Fig. 42A.2; Wherry et al, 1996).

In the future, routine use of preoperative imaging may help minimize bile duct injuries by identifying aberrant biliary anatomy. Already, some centers are examining the utility of preoperative CT cholangiography and MRI in preventing this complication (Hirano et al, 2006). Widespread adoption of this strategy will clearly be costly, but it could be justified: some

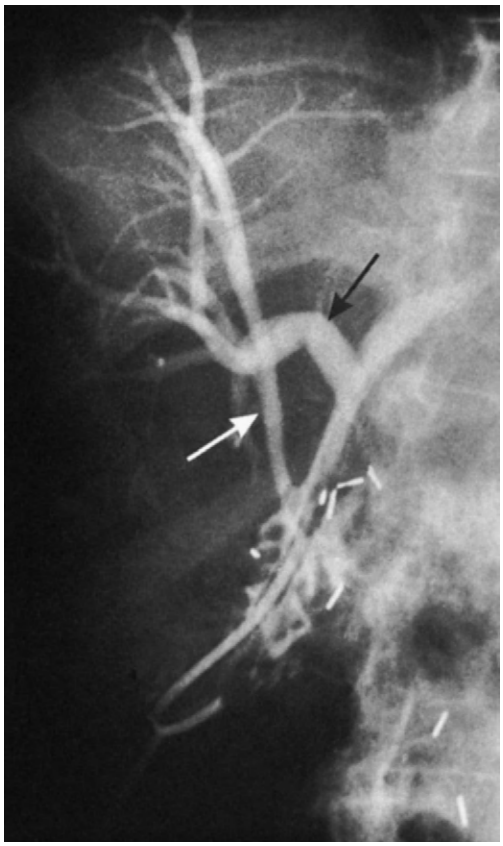


FIGURE 42A.2. The right anterior sectoral hepatic duct (*white arrow*) drains into the common hepatic duct, and the right posterior sectoral hepatic duct (*black arrow*) joins a main left hepatic duct. In this patient, cholecystectomy was accompanied by a biliary injury at the point of confluence of the common hepatic duct and the right anterior sectoral hepatic duct (Bismuth type 5). Repair has been carried out by Roux-en-Y hepaticojejunostomy.

imaging studies document right ductal aberrancy in the general population ranging from 4.8% to 8.4% (Kullman et al, 1996; Dusunceli et al, 2004). In some cases, the cystic duct is quite short, and misinterpretation of the anatomy can occur easily. Misinterpretation is especially likely if, on intraoperative cholangiography, the catheter has been advanced well into the CBD, and the proximal ducts are not visualized. The surgeon may mistake the common duct for the cystic duct, ligate it, and remove it with the attached gallbladder (Fig. 42A.3). This type of injury seems to be much more common after laparoscopic rather than open cholecystectomy and is well described (Davidoff et al, 1992). A related situation can occur in cases of long-standing cholelithiasis and chronic cholecystitis, resulting in obliteration of the cystic duct, which we will discuss later.

Vascular anomalies also are common, occurring in 20% of patients (see Chapter 1B). In the most common of these, the right hepatic arterial supply arises in part or in whole from the superior mesenteric artery. Such an aberrant vessel usually courses to the right of the portal vein, lateral and posterior to the CBD. During cholecystectomy, this vessel is prone to injury at the junction of the cystic and common hepatic ducts. Vascular injuries are not limited to patients with anatomic anomalies. The classic biliary injury during laparoscopic cholecystectomy, in which the surgeon mistakes the CBD for the cystic duct, is frequently associated with injury to the right hepatic artery, which will be discussed (Davidoff et al, 1992). This problem has been documented to occur in as many as 0.6% of patients after laparoscopic cholecystectomy and may not be apparent at the initial operation but may come to attention later as a hepatic artery pseudoaneurysm (Balsara et al, 1998; Nicholson et al, 1999). Rarely, concomitant vascular injury may involve both the right hepatic artery and right portal vein, which can be life threatening (Fig. 42A.4).

Ischemia

In the absence of overt injury, delayed biliary stricture formation may result from extensive periductal dissection and consequent interruption of the major ductal arterial supply (see Chapter 1B). Most of the arterial supply to the extrahepatic bile duct is provided by two small arteries that travel along the lateral duct borders in the 3 o'clock and 9 o'clock positions. Sixty percent of the blood supply runs upward from the major inferior vessels (retroduodenal, gastroduodenal), and approximately 38% runs downward from the right hepatic artery (Northover & Terblanche, 1979). Extensive circumferential dissection of the duct may disrupt this axial blood flow and has been proposed as a major mechanism of biliary stricture formation. Although there is no direct evidence to support this, it would seem reasonable not to pursue extensive dissection of the common duct during cholecystectomy. Also, damage to these vessels is likely to be a contributing, if not a central factor, in the formation of strictures attributed to electrocautery use.

Pathologic Factors

Patients with acute cholecystitis may have severe inflammation in the porta hepatis and triangle of Calot, which greatly distorts the anatomy. In addition, the gallbladder is often friable and difficult to grasp, and persistent oozing of blood often obscures the field. Some or all of these factors may conspire to preclude safe laparoscopic cholecystectomy. During the early era of laparoscopic cholecystectomy, acute cholecystitis was considered an absolute contraindication. However, as experience with laparoscopy grew, surgeons became more comfortable extending the indication to include acute cholecystitis. Several reports later documented that the laparoscopic approach not only is possible but also is safe in selected cases of acute cholecystitis (Kum et al, 1996; Wherry et al, 1996; Adamsen et al, 1997; Fletcher et al, 1999; Neri et al, 2003). As a result, laparoscopic cholecystectomy for acute cholecystitis is now widely practiced; in fact, the issue regarding timing of operation (early vs. delayed) has been settled (see Chapter 31; Casillas et al, 2008; Gurusamy et al, 2009). When laparoscopic cholecystectomy is performed for acute cholecystitis, studies have also revealed a greater potential for biliary injury (Kholdebarin et al, 2008). Fletcher and colleagues (1999) reported that complex cases that include patients with acute cholecystitis, cholangitis, and gallstone pancreatitis are associated with a dramatically increased incidence of bile duct injuries (1.7%), although acute cholecystitis alone is not an independent risk factor. Other authors have shown that acute cholecystitis increases the incidence of bile duct injuries twofold to threefold above baseline (Adamsen et al, 1997; Russell et al, 1996; Soderlund et al, 2005). In patients seen initially with acute cholecystitis, we recommend early operation by laparoscopic approach, even in patients with a history of prior open abdominal surgery. Given the increased risk of biliary injury in this setting, however, the

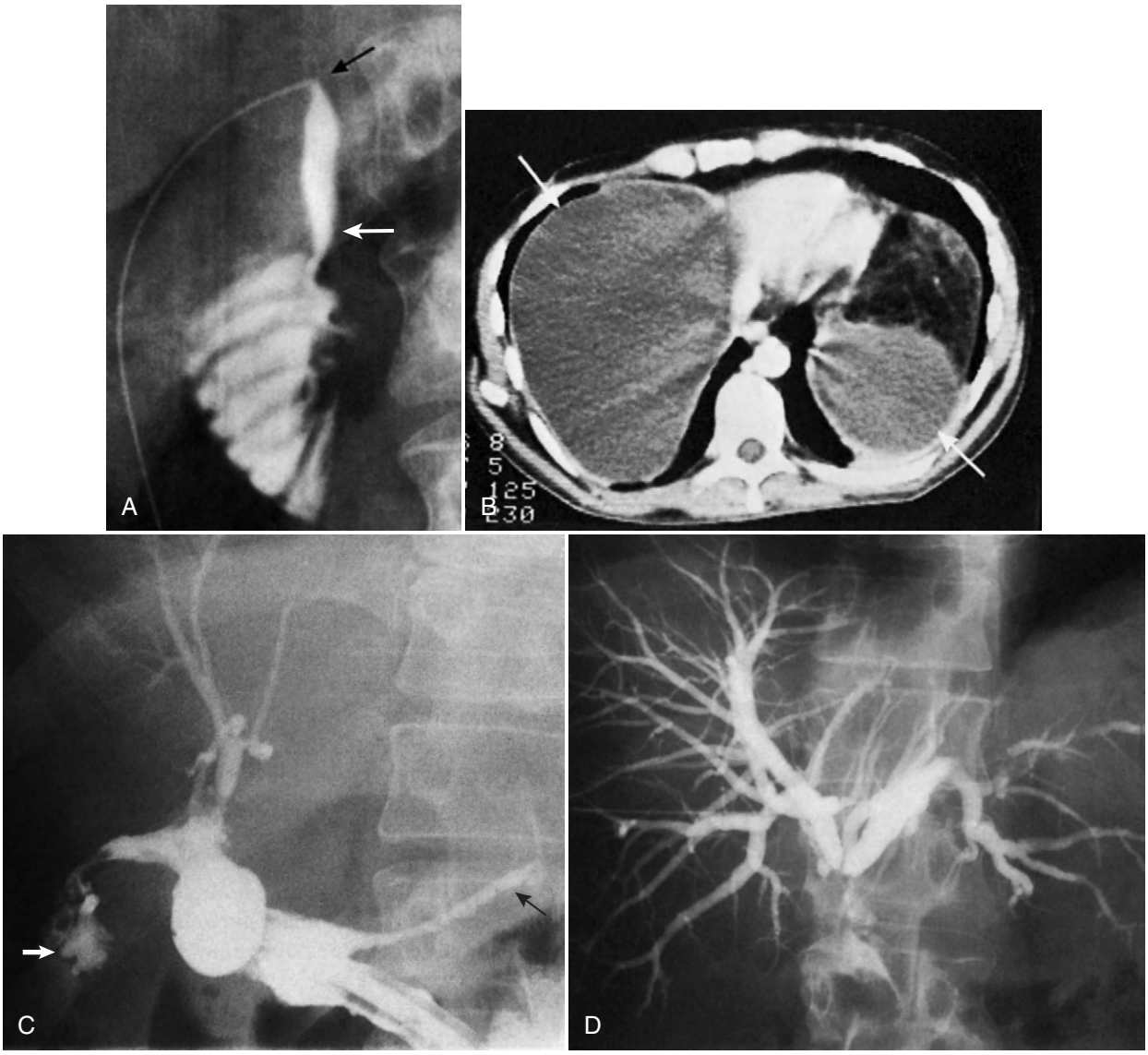


FIGURE 42A.3. **A,** Operative cholangiogram obtained after cannulation of the cystic duct. The cannula has entered the common bile duct (*black arrow*), and only the common bile duct has been outlined (*white arrow*). The common hepatic duct has not been visualized. The surgeon proceeded with cholecystectomy in the belief that he had cannulated the cystic duct. **B,** The patient became extremely ill after surgery and was referred. Computed tomographic scan revealed massive collections of intraperitoneal bile (*arrows*), which were drained. **C,** A subsequent fistulogram revealed a fistulous tract with connections to the right (*white arrow*) and left abdomen (*black arrow*). The right anterior sectoral hepatic duct also is seen. The patient, now well and free of jaundice, was monitored. **D,** Percutaneous transhepatic cholangiography obtained after the patient returned with jaundice showed that the fistula has closed, and a stricture had formed just below the biliary confluence (Bismuth type 3). Repair was performed by Roux-en-Y hepaticojejunostomy using an approach to the left hepatic duct and extending the dissection to the right.

threshold for conversion to an open procedure should always be low.

On occasion, the inflammatory reaction is so severe that even conversion to an open procedure does not clarify the anatomy. Fibrosis and inflammation within the triangle of Calot make dissection of the cystic duct particularly hazardous. In severe cases, the gallbladder neck and cystic duct may be fused to the common duct within a sheath of scar tissue. This finding should lead the surgeon away from an extensive dissection to define the cystic duct, which risks a major biliary injury. Placement of a cholecystostomy tube may be a safer approach. An alternative option is partial (subtotal) cholecystectomy with amputation of the gallbladder, well away from the cystic duct/common hepatic duct junction, and placement of a drain. This procedure is generally safe and effective, and in a review of 1100 patients, only 11.2% required operative reintervention (Soleimani et al, 2007). Moreover, centers have reported a significant decrease in the incidence of bile duct injuries since the introduction of laparoscopic subtotal cholecystectomy (Nakajima et al, 2009). In such heavily fibrosed cases, the cystic duct is nearly always obliterated, and postoperative biliary leak is infrequent.

A potentially more difficult problem is the small, contracted, fibrotic gallbladder with extensive surrounding inflammation, sometimes partially embedded into the liver and obliterating the triangle of Calot such that the gallbladder neck and cystic

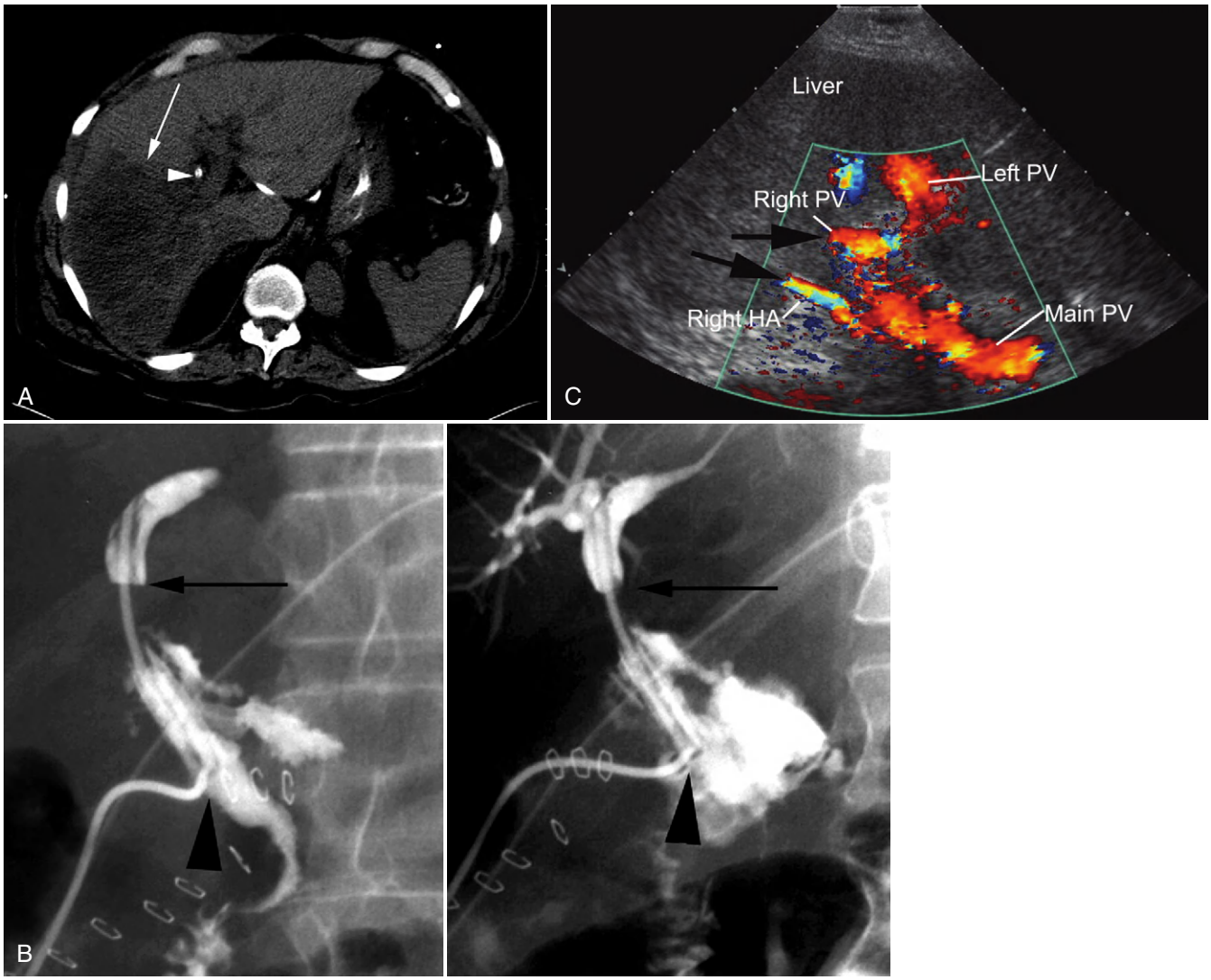


FIGURE 42A.4. A, Transaxial computed tomographic scan without intravenous contrast demonstrating the hypoperfused right lobe (*white arrow*) and an intraoperatively placed biliary tube (*arrowhead*). In this patient, the surgeon was confronted with significant bleeding during laparoscopic cholecystectomy and converted to open operation. Bleeding involved the right hepatic artery (*HA*) and portal vein (*PV*); these were suture ligated to control the hemorrhage. **B,** A tube cholangiogram demonstrates the "classic" biliary injury during laparoscopic cholecystectomy: the common bile duct was mistaken for the cystic duct, and a long section of the common duct was excised up to the common hepatic duct (*arrow*). The arrowhead points to the tube insertion site in the distal common duct. **C,** Doppler ultrasonography demonstrates lack of flow in both the right HA and PV (*arrows*).

duct are adherent to the common hepatic duct (Fig. 42A.5B). In such cases, the cystic duct is obliterated, and safe dissection in Calot's triangle is impossible. With long-standing disease, particularly associated with large impacted gallstones in the gallbladder neck, a cholecystocholedochal fistula is possible. A common hepatic duct stricture may be present, resulting from an impacted stone and the subsequent inflammatory response (Mirizzi, 1948; see Chapter 42B). A cholecystocholedochal fistula should be suspected in any patient with gallstones, jaundice, cholangitis, and imaging studies or operative findings that suggest an inflamed and contracted gallbladder. In these cases, an attempt to perform a total cholecystectomy should be abandoned, because this would lead the surgeon directly into the common hepatic duct (Sharma et al, 1998). Rather, partial cholecystectomy with extraction of the stones allows inspection of the depths of the gallbladder and is preferable. A rush of bile into the operative field at this point is strong evidence for a cholecystocholedochal fistula, because the cystic duct is nearly always obliterated. Because a biliary stricture often lies distal to the fistula, direct closure of the defect should be avoided, and it should instead be reconstructed as a cholecystocholedochoduodenostomy (see Chapter 42B and Fig. 42A.5B).

Technical Factors

General

Cholecystectomy is performed so commonly that it is easy to adopt a casual attitude toward the procedure; this is unwise, however, because some of these cases can be quite challenging. Also, although it is true that inexperienced or poorly trained surgeons cause many bile duct injuries, as we discussed earlier, even the most well-trained and experienced surgeons can cause

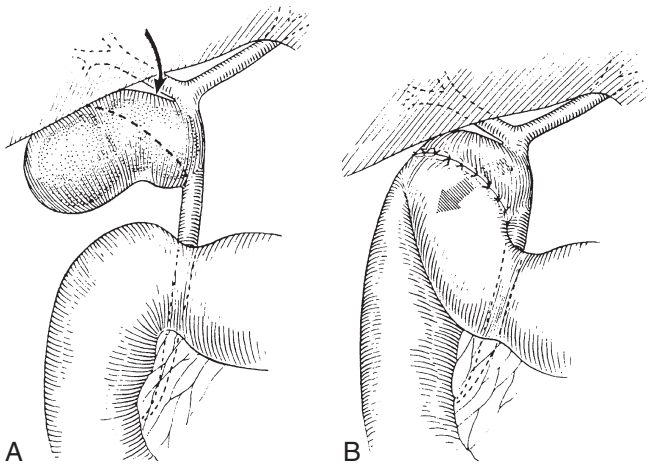


FIGURE 42A.5. A, Obliteration of Calot's triangle (*curved arrow*) by the inflammatory process accompanying severe chronic cholecystitis. The gallbladder is contracted around two large gallstones, one of which has eroded into the common hepatic duct, producing a cholecystocholedochal fistula. Such cases often present with obstructive jaundice or cholangitis. Complete cholecystectomy should not be attempted; it inevitably leads to biliary injury. Partial cholecystectomy (*dotted line*) can be performed with extraction of the calculi. **B,** Cholecystocholedochoduodenostomy can be done safely and with adequate drainage of bile.

an injury. It is imperative, therefore, that the surgeon adhere strictly to the basic tenets of cholecystectomy, either laparoscopic or open, to minimize the risk of biliary injury. Safe cholecystectomy requires clear visualization of the relevant anatomy, which demands proper exposure and modern high-resolution video equipment. Adequate assistance and retraction must be available, the incision must be adequate in length, and any trochars must be properly placed. It is imperative that no structure be ligated or divided unless its identity can be determined unequivocally.

Early reports of laparoscopic biliary injury cited bleeding and subsequent attempts to achieve hemostasis as major contributing factors to bile duct injury (Davidoff et al, 1992; Rossi & Tsao, 1994). At laparoscopy, even a small amount of blood obscures the field and hinders dissection. If necessary, an additional port should be placed for a high-powered suctioner/irrigator to precisely define the site of bleeding. Hemorrhage must be controlled, regardless of the approach, and blind placement of clips or indiscriminate use of electrocautery must be avoided. Early demonstration of the cystic artery is desirable, and it should be divided close to the gallbladder to avoid injury to the right hepatic or common hepatic artery.

Excessive traction on the gallbladder during cholecystectomy may tent the common duct upward, putting it at risk of injury if unrecognized. This mechanism does not seem to be as common at laparoscopic cholecystectomy, although other problems related to retraction may predispose to biliary injury at laparoscopy, which will be discussed later. Some authors have argued that the cystic duct–common hepatic duct junction should be precisely demonstrated before it is ligated and divided, even if this requires separating an adherent cystic duct and tracing it to its termination (Kune & Sali, 1981). We firmly believe that this is unnecessary and potentially hazardous; the risk of biliary injury with such extensive dissection is high and greatly outweighs the risk of a retained cystic duct stone.

The plane of dissection should be maintained as close to the gallbladder wall as possible to avoid entering the liver parenchyma. This is especially important when there is significant inflammation or fibrosis, and the ductal anatomy is unclear. Straying off the gallbladder wall may result in entry into the liver parenchyma and bleeding, further obscuring the field, or injury to a low-entry sectoral hepatic duct or a replaced right hepatic artery. In addition, the major right portal pedicles and branches of middle hepatic vein may be quite superficial in the liver substance with respect to the gallbladder fossa, and damage to these structures can occur if the plane of dissection is too deep. During a difficult open cholecystectomy, the advantage over the laparoscopic approach is that a finger can be inserted into the gallbladder to help define the proper plane.

The observation of bile draining from the gallbladder fossa always suggests the possibility of a biliary injury, perhaps to an aberrant right sectoral hepatic duct. It is tempting to ascribe such a finding to drainage from a subvesical duct of Lushka, a slender, 1- to 2-mm in diameter duct that passes from the right lobe in the gallbladder fossa to join the right hepatic or common hepatic duct (McMahon et al, 1995). In this situation, a major bile duct injury must be considered the leading diagnosis until disproved, and the surgeon is compelled to convert to an open procedure or to place a drain and investigate the cause postoperatively. Regarding the duct of Lushka, although some surgeons question its existence, several detailed anatomic and radiologic imaging studies have reliably identified its structure and course (Kocabiyik et al, 2009). Most patients with bile leaks attributable to a subvesical duct experience a delayed onset of symptoms and are usually seen in the first or second week following the procedure (Fig. 42A.6). In a review of nearly 10,000 patients, the incidence of bile leakage was 0.7%, of which 52% were leaks from subvesical ducts (Spanos & Syrakos, 2006).

The utility of routine cystic duct cholangiography is controversial (see Chapter 21), particularly with respect to reducing the incidence of biliary injury at laparoscopic cholecystectomy, which will be discussed later. Occasionally, operative cholangiography reveals a very small CBD with a filling defect, suggesting a small stone. In this situation, simple cholecystectomy without exploration of the common duct is probably safer than operative pursuit of a tiny stone in a small duct. Postoperative endoscopic cholangiography with stone extraction is nearly always possible if subsequently indicated. In general, exploration of a small caliber, otherwise normal-appearing common duct is frequently unrewarding, potentially dangerous, and more likely to result in postoperative symptoms than if such a stone were left in situ. Biliary strictures are more than just a theoretical concern after exploration of a small bile duct (Fig. 42A.7). Rarely, bile duct stones retained after cholecystectomy that are not removable by endoscopic means require reoperation (Fig. 42A.8; see Chapters 35 and 36). Under these circumstances, laparoscopic removal is usually possible via a transcholedochotomy approach (see Chapter 34). If this approach fails, an open exploration can often be avoided by placing a T-tube into the CBD for subsequent operative retrieval by intervential radiology techniques, which are successful in more than 95% of cases (Burhenne, 1980). When indicated at cholecystectomy or after failed attempts by other methods, open exploration of the CBD should be performed through a supraduodenal choledochotomy with careful exposure of a sufficient length of duct but without excessive dissection (see Chapters 29 and 35). Exploration must be gentle and performed only with soft bougies,

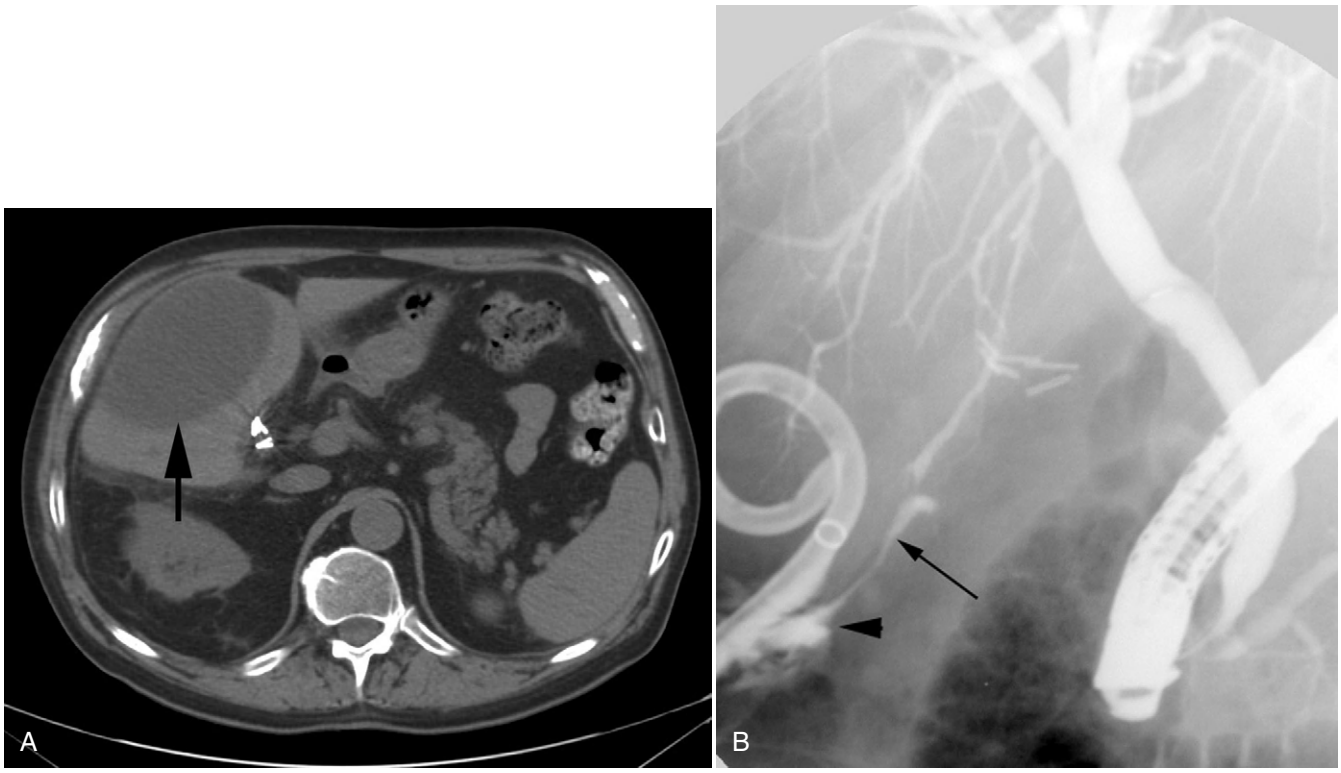


FIGURE 42A.6. **A,** Transaxial computed tomographic scan from a patient 2 weeks after elective laparoscopic cholecystectomy. The *arrow* points to perihepatic fluid collection consistent with a biloma. **B,** After percutaneous drainage of the biloma, the patient was evaluated by endoscopic retrograde cholangiopancreatography. The *arrow* points to the duct of Luschka; the *arrowhead* demonstrates contrast extravasation.

Fogarty-type balloon catheters, or a choledochoscope (rigid or flexible). Metal bougies such as Bake's dilators or stone forceps should be used with caution and should never be forced through the papilla of Vater into the duodenum; otherwise, secondary postinflammatory papillary stenosis may occur, or a false passage into the duodenum or pancreas may be created. After bile duct exploration, the choledochotomy should be closed with care, because this is also a potential source of biliary stricture (see Chapters 29 and 35).

Transduodenal sphincteroplasty probably is best reserved for patients with stones impacted in the distal bile duct (see Chapters 29 and 35). Stenosis or stricture of the distal CBD may occur after surgical or endoscopic sphincteroplasty or sphincterotomy. Side-to-side choledochoduodenostomy is an

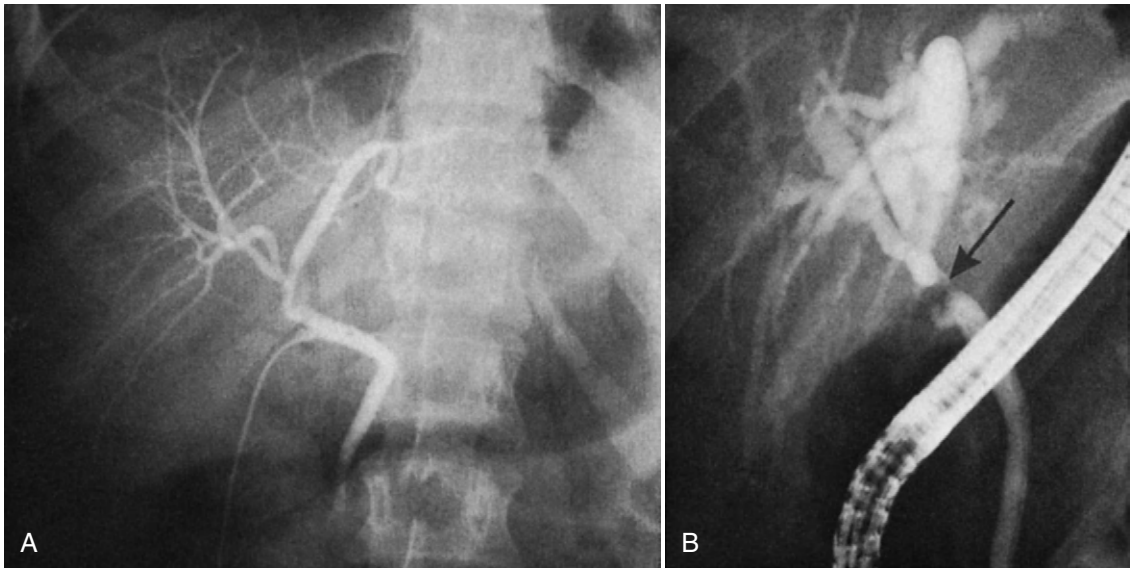


FIGURE 42A.7. **A,** Cystic duct cholangiogram obtained at cholecystectomy. A stone was suspected in a small-caliber common bile duct. Bile duct exploration was performed, but no stone was identified. **B,** Postoperatively, the patient developed recurrent attacks of cholangitis. Endoscopic cholangiogram showed a bile duct stricture at the previous choledochotomy site (*arrow*).

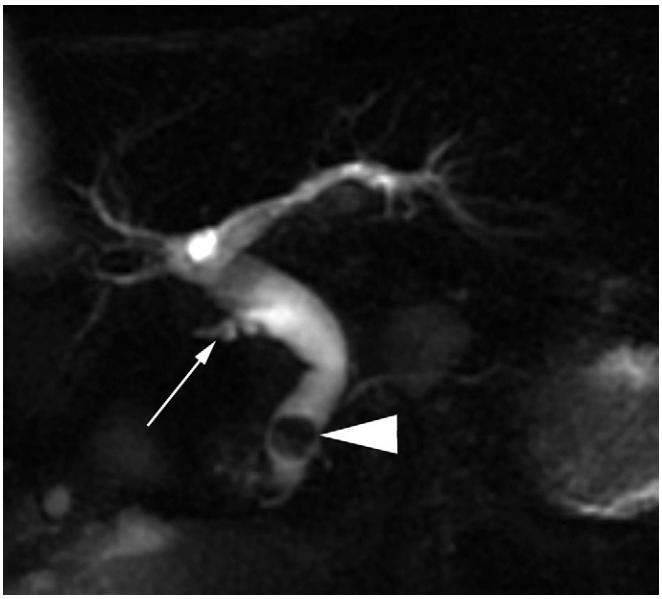


FIGURE 42A.8. Maximum intensity projection magnetic resonance cholangiopancreatographic, T2-weighed image demonstrates a large retained stone (*arrowhead*) within the common bile duct. This patient had previously undergone laparoscopic cholecystectomy and did not respond to postoperative removal by endoscopic means. The *arrow* points to cystic duct remnant.

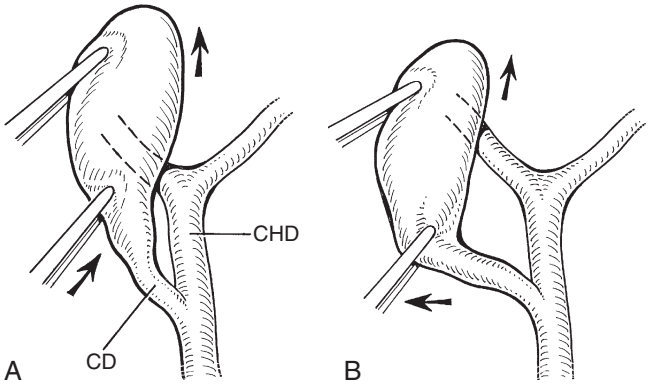


FIGURE 42A.9. Area of the triangle of Calot as it appears during laparoscopic cholecystectomy. **A,** Upward traction on the gallbladder, with insufficient lateral traction on the infundibulum, fails to open Calot's triangle adequately. This causes the cystic duct (*CD*) and common hepatic duct (*CHD*) to become aligned within the same plane. Injury to the CHD can occur during dissection of the CD because of its proximity or as a result of mistaking the CHD for the CD. **B,** Proper lateral traction on the infundibulum opens Calot's triangle, allowing safer dissection of the CD. In some cases, obliteration of Calot's triangle by dense fibrosis prevents adequate exposure of this area, even with adequate traction (see Fig. 42A.5).

option that should be considered in patients with multiple stones, primary stasis stones, or distal obstruction by stricture or papillary stenosis. The results are generally good, provided that the CBD is dilated to at least 15 mm in diameter, and a stoma of at least 2 cm can be created (Schein & Gliedman, 1981). Choledochoduodenostomy performed to a decompressed duct is more likely to result in stricture formation and cholangitis (see Chapter 29; Johnson & Stevens, 1969).

Laparoscopic-Specific Factors

Several technical factors specific to laparoscopic cholecystectomy predispose to biliary injury (see Chapter 34). Mistaking the common duct for the cystic duct is a frequent technical error (Davidoff et al, 1992; Gigot et al, 1997; Olsen, 1997). In the most common sequence of events, a long length of the common duct is excised up to the proximal common hepatic duct, which is either occluded or left to drain bile into the peritoneal cavity. This devastating injury—referred to as the "classic" laparoscopic injury, rarely seen at open cholecystectomy—also may be associated with damage to the right hepatic artery (Davidoff et al, 1992; Strasberg et al, 1995). Less severe injuries also may occur, such as lacerations of the duct wall or near-complete transections. Proper exposure is essential to avoid injuries arising from such anatomic misinterpretations. Maximum cephalad traction on the gallbladder fundus is necessary to expose the cystic duct and triangle of Calot. Concomitant lateral traction on the infundibulum is equally important, however, to open the angle between the cystic and common hepatic ducts. If lateral traction is inadequate, Calot's triangle is not opened sufficiently, and the course of the common duct is placed directly in line with that of the cystic duct (Fig. 42A.9; Rossi & Tsao, 1994; McMahon et al, 1995). The common duct may be damaged during dissection of the cystic duct because of its proximity, or because it is misidentified. Before any structures are divided, Calot's triangle must be cleared of all fatty and areolar tissue. The peritoneal reflection along the posterolateral aspect of the gallbladder should be opened to fully expose the junction of the gallbladder neck and cystic duct. At the completion of the dissection, only the cystic artery and cystic duct should be seen entering the gallbladder, and the bottom of the gallbladder fossa should be visible. The use of a 30-degree laparoscope has been advocated to improve visualization of this area (Hunter, 1991), and the resulting anatomically satisfying final view has been described by Strasberg (1995) as the "critical view of safety." The dissection should be maintained close to the gallbladder wall, and the cystic duct should be divided as close as possible to its junction with the gallbladder.

Routine intraoperative cholangiography has been advocated by many to minimize the incidence of laparoscopic biliary injuries (Way, 1992; Moossa et al, 1992; Asbun et al, 1993), but it remains controversial. In a meta-analysis encompassing more than 327,000 laparoscopic cholecystectomies, Ludwig and colleagues (2002) noted contribution of intraoperative cholangiography to incidence and outcome of CBD injuries during laparoscopic cholecystectomy and found injury rates to be halved in a routine cholangiogram group (0.21%) compared with a selective group (0.43%). A valid concern regarding the conclusions from these studies is that surgeons who use selective cholangiography do so appropriately in situations of inflammation or unclear anatomy inherently associated with increased risk of bile duct injuries. Thus, the injury rate under these circumstances can be artificially elevated, because the denominator —that is, the number cholecystectomies done without cholangiogram—is not typically included in the overall analysis. In a large review of cholecystectomies from Western Australia, Fletcher and colleagues (1999) reported that intraoperative cholangiography reduced the incidence of biliary injury twofold overall and eightfold in complex cases (acute cholecystitis, cholangitis, pancreatitis). In addition, some authors noted a strong inverse correlation between biliary injury and nonperformance

of cholangiography (Torkington et al, 1999). Cholangiography is clearly not preventive if the injury occurs after a normal study, or if the study serves only to identify an injury that already has been inflicted (Andren-Sandberg et al, 1985).

Other groups, however, have touted the lack of statistical benefit with the routine use of intraoperative cholangiography. A survey analysis of more than 184 Italian hospitals accounting for more than 56,000 operations demonstrated no significant difference between bile duct injury rate when cholangiogram was used routinely or selectively (Nuzzo et al, 2005). In contrast, several other reports have suggested that routine cholangiography may not reduce the incidence of biliary injury but may minimize injury severity and allow immediate recognition and definitive repair (Gigot et al, 1997; Woods et al, 1994; Carroll et al, 1996; Russell et al, 1996); this depends on proper interpretation of the study. In a review of 177 biliary injuries, Olsen (1997) found that only two of 32 cholangiographies were correctly interpreted, despite evidence of impending bile duct transection in most. The most common error was accepting an incomplete study as normal, without opacification of the right and left hepatic ducts. In a similar study, Stewart and Way (2003) showed that in their series of 252 bile duct injuries, cholangiograms were obtained in 43 patients, but only nine were correctly interpreted intraoperatively. They concluded that these injuries stemmed from a misperception that was often so compelling that adjunctive cholangiographic data was likewise misperceived. Failure to opacify the proximal bile ducts in their entirety should prompt the surgeon to strongly consider open conversion. Laparoscopic ultrasound has been described as an alternative to cholangiography for delineation of the cystic duct and identification of common duct calculi (Tomonaga et al, 1999). Recent studies demonstrate the efficacy of the technique as an alternative to cholangiography (Machi et al, 2009; Hublet et al, 2009), but it is not widely used.

Bile leakage occurs with greater frequency after laparoscopic cholecystectomy than after open cholecystectomy, which may be related to the use of clips rather than ties or suture ligatures (McMahon et al, 1995). Clips are less secure than sutures and may become dislodged if improperly placed or if manipulated after placement (Nelson et al, 1992; Fig. 42A.10). Reports of clip migration leading to complications such as choledocholithiasis and pancreatitis have also been reported (Raoul et al, 1992; Cetta et al, 1997; Dolay et al, 2007). Also, incomplete occlusion may occur if clips are placed across a thickened, rigid cystic duct or a cystic duct containing stones or if other tissues are included. When placing clips, it is important that the tips meet to ensure adequate occlusion. If both tips cannot be visualized as the clip is being applied, damage to adjacent structures may occur. If the clip does not fit across the entire width of the cystic duct, the surgeon must consider the possibility that the structure about to be divided is not the cystic duct but the common duct. If the anatomy is clear, and the cystic duct is simply thickened, placement of a ligature may be more appropriate (Michalowski et al, 1998). Also, using electrocautery in areas adjacent to clips should be avoided, because this may result in conduction of thermal energy to the adjacent common duct and lead to delayed biliary structure.

Location and Classification

The ease of management, operative risk, and outcome of biliary injuries vary considerably and depend on the type of injury and its location (Chapman et al, 1995). It has long been recognized that strictures involving the CBD or distal common hepatic duct are easier to repair than are more proximal injuries. The anatomic classification of Bismuth has been widely adopted in recognition of this fact (Fig. 42A.11; Bismuth & Lazorthes, 1981). In this classification scheme, five stricture types are recognized, reflecting the location with respect to the hepatic duct confluence (types 1 through 4) or the involvement of an aberrant right sectoral hepatic duct with or without a concomitant hepatic duct stricture (type 5; Table 42A.3).

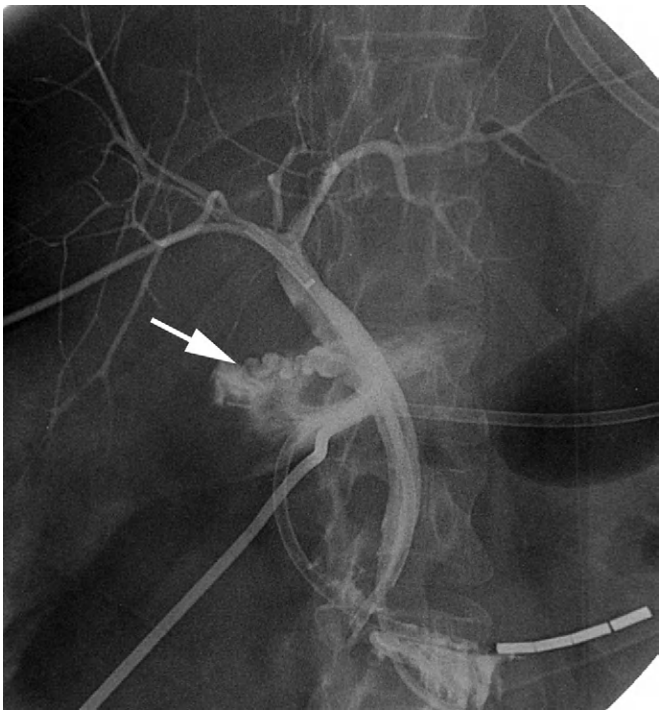


FIGURE 42A.10. Percutaneous transhepatic cholangiography on a patient who underwent laparoscopic cholecystectomy. A previously placed endoluminal stent failed to control bile leakage from the cystic duct stump (*arrow*). Note the percutaneous drain situated near the cystic duct remnant and the enteric feeding tube in the duodenum. This patient was managed nonoperatively.

The Bismuth classification is useful for localization and for prognosis after repair, but it does not encompass the entire spectrum of injuries that are possible. No provision is made for biliary leaks or major ductal injuries without stricture. Even within the group of patients with biliary leaks, there are varying degrees of severity. In an effort to fill this gap, Strasberg and colleagues (1995) proposed a comprehensive classification system that incorporates Bismuth's scheme but is much broader in scope (Fig. 42A.12). Injuries are classified as type A to type E, with the latter representing biliary strictures and further subdivided as E1 to E5 according to the Bismuth classification. *Type A* injuries are bile leaks from minor ducts still in continuity with the CBD. This encompasses the most common causes of biliary leaks seen after laparoscopic cholecystectomy—leakage from the cystic duct and from a subvesical duct of Luschka (see Figs 42A.6 and 42A.10). *Type B* injuries involve occlusion of part of the biliary tree, which for practical purposes almost always is an aberrant right sectoral hepatic duct. When this duct is transected without ligation, the injury is termed *type C*, reflecting the differences in presentation and management

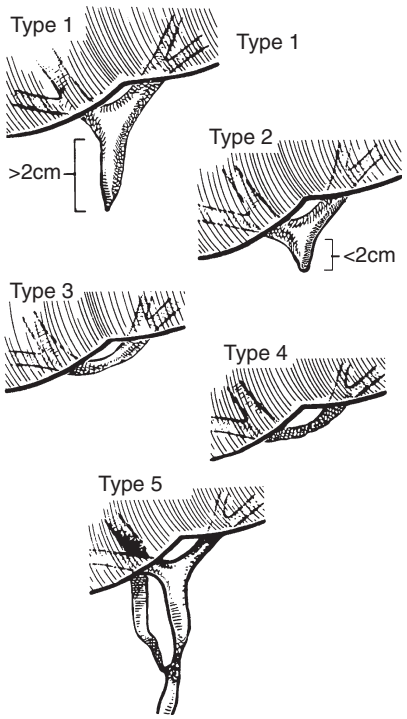


FIGURE 42A.11. Classification of bile duct strictures based on location with respect to the hepatic duct confluence (see Table 42A.3). *(From Bismuth H, 1982: Postoperative strictures of the bile duct. In Blumgart LH [ed]: The Biliary Tract: Clinical Surgery International. Edinburgh, Churchill Livingstone, pp 209-218.)*

between the two. A lateral injury to an extrahepatic bile duct is termed *type D*, which is similar to type A injuries in that the extrahepatic biliary tree remains in continuity but is classified separately to underscore the greater severity and potential need for major reconstruction (Fig. 42A.13).

The incidence of each type of biliary injury is difficult to ascertain with certainty. Most literature reports are derived from tertiary referral centers and are biased toward more severe injuries. Most surgical series focus on management of type E biliary strictures, whereas endoscopic and radiologic reports are concerned mainly with the treatment of biliary leaks. Type A injuries may be the most common, but many are managed successfully without referral and are underrepresented in reports from major centers (Strasberg et al, 1995).

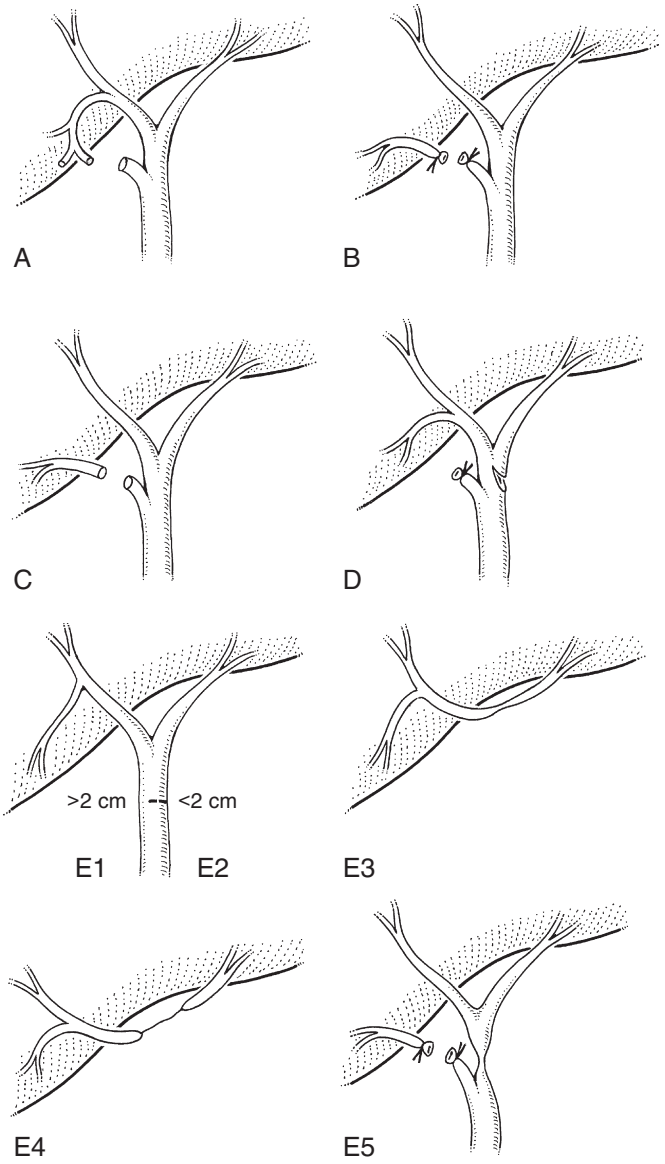


FIGURE 42A.12. Classification of laparoscopic biliary injuries according to Strasberg and colleagues (1995). Injuries are stratified from type A to type E. Type E injuries are subdivided further into E1 to E5 according to the Bismuth classification system.

Clinical Presentation

Most patients with postcholecystectomy biliary injuries, if not diagnosed at operation, come to medical attention early in the postoperative period. After open cholecystectomy, only about 10% of injuries are suspected after the first week, but nearly 70% are diagnosed within the first 6 months after operation (Pitt et al, 1982). By contrast, injuries after laparoscopic cholecystectomy seem to be recognized earlier (Davidoff et al, 1992; Lillemoe et al, 1997). This probably reflects differences in the pattern of injuries between the two approaches combined with a heightened awareness of the potential for injury at laparoscopy (Strasberg et al, 1995).

The clinical presentation depends on the type of injury; conversely, the type of injury may be inferred based on the clinical picture at presentation. Patients with significant bile leaks—types A, C, and D—generally present within the first week after operation, but some leaks may not become apparent for several weeks, and few are diagnosed intraoperatively (Strasberg et al, 1995). Most patients have abdominal pain coupled with fever

Table 42A.3

Bismuth Classification of Biliary Stricture

1. Low common hepatic duct stricture: hepatic duct stump >2 cm
2. Proximal common hepatic duct stricture: hepatic duct stump <2 cm
3. Hilar stricture with no residual common hepatic duct: hepatic duct confluence intact
4. Destruction of hepatic duct confluence: right and left hepatic ducts separated
5. Involvement of aberrant right sectoral hepatic duct alone or with concomitant stricture of the common hepatic duct

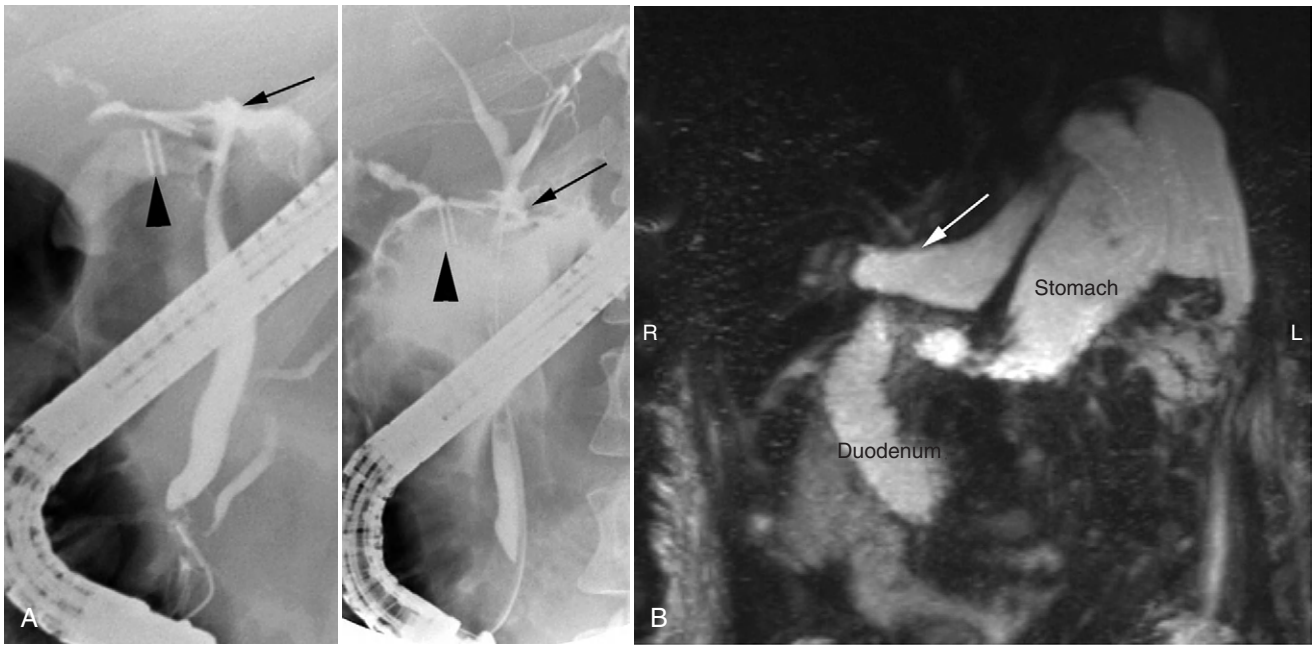


FIGURE 42A.13. A, Endoscopic retrograde cholangiopancreatography showing a Strasberg D injury. Early injection (*left*) shows contrast extravasation (*arrow*); *arrowhead* points to cyst duct clips. Higher pressure cholangiogram (*right*) shows contrast filling of the common duct and common hepatic duct. **B,** A coronal magnetic resonance cholangiopancreatography, T2-weighted image shows the biloma in the lesser sac. *Arrow* points to site of injury.

or other signs of sepsis, which is most common, or bile leakage from an incision. A few patients have none these signs and symptoms but rather have nonspecific complaints of weakness, fatigue, or anorexia. Elevated alkaline phosphatase levels are characteristic, as is mild hyperbilirubinemia, but markedly elevated serum bilirubin levels (>3 mg/dL) are uncommon (vanSonnenberg et al, 1993; Brooks et al, 1993).

Major injuries to the common duct (type E injuries) are more likely to be discovered intraoperatively, although most remain unrecognized until after operation. Similar to bile leaks, these injuries are diagnosed more often within the first few postoperative weeks, although patients with a slowly evolving stricture may not come to attention for several months (Strasberg et al, 1995), which is distinctly uncommon for patients with bile leaks. Most patients with these injuries present with jaundice often coupled with pain and occasionally sepsis. Jaundice is not always present early in the course of the illness. In some patients, the stricture may evolve slowly or cause only partial obstruction. Such patients may have nonspecific complaints, pruritus, or derangements in liver function tests (LFTs), any or all of which should prompt an investigation. In addition, patients with an isolated right sectoral hepatic duct injury (type B) or an internal biliary fistula may be seen initially with a history of unexplained fevers, pain, or general debilitation.

The findings on physical examination are often nonspecific. Jaundice, if present, is usually obvious, and there may be multiple skin excoriations from pruritus. Abdominal distension and pain may be seen in patients with bile peritonitis, whereas focal tenderness suggests a localized collection or abscess. Hepatomegaly may be seen with longstanding biliary obstruction. Splenomegaly or other signs of portal hypertension are uncommon, but if present, these should alert the surgeon to the possibility of concomitant portal venous injury or severe underlying hepatocellular damage. The presence of portal hypertension in association with a biliary stricture portends a poor outcome, and its identification is important not only for planning management but also in a medicolegal context.

Pathologic Consequences

Fibrosis

Biliary obstruction is associated with the formation of high local concentrations of bile salts at the canalicular membrane, and these initiate pathologic changes in the liver (Schaffner et al, 1971). Bile thrombi form within dilated centrilobular bile canaliculi, and secondary changes develop in adjacent hepatocytes. A complex cascade of molecular and cellular events ensues, collectively termed *fibrogenesis* (Friedman, 2008), which ultimately leads to the deposition of collagen and other extracellular matrix proteins and eventually to fibrosis and scarring around bile ducts and ductules (Maher & McGuire, 1990; Jarnagin et al, 1994; Friedman, 1997; see Chapter 6). As this process progresses, mechanical interference with bile flow develops in these intrahepatic biliary radicles and perpetuates cholestasis.

Fibrosis is accompanied by liver cell hyperplasia (Weinbren et al, 1985); this is not true in secondary biliary cirrhosis, because the lobular structure of the liver is usually well preserved (Fig. 42A.14) and the marked fibrosis that occurs in advanced cases only rarely progresses to true cirrhosis. This knowledge is important in planning therapy because many of these pathologic changes are reversible (Duffield et al, 2005). A histologic return of normal liver parenchyma is seen after relief of obstruction in both animal and human models (Sikora et al, 2008; Kirkland et al, 2009), which correlates to the return to near-normal liver function after relief of biliary obstruction (Blumgart, 1978). Fibrosis also may develop in the extrahepatic

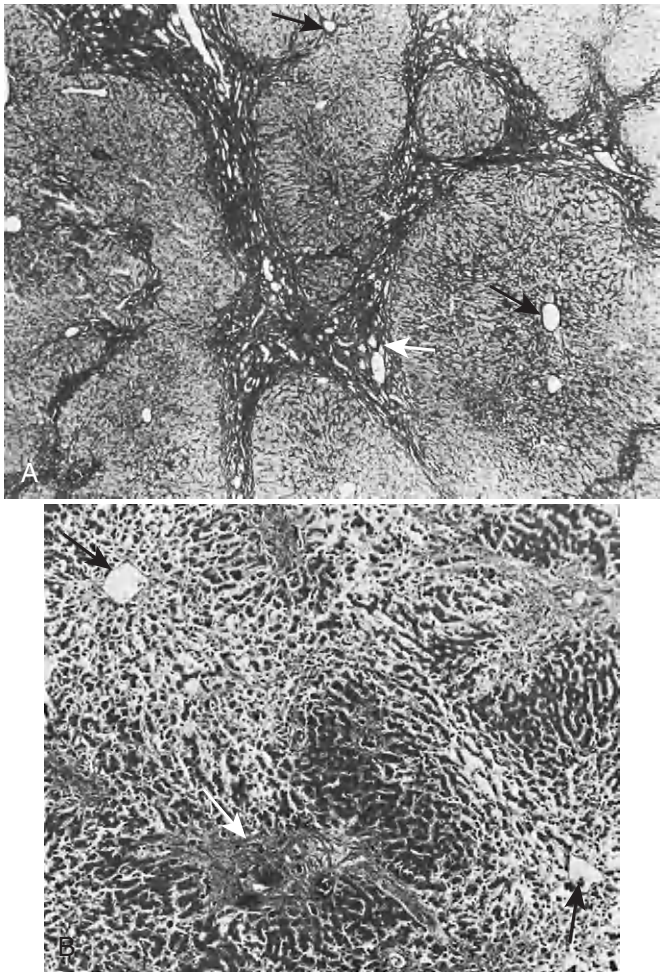


FIGURE 42A.14. A, Photomicrograph showing the effect of long-standing biliary obstruction secondary to benign biliary stricture. Hepatic fibrosis is present, but with preservation of the basic hepatic architecture, with the portal tract (*white arrow*) and hepatic venous radicles (*black arrows*) maintaining their normal relationships. The fibrosis extends between the lobules, but the pattern is not one of true cirrhosis, in which there is destruction of the basic hepatic architecture. **B,** Extensive fibrosis with a substantially normal relationship of hepatic venous radicles (*black arrows*) to portal tracts (*white arrow*) in a patient with portal hypertension. *(From Weinbren K, et al, 1985: Structural aspects of the liver in patients with biliary disease and portal hypertension. J Clin Pathol 38:1013-1020.)*

ducts proximal to the stricture, which is especially likely after biliary intubation. Upward retraction of the ducts is accompanied by a sequence of mucosal atrophy, squamous metaplasia, inflammatory infiltration, and further fibrosis in the subepithelial layers of the ducts.

It usually takes several years for liver fibrosis and portal hypertension (see Chapter 70) to become evident, although it may manifest 2 years after the development of the stricture. Major stigmata of hepatocellular dysfunction, such as spider angiomata and encephalopathy, are uncommon in benign biliary obstruction and should raise the possibility of preexisting parenchymal disease (e.g., chronic hepatitis, alcoholic liver disease). If liver biopsy reveals significant primary hepatocellular disease in association with a benign stricture, the prognosis is especially poor.

Atrophy

The distribution of liver mass is regulated by a poorly understood balance of bile flow, portal venous flow, and hepatic venous flow. Segmental or lobar atrophy may result from portal venous obstruction or bile duct occlusion in the affected area (see Chapter 5). Unilobar atrophy is associated with hypertrophy of the contralateral lobe and may present diagnostic and operative difficulties. Liver lobe atrophy and compensatory hypertrophy is frequently found in benign strictures and may be associated with asymmetric involvement of lobar or sectoral hepatic ducts, interference with portal venous blood supply, or decreased portal perfusion owing to secondary fibrosis. In benign strictures, the dilated ducts within the atrophic segments often are filled with infected bile and debris, and even though drainage of an atrophic segment would not be effective in relieving jaundice, cholangitis may continue unabated unless satisfactory drainage of the atrophic and hypertrophic segments is achieved.

The presence of significant atrophy and compensatory hypertrophy greatly influences the approach to repair. The most common situation is gross hypertrophy of the left lobe accompanied by right lobe atrophy (Czerniak et al, 1986). Anastomosis in the region of the hilum is made difficult by the rotational deformity and anatomic distortion imposed by this condition (see Chapters 5 and 29). A thoracoabdominal approach to such strictures provides more direct exposure and access for repair by allowing rotation of the liver to the left (Bismuth & Lazorthes, 1981). Recent reports verify that the presence of atrophy and contralateral hypertrophy are associated with significantly longer reconstructive operations, higher intraoperative blood loss, and greater blood transfusion requirements (Pottakkat et al, 2009). Similar problems may occur in bile duct strictures after right hepatic resection.

Portal Hypertension (See Chapter 70)

It is estimated that approximately 15% to 20% of patients with benign biliary stricture have concomitant portal hypertension (Blumgart & Kelley, 1984; Chapman et al, 1995). Patients with biliary strictures may develop portal hypertension as a result of secondary hepatic fibrosis or direct damage to the portal vein. Alternatively, portal hypertension may be due to preexisting liver disease. It is important that these patients undergo further workup, including a liver biopsy, to exclude underlying chronic parenchymal disease. Iatrogenic biliary injuries are often the subject of medicolegal proceedings, and precise documentation of all injuries is essential to provide an accurate assessment of the cause of symptoms and prognosis. The outcome of patients with biliary strictures and portal hypertension is much worse than for patients without portal hypertension, with an in-hospital mortality rate of 25% to 40% (Blumgart & Kelley, 1984; Chapman et al, 1995). It has been suggested, however, that adequate biliary drainage may be followed by some resolution of fibrosis and perhaps a reduction in portal pressure (Blumgart, 1978).

Management

Successful management of patients with postcholecystectomy bile duct injuries requires careful planning. The importance of thorough investigation and patient preparation cannot be overemphasized. Before any intervention, the surgeon must define completely the type and extent of injury and treat

life-threatening coexisting conditions—sepsis, cholangitis, ongoing biliary leakage, and abscess—that reduce the likelihood of a successful outcome. Hasty treatment decisions based on incomplete data are more likely to exacerbate an already difficult situation. Imaging studies play a central role in assessing patients with biliary injuries and should be directed at answering the following questions: Is there a subhepatic bile collection or abscess? Is there ongoing bile leakage? What is the level and extent of injury in the biliary tree? Are there associated vascular injuries? Is there evidence of lobar atrophy?

Radiologic Investigations (See Chapters 13 and 15 Through 18)

Duplex ultrasonography is an excellent, noninvasive means of showing intrahepatic ductal dilation and may reveal a subhepatic fluid collection or evidence of vascular damage. Although ultrasound may provide valuable information regarding the level of biliary injury, it is of little value in assessing the extent of a stricture and is of no value if the biliary tree is decompressed.

Computed tomography (CT) is probably the best initial study, the results of which help direct further investigations. A good quality CT scan shows a dilated biliary tree and helps localize the level of ductal obstruction in patients with strictures. In addition, CT identifies fluid collections or ascites, which may suggest the possibility of vascular damage, and it reveals lobar atrophy.

In patients with biliary strictures, complete delineation of the level and extent of injury is necessary. All branches of the right and left intrahepatic biliary tree must be outlined, particularly in cases of high bile duct stricture and recurrent stricture after previous reconstruction. Displaying the hepatic duct confluence (if intact) and the left ductal system and its branches is especially important in selecting the appropriate reconstruction. Percutaneous transhepatic cholangiography (PTC) is much more likely than endoscopic retrograde cholangiopancreatography (ERCP) to provide this information, and PTC remains the standard investigation in this setting (Fig. 42A.15).

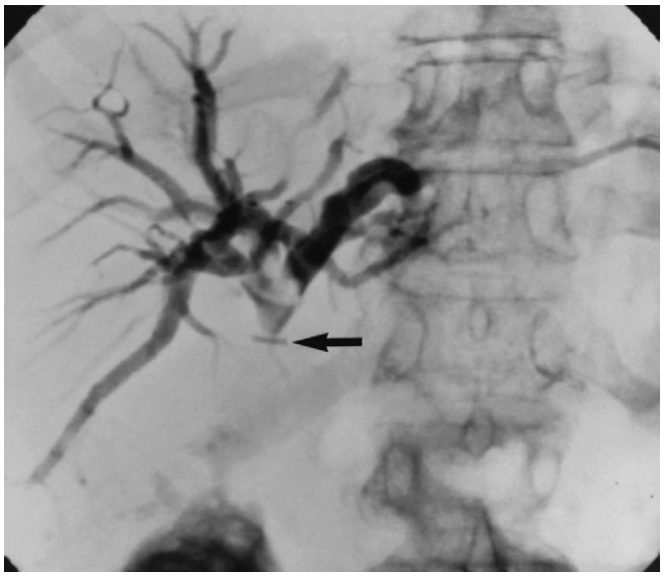


FIGURE 42A.15. Percutaneous transhepatic cholangiography showing a surgical clip occluding the common hepatic duct just below the confluence (*arrow*). All major branches of the proximal biliary tree are outlined.

Drainage catheters should be left in place following PTC if a complex injury is identified on cholangiogram, because palpation of the catheter intraoperatively often helps guide identification of ductal structures later during definitive repair. The risk of cholangitis can be reduced with prophylactic antibiotics.

Magnetic resonance cholangiopancreatography (MRCP) has emerged as a valuable tool in evaluating proximal bile duct injuries (Coakley et al, 1998). This noninvasive modality provides striking images of the biliary tree and yields anatomic information in a single study that was previously obtainable only with CT and PTC (Fig. 42A.16). Multiple studies have now confirmed the high accuracy and detailed information provided by MRCP (Bujanda et al, 2003; Jarnagin et al, 1994; Ragozzino et al, 2004). However, in some cases involving severely distorted anatomy as a result of atrophy, hypertrophy, or dense scarring, preoperative PTC and catheter placement should still be strongly considered, not only for additional cholangiographic information or intraoperative guidance but also because catheters can be easily exchanged for soft tubing to stent across worrisome small caliber anastomoses.

ERCP is seldom of value in the precise diagnosis of complete proximal bile duct strictures because there is often discontinuity of the CBD preventing visualization of the intrahepatic ductal system. ERCP may be more helpful for incomplete strictures (stenoses) and is appropriate for patients with a history of sphincteric damage at previous common duct exploration, or if there is suspicion of papillary stenosis or other periampullary pathology. ERCP also has a role in the diagnosis and treatment of patients with bile leakage from the cystic duct stump or from a laceration of the common duct (Brooks et al, 1993). These patients have evidence of an intraabdominal fluid collection on CT. After percutaneous drainage, biliary scintigraphy (e.g., hepatobiliary iminodiacetic acid [HIDA] scan) can be used to establish the presence of a persistent bile leak. ERCP may then be applied to identify the location of the leak, and placement of a stent may reduce or eliminate bile leakage; however, many bile leaks resolve with percutaneous drainage alone, and ERCP is probably unnecessary in the absence of radiographic or clinical evidence of ongoing bile drainage (Brooks et al, 1993).

Isotopic scanning techniques may be valuable in assessing bile duct strictures, particularly the functional assessment of incomplete strictures, previous biliary reconstructions, and isolated sectoral hepatic duct strictures (see Chapter 15). HIDA scanning offers a dynamic and quantitative assessment of liver function and of the clearance of bile across anastomoses and stenoses (Fig. 42A.17; McPherson et al, 1982). In patients with hepatocellular disease, HIDA scanning may be valuable in distinguishing the contribution of the biliary obstruction from that of the intrinsic liver disease to the overall biochemical and symptomatic picture. In such cases, the bilirubin level may be normal, but the alkaline phosphatase level is increased. HIDA scanning also is valuable during follow-up of patients after surgical repair. Because it can be repeated and is noninvasive, it is of particular value in showing anastomotic patency and function when no tube has been left across the anastomosis at the time of repair (see Fig. 42A.17). An isolated sectoral hepatic duct stricture is suggested by delayed clearance of isotope from a portion of the liver.

Arteriography and delayed-phase portography (see Chapter 19) can be obtained to confirm vascular injury on the initial studies, a suspicion of portal hypertension from the history and physical examination, or a history of excessive bleeding at the

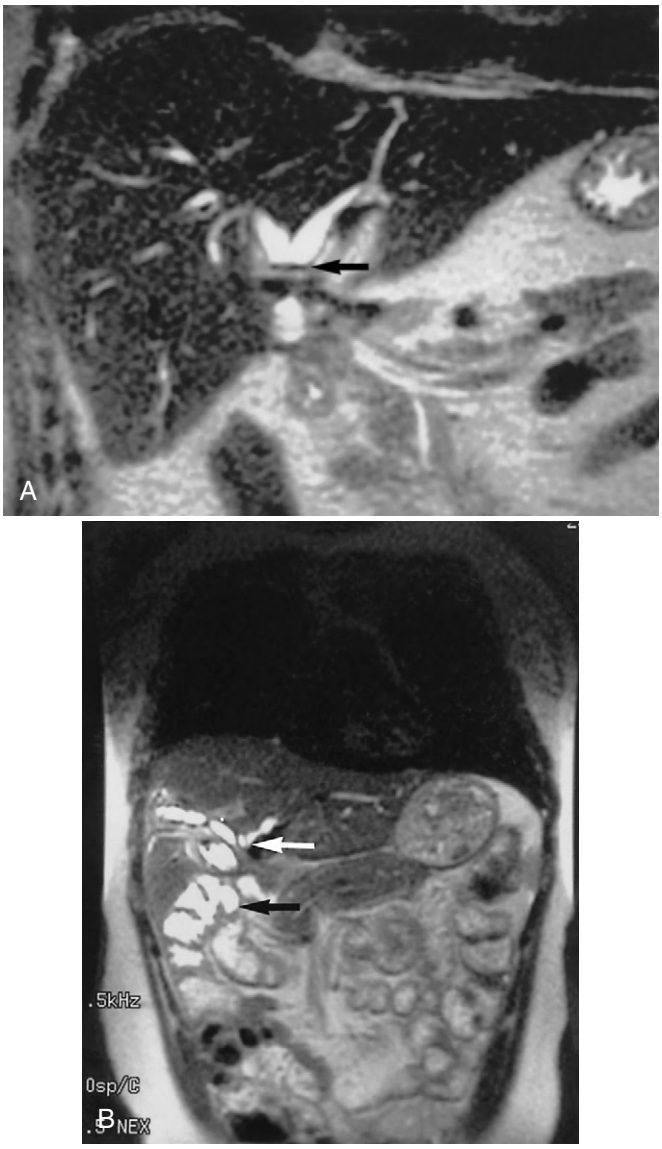


FIGURE 42A.16. A, Coronal single-shot fast spin-echo magnetic resonance cholangiopancreatography (MRCP) showing a surgical clip (*arrow*) occluding the common hepatic duct just below the confluence. **B,** Coronal single-shot fast spin-echo MRCP in a young woman with recurrent cholangitis after multiple attempts to repair a postcholecystectomy bile duct injury. The hepatic duct confluence (*white arrow*) is shown. Excess fluid was noted in the adjacent colon (*black arrow*), suggesting a fistula from the biliary tree to the hepatic flexure. Surgical findings confirmed a fistula from the right posterior sectoral hepatic duct, which had been excluded from the anastomosis. *(From Coakley FV et al, 1998: Complex postcholecystectomy biliary disorders: preliminary experience with evaluation by means of breath-hold MR cholangiography. Radiology 209:141-146.)*

time of cholecystectomy (Li et al, 2008). A biliary injury in the setting of portal hypertension dramatically increases the morbidity and mortality of operative intervention, and its presence should redirect the management approach (Chapman et al, 1995). The combination of biliary and vascular injuries often leads to segmental or lobar atrophy, but it may also be seen with long-standing biliary obstruction alone. An atrophic lobe may be evident on the initial ultrasound or CT scan and appears as a small, often hypoperfused area with dilated, irregular, and crowded bile ducts (Fig. 42A.18). Isotopic scanning may show what appears to be a filling defect in the affected area. It is important to recognize lobar atrophy on the cross-sectional imaging studies, not only because it is an indicator of concomitant vascular injury needing further evaluation, but also because it would change the operative approach during repair (see Chapter 29). In addition, patients with combined bile duct and hepatic artery injuries seem to be at increased risk for severe complications, such as hepatic necrosis and abscess, after reconstructive surgery. A patient undergoing biliary reconstruction in the setting of hepatic artery occlusion may also be at greater risk of late stricture recurrence (Gupta et al, 1998; Schmidt et al, 2005).

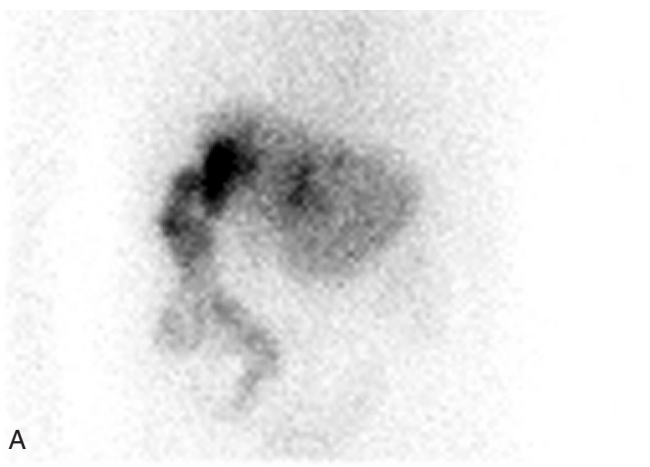
Occasionally, injection of contrast material into an established biliary fistula or percutaneous drain outlines the ductal system (Fig. 42A.19). Such studies may complement information provided by formal PTC, particularly if the fistula or tube tract drains an excluded sectoral duct (see Chapter 42B). Because bacterial colonization or biliary infection is inevitable in such cases, it is wise to administer prophylactic antibiotics before and after these studies.

Preoperative Preparation

In general, operative repair of bile duct injuries need not be rushed, the exceptions being treatment of bile duct injuries recognized at the time of initial cholecystectomy or, rarely, emergency treatment of suppurative cholangitis or peritonitis. For most patients, there is ample time to treat coexisting conditions and to perform a full investigation, both of which increase the likelihood of a successful outcome (Stewart & Way, 1995; Chapman et al, 1995).

Cholangitis is a frequent occurrence in patients with bile duct strictures, especially after ductal intubation (see Chapter 43). Administration of intravenous antibiotics is important prior to surgical treatment, and the results from bile cultures obtained at PTC should be used to direct therapy. Patients with severe cholangitis and sepsis are unlikely to respond to antibiotics alone and should be submitted to percutaneous drainage before surgery. Preoperative antibiotics are usually adequate to manage milder attacks and should be used in patients with no clinical evidence of cholangitis, given the high incidence of bacterial contamination. Antibiotic regimens should take into account the frequent presence of anaerobic organisms and enterococci in patients with biliary obstruction (Thompson et al, 1990; Hochwald et al, 1999). We begin antibiotics immediately before operation and continue appropriate treatment for 5 to 7 days postoperatively if cholangitis is a preoperative feature. Although no firm data exist to guide the duration of treatment, the markedly increased incidence of postoperative infectious complications in patients with endoscopic or percutaneous stents suggests that a prolonged course of treatment is justified (Hochwald et al, 1999). These data further suggest that jaundice without evidence of cholangitis is not an indication for biliary intubation.

Anemia should be corrected, if necessary, by blood transfusion; coagulation defects, which typically manifest as a prolongation of the prothrombin time, should be treated with vitamin K or fresh frozen plasma. Patients with prolonged illness may be seen with malnutrition (see Chapter 24). Enteral feedings through a fine-bore nasal catheter may be successful in some cases but may not be tolerated in sufficient amounts, and parenteral nutrition may be necessary. Despite these measures,



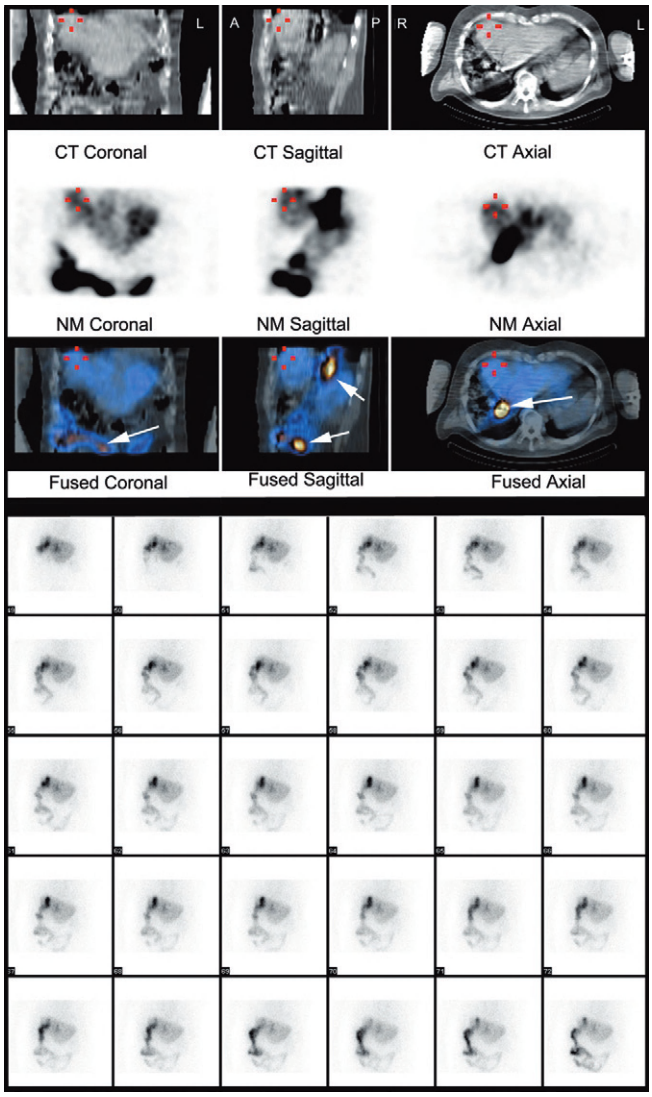


FIGURE 42A.17. A, Hepatobiliary iminodiacetic acid (HIDA) scan, anterior view of the liver 5 minutes after the intravenous injection of 5 mCi of technetium 99m–Choletec in a patient after right hepatectomy and hepaticojejunostomy for a benign stricture. This shows rapid visualization of liver with slight heterogenous distribution of the tracer throughout the liver, major bile ducts, and early filling of the Roux-en-Y limb. **B,** Additional single-photon emission computed tomography of the liver was obtained (*upper panels*). *Arrows* in the fused nuclear medicine (*NM*) and computed tomographic (*CT*) images correspond to high levels of γ-radiation emission; *lower panels* correspond to the HIDA scan with 1-minute sequential frames in the same patient.

however, weight gain is sometimes difficult to achieve, and to date no prospective randomized trials have shown a benefit from short-term preoperative nutritional support. A significant external bile fistula predisposes to excessive fluid and electrolyte loss and may lead to hyponatremia and acidosis (McPherson et al, 1982). It is imperative to correct fluid deficits and electrolyte imbalances before operation (see Chapter 24).

The preoperative management of complications of biliary injuries, such as biliary peritonitis, subphrenic or subhepatic abscess, hemorrhage from erosive gastritis or esophageal varices, or hepatic failure secondary to fibrosis, is important; usually, these must be addressed before biliary reconstruction can be considered. In general, drainage of intraabdominal abscesses and control of gastrointestinal hemorrhage takes priority; however, if systemic sepsis arises from an obstructed biliary tree, a factor that may contribute to other complications, immediate biliary drainage is essential. In such desperately ill patients, it is preferable to perform rapid percutaneous drainage to allow further resuscitative measures with intravenous antibiotics and hydration to prevent renal insufficiency. Management of portal hypertension and external bile fistula occurring in association with stricture is addressed subsequently.

Surgical Treatment

The most appropriate management of bile duct injuries depends on the injury type and whether or not the injury is diagnosed immediately or at some time after operation.

INJURY RECOGNIZED AT INITIAL OPERATION. If injury to the extrahepatic biliary tree is recognized at the time of initial cholecystectomy, the surgeon should consider his or her experience and ability to repair it immediately. The advice of a more



FIGURE 42A.18. Computed tomographic scan showing severe atrophy of the right lobe. The right lobe is hypoperfused and small and is clearly demarcated from the left lobe (*black line*). Notice the markedly increased size of segment IV and the left lateral segment (*white line*) and the dilated and crowded ducts in the small right lobe.

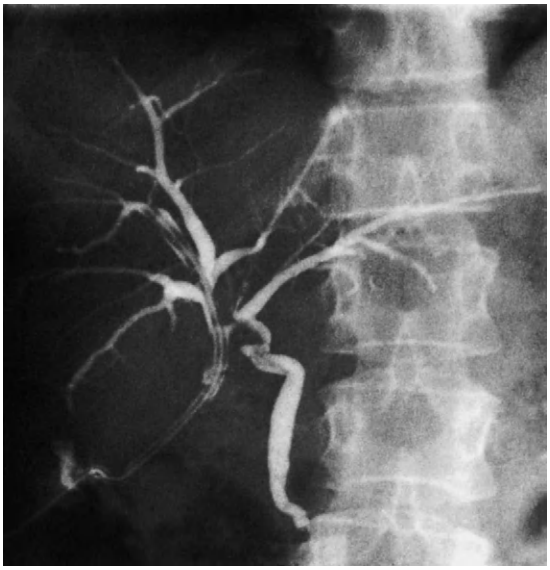


FIGURE 42A.19. Injection of contrast material into a tube that had been placed into the ductal system after a hilar ductal injury recognized at operation. The patient was referred draining approximately 200 mL of bile per day, but with normal liver function test (LFT) results and no fever. The tube was passed into the right hepatic ductal system, but filling of the entire intrahepatic biliary tree is seen with what appears to be a complete division of the common hepatic duct; a fistulous connection has developed between the left hepatic ductal system and the common hepatic duct. The tube was withdrawn and no repair was performed. Subsequent atrophy of the right liver occurred, but the patient was well and symptom free with normal LFT results over a 4-year follow-up period.

experienced surgeon should be sought if possible. The situation is not immediately desperate, and there is always time to wait a short while for another opinion and for additional assistance. Substantial evidence suggests that immediate open conversion and repair by an experienced surgeon is associated with reduced morbidity, shorter duration of illness, and lower cost (Stewart & Way, 1995; Savader et al, 1997). A recent multivariate analysis of bile duct injuries by Stewart and Way (2009) identified timing of biliary reconstruction as being insignificant when patient preoperative condition, complete cholangiography, surgical technique, and surgeon experience are optimized.

Despite the apparent ability to perform biliary reconstruction electively, several studies have cited the benefits of early referral to a tertiary center, as such institutions have specialized hepatobiliary surgeons and radiologists to diagnose and treat biliary complications in a timely fashion (Sicklick et al, 2005; Fischer et al, 2009). Each failed repair is associated with some loss of bile duct length (Tocchi et al, 1996) and greatly exacerbates an already difficult situation. This is particularly true of injuries involving the biliary confluence, in which failure of the initial repair and loss of bile duct length may result in isolation of the right and left hepatic ducts; repair becomes more difficult, and the likelihood of a successful outcome is reduced (Chapman et al, 1995). If the surgeon cannot effect a reasonable repair, and competent help is unavailable, drains should be placed to control any biliary leak, and the patient should be referred to a specialist center.

The damaged area of bile duct requires careful dissection to define the extent of injury. To accomplish this dissection without making matters worse, the laparoscopic approach must be abandoned in favor of a generous right subcostal, extended subcostal, or chevron incision. Additional assistance should be obtained to aid in exposure. Operative cholangiography may be helpful at this point to delineate the anatomy and the type of injury. Regardless of the location of the lesion, initial repair of the damage recognized at the time of cholecystectomy should have two basic aims: 1) maintenance of ductal length below the hilus without sacrifice of tissue and 2) avoidance of uncontrolled postoperative bile leakage.

The initial intervention may not be the final definitive reconstruction; this is particularly true of injury to small ducts that may be difficult to repair. The prime aims of maintaining length and preventing fistulation should guide the surgeon, rather than elaborate attempts at reconstruction under adverse circumstances. It is probably safer to provide external drainage by means of a tube inserted proximally into the bile duct and to refer the patient for specialist treatment, rather than to complicate the situation with a repair that is likely to fail and lead to further damage.

The injury in most cases involves complete transection with or without excision of a length of common duct. Occasionally, only an aberrant right sectoral hepatic duct is involved (Bismuth type 5), although this too may be associated with concomitant injury to the common hepatic duct or CBD. Durable reestablishment of biliary-enteric continuity is difficult when the ducts are small and decompressed, and referral to a specialist unit is crucial in this situation.

Two options are available for repairing a complete duct transection. The first is end-to-end repair over a T-tube. This repair is feasible only if the transected ends can be apposed without tension, which usually requires full mobilization of the duodenum and head of the pancreas. The anastomosis is created using a single layer of interrupted absorbable sutures with the T-tube brought out of the bile duct away from the anastomotic line. Silk sutures should be avoided for all biliary reconstructions, because they can promote an inflammatory reaction and act as a nidus for stone formation. End-to-end anastomoses are

associated with a high incidence of late stricture formation, up to 60% (Csendes et al, 1989; Pellegrini et al, 1984; Rossi & Tsao, 1994; Stewart & Way, 1995). Other reports support the use of end-to-end repair, because more than two thirds of the associated complications, such as stricture or leak, can be managed nonoperatively (de Reuver et al, 2007). In general, we recommend Roux-en-Y hepaticojejunostomy, which will be discussed later; this approach is more likely to give better long-term results.

An injury to the lateral duct wall may be amenable to direct suture repair, and relatively small and simple lacerations may be repaired with interrupted 4-0 or 5-0 absorbable suture. The area of injury should be adequately exposed, but extensive dissection risks further injury and late stricture formation. Some authors recommend T-tubes for all such repairs, but they are probably unnecessary for small lacerations, and their placement into a decompressed bile duct may exacerbate the injury (Rossi & Tsao, 1994). An analogous situation is primary choledochorrhaphy after CBD exploration, and several authors have reported excellent results without using T-tubes (Sheen-Chen & Chou, 1990; Sorensen et al, 1994; Tu et al, 1999). Long, lateral injuries that are not circumferential may be impossible to repair transversely without compromising the lumen, and direct repair over a T-tube is likely to result in future stenosis. Some authors have suggested that vein patches may be used to cover such defects (Ellis & Hoile, 1980), whereas others have described using the cystic duct stump or pedicled flaps of jejunum (Okamura et al, 1985).

Although these approaches may have merit in some situations, we prefer instead to use a Roux-en-Y loop of jejunum as a serosal patch (Fig. 42A.20). A T-tube is placed across the defect, and its long limb is led out through the Roux loop and exteriorized through the abdominal wall. This approach has several advantages: First, bile duct length is maintained. Second, the jejunal serosa is used to cover the defect, secured in place with fine, interrupted absorbable sutures to the bile duct wall without attempting direct approaches to the ragged edge of the damaged duct. Finally, the T-tube provides biliary decompression across the jejunum so that when it is removed, any leaking bile drains into the bowel lumen rather than the abdominal cavity. This method may be particularly useful to an inexperienced surgeon in a difficult situation.

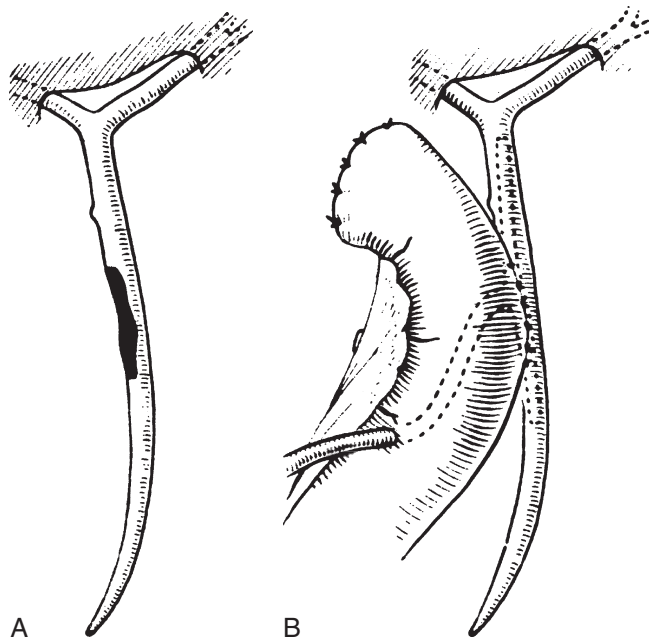


FIGURE 42A.20. Method of repair of a noncircumferential laceration to the bile duct wall. **A,** Injury is lateral with loss of ductal wall over some considerable length. **B,** A Roux-en-Y loop of jejunum is prepared and brought up. A T-tube is placed within the injured bile duct, and the long limb is led out across the jejunal loop, which is secured to the bile duct as a serosal patch over the defect.

INJURY RECOGNIZED IN THE IMMEDIATE POSTOPERATIVE PERIOD. Biliary injuries not appreciated intraoperatively may appear in the first few days after operation. The mode of presentation may be bile drainage through the wound, bile peritonitis, or progressive jaundice, depending on the injury type. In the setting of an external biliary fistula (see Chapter 42B), the essential consideration in management is to avoid early reoperation. It is wiser to take full stock of the situation, to carry out appropriate investigations as described earlier, and to keep the patient well nourished and free of infection. If fistulography or other studies reveal continuity between the biliary system and the gastrointestinal tract, a prolonged period of drainage is warranted and may result in spontaneous closure, provided that there is no distal obstruction to bile flow. This is particularly true of bile leakage from the cystic duct or a subvesical duct of Luschka (type A) or from a noncircumferential laceration (type D).

More severe lacerations or complete transections of the common duct or an aberrant right sectoral hepatic duct with ongoing bile leakage require careful consideration. Because the biliary tree is decompressed, the proximal ducts are small in caliber. Immediate surgical treatment of these injuries is difficult. Adequate repair requires exposing healthy bile duct mucosa within a sufficiently dilated proximal duct to allow precise anastomosis. In the setting of a decompressed biliary tree and significant inflammation, this exposure can be quite demanding or even impossible. A delayed approach remains the most appropriate course of action, because such fistulas also may close without operative intervention, and this may be associated with eventual proximal duct dilation and easier subsequent repair (see Fig. 42A.3). If fluid losses from the biliary fistula remain high over a prolonged period, a useful but rarely used technique is creation of a temporary internal fistulojejunostomy, with definitive repair deferred for a later date (Smith et al, 1982). Alternatively, placement of an endoscopic or percutaneous stent across the defect may reduce output from the fistula, hasten closure, and make management easier. Long-term results of such interventions have shown excellent results, and oftentimes more than 90% of patients with peripheral leaks or strictures can be treated endoscopically (Weber et al, 2009). Some authors advocate early endoscopic sphincterotomy to decrease the relative resistance of transpapillary bile drainage to promote closure (Liguory et al, 1991; Abdel et al, 1996; Inui et al, 1998; Fujii et al, 1998). Although these approaches are occasionally useful, no evidence is available to show that they provide a significant advantage, and a waiting period of 2 to 3 weeks is recommended, because most fistulas close or decrease substantially.

Patients with bile peritonitis are often desperately ill, especially if the bile is infected, although some patients with sterile bile may accumulate large volumes without overt signs of sepsis

(see Fig. 42A.3B). Drainage of the bile collection and control of ongoing bile leak is the primary objective and often requires percutaneous abscess drains in combination with percutaneous biliary catheters. Definitive repair is seldom possible initially, with the bile ducts collapsed, deeply bile stained, and friable; repair is best delayed, until the biliary leak has been controlled completely, and the patient has been fully resuscitated.

INJURY PRESENTING AT AN INTERVAL AFTER INITIAL OPERATION. Many patients seen a long time after cholecystectomy have biliary strictures. The principles of managing late bile duct stenoses and strictures include 1) exposure of healthy proximal bile ducts draining all areas of the liver, 2) preparation of a suitable segment of distal mucosa for anastomosis, and 3) creation of a mucosa-to-mucosa sutured anastomosis of the bile ducts to the distal conduit, which is almost always a Roux-en-Y loop of jejunum.

It may be necessary to consider a staged approach to stricture repair in the presence of intraabdominal infection, portal hypertension, or poor general condition of the patient. Repair attempts in the face of uncontrolled local infection, acute complications of portal hypertension, or general debilitation are doomed to fail. The initial approach in such cases should be limited to establishing external bile drainage, controlling sepsis, and treating other coexisting conditions that are life threatening. In this manner, the clinical condition of the patient may be improved before attempts at definitive repair (Cattell & Braasch, 1959). In a patient with portal hypertension, initial interventional radiologic management by percutaneously placed biliary drainage catheters is probably safer than operation, given the danger of intraoperative hemorrhage (Pellegrini et al, 1984).

Technical Approaches to Biliary Repair (See Chapter 29)

END-TO-END DUCT REPAIR. Excision of the stricture with end-to-end anastomosis was one of the earliest techniques used for reconstruction (Cattell & Braasch, 1959). This repair reestablishes normal anatomic continuity and drainage via an intact sphincter of Oddi. Such an approach has been tried even for high strictures after extensive mobilization of the duodenum and common duct. End-to-end repair is associated with a 50% to 60% incidence of long-term failure (Csendes et al, 1989; Pellegrini et al, 1984; Stewart & Way, 1995). These figures reflect the failure rates in the most favorable of cases, because patients with more extensive injuries usually were submitted to biliary-enteric anastomosis (Rossi & Tsao, 1994). These data suggest that end-to-end repair has a limited role in the surgical treatment of benign biliary strictures.

BILIARY-ENTERIC REPAIR. For most cases of bile duct transection or stricture, biliary-enteric anastomosis is the procedure of choice. For strictures of the retropancreatic or immediate supraduodenal portion of the CBD, choledochoduodenostomy is an ideal procedure. The anastomosis may be performed either side-to-side or end-to-side (see Chapter 29). This technique is appropriate only in the setting of a dilated bile duct and almost certainly would result in recurrent stricture if created to a decompressed duct. Most postcholecystectomy strictures are not amenable to choledochoduodenostomy, because such low injuries are unusual in contrast to postgastrectomy strictures, which often involve the distal bile duct. Strictures involving the common hepatic duct are more difficult to manage, especially strictures involving the biliary confluence, and they almost always require Roux-en-Y hepaticojejunostomy for reconstruction. The technical aspects of biliary-enteric anastomosis have been described (Voyles & Blumgart, 1982; Blumgart & Kelley, 1984) and are outlined in Chapter 29.

There are a variety of approaches to the proximal hepatic ducts. When the stricture is below the confluence (Bismuth type 1 or 2), a direct anastomosis to the hepatic duct stump is usually straightforward. By contrast, when the stricture encroaches on the confluence of the right and left hepatic ducts (type 3) or extends proximally so as to isolate the ducts (type 4), the problem becomes more complex, and good results are more difficult to achieve. The choice of surgical approach should be tailored to the height and extent of the lesion. The technical descriptions that follow should be read in conjunction with Chapter 29.

An important feature is early division of the falciform ligament back to the diaphragm and freeing the liver of adhesions. Dissection should begin in the right subhepatic area, and it is usually necessary to mobilize completely the hepatic flexure of the colon, starting from below and working upward and medially. The duodenum often adheres to the undersurface of the liver and to the hilar structures, particularly in the area of the stricture. The surgeon may encounter an internal bile fistula to the duodenum or may injure the duodenal wall during this portion of the dissection, either of which would require repair.

Attempts to identify the duct below the stricture are unnecessary, because the distal duct generally cannot be used for anastomosis; it is usually encased in dense scar tissue, and extensive dissection to free it risks injury to the hepatic artery and portal vein. The essential point is identification of the bile ducts proximal to the stricture, and a systematic, careful, and patient approach is necessary. Dissection in the area lateral to the hepatic artery pulsation allows identification of the common hepatic duct. Although this approach is reasonable in patients with relatively low strictures (Bismuth type 1), it is inappropriate in most cases. It is generally much easier and safer to expose the left hepatic duct by lowering the hilar plate at the base of segment IV (quadrate lobe). Often this area has not been disturbed by the previous surgeon and is likely to be relatively free of adhesions. This maneuver delivers the left hepatic duct and the biliary confluence from the undersurface of the liver and makes identification of the strictured area much easier. Adhesions posterior to a damaged duct may be dense, and extensive dissection in this situation risks injury to the underlying portal vein. It is generally unnecessary to come around the scarred area completely, provided that the posterior wall of the duct above the stricture can be elevated sufficiently for anastomosis.

Strictures at or above the level of the biliary confluence are much more challenging. Adequate exposure of the bile ducts is usually achievable by dissecting the left hepatic duct system. This approach is based on the anatomic studies of Couinaud (1953, 1955; Hepp & Couinaud, 1956) and is well described (Bismuth et al, 1978; Blumgart & Kelley, 1984). For type 2 and type 3 strictures, biliary-enteric anastomosis to the left hepatic duct provides complete drainage of the left and right ductal systems. For type 4 strictures, however, the confluence is obliterated, and it is necessary to provide drainage of the right lobe as well, often by dissection across the stricture and creation of a second anastomosis to the right ductal system. Occasionally, mobilization or even partial excision of the quadrate lobe may be necessary in some type 4 strictures.

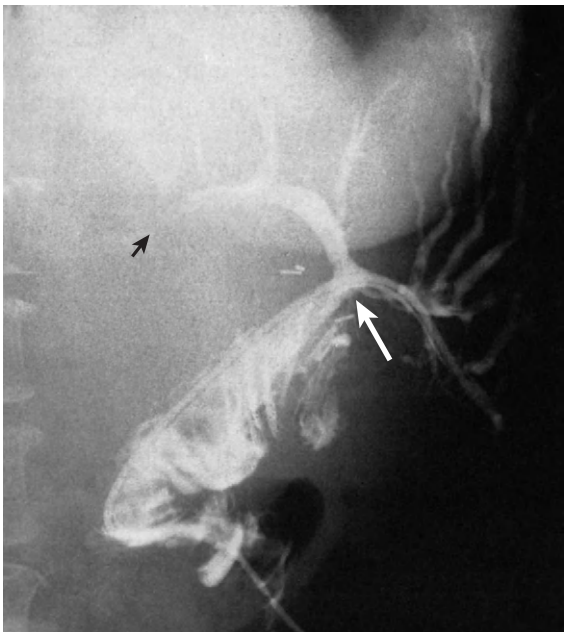


FIGURE 42A.21. Roux-en-Y hepaticojejunostomy to the segment III duct after postcholecystectomy stricture initially treated by hepaticojejunostomy, using the mucosal graft technique with a transhepatic tube through the right liver. At referral, the patient had a grossly atrophic right lobe and a high bile duct stricture (*black arrow*). At operation, the left hepatic duct was exposed using the ligamentum teres approach, and anastomosis was carried out (*white arrow*). Subsequent repeat stricture occurred 1 year later and was treated by refashioning of the anastomosis and subsequent transtubal balloon dilation with a satisfactory outcome. The patient was well and symptom free 2 years after operation.

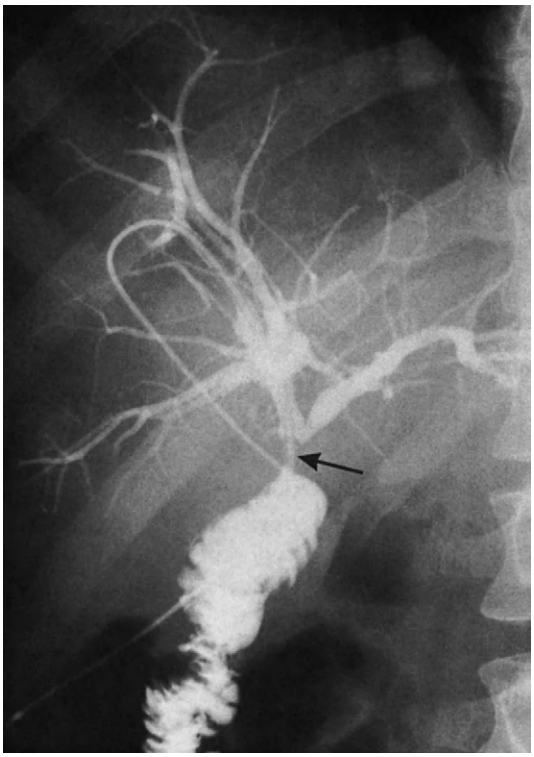


FIGURE 42A.22. Cholangiogram obtained by injection of a U-tube was used to develop a mucosal graft repair of a high bile duct stricture done 2 weeks before this radiograph was obtained. It was considered that there were no ducts visible at the hilus of the liver that would allow formal anastomosis. The mucosal graft is already widely separated from the biliary confluence (*arrow*). Repair was done by an approach to the left hepatic duct. A wide anastomosis was obtained easily, and the patient was well and symptom free with normal liver function tests 3.5 years after operation.

Although most high strictures may be approached and managed as described previously, it is occasionally difficult to expose the left hepatic duct because of adhesions or fibrosis. Excessive bleeding may be encountered, or a large, overhanging quadrate lobe may prevent access to the left duct. Occasionally, the extrahepatic length of the left duct, normally much greater than the right, is short, and access to it is difficult. In such instances, repair can be accomplished by dissection of the left duct within the umbilical fissure, known as the *ligamentum teres* or *round ligament approach* (Fig. 42A.21; Soupault & Couinaud, 1957). This approach rarely is indicated for benign strictures and should not be used unless the biliary confluence is intact, so that a left-sided anastomosis would drain the entire liver.

The mucosal graft procedure of Smith (1964, 1969) is a procedure of historical interest only. This method was introduced for treating high strictures in which hilar dissection was thought to be impossible, and the proximal ducts could not be delivered for mucosa-to-mucosa anastomosis. The object of the procedure is to use a transhepatic tube to draw the jejunal mucosa high up into the hepatic ducts and allow apposition. The procedure was claimed to be easier and quicker, because no sutures were inserted. The transhepatic tube was left in place for 2 to 6 months, occasionally longer for difficult cases. Initially hailed as an important advance in technique (Kune & Sali, 1981), it is now clear that the dome of the jejunal mucosa drawn into the hepatic ducts may block significant secondary intrahepatic ducts, occluding and isolating segments of liver tissue (Blumgart, 1978; Blumgart et al, 1984). In addition, the mucosa may slip away postoperatively, and the jejunal loop may become detached (Fig. 42A.22). Recurrent stricture at the site of previous mucosal grafting is common (Blumgart & Kelley, 1984). This technique fell out of favor after several series of complex biliary strictures documented good to excellent long-term results using biliary-enteric anastomotic techniques without using the mucosal graft approach (Schol et al, 1995; McDonald et al, 1995; Chapman et al, 1995; Stewart & Way, 1995; Nealon & Urrutia, 1996; Tocchi et al, 1996; Lillemoe et al, 1997).

LIVER SPLIT AND LIVER RESECTION. To expose the bile ducts for repair, it is sometimes necessary to open the liver tissue as a hepatotomy (Blumgart, 1980). The most frequent situations involve opening the umbilical fissure to obtain access to the segment III duct or extending the subhepatic approach to expose the origin of the right hepatic duct. This latter approach involves opening the liver in the line of the gallbladder fossa. Upward mobilization of the entire quadrate lobe by this maneuver combined with opening the umbilical fissure facilitates access for selected type 4 strictures, especially when approaching the right hepatic ducts is difficult. Fiddian-Green and colleagues (1988) described a similar approach. Resection of the lower parts of segments IV and V to obtain exposure to the hilar plate has been described for Strasberg E3 injuries; in this setting, the surgeon must be diligent to stay away from the hepatoduodenal ligament (Sirichindakul et al, 2009). Division

of liver tissue in this setting must be accomplished patiently, because it may be accompanied by significant hemorrhage. These techniques are unnecessary if approaches to the left duct are possible. Actual liver resection is rarely necessary for exposure of the bile ducts in benign postcholecystectomy strictures. Most often, excision of the anterior portion of the quadrate lobe is done if exposure of the umbilical fissure and incision in the gallbladder bed are insufficient to expose the ducts in difficult type 4 strictures.

More rarely, benign strictures may be treated by means of an intrahepatic hepaticojejunostomy as described by Longmire and Sandford (1948, 1949), which involves resection of a portion of the left lateral segments (II and III) and anastomosis to ducts exposed on the cut surface of the liver. In general, this procedure is difficult and potentially dangerous, because the liver is often fibrous, and resection is met by a fair degree of hemorrhage. The bleeding vessels are generally in close proximity to the ducts needed for anastomosis. The use of this procedure is limited to cases in which there is left-sided hypertrophy (Czerniak et al, 1986), and it is rarely the only option available to secure access to the bile ducts.

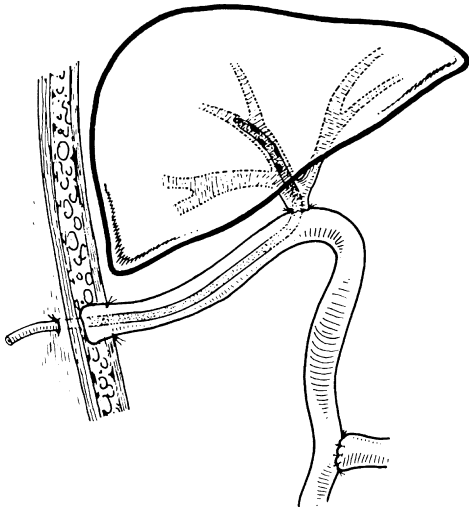


FIGURE 42A.23. Hepaticojejunostomy with a long, defunctionalized Roux limb with the end secured subcutaneously or subperitoneally to allow access for future diagnostic or therapeutic studies.

ISOLATED SECTORAL HEPATIC DUCT INJURIES. Injuries to aberrant or "low entry" right sectoral hepatic ducts can be particularly difficult to diagnose and manage. Patients with a stricture but no bile leak (type B) may remain asymptomatic for months or years after the injury and only then present with pain or evidence of cholangitis. Some patients may remain essentially asymptomatic and come to attention because of abnormal LFTs. These injuries are not associated with jaundice, unless concomitant stricture of the common hepatic duct (type E5) is present. Long-standing obstruction may result in atrophy of the corresponding hepatic sector drained by the occluded duct (right anterior or right posterior). Some of these patients will have had ERCP in the course of their evaluation that was interpreted as normal, but in retrospect, it is found to actually show partial nonfilling of the right biliary tree. Biliary drainage to a Roux-en-Y loop of jejunum should be done in symptomatic patients. In patients with symptoms, especially recurrent cholangitis, and evidence of liver atrophy, drainage alone may be insufficient, and resection of the atrophic sector may be required. Asymptomatic patients may not require intervention, especially if the injury was remote, and significant atrophy is already evident; however, patients with a relatively recent injury and no atrophy probably are best served with operative drainage to prevent future problems (Strasberg et al, 1995).

Patients with sectoral hepatic duct injuries associated with biliary leak (type C) are a particularly difficult group to manage. After appropriate initial investigation, control of biliary leak, and resuscitation, reconstruction to a Roux-en-Y jejunal loop should be performed. Because the transected duct is small and decompressed, achieving good results is difficult even in experienced hands, and restenosis is common. It has been suggested that percutaneous transhepatic drainage of the affected duct before operation (Lillemoe et al, 2000; Strasberg et al, 1995) and prolonged postoperative anastomotic stenting are crucial for successful management (Lillemoe et al, 2000). We believe that neither of these maneuvers is necessary as a matter of routine, but they may be helpful in selected cases.

COMBINED MODALITY APPROACHES. The standard surgical techniques of biliary reconstruction described previously are suitable for most cases. In the most complex and difficult strictures, and especially in the presence of intrahepatic strictures and stones, even optimal surgical management is met with a disappointingly high incidence of postoperative intrahepatic stone formation, cholangitis, and recurrent stricture. Interventional radiologic and endoscopic techniques, used as primary therapy in this setting, are similarly unsuccessful because of recurrent cholangitis associated with stent occlusion or recurrent stricture after balloon dilation. Often, nonoperative techniques are technically impossible because of limited access.

Under such adverse circumstances, when the risk of recurrent stricture or stone formation is believed to be high, hepaticojejunostomy may be performed over a transjejunal tube brought to the exterior across the blind end of the Roux limb. The defunctionalized Roux limb is deliberately left long, and the end is secured subcutaneously or subperitoneally (Fig. 42A.23); this allows easy subsequent access for cholangiography, cholangioscopy, dilation, or stone removal. The blind end of the Roux limb may be reaccessed by percutaneous puncture under fluoroscopic guidance or via a small incision made under local anesthetic for late diagnostic or therapeutic procedures long after the transjejunal tube has been removed. In our experience, this approach is rarely necessary but can provide an improved chance of excellent outcome in difficult cases and may spare the patient the need for repeated major surgical intervention months or years later (Schweizer et al, 1991; McPherson et al, 1998). It is generally unnecessary to add the morbidity of a formal stoma, although such an approach has been reported (Barker & Winkler, 1984).

HEPATIC RESECTION. Patients who have undergone prior unsuccessful repairs or have concomitant vascular injury or long-standing cholangitis often develop sectional duct strictures or interruptions between the right-sided and left-sided biliary tree, effectively precluding biliary-enteric revision. Such patients may require formal liver resection to eliminate atrophied liver or the biliary duct confluence. The surgical aim in such instances is to create a more functional biliary-enteric anastomosis using the remnant liver. Although mostly described as isolated cases

(Uenishi et al, 1999; Heinrich et al, 2003), Laurent and colleagues (2008) reported their experience with 18 cases of formal resections (14 right hepatectomies, 3 left hepatectomies, and 1 left trisectionectomy) for benign biliary stricture (see Chapter 90B). At a median follow-up of 8 years, 94% of patients had good or excellent results. Another report described eight patients who underwent either right hepatectomy or left lateral sectionectomy, and it demonstrated similar, excellent results (Thomson et al, 2007). Hepatic resection remains an important option in the treatment of refractory benign bilary stricture, especially in patients suffering from recurrent bouts of cholangitis or sepsis.

LIVER TRANSPLANTATION. Transplantation for iatrogenic biliary injury can be performed acutely but is usually done because of a devastating combined vascular and biliary injury (Felekouras et al, 2007; Zaydfudim et al, 2009). Only rarely does secondary biliary fibrosis resulting from longstanding biliary obstruction progress to true cirrhosis (see Chapter 97A). In such cases, orthotopic liver transplantation should be considered as an alternative to biliary reconstruction. Thomson and colleagues (2007) reported their series of 14 patients who either underwent hepatic resection or transplantation for secondary biliary cirrhosis. Of the five patients who ultimately required transplant for survival, two were deemed unsuitable for the procedure, one died awaiting an organ, and two underwent the procedure. Even in experienced transplantation centers, surgical reconstruction is preferred for most patients with benign strictures.

PORTAL HYPERTENSION AND BILIARY STRICTURE. Patients with coexisting portal hypertension and biliary stricture are an especially difficult group to manage (see Chapter 70). This combination has been reported in 10% to 20% of patients at the time of referral (Blumgart & Kelley, 1984; Chapman et al, 1995). Portal hypertension may result from secondary biliary fibrosis or direct injury to the portal vein, or coincident hepatocellular disease may be evident from alcohol abuse, chronic hepatitis, or other causes. The presence of splenomegaly or a history of gastrointestinal bleeding in a patient with biliary stricture should prompt further investigation with esophagogastroduodenoscopy and angiography with delayed-phase splenoportography. Bleeding esophageal varices, particularly if accompanied by hypersplenism or ascites, render the overall prognosis far worse (Chapman et al, 1995; Way & Dunphy, 1972). Collateral venous channels in the subhepatic region and within adhesions make dissection difficult and bloody. Patients with portal hypertension often have a proximal stricture, and some have had multiple previous attempts at repair, further reducing the likelihood of a successful outcome.

In seriously ill patients with jaundice and portal hypertension, it is preferable to attempt nonoperative stenting or balloon dilation than to proceed to immediate definitive repair (Fig. 42A.24; Toufanian et al, 1978; Molnar & Stockum, 1978; Teplick et al, 1980; Schwarz et al, 1981; Pellegrini et al, 1984). In the face of severe gastrointestinal bleeding, initial measures must be directed at stopping the hemorrhage and resuscitating the patient (see Chapters 75A and 75B). If bleeding continues, consideration should be given to immediate splenorenal or transjugular intrahepatic portosystemic shunting (TIPS; see Chapter 76) to achieve control, with bile duct reconstruction deferred until a later date. Occasionally, successful biliary-enteric reconstruction can be done under these circumstances with no need to create an intraoperative vascular shunt (Perakath et al, 2003; Agarwal et al, 2008). The best and most convenient form of operative shunt is the splenorenal shunt (see Chapter 76C). TIPS has a limited patency, and such shunting is used most often as a bridge to transplantation. The risk of biliary injury and subsequent biliary-venous fistula is high in the setting of a dilated biliary tree and seems to be a major mechanism of early shunt failure (Jalan et al, 1996; Saxon et al, 1998). TIPS is unlikely to play a major role in the management of these patients; instead, percutaneous drainage or balloon dilation may be used along with the measures described earlier.

If hemorrhage is encountered during stricture repair, hepaticostomy drainage may be performed as an initial measure, and a splenorenal shunt may be undertaken at a later date. Bile duct stricture repair done at the time of the shunting procedure can be extremely difficult and in any event is unwise at a time of severely compromised liver function. Occasionally, patients present with variceal hemorrhage after an otherwise successful stricture repair (Fig. 42A.25). In these instances, portosystemic shunting may be indicated as an emergency measure or, preferably, after initial conservative management. Injection sclerotherapy may control the bleeding successfully and obviate the need for operative intervention (see Chapter 75B).

RESULTS OF BILIARY RECONSTRUCTION. Given the wide spectrum of injuries that are possible at laparoscopic cholecystectomy, it is difficult to assess fully the results of operative repair. Most surgical series report results of repair of biliary strictures (type E) and do not address operative intervention for other injury types. In addition, many patients are subjected to immediate repair at the time of initial injury; the more difficult cases and the failures generally are referred to specialist units, but the long-term outcome of the other cases is often not reported. As a result, most literature reports—generated from tertiary referral centers—include significant numbers of patients requiring difficult reconstructions or with multiple previous repair attempts, which may underestimate the overall success rate. Relatively few reports with sufficient follow-up focus on the results of repair of laparoscopic injuries alone (Table 42A.4). It remains to be determined whether the results of repair of bile duct strictures after open cholecystectomy or other procedures can be extrapolated to repair of laparoscopic injuries. It has been suggested that laparoscopic bile duct injuries may have a less satisfactory outcome because of the more complex nature of many of these injuries and the frequent inflammation and fibrosis secondary to bile leakage (Lillemoe et al, 1997).

OPERATIVE MORBIDITY AND MORTALITY. Several studies have suggested significant morbidity associated with repair of benign strictures (Blumgart et al, 1984; Kune & Sali, 1981). The most common postoperative complications seen were intraabdominal abscess, wound infection, cholangitis, sepsis, biliary fistula, postoperative hemorrhage, and pneumonia. The perioperative mortality rate in many series ranged from 5% to 8% (Cattell & Braasch, 1959; Warren et al, 1982; Way & Dunphy, 1972); however, since the 1990s, several authors have documented a considerable decline in mortality, with many citing no perioperative deaths (see Table 42A.4). These figures generally do not take into account patients who die as a result of biliary tract–related sepsis while awaiting definitive treatment. Factors frequently associated with perioperative death include advanced age, significant comorbid medical conditions,

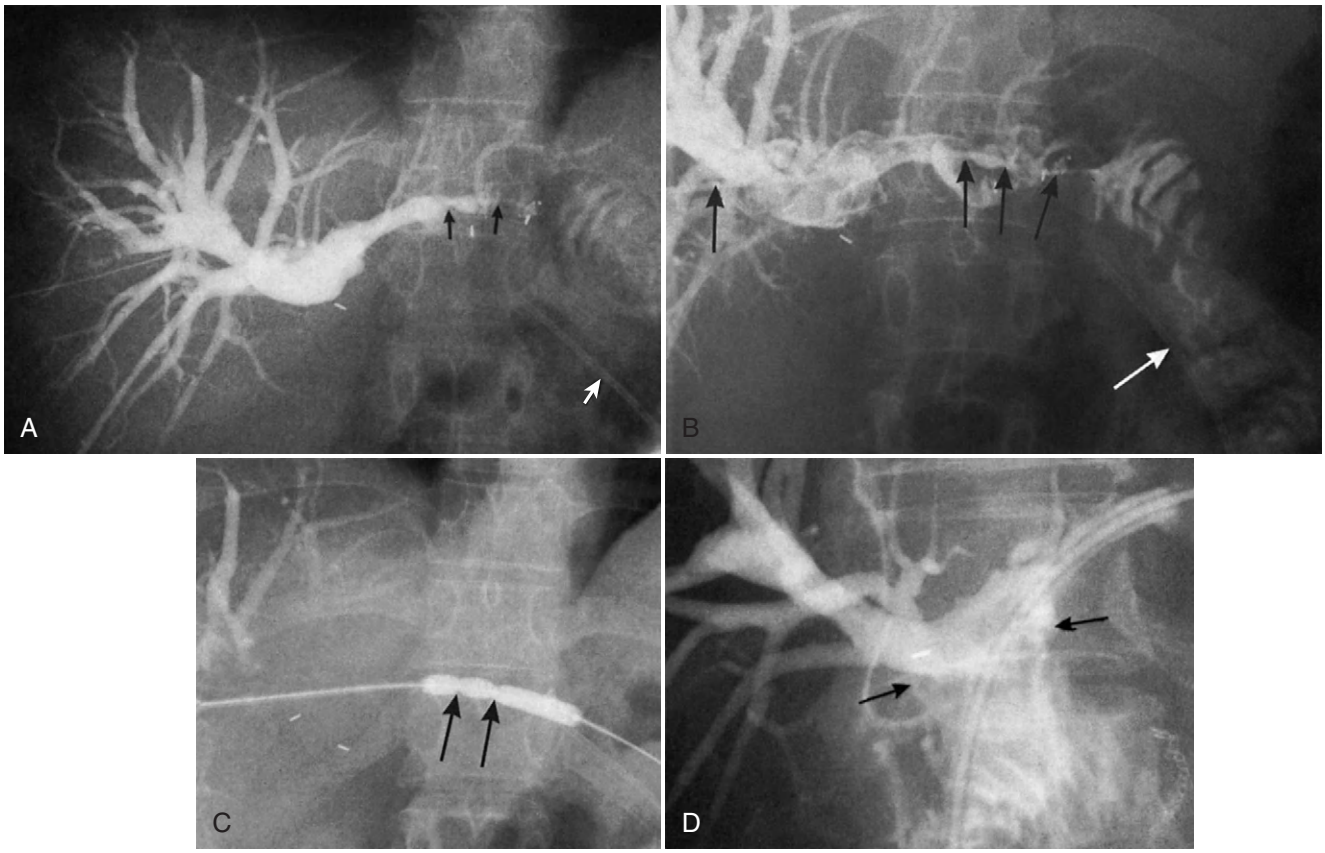


FIGURE 42A.24. A, Percutaneous transhepatic cholangiography showing a high (type 3) postcholecystectomy biliary stricture in a patient after cholecystectomy, during which there had been excision of the entire common hepatic duct. This was followed by two attempts at a mucosal graft repair and a left-sided hepaticojejunostomy by the Longmire-Sandford procedure. After failure of this operation, percutaneous intubation of the biliary ductal system was undertaken from the right side with attempted balloon dilation of the hepaticojejunostomy on three consecutive occasions. The radiograph shows the area of the hilus, marked by a surgical clip, and two strictures in the left hepatic ductal system, one just proximal to and the other at the hepaticojejunostomy (*black arrows*). A free endoprosthesis is seen (*white arrow*) lying in the jejunum. **B,** Cholangiogram obtained during attempted balloon dilation of the stricture reveals the passage of the catheter (*black arrows*) and the biliary system full of clot. The guidewire crosses the stricture, and a free endoprosthesis lies within the jejunal loop (*white arrow*). This procedure was followed by a severe episode of hemobilia requiring blood transfusion. **C,** Radiograph obtained during balloon dilation clearly shows the two strictures (*arrows*). **D,** Roux-en-Y hepaticojejunostomy was performed by the left hepatic duct approach, and a wide anastomosis was obtained (between the *arrows*). The previous hepaticojejunostomy to the left lobe was dismantled, and the new anastomosis was splinted by a tube passed through the left hepatic ductal system. The tube was removed 2 months later, and the patient was well and symptom free with normal liver function test results 2 years after operation.

and biliary sepsis. Significant underlying liver disease is perhaps the most important predictor of adverse outcome. Chapman and colleagues (1995) reported a perioperative mortality rate of 23% in patients with biliary strictures and portal hypertension subjected to any operative procedure.

A significant proportion of patients in many reports were referred after one or more repair attempts. Failed repairs nearly always render subsequent attempts more difficult and have a negative impact on the ultimate outcome. The reported morbidity and mortality rates reflect this point and underscore the serious nature of these injuries. Nevertheless, in experienced hands, operative repair of biliary strictures is a relatively safe procedure, and this fact must be considered when comparing surgery with nonoperative techniques.

LONG-TERM RESULTS AND FOLLOW-UP. Several factors must be considered when analyzing the long-term results of biliary reconstruction. First, there is no consistently used algorithm for postoperative investigation. Likewise, the measures used to assess outcome vary considerably. Approaches to follow-up range from simple observation and measurement of LFTs to performance of cholangiography or HIDA scans. Consistency in analyzing long-term results is important and should include an assessment of symptoms, LFTs, and radiographic studies. Such a triad of criteria is useful for clarifying the results and is the only way to compare accurately the results from various series or interventions (Table 42A.5; Schweizer et al, 1991). In addition, long-term follow-up is crucial in analyzing the final results of any series and when comparing different treatment modalities. Pitt and colleagues (1982) reported that two thirds of recurrent strictures were apparent within 2 years, but 20% were diagnosed 5 or more years after the initial repair. Similarly, Tocchi and colleagues (1996) observed that 40% of restrictures were identified more than 5 years after the initial operation. Complete and accurate assessment of the results of surgery or any other intervention requires a minimum follow-up of 5 years, but probably longer (Bismuth, 1982).

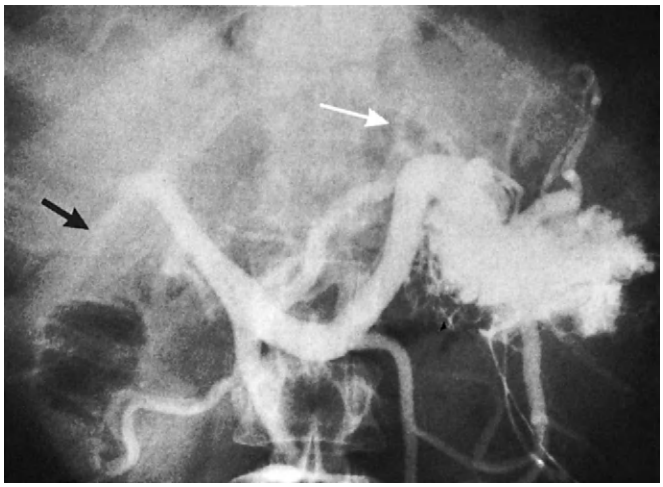


FIGURE 42A.25. Splenoportography in a patient with benign bile duct stricture and a history of vascular injury at the initial operation. The patient presented with portal hypertension and bleeding esophageal varices. Only a portion of the right portal venous vasculature is outlined (*black arrow*). Note varices in the area of the gastric fundus (*white arrow*). Percutaneous transluminal cholangiography revealed a stenosis near the biliary confluence, but not a complete obstruction, and liver biopsy showed hepatic fibrosis. Biliary reconstruction was not undertaken; instead, the patient was managed with a splenorenal shunt and has remained well for several years, and repair of the stricture has never been necessary.

Numerous studies assessing the impact of postcholecystectomy bile duct injuries on quality of life (QoL) in long-term follow-up have reported mixed results. Three studies showed significant impairment in several measured QoL categories (Boerma et al, 2001; Moore et al, 2004; de Reuver et al, 2008), whereas three others showed minimal (Melton et al, 2002) or no difference (Sarmiento et al, 2004; Hogan et al, 2009) compared with a matched cohort. Tornqvist and colleagues (2009) analyzed more than 374,000 laparoscopic cholecystectomies over 40 years' time in Sweden and identified 1386 injuries requiring reconstructive surgery; of note, injured patients had a fourfold increase in the risk of death from liver disease and a signficantly decreased overall survival. However, differences in study design and in the QoL instrument used make direct comparisons between studies difficult. In addition, pending litigation, which is common in such cases, is a potential confounding variable that likely has some influence on the results. Nevertheless, QoL measurement adds another dimension to the assessment of long-term outcome.

Several specialist centers reported satisfactory outcomes in 80% to 90% of patients reconstructed with Roux-en-Y biliary-enteric anastomosis, (see Table 42A.4). Many of these studies also identified factors associated with an adverse outcome (Table 42A.6). Chapman and colleagues (1995) found that long-term failure and the need for reintervention were significantly greater in patients with injuries involving the biliary confluence and those subjected to three or more repair attempts before referral. Tocchi and colleagues (1996) observed that the best results correlated directly with the degree of biliary ductal dilation, independent of stricture location. A report from Schmidt and colleagues (2005) confirmed that a repair in the presence of uncontrolled infection, a concomitant hepatic arterial injury, and injury location (i.e., at or above the bifurcation) were independent predictors of the development of major biliary complications. Surgeon experience and the type of repair also are important determinants of outcome. In the series reported by Stewart and Way (1995), primary end-to-end repairs over a T-tube were always unsuccessful when the duct had been completely transected.

Many authors have advocated the use of anastomotic stents (Smith, 1969; Crist et al, 1987; Lillemoe, 1997), but the impact

Table 42A.4

Selected Series Reporting Outcome After Repair of Benign Biliary Strictures

Reference	No. Patients	Mechanism of Injury	Previous Repair Attempt	Morbidity/ Mortality	Successful Outcome	Follow-up
Chapman et al, 1995	122	OC (all)	80 (66%)	NR/1.8%*	76%	86 mo
McDonald et al, 1995	45	OC, 26 LC, 16 Other, 3	11 (24%)	36%/0	95%†	55 mo
Stewart & Way, 1995	45	LC (all)	27 (60%)	4%/0	94%	NR
Tocchi et al, 1996	84	OC, 60 CBDE, 4 Trauma, 4 Other, 16	4 (5%)	21%/2.2%	83%‡	108 mo
Lillemoe, 1997	59	LC (all)	15 (25%)	NR/0	92%‡	33 mo
Frilling et al, 2004	40	LC (all)	10 (25%)	NR/5%	82.5%	16 mo (median)
Schmidt et al, 2005	54	LC and OC, 22	41%	NR/1.9%§	92.6%	61.9 mo (median)

Most repairs were performed as hepaticojejunostomy or choledochojejunostomy (Roux-en-Y). *Previous repair attempt* refers to the number and percentage of patients referred after at least one attempt at repair. *Successful outcome* refers to the percentage of patients requiring no further intervention after initial, definitive surgical management at the reporting institution; most series reported salvaging some of the initial failures with interventional radiologic or further surgical intervention.

*Postoperative deaths in two patients subjected to mucosal grafts; no deaths occurred in patients submitted to direct biliary-enteric repair.

†Includes some asymptomatic patients with mild elevations of liver function tests.

‡Includes patients with excellent or good outcomes.

§A total of five deaths occurred during the follow-up period with one perioperative death.

CBDE, common bile duct exploration; LC, laparoscopic cholecystectomy; NR, not reported; OC, open cholecystectomy

Table 42A.5

Suggested Criteria for Assessing the Late Results of Biliary Stricture Management

Classification	Symptoms	Biochemistry*	Radiology†
Excellent	None	Normal	Normal
Good	None	Elevated	Abnormal
Fair	Improved	Elevated	Abnormal
Poor	Persistent/worse	Elevated	Abnormal

*Serum bilirubin and alkaline phosphatase
†Hepatobiliary iminodiacetic acid scan or cholangiography or both

Table 42A.6

Factors Associated with Stricture Recurrence or Poor Outcome After Operative Reconstruction

Proximal stricture (Bismuth types 3 and 4)
Multiple prior attempts at repair
Portal hypertension
Hepatic parenchymal disease (cirrhosis or hepatic fibrosis)
End-to-end biliary anastomosis
Surgeon inexperience
Intrahepatic or multiple strictures
Concurrent cholangitis or hepatic abscess
Intrahepatic stones
External or internal biliary fistula
Intraabdominal abscess or bile collection
Hepatic lobar atrophy
Advanced age or poor general health

of such stents on long-term patency is questionable. We and other authors rarely use stents, and we get excellent results (Bismuth, 1982; Bismuth et al, 1978; Stewart & Way, 1995; Tocchi et al, 1996). Transanastomotic stents seem to have little impact on outcome and probably should not be used routinely. Although stents may be useful in selected cases, they cannot prevent the inevitable failure of a poorly constructed anastomosis.

The results of surgical reconstruction for injuries other than those involving the main extrahepatic bile duct have not been reported in great numbers and are not known precisely. Lillemoe and colleagues (2000) reported the results of 9 cases of reconstruction for isolated sectoral hepatic duct strictures over an 18-year period. All patients in this series incurred injuries to aberrant right sectoral hepatic ducts at laparoscopic or open cholecystectomy, and all had associated bile leaks. After Roux-en-Y hepaticojejunostomy, six (66.6%) of the nine patients had a successful outcome, whereas three patients developed late strictures that required reintervention. Colovic (2009) likewise analyzed 19 patients with isolated segmental, sectoral, and right hepatic duct injuries over a 26-year period. Twelve patients underwent surgical reconstruction, and the rest were managed expectantly or with percutaneous drainage with good to excellent results.

Patients with recurrent strictures after reconstruction at a specialist unit may be salvaged with further intervention, either anastomotic revision or balloon dilation. Several authors have reported some measure of success with surgical revision in these patients (Chapman et al, 1995; Lillemoe et al, 1997; Stewart & Way, 1995; Tocchi et al, 1996; Walsh et al, 2004). The likelihood of a good outcome is less than with the initial reconstruction, however. In the series reported by Chapman and colleagues (1995), 11 of 22 operative failures were treated a second time successfully and had satisfactory outcomes, but this was substantially lower than the nearly 80% success rate after the initial repair. Other groups have reported nearly equivalent surgical outcomes for reoperated patients when compared with primary repairs at the same institution (Pottakkat et al, 2007). As discussed previously, the loss of bile duct length associated with a failed repair is a major factor that limits the success of subsequent interventions.

Duodenal ulceration has been reported in 10% of patients after Roux-en-Y biliary-enteric reconstruction and constitutes an additional cause of late morbidity (McArthur & Longmire, 1971; Sato et al, 1982). Most patients respond to antiulcer medication, but some may develop significant hemorrhage.

NONOPERATIVE APPROACHES. Advances in interventional radiology have resulted in a broader application of nonoperative approaches to bile duct stricture (see Chapter 28). The largest reported experience has been with percutaneous balloon dilation. With this technique, the biliary tree is accessed percutaneously, and a guidewire is passed through the stricture. The stricture is dilated with an angioplasty-type balloon catheter, after which a transhepatic stent is left in place for follow-up cholangiography and repeat dilation. In most cases, multiple dilations and prolonged biliary intubation are required. Early results have been encouraging, with several authors reporting good results in 55% to 85% of patients (Vogel et al, 1985; Mueller et al, 1986; Williams et al, 1987; Moore et al, 1987; Pitt et al, 1989; Lillemoe, 1997).

These results must be viewed with considerable caution, however. First, the mean follow-up in most of these studies was less than 3 years, which is insufficient to make a definitive comment regarding long-term efficacy. However, Cantwell and colleagues (2008) reported their long-term results with balloon dilation of 85 patients with benign postoperative biliary stricture and reported that most patients (61.9%) were successful after the first dilation, and 75% of patients had clinical patency after multiyear (mean, 8 years) follow-up. Second, balloon dilation is limited in its application to patients in whom biliary continuity is intact or has been restored by a previous attempt at repair; it has no role for strictures at or above the confluence and cannot be used if the bile duct has been transected (Lillemoe et al, 1997). Third, complications related to balloon dilation or to the percutaneous catheter are frequent and include hemobilia, bile leak, and cholangitis in 20% of patients.

Another nonoperative approach used is endoscopic stenting. With this technique, multiple plastic or metallic stents are placed across the stricture endoscopically, necessitating removal at a later date. Kassab and colleagues (2006) reported their experience with 88 patients with benign biliary stricture after

cholecystectomy who underwent endoscopic stenting during ERCP. They reported that 69.1% of patients were successfully treated, with a mean of 1.6 stents placed for an average duration of 14 months and no stricture recurrence at a mean follow-up of 28 months after stent removal. Other groups have reported higher success rates, albeit at shorter follow-up intervals (Kuzela et al, 2005; van Boeckel et al, 2009). As with balloon dilation, the results of stenting are tempered with caveats of short follow-up periods and no randomized studies.

Comparing the results of balloon dilation or endoscopic stenting with operative reconstruction is difficult because of differences in the types of injuries selected for each type of treatment, inconsistencies in defining successful outcomes, and differences in reporting complications and length of follow-up. To date, no randomized studies have compared these techniques. In two retrospective analyses, biliary reconstruction was more likely to result in a successful outcome: 89% versus 52% (Pitt et al, 1989), 92% versus 64% (Lillemoe et al, 1997), and 94% versus 58% (Misra et al, 2004). Because balloon dilation requires multiple readmissions and repeat interventions, the overall cost and morbidity seem to be similar to that of operatively treated patients (Pitt et al, 1989). The data suggest that, in most cases, biliary-enteric anastomosis is more effective and provides more durable relief of symptoms than balloon dilation, although balloon dilation is preferable in patients who otherwise would not tolerate an operation; it may be tried as an initial treatment in patients with biliary anastomotic strictures, for which the success rate seems to be greater than for primary bile duct strictures (Millis et al, 1992).

BILE DUCT INJURY AFTER OTHER OPERATIONS

Nontraditional Cholecystectomy

The advent of novel surgical technologies has ushered in a new potential for causation of iatrogenic biliary stricture. Natural orifice translumenal endoscopic surgery (NOTES)—a technique to obtain intraabdominal access via transgastric, transvaginal, transvesical, or transcolonic routes—has been recently applied for cholecystectomy. Multiple groups have described both the feasibility and safety of the technique (Chamberlain & Sakpal, 2009) as well as the ability to achieve Strasberg's critical view of safety (Auyang et al, 2009). However, hepatic complications, including bile leak and hepatic injury (Zornig et al, 2009; Salinas et al, 2010; Chow et al, 2009), have occurred in addition to other NOTES-specific complications such as gastric hematoma, abdominal sepsis, and esophageal perforation.

Another recent surgical trend is single-incision laparosopic surgery (SILS) to perform cholecystectomy via a single port at the umbilicus. Similar to NOTES, complications include hepatic injury, cystic artery hemorrage, and biliary leakage (Palanivelu et al, 2008; Tacchino et al, 2009). As with any new technology, initial results are tempered by the anticipated learning curve. An important limitation for both SILS and NOTES for cholecystectomy is inadequate retraction and maneuverability of the gallbladder to achieve critical views. Percutaneous large-bore–needle T-fasteners inserted into the gallbladder for retraction are fragile and may increase the likelihood of bile leakage. The effect on iatrogenic biliary injury remains to be seen with these techniques. On the other hand, the implementation of robotic technologies in theory gives the ability for more refined movement and views. Groups have already reported using robotic surgical platforms as a salvage mechanism for completion cholecystectomy, as it is believed the increased precision allows for better visualization and dissection in a hostile abdomen than that provided by traditional open or laparoscopic approaches (Kohn & Martinie, 2009). These new techniques need further careful safety evaluations before they should be widely accepted. The authors believe that the minor cosmetic benefit of these procedures does not outweigh the unknown potential harmful affects when compared with the standard laparoscopic approach.

Biliary Reconstructive Operation

Postoperative stricture or fistula can complicate procedures that require biliary-enteric anastomoses, such as reconstruction after pancreaticoduodenectomy, bile duct resection for mid–bile duct tumors, and excision of choledochal cysts. Typically, these procedures involve choledochoenteric or hepaticoenteric anastomosis. Late strictures after such procedures are most likely to occur when enteric anastomosis is performed to a normal caliber duct, or when the duct itself is diseased, as in cases of choledochal cysts. When biliary-enteric anastomosis has been performed for longstanding biliary obstruction, the duct is dilatated and thickened. In these cases, the anastomosis is usually easy to construct, and late stenosis is uncommon (Tocchi et al, 1996). In most cases, stricture of a biliary-enteric anastomosis after resection for malignancy is the result of cancer recurrence. However, in a retrospective study of 1595 patients, no difference was apparent in postoperative stricture rate (2.6%) between benign and malignant indications for resection following pancreaticoduodenectomy (House et al, 2006). Only 9% of strictures were caused by recurrent malignant disease, and preoperative biliary drainage and postoperative biliary stenting were the only risk factors for stricture.

Late stricture may also occur after side-to-side choledochoduodenostomy performed for choledocholithiasis or as a bypass procedure for chronic pancreatitis. This complication is rare if the anastomosis is performed to a sufficiently dilated duct (at least 1.5 cm), and the final diameter of the anastomosis is at least 2 to 2.5 cm (Schein & Gliedman, 1981; Escudero-Fabre et al, 1991). The so-called sump syndrome after choledochoduodenostomy—in which particulate matter, stones, and food debris accumulate and stagnate in the distal, "blind" end of the common duct—is an occasional cause of recurrent cholangitis that can result in anastomotic stricture (Matthews et al, 1993; Venerito et al, 2009). Endoscopic management, consisting of sphincterotomy with or without balloon dilation of the anastomosis or even placement of an occlusion device, has been reported for this condition (Baker et al, 1985; Ell et al, 2006). This approach may not be adequate, however, to remove the thick, infected debris that is often densely adherent to the wall of the inflamed distal CBD, and restricture of the anastomosis is common. We prefer reoperation, with end-to-side hepaticojejunostomy, Roux-en-Y, to prevent persistent regurgitation of intestinal contents and to remove the "sump" permanently (Matthews et al, 1993). When dissection in the hilus is rendered hazardous because of dense scarring, an alternative maneuver is to perform a pyloric exclusion and gastrojejunostomy, which accomplishes the same objective of preventing reflux of intestinal contents into the biliary tree.

Recurrent cholangitis after biliary-enteric anastomosis almost invariably is attributed to anastomotic stricture; however, this assumption has been questioned (Goldman et al, 1983). Some patients develop repeated episodes of cholangitis despite apparently free drainage of bile through the anastomosis in the absence of a clear stricture. In these cases, there may be an overlooked intrahepatic stricture or intrahepatic stone disease (Matthews et al, 1993) or even parasitic infection (Mercado et al, 2006).

Gastric Resection

Injury to the bile duct at gastrectomy is particularly likely when the pyloric region and duodenal bulb are severely distorted or inflamed (Florence et al, 1981). The most common situation is biliary injury during Billroth II gastrectomy. Patients may be seen with jaundice or biliary fistula in the postoperative period, which may be mistakenly attributed to a duodenal stump leak. Less commonly, bile duct injury occurs during gastrectomy (Fig. 42A.26), which can result in biliary stricture. Chronic inflammation from a duodenal ulcer or deeply placed sutures for management of hemorrhage can present with a delayed distal bile duct stricture or papillary stenosis (Fig. 42A.27).

Repair of the damaged bile duct after gastrectomy is usually not difficult. The stricture typically lies close to the proximal, divided end of the duodenum, and it is a simple matter to identify the biliary tree and perform a direct anastomosis at or near the duodenal stump. Occasionally, the entire first and second portion of the duodenum has been disconnected from the pancreatic head. One approach to such cases is repair with a retrocolic Roux-en-Y segment and envelopment of the pancreatic head in the open end of the jejunum.

Hepatic Resection

Biliary injury during hepatic resection is uncommon in experienced hands, but it can occur, particularly when resection is done for lesions near the hilus. In such instances, we recommend that the bile duct be freed from the tumor by careful dissection of hilum and clear identification of the right and left main ducts. Special care should be exercised when using the pedicle ligation and stapler technique to prevent inadvertent injury or complete occlusion of the left bile duct in right-sided resections (Fig. 42A.28). If there is a suspicion of iatrogenic ductal injury that cannot be readily identified, or if the biliary anatomy is unclear, intraoperative cholangiography should be performed; deliberate choledochotomy with passage of fine bougies into the right and left ducts may assist identification. If a choledochostomy has been performed, a T-tube usually is inserted.

The management of injuries that occur after partial hepatectomy can be extremely difficult (Johnson et al, 1979; Smith et al, 1982; Matthews et al, 1991). The problems are similar to

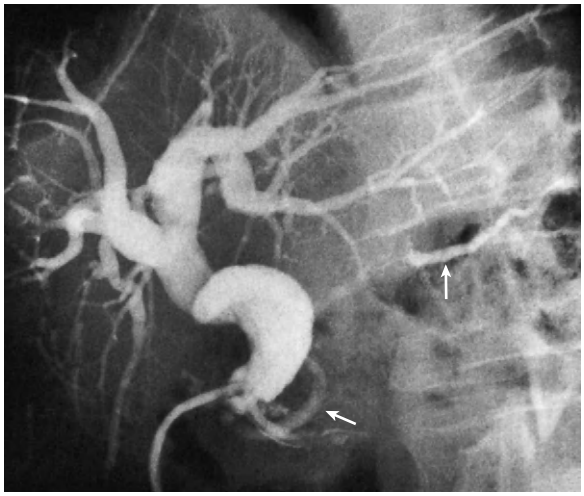


FIGURE 42A.26. A patient with ampullary disconnection that occurred during Billroth I gastrectomy. The duodenal loop was completely detached from the periampullary area. A fistulogram obtained through a T-tube that had been left in situ shows the biliary tree and the pancreatic duct (*arrows*). *(Courtesy Dr. H. Gooszen, University of Leiden, The Netherlands.)*

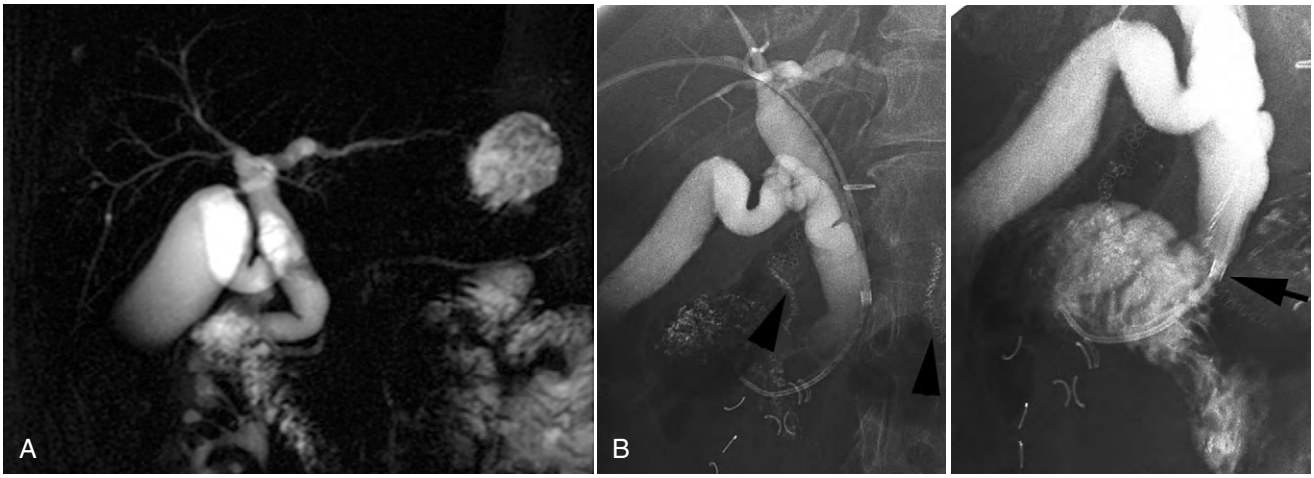


FIGURE 42A.27. A, Magnetic resonance cholangiopancreatographic (maximum-intensity projection), T2-weighted images demonstrating diffuse dilation of the common bile duct. The patient had undergone a gastrectomy with a Billroth II reconstruction for bleeding ulcer disease 15 years prior and presented with abdominal pain and normal liver function tests. A postgastrectomy bile duct stricture was suspected, but intraoperative findings showed papillary stenosis with a pinpoint opening. **B,** Percutaneous transluminal cholangiography (*right*) shows distal bile duct coming to a point at the level of the ampulla (*arrow*) and staple lines (*arrowheads, left*) from prior gastrectomy.

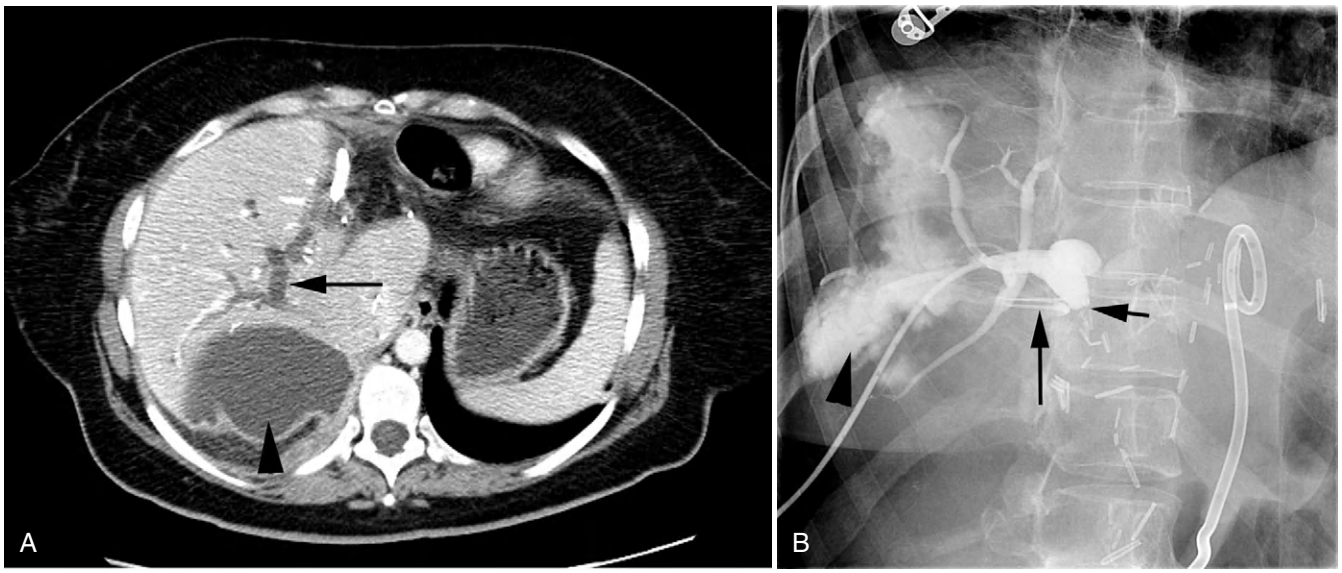


FIGURE 42A.28. A, Transaxial computed tomographic scan showing dilatated intrahepatic bile ducts (*arrow*) and biloma (*arrowhead*). This patient had undergone a right hepatectomy and segment II resection for metastatic colorectal cancer. A large tumor deposit was located at the bifurcation, and the bile duct was divided using a vascular stapler, which incorporated the left bile duct and resulted in complete biliary obstruction. **B,** Percutaneous transluminal cholangiography shows the obstruction of the bile duct at the hilum (*short arrow*). Contrast extravastion is seen (*long arrow*), resulting in biloma (*arrowhead*).

those encountered with liver atrophy discussed earlier. A biliary fistula after liver resection should be treated expectantly for a long time, because many resolve spontaneously. Operative repair should be undertaken only for persistent fistula despite continued observation or for jaundice or recurrent episodes of cholangitis.

Other Procedures

Late biliary stenosis may follow any other procedure requiring dissection in or near the porta hepatis, such as portocaval shunt or lymphadenectomy (Ishizuka et al, 1998). Biliary strictures also have been described after external-beam radiation therapy (Schmets et al, 1996) and after endoscopic injection of sclerosant into a bleeding duodenal ulcer (Luman, 1994). Bile duct strictures also may complicate orthotopic liver transplantation (see Chapter 98A), although their frequency seems to have decreased (Calne, 1976; Colonna et al, 1992; Vougas et al, 1996; Macfarlane et al, 1996; Lemmer et al, 1997; Wojcicki et al, 2008). Direct end-to-end choledochostomy has been the preferred method of reconstruction, but Roux-en-Y choledochojejunostomy also is used (Lopez-Santamaria et al, 1999). The use of T-tubes after biliary reconstruction, once considered essential, has been shown to offer no significant benefit (Vougas et al, 1996), and their routine use has been discontinued in many centers (Macfarlane et al, 1996; Vougas et al, 1996; see Chapter 35). Hepatic artery thrombosis is an uncommon but well-recognized cause of biliary stricture after liver transplantation (Colonna et al, 1992; Orons et al, 1995; Sanchez-Urdazpal et al, 1993; see Chapter 100). Late stricture is seen in 10% to 15% of cases (Macfarlane et al, 1996; Vougas et al, 1996), which is much lower than the reported rate of recurrent stricture after direct anastomosis for bile duct injuries. Many of these patients require operative revision, but some may be managed successfully with endoscopic or interventional radiologic approaches (Colonna et al, 1992; Lemmer et al, 1997; Macfarlane et al, 1996). In addition, the burgeoning of living donor transplantation has exposed the potential for significant biliary injury to the donor, a problem that seems to be uncommon in experienced hands (see Chapters 98B and 100; Lo, 2003; Liu et al, 2005).

BILE DUCT INJURY RESULTING FROM BLUNT OR PENETRATING INJURY

Hepatic, pancreatic, and biliary injuries from trauma are discussed more fully in Chapters 102, 103, and 104. The gallbladder or biliary tree may be damaged by blunt (Fig. 42A.29) or penetrating abdominal injuries. The CBD is susceptible to disruption from deceleration injuries, usually at the level of the pancreaticoduodenal junction, where it is relatively fixed compared with the more proximal duct. Delayed common duct stricture has been reported after blunt abdominal trauma (Yoon et al, 1998; Horiguchi et al, 1998). Late problems also may arise after hepatic trauma, in which prolonged fistulization occurs from a segment of liver isolated by the injury, particularly when bile drains from a large portion of the liver through the fistulous tract.

Management of ductal injuries depends on the extent of associated injuries. Major hemorrhage and other life-threatening injuries take priority, and in this setting, external diversion of bile flow through a tube passed proximally into the duct prevents bile leak and allows for later definitive repair. Roux-en-Y biliary-enteric reconstruction is the preferred approach for complete ductal transections (Degiannis et al, 2001). Traumatic strictures are probably also best approached in this manner, although successful dilation has been reported (Horiguchi et al, 1998). Management of persistent bile leak after liver injury is a much more difficult problem, because the fistula may persist even after prolonged observation. The possibility of an associated distal stricture, which perpetuates bile drainage, should be excluded. One approach to management is

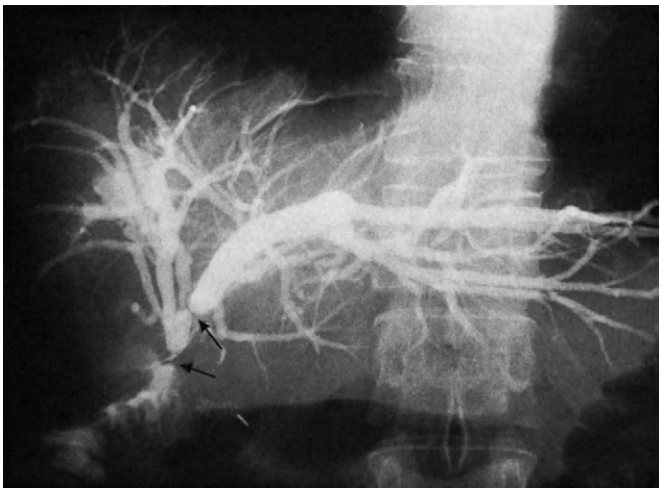


FIGURE 42A.29. Percutaneous transluminal cholangiography in a young man with recurrent attacks of cholangitis 1 year after repair of a biliary stricture at the site of damage to the common hepatic duct associated with a liver injury that necessitated right hepatectomy. Two strictures are present: one at the site of previous hepaticojejunostomy and the other in the main left hepatic duct (*arrows*). Rotation of the liver had made an approach to the left duct difficult. Hepaticojejunostomy was refashioned in the area of the confluence, and the stricture within the left hepatic duct was treated by subsequent balloon dilation with a good result.

by anastomosis of a well-developed fistula tract to a loop of jejunum (fistulojejunostomy) or to the gallbladder. Fistulojejunostomy may yield a permanent cure, although late stenosis or stricture still may develop, for which secondary repair must be performed (Smith et al, 1982). Resection of an isolated segment of liver that is the source of the drainage is difficult and seldom warranted, and direct oversewing of the fistula is rarely successful.

POSTINFLAMMATORY BILIARY STRICTURES

Longstanding Cholelithiasis

Repeated attacks of cholecystitis may result in progressive fibrosis and shrinking of the gallbladder, which ultimately obliterates the triangle of Calot, as described earlier. The inflammatory process may spread to involve the common hepatic duct, causing inflammatory stenosis and resulting in jaundice and cholangitis (Mirizzi, 1948; see Chapter 42B). The presentation may be associated with a history of acute or chronic cholecystitis, and an overt stricture may be present at the time of cholecystectomy. Intraoperative cholangiography may be difficult to obtain, and inadvertent bile duct injury may ensue during attempts to remove the gallbladder. A large stone in the region of the Hartmann pouch may erode into the common hepatic duct and cause a cholecystocholedochal fistula (see Fig. 42A.5). In such cases, attempts to remove the gallbladder result in injury to the common hepatic duct or removal of a portion of the duct. Patients with long-standing gallstones and jaundice should never be submitted to operation without preliminary percutaneous or endoscopic cholangiography.

Patients with inflammatory strictures of the common hepatic duct in association with chronic cholelithiasis may be seen with radiologic features that are indistinguishable from cholangiocarcinoma (see Chapter 50B); this possibility must be considered in all patients suspected to harbor a tumor at the biliary confluence with coincident choledocholithiasis (Hadjis et al, 1985; Standfield et al, 1989; Wetter et al, 1991). Biliary cytology and percutaneous biopsy generally are not helpful, because a benign result never excludes a malignancy; the diagnosis usually is established at operation.

Chronic Duodenal Ulcer

Chronic duodenal ulcer can cause inflammation and fibrosis in the entire periampullary area and result in distal biliary stricture or choledochoduodenal fistula. The presentation is typically that of jaundice and cholangitis in a patient with a long history of duodenal ulcer. The advent of acid-reducing agents has greatly reduced the incidence of complications related to peptic ulcer disease, and such problems are now rarely seen.

Recurrent Pyogenic Cholangitis

Recurrent pyogenic cholangitis is addressed in detail in Chapters 39 and 40. This condition is seen mainly in Southeast Asia and is associated with intrahepatic calcium bilirubinate stones and intrahepatic strictures (Ong, 1962; Maki et al, 1972; Choi et al, 1982; Chen et al, 1984). Recurrent episodes of cholangitis and sepsis are the major threat to life in these patients, along with a significantly increased risk of cholangiocarcinoma (Sato et al, 1995, 1998; Chijiiwa et al, 1995; Chu et al, 1997). Hepatic resection combined with Roux-en-Y biliary-enteric reconstruction is effective in relieving symptoms and clearing stones. This is particularly true if the disease is unilateral, but even patients with bilateral disease may benefit from a combination of resection and postoperative balloon dilation and stone extraction (Jeng et al, 1996). Because of the high incidence of recurrent stricture and stone formation, a team approach that includes experienced surgeons, interventional radiologists, and gastroenterogists is required to obtain the best results (Kim et al, 1998). Careful operative planning is important, and the operation can be tailored to help provide future access to the biliary tract. For example, we have sucessfully used a Roux-en-Y biliary-enteric reconstruction that not only includes the long-segment limb anchored to the abdominal wall for interventional radiology access, but a jejunogastrostomy is also constructed, using the proximal end of the Roux limb, for easy endoscopic access in patients at high risk for recurrent stones (Fig. 42A.30). Some authors have reported success using balloon dilation combined with transhepatic choledochoscopic lithotripsy, either as initial therapy or for recurrent stones after surgery (Yoshida et al, 1998; Sheen-Chen et al, 1998). Numerous patients have advanced parenchymal disease at presentation and die as a result of related complications despite aggressive intervention (Chijiiwa et al, 1995).

Chronic Pancreatitis (See Chapter 55)

Chronic pancreatitis is a well-known cause of distal bile duct stenosis and stricture. The incidence of biliary stricture in these patients is difficult to know with certainty, but it has been reported in 30% of patients (Sarles & Sahel, 1978). The characteristic lesion is a long, narrow stricture involving the retropancreatic portion of the CBD (Fig. 42A.31), but other variants

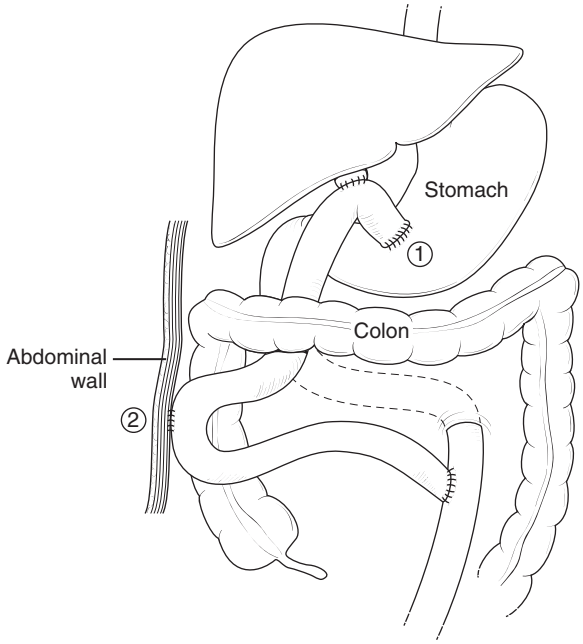


FIGURE 42A.30. Surgical reconstruction option for patients with recurrent pyogenic cholangitis. Note the jejunogastrotomy (*1*) constructed from the proximal end of the Roux limb to the antrum for easy endoscopic assess. A long-segment jejunal Roux limb is used and is anchored to the abdominal wall (*2*) for interventional radiology access for future therapeutic or diagnostic studies in patients at high risk for recurrent stones.

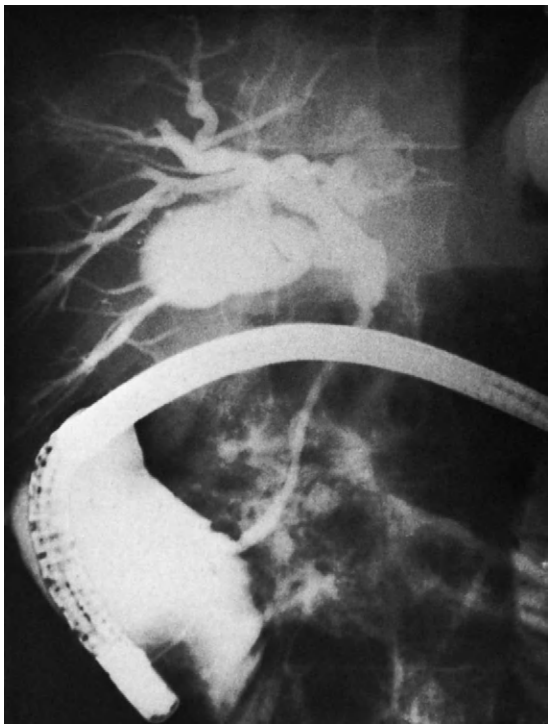


FIGURE 42A.31. Retrograde cholangiography in a patient with biliary stricture related to pancreatitis. Note the long stricture in the common bile duct as it passes through the head of a calcified pancreas. The stricture is a result of pancreatitis from alcohol ingestion, and the patient's symptoms were of intermittent attacks of jaundice and pain. The pancreatic duct could not be delineated; management included laparotomy and choledochojejunostomy.

have been described (Sarles & Sahel, 1978; Barthet et al, 1994). Although more common in association with alcohol-related chronic pancreatitis, it may occur in chronic pancreatitis unrelated to alcohol use. In addition to jaundice, pain is common, which may be intermittent and similar to biliary colic; cholangitis and fever are less frequent (Stabile et al, 1987; Kalvaria et al, 1989; Barthet et al, 1994).

The diagnosis of bile duct stricture usually is made by MRCP. The radiologic appearance is typically a long stenosis of the retropancreatic portion of the CBD. The fibrotic process also may affect the proximal duct gradually over a prolonged period so that it is relatively nondistensible, and the proximal duct may exhibit little dilation, as one would expect from a stricture from other causes. Occasionally, the stenosis is shorter in length, however, or it may involve only the immediate papillary area. Contrast medium usually, but not always, traverses the stenosis and flows into the duodenum. Differentiating a stricture related to pancreatitis from malignant obstruction may be difficult. Although the long, tapering, narrow stricture of the bile duct is characteristic of chronic pancreatitis, especially when associated with demonstrable pancreatic ductal abnormality on ERCP, carcinoma still may be present, and one must use extreme caution to avoid an erroneous diagnosis.

The presence of a bile duct stenosis or stricture in association with chronic pancreatitis is not an indication for therapy. Quite severe stenosis may be found in the presence of absolutely normal LFTs and in patients who have never had jaundice. If cholestasis or cholangitis occurs, however, biliary bypass becomes necessary. Occasionally, operation is necessary in the management of chronic pancreatitis, and if it is known that a high-grade biliary stricture is present, biliary bypass may be performed concomitantly. In a series of 240 patients with chronic pancreatitis, 39 of whom came to operation, nine had symptomatic biliary obstruction, and 13 were subjected to some form of biliary-enteric anastomosis, either alone or associated with excisional surgery for pancreatic disease. Most patients with CBD stenosis associated with chronic pancreatitis can be managed without biliary bypass (Kalvaria et al, 1989; Smits et al, 1996). Temporary endoscopic biliary stenting may be useful in some cases and may be definitive therapy in 10% to 25% (Barthet et al, 1994; Itani & Taylor, 1995; Smits et al, 1996).

For patients requiring biliary bypass, side-to-side choledochoduodenostomy may be used, but this is often not the best option, because the surrounding inflammatory reaction may render the duodenum rigid and less mobile. Also, the CBD may be involved in periductal fibrosis and may be only minimally dilated. Roux-en-Y choledochojejunostomy is the preferred reconstructive approach. Cholecystojejunostomy should not be used, and transduodenal sphincteroplasty is generally not suitable because of the great length of the stricture. Biliary-enteric anastomosis generally affords excellent long-term relief of obstruction, but relief from chronic pain associated with the pancreatitis itself is unusual (Barthet et al, 1994; Stabile et al, 1987).

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PART 5: Biliary Tract Disease

SECTION I: Inflammatory, Infective, and Congenital

C. Biliary Infection and Infestation

CHAPTER 43

Cholangitis

Cherif Boutros and N. Joseph Espat

OVERVIEW

Cholangitis, or bile duct inflammation, is generally associated with infection in the presence of biliary obstruction. It should be considered a clinical emergency that requires urgent multidisciplinary care comprising intravenous (IV) fluids, broad-spectrum parenteral antibiotics, and, most importantly, biliary decompression. The most common cause for cholangitis, as we have defined it, is choledocholithiasis and pathologies that similarly result in the obstruction of the biliary tree. For "true" cholangitis to develop, obstruction of bile flow contaminated by bacteria or fungi is necessary. As such, in the absence of both of these conditions, cholangitis is uncommon.

Approximately 80% of patients with cholangitis will clinically improve with IV fluids and antibiotics; however, definitive biliary decompression is still likely necessary. Patients who fail to improve or those who deteriorate within 12 hours of instituting medical therapy should undergo emergent biliary decompression by either endoscopic or percutaneous drainage procedures. The specific procedure selected for decompression should be based upon the type and suspected location of the obstruction. In general terms, a low biliary obstruction is best decompressed endoscopically, but obstruction proximal to the bifurcation or from biliary-enteric anastomoses should be decompressed percutaneously.

Procedures to achieve a goal beyond decompression—such as papillotomy, balloon stricture dilation, or biliary tract debris clearance—should be avoided in the setting of recent or present sepsis. Emergent operative exploration and decompression of the bile duct is rarely indicated and is associated with high mortality. Operative biliary decompression should be reserved only for those patients who fail nonoperative decompression. The extent of operative biliary decompression should, in most cases, be limited to T-tube type decompression of the common bile duct (CBD) with deferred definitive management of the biliary obstruction, until the sepsis has resolved, and the patient's condition has improved. Continuation of antibiotic therapy should be guided by the persistence of residual biliary obstruction because of the increased risk of recurrent cholangitis.

CHOLANGITIS

Cholangitis is not a single disease with a well-defined clinical appearance but rather a spectrum of disease that presents variably with a wide range of severity. The appearance and course of cholangitis ranges from mild, intermittent, and recurrent episodes of abdominal pain, jaundice, fever, and chills as described by Charcot in 1877 to a rapidly progressive systemic illness that results in shock, coma, and death as described by Reynolds and Dargan (1959).

The development of cholangitis requires the presence of three factors: 1) obstruction of bile flow, 2) colonization of the bile with bacteria (bactobilia) or fungi, and 3) elevation of intraductal biliary pressure. The most common causes of biliary obstruction associated with cholangitis are calculi, benign and malignant strictures, obstructed stents, and parasites (Table 43.1; see Chapters 7 and 11). The management of cholangitis should follow three principles: 1) vigorous resuscitation and hemodynamic support, 2) broad-spectrum parenteral antibiotics, and 3) relief of biliary obstruction (decompression). Figure 43.1 provides a suggested management algorithm for patients with cholangitis.

All patients being treated for cholangitis should be aggressively resuscitated, administered appropriate IV antibiotics, and closely monitored. Most patients (85%) will clinically improve over the ensuing 12 to 24 hours, after which time semielective imaging of the biliary tree by ultrasound (US), computed tomography (CT), and/or magnetic resonance cholangiography (MRC) is indicated to diagnose the location and cause of the underlying biliary obstruction. However, it cannot be overstated that the definitive treatment for cholangitis is biliary decompression.

Table 43.1

Causes of Cholangitis

1. Biliary stones
   - a. Choledocholithiasis
   - b. Hepatolithiasis
   - c. Mirizzi syndrome
2. Benign biliary strictures
   - a. Biliary surgery
   - b. Chronic pancreatitis
   - c. Primary sclerosing cholangitis
   - d. Orthotopic liver transplantation
   - e. Cholangiography in patients with AIDS
3. Malignant biliary obstruction
   - a. Pancreas
   - b. Bile duct/gallbladder
   - c. Ampulla
   - d. Duodenum
4. Nonsurgical biliary interventions
   - a. ERCP
   - b. PTC
   - c. Biliary stents
5. Parasitic infection
6. Miscellaneous

AIDS, acquired immunodeficiency syndrome; ERCP, endoscopic retrograde cholangiopancreatography; PTC, percutaneous transhepatic cholangiography

Modified from Bornman PC, et al, 2003: Management of cholangitis. Hepatobiliary Pancreat Surg 10:406-414.

Pharmacologic Treatment for Cholangitis

The pharmacologic treatment of cholangitis differs from that of acute cholecystitis in the need for more specific and broader antimicrobial therapy dictated by the patient's underlying pathology and clinical condition. Culture-identified bacteriology of the biliary tree has changed over the past 40 years. Previously, the gram-negative aerobes *Escherichia coli* and *Klebsiella,* gram-positive aerobes, and enterococci were the most common isolates identified from patients with cholangitis (Helton, 1987). More recently, infections have been polymicrobial in 30% to 80% of cases (Westphal & Brogard, 1999). In some studies, anaerobes have been detected in more than 15% of patients but rarely as the sole isolate. *Bacteroides* and *Clostridium* species are the most frequently cultured anaerobes, and anaerobic bacteria are commonly isolated from biliary tract specimens from patients who have a history of biliary surgery, especially those with a biliary-enteric anastomosis or chronic biliary tract infection and the elderly. Cholangitis arising from anaerobic organisms is reported to be associated with a more severe clinical illness compared with purely aerobic infections (Csendes et al, 1996; see Chapter 11).

Bacteremia in acute cholangitis has been demonstrated to be the result of increased bile duct pressure that favors the reflux of bacteria into the blood and lymphatic circulation (Csendes et al, 1995); it has been reported in 21% to 71% of patients with cholangitis (Cotton et al, 1991; Csendes et al, 1996; see Chapter 7). The organisms isolated reflect a similar distribution to that of biliary cultures, except for anaerobes and enterococci, which are infrequently found in blood cultures.

A variety of antibiotic regimens and combinations have been compared in prospective randomized clinical trials to establish efficacy, safety, and toxicity profiles. Monotherapy with broad-spectrum agents, such as a third- and fourth-generation cephalosporins (cefotaxime, cefipime), and a ureidopenicillin (mezlocillin, piperacillin) combined with a β-lactamase inhibitor (ticarcillin-clavulanate, piperacillin-tazobactam) or quinolone (ciprofloxacin) have been reported to be as effective in treating patients with cholangitis as metronidazole or clindamycin in combination with an aminoglycoside or a third-generation cephalosporin and ampicillin (Sung et al, 1995; Thompson et al, 1993).

In a multicenter comparative study of cefepime versus broad-spectrum antibacterial therapy in moderate and severe bacterial infections (Badaro et al, 2002), cefepime was demonstrated to achieve a higher cure rate compared with broad-spectrum combination therapy as an initial empiric treatment for hospitalized patients with moderate to severe community-acquired infections.

Carbapenems, ureidopenicillins, and fluoroquinolones offer good coverage for gram-negative aerobes (Mazuski et al, 2002), but piperacillin offers the advantage of gram-positive coverage, including enterococci, as well as anaerobic coverage (Thompson et al, 1990). Tazobactam, a β-lactamase inhibitor, extends the spectrum to cover organisms that have acquired resistance. These regimens are sufficient for most patients presenting with de novo cholangitis who have not yet been hospitalized, operated upon, or instrumented (Table 43.2). Again, it is emphasized that although hydration and antibiotics may improve the clinical condition in up to 80% of patients with acute cholangitis, 20% with clinical sepsis will require urgent biliary decompression.

For patients with a previously instrumented biliary tract (endoscopic retrograde cholangiopancreatography [ERCP], placement of a biliary stent), a previous biliary operation, or prolonged hospitalization, the cholangitis is likely to be associated with resistant flora such as *Pseudomonas* or *Serratia* species. Liver transplant patients who develop cholangitis have been observed to have *Candida* and/or *Enterococcus* in the biliary tree. Interestingly, vancomycin-resistant enterococci (VRE) are common in liver transplant patients (Schlitt et al, 1999). When *Candida* and/or *Enterococcus* are cultured, these should be treated with amphotericin and one of the streptogramins (quinupristin/dalfopristin [Synercid] or oxazolidinone linezolid [Zyvox], respectively). For all hospitalized patients, antibiotic coverage should always take into consideration the local resistance patterns ("antibiotic-gram") of specific pathogens.

Duration of Antibiotic Therapy for Cholangitis

No randomized clinical trials have firmly established the duration of antibiotic therapy for the treatment of cholangitis. However, general guidelines are for antibiotic therapy to continue until biliary obstruction is completely relieved, biochemical liver function tests have improved or normalized, and the patient is afebrile for at least 48 hours. After successful biliary drainage by ERCP, a retrospective study comparing short-duration antibiotic therapy (3 days) with longer antibiotic coverage showed that 3 days of antibiotic therapy appears sufficient when adequate drainage has been achieved and fever is abating (van Lent et al, 2002).

Patients at risk for recurrent cholangitis, such as those with residual calculi or incompletely relieved obstruction

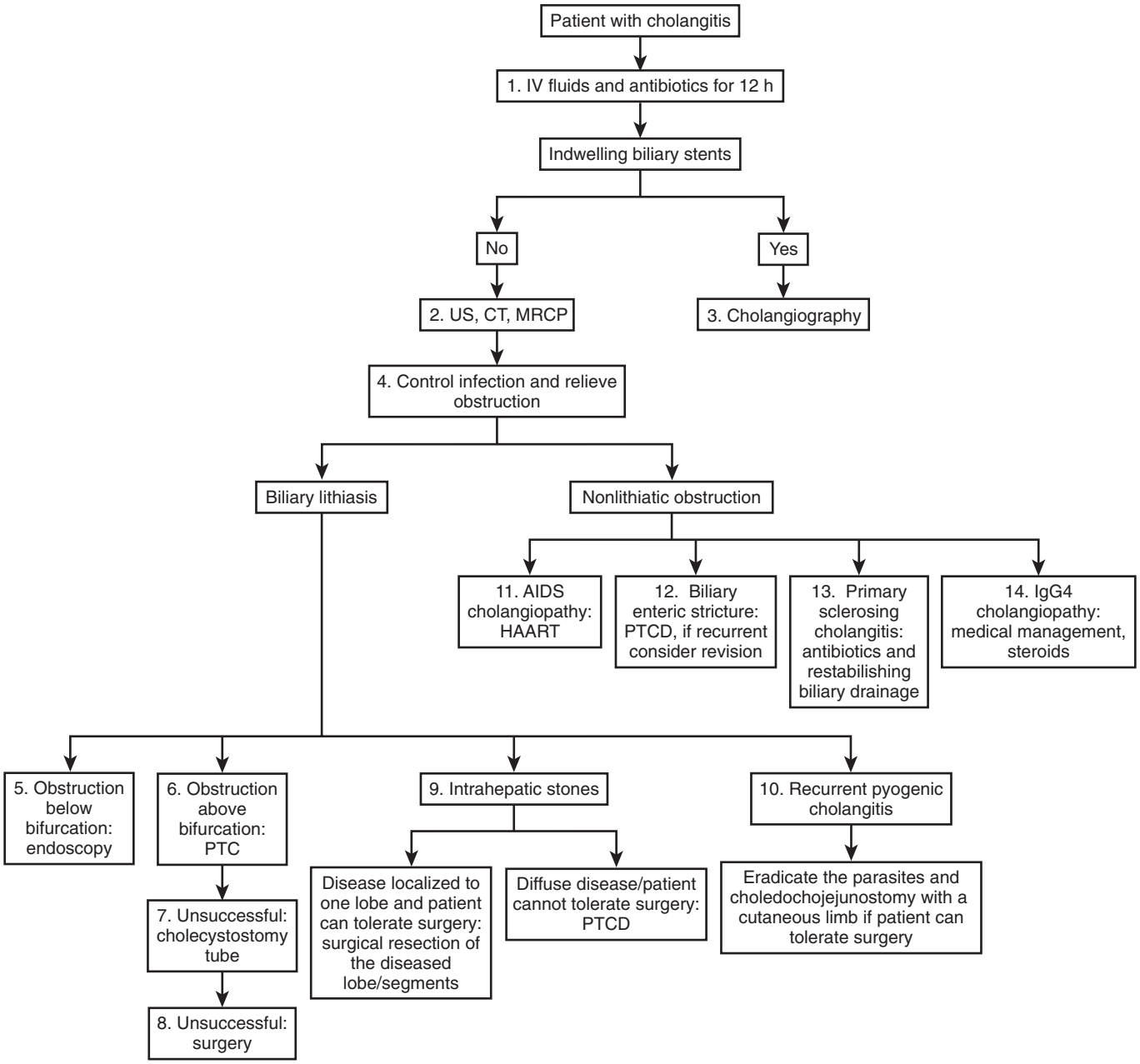


FIGURE 43.1. Suggested algorithm for management and interventions in the treatment of cholangitis. AIDS, acquired immunodeficiency syndrome; CT, computed tomography; HAART, highly active antiretroviral therapy; IgG4, immunoglobulin G4; IV, intravenous; MRCP, magnetic resonance cholangiopancreatography; PTC, percutaneous transhepatic cholangiography; PTCD, percutaneous transhepatic cholangiography and drainage; US, ultrasound.

Table 43.2

Pharmacologic Parameters Relevant to Antibiotic Therapy or Prophylaxis of Biliary Sepsis

					CLINICAL RELEVANCE OF THE PARAMETERS FOR		
	THERAPEUTIC CLASS						
PARAMETER	Aminoglycosides	Quinolones	Penicillins	Cephalosporins	Treatment of Acute Infections	Prophylaxis	Maintenance Therapy
Oral bioavailability	No	++	+/++	+/++	No	Yes	Yes
Distribution in tissues	+	+++	++	++	Yes	Yes	More or less
Ratio of concentration to MIC for *Escherichia coli*							
In blood	+++	+++	++	+++	Yes	Yes	More or less
In bile	+	+++	++*	+/+++†	Yes	No	Yes

*Ureidopenicillins

†Anionic cephalosporins with molecular weight >500 (e.g., cefpiramide, cefoperazone, ceftriaxone, cefotetan, cefixime)

MIC, minimum inhibitory concentration

From Westphal JF, Brogard JM, 1999: Biliary tract infections: a guide to drug treatment. Drugs 57(1):81-91.

from any cause, should remain on oral antibiotics until the biliary obstruction is completely relieved. Acceptable oral antibiotics for these types of patients include trimethoprim/sulfamethoxazole and levofloxacin or ciprofloxacin alone or in combination with metronidazole.

Diagnostic Imaging Studies

Various noninvasive modalities are available to image the biliary tree and gallbladder: transabdominal ultrasonography (TUS), radionuclide imaging (e.g., hepatoiminodiacetic acid [HIDA]), CT, MRC, and CT cholangiography.

Transabdominal Ultrasound

TUS (see Chapter 13) is the least expensive and most universally available imaging modality to evaluate the biliary tree and gallbladder. As such, it is the preferred first diagnostic test when evaluating a patient with acute cholecystitis and/or cholangitis. US can reliably demonstrate intrahepatic and extrahepatic biliary dilation, but this can be absent in the case of an acute obstruction. In the presence of gallstones less than 10 mm in size and dilation of the CBD greater than 10 mm, CBD obstruction by gallstones is likely (Abboud et al, 1996). The sensitivity of US to detect CBD stones varies between 20% and 75%, with increased sensitivity in the case of multiple large stones within a dilatated CBD and less sensitivity in the case of stone impaction in the retropancreatic segment of the CBD.

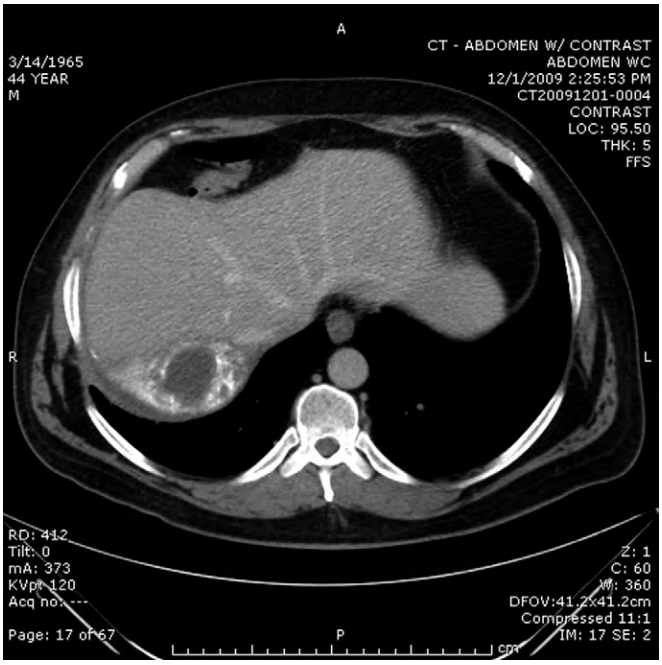


FIGURE 43.2. Abdominal computed tomographic scan demonstrating a hepatic abscess involving the right hepatic lobe with surrounding inflammatory changes.

Computed Tomography

Non–contrast-enhanced CT scan (see Chapter 16) overcomes the technical limitations of US, as it can detect impacted stones in the retropancreatic CBD segment; when performed with 2- to 3-mm slices, its sensitivity for detecting small stones is reported to range between 65% and 80% (Neitlich et al, 1997). However, because up to 25% of gallstones will have the same density as bile, the sensitivity of noncontrast CT does not exceed 80%.

In the case of cholangitis, intravenous (IV) contrast–enhanced CT scan can reveal inflammation and demonstrate thickness of the bile ducts. The arterial phase should reveal peripheral or periductal hypervascularization (Arai et al, 2003). Another important role for CT is to detect the complications of cholangitis, such as hepatic abscess (Fig. 43.2) and pylephlebitis (suppurative thrombosis of the portal vein). Finally, CT can reveal etiologies of biliary obstruction, other than a CBD stone, such as a tumoral mass; however, contrast material is associated with a risk of hypersensitivity or induced renal toxicity, particularly in underresuscitated patients or in the presence of hemodynamic instability.

Magnetic Resonance Cholangiopancreatography

Magnetic resonance cholangiopancreatography (MRCP; see Chapter 17) provides imaging in a noninvasive manner that allows visualization by emphasizing the hyperintensity of stationary liquids, thus the use of this modality precludes the need for contrast injection to fully visualize the biliary system. Images obtained by MRCP are similar to those obtained by cholangiogram: stones appear as hypointense defects (lacking liquid) within the biliary system. However, MRCP cannot differentiate stones from air bubbles, sludge, or blood clots—all these lack liquid. A further limitation of MRCP is that it cannot detect stones less than 3 mm in size, nor can it detect impacted stones in the ampulla, which require evaluation of T1 images before and after gadolinium injection. The overall sensitivity of MRCP to detect CBD stones is 80% to 100%, and its specificity is excellent, varying between 90% and 100% (Hakansson et al, 2002; Kondo et al, 2001; Soto et al, 2000). It is important to recall that MRCP is purely a diagnostic modality, it is not therapeutic.

Endoscopic Ultrasound

Endoscopic ultrasound (EUS; see Chapter 14) is an invasive procedure that requires sedation or general anesthesia. Once it has been passed through the stomach and into the duodenum, the US probe is in close relationship to the CBD; by using a high US frequency (7.5 to 12 MHz), the resolution of EUS is exceptional (<1 mm), making it the gold standard in the detection of small gallstones or other obstructive etiologies. The major limitations of EUS are that it cannot be performed in patients with altered anatomy, such as those with a prior distal gastrectomy or gastric bypass, or in the presence of a significantly calcified pancreas or hilar biliary pathology.

Direct Cholangiography

Although historically considered the reference radiologic modality, direct cholangiography (see Chapter 18) for purely diagnostic purposes has been supplanted by less invasive cross-sectional imaging alternatives, which also provide additional anatomic detail related to adjacent organs to allow a more complete assessment. Retrograde or percutaneous cholangiography is largely limited to the first step of a therapeutic procedure (Gallix et al, 2006).

In addition to its inferior image quality, there are various complications associated with the use of direct

cholangiography, including biliary infection, pancreatitis, and hemorrhage (Vidal et al, 2004).

MANAGEMENT OF CHOLANGITIS

Extrahepatic Biliary Stone Obstruction: Procedures for Biliary Decompression

When performed in a timely manner, biliary decompression and successful drainage are the cornerstones of acute cholangitis treatment. Several techniques can be used to ensure effective biliary drainage. A review of these techniques with the Tokyo guidelines was recently published (Tsuyuguchi et al, 2007).

The preferred method and route to relieve biliary obstruction, and the ultimate success of biliary drainage, depends upon a number of factors that include availability of the technique (endoscopic, percutaneous, or operative), local expertise, etiology, location and severity of obstruction, and the presence of comorbid medical conditions. Patients who do not respond to initial medical treatment within 12 to 24 hours should undergo emergent, nonoperative decompression of the biliary tract. When the obstruction is believed to be below the bile duct bifurcation, the preferred initial approach is endoscopic (Kumar et al, 2004).

Endoscopic Biliary Decompression (See Chapters 27 and 36)

ERCP and biliary decompression should be performed only after patients have been resuscitated and given systemic antibiotics, although an exception can be made for patients who do not respond to initial medical therapy or those who clinically deteriorate within 12 hours of beginning treatment. If the patient has mild to moderate cholangitis and is stable, an effort can be made to definitively clear the duct of calculi. However, if the patient is septic with hemodynamic instability, or if there is purulence within the duct, efforts to clear the duct completely should be deferred to another time, when the patient is more stable, and sepsis has resolved.

The procedure should be carried out in a monitored setting (endoscopy lab, intensive care unit, or operating theater) under either conscious sedation or general anesthesia. A side-viewing scope is used to visualize and cannulate the ampulla of Vater. Contrast is injected into the CBD under real-time fluoroscopy only in an amount that allows the level of the obstruction to be visualized, and a guidewire is passed across the obstruction. In acutely ill or septic patients, biliary decompression should be obtained with the least amount of manipulation and effort, and extended maneuvers to remove calculi or perform sphincterotomy should be avoided. A convenient method of decompression is with external nasobiliary drainage (ENBD), a drainage procedure done by placing a 5- to 7-Fr tube using a guidewire technique. ENBD has the advantage of being an effective drainage tool, without the need of a sphincterotomy, and it provides access for biliary cultures.

Another biliary drainage modality is internal drainage using a 7- to 10-Fr plastic stent in the bile duct, using a guidewire after selective cannulation of the bile duct. Two stent shapes are available: a *straight type* with flaps on both sides and a *pigtail type* to prevent dislocation. Advantages of this approach include minimal or absent discomfort and limited electrolyte or fluid shifts relative to transnasal biliary drainage. Disadvantages include the potential for stent clogging or loss of patency, risk of dislodgement, and the technical disadvantage for a sphincterotomy when a stent larger than 7 Fr is inserted.

In cases of difficult biliary cannulation, an endoscopic sphincterotomy (EST) may be performed. A common EST technique is to perform a high-frequency electric surgical incision of the duodenal papilla, using a sphincterotome selectively inserted into the bile duct. In contrast to EST for stone removal, when performed for drainage, only a limited incision is necessary. Bleeding, retroduodenal perforation, and pancreatitis are the most common complications after ERCP and sphincterotomy. Morbidity and mortality rates are much higher with sphincterotomy than with nasobiliary catheter drainage when patients are critically ill (Boender et al, 1995; Chawla et al, 1994; Leese et al, 1986). Complications commonly reported with EST are hemorrhage (2% to 3%) and pancreatitis (1.9% to 5.4%), and mortality rate is 0.4% to 1.3% (Cotton et al, 1991; Freeman et al, 1996).

Contraindications

Sphincterotomy is contraindicated in the presence of coagulopathy, systemic sepsis, and hemodynamic instability, with the exception of those patients who have clinically deteriorated after initial medical therapy.

As stated, emergent sphincterotomy to decompress the bile duct should be avoided in septic patients, and especially in elderly patients, because of potentially high mortality rates (18.8%). In the elderly, endoscopic drainage alone has been observed to result in lower morbidity (16.7%) and mortality (5.6%) rates than surgical (87.5% and 25.0%, respectively) or percutaneous drainage (36.4% and 9.1%, respectively) (Boender et al, 1995; Sugiyama & Atomi, 1997). It is important to emphasize that once control of sepsis has been achieved, sphincterotomy and more optimal biliary imaging can be obtained, thus defining the underlying obstruction and enabling definitive treatment for either a stone, tumor, or stricture (Lee et al, 2002).

Percutaneous Transhepatic Cholangiography and Drainage (See Chapters 28, 32, and 36)

Retrospective analyses and prospective randomized trials have shown that urgent endoscopic drainage is an effective treatment for suppurative cholangitis and results in a better clinical outcome than surgical drainage (Hui et al, 2002); however, in an unstable patient, ERCP should not be performed; percutaneous transhepatic decompression is a better alternative, despite the limitation of not treating the cause of the obstruction (Gould et al, 1985; Kadir et al, 1982).

Percutaneous transhepatic cholangiography and drainage (PTCD) is especially valuable in the presence of a hilar obstruction (Nomura et al, 1997), having been reported to be useful in cases of malignant biliary obstruction, particularly when used in combination with definitive decompressive adjuncts, such as expandable metallic stents. In a series of 233 patients with malignant biliary obstruction requiring biliary drainage, with decompression achieved by PTCD and placement of metallic stents and/or plastic tubes, improvement in survival was reported after either chemotherapy, radiotherapy, or brachytherapy at 1, 3, 6, and 12 months of 97.96%, 95.92%, 89.80%, and 32.59%, respectively. Most notable was the observation that the patency rates for biliary stents at 1, 3, 6, and 12 months were 97.96%, 93.86%, 80.93%, and 56.52%, respectively.

These results strongly suggest that for patients with malignant biliary obstruction, biliary decompression with PTCD, using internalized stents for biliary patency, approaches the duration of patient survival (Qian et al, 2006).

Standard Procedure

Deciding which side of the liver to drain initially depends on the underlying pathology and the location of the obstruction within the biliary tree. Therefore, US and/or CT of the liver should be obtained to assess anatomy, liver lobe atrophy, distribution of dilated intrahepatic ducts, and to identify the likely cause and location of the obstruction. When the left hemiliver is punctured, it is preferable to enter into the segment III or IV bile duct through the left lateral segment or the umbilical fissure. When the right hemiliver is punctured, an intercostal approach is often used, preferably aimed toward the main segment VI duct. A Chiba needle is used under real-time fluoroscopy, and contrast is slowly injected, until a biliary division is entered. It is important to remember not to inject contrast under pressure into the biliary tree to avoid cholangiovenous reflux of bacteria and endotoxin. Once the biliary tree is accessed, a guidewire is placed, passed, and advanced distally to traverse the point of obstruction. If the point of obstruction cannot be traversed, a locking pigtail catheter is placed to decompress the biliary system proximal to the point of obstruction. In the septic or unstable patient, it is not recommended to attempt complete clearance of the biliary tree—the goal is decompression.

Although no studies directly compare percutaneous to endoscopic drainage in the setting of acute cholangitis, PTCD should applied to those patients who are not candidates for, or who have failed, endoscopic drainage. PTCD is potentially more morbid, with known complications that include intraperitoneal hemorrhage (2.5%) and biliary peritonitis (1.2%) with a mortality rate as high as 1.7%. In patients with proximal biliary obstruction, percutaneous drainage is clearly preferred, especially in an ill patient (Paik et al, 2009).

Complications from PTCD can be severe and may require additional procedures. The most frequently encountered complications are catheter dislodgement, hemobilia, catheter obstruction, cholangitis, hemoperitoneum, and choleperitoneum (Gazzaniga et al, 1991). The spillage of infected bile into the subdiaphragmatic and perihepatic space may lead to peritonitis and prolonged fever and may eventually require operative drainage.

Mortality rates are substantial after unsuccessful endoscopic drainage of cholangitis from hilar obstruction (Ducreux et al, 1992). Hence, rather than endoscopic drainage, PTCD is indicated for such lesions. If PTCD is unsuccessful or unavailable, the patient should undergo emergent percutaneous cholecystostomy tube decompression, if the cystic duct is patent, and the obstruction is below the cystic duct–CBD union. Because of its high mortality rate (>30%), emergency laparotomy and CBD decompression via a T-tube should only be used as a last resort, when nonoperative modalities are unavailable or unsuccessful (Lai et al, 1992).

Contraindications

PTCD should not be performed in the hemodynamically unstable or otherwise seriously ill septic patient, except in those who have clinically deteriorated after initial aggressive medical therapy. PTCD should be used only if endoscopic drainage fails for lower bile duct obstruction, and it should not be used as the primary means of decompression in the patient with ascites.

Open Common Bile Duct Exploration (See Chapters 29 and 35)

Patients with acute cholangitis are preferentially treated with noninvasive drainage procedures, such as endoscopic drainage or PTCD; only the minority should be candidates for open surgical drainage. However, open drainage may be indicated for patients who cannot undergo such noninvasive drainage procedures, most commonly for anatomic reasons that may include a prior Roux-en-Y choledochojejunostomy or gastric bypass procedure. In open drainage, the goal is to decompress the biliary system as quickly and effectively as possible. Simple procedures such as T-tube placement without choledocholithotomy are recommended, because prolonged operations should be avoided.

During open CBD exploration, exposure should be obtained along the free border of the lesser omentum, above the duodenum. When dense adhesions are encountered, or the anatomy is unclear, aspiration with a fine needle facilitates the localization of the CBD. Once identified, an anterior vertical incision is made parallel to the long axis of the duct on the distal CBD, with stay sutures placed on either side. It is important to emphasize that a vertical, rather than horizontal, incision should be performed; a horizontal incision is limited in extension, yields a stenotic area when closed, and may interrupt the axial arterial blood supply of the CBD, which courses along the 3 o'clock and 9 o'clock positions along the lateral aspects of the bile duct. A T-tube should be placed in the CBD above the level of the obstruction to externally decompress the biliary system and enable bile duct closure. The benefits of T-tube placement and decompression are maintenance of biliary ductal patency in the setting of edema and allowance of subsequent access to the biliary tract. Usually, the T-tube is kept in place for 4 to 6 weeks and is removed after a normal cholangiogram (Verbesey & Birkett, 2008).

Intrahepatic Biliary Stone Obstruction (See Chapters 39 and 44)

Patients with complex hepatolithiasis represent a difficult problem, as intrahepatic stones are more difficult to access and remove endoscopically and are often associated with intrahepatic biliary strictures. The resulting cholangitis is characterized by high treatment failure and high recurrence rate. In the past, surgical management consisting of hepatic resection and/or hepaticojejunostomy was the only option for patients with complex hepatolithiasis, with the goal of preventing recurrent cholangitis. Currently, a nonsurgical approach consisting of PTCD followed by cholangioscopy, biliary stricture balloon angioplasty, and lithotripsy is preferred to avoid the morbidity and mortality associated with surgical treatment, especially in debilitated elderly patients with significant comorbidities (Chiang et al, 1994). For patients whose intrahepatic stones have been successfully removed, compared with those whose removal failed, the recurrence of cholangitis is delayed (Cheung, 1997; Yeh et al, 1995).

When the percutaneous approach is unsuccessful, and the patient can tolerate a major operation, hepatic resection should

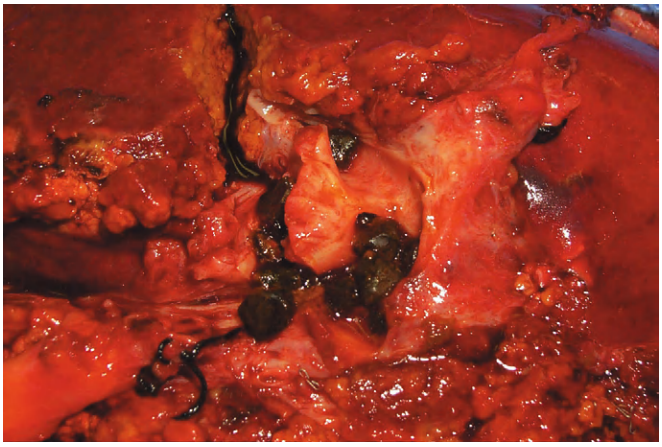


FIGURE 43.3. Intraoperative picture of intrahepatic biliary stones with strictures and microabscesses.

still be offered (Yeh et al, 1995). In a selected group of patients with disease localized to one lobe or a few segments, hepatic resection removes the stones and the associated pathologic changes, including ductal stricture, fibrosis, and microabscess (Fig. 43.3). In a series of 174 patients with intrahepatic stones treated with liver resection or percutaneous choledochoscopy (Cheung & Kwok, 2005), the overall success rate in the surgical group was 98.0%, and the 5-year cholangitis recurrence rate was 13.3%. For the percutaneous choledochoscopic–treated group, the overall success rate was 70.5%, and the 5-year cholangitis recurrence rate was 43.2% and 26.4% for those with and without stricture, respectively. Bilateral stones, the presence of stricture, and the presence of hepatic parenchymal atrophy were demonstrated to be significant risk factors for a poor long-term outcome after stone removal alone.

It is generally acceptable to offer liver resection to patients with associated atrophy of the involved segments, mostly those in whom the left lobe was involved, because of the reduced operative risk. Resection of nonatrophic stone-bearing segments is more controversial. In patients with biliary stricture, liver resection can reduce the reported high rate of restenosis; regardless of whether dilation of the stricture was successful, the associated rate of recurrent cholangitis has been reported to be upward of 35% (Jan & Chen, 1995). In patients without stricture yet with numerous stones, resection may be considered to eliminate the risk of future cholangiocarcinoma, which is reported in 5% to 16% of patients (Chen et al, 1993; Chijiiwa et al, 1993; Liu et al, 1998).

Two additional nonsurgical approaches for the treatment of intrahepatic stones are discussed, namely, the transhepatic percutaneous intracorporeal electrohydraulic shock-wave lithotripsy (ICSWL) and yttrium-aluminum-garnet (YAG) laser lithotripsy. In ICSWL, PTCD is placed, and the infection is allowed to resolve. At separate settings, the PTCD catheter is exchanged for larger biliary catheters to enable the formation of a well-formed tract. Once the tract is a sufficient size (at least 14 Fr), downstream stones can be crushed with mechanical lithotriptors or contact shock-wave lithotripsy under direct endoscopic visualization. When stone debris is removed, distal strictures can be traversed with an angioplasty balloon catheter and dilated. As such, multiple treatment sessions are required to successfully and safely clear the duct to avoid sepsis (Bonnel et al, 1991).

Although an important procedure in the armamentarium, fragmentation with ICSWL requires additional therapies for removal of stone fragments in 50% of patients (Bland et al, 1989). It requires general anesthesia or regional blocks that may be avoided with percutaneous techniques. The most obvious advantage is avoidance of the percutaneous biliary catheter, which gives some patients discomfort. When combined with endoscopic removal, ICSWL can achieve stone clearance for 94% to 96% of patients (Harz et al, 1991; White et al, 1998).

A more recent nonsurgical approach involves laser application. This technique consists of percutaneous access to the biliary tree with percutaneous holmium: YAG laser lithotripsy ablation of bile duct stones (Hazey et al, 2007). Depending on the location of the stones and anatomic considerations, the left, right, or both systems may be accessed via percutaneous transhepatic cholangiography (PTC) techniques. The catheter is upsized to 12- or 14-Fr over several weeks to allow for passage of a videocholedochoscope. Passage of an endoscope and direct visualization of the calculi is all that is required to pass energy via the laser and fragment the stones. Once the stones are fragmented, the debris is flushed out the access catheter, or it may pass through the sphincter of Oddi into the duodenum. Frequently, the sphincter has been rendered incompetent by a previous endoscopic sphincterotomy.

The medical literature is replete with studies outlining percutaneous access and removal of primary hepatolithiasis using YAG laser therapy in Asian patients, with clearance rates of 76.8% to 100% (Chen et al, 2005; Cheung et al, 2003; Shamamian & Grasso, 2004). Primary intrahepatic stones have frequently required more treatments (average, 3.9) than secondary intrahepatic calculi (average, 2.6) (Shamamian & Grasso, 2004). The clearance rates diminished significantly for patients with intrahepatic strictures: 58% in the presence of stricture versus 100% in cases with no stricture (Huang et al, 2003). Similarly, presence of stricture is associated with a high recurrence rate of 51.6% (Jan & Chen, 1995) to 63.2% (Huang et al, 2003).

In the Western literature, fewer YAG laser applications for hepatolithiasis are reported. In a relatively small series, Hazey and others (2007) reported that all patients (n = 13) undergoing percutaneous holmium:YAG laser lithotripsy and ablation of their biliary calculi were successfully treated; the average number of treatments required for stone clearance was 1.6 (range, 1 to 3), no patients required more than three treatments, and 3 of the 13 patients were treated solely as outpatients.

Recurrent Pyogenic Cholangitis (See Chapter 44)

Recurrent pyogenic cholangitis (RPC), previously called *oriental cholangiohepatitis,* was first described in 1930 by Digby. This clinical entity is most common among Southeast Asians and is characterized by recurrent episodes of bacterial cholangitis that occur in association with bile duct strictures, segmental biliary dilation with bile stasis, recurrent episodes of obstructive jaundice and ascending cholangitis, pigmented biliary calculi, and biliary cirrhosis.

A possible association between biliary helminthic infection and hepatolithiasis has been suggested (Huang et al, 2005; see Chapter 45). *Ascaris lumbricoides, Clonorchis sinensis, Opisthorchis viverrini, O. felineus,* and *Fasciola hepatica* are pathogens that

often lead to the initial epithelial damage (Abdalian & Heathcote, 2006). *Ascaris lumbricoides,* a round worm, is a common cause of cholangitis in tropical and subtropical countries. Mature adult worms lodged in the biliary system are responsible for a variety of disease processes that include cholangitis, cholecystitis, gallstone formation, and pancreatitis. In the case of cholangitis secondary to *Ascaris* infection, the worms are located in the CBD in 95% of cases, and they can be seen in 86% of cases during endoscopic examination (Sandouk et al, 1997).

The goal of treatment is to eradicate the parasites with mebendazole and eliminate all biliary stones and strictures. As optimal management of stones and strictures will often require multiple treatment sessions, it is usually advised that patients be capable of tolerating a major operation, which may include choledochojejunostomy or hepaticojejunostomy with a biliary access procedure, so that the biliary tree can be readily accessed to clear recurrent stones and to dilate recurrent intrahepatic strictures.

Choledochojejunostomy with a cutaneous limb offers a number of distinct advantages over previous approaches in the management of RPC (see Chapter 29). Following standard cholecystectomy, a portion of the common duct is isolated for choledochoenteric anastomosis. A 60- to 70-cm segment of bowel is used for the Roux-en-Y limb, and a side-to-side choledochojejunostomy is then constructed 10 to 15 cm from the end of the jejunal limb. The blind limb of the jejunal access loop is then brought through the fascia of the abdominal wall in the right upper quadrant at a point that will allow straight access to the biliary tree. Lateral placement of the bowel, just below the skin, will help ensure that the interventional radiologist's hands and instruments are not in the fluoroscopy beam. Although gross stones are removed, no attempt is made at complete clearance of the CBD or hepatic radicles. After closure of the abdomen, the stoma is matured in a "turn-back" fashion. The availability of the cutaneous stoma greatly facilitates subsequent treatment of the residual stones and strictures. After completion of radiologic treatment, the stoma is mobilized, closed, and left buried in the subcutaneous tissues for future access (Gott et al, 1996).

The treatment described above is far less radical with less morbidity and mortality than hepatic resection previously offered to patients with RPC, without sacrificing hepatic parenchyma that can potentially recover subsequent to biliary decompression. At the same time, the bypass provides effective initial biliary drainage of the biliary tree and alleviates any immediate biliary sepsis.

Clearance of residual stones and dilation of strictures is easily accomplished on an outpatient basis. The treatment of recurrent stones or strictures is greatly simplified by access to the cutaneous jejunal limb, and it avoids the need for high-risk reoperative biliary procedures (Gott et al, 1996).

Nonlithiatic Biliary Obstruction

As previously mentioned, biliary stones are responsible of *most* cases of biliary obstruction; other less frequent causes can produce either an extrahepatic obstruction, as in AIDS cholangiopathy or cholangitis as a result of stricture of a biliary enteric anastomosis, or a mixture of hepatic and extrahepatic obstruction, as in the case of primary sclerosing cholangitis (PSC) and immunoglobulin G4 cholangitis.

AIDS Cholangiopathy

First described in 1986 (Margulis et al, 1986), AIDS cholangiopathy occurs in patients with advanced HIV infection. It occurs with acalculous cholecystitis, focal distal biliary stricture at the papilla of Vater, or multifocal biliary strictures similar to what is seen in primary sclerosing cholangitis. These patients are often colonized with cryptosporidia or microsporidia, but it is not clear whether treatment directed at these organisms with albendazole makes any short- or long-term difference in their outcome (Bird et al, 1995).

AIDS cholangiopathy typically occurs in patients with very low CD4 lymphocyte counts (median, 26.5 × 106/L). It is very unusual to see cholangiopathy in patients with CD4 lymphocyte counts greater than 100, because most of the opportunistic infections typical of this disorder occur only in late stages of the disease.

The prognostic factors in patients with AIDS cholangiopathy have been studied by Ko and colleagues (2003). In this retrospective analysis, the authors evaluated 94 patients with AIDS cholangiopathy who were diagnosed at the San Francisco General Hospital between 1983 and 2001. Patient outcome (death) was subsequently correlated with a number of collected variables via multivariable logistic regression. Mean survival was 9 months in those patients with cholangiopathy, with those on highly active antiretroviral therapy (HAART) having a significantly prolonged duration of survival. The presence of opportunistic infections and an elevated alkaline phosphatase level (>1000 U/L) were negative prognostic indicators of survival. Interestingly, endoscopic sphincterotomy, the type of cholangiopathy, and CD4 lymphocyte counts did not correlate with survival.

ERCP in patients with AIDS cholangiopathy is helpful as a diagnostic tool; however, therapeutic ERCP is helpful only in reducing pain, not in extending survival. Additionally, as a result of the advances in HIV management, this disorder is becoming a rarity, and ERCP should only be considered in those patients with very low CD4 lymphocyte counts after other noninvasive diagnostic modalities have been exhausted. The presence of opportunistic infections and a very low CD4 count are markers of advanced disease, and the emphasis should be on the HIV disorder, not on the AIDS cholangiopathy.

The goal of therapy of both is directed toward elevating the CD4 count and decreasing the viral loads, which can only be obtained by HAART. A multidisciplinary approach to this disorder is critical, particularly because the disease rapidly changes, depending on therapy. With the changing modalities of treatment, it is hoped that AIDS cholangiopathy might become a disorder of historical interest only (Enns, 2003).

The overall prognosis of patients with AIDS cholangiopathy is poor, because the disease itself is believed to be a manifestation of advanced HIV. As previously mentioned, the survival of patients is not affected by endoscopic therapy (Cello & Chan, 1995). Survival rates were low, with 1- and 2-year survival as low at 14% to 41% and 8%, respectively, with a mean reported survival of 7 to 12 months (Bouche et al, 1993; Cello & Chan, 1995). For survivors, an association with subsequent cholangiocarcinoma has also been reported (Hocqueloux & Gervais, 2000).

Biliary-Enteric Strictures

Patients with a history of a previous Roux-en-Y hepaticojejunostomy or choledochojejunostomy who are seen with

cholangitis present a complex situation. Initially, a PTCD and balloon dilation of the stricture should be performed, as it is a simple and effective procedure. However, the incidence of long-term restenosis (follow-up period of 5 to 7.5 years) is high—up to 45% (Jan et al, 1994). In the case of recurrent cholangitis after PTCD dilation, every consideration should be given to operative revision of the biliary enteric anastomosis, provided that the patient can safely undergo operation.

Primary Sclerosing Cholangitis

PSC (see Chapter 41) is an idiopathic inflammatory process that affects the biliary tree, resulting in patchy areas of fibrosis and obstruction that are often associated with biliary infection. The diagnosis of PSC is based on selection and exclusion criteria. A persistent twofold or threefold elevation of the alkaline phosphatase level is typical (Gordon, 2008). Protoplasmic-staining antineutrophil cytoplasmic antibodies are present in 80% of cases of PSC, but this finding is not specific (Mulder et al, 1993). The radiologic inclusion criteria include the presence of diffusely distributed strictures of the biliary system seen on cholangiography and characteristic hepatic histology. The histology, classified by Ludwig and colleagues (1981), includes four stages: 1) periportal hepatitis, 2) periportal hepatitis and fibrosis, 3) fibrosis extending beyond the limiting plate, and 4) biliary cirrhosis.

Various diseases are associated with PSC: inflammatory bowel disease (IBD), celiac sprue, sarcoidosis, chronic pancreatitis, rheumatoid arthritis, retroperitoneal fibrosis, thyroiditis, and vasculitis. Patients with PSC also have a substantial predisposition to develop cholangiocarcinoma.

The mainstay of treatment for PSC consists of providing appropriate antibiotic coverage for the bactobilia and reestablishing biliary drainage to the intestinal tree. Long-term antimicrobial prophylaxis is necessary in many patients because of multiple intrahepatic partial biliary strictures; however, no medical therapy is available that can halt the progression of the disease or prevent the development of cholangiocarcinoma. The only effective treatment for advanced PSC is orthotopic liver transplantation (OLT), which in the absence of cholangiocarcinoma has a 5-year survival of up to 89%. Patients with cholangiocarcinoma who undergo OLT have a high risk of recurrence and a dramatically worsened survival if this occurs; therefore the identification of patients with deterioration in liver function sufficient to warrant OLT before they develop cholangiocarcinoma remains a central goal in the management of PSC.

Current management of PSC includes medical therapy with the use of choleretic immunosuppressive and antifibrinogenic agents, surgical management for reconstruction of the biliary tract and colon resection in patients with ulcerative colitis, with liver transplantation reserved for end-stage PSC (Gordon, 2008).

Immunoglobulin G4–Associated Cholangitis

Although the systemic diseases associated with immunoglobulin G4 (IgG4) have been recognized since the 1960s (Sarles et al, 1961), the credit for the first description IgG4 cholangitis belongs to Montefusco and colleagues (1984), who described a series of case reports of patients with combined pancreatic and extrapancreatic disease associated with IgG4. The predominant extrapancreatic feature noted was sclerosing cholangitis with PSC-like features.

In the largest reported cohort to date, which includes 53 patients, Ghazale and colleagues (2008) described the most frequent clinical signs and symptoms at presentation of IgG4 cholangitis: jaundice (77%), weight loss (51%), mild to moderate abdominal pain (26%), steatorrhea (15%), and new-onset diabetes (8%). The diagnostic criteria for IgG4 cholangitis are either having a previous diagnosis of IgG4-related pancreatic/biliary disease or two or more of the following: elevated serum IgG4, other manifestation of a systemic disease, or bile duct biopsy showing more than 10 IgG4-positive cells per high-powered field (HPF) with a documented response after 4 weeks of steroid therapy (Ghazale et al, 2008).

Cholangiographic studies do not reveal pathognomonic findings; they show either a picture of intrahepatic bile duct involvement similar to PSC and/or extrahepatic biliary strictures similar to those found with cholangiocarcinoma and pancreatic cancer. As it is difficult to differentiate IgG4-associated cholangitis from PSC, many studies have investigated the clinical and laboratory findings that correlate with the diagnosis of IgG4. A recent review (Alderlieste et al, 2009) reported significant differences between IgG4 and PSC in the age at onset, occurrence of diabetes mellitus and IBD, salivary gland swelling, and elevated serum IgG4 levels (Table 43.3). Liver or biliary biopsy can help to differentiate IgG4 cholangitis from PSC or pancreatic or biliary cancer. Liver histology in IgG4-associated cholangitis is characterized by lymphoplasmacytic infiltrates within and around bile ducts and obliterative phlebitis and fibrosis leading to sclerosis of the bile ducts. Numbers of IgG4-bearing plasma cells, mainly found in the portal tracts, are significantly higher than in patients with other hepatopathies—including PSC, primary biliary cirrhosis, autoimmune hepatitis, and chronic viral hepatitis—and correlate to serum IgG4 levels, decreasing on

Table 43.3

PSC and IAC: Differences in Clinical Presentation, Immunopathologic Features, and Treatment Response

	PSC	IAC
Age (yr)	25 to 45	65
Male gender	65%	80%
Response to steroids	–	+++
Association with IBD	+++	–
Association with cholangiocarcinoma	+++	?
Other organ involvement	?	+++
Histologic findings	Obliterative cholangitis and cirrhosis	Abundant IgG4-positive plasma cells
Dominant cholangiographic findings	Bandlike strictures with a beaded appearance	Segmental strictures and distal bile duct strictures
Elevated serum IgG4	7% to 9%*	~70%

*As the authors of this table suggest, within their cohort of PSC patients, some of the patients with elevated IgG4 levels may be misdiagnosed IAC patients.

IBD, inflammatory bowel disease; IgG4, immunoglobin G4; IAC, immunoglobulin-associated cholangitis; PSC, primary sclerosing cholangitis

From Alderlieste YA, et al, 2009: Immunoglobulin G4–associated cholangitis: one variant of immunoglobulin G4–related systemic disease. Digestion 79(4):220-228.

corticosteroid treatment (Kamisawa, 2008; Umemura et al, 2007). Endoscopic biopsy specimen of biliary epithelium revealed more than 10 IgG4-positive cells/HPF in 88% of 16 patients with IgG4 cholangitis who underwent biopsy (Ghazale et al, 2008). Accurate diagnosis is of utmost importance to prevent unnecessary surgery and avoid delayed diagnosis of a potentially fatal malignancy.

CHOLANGITIS AND INTRAABDOMINAL HEPATIC ABSCESS

Inadequately managed cholangitis can be complicated by liver, gallbladder, and subphrenic abscesses (see Chapter 66). In general, these abscesses should be treated following standard surgical principles of drainage and broad-spectrum antibiotics, until the fever resolves and liver function tests return to normal (Rintoul et al, 1996).

Untreated pyogenic liver abscesses are almost uniformly fatal. Traditionally, treatment consists of antibiotic administration and drainage of purulent collections. Although this remains the standard approach to the patient with hepatic abscess, some investigators have advocated the use of antibiotics alone in selected patients (Pearce et al, 2003).

Over the past decade, percutaneous aspiration of pyogenic liver abscess without catheter drainage has also gained increased attention. Retrospective series have reported percutaneous aspiration success rate in combination with antibiotic therapy to be in the range of 58% to 88%, which is comparable to the results of catheter drainage (Barakate et al, 1999; Johannsen et al, 2000; Seeto & Rockey, 1996). However, it is important to mention that no randomized trial comparing percutaneous aspiration and catheter drainage of liver abscesses has been performed.

Antibiotics should be started as soon as possible, once the diagnosis of pyogenic liver abscess is suspected. Blood specimens for culture should be obtained before initiating empiric therapy, but delaying therapy until abscess material is obtained is potentially dangerous and ill advised. The suspected origin of infection should be considered when choosing initial antimicrobial therapy, because it will predict the most likely pathogens. Pyogenic liver abscesses that arise in a patient with biliary disease often include enterococci and enteric gram-negative bacilli. Pyogenic liver abscesses from a colonic or pelvic source are more commonly the result of coliforms and anaerobes. Metronidazole should be included in the initial therapy for most cases of pyogenic liver abscess to empirically treat both anaerobes, especially *Bacteroides fragilis* and *Entamoeba histolytica,* while the specific etiology is being evaluated. Once microbiologic data are obtained, antibiotic therapy should be tailored to the organisms isolated and their respective antibiotic susceptibility profiles (Johannsen et al, 2000).

Pyogenic liver abscesses are usually treated initially with parenteral antibiotic therapy for 2 to 3 weeks, and patients subsequently complete a 4- to 6-week course of oral antibiotics (Pitt, 1990). In general, abscesses completely resolve after a full course of therapy. On occasion, a residual cavity persists despite prolonged therapy; if the size of this cavity is stable on serial imaging studies, and the patient is asymptomatic, antibiotics can be stopped and the patient observed closely for the development of recurrent fevers or abdominal pain. In these situations, a follow-up CT scan is recommended 1 to 2 months after cessation of therapy.

SUMMARY

Cholangitis is not a single clinical process but rather a wide spectrum of disease that presents variably with a broad range of severity. In the setting of acute cholangitis, intervention should begin with resuscitation, parenteral antibiotics, and biliary decompression. The imaging and procedural modalities used in the treatment of affected patients requires a thorough understanding of the etiology and should be tailored to the specific causation. It cannot be overemphasized that untreated cholangitis-associated sepsis is almost universally fatal, and the potential for the progression from mild to moderate to severe cholangitis can be rapid and irreversible.

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CHAPTER 44

Recurrent pyogenic cholangitis

See Ching Chan, Sheung Tat Fan, and John Wong

OVERVIEW

Recurrent pyogenic cholangitis (RPC) is characterized by repeated bacterial infections of the biliary tract as a result of stones and bile duct strictures (see also Chapters 7, 11, 39, and 43). This condition was first described in Hong Kong by Digby in 1930, and the name *recurrent pyogenic cholangitis* was first coined by Cook in 1954. RPC has many synonyms, including *Oriental cholangiohepatitis* (Stock & Fung, 1962), *Hong Kong disease* (Mage & Morel, 1965), *intrahepatic stones* (Wen & Lee, 1972), *hepatolithiasis* (Nakayama et al, 1980), *primary cholangitis* (Choi et al, 1981), and *Oriental infestational cholangitis* (Seel & Park, 1983). It is prevalent in East Asia (Balasegaram, 1972; Chang & Passaro, 1983; De & Acharya, 2001; Maki et al, 1964; Nakayama et al, 1980; Ong, 1962; Seel & Park, 1983). With ease of travel and increasing migration from Asian countries, RPC is being encountered more frequently in Western countries, particularly in cities where Asian emigrants congregate (Al-Sukhni et al, 2008; Harris et al, 1998; Nguyen et al, 2009). RPC should not be regarded as a curiosity peculiar to Asia but rather as a disease that may affect Asians wherever they live.

RPC affects the young and the elderly of those who were of the lower socioeconomic classes growing up. There is no gender difference in incidence. In the past, RPC was one of the most common surgical emergencies, but the incidence has declined in recent years, particularly in urban centers (Nakayama, 1982). The overall incidence of RPC has decreased in Japan, from 50% of the cases of biliary stones in the pre–World War II years to 20% (Nakayama et al, 1980) despite advances in diagnostic techniques. In Hong Kong today, 12% of biliary stone cases are due to RPC (Fan et al, 1991a).

ETIOLOGY AND PATHOGENESIS

The exact etiology of RPC continues to be elusive and is probably multifactorial. The likely initiating event is the establishment of infection by bowel microorganisms in the small biliary radicles (see Chapter 43). Experimental and clinical studies (Nakayama et al, 1980; Ong, 1962) indicate that the organisms isolated from portal vein blood, common duct bile, and liver biopsy specimens are predominantly of bowel origin (see Chapter 11). Although bowel organisms may reach the liver under ordinary circumstances, clinical infection does not occur except when bowel infection is severe, the organism is of particular virulence, or the host defense in the liver is compromised. In RPC, numerous organisms may enter the portal vein during a serious attack of enteric infection, which was previously common in Asia. As this condition often affects the lower socioeconomic classes, malnutrition and perhaps infection by flukes and worms may reduce the capacity of the liver to clear enteric bacteria effectively.

Once the organisms are established in the liver, infection begins in the cholangioles and subsequently involves the rest of the portal triads. If the infection is severe, the hepatocytes show vacuolation and may undergo necrosis, hence the name *cholangiohepatitis.* Hepatocellular damage is usually mild, if the infection is confined to the cholangioles. If cholangiolitis spreads to the larger intrahepatic ducts and to the common bile duct (CBD), hepatocellular damage is severe. Resolution of infection in the early phases restores normal morphology, but more intense or repeated infection may result in fibrosis of intrahepatic ducts or cholangitic liver abscess formation.

Whether stones or strictures develop first is not clear (see Chapter 39). Endoscopic retrograde cholangiopancreatography (ERCP) of the bile ducts in RPC (Lam et al, 1978) suggests that structural changes may occur in the ducts before stones are demonstrable, and strictures are often seen at cholangiography in the absence of stones. Conversely, stones are also found in the intrahepatic ducts when no significant narrowing of the ducts is discerned. In advanced cases, strictures are associated with extensive formation of stones, which can fill the ducts throughout the liver. Cisternal dilation of a duct may not be associated with very tight stenosis, and the cavernous ducts do not contain many stones; perhaps some ball-valve mechanism is responsible for these changes. In some patients with acute attacks, stones are not found, but infected, viscous bile permeates the entire biliary tree, which may represent the early stages of precipitation of bile before discernible stones are formed (see Chapter 7). Whatever the sequence of development, repeated or severe infection leads to transmural inflammation of the ducts and results in stenosis in the larger ducts, forming weblike strictures, and in the smaller peripheral ducts, showing more tubular narrowing. As a result of obstruction, together with parenchymal damage to the adjoining liver, the rest of the ducts dilate.

The calculi formed in RPC are pigmented bilirubinate stones (see Chapter 39). Infection in the bile duct changes the bile from a supersaturated solution to an insoluble precipitate. It is postulated that β-glucuronidase, derived from *Clostridium perfringens* and *Escherichia coli,* splits the bilirubin diglucuronide into free bilirubin, and the ionized unconjugated bilirubin together with ionic calcium precipitates to form insoluble calcium bilirubinate, which with time coagulates and consolidates into stones (Leung et al, 2001; Maki, 1966; Nakayama et al, 1980).

Although positive bile cultures are commonly obtained in patients with Western-type stones lodged in the CBD, when the stones are confined to the gallbladder, the incidence of infection is low. In contrast, regardless of whether the stones are located

in the gallbladder or the CBD, the incidence of positive bile cultures in RPC is high (Suzuki et al, 1984; Tabata & Nakayama, 1981), a finding that favors infection as the primary step in the etiology of RPC. It also has been shown that in affected intrahepatic ducts, the number of mucous glands in the epithelial lining is increased (Nakanuma et al, 1988; Terada & Nakanuma, 1988). The integrated role of bacteria and mucus in the lithogenesis of hepatolithiasis was shown in a study by Zen and colleagues (2002), who found that lipopolysaccharide could induce overexpression of gel-forming apomucin (MUC2 and MUC5AC) in biliary epithelial cells via synthesis of tumor necrosis factor (TNF)–α and activation of protein kinase C. Mucin hypersecretion contributes to more stone formation by impeding bile flow and creating a nidus for pigment deposition (Sasaki et al, 1998). Augmented expression and secretion of trefoil factor family protein, a mucin-associated protein important for mucosal defense and repair, together with gel-forming apomucin may play a role in lithogenesis (Sasaki et al, 2004).

Once formation has started, the stones enlarge; where they finally reside depends on whether they can pass through existing strictures. When the stones are larger than the strictures, they are trapped proximally and increase in size as layers of calcium bilirubinate become encrusted on their surface. If the stones are small, they may pass into the common duct and egress through the ampulla into the duodenum, or they may be held in the common duct and enlarge. At any site, stones trapped in the liver or the common duct perpetuate infection and cause further inflammation and scarring of the duct wall.

An association with infection by *Clonorchis sinensis* and *Ascaris lumbricoides* has been implicated in the past (Fung, 1961) and is still commonly regarded as causally significant (see Chapter 45; Rana et al, 2007). However, in countries where clonorchiasis is absent, such as the Philippines, RPC remains prevalent; and in Japan, where clonorchiasis is endemic, RPC is on the decline. Other evidence against clonorchiasis as a causal factor is that *Clonorchis* ova are isolated from the stools of only 25% of patients with RPC, and ascariasis is present in only 5% (Ong, 1962). It is indisputable that clonorchiasis is a serious infection that may cause structural changes in the intrahepatic and extrahepatic bile ducts (Hou, 1956). Although the cholangiographic changes of clonorchiasis are distinctly different from the changes of RPC (Choi et al, 1984), in that the terminal ducts are dilated rather than narrowed, the predominant and more severe changes are seen in the left duct. This occurrence corresponds to the distribution of RPC, a finding that still defies explanation.

Even if clonorchiasis and ascariasis are merely coincidental infections, they may become a nidus for stone formation (Teoh, 1963). Ascariasis probably plays no role in RPC except as a source of foreign bodies, and clonorchiasis may be a contributory factor in countries where RPC is endemic.

PATHOLOGY

The primary pathologic changes are infection and fibrosis with strictures and stone formation in the bile ducts, with other changes being consequences of these main events. The consequences of repeated infection are progressive biliary epithelial and hepatocellular damage, as discussed previously. Suggested sequential changes in the bile ducts in RPC have been documented in detail by Lam and others (1978). These changes include loss of parallelism of duct walls, excessive branching, abrupt termination or "arrowhead" formation of smaller ducts, and development of strictures (Fig. 44.1).



FIGURE 44.1. Endoscopic retrograde cholangiopancreatography showing early recurrent pyogenic cholangitis changes with extensive branching and dilation of the left intrahepatic ducts proximal to the intrahepatic ductal strictures.

Strictures may be found anywhere in the biliary tree but are more common in the major hepatic duct branches, especially in the left liver and in the intrahepatic ducts. When in the extrahepatic ducts, strictures are weblike, situated toward the lower end; if the obstruction is severe, proximal dilation is marked (Fig. 44.2). Strictures in the hepatic ducts also extend over a short distance and are usually intrahepatic, but they may extend to the extrahepatic portion (Fig. 44.3). In the smaller intrahepatic ducts, the strictures are longer, and there may be a pattern of tubular narrowing over a length of duct (Fig. 44.4; also see Fig. 44.1).

The left duct is more frequently and severely affected than the right. Left duct involvement alone is found in 40% of cases of intrahepatic disease, right duct involvement alone is found in 20%, and involvement of both ducts is found in 40%. No satisfactory explanation has been offered for this finding, but it has been suggested that the left duct is more horizontal, and bile in the left duct may not drain as well as bile in the right duct. On the right side, one would expect the incidence of intrahepatic stones to be higher, if the right posterior hepatic duct joins the left hepatic duct at a sharp angle; however, a detailed study of the confluence patterns of segmental hepatic ducts did not show a causal relationship (Kitagawa et al, 2003).

Proximal dilations behind the strictures are an expected secondary phenomenon. These dilations sometimes can be so large as to be called *cisterns* (Maki et al, 1964), and little liver parenchyma remains in such affected segments (Fig. 44.5). In these dilated ducts, relatively fewer stones are found (Fig. 44.6). Dilated segments taper toward the strictures, which are thick and fibrous; when operative plastic repair of such strictures is attempted, restenosis is common as a result of ongoing fibrotic changes in the diseased ductal tissues, and failure can be expected in most cases.

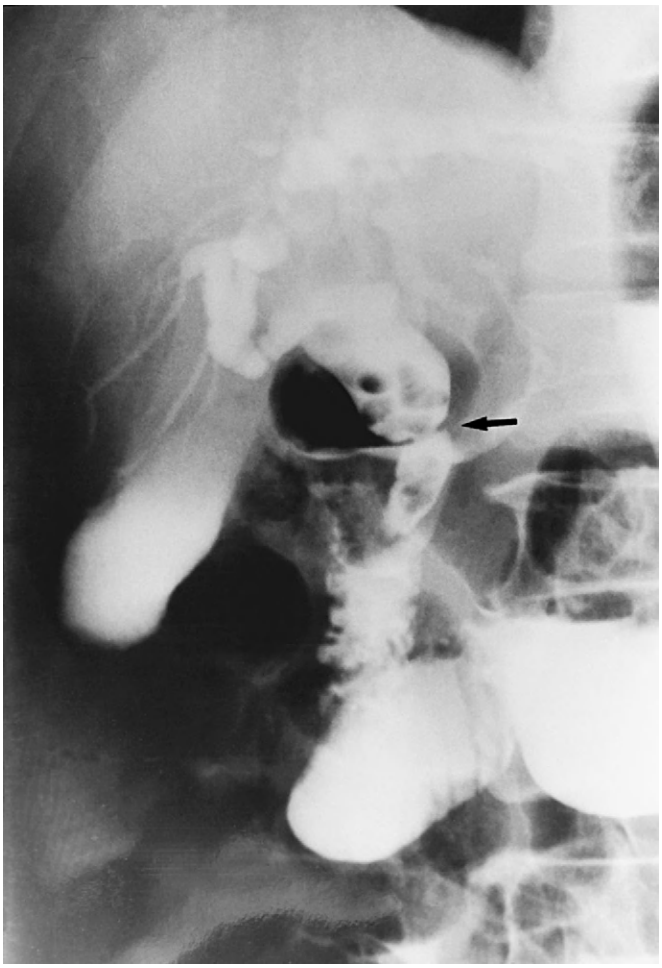


FIGURE 44.2. Stricture of the distal common bile duct in recurrent pyogenic cholangitis (*arrow*). It is weblike, and proximal dilation is seen, with stones above and below the stricture. The gallbladder is unremarkable.



FIGURE 44.3. T-tube cholangiogram shows tight strictures at the confluence of the left and right hepatic ducts and the common hepatic duct.

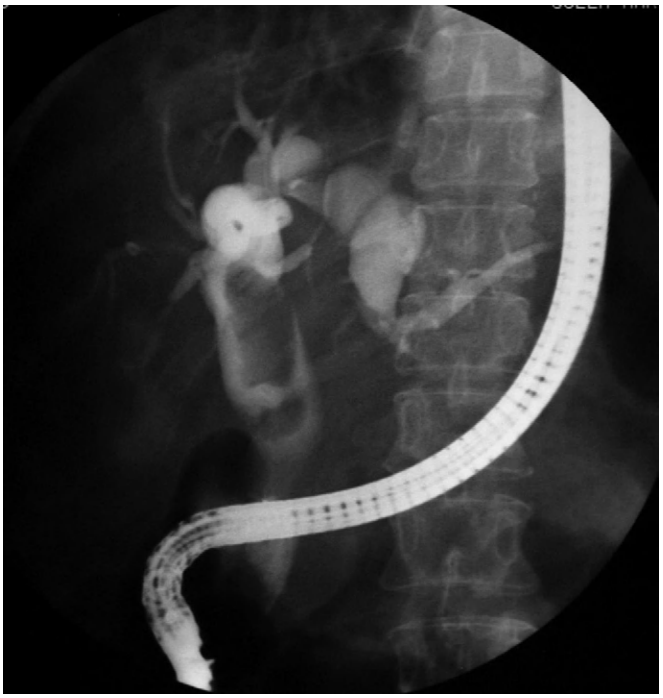


FIGURE 44.4. Recurrent pyogenic cholangitis affecting the extrahepatic and, bilaterally, the intrahepatic ducts. Many stones are present in the liver proximal to the strictures.

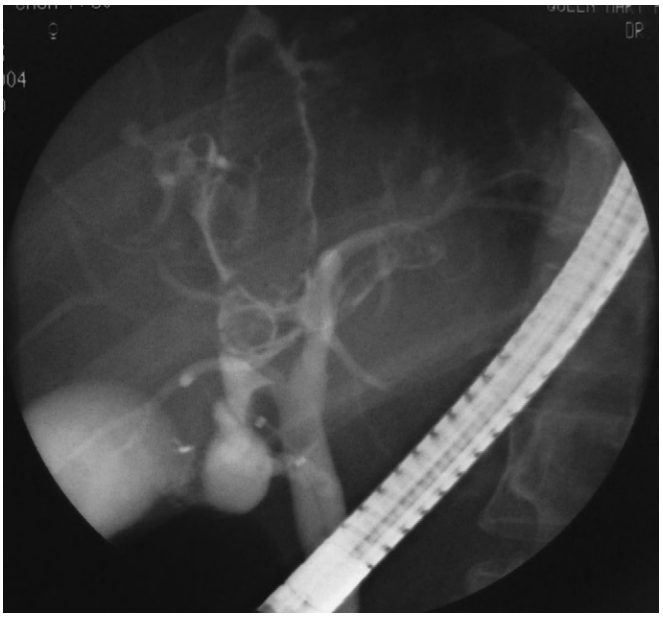


FIGURE 44.5. The right segmental duct is obstructed, and the proximal ductal system has become grossly dilated to form cisterns. Few stones are seen within the duct. The resected specimen is shown in Figure 44.6.

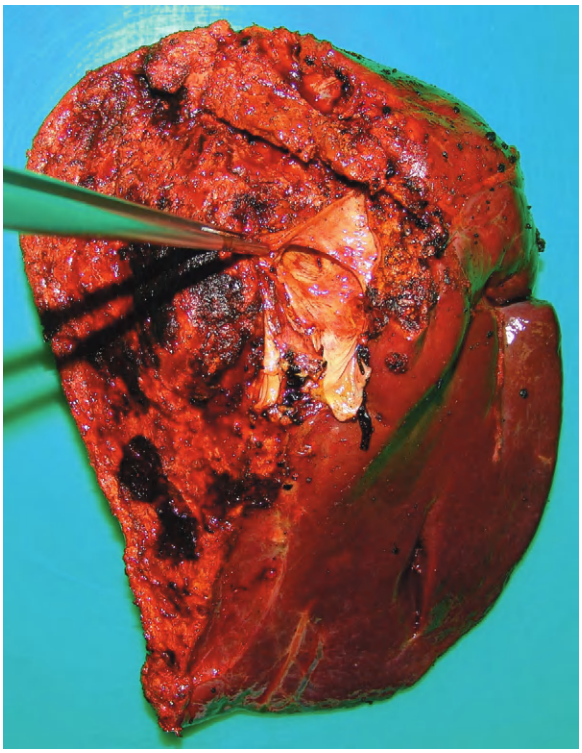


FIGURE 44.6. Resected specimen of the right segmental duct (endoscopic retrograde cholangiopancreatography is shown in Fig. 44.5) showing saccular enlargement of the intrahepatic ducts with stones. The surface is hemorrhagic, and the duct walls are thick.

The gallbladder is diseased in approximately 20% of patients with RPC, but in many patients with extensive ductal disease, the gallbladder is normal (see Figs. 44.2, 44.17A, and 44.19). When stones are found in the gallbladder, disease is invariably present elsewhere. In the acute attack, and when common duct obstruction is severe, the gallbladder may be grossly distended, and empyema, gangrene, or perforation may develop. When a normal gallbladder is left behind after drainage procedures to the common duct, the risk of developing a complication arising from the gallbladder that would require operation is small. When an operation is performed for patients with RPC, it is justified, although perhaps not recommended, to leave an apparently normal gallbladder when stones are found only in the bile duct.

All stones recovered in RPC patients are bilirubinate stones: soft, pigmented, earthy stones that are very friable and crumble when pressed between the fingers. Application of forceps to these stones leads to fragmentation, and the small pieces usually left behind can be flushed out with saline (Fig. 44.7). The stones are irregular in shape and conform to the configuration of the bile duct in which they reside; when packed together, some may have facets. Their size varies from greater than 4 cm to almost microscopic, and in a single patient, a continuum in size may be seen, in contrast to the stepwise size change observed in Western-type mixed stones (Fig. 44.8).

In the fresh state, the stone surface is covered with mucus or a film of viscous bile. In some stones, the outer color may be almost black from prolonged exposure to bile; in others, it is orange or green. Flakes of more recently deposited bile debris are separated from the surface when gently scraped, exposing a lighter colored interior, which may appear laminated. Some stones show no organized structure and disintegrate with slight compression into irregular, powdery clumps. A nidus may sometimes be identified, and microscopic examination of this area may show dead parasites or clumps of bacteria or cells (Teoh, 1963).

In approximately 10% of patients, stones are absent, and the bile duct is filled with biliary debris, termed *biliary mud*. This debris is composed of mucus, pus, parasites, altered bile products, microcalculi, and desquamated epithelium, all mixed to form a thick, porridge-like material that exudes from the duct when it is opened. This material may also coexist with stones. In an acute attack, this soft, infected material with or without stones is more commonly encountered.

At operation for an acute problem, the liver appears "cholangitic": congested, bile stained, soft, and prone to bleeding easily. In the quiescent phase, avascular adhesions are found between the surface of the liver and the parietal peritoneum—evidence of previous, resolved acute episodes. In long-standing cases, the adhesions are dense and vascular and contain pockets of pus, which are due to rupture of cholangitic liver abscesses into the peritoneal cavity. Scars on the liver surface indicate previous attacks and dilated bile ducts and may appear prominently, especially from the undersurface of the left lobe (Fig. 44.9). When the left lobe is atrophic, compensatory hypertrophy of the right lobe is seen. Conversely, in the rare situation of severe right lobe disease, the left lobe may be massive, and the liver hilum anatomy may be grossly distorted (Fig. 44.10). Even when the external appearance is normal, intrahepatic disease may be extensive, and stones are easily palpable through the surface.

Biliary cirrhosis and liver failure are possible complications (Jeng et al, 1989) and usually follow long-standing severe disease that has failed to improve with multiple operations, some of which may be associated with stricture of the biliary-enteric anastomosis (see Chapters 29 and 42A). When cirrhosis has developed, portal hypertension and bleeding esophageal varices may ensue. Further corrective biliary surgery is feasible only after decompression by portosystemic shunting (see Chapter 76).

Stones at the lower end of the CBD may cause two additional complications in addition to biliary obstruction: choledochoduodenal fistula and acute pancreatitis. Choledochoduodenal fistula is not serious, but it may be confusing to the endoscopist and the radiologist. Acute pancreatitis is an important potential consequence of RPC. In Hong Kong, acute pancreatitis was once associated with RPC in approximately half of all patients (Ong et al, 1971), and in approximately 20% of patients with RPC, a high serum amylase level was recorded, although many cases were clinically silent.

Although rare, abscesses in the left liver may rupture into the pericardial cavity and cause cardiac tamponade (Fan & Wong 1997). Abscesses in the right liver may rupture to form a pleurobiliary or bronchobiliary fistula (Wei et al, 1982). These abscesses also may bleed into the abscess cavity (Fig. 44.11) or bile duct (Joo et al, 2003), rupture into the abdominal cavity or into adjacent hollow viscera, or extend into the subphrenic or subhepatic spaces.

A chronic abscess may be indistinguishable clinically, at operation or on contrast studies, from cholangiocarcinoma, and it may be identified as such only through detailed histologic

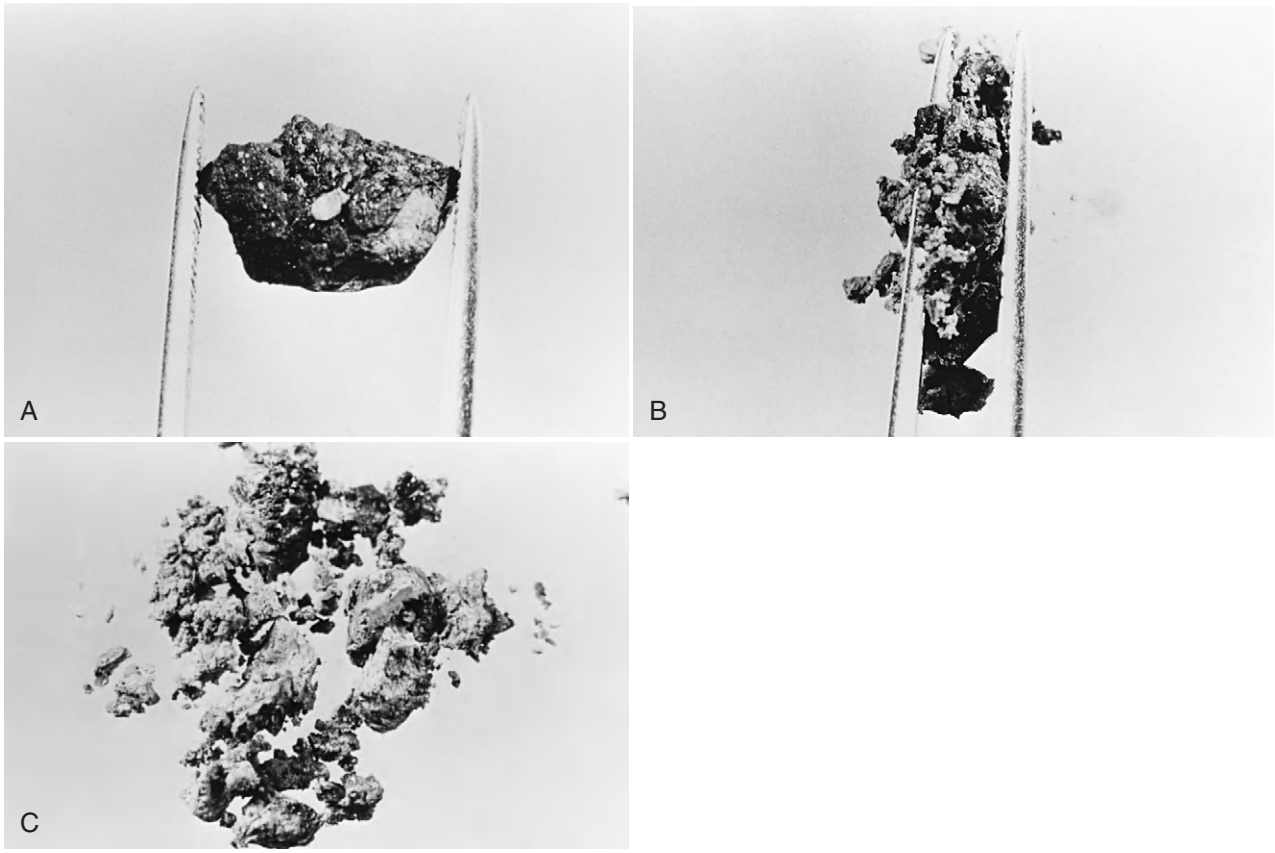


FIGURE 44.7. A, Recurrent pyogenic cholangitis stone is placed between tissue forceps. **B,** The stone is crushed easily by gentle pressure. **C,** Stone fragmenting into soft amorphous masses.

examination after resection. As with hepatolithiasis, an increased incidence of cholangiocarcinoma owing to clonorchiasis has been noted (see Chapter 50; Hou, 1956; Ohta et al, 1984).

Whether cholangiocarcinoma is coincidental or etiologically related to RPC is controversial. The nearly constant presence of severe clonorchiasis in patients with cholangiocarcinoma supports a cause-and-effect relationship (Belamaric, 1973). Cholangiocarcinoma is found in 2% to 13% of patients with intrahepatic stones (Chen et al, 1989; Chu et al, 1997; Ohta et al, 1984, 1988). Autopsy studies suggest that recurrent cholangitis can induce progressive changes, leading to atypical epithelial hyperplasia and cholangiocarcinoma (Ohta et al, 1984). The tumor may take the form of a nodular or papillary growth, and stones may be found within the tumor mass or within the ductal lumen with tumorous invasion (Fig. 44.12). Cholangiocarcinoma should be suspected whenever a mass lesion is seen on imaging studies (Fig. 44.13); however, inflammatory pseudotumor (see Chapter 48) is also present in patients with RPC (Yoon et al, 1999). The imaging characteristics are nonspecific; only resection and pathologic examination can reliably differentiate the two conditions.



FIGURE 44.8. Gradation of sizes of irregular recurrent pyogenic cholangitis stones. The surfaces are bile stained, but the interior is lighter in color. The shape of the stones molds to the contours of the intrahepatic ducts.

Thrombophlebitis of major portal vein branches may develop when adjacent large biliary ducts are affected by RPC, causing extensive periductal inflammation (Fig. 44.14). The degreee of portal vein obstruction correlates well with the degree of liver atrophy (Kusano et al, 1991; see Chapter 5). When the hepatic veins become thrombosed, pulmonary emboli may develop; in rare instances, this can lead to pulmonary hypertension (Lai et al, 1968). Microscopically, the portal triads are infiltrated with inflammatory cells, and the cholangioles are filled with pus. In severe attacks, neutrophils are also seen in the sinusoids of the lobules, and adjacent hepatocytes undergo vacuolation. The larger bile ducts show acute inflammatory changes initially, but with repeated attacks, the ducts

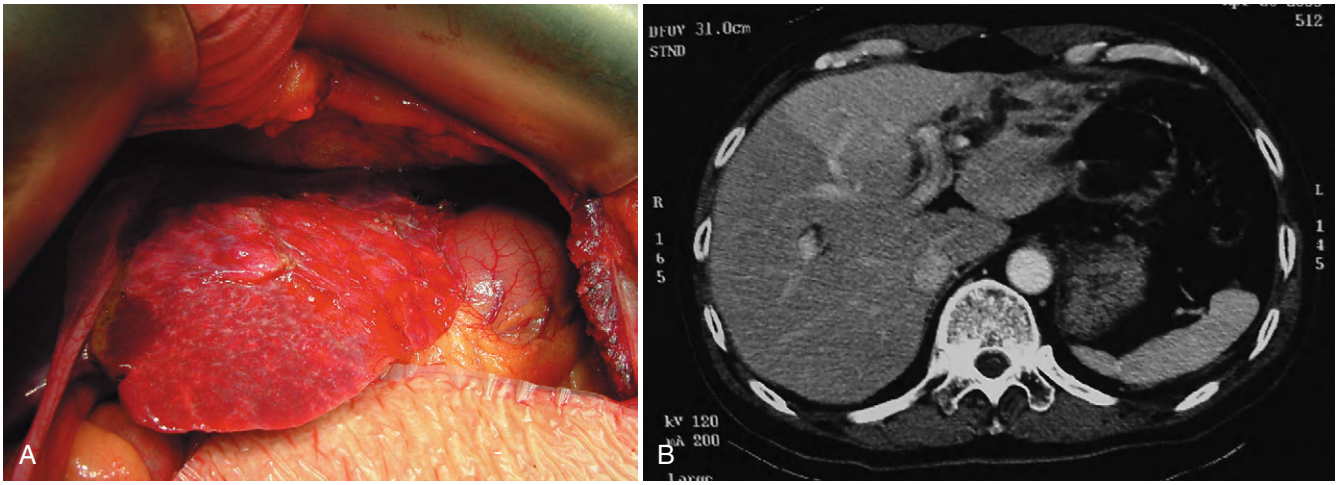


FIGURE 44.9. **A,** At laparotomy, the left lateral segment appears cholangitic with scars, and dilated ducts are seen on the surface. Stones may be palpable in the dilated ducts through the atrophic liver parenchyma. **B,** Computed tomographic scan of the same patient shows the typical features of this condition.



FIGURE 44.10. Computed tomographic scan of a patient with recurrent pyogenic cholangitis shows right lobe atrophy and shifting of the liver hilum toward the right side. Stones are located within the right duct.



FIGURE 44.12. Right hepatectomy specimen of the same patient as in Figure 44.13, showing tumor mass (*arrowheads*) growing within the dilated bile duct; a black stone is seen within a branch of the bile duct (*arrow*).

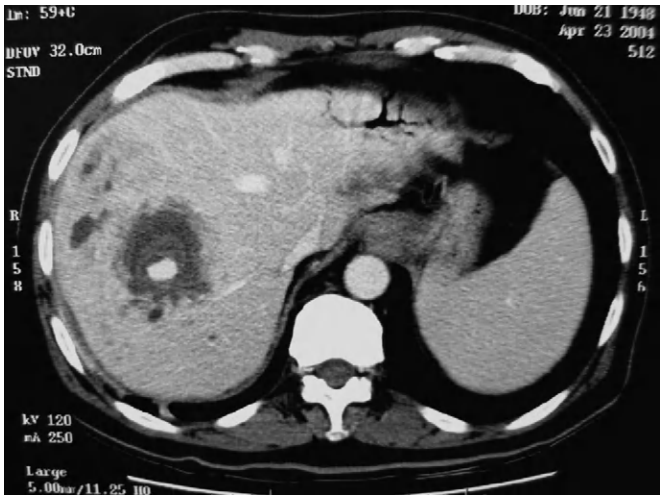


FIGURE 44.11. Computed tomographic scan of a patient with liver abscess that has produced a mycotic aneurysm.



FIGURE 44.13. CT scan of a patient with recurrent pyogenic cholangitis shows a dilated right duct with a soft tissue mass within (*arrowheads*).

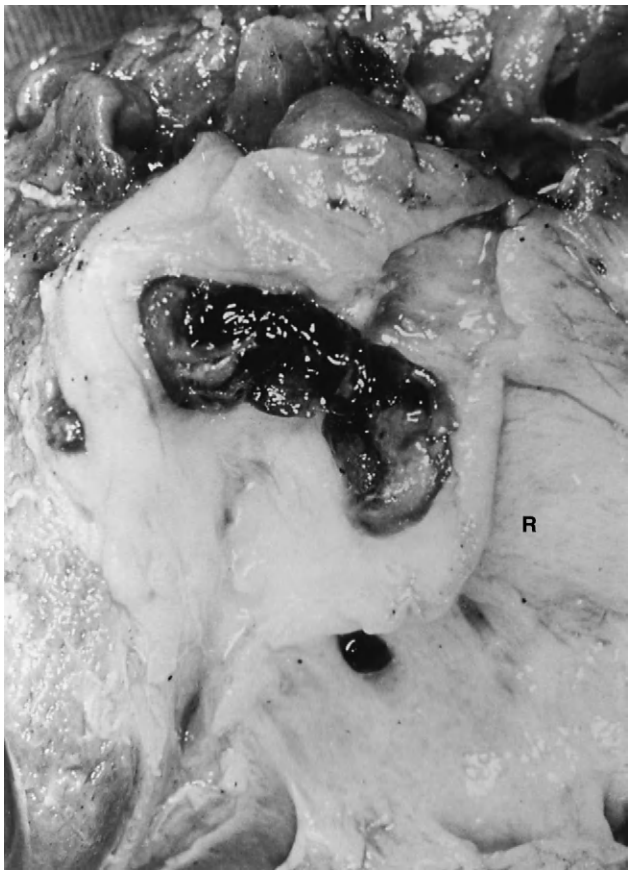


FIGURE 44.14. Thrombophlebitis of the right branch of the portal vein in severe recurrent pyogenic cholangitis affecting the right hepatic duct (*R*). The vein wall is thickened with white fibrous tissue.



FIGURE 44.15. Photomicrograph of a large intrahepatic duct affected by recurrent pyogenic cholangitis. The wall is thick and fibrosed, the epithelial lining in the duct lumen is denuded, and glandular proliferation extends into the depths of the thickened duct wall (hematoxylin and eosin stain, ×67.)

become thickened, surface mucosal lining is lost, and marked glandular proliferation advances into the thickened duct wall and beyond (Fig. 44.15). With repeated attacks, many of the glands undergo metaplasia, and fibrosis may extend far beyond the already thickened duct wall into the adjoining liver parenchyma, which undergoes degeneration and necrosis.

CLINICAL FEATURES

In contrast to biliary calculous diseases seen in Western countries (see Chapter 30), RPC affects men and women equally, with a predilection for the lower socioeconomic classes. In Hong Kong today, with improved socioeconomic conditions, there are fewer new cases and fewer young patients with RPC. In a survey, the median age of patients with RPC was 59.5 years, and 56% had previous biliary operations for biliary stone disease (Liu et al, 1998).

The symptoms of RPC are not in themselves distinctive and are characteristic of acute cholangitis: pain, fever, and jaundice (Charcot's triad; see Chapter 43). The pain is right hypochondrial or epigastric, and it may be distending, sharp, gnawing, or cutting, with frequent radiation to the back. It is constant, seldom colicky, and lasts for hours. Nausea is common, but vomiting is unusual. If the body temperature is elevated, septicemia or liver abscess must be suspected; the temperature chart often shows spikes rather than a continuous fever. Jaundice is seldom marked and may be just clinically perceptible, indicating incomplete obstruction. Pruritus is rarely a complaint, and the patient does not note pale stools. More typically, the patient is aware of the passage of tea-colored urine.

Physical examination in the acute attack reveals a restless patient, slightly jaundiced, and unwell. The abdomen may bear the scars of previous surgery. Tenderness is elicited in the epigastrium or right hypochondrium, and there is guarding. The liver is enlarged in 60% of patients, but this may be masked by guarding. Similarly, a distended gallbladder may not be palpable. The spleen is enlarged in 25% of patients.

Should the abdominal signs deteriorate, indicating worsening peritonitis, or if generalized peritonitis is present, emergency operation or nonoperative intervention is mandatory. In elderly patients, abdominal signs may be minimal, even in septicemic patients, and reliance on physical findings alone may delay a decision to operate until the patient is in shock. Even when shock is present, there still may be a reluctance to operate on these elderly patients for lack of convincing abdominal signs. A transient increase in blood pressure in a patient with acute cholangitis may be a prelude to shock and must be regarded as a sign of impending deterioration rather than a positive response to treatment. In between attacks, there are few if any significant clinical features. Recent weight loss in elderly patients known to have RPC should raise the suspicion of development of cholangiocarcinoma, and it should also be suspected during follow-up when a patient's serum alkaline phosphatase increases markedly (Kim et al, 2003), or when intrahepatic stones involving both lobes have not been completely cleared in previous operations (Jan et al, 1996).

INVESTIGATIONS

Routine hematologic and biochemical tests are consistent with bacterial infection of an obstructed bile duct and do not distinguish patients with RPC from patients with infectious processes from other causes. Leukocytosis is present, and liver function tests show an obstructive picture with a moderate elevation of

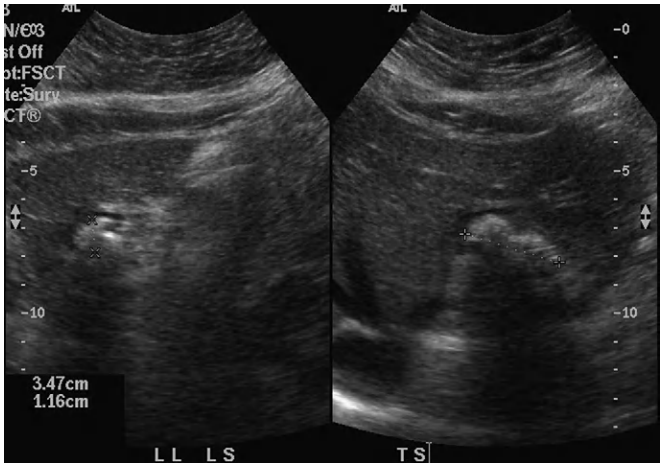


FIGURE 44.16. Ultrasound of a patient with recurrent pyogenic cholangitis. The intrahepatic stone produces an acoustic shadow, a feature not always demonstrable.

the bilirubin level and high serum alkaline phosphatase and γ-glutamyltransferase (GGT) levels. Occasionally, patients with RPC have completely normal liver biochemistry, even during an acute attack.

Imaging studies are important for the diagnosis of the disease, evaluation of the extent of involvement, and formulation of treatment plans for eradication of stones and strictures. Ultrasonography (US), computed tomography (CT), cholangiography, and magnetic resonance imaging (MRI) are complementary to each other in achieving such goals (see Chapters 13, 16, and 17).

When applied optimally, US diagnoses the size of the common and intrahepatic ducts and the location of stones. It also shows liver abscesses, biloma, or tumor if any of these are present. Color Doppler US is useful in studying portal vein hemodynamics. Intrahepatic stones are readily identified if they cast sonic shadows (Fig. 44.16), but some stones found in RPC are isoechoic and may be isoechoic with respect to the surrounding tissue (Federle et al, 1982). This fact, combined with the propensity of these stones to form biliary casts, may lead to failure of US to identify intrahepatic stones in some cases (Chau et al, 1987). Another deficiency of US in the imaging of this disease is related to pneumobilia, which may produce highly reflective echoes and acoustic shadowing that simulates stones (Federle et al, 1982). Pneumobilia is a common finding in patients with RPC who have undergone biliary-enteric drainage procedures. In 30% of patients with RPC, prominent periportal echogenicity is found (Chau et al, 1987). These changes could represent pericholangitis and periportal fibrous thickening found in advanced stages of RPC, a finding that should prompt the ultrasonographer to search for other evidence of RPC.

CT is more expensive than US, but it provides imaging that is largely free from observer bias and operator-dependent interpretation. In addition to providing the information offered by US, it can accurately differentiate intrahepatic stones from pneumobilia, which may be confusing on US, and can provide accurate topographic localization for drainage of liver abscess (Fan et al, 1990). In RPC, some stones may become less conspicuous on postcontrast scans against the contrast-enhanced hepatic parenchyma (Fig. 44.17), and examination of a noncontrast scan is mandatory to avoid a false-negative interpretation. On CT scan, volumetric and contour alteration of the liver can be readily seen; liver lobe atrophy, hypertrophy, and rotation of the liver hilum are present in longstanding cases (see Fig. 44.10), and parenchymal changes can also be detected. During an acute attack, persistent segmental enhancement is observed in 36% of patients (Chan et al, 1989), representing parenchymal suppuration analogous to the angiographic finding of diffuse hypervascularity and arteriovenous shunting described for the disorder (Freeny, 1980).

US and CT are complementary examinations to cholangiography (see Chapter 18), which provides clear delineation of the ductal anatomy. The pattern of ductal disease can be so diverse in IPC that detailed delineation of the entire biliary tract is essential. ERCP and percutaneous transhepatic cholangiography (PTC) are the direct cholangiographic methods of choice

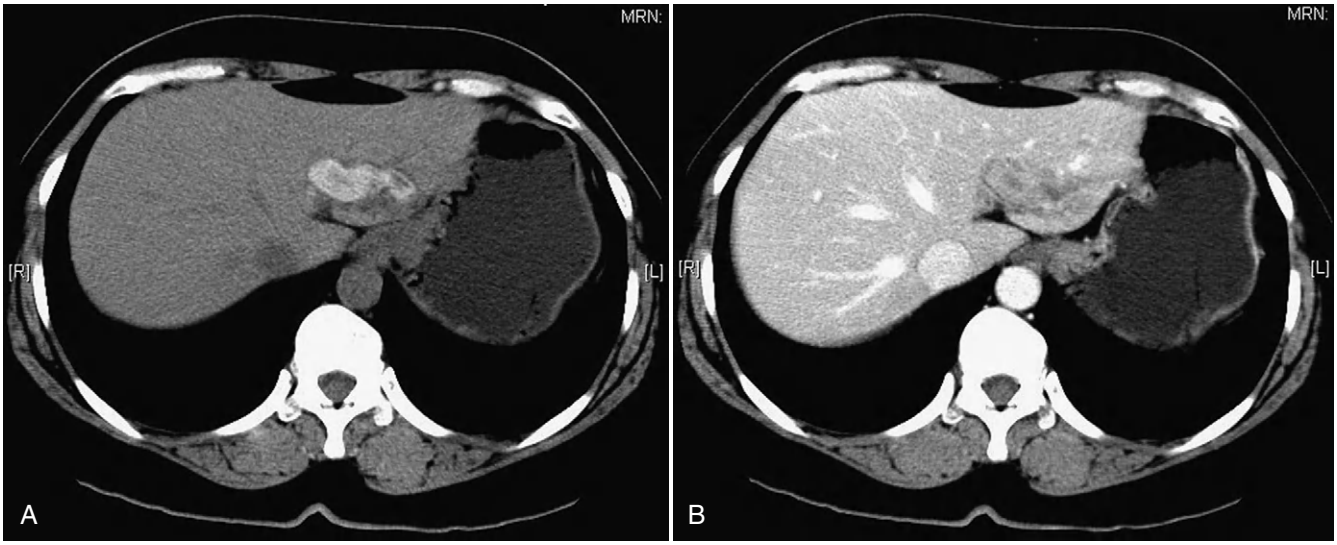


FIGURE 44.17. A, Computed tomographic (CT) scan shows obvious intrahepatic stones on a noncontrast film. **B,** CT scan shows the stones being masked by parenchymal contrast enhancement.

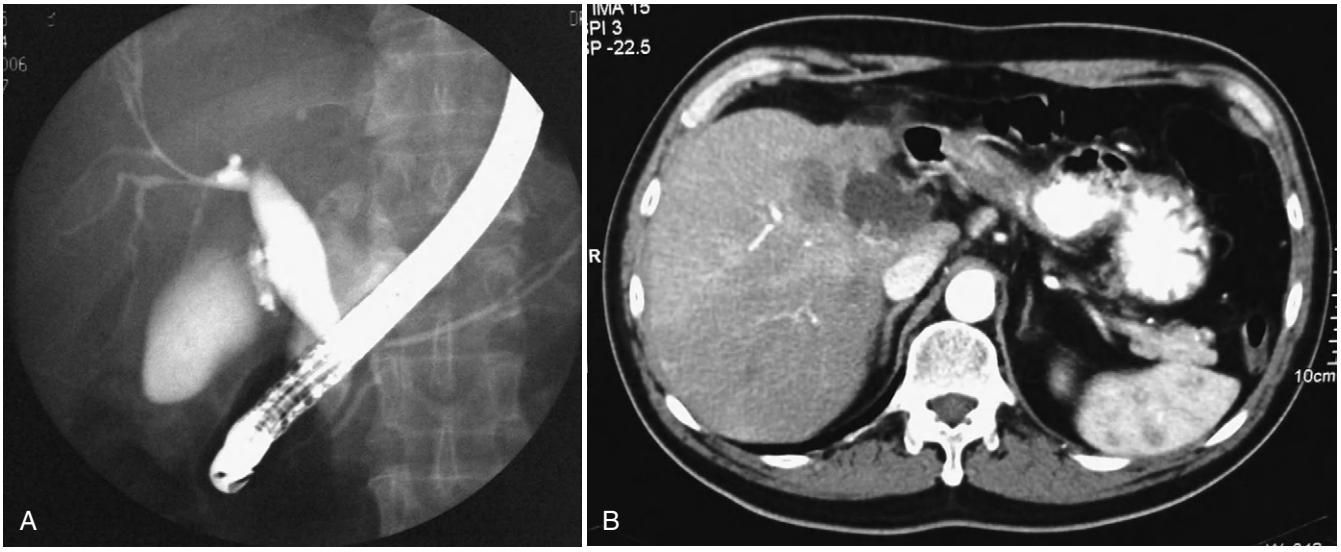


FIGURE 44.18. A, Endoscopic retrograde cholangiopancreatography shows an apparently normal cholangiogram. On closer examination, a lack of intrahepatic ductal filling is present on the left side. **B,** Computed tomographic scan of the same patient shows that the absent intrahepatic filling is due to stricture of the left duct leading to cisternal dilation. Multiple stones are present inside the dilated duct.

for RPC. We generally prefer to perform ERCP first, because the extrahepatic ducts, which are affected in more than 50% of patients with RPC, are better visualized. PTC is preferred when there has been a hepaticojejunostomy or choledochojejunostomy and when a stone or stricture located at a confluence of bile ducts prevents filling of the intrahepatic ducts. US can be useful in this instance by guiding percutaneous puncture of the targeted bile duct and by offering greater safety (Nakayama & Koga, 1984). On interpreting cholangiograms obtained in patients with this condition, care should be exercised in looking for missing segmental ducts, especially with a paucity of intrahepatic filling (Fig. 44.18). Correlation with US or CT may yield useful information in defining the cause of repeated attacks of cholangitis in patients who apparently have cleared all stones.

Similar to CT and US, MRI is a sensitive modality for showing the volume and contour changes in RPC. Contrast-enhanced T1-weighted MRI can show acute suppurative changes by enhancement of the ductal walls and parenchyma. Periportal inflammation is seen on MRI as an intermediate signal between that of the liver and bile on T2-weighted images (Chan et al, 1997). T2-weighted images are best for showing ductal dilation and stones, because bile appears with high signal intensity, whereas stones (without free protons) are signal void and appear as an intraductal filling defect (Fig. 44.19). Compared with US and CT, MRI is slightly better in detecting intrahepatic stones, ductal dilation, and strictures (Kubo et al, 1995), however, the presence of pneumobilia, which is also signal void, may adversely affect the stone detection rate. Three-dimensional display of the biliary system by MRI cholangiography (see Chapter 17) is indicated when ERCP cannot be performed, and it may supplant direct cholangiography for diagnostic purposes (Fig. 44.20; Soto et al, 1996). MRI cholangiography is more sensitive than ERCP in detecting intrahepatic stones, because intrahepatic stricture inhibits filling of intrahepatic branches by contrast material in ERCP, and MRI cholangiopancreatography may replace ERCP in situations in which a therapeutic procedure is not mandatory (Kim et al, 2002).

MANAGEMENT

Most patients present with an acute attack, which is often not their first. The acute attack usually resolves with antibiotic and surgical or endoscopic treatment, and the patient undergoes detailed radiologic examination. In particular, the site of the strictures, location of stones, size of the ducts, volume of the liver parenchyma involved, and any associated complications



FIGURE 44.19. Magnetic resonance imaging shows coronal plane of a patient with recurrent pyogenic cholangitis. Cisternal dilation of intrahepatic ducts and stone (*arrow*) are seen, whereas the common bile duct (*CBD*) is normal in caliber. *(Courtesy Dr. F.L. Chan.)*



FIGURE 44.20. Magnetic resonance imaging cholangiopancreatography shows large common bile duct stones and irregular caliber of intrahepatic ducts in a patient with recurrent pyogenic cholangitis. The gallbladder does not contain stones. *(Courtesy Dr. F.L. Chan.)*

can be ascertained before a decision is made regarding the need for or type of operation to be performed. Definitive treatment by liver resection is often indicated. Patients for whom liver resection is not recommended are few, and those generally include frail patients who have minimal ductal strictures and in whom stones are absent and also the rare patients whose bile ducts are filled with *C. sinensis* and whose attack of cholangitis is presumably due to bacterial infection on top of a heavy infection by flukes.

Acute Attack

The goal of treatment of an acute attack is to provide noninvasive conservative measures. This phase of treatment is regarded as preoperative or preinterventional. Intravenous fluids, broad-spectrum antibiotics, and analgesics are given, and the gastrointestinal tract is rested. Antibiotics must cover gram-positive and gram-negative organisms, particularly *E. coli, Klebsiella* species, and anaerobes, especially in patients with a previous biliary-enteric anastomosis (Sheen-Chen et al, 2000). Patients who come to medical attention in shock or whose condition is unstable must receive surgical or nonsurgical intervention without delay.

Conservative treatment for an acute attack fails in about 30% of patients. Complications occur in approximately 35% of the patients who required emergent operative, endoscopic, or radiologic procedures (Chen et al, 1984; Fan et al, 1991b). A retrospective analysis suggested that failure of conservative treatment is more likely to occur with obstruction of the entire biliary tract by stones or strictures in the common duct than when the biliary obstruction involves an isolated segment only. In other words, sepsis involving the entire biliary tract seems to be more serious than sepsis with segmental involvement. Factors such as age, incidence of comorbidities, previous surgery, bacteremia, bacterial strains resistant to antibiotics, and multiplicity of bacterial cultures seem to be less important determinants (Fan et al, 1991b).

Failure of conservative treatment is evidenced by persistent fever, mental obtundation, spreading signs of peritonitis, tachycardia, oliguria, and hypotension. Urgent biliary decompression is required before the patient lapses into irreversible shock and death. This is achieved by an endoscopic, radiologic, or operative approach.

Surgical Treatment During an Acute Attack

In an acute attack, the operation is aimed at saving the patient's life by decompressing the obstructed bile duct and providing free biliary drainage. The standard approach is exploration of the CBD through a choledochotomy and insertion of a large-bore T-tube. The common duct is often a few centimeters in diameter and very thick walled. When the CBD is extremely large and fibrosed, the normal anatomy is distorted; in this situation, recognition may not be straightforward, especially with a history of previous operation. When the duct is opened, thick, infected biliary mud or pus exudes. After this material has been aspirated, stones within the duct are removed with forceps gently, to avoid fragmentation; a scoop is useful in retrieving soft stones and thick mud (see Chapters 29 and 39).

Intrahepatic strictures and stones are not dealt with definitively at the emergency operation, but intrahepatic ductal infection must be relieved by dilation of strictures with graduated sounds. When tight strictures are dilated, a gush of infected bile emerges from the duct. To establish the drainage and decompression of the intrahepatic segmental ducts, a transhepatic tube can be inserted on the same principle as a percutaneous transhepatic biliary drain inserted by radiologic means (Fan & Wong, 1996). During exploration of the CBD, irrigation of the bile duct with warm saline solution must be done gently, because syringing at high pressure may induce bacteremia. For this reason, among others, choledochoscopic examination of the intrahepatic duct should not be performed. Choledochoscopy can be done for the lower end of the CBD, provided that the choledochotomy is large and allows free egress of saline.

After the common duct is cleared, patency of the lower end can be established by gently passing a biliary Fogarty catheter. Inflation of the Fogarty catheter without choledochoscopic guidance is not recommended, because inflation of the balloon at the sphincter of Oddi may damage the sphincter or induce acute pancreatitis. Similarly, blind passage of a biliary sound is not recommended, because it may create a false passage or damage the sphincter of Oddi. Digital exploration also is helpful to detect stones and strictures in the CBD and the proximal hepatic ducts, but it is not reliable in ascertaining complete clearance of stones.

After bile flow from both lobes of the liver is established, a large-bore T-tube is inserted in the CBD, and the choledochotomy is closed with absorbable sutures. This T-tube allows debris to pass unimpeded, and because residual stones are found in more than 30% of patients after emergency exploration, it affords a large tract for percutaneous manipulation after operation.

Whether additional procedures are required depends on the presence of concomitant pathology and the condition of the patient. Cholecystectomy and cholecystostomy are not routinely performed, unless the condition of the patient is satisfactory; acute cholecystitis, empyema, or gangrene of the

gallbladder is present; or the gallbladder is extremely distended. When the condition of the patient is not satisfactory, the presence of stones in an otherwise normal gallbladder is not an indication for cholecystectomy during operation for an acute attack. Palpable liver abscesses are drained externally. Smaller, multiple abscesses should resolve with adequate biliary drainage and antibiotics. If the cardiovascular condition of the patient is stable, hepatic resection can be performed safely for multiple liver abscesses in a destroyed left lateral segment (Fan et al, 1993a).

A stone impacted at the lower end of the CBD that cannot be extracted via a choledochotomy is left in situ, if there is no associated acute pancreatitis. In the presence of acute pancreatitis, removal through a transduodenal sphincteroplasty is mandatory, because pancreatitis may progress (see Chapter 35). This operation can be performed with low risk (Ong et al, 1979). Although it may be argued that such an impacted stone may be left for endoscopic removal, this strategy entails further intervention in the immediate postoperative period, using a procedure that is not without risk; in addition, it does not offer the assured success of surgical removal at the same operation. The patient may lose a large volume of bile in the postoperative period, leading to hyponatremia, hypokalemia, metabolic acidosis, and dehydration. An alternative to transduodenal sphincteroplasty for an impacted stone at the lower end of the CBD is fragmentation of the stone using electrohydraulic lithotripsy (Fan, 1989). In experienced hands, this procedure is safe and quick, and transduodenal sphincteroplasty can be avoided.

Postoperatively, the patient's improvement is usually dramatic. Patients who undergo operation for septic shock may need a prolonged convalescence in the intensive care unit to recover from hepatic and renal dysfunction; temperature, pulse rate, and blood pressure may take some time to return to normal levels. Some of these critically ill patients remain in shock and subsequently die of multiple organ failure, sepsis, and generalized bleeding secondary to coagulation defects.

Patients with heavy *C. sinensis* infections may pass large volumes of thin bile through the T-tube despite demonstrated patency of the lower end of the CBD. The mechanism for this choleresis is unknown. Praziquantel should be given to eradicate the infection, and adequate fluid and electrolyte replacement must be given to avoid complications.

Nonoperative Treatment of an Acute Attack

Biliary decompression can be achieved by endoscopic papillotomy (see Chapters 27, 36, 37, and 39) and nasobiliary catheter or large-bore endoprosthesis insertion (Lam, 1984). Biliary decompression has the advantage of immediate relief of biliary obstruction if the site of obstruction is within the CBD, but it is not beneficial if the disease is mainly intrahepatic. In this situation, percutaneous transhepatic biliary drainage (see Chapters 28 and 32) of the obstructed segmental ducts under US guidance may be helpful (Heffernan et al, 2009; Huang & Ker, 1988). The drainage tubes used in these procedures are small, and the lumen is even smaller; these can be blocked easily in the presence of thick, infected bile and soft stones (Takahashi et al, 1990). Because multiple strictures are often present inside and outside the liver, a single drain is inadequate in affording total decompression.

Careful assessment of the clinical condition after endoscopic or radiologic biliary decompression is necessary. If the patient's condition does not improve, further imaging is necessary to identify the location of sepsis. Possible causes of ongoing sepsis may include empyema of the gallbladder with perforation and bile peritonitis, one or more undrained segmental ducts, liver abscess, and blockage of the lumen of a previously placed drainage tube by thick bile. Regardless of the cause of sepsis, prompt surgical intervention is indicated.

In the past, biliary decompression was performed when a patient's condition deteriorated or failed to improve after conservative treatment. The mortality of this approach is about 10% and is unacceptable. With the availability of emergency endoscopic service, we advocate emergency ERCP and endoscopic decompression within 24 to 48 hours of admission, hoping to avoid surgical intervention at the time of an unfavorable physiologic condition. ERCP is the best initial step, because the pathology leading to failure of conservative treatment usually resides in the CBD (Fan et al, 1991a, 1991b), and adequate decompression can be achieved by the use of a large-bore endoprosthesis. With this approach, there is almost no hospital mortality for an acute attack (Liu et al, 1998); however, the condition of the patient must be meticulously observed. If a sign of immediate improvement is not apparent, the patient must be considered for surgical intervention.

Definitive Surgery

The goals of elective definitive surgery are to clear the biliary tract of stones, to bypass or enlarge the strictures, to provide adequate biliary drainage, and, where necessary, to provide percutaneous access to the biliary tract. Because the disease affects the biliary tract at different sites and with varying degrees of severity, many procedures have been developed to deal with the different circumstances. These procedures include common duct exploration, hepatotomy, partial hepatectomy, hepaticocutaneous jejunostomy, and stricturoplasty. A complete and exact imaging study to outline the location of stones and strictures and the degree of segmental liver atrophy is mandatory in planning elective definitive treatment.

In general, RPC can be arbitrarily divided into simple and complicated cases depending on the absence or presence of intrahepatic strictures. For simple cases, cholecystectomy, exploration of the common duct, and choledochoscopy with or without hepaticojejunostomy suffice. For complicated cases, hepaticocutaneous jejunostomy, stricturoplasty, and partial hepatectomy are additional procedures needed to circumvent intrahepatic ductal strictures and to eradicate impacted stones.

Approach to the Biliary Tract

Similar to the operations performed for an acute attack, a choledochotomy or hepaticodochotomy is made for initial exploration of the bile duct. In patients with predominantly intrahepatic involvement, the hepaticodochotomy can be extended up into the right or left duct. By such an extension, pathology located at the confluence involving the main right or left duct can be readily approached. The orifice of the right posterior sectoral duct, especially when it joins the left duct, can be exposed for removal of an impacted stone. If a stricture is found at this orifice, dilation or stricturoplasty (Fan & Wong, 1996) can be performed.

Exposure of the CBD is sometimes difficult when it is obscured by dense adhesions as a result of previous operations or by a pericholedochal venous plexus related to portal vein thrombosis or portal hypertension. On occasion, the CBD

becomes posterior to the portal vein as a result of left lobe hypertrophy and right lobe atrophy (see Chapters 1B and 5; Czerniak et al, 1986). In these situations, the biliary system can be approached by extraperitoneal mobilization of the duodenum followed by transduodenal sphincteroplasty (see Chapter 35; Choi et al, 1982) or dissection of the left duct (Blumgart & Kelley, 1984) or the segment III duct (see Chapters 29 and 42; Dudley et al, 1979). Sometimes, dilated intrahepatic ducts with or without impacted stones are palpable on the surface of the liver, or they can be located by intraoperative US. In this situation, access to the intrahepatic ducts can be achieved by direct hepatotomy (Zhang et al, 1997). This method causes little bleeding if the parenchyma is thin but massive bleeding if the stones are deeply seated. Careful Doppler and US assessment must be done before a decision is made to proceed with direct hepatotomy.

Removal of Stones During Laparotomy

When the biliary tract is opened, stones can be readily removed by forceps, scoops, a Fogarty catheter, or saline flushing. Intraoperative flexible choledochoscopy (see Chapter 21) is mandatory to discover and remove additional stones, and extraction of stones can be difficult when they are impacted, situated behind strictures, or positioned within sharply angulated ducts, such as the right posterior sectoral or segment IV ducts (Fan et al, 1991a; Jeng et al, 1994; Mahadeva et al, 2003). The difficulty can be circumvented by electrohydraulic lithotripsy (Fan et al, 1989), which involves introduction of an electrohydraulic probe through the working channel of a flexible choledochoscope. Under direct visual control, the probe is brought into contact with the stone, which is disintegrated by sparks generated by the electrohydraulic lithotripter. The lithotripter should be applied cautiously, because a probe in contact with the ductal wall may damage the wall and lead to hemobilia. A holmium:yttrium-aluminum-garnet laser (Uchiyama et al, 2002) and a new-design plasma shock-wave lithotripter (Xu et al, 2002) may be viable alternatives, because they do not damage the ductal wall, and they work to clear intrahepatic stones in almost 100% of cases.

Cholecystectomy

Emergent cholecystectomy has been recommended by some authors only when gallbladder disease is present. This approach is justified, because a normal gallbladder left in situ has only rarely required subsequent removal for acute complications, it might act as a sentinel of distal obstruction in the bile duct, and it may be used for further biliary operation should the need arise. For RPC, these reasons are not compelling, therefore it is prudent to remove the gallbladder at the first opportunity in an elective situation.

Biliary Drainage Procedures

Additional drainage procedures, such as transduodenal sphincteroplasty (see Chapter 35) and choledochojejunostomy or hepaticojejunostomy (see Chapters 29 and 42), are carried out when specific indications are present. For sphincteroplasty, these indications include stenosis at the ampulla of Vater or distal common duct, a stone impacted at the lower end, or residual small stones in the intrahepatic ducts. In addition, the duct wall should not be thickened. Transduodenal sphincteroplasty is performed in the standard manner (Chapter 35). An extraperitoneal approach for this operation has been described (Choi et al, 1982) and is particularly useful for patients who have had multiple previous operations. A high transverse incision is used, and the duodenum is identified by its anterior relationship to the kidney. After the sphincteroplasty has been completed, the common duct is explored from below, and residual stones are extracted. Although a supraduodenal choledochoduodenostomy suffices for some of the indications listed, and the anastomosis allows passage of an endoscope for diagnosis or therapy, the disadvantage is possible development of the sump syndrome and liver abscess, because food debris may reflux into the partially obstructed segmental duct (Rumans et al, 1987). Conversion from choledochoduodenostomy to hepaticojejunostomy may be required in these situations. Choledochojejunostomy or hepaticojejunostomy (see Chapter 29) is carried out most commonly for a stricture in the intrapancreatic portion of the CBD or for a dilated thickened CBD that has lost its elasticity. It is performed with the hope that newly formed stones may pass into the bowel. In this instance, sphincteroplasty may not suffice, because the common duct may act as an inert sac and may drain inadequately.

Hepaticojejunostomy is also required when a stricture is present in the common hepatic duct. When the stricture involves the common hepatic duct at or near the confluence, biliary-enteric anastomosis to the left hepatic duct or segment III duct is necessary. When stricture involves the right and left ducts simultaneously in their immediate extrahepatic portion, the difficulty in treatment is increased (see Fig. 44.20); it may be possible to resect the strictures and to perform a bilateral hepaticojejunostomy (Figs. 44.21 and 44.22).

Hepaticocutaneous Jejunostomy

Hepaticojejunostomy is constructed with the hope of providing adequate drainage to the biliary tract for unimpeded passage of newly formed intrahepatic stones. Intrahepatic strictures proximal to the hepaticojejunal anastomosis impede free drainage of bile and passage of stones. Reoperation for recurrence of stones after hepaticojejunostomy becomes increasingly difficult and hazardous. Percutaneous access to the biliary tract may be achieved by flexible choledochoscopy, if the Roux-en-Y limb of the hepaticojejunostomy can be extended to the cutaneous level and opened as a stoma (see Chapter 29; Fan et al, 1993b; Fang & Chou, 1977). Via the stoma, it is possible to perform unlimited sessions of choledochoscopy, until all stones are removed, and all strictures are adequately dilated (Figs. 44.23 to 44.25). The stoma is closed and buried under the skin, so it may be reconstructed as a stoma for diagnostic and therapeutic purposes when recurrence of disease is suspected.

The operative procedure of hepaticocutaneous jejunostomy is simple, but it is imperative to construct a relatively straight and short loop from the skin to the biliary-enteric anastomosis; choledochoscopy through a redundant loop of small bowel is difficult, and access to the intrahepatic branches may be impossible. A variety of methods are effective for construction of a hepaticocutaneous jejunostomy (Hutson et al, 1984). In patients with RPC and numerous abdominal operations, a simpler attachment of a part of the circumference of the long limb of the jejunal loop to the abdominal wall is possible (see Fig. 44.25D).

Postoperative Choledochoscopy and Extraction of Stones

During the definitive operation, intraoperative choledochoscopy is performed, and as many stones as possible are extracted. Complete clearance of stones is sometimes impossible because

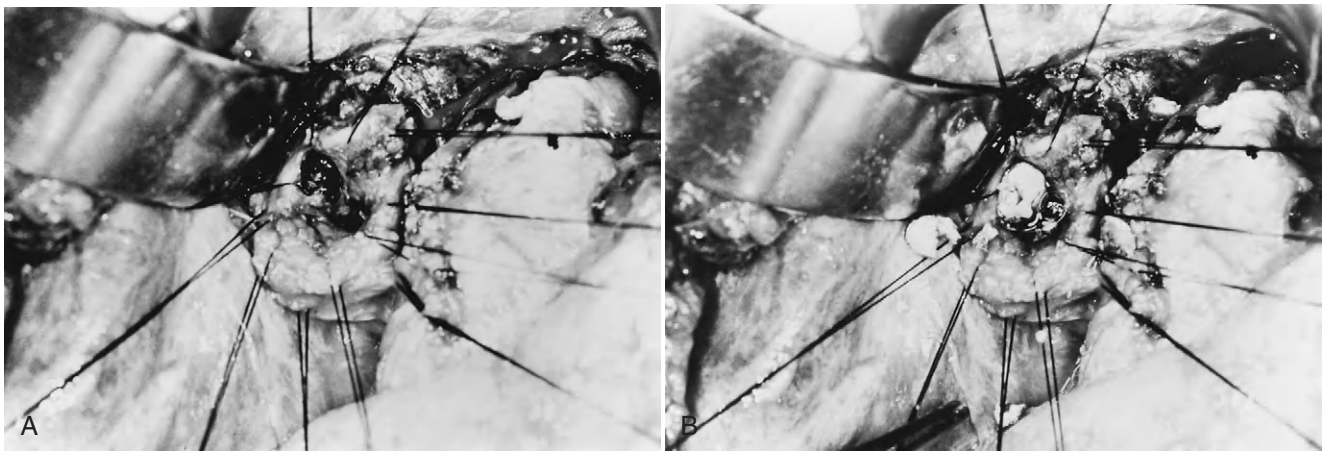


FIGURE 44.21. A, Stricture of the right hepatic duct at the porta hepatis. A stone can be seen within the stricture. **B,** Application of forceps on the stone results in fragmentation, showing the paler interior of the stone.

of the presence of a huge number of stones, or because many more stones are discovered only on postoperative cholangiogram. Postoperative choledochoscopy is required via the T-tube tract, or a cutaneous stoma is required. With numerous sessions of choledochoscopy aided by electrohydraulic lithotripsy, complete stone clearance can be achieved in 90% of patients (Table 44.1; Fan et al, 1991a). A similar complete stone-clearance rate can also be achieved by choledochoscopy via a percutaneous transhepatic biliary drain (PTBD) tract, which is favored by some authors (Cheung et al, 2003; Huang et al, 2003; Lee et al, 2001; Pitt et al, 1994).

The merits of choledochoscopy via a cutaneous stoma or PTBD tract are compared in Table 44.2. Generally, choledochoscopy via a cutaneous stoma is preferred for patients with many stones and strictures, because introduction of the choledochoscope is not painful, approach to the orifices of the segmental ducts is direct, extraction of stones from intrahepatic ducts is not limited, and lost access is not a concern. Bile may induce excoriation of skin, however, especially when the stoma adhesive cannot be applied properly. The location of the stoma has to be planned carefully before the operation to avoid scarred areas. On the contrary, bile leakage is not a major problem with PTBD, but the presence of the drainage tube can be a nuisance. Finally, creation of a PTBD pathway is less cumbersome than hepaticocutaneous jejunostomy but not entirely free of serious complications, such as injuries to the hepatic artery and portal vein. Despite the pros and cons, the two routes of access should not be considered mutually exclusive, but rather complementary, for complete clearance.

Choledochoscopic extraction of stones is generally effective, but occasional large stones may prove difficult and may defy fragmentation by electrohydraulic lithotripsy. Extracorporeal shock-wave lithotripsy (ESWL) is an alternative, and resultant stone fragments may either be extracted endoscopically or passed spontaneously (Adamek et al, 1999; Sackmann et al, 2001).

ERCP has been advocated as a sole modality for eradication of intrahepatic stones (Okugawa et al, 2002). With the aid of the "mother-baby" endoscope system, the complete stone removal rate is about 64%. Considering cost and efficacy, ERCP is considered supplementary to PTBD in difficult situations and is the treatment only in patients who are unfit for surgery.

Access to the biliary tract using the gastroscope via choledochoduodenostomy or interposition duodenojejunostomy has

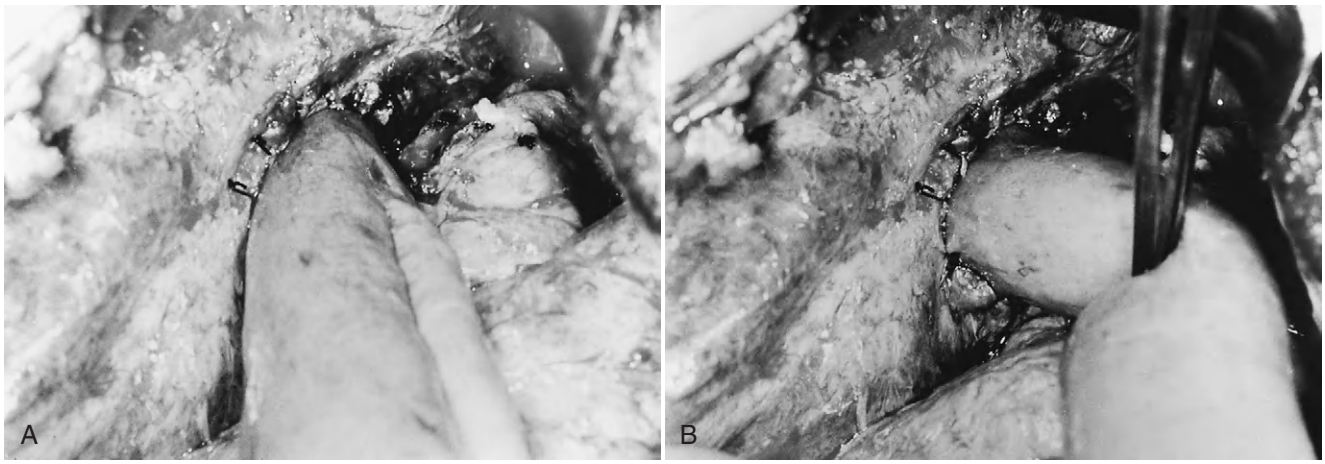


FIGURE 44.22. A, Hepaticojejunostomy performed after the stricture shown in Figure 44.21 had been excised and stones had been cleared from the intrahepatic duct. **B,** Posterior aspect of the hepaticojejunostomy shows the anastomosis is essentially intrahepatic.



FIGURE 44.23. **A,** Percutaneous transhepatic cholangiography of a patient who had undergone six previous operations for recurrent pyogenic cholangitis, including a left hepatectomy, a choledochojejunostomy, and a hepaticojejunostomy. The right duct is packed with stones proximal to an intrahepatic duct stricture, and the enteric anastomosis is patent. **B,** Postoperative appearance of the abdomen of the same patient. The end of the right intrahepatic duct was anastomosed to the side of a jejunal loop, the proximal end of which was brought out as a cutaneous stoma for permanent access to the intrahepatic duct.

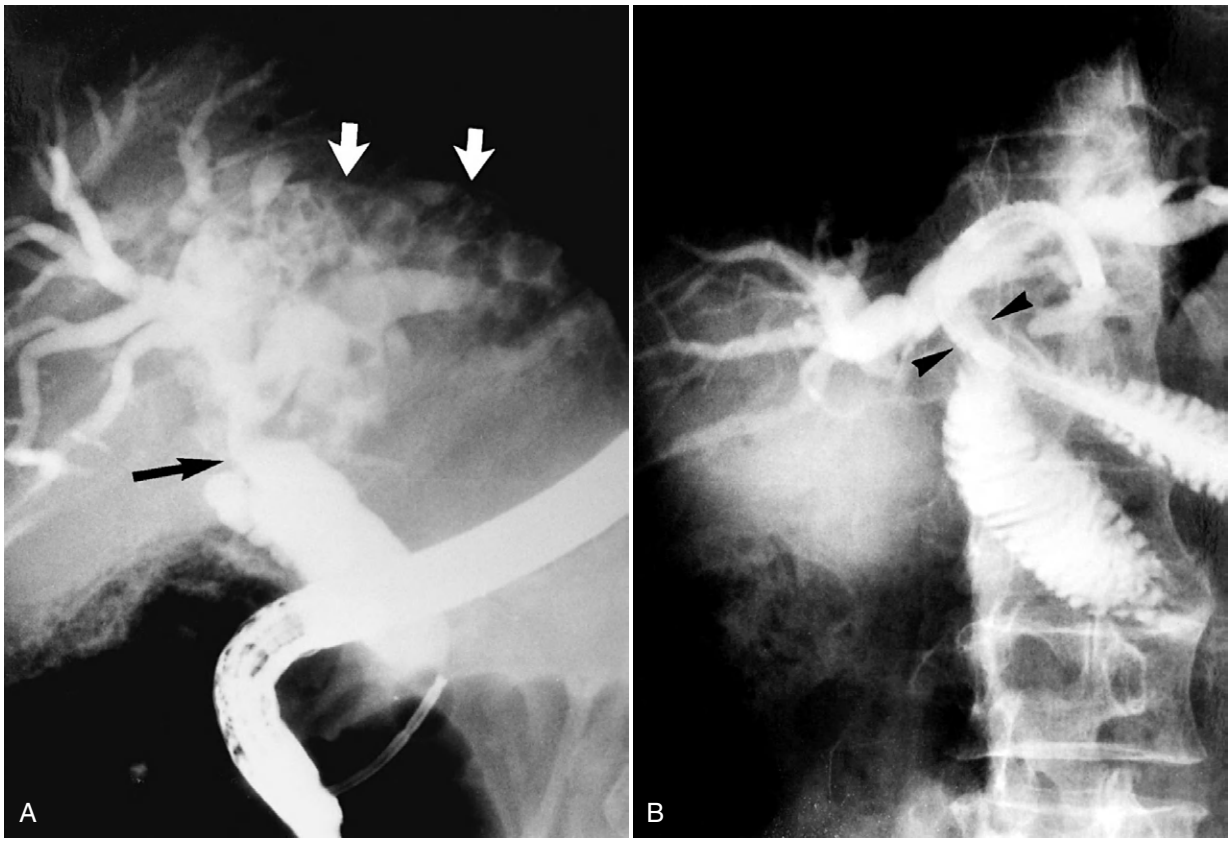


FIGURE 44.24. **A,** Cholangiogram of a patient with stricture at the common hepatic duct (*black arrow*) and numerous stones inside dilated left ducts (*white arrows*). **B,** Hepaticojejunostomy is constructed at segment III duct (*arrowheads*), and a flexible choledochoscope is shown passing through the anastomosis deeply into peripheral branches of left ducts. All stones have been cleared.

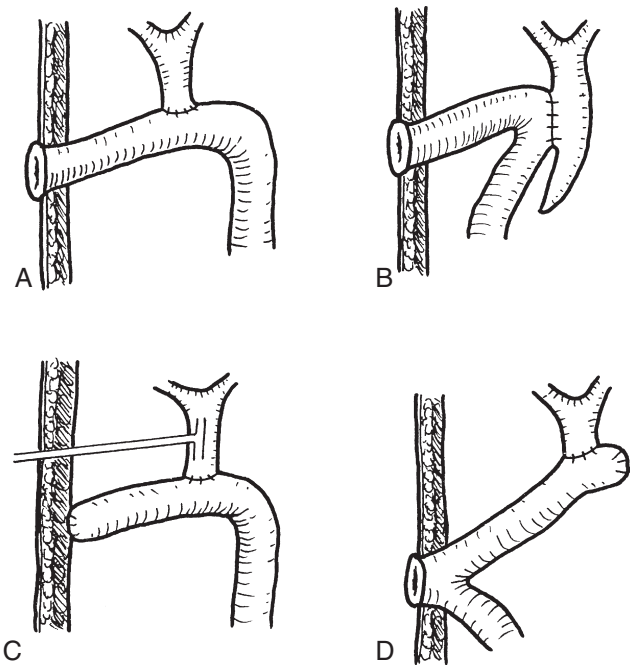


FIGURE 44.25. Diagram showing the standard operation of hepaticocutaneous jejunostomy (**A**) and modifications in selected circumstances (**B** through **D**). Method **B** is used when separation of the common bile duct from the portal vein is dangerous. Method **C** is used when a stoma is not required immediately after the operation. Method **D** is used when the patient has had a previous choledochojejunostomy (see Chapter 35).

been considered (Cunha et al, 2002; Ramesh et al, 2003). Although these techniques have the advantage of having no cutaneous stoma or percutaneous tube, both have the disadvantage of poor access to the small intrahepatic ducts by the gastroscope. With stenosis, food reflux into the intrahepatic duct cannot return freely to the duodenum, and the incidence of ascending cholangitis and liver abscess may be higher in these cases.

Hepatic Resection

Partial hepatectomy is indicated for destroyed liver segments, multiple cholangitic liver abscesses, and concomitant cholangiocarcinoma (see Chapter 90B; Cheung & Kwok, 2005; Fan et al, 1993a; Jeng et al, 1996; Otani et al, 1999). In the past, hepatic resection for RPC was confined largely to left lateral segmentectomy and occasionally left hepatectomy, because intrahepatic stones are located mainly in the left intrahepatic ducts. More recently, left hepatectomy instead of left lateral segmentectomy has been recommended, because ductal strictures are usually near the confluence of the right and left ducts. After hepatectomy, the ductal stricture is dilated, and the left ductal stump and the right and common ducts are explored for removal of intraductal stones. Thorough clearance of stones reduces the need for exploration of the CBD separately (Hwang et al, 2008). Right hepatectomy was once rarely performed, considered too dangerous and undesirable for a nonmalignant condition. However, with improved surgical technique and anesthetic care (see Chapter 22), more and more right hepatectomies are performed safely for RPC associated with impacted stones, an atrophic right lobe, or concomitant cholangiocarcinoma

Table 44.1

Comparison of Patients Treated in 2 Decades at Queen Mary Hospital

	1984-1989*	1991-1996†
No. patients	137	96
Age (median)	56	59.5
Intrahepatic strictures	46 (33.6%)	31 (32.3%)
Emergency ERCP	1 (0.7%)	61 (63.5%)
Partial hepatectomy	44 (32.1%)	55 (57.3%)
Hepaticocutaneous jejunostomy	19 (13.9%)	70 (72.9%)
Right hepatectomy	1 (0.7%)	5 (5.2%)
Stone clearance rate	114 (83.2%)	96 (100%)
Hospital mortality	4 (2.9 %)	1 (1.0%)
Stone recurrence rate	18 (13.1%)	3 (3.1%)

*Fan et al, 1991a
†Liu et al, 1998
ERCP, endoscopic retrograde cholangiopancreatography

(Table 44.2 and Fig. 44.26; also see Table 44.1 and Fig. 44.12) (Hung & Lin, 1997; Liu et al, 1998).

The technique of partial hepatectomy for RPC is not different from the standardized procedures (see Chapters 90 to 93). Modification is needed, however, when difficulty is encountered. When right hepatectomy is indicated for an atrophic right lobe, a thoracoabdominal approach may be indicated (see Fig. 44.10). If the inflow and outflow vascular dissection is difficult because of previous operation or infection, it may be wise to proceed to parenchymal transection directly and to achieve vascular control within the liver parenchyma. Furthermore, mobilization of the right liver can result in bacteremia; therefore the anterior approach is preferred (Liu et al, 2003). Adhesion of the left lateral segment to the adjacent viscera owing to repeated infection and rupture of liver abscess may predispose to injury to the vagus nerve, diaphragm, and the phrenic veins and to a higher incidence of postoperative septic complications (Fan et al, 1993a). The complication rate of hepatectomy for RPC is approximately 40%, half of which are of wound infections (Cheung & Kwok, 2005; Lee et al, 2009), and good correlation

Table 44.2

Comparison of Choledochoscopy via PTBD vs. Hepaticocutaneous Jejunostomy

	Via PTBD Route	Via Jejunal Loop
Choledochoscopy	Painful at skin entry site	Painless
Stone extraction	Stone fragments possibly too large for the tract	No limitation
Approach to intrahepatic duct by choledochoscope	Difficult to bend over angulation into segmental ducts	Theoretically easy
Loss of access	Tract disruption after repeated use	Redundant loop
Wound complication	Granuloma around skin entry site	Skin excoriation by bile

PTBD, percutaneous transhepatic biliary drain

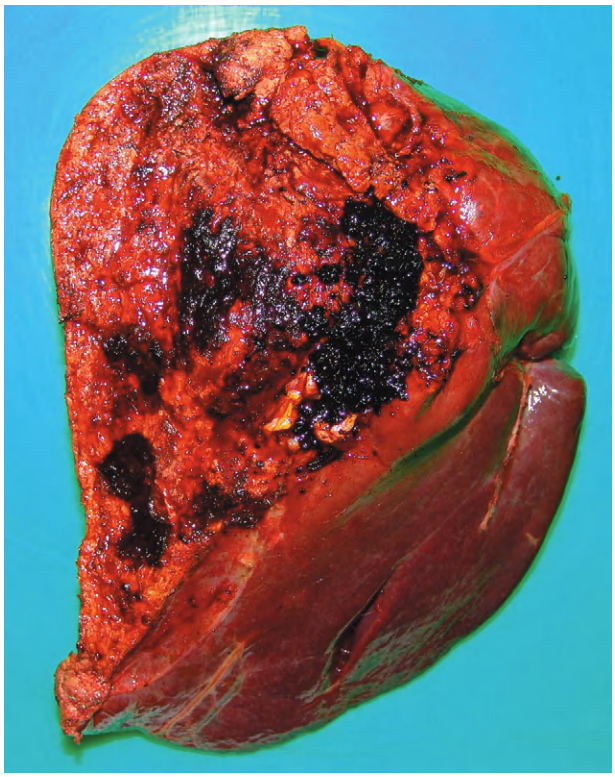


FIGURE 44.26. Resected specimen of the right lobe in which the ducts are packed with stones. Despite a significant residual functional parenchyma, the frequency and severity of symptoms of recurrent pyogenic cholangitis necessitated resection.

is found between the preoperative or intraoperative bile culture and wound infection culture (Lee et al, 2009). An appropriate choice of antibiotic and wound protection during the operation may lower the incidence of wound infections. With advances in the laparoscopic surgery technique, left lateral segmentectomy and even left hepatectomy could be performed in selected patients with an atrophic segment using a hand-assisted device (see Chapter 90E; Chen et al, 2004; Tang & Li, 2003). Such an approach is generally feasible for patients who have not undergone multiple operative procedures and without excessive perihepatic infection and adhesions, although with increasing experience, even these patients are potentially amenable to a laparoscopic resection. Longer follow-up is needed, however, before laparoscopic resection can be considered a standard technique for RPC.

Treatment for Intrahepatic Duct Strictures

Strictures located in the extrahepatic bile duct may be treated or circumvented by hepaticojejunostomy performed proximal to the stricture (e.g., at the confluence, left hepatic duct, or segment III duct; see Chapters 29 and 42). Intrahepatic duct strictures associated with liver atrophy or numerous cholangitic abscesses are best treated by partial hepatectomy. If significant thickness of the liver parenchyma is still present, the stricture is best treated by instrumental dilation (Cheng et al, 2000). After adequate dilation and removal of stones, however, such strictures may recur, and the stoma of the hepaticocutaneous jejunostomy, if present, has to be reopened for repeat dilation. Intrahepatic duct strictures have been treated by self-expanding metallic stents with a reported patency rate of approximately 60% (Jeng et al, 1999; Tsukamoto et al, 2004; Yoon et al, 1997). However, the use of such stents for benign biliary stricture is still controversial. For patients who have refractory intrahepatic biliary strictures and who refuse surgery, self-expanding metallic stents are a potential option, but at present, these should be considered only as a secondary alternative when surgery is impossible.

Liver Transplantation

Bilateral and extensive presence of intrahepatic stones far out into the peripheral ducts may not be amenable to resection and endoscopic treatment. Established secondary biliary cirrhosis, which results in liver failure and bleeding esophageal varices, is an indication for the ultimate treatment of RPC by liver transplantation. The possibility of the development of cholangiocarcinoma with time needs to be addressed, and vascular adhesions from previous operations and portal hypertension renders total hepatectomy of the native liver difficult and potentially hazardous (Strong et al, 2002).

RESULTS OF TREATMENT

Short-Term Results

The short-term results of the treatment of RPC is measured by the mortality, stone clearance, and stone recurrence rates. The outcome depends on the level of scrutiny for residual stones by various types of imaging and on the experience of the team, especially in choledochoscopy. The best results are achieved after good imaging studies, selection of the appropriate procedure for the individual case, and vigilant postoperative choledochoscopy before removal of the T-tube or closure of the cutaneous stoma. Our series indicate that the increasing use of aggressive treatment—such as partial hepatectomy, hepaticocutaneous jejunostomy, and diligent postoperative choledochoscopy—can lead to a 100% stone clearance rate and 3% stone recurrence rate after a median follow-up period of 26 months, with a mortality rate of only 1% (see Table 44.1).

Long-Term Results

The long-term result is best measured by the reappearance of stones and strictures after 5 years of follow-up and by the occurrence of portal hypertension, bleeding esophageal varices, ascites, liver failure, and cholangiocarcinoma. With respect to the location of the disease, patients with simple disease patterns can be expected to do well in the long-term with drainage procedures, whereas patients with complicated disease patterns are expected to have a 30% recurrence of symptoms (Chijiiwa et al, 1995; Jan et al, 1996). Along with recurrence of stones and strictures, progressive liver damage leads to portal hypertension, liver failure, and cholangiocarcinoma. About 10% to 20% of patients may eventually die of the disease, and the occurrence of complications is related to the failure to eradicate stones completely at the time of treatment (Jan et al, 1996).

Treatment is difficult in cases of RPC complicated by liver failure and portal hypertension. Liver transplantation is the only way to salvage these patients, but it is problematic because of the presence of dense perihepatic vascular adhesions resulting from previous infection, multiple abdominal operations, and cholangitic liver abscesses rupturing into the perihepatic

region. Torrential bleeding on mobilization of the liver may occur. This hemorrhage, together with the underlying sepsis, results in a much higher risk than in other patients undergoing liver transplantation. The number of patients with RPC having liver transplantation is small, and the hospital mortality rate has been reported to be 33% (Krissat et al, 1998). If liver transplantation is performed before multiple biliary procedures, the outcome seems to be acceptable (Chen et al, 2008; Strong et al, 2002).

CONCLUSION

To achieve optimal results in treating RPC, a judicious choice of a combination of treatment modalities by a dedicated multidisciplinary team is mandatory. Although it may not be possible to prevent recurrence of stones and strictures in all patients, the construction of a permanent percutaneous access to the biliary tract can facilitate the overall management and reduce the magnitude of subsequent procedures. For less complicated cases, complete removal of the stones and dilation or bypass of all strictures combined with vigilant follow-up can prevent disease recurrence. In the case of establishment of secondary biliary cirrhosis and liver failure, an early decision on liver transplantation must be made before the operative risk has become excessively high.

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CHAPTER 45

Biliary parasitic disease

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PARASITIC INFECTIONS

Parasitic infections of the biliary tract are a common cause of biliary obstruction in tropical developing countries and less frequently in developed countries. These infections are important, because they can lead to serious complications such as cholelithiasis (see Chapters 30, 35, and 39), recurrent pyogenic cholangitis (Chapter 44), cirrhosis (Chapter 70), pancreatitis (Chapter 53), and cholangiocarcinoma (Chapters 50A and 50B). The most common parasites of the biliary tract reported in humans are *Fasciola*, *Opistorchis*, *Clonorchis*, and *Ascaris* species. They have a wide geographic distribution, complicated life cycles, and various clinical manifestations with several diagnostic options available to detect them and multidisciplinary treatments. Millions of people are infected by these parasites, and surgical complications occur quite often.

Fascioliasis

Fascioliasis, or distomatosis, is a zoonosis caused by *Fasciola hepatica* or *F. gigantica* (Trematoda: Fasciolidae). The infection is distributed globally on all continents, but *F. hepatica* predominates in temperate zones, whereas *F. gigantica* is found in most tropical regions. In approaching a patient with suspected fascioliasis, epidemiologic (Table 45.1), clinical (Table 45.2), and imaging features (Table 45.3) can provide clues for the diagnosis before ordering a diagnostic test to confirm the infection. An algorithm for diagnosis and management is recommended and summarized in Figure 45.1.

Epidemiology

F. hepatica infection was first documented in the Gallo-Roman period (Da Rocha et al, 2006). Today, the estimated number of human infections ranges from 2.4 million to 17 million, and 91.1 million are at risk of infection around the world (Keiser & Utzinger, 2005). In the past, fascioliasis was limited to specific and typical geographic areas, but it is now widespread throughout the world. According to the reported cases, *F. hepatica* transmission has increased in Europe, the Americas, and Oceania, and in Africa and Asia, where *F. gigantica* and *F. hepatica* overlap. The geographical distribution is determined by the intermediate host (*Lymnaea* spp.) and certain other conditions such as climate, alimentary behaviors, and poverty.

Examples of countries with estimates of the infected population include 830,000 in Egypt, 742,000 in Peru, 360,000 in Bolivia, 37,000 in Yemen, 20,000 in Ecuador, and 10,000 in Iran (Haseeb et al, 2002). Furthermore, other countries that have reported a significant number of cases in years include Argentina (Kleiman et al, 2007), Venezuela (Incani et al, 2003), Chile (Llanos et al, 2006), Ecuador (Trueba et al, 2000), Mexico (Cruz-Lopez et al, 2006), Turkey (Kaya et al, 2006; Turhan et al, 2006), Thailand (Aroonroch et al, 2006), Japan (Inoue K, et al, 2007), Korea (Lee & Kim, 2006), the United States (Fullerton et al, 2006; Graham et al, 2001), Tunisia (Khelifi et al, 2006), and Lebanon (Birjawi et al, 2002), among others. The majority of reported cases in these countries are related to complications from the infection, and the current number of cases is undoubtedly underestimated. On the other hand, globalization and migration of populations from rural areas to large cities have led to a number of cases of fascioliasis in nonendemic areas. In fact, because of clinicians' lack of familiarity with this parasitic infection in nonendemic areas, the diagnosis can be delayed, which increases the rate of complications (Kang, 2008).

Fascioliasis is distributed globally, with the most affected area in the world being the Andean region of South America. In fact, more than half of the population may carry the infection in some selected regions, with prevalence ranging from 6% to 68% (Marcos et al, 2005b, 2007a; Parkinson et al, 2007). New evidence has shown that proximity of medium- to high-income industrialized cities to rural areas creates a potential source of infection in nonendemic areas because of the importation of contaminated vegetables to the high-consuming markets of big cities. Thus it is not uncommon to see cases of fascioliasis in nonendemic areas. Another factor that contributes significantly to the dissemination of the infection to new areas is the highly adaptable capacity of both the parasite and the lymnaeid snail hosts to challenging meteorologic conditions (e.g., 4200 meters above sea level, Andean Altiplano). Paleoparasitologic studies have shown that the introduction of *F. hepatica* and its snail host from Europe into the Americas has been relatively recent. Today, fascioliasis as a result of *F. hepatica* is the vector-borne disease with the widest latitudinal, longitudinal, and altitudinal distribution known. These key factors explain the wide geographical distribution of the disease (World Health Organization [WHO], 2007).

The epidemiologic pattern of transmission of fascioliasis can be classified as follows (Mas-Coma et al, 1999): 1) cases imported to areas where neither human nor animal fascioliasis is transmitted; 2) autochthonous, isolated, nonconstant cases of sporadic infection in areas where animal fascioliasis is present; 3) endemic fascioliasis (hypoendemic ≤1%, mesoendemic 1% to 10%, hyperendemic ≥10%); 4) epidemic fascioliasis (i) in animal endemic areas and (ii) in human endemic areas. Epidemiology is an important determinant of the initial evaluation of a patient with probable fascioliasis.

Life Cycle

The adult *F. hepatica* flukes are large, flat, brown, and leaf shaped with a broad anterior portion covered with scalelike spines. Flukes measure approximately 25 to 30 mm by 10 to 15 mm, although *F. gigantica* can measure up to 75 mm. The

Table 45.1

***Fasciola hepatica* Infection in Endemic Areas in Peru**

Risk Factor	OR (95% CI)	*P* Value	Reference
Multivariate Analysis			
Drinking emollients	5.2 (1.7-15.6)	.05	Marcos et al, 2004
Living close to irrigation channels	17.2 (2.8-106.7)	.05	
Eating salads	3.3 (1.2-9.0)	.05	Marcos et al, 2005
Drinking alfalfa juice	4.5 (1.7-11.1)	.001	Marcos et al, 2006
Familiarity with aquatic plants	4.3 (1.7-10.5)	.001	
Univariate Analysis			
Water supply from channels	2.4 (1.1-5.3)	.03	Marcos et al, 2006
Consumption of aquatic plants	2.5 (1.1-5.6)	.028	
Breeding five or more heads of cattle	2.5 (1.1-5.6)	.028	
Owning dogs	3.2 (1.3-8.1)	.1	
Defecation site in fields	2.6 (1.3-5.6)	.01	
Familiarity with aquatic plants	3.9 (1.8-8.3)	.0001	
Breeding more than five sheep	0.3 (0.1-0.7)	.003	

These studies were performed in the Andean region of South America. Risk factors in other parts of the world may be similar.
OR, odds ratio; CI, confidence interval

Table 45.3

Clinical Manifestations, Laboratory Data, and Imaging in Fascioliasis

Clinical Picture	Imaging and Laboratory Results
Acute	
Prolonged fever (weeks or months)	Eosinophilia (any cell count)
Abdominal pain (mostly upper abdomen)	Anemia
Hepatomegaly	Anicteric hepatitis
Weight loss	Biliary hemorrhage or hemobilia
Urticaria	Subscapular hematoma or hepatic rupture (seen on CT)
Ectopic lesions*	Hepatic abscesses
	Tracklike lesions on CT
Chronic	
Abdominal pain in right upper quadrant	Eosinophilia (sometimes)
Biliary colic	Cholestasis
Nausea and vomiting	Hepatic abscesses
Recurrent or intermittent jaundice	Liver fibrosis and ultimately cirrhosis
Uritcaria	Necrotic granuloma (increased ALT and AST levels)
	Cystic tumors
	Cholangitis caused *by Klebsiella, Escherichia coli, Enterococcus* spp.
	Choledocolithiasis
	Eosinophilic cholecystitis
	Achalcolous cholecystitis

*Ectopic migration and other clinical manifestations. Acute stage: migratory nodule under the skin or peritoneal cavity, arthralgias, lymphadenopathies, hemolytic anemia, seizures, pleural effusion. Chronic stage: subcutaneous nodules and gastric nodules.
CT, computed tomography; ALT, alanine aminotransferase; AST, aspartate aminotransferase

adult fluke lives in the common and hepatic bile ducts of the human or animal host, and animals susceptible to becoming reservoir hosts for *Fasciola* species include mainly cattle, sheep, pigs, buffaloes, and donkeys, although it has been also reported in horses, dogs, goats, llamas, alpacas, dromedaries, and camels. The eggs are oval, yellowish brown, and measure approximately 130 to 150 by 60 to 90 µm (Fig. 45.2).

The life cycle begins when the parasite eggs in stools are deposited in tepid water (22° C to 26° C); miracidia appear, develop, and hatch in 9 to 14 days. These miracidia then invade many species of freshwater snails, in which they multiply as sporozoites and redia for 4 to 7 weeks. They leave as free-swimming cercaria that subsequently attach to watercress, water lettuce, alfalfa, mint, parsley, or khat. Free-swimming cercaria may remain suspended in water and encyst over a few hours, and infection of the human host begins after consumption of plants or water contaminated with the metacercariae. In the first week, the larvae excyst in the duodenum and migrate through the bowel wall and peritoneal cavity; after 4 weeks, the juvenile larvae penetrate the liver through the Glisson capsule to initiate the acute larval, hepatic, and invasive stages of human infection.

Sometimes the larvae deviate to other locations; these are called *extrahepatic forms* or *ectopic infections.* Maturation from juvenile larvae into adult flukes takes approximately 3 to 5 months, during which time the larvae mature and migrate through the liver into the large hepatic and common bile ducts (Fig. 45.3). Mature flukes consume hepatocytes and duct epithelium and reside for years in the hepatic and common bile ducts and occasionally in the gallbladder. Adult fluke worms produce eggs within 4 months after infection (range, 3 to 18 months); these eggs traverse the sphincter of Oddi and intestine and then continue the cycle of infection. Of note, acute and chronic stages can overlap; this is commonly seen in endemic areas, and it is not unusual to find eggs in the stool samples of patients with acute infection.

Table 45.2

Epidemiology of Human Fascioliasis

Geographic Area	Risk Factors	Population at Risk
Latin America (Andean region)	Watercress	Children in endemic areas
Europe	Drinking alfalfa juice	Travelers
Africa	Green vegetables	Women
Asia	Contaminated water	Vegetarians
Australia	Travel to endemic areas	
	Living close to irrigation canals	
	Eating salads	

Risk Factors

The main source of infection is the consumption of metacercariae-contaminated raw vegetables—such as watercress, lettuce, alfalfa juice, and mixed green salads—or

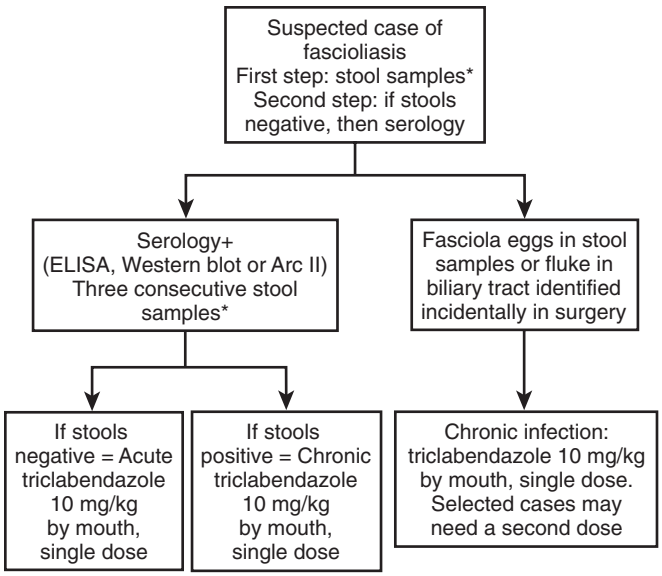


FIGURE 45.1. Summary of management and treatment of a suspected patient with fascioliasis. *Three consecutve stool samples must be examined by a sedimentation technique (Lumbreras, 1962) before ruling out the infection. Stool examination is preferred over serology because of cost effectiveness and availability. In highly suspected cases, a trial of triclabendazole is warranted. Single-dose triclabendazole 10 mg/kg has a cure rate greater than 90%. A second single dose may be used in selected cases (e.g., high intensity of infection in feces, large numbers of parasites in surgery, refractory cases). ELISA, enzyme-linked immunosorbent assay.

contaminated water from man-made irrigation channels (Marcos et al, 2004, 2005a). Because of epidemic obesity, alimentary habits have changed; for example, higher consumption of green vegetables has led to an increase in the risk for fascioliasis, because it requires vegetables imported from endemic areas (Marcos et al, 2007b). The infection has been also seen in people who have eaten salads in luxury restaurants or hotels in endemic countries, and watercress has traditionally been the



FIGURE 45.2. Adult egg of *Fasciola hepatica* in microscopic examination of stools by the rapid sedimentation technique.

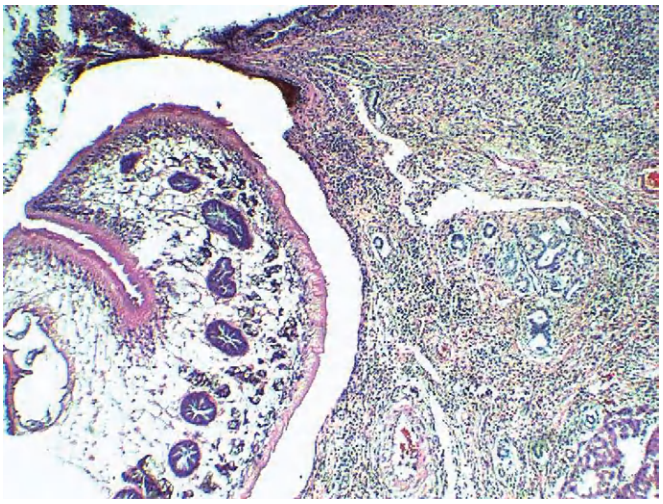


FIGURE 45.3. Liver biopsy of an infected rat with *Fasciola hepatica*, adult parasite in a bile duct.

most common known source of infection. Nonetheless, a large variety of plants have been described in recent years, such as *Medicago sativa* (alfalfa in juice) in Peru; *Taraxacum dens leonis* (dandelion leaves), *Valerianella olitoria* (lamb's lettuce), and *Mentha viridis* (spearmint) in France; green leafy *Nasturtium* spp. and *Mentha* spp. in Iran; *Juncus andicola* and *J. ebracteatus* (Juncaceae), *Mimulus glabratus* (Scrophulariaceae), and *Nostoc* species (Cianofitas) in the Bolivian Altiplano (Bjorland et al, 1995; Mas-Coma et al, 1999).

More women are affected than men, with higher prevalence rates, more severe infections, and with more reported liver or biliary complications (Marcos et al, 2006). Although, the differences are not well understood, alimentary habits, immunologic factors, and proximity to contaminated sources may play a role; for example, children are affected more than adults (Marcos et al, 2007c) likely because of alimentary habits. Reinfection is commonly seen in highly endemic areas, and the parasite can live in the biliary tract for a long time—between 9 and 13.5 years.

Epidemiologic studies have been carried out in endemic areas to measure the impact of alimentary habits on the acquisition of infection. Drinking beverages made from watercress or alfalfa leaves, called *emollients,* and living close to irrigation channels were found to be risk factors in a multivariate analysis in the Andean region (Marcos et al, 2004). Eating salads is the common factor among infected families, and it carries a 3.3-fold increased risk of acquiring the infection (Marcos et al, 2005b). In a logistic regression analysis, an age- and gender-matched case-control study comparing 60 infected children found that drinking alfalfa juice carries a 4.5-fold increase in the risk of acquiring fascioliasis, and familiarity with aquatic plants carries a 4.3-fold increased risk (Marcos et al, 2006). Therefore aquatic plants—watercress, alfalfa, and others—and the irrigation channels that carry the metacercariae play a key role in the transmission of fascioliasis in Andean endemic areas. Hypothetically, exportation of plants or other products could lead to transmission in nonendemic areas. Treatment of contaminated plants with high doses of potassium permanganate decreases metacercariae viability and could be used to prevent infection (Ashrafi et al, 2006), although its impact in endemic

Table 45.4

Imaging Findings in Fascioliasis

Ultrasonography	Computed Tomography	Magnetic Resonance Imaging
Focal areas Multiple nodules Irregular lesions Variable or increased echogenicity Single complex mass Complex cystic mass Parasites moving in gallbladder	Multiple hepatic metastatic-like lesions Change in position, attenuation, shape in time Abscess-like lesions Low-density serpiginous tortuous tunnel-like branching Subscapular hematoma Cystic calcifications Glisson's capsule contrast enhancement Single non–contrast-enhanced hypodense irregular mass	Homogenous hyperintense T2-weighted turbo spin-echo image Subscapular multiple hypointense areas Hypointense T1-weighted 3D gradient-echo image

3D, three-dimensional

areas has not yet been tested. A summary of risk factors with studies reporting odds ratios is presented in Table 45.4.

Clinical Manifestations

Fascioliasis has two distinct clinical phases: acute and chronic. Signs and symptoms depend on the worm burden, duration, and phase of infection. In general, the *chronic infection* is usually diagnosed in epidemiologic studies in endemic areas as a cause of biliary obstruction or in routine stool tests for other reasons. On the other hand, the *acute infection* has a more florid clinical picture that brings the patient to the emergency room. The clinical manifestations are so variable that mild right upper quadrant pain may call for a step-by-step workup that can lead to the final diagnosis of fascioliasis (Behar et al, 2009).

ACUTE INFECTION

The first acute or invasive phase lasts from 3 to 5 months and is caused by the migration of the immature larvae from the duodenum to the liver. Finally reaching the bile ducts, parasites migrate through the liver parenchyma and digest hepatic tissue, causing intense inflammation and hemorrhage proportionate to the number of worms. Migration tracks can be observed in histologic sections, and flukes sometimes die, leaving cavities filled with necrotic debris; these are eventually replaced by scar tissue. Symptoms include prolonged fever, hepatomegaly with abdominal pain, and mild eosinophilia (early infection) or hypereosinophilia (mid- or late-acute infection). Multiple hypodense lesions can be seen on CT scan, similar to metastases (MacLean & Graeme-Cook, 2002). Of note, one of the most frequent manifestations in this acute phase is hypereosinophilia, which is seen in almost all cases. If no eosinophilia is detected at the initial visit, it may be too early in the acute infection; a repeated cell blood count 3 to 5 days later will detect a significant increase in the eosinophil count. Absence of persistent eosinophilia reduces the suspicion for acute infection. In summary, acute fascioliasis is a clinical syndrome similar to acute cholecystitis with significant eosinophilia.

The acute phase presents itself with subcapsular hematomas, hepatic cysts, residual hepatic calcifications, and severe anemia. Hyperbilirubinemia is absent in the acute phase (Marcos et al, 2008b), which distinguishes it from other forms of acute hepatitis. Other manifestations are anorexia, weight loss, nausea, vomiting, cough, diarrhea, urticaria, lymphadenopathies, and arthralgias (Marcos et al, 2005c). Occasionally, the juvenile larvae reach other anatomic locations, such as the subcutaneous tissue, pancreas, eye, brain, and stomach wall, among others (Rana et al, 2007).

CHRONIC INFECTION

The chronic phase begins approximately 3 to 6 months after the consumption of the metacercariae, when the parasite reaches the bile ducts. By macroscopic examination, the liver has large, dilated, thick-walled, and calcareous bile ducts with yellowish brown bile. By microscopic examination, the bile ducts have a thickened hyperplastic wall with marked fibrosis (Haridy et al, 1999; Marcos et al, 2007c). Symptoms usually reflect biliary obstruction with colicky pain in the right upper quadrant, epigastric area, or upper abdomen (Rana et al, 2007; Maco et al, 2003; Jimenez et al, 2001). It can also be a silent, potential threat: the parasites can survive for longer than 10 years, and infection is commonly asymptomatic (Marcos et al, 2004).

Liver function tests during this phase are consistent with an extrahepatic cholestasis syndrome (Dobrucali et al, 2004) that can lead to surgery to treat the biliary obstruction (Jimenez et al, 2001). Moreover, an increase in liver enzymes can be present with minimal symptoms in endemic areas. In Egypt, it was found that patients with fascioliasis had significant liver enzyme abnormalities: elevation of alanine aminotransferase in 21.5% of the patients, aspartate aminotransferase in 21.9%, total bilirubin in 16.5%, gamma-glutamyltransferase in 80.6%, and alkaline phosphatase in 76.4% was reported. Excluding viral liver infections, *F. hepatica* infection is a significant cause of cholestasis in endemic areas ($P < .05$) (El-Shazly et al, 2005).

Imaging abnormalities were also found on ultrasound (US), including hepatomegaly, splenomegaly, periportal fibrosis, thickened gall bladder wall, dilated common bile duct, parasites in the gallbladder and common bile duct, stones in the gallbladder, stones in bile duct, cystic lesions in the liver, focal lesions in the liver, and ascites (El-Shazly et al, 2001).

Fasciola may also cause acute eosinophilic cholecystitis (Umac et al, 2006) along with pruritus and intermittent jaundice (Umac et al, 2006; Marcos et al, 2002). The parasites appear as small intrahepatic cystic lesions (Aroonroch et al, 2006) or as a large, multiloculated cyst that causes abscesses. On imaging parasites may appear very similar to echinococcosis (Maeda et al, 2008). Bacterial superinfection of *Fasciola* cysts is a complication of the chronic phase. Recent studies in a rat model have shown a significantly increased risk of bacterobilia in the chronic infection (Valero et al, 2006) and with gallstones (Valero et al, 2003). Even after successful treatment, abdominal pain and weight loss may still be present in approximately 2% to 4% of patients for several months (Rondelaud et al, 2006), and morbidity in these patients is significant.

Eosinophilia is absent in approximately half of the chronic cases. Upon admission to a tertiary health center, 47% of 277 complicated cases had eosinophilia (Blancas et al, 2004). A similar percentage was found in 101 chronic cases from the Andean region and other endemic areas: 48% had eosinophilia above normal levels, and only 14% had more than 1000

eosinophils/mL (Alban et al, 2002). In another study, about half of a group of 61 children in the Peruvian Altiplano with chronic fascioliasis had eosinophilia (Marcos et al, 2002). In Turkey, two (11%) of 18 subjects with fascioliasis had eosinophilia (Turhan et al, 2006).

Eosinophilia is present in a minority of cases of fascioliasis in the chronic phase. If present, it is generally mild (Gil-Gil et al, 2006). Few cases in the chronic phase have high-grade eosinophilia, in contrast with the acute phase, which presents with hypereosinophilia in almost all cases. Finally, a wide variety of other infectious agents are associated with eosinophilia, such as *Strongyloides stercoralis, Ascaris lumbricoides,* and hookworms or other helminths. Despite the fact that these are the most common parasitic causes of eosinophilia, they do not typically cause hepatic lesions, nor do they reach the high levels that we observe in patients with acute fascioliasis.

Another presentation of the chronic infection is hemobilia as a result of ulcerative lesions in the biliary tract caused by the adult parasite (see Chapter 105; Bahçecioglu et al, 2007). A granulomatous chronic inflammation may also be triggered by parasite ova in the liver or in other anatomic locations (Marcos & Terashima, 2007; Naresh et al, 2006). New data developed in an animal model have demonstrated a persistent immune suppression in advanced chronic infection (Gironès et al, 2007), suggesting that the infected host may be susceptible during the chronic phase to any Th2-suppression–dependent infection. Hence, a chronic immunosuppression may predispose to bacterial infection that can be life threatening.

An association exists between fascioliasis and liver fibrosis. It appears that hepatic fibrosis may evolve in some susceptible hosts, depending on the time and burden of infection. For instance, almost 50% of cattle infected chronically by fascioliasis had cirrhosis (Marcos et al, 2007c). In addition, hepatic cirrhosis has been reported in infected children (Almendras-Jaramillo et al, 1997; Marcos et al, 2005a) and adults (Heredia et al, 1984; Sanchez-Sosa et al, 2000), especially those with high-density infections. New data on the pathogenesis of hepatic involvement associated with *F. hepatica* infection have implicated cathepsin L1 and its collagenolytic function associated with tissue-invasion (Stack et al, 2007), with proteolytic activity leading to collagen type I expression and ultimately to hepatic fibrosis. The chronic infection can also have a negative impact on the nutrition and health of children in endemic areas.

Imaging Studies

The most common imaging findings in fascioliasis are summarized in Table 45.3.

ABDOMINAL ULTRASOUND. Findings in the acute phase include focal areas of increased echogenicity, multiple nodular or irregular lesions of variable echogenicity, or a single, complex mass in the liver that resembles malignancy mimicking malignancy (Cosme et al, 2001, 2003). In frequent travelers, an abnormal liver US showing a complex cystic lesion warrants a workup for fascioliasis or other parasitic disease, such as echinococcal infection. In the chronic phase, US is even less specific, although the adult parasites can be visualized in the gallbladder (Bonniaud et al, 1984; Kabaalioglu et al, 1999; Gonzales-Carbajal et al, 2001). Overall, the detection rate is extremely low if used as the sole diagnostic tool. For instance, of 76 subjects with chronic fascioliasis evaluated by means of abdominal US, only 11 patients (14%) had visualized parasites, and in only two cases (2.6%), the parasites were spontaneously moving into the gallbladder. Therefore, the detection-rate of *F. hepatica* chronic infection by US is disappointingly low (Richter et al, 1999) and not specific (Turhan et al, 2006).

COMPUTED TOMOGRAPHY. The most common computed tomography (CT) findings include multiple hepatic metastasis-like lesions that change in position, attenuation, and shape over time (Marcos et al, 2008). Initial lesions may be easily confused with hepatic metastases. Other findings are hepatomegaly, tract-like hypodense lesions with subcapsular location, subcapsular hematoma, and cystic calcifications (Marcos et al, 2008; Loja et al, 2003). The hepatic lesions correlate with the time of infection. Early infection is associated with contrast enhancement of the Glisson capsule as a result of inflammation stimulated as the juvenile parasite penetrates the liver capsule. This occurs in the early stage of the acute infection (first month of infection). In the intermediate stage (after the first month), multiple hypodense nodular areas (abscesslike lesions) or low-density serpiginous, tortuous, tunnel-like branching lesions that range from 2 to 10 mm are created by parasite migration through the liver and are typically visualized in the subcapsular region (MacLean & Graeme-Cook, 2002; Gonzalo-Orden et al, 2003). In the late stage (≥3 months), a necrotic granuloma is seen that appears as a single, non–contrast-enhanced hypodense irregular mass in the liver parenchyma, more central than peripheral (Kim KA et al, 1999; Noyer et al, 2002). Finally, part of the differential diagnosis of liver calcification is fascioliasis, which generally means an old infection of at least 6 months' duration. Although the characteristics of these cyst calcifications seem to be unique to fascioliasis, this finding adds a new agent to the list of infectious diseases associated with tissue calcifications, such as echinococcosis, paragonimiasis, histoplasmosis, toxoplasmosis, and others.

MAGNETIC RESONANCE IMAGING (MRI). Only a few cases visualized on MRI imaging have been reported. T2-weighted turbo spin-echo MRI showed a homogeneous hyperintense area in a subcapsular location containing multiple hypointense areas. A T1-weighted three-dimensional gradient-echo image displayed homogeneous contrast enhancement (Orlent et al, 2007). The hypodense lesions observed in the CT scan are of hypointense signal in T1-weighted imaging and hyperintense in T2 (Kabaalioglu et al, 2000; Aksoy et al, 2006).

Diagnosis

The diagnosis of the acute phase of fascioliasis is confirmed by serology or response to therapy. Accurate identification of early disease has been difficult because of the lack of a confirmatory test; the serologic test that requires medium-high technology is not available in most endemic areas. Nonetheless, if the pretest probability or clinical suspicion is unequivocally high, an antiparasitic trial is warranted. Diagnostic criteria are significant clinical improvement and decreasing levels of eosinophils in the 3 to 5 days after a trial of triclabendazole (Marcos, 2008b). The results of the serology and stool sampling, the possible stage of the infection, and the clinical significance are illustrated in Figure 45.4.

ACUTE PHASE. Among the serologic tests developed in the last few years, an enzyme-linked immunoabsorbent assay (ELISA) detects the antibodies against cathepsin L1 and is highly

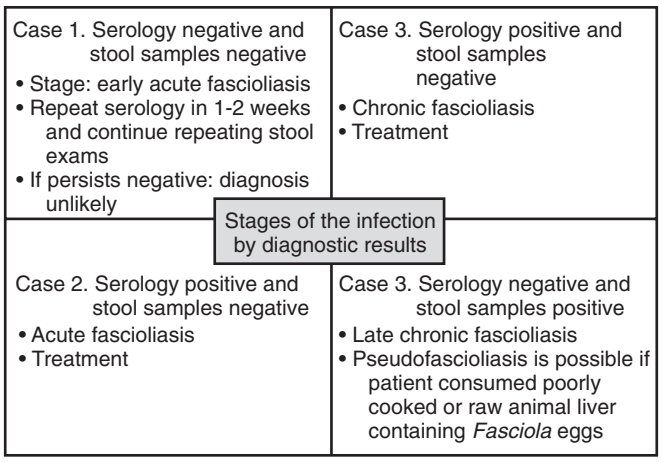


FIGURE 45.4. Most common possible scenarios of diagnostic results in fascioliasis. Cases 2 and 3 are the most common found in clinical practice. Cases 1 and 4 are uncommon.

sensitive and specific for the acute phase of fascioliasis. It is also called *Fas2-ELISA* (cathepsin L1–based antibody), and it is more specific than Western blot and Arc II (Espinoza et al, 2005, 2007). This ELISA has been tested in 634 infected children from endemic areas in Peru and has been found to have a sensitivity of 92.4% and a specificity of 83.6%, with a negative predictive value of 97.2% (Espinoza, 2007). Acute *F. hepatica* infection must be considered in patients with eosinophilia, prolonged fever, abdominal pain, multiple hepatic abscesses, or metastases-like lesions in the peritoneum or liver before starting multiple diagnostic tests. Recognizing the clinical scenario early may allow timely and noninvasive identification of this infection.

CHRONIC PHASE. The gold standard test for the chronic infection is the visualization of the parasite eggs in the stool of the host. A serologic test is used when an adequate stool test is persistently negative despite a high pretest probability. A sedimentation technique must be performed on serial stool specimens (at least three) from different days to increase the likelihood of detecting the eggs in the stools, and an experienced technician is required. The intermittent deposition of parasite ova in the biliary duct can decrease the sensitivity of the sedimentation technique. Again, a high pretest probability warrants a trial of triclabendazole. The sedimentation technique that can be performed in any laboratory in the world is the rapid sedimentation technique (RST) described by Lumbreras and colleagues (1962) in Peru. This test is inexpensive, easy to perform, and highly sensitive, with a higher sensitivity than the ether-formalin concentration method (Marcos et al, 2007a). The Kato-Katz technique may be used to measure the intensity of infection (Katz et al, 1972), and it can be also helpful for the diagnosis.

***Fasciola* and Liver Fibrosis.** *F. hepatica* infection causes bile duct hyperplasia (Hamir & Smith, 2002), increased levels of proline (Campbell et al, 1981; Wolf-Spengler & Isseroff, 1983), and type I and III collagen in the liver (Mark & Isseroff, 1983); these anomalies are similar to the progression observed in cirrhosis and other pathologic conditions, including wound healing. However, few studies have attempted to identify factors associated with liver fibrosis, which is a significant clinical outcome of the infection (Marcos et al, 2007c; Perez et al, 1999; Phiri et al, 2006; Shirai et al, 2006). In addition, liver cirrhosis has been reported in both children and adults with fascioliasis (Almendras-Jaramillo et al, 1997; Heredia et al, 1984; Marcos et al, 2005a; Sanchez-Sosa et al, 2000). In cirrhotic patients in an endemic country, 9.1% were positive for Fas2-ELISA (Marcos et al, 2009b). In conclusion, the chronicity of the infection can lead to liver fibrosis.

DIAGNOSIS OF FASCIOLIASIS BY SURGERY. In the cases reported in the literature, the majority that underwent a surgical or invasive procedure were patients in the chronic phase of the infection whose initial clinical problem was biliary obstruction and choledocholithiasis (Kim et al, 2006). The detection rate of the adult parasite in operations of the biliary tract is low. In a series of 162 cases of cholecystectomy in an endemic area, only 1.2% had *F. hepatica* in the gallbladder (Alban et al, 2002); however, several cases have been diagnosed in the operating room incidentally.

Because the chronic phase may be seen with or without very mild eosinophilia, a high level of suspicion should always be maintained in cases of biliary obstruction in endemic areas or in immigrants or travelers from endemic areas. Nine cases have been diagnosed and managed by endoscopic retrograde cholangiopancreatography (ERCP), and only two had mild eosinophilia (Bahçecioglu et al, 2008; Diaz Fernandez et al, 2005; Gulsen et al, 2006). A single dose of triclabendazole must be given after the procedure to ensure elimination of any parasites missed by endoscopy or remaining in other anatomic locations. The adult parasite can also be found during an elective laparoscopic cholecystectomy (Bulbuloglu et al, 2007).

Even in highly endemic areas, the diagnosis can be missed initially, and cases of parasites accidentally obstructing percutaneous biliary drainage catheters have been reported (Maco et al, 2003). Clinical judgment is mandatory when biliary obstruction is associated with cholangitis that requires surgical intervention. In cases of biliary obstruction, both surgical intervention to manage the obstruction and antiparasitics are the cornerstones in the treatment when clinically indicated.

Interestingly, fascioliasis can be misdiagnosed as echinococcal because the former may have a strong cross-reactivity in the ELISA. Patients may end up with surgical intervention to remove the pseudocyst of *Echinococcus*, when parasites of *F. hepatica* were causing an intrahepatic cyst (Das et al, 2007). In other situations, adult parasites were found when trying to remove a possible malignancy or metastasis-like lesion from the colonic wall (Makay et al, 2007), neck (Marcos et al, 2009a), epidural space (Vatsal et al, 2006), eye (Dalimi & Jabarvand, 2005), and breast (Naresh et al, 2006).

When fascioliasis affects the pancreatic duct (Parsak et al, 2007), the management, either surgical or conservative, should be individualized. However, when indicated, drainage can be a reasonable approach, followed up by a trial of triclabendazole with antispasmodics to reduce the severe abdominal pain experienced after the death of the parasite. Complications such as pancreatic duct obstruction and consequent pancreatitis may be life threatening, but they are rare (Echenique-Elizondo et al, 2005).

In cases of cholangitis (Ait Ali et al, 2002), emergent percutaneous drainage is recommended, because despite the antiparasitic medication, the dead parasites will remain in the biliary duct for a few days before being released, thus interrupting the

drainage through the ampulla of Vater. The most common organisms identified in an animal model were *Escherichia coli* (45%), *Enterococcus faecalis* (45%), and *Klebsiella pneumonaie* (10%) (Valero et al, 2006). No data in humans are available, but the fact that *E. faecalis* is present in almost half of the cases of bacterobilia in the animal model should be taken with special consideration for antibiotic choice. It is recommended that a single antibiotic be given, such as a β-lactam/lactamase inhibitor for mild to moderate infection or a carbapenem for severe infection. A combination therapy of cephalosporin or fluoroquinolone is also acceptable. Ideally, antimicrobial therapy should be adjusted according to the organism identified, with susceptibilities to common antimicrobials.

The literature reveals several diagnoses of fascioliasis that have been made in the operating room. Although an uncommon presentation in a nonendemic area, lack of familiarity by the clinician can underestimate the impact of fascioliasis.

In summary, a patient who comes from endemic areas and who presents with a clinical picture similar to acute cholecystitis, normal US, or abscesslike lesions by imaging, the diagnosis of fascioliasis should be considered. Furthermore, during a diagnostic laparoscopy, metastatic-like liver lesions with eosinophilia are strongly suggestive of acute fascioliasis.

Treatment

Triclabendazole is the treatment of choice for both phases of *Fasciola* infection (Keiser & Utzinger, 2007a). The cure rate exceeds 90% for acute stages after a single dose of 10 mg/kg (Marcos et al, 2009), and similar results have been obtained in the therapy of chronic infection (Apt et al, 1995; Talaie et al, 2004; El-Tantawy et al, 2007). This drug has a better absorption with a fatty meal, and the most frequent adverse event is biliary colic caused by the passage of dead or dying parasites through the bile ducts. Triclabendazole was introduced in the early 1980s for the treatment of *F. hepatica* infections in livestock, and it has been placed on the WHO List of Essential Medicines (http://www.who.int/medicines/publications/essentialmedicines/en/) because of its efficacy and cost effectiveness.

Treatment of fascioliasis with triclabendazole was shown to reduce the prevalence significantly, from 5.2% to 1.2% in 7 years (Abdussalam et al, 1995). However, the intensive use of triclabendazole has resulted in the development of resistance in animals (Mottier et al, 2006; Alvarez-Sanchez et al, 2006). On the other hand, in places where triclabendazole for humans is not available, the veterinary form can be effective as well. In Peru, a single dose of 10 mg/kg cured 96%, whereas 10 mg/kg for 2 days cured 100% with no major adverse effects registered (Terashima et al, unpublished data). The most important adverse effect was abdominal pain or biliary colic during the first week of treatment. This pain is likely caused by the passage of dead or dying parasites through the bile ducts (Millan et al, 2000; Richter et al, 1999). Antispasmodics may decrease or completely alleviate the transitory episodes of abdominal pain and should be used in most cases at the beginning of the therapy or even before the first dose.

A single dose of triclabendazole is effective and tolerable, without major side effects, and it may also be used as a diagnostic tool (Marcos et al, 2007c). However, given the unlikelihood of any new drugs against *F. hepatica* being developed in the foreseeable future, the emergence of resistance represents an important threat (Alvarez-Sanchez et al, 2006), although resistance in humans has not been reported.

Many years ago, parenteral dehydroemetine at doses of 1 mg/kg for 10 days was used. Then, bithionol was applied at doses of 30 to 50 mg/kg every third day for a total of 10 to 15 doses, although it is cardiotoxic and very expensive. Other drugs, such as nitazoxanide, have been evaluated for fascioliasis, but cure rates have been disappointingly low. Adult patients who received a 7-day course of nitazoxanide had a cure rate of 60%, but the rate was only 40% in children (Favennec et al, 2003). Because of this, and because of the increasing triclabendazole resistance in animals, new drugs have been evaluated and tested in animals with fascioliasis. For instance, artesunate, artemether, and OZ78 have fasciocidal properties in animals, and they are promising drugs for the near future, should resistance to triclabendazole become a problem (Keiser et al, 2007a, 2009). Albendazole, metronidazole, and praziquantel are not recommended for fascioliasis treatment.

Future Directions and Vaccines

Because fascioliasis constitutes a major economic impact, development of effective vaccines would be an important advance. Preliminary studies in animals have reported significant advances (McManus & Dalton, 2006; Spithill & Dalton, 1998). Cysteine proteinases released by *F. hepatica* play a key role in parasite feeding and migration through host tissues and in immune system evasion. A recombinant cysteine proteinase (CPFhW) expressed as inclusion bodies in *E. coli* was used for enteral vaccination of rats against fascioliasis. In that study, oral vaccination reduced the parasite burden by 78% to 80% after a challenge with metacercariae (Kesik et al, 2007). The glutathione transferase superfamily (GST) from liver fluke plays phase II detoxification and housekeeping roles and has been shown to contain protective vaccine candidates (Chemale et al, 2006). Promising future research will yield meaningful immunologic targets to prevent the infection, especially in the well-recognized endemic areas and particularly in children, but so far the vaccines are targeted only to animals.

Clonorchiasis and Opisthorchiasis

Liver fluke infection caused by trematodes belonging to the family Opisthorchiidae—*Opisthorchis viverrini*, *O. felineus*, and *Clonorchis sinensis*—is a major public health problem in many parts of the Far East, Southeast Asia, and Eastern Europe. Clonorchiasis is an infection caused by *Clonorchis sinensis*, the Chinese or Oriental liver fluke, whereas opisthorchiasis is caused by *O. viverrini* and *O. felineus* (class Trematoda). Migration and global tourism are responsible for cases diagnosed in areas where the disease is not endemic.

C. sinensis and *O. viverrini*, small Asian liver flukes 8 to 15 mm in length, are very similar in adult morphology and genetics but differ in geographic distribution (Park, 2007). There are 601 million and 79.8 million people at risk of infection with *Clonorchis* and *Opisthorchis*, respectively, and *C. sinensis* is endemic in northeast China, southern Korea, Japan, Taiwan, northern Vietnam, and the far eastern part of Russia (Rim, 2005), and *O. viverrini* is endemic in Laos, Thailand, Vietnam, and Cambodia. *O. felineus* infection is the most prevalent foodborne liver fluke infection of humans in Russia, Ukraine, and Kazakhstan. In Thailand, approximately 6 million people are infected with *O. viverrini* (Kaewpitoon et al, 2008). In China, *Clonorchis* infections have more than tripled over the last decade, with 15 million people infected in 2004 (Lun et al, 2005).

Similar to fascioliasis, the geographic pattern of these small flukes is not uniform. For instance, in Thailand, the greatest prevalence of opisthorchiasis is in the north (19.3%) and northeast (15.7%) compared with the central (3.8%) and southern regions (0%). In general, the infection is acquired by eating raw or uncooked cyprinoid fish products in rural areas or dishes such as koi-pla (Sayasone et al, 2007). Some cases are commonly documented in North America, mainly imported by Asian immigrants.

Life Cycle

Fish-borne trematodes have a complicated life cycle with two intermediate hosts. Starting from a human host, the adult worms deposit fully developed eggs; the eggs are then passed to the environment through the feces, and they must get into water to hatch and to infect their first intermediate host, a freshwater snail. After being ingested by a suitable snail, the eggs release miracidia, which undergo several developmental stages in the snail: as sporocysts, redia, and cercaria. The snail intermediate hosts for *Opisthorchis* are *Bithynia goniompharus, B. funiculata, and B. siamensis. Parafossarulus manchouricus* often serves as a first intermediate host for *C. sinensis,* and snail hosts also include other *Bithynia*, *Tarebia*, *Alocinma,* and *Bulimus* species. Once inside the snail's body, the miracidium hatches from the egg and parasitically grows inside of the snail, where it develops into a sporocyst that houses the asexual reproduction of redia, the next stage. The redia themselves house the asexual reproduction of free-swimming cercaria. This system of asexual reproduction allows for an exponential multiplication of cercaria individuals from one miracidium. Once the redia mature, having grown inside the snail body until this point, they actively bore out of the snail body into the freshwater environment and seek out fish. Cercariae are released from the snail and then penetrate freshwater fish—the second intermediate host (*Cyclocheilichthys* and *Puntius* spp., *Hampala dispar*), encysting as metacercariae in the muscles or under the scales. Once inside the fish muscle, the cercaria creates a protective metacercarial cyst with which to encapsulate their bodies. This protective cyst proves useful for when the fish muscle is consumed by a human or other host, such as a cat, dog, pig, or any other fish-eating mammal. The acid-resistant cyst enables the metacercariae to avoid being digested by the gastric acids and allows them to reach the small intestine unharmed.

Reaching the small intestine, the metacercariae navigate toward the human liver—the final habitat. In contrast with the larger *F. hepatica* fluke, metacercariae of *Opisthorchis* and *Clonorchis* migrate through the ampulla of Vater after excysting in the duodenum; they then travel into the bile ducts, where they mature into adult worms within 4 weeks and deposit yellow, operculated eggs. The parasites may live for up to 45 years in the liver of a human host, producing 1000 to 2500 eggs per day. The adult flukes, measuring 10 to 25 mm by 3 to 5 mm, reside in medium-sized and small intrahepatic bile ducts and, occasionally, in the extrahepatic bile ducts, gallbladder, and pancreatic duct.

Clinical Manifestations

Clonorchiasis and opisthorchiasis infections are associated with a number of hepatobiliary diseases but mainly with disease in the biliary tract, because these flukes do not penetrate the liver parenchyma as they do in fascioliasis. The frequency and types of pathology and clinical disease seem to differ for *C. sinensis* and *O. viverrini*. For example, cholelithiasis is one of the more serious complications of clonorchiasis but is a rare complication of opisthorchiasis. In both species the prominent inflammatory process within the biliary tract is the main pathologic characteristic of these infections that can sometimes lead to cholangiocarcinoma, especially with *O. viverrini*.

Flukes can occasionally gain access to the pancreatic tract, where they can cause obstruction and pancreatitis. The pathologic and clinical consequences of opisthorchiasis are related to the intensity and duration of cumulative infections. Because adult flukes are long lived, they can produce eggs and symptoms long after the human host has emigrated from the area. Most people with these Asian fluke infections have no symptoms, and only 5% to 10% of those heavily infected have nonspecific chronic symptoms such as right upper quadrant abdominal pain, flatulence, and fatigue. Cholangiocarcinoma is a known complication.

***Clonorchis sinensis*.** Acute infection by *C. sinensis* is usually asymptomatic, but some patients may have fever, rash, malaise, and right upper quadrant abdominal discomfort. Chronic infection reflects the worm burden and may appear as recurrent pyogenic liver cholangitis (see Chapters 43 and 44), cholecystitis (see Chapter 31), obstructive jaundice, hepatomegaly, cholecystitis, multiple hepatic tumours (Liao et al, 2006), and cholelithiasis (Park & Son, 2008; Stunell et al, 2006). An association between clonorchiasis and cholangiocarcinoma has also been reported (Choi et al, 2006). Severe *C. sinensis* infection is a significant risk factor for malignant changes in bile ducts and surrounding liver tissues occurring as a result of direct contact with *C. sinensis* worms and their excretory-secretory products.

***Opisthorchis viverrini*.** In acute *O. viverrini* infection, only 5% to 10% of heavily infected patients have nonspecific symptoms, such as right upper quadrant abdominal pain, flatulence, fatigue, and a hot sensation over the abdomen. In the chronic phase, mild hepatomegaly occurs, mainly in more heavily infected patients (egg counts >10,000 eggs/g). Jaundice and splenomegaly are not observed, but intrahepatic duct stones and recurrent suppurative cholangitis are common manifestations of opisthorchiasis. Whenever jaundice and ascending cholangitis are detected, fluke-related cholangiocarcinoma should be suspected.

***Opisthorchis felineus*.** Infection with *O. felineus* usually follows consumption of raw, slightly salted, and frozen fish ("stroganina"). Acute symptoms occur 2 to 4 weeks after eating raw fish. These include high-grade fever, nausea, vomiting, abdominal pain, malaise, arthralgias, lymphadenopathy, and skin rash (Tselepatiotis et al, 2003). Peripheral eosinophilia is a common finding, especially during the first 2 to 6 weeks of the infection, together with raised liver enzymes. In chronic infection, eosinophilia is usually milder, but patients may present with suppurative cholangitis and liver abscess as a result of biliary obstruction.

Consequences of Chronicity of Infection

Carcinogenesis associated with helminth infections is a complex process that may involve several different mechanisms, but chronic inflammation is a key feature. The human liver fluke *O. viverrini* infects millions of people throughout Southeast Asia and is a major cause of cholangiocarcinoma, or cancer of the

bile ducts. The mechanisms by which chronic infection with *O. viverrini* results in cholangiocarcinogenesis are multifactorial, but one such mechanism is the secretion of parasite proteins with mitogenic properties into the bile ducts, driving cell proliferation and creating a tumorigenic environment. A possible pathway for the development of cholangiocarcinoma is the presence of Ov-GRN-1, a major growth factor present in *O. viverrini* excretory-secretory products that induces proliferation of host cells, which supports a role for this fluke protein to establish a tumorigenic environment.

In general, these flukes cause inflammation around the biliary tree that leads to severe hyperplasia of epithelial cells, metaplasia of mucin-producing cells in the mucosa, and progressive periductal fibrosis. There are clear associations between *O. viverrini* infection and cholangiocarcinoma in the context of the intensity of infection, parasite-specific antibody response, and abnormalities of the biliary tract.

The higher the intensity of anti–*O. viverrini* antibody titers, the higher the risk for cholangiocarcinoma (Honjo et al, 2005). The International Agency for Research on Cancer recognizes this parasite as a category I carcinogen. The lesions that predispose to malignant changes in *O. viverrini* are evident as a dilation of subcapsular medium and large bile ducts with a prominent fibrotic wall, periductal inflammatory cell infiltration, goblet cell metaplasia, epithelial and adenomatous hyperplasia, and periductal fibrosis. The pathogenesis of *O. viverrini*–mediated hepatobiliary changes may be due to mechanical irritation or to its metabolic products (Sriamporn et al, 2004). Several N-nitroso compounds and their precursors occur at low levels in fermented food, such as preserved mud fish paste (*pla ra*), a condiment ubiquitous in the cuisine of northeastern Thailand and Laos (Sripa et al, 2007). The study of *O. viverrini* genes should expedite molecular studies of cholangiocarcinogenesis and accelerate research focused on developing new interventions, drugs, and vaccines that might help in controlling *O. viverrini* and related flukes (Laha et al, 2007). Similarly, recent studies show a strong association between *C. sinensis* and the development of cholangiocarcinoma (Choi et al, 2006). For instance, a recent epidemiologic study in Korea correlates the prevalence of *C. sinensis* and the incidence rate of cholangiocarcinoma: *C. sinensis* prevalence was 2.1% in Chuncheon, 7.8% in Chungju, and 31.3% in Haman; cholangiocarcinoma incidence rate was 0.3, 1.8, and 5.5 per 100,000 population, respectively (Lim et al, 2006). Hepatocellular carcinoma also has been associated with clonorchiasis, along with hepatitis B virus and alcohol consumption as cofactors (Tan et al, 2008). It seems plausible that cholangiocarcinogenesis associated with clonorchiasis is the cumulative end result of a multifactorial carcinogenic mechanism, although the mechanisms involved are not completely understood.

Improving diagnosis with new serologic tests may be helpful, but such tests cannot distinguish between recent or past infection. Currently, the Ov-CP-1–based ELISA shows a sensitivity of 95% and specificity of 96% in serum coinfected with hookworm, minute intestinal fluke, *S. stercoralis*, *Taenia* spp., *Giardia lamblia,* and *E. coli* infection (Watthanakulpanich et al, 1997). The sensitivity and specificity are similar to other studies using an ELISA based on recombinant trematode cysteine protease such as *C. sinensis* (sensitivity 81.3% to 96%, specificity 92.6% to 96.2%) (Nagano et al, 2004; Zhao et al, 2004).

Human clonorchiasis and opisthorchiasis are primarily diagnosed by the detection of eggs in feces. The Kato-Katz method is accepted as the best for fecal examination, although sometimes the eggs may not be detected because of biliary obstruction or intermittent egg excretion similar to that encountered with fascioliasis. In light infections, with less than 10 adult worms in the biliary tract, a polymerase chain reaction (PCR) detecting the DNA of the adult parasite in stools may be helpful (Duenngai et al, 2008). Intrahepatic duct dilation is the most common finding on US imaging (76% of patients), and increasing periductal echogenicity and gallbladder sludge are seen only in patients with heavy infection (Choi et al, 2005). Recently, Ruangsittichai and colleagues (2006) reported high sensitivity and specificity using a recombinant eggshell protein with potential for the serodiagnosis of human opisthorchiasis. However, detection of *O. viverrini* DNA is expensive and requires skillful personnel.

Treatment

Praziquantel, a derivative of pyrazino isoquinoline, is the drug of choice for *O. viverrini*, *O. felineus,* and *C. sinensis* treatment. For *O. viverrini*, a single dose (40 to 50 mg/kg) of praziquantel treatment is indicated, with a cure rate between 91% and 97%. For clonorchiasis, the recommended dose of praziquantel is 25 mg/kg three times at 5-hour intervals in 1 day (total dose 75 mg/kg), with a cure rate of 83% to 85% (Rim, 2005).

Future Directions

Opisthorchis and *Clonorchis* are medically important foodborne trematodes endemic in Asian countries, and infection is associated with cholangiocarcinoma and other hepatobiliary diseases. The epidemiology is found in some rural areas because of the tradition of eating raw or uncooked fish products.

Other Parasitosis of the Biliary Tract

Ascaris lumbricoides infections are endemic in tropical countries. *A. lumbrocoides* may occasionally migrate from its normal habitat in the small bowel to other locations, such as the biliary tract or pancreatic duct. Because of the high intensity of infection in endemic areas, *A. lumbrocoides* is more often seen as a clinical picture of jaundice, abdominal right upper quadrant pain, and fever, although it can occasionally cause biliary obstruction and result in obstructive jaundice or pancreatitis.

Occasionally, ERCP may diagnose parasitosis of the biliary tract. For example, of 3548 ERCPs performed for extrahepatic cholestasis, cholangitis, and choledocolithiasis (see Chapters 31, 43, and 44) in a moderate endemic area in Eastern Europe, only 24 (0.66%) were found to show biliary parasitosis, such as hydatid cystic disease (n = 16; see Chapter 68); in addition, 8 showed partial obstruction of the biliary tract, and 8 had ruptured cysts; *F. hepatica* (n = 4) and *A. lumbricoides* (n = 4) were also found. Endoscopic sphincterotomy was performed, after which the choledochus was examined carefully using a balloon catheter and basket procedure. ERCP is very useful in the therapy of biliary parasitic infections. The treatment for *Ascaris* in the biliary tract is elimination of the adult parasite through the endoscope, followed up by a single, oral dose of albendazole (400 mg).

Hepatic hydatid cyst rupture into the biliary tree occurs in 5% to 25% of patients and constitutes the most common complication of hepatic echinococcal cysts (see Chapter 68). In this setting, ERCP plays a pivotal role in the therapeutic management of the disease, even as a definitive therapy in some cases.

However, oral albendazole (400 mg) twice a day can be started prior to the procedure. Typically, the ERCP will show a global dilation of the biliary tree with several laminated defects occupying the distal common bile duct with multiple white germinative membranes; a sphincterotomy will help eliminate the membranes causing the obstruction. The treatment of choice for hepatic echinococcosis usually involves antihelmintic therapy and surgical resection or percutaneous aspiration. However, when hydatid material, comprising daughter cysts and hydatid membranes, is released into the biliary tree through a fistulous tract, an ERCP is mandatory before surgery to ensure the retrieval of hydatid biliary material to treat or prevent biliary obstruction complications, mainly acute cholangitis. Regardless of management, antihelmintic drugs should always be started prior to endoscopic or surgical therapy to inactivate intracystic material and minimize allergic disorders or postoperative recurrence.

References are available at expertconsult.com.

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CHAPTER 46

Bile duct cysts in adults

Saboor Khan and David M. Nagorney

BILE DUCT CYSTS

Bile duct cysts typically are a surgical problem of infancy or childhood (Altman, 1994); however, in nearly 20% of patients, the diagnosis is delayed until adulthood. Although clinically similar, the presentation and therapeutic strategies for bile duct cysts in adults may differ substantially from those of younger patients. In contrast to the pediatric experience, adult patients have an increased rate of associated hepatobiliary pathology (Nagorney et al, 1984a; Powell et al, 1981; Rattner et al, 1983), and they often are first seen with complications of previous cyst-related procedures (Gigot et al, 1996; Nagorney et al, 1984a; Ono et al, 1982; Todani et al, 1984a). The surgical management of bile duct cysts in adults is thus complicated by coexisting hepatobiliary disease and the added technical difficulties of reoperative biliary surgery. Despite the heterogeneity of the disease and the absence of clinical trials, a consensus on the management of extrahepatic bile duct cysts has been established: excision is best. However, the management of intrahepatic bile duct cysts remains problematic, and the method of choice for reestablishing bilioenteric continuity after excision is debatable. This chapter examines the spectrum of hepatobiliary pathology encountered in adults with bile duct cysts and describes the alternative surgical approaches for managing such patients.

DIAGNOSIS

Classification

Bile duct cysts are classified on the basis of site, extent, and shape of the cystic anomaly of the ductal system. Although the term *choledochal cyst* is often used, *bile duct cyst* is semantically more appropriate because cystic dilation can occur anywhere throughout the biliary ductal system, not just in the common bile duct (choledochus). The first coherent classification of extrahepatic bile duct cysts was proposed by Alonso-Lej and colleagues in 1959. Cysts were classified into three types: *type I* is a fusiform or saccular dilation of the common hepatic and common bile duct, *type II* is a supraduodenal diverticulum of the common hepatic or common bile duct, and *type III* is an intraduodenal diverticulum of the distal common bile duct or choledochocele. Although this classification did not include intrahepatic bile duct cysts, this simple and practical scheme has provided the basis for all other classification systems.

The recognition of intrahepatic bile duct cysts prompted modification of the Alonso-Lej classification system, and in 1958, Caroli and colleagues described the entity of multiple intrahepatic bile duct cysts in the absence and presence of extrahepatic cysts. Although initially described as an entity of multiple saccular dilations of only the intrahepatic ducts, the term *Caroli disease* has been broadly applied to describe any patient with intrahepatic bile duct cysts, regardless of the presence of extrahepatic bile duct cysts or the shape of the intrahepatic cysts (Dayton et al, 1983). Caroli disease represents a spectrum of diseases that may include such variants as cysts with congenital hepatic fibrosis or Grumbach disease (see Chapter 70A; Grumbach et al, 1954). Todani refined the classification system of bile duct cysts by combining the Alonso-Lej classification and the variants of Caroli disease (Todani et al, 1977). The comprehensive Todani classification system is shown in Fig. 46.1.

Matsumoto also modified the Alonso-Lej classification system based not only on the location of the cyst but also on the configuration of cysts (Matsumoto et al, 1977a). To date, clinical management of bile duct cysts is dictated by cyst location, not configuration; therefore there is little clinical rationale for adoption of the more detailed classification scheme (Kamisawa et al, 2005; Komi et al, 1992; Matsumoto et al, 1977b), although further additions to the Todani classification have been suggested (Calvo-Ponce et al, 2008; Conway et al, 2009).

ETIOLOGY

Multiple theories have been proposed to explain the origin of bile duct cysts. The most widely accepted hypothesis is that cystic dilation of the bile ducts is related to an anomalous arrangement of the pancreaticobiliary ductal junction (Babbitt,

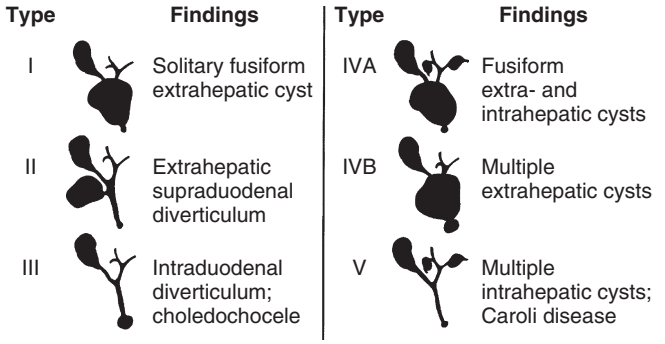


FIGURE 46.1. Classification of bile duct cysts.

1969; Cheng et al, 2004; Komi et al, 1992; Okada et al, 1990; Todani et al, 1984b; Wiedmeyer et al, 1989). The pancreaticobiliary junction is proximal to the sphincter of Oddi (Fig. 46.2) (Nagata et al, 1986). An anomalous pancreaticobiliary junction is often associated with a long common channel that predisposes to reflux of pancreatic juice into the biliary tree, leading to inflammation, ectasia, and, ultimately, to dilation. This postulate has been supported by biliary manometric studies (Iwai et al, 1986), high concentrations of pancreatic enzymes in cyst fluid (Todani et al, 1990), and histopathologic studies of ductal epithelial hyperplasia, round cell infiltration, and marked ductal fibrosis (Oguchi et al, 1988). Moreover, experimental canine studies of pancreaticocholecystostomy and pancreaticocholedochostomy have resulted in cystic dilation of the extrahepatic bile duct (Oguchi et al, 1988; Ohkawa et al, 1981). Pancreaticobiliary maljunction, or *anomalous union*, defined as union of the pancreatic and biliary duct outside of the duodenal wall, has also been implicated in biliary tract cancer even in the absence of a biliary cyst (Funabiki et al, 2009; Horaguchi et al, 2005).

Reports of choledochal cysts of the same type in family members suggest that a hereditary factor may contribute, albeit rarely, to bile duct cysts (Iwafuchi et al, 1990). Finally, oligoganglionosis in the distal neck of the cyst may account for some bile duct cysts. The reduction in ganglion cells in the narrow portion of the cyst wall may be the biliary equivalent of Hirschsprung disease of the colon (Kusunoki et al, 1988).

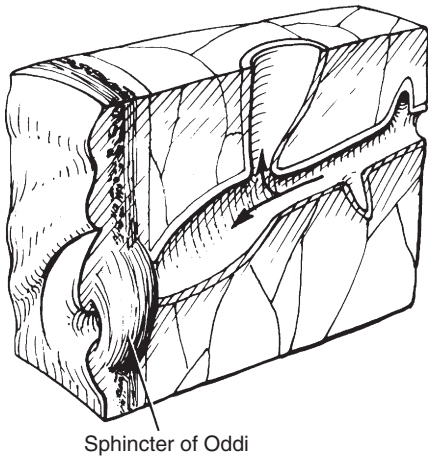


FIGURE 46.2. A long common channel, as shown in this figure of the pancreaticobiliary ductal confluence, is the most accepted cause of choledochal cysts.

DEMOGRAPHICS

Bile duct cysts are an uncommon finding, with fewer than 4000 cases reported (Flanigan, 1975; Powell et al, 1981; Yamaguchi, 1980). Estimates of the actual clinical incidence range from one in 13,000 to one in 2 million patients (Olbourne, 1975), and biliary cysts account for approximately 1% of all benign biliary disease (Saxena et al, 1988). The estimated prevalence of bile duct cysts by type (Todani classification), based on a review of the current literature, is shown in Table 46.1. The true prevalence of bile duct cysts by current classification schemes is underestimated here because classification is often not detailed. The frequency of bile duct cyst in decreasing order is the type I choledochal cyst (79%), followed by type IV (13%), then type III, or choledochocele (4%), and type II (2.6%). Multiple intrahepatic bile duct cysts without an extrahepatic component (Caroli disease) occur in fewer than 1% of all patients with biliary cystic disease. The distribution of cyst types encountered in adults is similar to that in infants and children (Gigot et al, 1996; Nagorney et al, 1984a; Ono et al, 1982), except type IV cysts are more frequent in adults (Todani et al, 1978, 1984a).

A marked population prevalence has been seen in Japan (Flanigan, 1975; Powell et al, 1981; Yamaguchi, 1980), where more than one third of reported cases have occurred. Although the number of reported cases has increased recently, this finding probably reflects advances in diagnosis through improvements in hepatobiliary imaging rather than a true increase in incidence.

A female preponderance among patients with bile duct cysts is well known, regardless of cyst type. In Flanigan's (1975) collected series of 820 cases, 81% of the patients were female. A similar female/male ratio has been found in adults (Powell et al, 1981). Current theories on the pathogenesis of bile duct cysts have not implicated sex hormones or congenital intrauterine endocrine disturbances as possible factors.

CLINICAL FEATURES

Choledochal cysts may remain asymptomatic for many years. Initial clinical presentation in adulthood (age >16 years) occurs in fewer than 20% of all patients with common duct cysts (Flanigan, 1975). Diagnosis may be an incidental finding on imaging studies for unrelated processes. If symptomatic, bile duct cysts usually present with symptoms mimicking calculous biliary tract disease, regardless of cyst type. Symptoms are typically intermittent, recurrent epigastric or right hypochondrial pain, abdominal tenderness, fever, and mild jaundice—the most common initial findings. The pain may radiate to the right infrascapular region or to the mid back, and it generally persists for hours. Abdominal pain or discomfort is often overshadowed by fever and rigors, which may occur repeatedly for several days. An abdominal mass is uncommon in adults; however, if a mass is present, cyst-associated malignancy must be strongly suspected. Biliuria heralds the onset of clinical jaundice. Nausea, vomiting, and anorexia may accompany other symptoms; if cholangitis persists, the jaundice deepens and overt signs of sepsis may evolve.

Approximately 15% of adults with common duct cysts present with overt evidence of cirrhosis or hepatic fibrosis from

Table 46.1

Prevalence of Bile Duct Cysts by Todani Classification: Literature Review of Cyst Type

Author, Year	I	II	III	IV	V
Alonso-Lej et al, 1959	86	4	4	–	–
Lee et al, 2004	86	2	5	–	–
Flanigan, 1975	659	23	42	19	–
Yamaguchi, 1980	682	18	12	166	–
Powell et al, 1981	255	7	13	60	–
Ono et al, 1982	21	–	–	1	–
Deziel et al, 1986	18	1	2	6	4
Nagata et al, 1986	21	–	1	5	–
Tan & Howard, 1988	31	0	1	2	1
Hopkins et al, 1990	5	–	–	2	–
Joseph, 1990	45	1	2	3	1
Lopez et al, 1991	15	2	5	1	–
Chijiiwa and Koga, 1993	26	2	–	18	–
Lipsett et al, 1994	22	1	2	17	–
Scudamore et al, 1994	8	–	1	14	–
Swisher et al, 1994	21	1	2	4	5
Hewitt et al, 1995	8	1	–	4	–
Stain et al, 1995	22	1	–	4	–
Chen et al, 1996	41	1	–	14	4
Gigot et al, 1996	19	1	–	11	–
Kouraklis et al, 1996	5	4	1	–	–
Benhidjeb et al, 1994	6	3	3	–	–
Chaudhary et al, 1997	9	–	–	7	1
Jesudason et al, 1997	10	–	–	4	–
Belli et al, 1998	8	–	2	3	–
TOTAL	2129	73	98	365	16
Percentage of total	79.4%	2.7%	3.7%	13.6%	0.6%

Subclassifications of type IV cysts generally are not reported.

chronic biliary obstruction. Such patients typically have had multiple operations for complications of type I or IVA cysts or Caroli disease. Hepatomegaly and splenomegaly are common in patients with cirrhosis and portal hypertension. Hematemesis, melena, and ascites may accompany portal hypertension; however, cholangitis remains the most common initial symptom complex in adults, whether or not cirrhosis is present. Interestingly, other signs of chronic liver disease—muscle wasting, fatigue, spider angiomas, and pruritus—are uncommon. Liver failure is seen late in Caroli disease.

Clinical pancreatitis is present in nearly 30% of patients with choledochal cysts (Nagorney et al, 1984a). In contrast to patients with cholangitis, patients with pancreatitis have more intense and prolonged epigastric pain and vomiting. Fever and jaundice are less prominent. Weight loss, although unusual, is noteworthy because nearly 70% of adults with this finding will harbor an associated bile duct malignancy (see Chapter 50B).

IMAGING

Accurate preoperative diagnosis can be achieved by using the routine diagnostic armamentarium for patients with suspected biliary tract disease: abdominal ultrasonography (US), computed tomography (CT), percutaneous transhepatic cholangiography (PTC), endoscopic retrograde cholangiopancreatography (ERCP), and magnetic resonance cholangiography (MRC) (Fig. 46.3). Current reviews of the diagnostic imaging modalities of bile duct cysts with representative images are referenced (Kim et al, 1995; Savader et al, 1991a, 1991b). Although hepatobiliary scintigraphy has also been useful in identifying bile duct cysts, its value is limited because the information is functional and not anatomic; it is therefore only complementary to US, CT, and direct cholangiography. In general, bile duct cysts are typically recognized serendipitously in adults, unless a past diagnosis had been established before adulthood.

The noninvasiveness and accuracy of US, combined with its ability to image adjacent viscera, support its use as the initial investigative procedure (see Chapter 13). Real-time US is favored because of its speed and ease of application. Moreover, the ability of real-time US to scan multiple planes adds a distinct advantage in defining the extent of the dilation. The sonographic features of choledochal cysts have been well defined for type I choledochal cysts and the variants of Caroli disease (Bass et al, 1977; Morgan et al, 1980; Todani et al, 1978; Young et al, 1990). US of type I cysts simply shows an irregular hypoechoic segmental dilation of the extrahepatic bile duct. Focal duct wall thickening or nodularity should arouse suspicion for cancer in an adult. Stones within the cyst can also be identified by typical

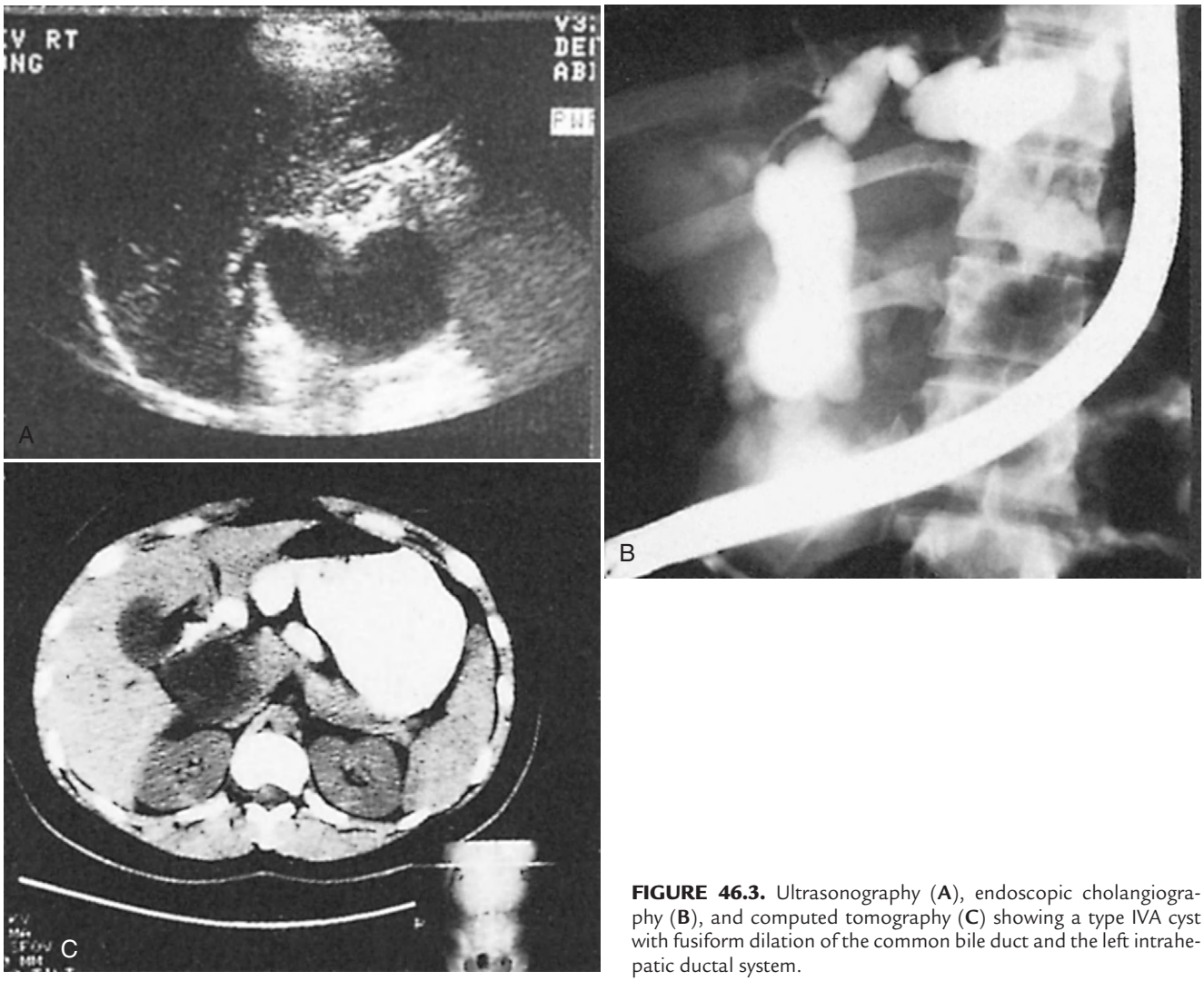


FIGURE 46.3. Ultrasonography (**A**), endoscopic cholangiography (**B**), and computed tomography (**C**) showing a type IVA cyst with fusiform dilation of the common bile duct and the left intrahepatic ductal system.

echogenic features and acoustic shadowing. The absence of septations on US will distinguish choledochal cysts from extrahepatic biliary tumors, such as cystadenomas (Nagorney et al, 1984b). Although the sensitivity of US is excellent for cysts involving the bile duct proximal to the pancreas, US is limited in adults in identifying choledochoceles because of the small size of these cysts and the frequency of bowel gas overlying the terminal common bile duct.

Caroli disease is clinically recognized by multiple cysts adjacent to the major intrahepatic bile ducts on US (Bruneton et al, 1983). Cysts may be unilobar or bilobar, and confirmation of communication of the intrahepatic cysts to the bile ducts can be confirmed by scintigraphy (Sty et al, 1978) or using CT with biliary contrast medium (Musante et al, 1982).

CT combined with intravenous cholangiography is useful for demonstration of cyst communication with the biliary tract (see Chapter 16; Hoglund et al, 1990). Intravenous cholangiography is performed 2 hours before abdominal CT scanning. The sensitivity of CT allows for accurate identification of accumulated contrast material within the cyst, if communication is present, and for accurate definition of the bile duct cyst (Tohma et al, 2009).

Direct cholangiography is the preferred diagnostic modality for accurate definition of the type of choledochal cyst (see Chapter 18). Indeed, cyst classification is based on cholangiographic features (Matsumoto et al, 1977a; Todani et al, 1977). All bile duct cysts communicate with the ductal system. Direct cholangiography is a prerequisite to operation because it has the advantage of being able to define the configuration and extent of the cyst; it also can identify ductal strictures, stones within the biliary and pancreatic ducts, and polypoid filling defects that suggest ductal malignancy. In addition, direct cholangiography is essential in defining the relationship of the distal bile duct in the type I cyst or the extrahepatic component of type IVA cyst to the pancreatic duct. The base of the extrahepatic choledochal cyst typically joins the pancreatic duct 2 to 4 cm proximal to the duodenum (Fig. 46.4), resulting in a long common channel (ampulla) (Jona et al, 1979; Komi et al, 1992; Ono et al, 1982; Rattner et al, 1983). The angle of fusion between the distal bile duct and pancreatic duct varies widely and has led to subclassifications of cyst type (Komi et al, 1992). Anatomic definition of the pancreatic biliary ductal junction is of key importance to avoid intraoperative damage of the pancreatic duct during cyst excision, recognize stones impacted within



FIGURE 46.4. Endoscopic retrograde cholangiopancreatogram shows the most frequent anomaly of the bile duct, cyst, and pancreatic duct anatomy with perpendicular fusion of the distal bile duct or cyst to the pancreatic duct and the presence of a long common channel.

the common channel or junction, and exclude distal tumors. Regardless of method, complete cholangiographic visualization of the entire biliary and pancreatic ductal systems is essential in patients with choledochal cysts because failure to recognize pancreatic duct anomalies or segmental areas of dilation within the liver parenchyma may lead to sepsis, subsequent cholangitis, pain, pancreatitis, and eventual reoperation.

There are advantages and disadvantages of PTC and ERCP for assessing choledochal cysts. Regardless of method, large volumes of radiographic contrast may be required for complete visualization of the bile ducts. Adults without previous cystenterostomy are probably best evaluated by ERCP because it provides better visualization of an abnormal pancreaticobiliary ductal junction (Savader et al, 1991b; Komi et al, 1992). Carcinoma can be excluded by biopsy or brush cytology, and intracystic stones can be extracted after papillotomy to relieve severe cholangitis before surgery. Endoscopy also allows visualization of the esophagus and stomach to exclude signs of portal hypertension. The endoscopist should attempt to examine the ductal bifurcation and the lining of the cyst, if a patent cystoduodenostomy allows introduction of the endoscope into the biliary tree. Endoscopically directed biopsy of intracystic masses should be performed to exclude malignancy. Obstructing balloons should be available to ensure that complete radiographic filling of the biliary tree is possible, especially in patients with prior cystoduodenostomy. Endoscopy of the cyst through a cystenterostomy may also permit diagnosis of intraductal stenoses by membranes or septa at the confluence of the major bile ducts in patients with type IVA cysts (Ando et al, 1995). The procedure of choice for type III cysts or choledochoceles is ERCP because endoscopic papillotomy is potentially therapeutic (Sarris & Tsang, 1989; Venu et al, 1984).

PTC is an effective alternative to ERCP in the diagnosis of choledochal cysts. Because of endoscopic limitations imposed by the Roux-en-Y jejunal limb, PTC is particularly advantageous in patients with previous Roux-en-Y cystenterostomy and in patients with type IV bile duct cysts, in whom ductal strictures or tumors prevent complete visualization of intrahepatic cysts by ERCP (Savader et al, 1991b). The major diagnostic disadvantage of PTC is occasional failure to clearly define the pancreaticobiliary junction. Percutaneous biliary drainage (PBD) may be performed after PTC when indicated for control of biliary sepsis or to aid surgical reconstruction. PTC is particularly limited in patients with a widely patent cystenterostomy or huge extrahepatic cysts, because intracystic contrast is often superimposed over the pancreaticobiliary junction and obscures its radiographic definition.

MRC provides a noninvasive method of imaging the bile ducts and its anomalies (see Chapter 17), and it has been shown to provide an accurate anatomic definition of bile duct cysts in neonates, infants, and young children (Fitoz et al, 2007; Miyazaki et al, 1998). In a recent study, MRC reliably diagnosed biliary cystic disease in 74 (96%) of 76 patients with an accuracy of 86% for ductal anomalies (Park et al, 2005); however, it was less effective in detecting minor ductal anomalies and small cysts (Shaffer, 2006). MRC application to adults can be anticipated because image acquisition in adults is not hindered by the technical difficulties met when performing these studies in children. The limitation of MRC for bile duct cysts has related to its inability to clearly define the pancreaticobiliary junction (diagnostic accuracy, 69%) and its lack of therapeutic capability.

ASSOCIATED HEPATOBILIARY PATHOLOGY

Additional hepatobiliary pathology is frequently associated with bile duct cysts in adults. Cystolithiasis, hepatolithiasis, calculous cholecystitis, pancreatitis, cholangiocarcinoma, intrahepatic abscess, and cirrhosis with portal hypertension are potential problems that may either precipitate or complicate treatment. Although spontaneous perforation of bile duct cysts has been reported in infants and children, that complication has not been recognized in adults (Ando et al, 1998). Studies in adults suggest that nearly 80% of adults with bile duct cysts have complications from one or more of the conditions listed above (Nagorney et al, 1984a; Ono et al, 1982). A recent study suggests that complications in adults may decrease if excision is used routinely in infants and children (Gigot et al, 1996).

Cystolithiasis is the most frequent accompanying condition in adults with bile duct cysts. In contrast to the low prevalence of cystolithiasis in pediatric patients (Flanigan, 1975; Matsumoto et al, 1977a, 1977b; Rattner et al, 1983), the prevalence of intracystic stones has ranged from 2% to 72% in adults (Chijiiwa & Koga, 1993; Nagorney et al, 1984a; Todani et al, 1988). Although their composition has not been analyzed biochemically, most intracystic stones have been described as soft, earthy, and pigmented in appearance, thus supporting bile stasis as a primary etiologic factor (Matsumoto et al, 1977a, 1977b). These stones typically are associated with thick, viscous bile that may form bile duct or cyst casts. Cystolithiasis frequently complicates anastomotic strictures after previous

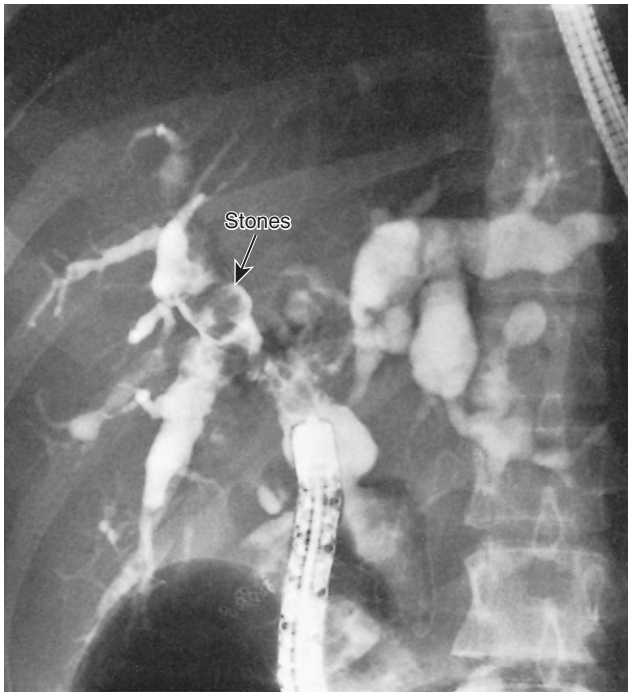


FIGURE 46.5. Endoscopic retrograde cholangiogram of a type IVA bile duct cyst showing multiple intrahepatic stones and a patent choledochoduodenostomy.

cystoenterostomies, which suggests that stasis and infection are major factors contributing to the pathogenesis of these stones.

Hepatolithiasis has been recognized with increasing frequency with long-term follow-up and may occur with or without evidence of anastomotic stricture (Fig. 46.5) (see Chapter 7; Deziel et al, 1986; Gigot et al, 1996; Uno et al, 1996). Some patients will have a complete or partial stricture of the cystenteric anastomosis, and hepatolithiasis develops as a consequence of proximal bile stasis or migration of intracystic stones. Hepatolithiasis usually occurs in type IV bile duct cysts. A recent study has shown that more than 80% of type IV bile duct cysts are associated with either a membranous or septal stenosis of the major lobar bile ducts near the confluence (Ando et al, 1995). Stenosis of the major ducts should be assessed in all patients with hepatolithiasis. Intrahepatic stones may be sequestered in segmental ducts, leading to further localized intrahepatic ductal dilation or subsequent intrahepatic abscess formation.

Gallbladder disease is a frequent complication for patients with bile duct cysts. Gallbladder disease can occur de novo, leading to the incidental discovery of bile duct cysts, or it can evolve after treatment for bile duct cysts. In particular, a gallbladder that is not excised as part of the initial treatment for symptomatic bile duct cysts is frequently a subsequent source of biliary tract disease. Both acute and chronic cholecystitis, with or without stones, has been recognized in these patients. Similar to stones within cysts, stones in noncystic portions of the bile duct are typically bilirubinate in appearance. Stasis is probably the primary etiologic factor in such cases.

The association of pancreatitis with choledochal cysts is a well-recognized entity, particularly in adults (see Chapter 53). The prevalence has ranged from 2% to 70% (Lipsett et al, 1994; Nagorney et al, 1984a; Okada et al, 1990; Rattner et al, 1983; Swisher et al, 1994). The true incidence of pancreatitis is difficult to determine because the diagnosis is based on the clinical findings of epigastric pain, nausea and vomiting, and hyperamylasemia. Another clinical condition, the common channel syndrome (Jona et al, 1979) or pseudopancreatitis (Todani et al, 1990), may mimic these findings completely, thus overestimating the true incidence of pancreatitis. Whether differentiation between these two entities has clinical or therapeutic significance is unclear. Pancreatitis associated with bile duct cysts typically is mild. The pattern of pancreatitis is acute and often relapsing, but objective pancreatic dysfunction seldom occurs. Chronic pancreatitis associated with bile duct cysts is rare.

The pathogenesis of pancreatitis in patients with choledochal cysts is primarily related to the anomalous pancreaticobiliary ductal anatomy and the presence of cystolithiasis or cholelithiasis. Several authors have confirmed that the base of the extrahepatic cyst or distal common bile duct in type I or IV cysts joins the main pancreatic duct more proximally than normal, resulting in a long common channel (Jona et al, 1979; Nagorney et al, 1984a; Ono et al, 1982; Rattner et al, 1983; Swisher et al, 1994). Obstruction of the pancreatic duct at the pancreaticobiliary junction or distally in the common channel (ampulla) by stones is postulated as the precipitating factor. A few studies (Nagorney et al, 1984a; Rattner et al, 1983) have shown an association between biliary tract stones in patients with choledochal cysts and pancreatitis, and stone impaction within the pancreaticobiliary junction may cause pancreatitis (Fig. 46.6). An alternative mechanism for pancreatitis is bile reflux into the pancreatic duct (Okada et al, 1983; Swisher et al, 1994); although the anatomy of the pancreaticobiliary ductal system is conducive to bile reflux, little evidence is available to support this theory. Some patients with bile duct cysts and pancreatitis have normal pancreaticobiliary anatomy (Swisher et al, 1994), and some patients with choledochoceles also may have recurrent acute pancreatitis (Martin et al, 1992; Masetti et al,

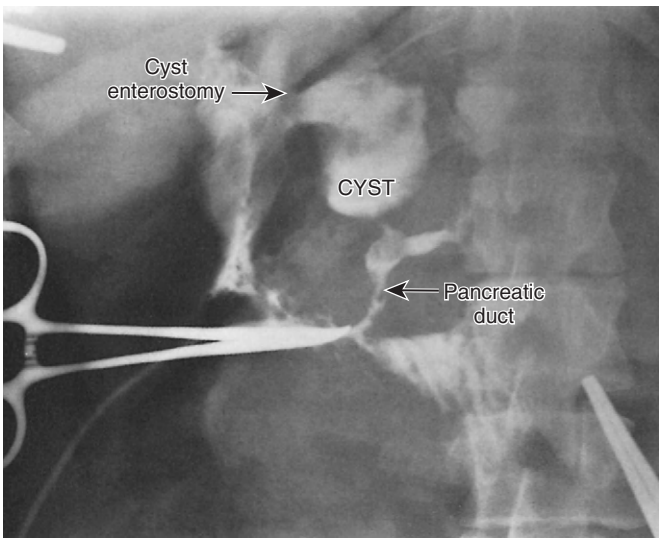


FIGURE 46.6. Intraoperative cholangiopancreatography in a patient with clinical pancreatitis and a type I cyst shows a stone impacted in the anomalous junction of the distal common bile duct and pancreatic duct. Previous cystenterostomy is also identified.

1996). Thus pancreatitis associated with bile duct cysts has multiple potential causes.

A significant association between bile duct cysts and hepatobiliary malignancy is well established (Dayton et al, 1983; Fieber & Nance, 1997; Flanigan, 1977; Komi et al, 1989; Rossi et al, 1987; Todani et al, 1979; Tsuchiya et al, 1977). The incidence of cancer associated with bile duct cysts ranges between 2.5% and 28% (Fieber & Nance, 1997; Flanigan, 1975; Ono et al, 1982). Hepatobiliary malignancies arising within or associated with bile duct cysts have included cholangiocarcinoma or adenocarcinoma, adenocanthoma, squamous cell carcinoma, anaplastic carcinoma, bile duct sarcoma, hepatocellular carcinoma, pancreatic carcinoma, and gallbladder carcinoma (Fieber & Nance, 1997; Ono et al, 1982; Todani et al, 1979, 1987; Tsuchiya et al, 1977). Cholangiocarcinoma is the most common malignancy associated with bile duct cysts (see Chapter 50), and its incidence is approximately 20 times greater than the incidence of bile duct carcinoma in the general population (Flanigan, 1975). The incidence of cyst-associated malignancy is age related, increasing from 0.7% in the first decade of life to more than 14% after age 20 years (Voyles et al, 1983). The mean age of patients with cancer associated with bile duct cysts is 32 years (Ono et al, 1982). These findings underscore the necessity for a high index of suspicion of carcinoma in adults with biliary cystic disease.

Malignancies associated with bile duct cysts may arise within the cyst or elsewhere within the liver or pancreaticobiliary tract. Indeed, only 57% of tumors are intracystic (Fig. 46.7) (Flanigan, 1977), and they may occur after cyst excision (Ishibashi et al, 1997; Nagorney et al, 1984b). Malignancies may be associated with any type of bile duct cyst, although the prevalence of cancer is significantly greater in type I and IV cysts. Caroli disease (type V) is also associated with an increased incidence of carcinoma (Dayton et al, 1983).

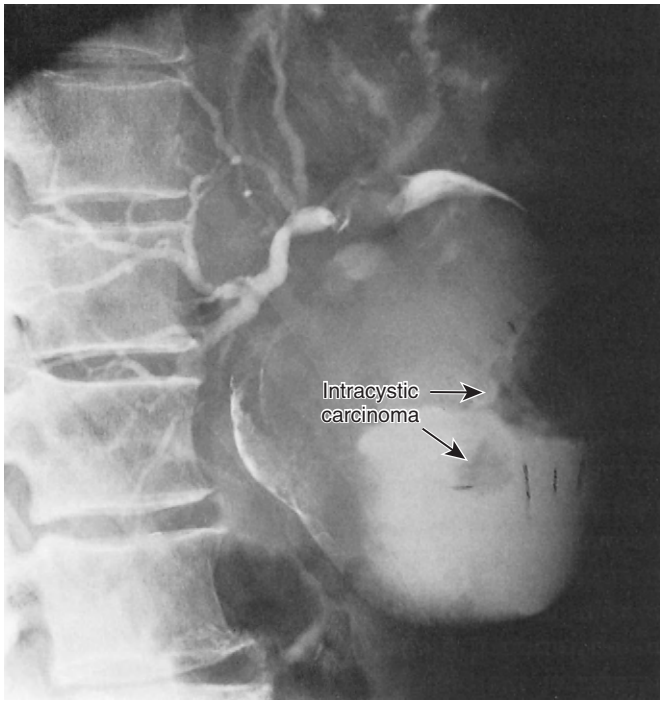


FIGURE 46.7. Percutaneous transhepatic cholangiography of a type I choledochal cyst with a polypoid intracystic cholangiocarcinoma.

The etiology of cyst-associated malignancies is unknown. Bile stagnation with the development of intrabiliary carcinogens leading to epithelial malignant degeneration is postulated as the most likely mechanism (Flanigan, 1977; Todani et al, 1979). Unconjugated deoxycholate and lithocholate have been associated with biliary metaplasia and mutagenicity, which may lead to neoplasia. Secondary bile acids have been found in bile duct cysts with cancer (Reveille et al, 1990), although neither their relative or absolute concentration in patients with bile duct cysts has differed in the presence or absence of cancer (Chijiiwa et al, 1993), thus suggesting other factors as primary carcinogens. An association between cystolithiasis and malignancy has not been established, although stasis and bacterial overgrowth associated with stones may lead to secondary bile acid formation. Long-term survival of patients with bile duct cysts and malignancy is rare. Delayed diagnosis, advanced stage of disease, intraabdominal seeding from previous operations, and tumor multicentricity generally preclude curative resection. Whether primary prophylactic excision of cysts in childhood can reduce the incidence of malignancy is unknown (Ono et al, 1982; Voyles et al, 1983).

Rare hepatobiliary problems arising in adults with common duct cysts include intrahepatic abscess and portal hypertension. Both conditions usually result from recurrent cholangitis and biliary obstruction after strictures of prior cystenterostomies. Large solitary hepatic abscesses represent an end stage of obstructive cholangitis and are usually completely obstructed, pus-filled intrahepatic cysts (see Chapters 43 and 66). These intrahepatic abscesses occur predominantly in the left intrahepatic duct (Mercadier et al, 1984; Ramond et al, 1984) and may be related partly to angulation of the left main duct. Adjacent liver parenchyma is fibrotic and atrophic and may harbor miliary abscesses within the peripheral bile duct radicles.

Portal hypertension associated with choledochal cysts may be due to secondary biliary cirrhosis or fibrosis, portal vein thrombosis, or Caroli disease with congenital hepatic fibrosis (see Chapter 70A; Kim, 1981; Martin & Rowe, 1979; Ono et al, 1982). Portal hypertension in adults generally is preceded by numerous operations for cyst drainage (Chaudhary et al, 1997; Hewitt et al, 1995; Lipsett et al, 1994). Portal hypertension in patients with bile duct cysts is manifested clinically by hepatosplenomegaly, hematemesis, melena, or ascites. Portal hypertension causes a hypervascularity of the hepatoduodenal ligament with prominent pericholedochal varices. Hepatic functional reserve deteriorates progressively, and hepatic coma and renal failure may be precipitated by recurrent cholangitis.

TREATMENT

General Principles

The surgical management of adults with bile duct cysts is based on cyst type and the presence of associated hepatobiliary pathology. The aims of preoperative management are complete cholangiographic definition of the extent of the cystic process and associated ductal pathology and control of biliary infections. Any patient with recurrent symptoms after prior cyst-related operations must be evaluated for anastomotic stricture, ductal stones, biliary tract malignancy, cirrhosis, and portal hypertension. Broad-spectrum antibiotics concentrated in bile and effective against proximal enteric bacteria are preferred for control of biliary infections. When sepsis fails to resolve with

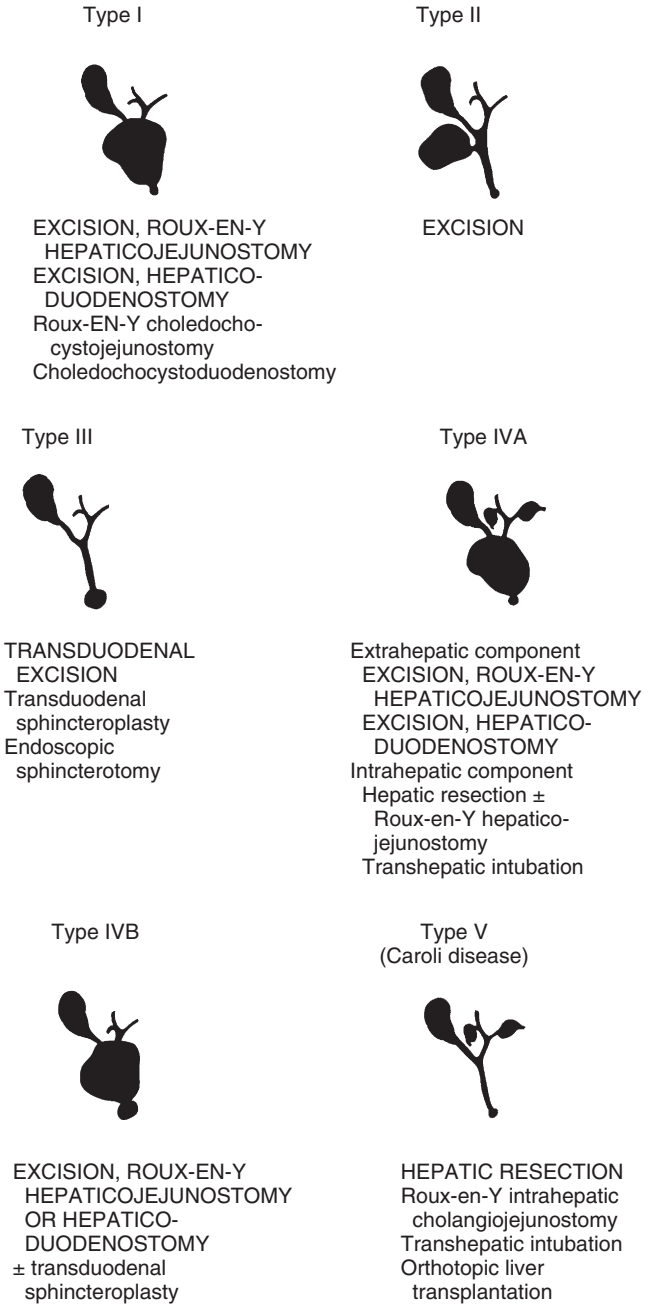


FIGURE 46.8. Surgical options for treatment of choledochal cysts. The preferred treatment appears in capital letters.

intravenous antibiotics, percutaneous or endoscopic drainage of infected bile duct cysts usually controls the infections before definitive operation.

The definitive treatment of bile duct cysts is surgical (Todani et al, 1978). The therapeutic alternatives for the treatment of each type of bile duct cyst are shown in Fig. 46.8. In general, all bile duct cysts should be excised and bile flow reestablished by mucosa-to-mucosa bilioenteric anastomosis (see Chapter 29). If complete excision is not feasible, partial cyst excision and Roux-en-Y cystojejunostomy to an epithelial-lined portion of the cyst remnant is preferred; external drainage alone has no role in the management of bile duct cysts. Cholangioscopy can be used in adults to exclude retained ductal stones and ductal malignancy (see Chapter 21). Finally, long-term follow-up must be maintained in adults because of the age-related risk of malignancy and the frequency of late anastomotic strictures in patients treated without cyst resection.

Type I Cyst

The treatment of choice for type I choledochal cysts in adults is total cystectomy and Roux-en-Y hepaticojejunostomy. Cyst excision eliminates the primary site of bile stasis and permits a bilioenteric anastomosis of normal jejunum and epithelial-lined proximal bile duct. The theoretical advantages of this approach include a reduced incidence of anastomotic stricture, stone formation, cholangitis, and intracystic malignancy. The advantages of a mucosa-to-mucosa anastomosis have been extrapolated from similar biliary reconstructions for other biliary tract problems: benign strictures, common bile duct stones, and suppurative cholangitis (see Chapter 42A).

Reduction in risk of malignancy is based on three presumptions: 1) the potential carcinogenic effect of pancreatic secretions is eliminated because of total diversion from the biliary tract; 2) the production of mutagenic secondary bile acids are reduced because bacterial overgrowth in the bile is less frequent; and 3) abnormal cyst epithelium is excised. The clinical results of cyst excision and Roux-en-Y hepaticojejunostomy have been excellent. Morbidity and mortality rates of excision have not been greater than that of drainage by Roux-en-Y choledochocystojejunostomy (Flanigan, 1975; Nagorney et al, 1984a; Ono et al, 1982; Rattner et al, 1983; Stain et al, 1995; Todani et al, 1978). Moreover, most reports with late follow-up have confirmed that the majority of patients remain asymptomatic following excision (Chen et al, 1996; Chijiiwa et al, 1993; Gigot et al, 1996; Nagorney et al, 1984a; Ono et al, 1982; Rattner et al, 1983; Uno et al, 1996), although recurrent cholangitis from anastomotic strictures occurs in 10% to 25% of patients (Chijiiwa & Tanaka, 1994; Gigot et al, 1996; Ono et al, 1982; Rattner et al, 1983; Uno et al, 1996).

Although reduction of malignancy by cyst excision has been suggested (Todani et al, 1987), cancer has developed after cyst excision (Nagorney et al, 1984a; Yamamoto et al, 1996). Previous cystenterostomy predisposes to ongoing risk of malignancy, and although such procedures are inadequate therapy for biliary cystic disease, they do not preclude definitive cyst excision (Gigot et al, 1996; Ono et al, 1982; Todani et al, 1988). Although morbidity is increased, low mortality rates and excellent long-term functional results can be achieved in adults with previous cystenterostomy, and reoperation and cyst excision should generally be undertaken. Bilioenteric continuity can be reestablished by hepaticoduodenostomy after cyst excision, although this method has been used infrequently in adults (Todani et al, 1981). An advantage of hepaticoduodenostomy is that the residual biliary epithelium is partially accessible to direct visualization by endoscopy (Todani et al, 1988). Technical factors influencing choice of hepaticoenterostomy (Roux-en-Y hepaticojejunostomy vs. hepaticoduodenostomy) include aberrant hilar ductal anatomy, ductal strictures, ductal size, and hilar arterial anatomy (Todani et al, 1998). Mobility of the duodenum is an important factor and may limit its use in some patients.

Cyst excision in adults differs technically from the approach generally advocated for pediatric patients (Altman, 1994; Lilly,

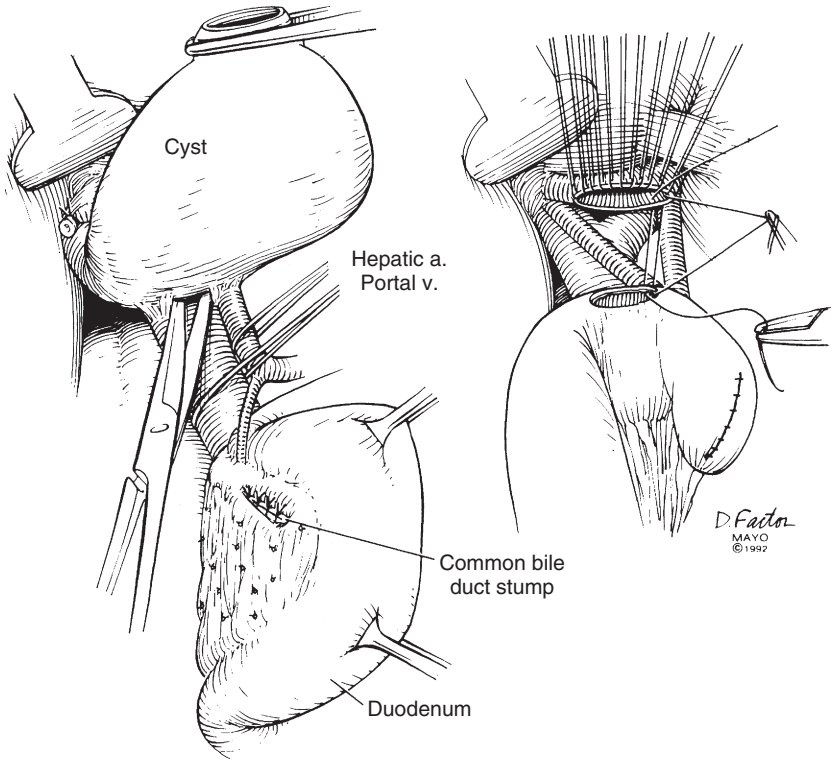


FIGURE 46.9. Isolation of vascular structures, complete excision of the cyst with closure of the distal stump, and bilioenteric reconstruction with hepaticojejunostomy with a Roux-en-Y loop. a., artery; v., vein.

1979). Most adults have had prior cyst drainage procedures, which may result in dense subhepatic adhesions. Recurrent cholangitis may result in epithelial degeneration or ulceration that can obscure or mimic malignancy, and regenerative epithelium may be densely adherent to the cyst wall. Although the vascularity of the pericholedochal tissue may increase, hypervascularity is most often limited to the ductal wall. In contrast to reports in pediatric patients (Lilly, 1979), complete dissection of the intracystic epithelium from the posterior cyst wall after excision of the anterior wall may be difficult. Because of the age-related incidence of cancer and its often occult operative and radiographic manifestations, total cyst excision to remove all intracystic epithelium is essential in adults. Only extensive hypervascularity from portal vein thrombosis or secondary biliary cirrhosis with portal hypertension would preclude excision.

Technically, cyst excision in adults can be accomplished by initially mobilizing the gallbladder from its bed to dissect the cyst away from the hilar structures. The portal vein is identified. Isolation and proximal control of the hepatic artery before dissection of the posterior cyst wall can be very helpful, especially if hypervascularity and dense adhesions are encountered. Before division of the cyst, the distal cyst is dissected from the pancreas to identify the pancreaticobiliary ductal junction (Ando et al, 1996). The intrapancreatic portion of the cyst is separated from the pancreas along the loose areolar plane between these structures. Meticulous fine suture ligature of collateral vessels will prevent potentially troublesome postoperative hemorrhage. Knowledge of the anatomy by preoperative cholangiography becomes particularly important to avoid damage to the pancreatic ducts. The cyst is transected distally within the head of the pancreas, and the distal bile duct is ligated carefully to prevent narrowing of the pancreatic duct. The cyst is mobilized proximally to the ductal confluence. After confirmation of the ductal confluence, the proximal cyst is transected, and the cyst is removed. Bilioenteric flow is reestablished through a wide mucosa-to-mucosa Roux-en-Y hepaticojejunostomy at the level of the hilum (Fig. 46.9) or with a hepaticoduodenostomy. If a previous cystenterostomy has been performed, the same technique is used for excision after the cystenterostomy has been divided. An existing Roux loop can be reused for the new anastomosis. Hepatic arteries should be positioned posterior to the cystenterostomy to reduce potential injury in case of reoperation.

Portal hypertension secondary to biliary cirrhosis and inflammatory adhesions from severe pancreatitis or past drainage procedures may preclude cyst excision. In these circumstances, Roux-en-Y choledochocystojejunostomy is the preferred alternative treatment for type I choledochal cysts. Preoperative morbidity and mortality rates are similar to that of cyst excision. Adequate long-term functional results from Roux-en-Y cyst drainage can be expected in 60% to 70% of patients (Nagorney et al, 1984a; Ono et al, 1982; Rattner et al, 1983). Long-term results are improved by partial cyst excision in an effort to ensure a mucosa-mucosa bilioenteric anastomosis (Gigot et al, 1996). When either excision or Roux-en-Y drainage is performed, intraoperative choledochoscopy to exclude retained ductal stones and to biopsy the abnormal epithelium to exclude malignancy is advised. In patients with recurrent acute pancreatitis and unresectable cysts, intracystic closure of the base of the cyst proximal to its junction to the pancreatic duct or concurrent transduodenal sphincteroplasty

should be used to prevent further episodes of pancreatitis (Rattner et al, 1983; Nagorney et al, 1984a). Careful long-term follow-up is essential because of the late development of malignancies, recurrent ductal stones, and anastomotic stricture (Chijiiwa & Tanaka, 1994; Fieber & Nance, 1997; Todani et al, 1998; Uno et al, 1996).

Portal decompression may be required before biliary reconstruction in patients who develop portal hypertension (Nagorney et al, 1984a). Preoperative assessment of these patients should include hepatic arteriography and portography. In general, central splenorenal shunts are preferred because portal decompression can be performed in an area distant from the subhepatic pericystic inflammation. In general, drainage is undertaken 6 to 12 weeks after portosystemic shunting. Alternatively, transjugular intrahepatic portosystemic stenting (TIPS) could be used for preoperative portal decompression (see Chapter 76E).

Type II Cyst

The treatment of choice for type II bile duct cysts is excision (Flanigan, 1975; Powell et al, 1981). Due to the low incidence, however, experience is limited, although reported results after excision have been excellent (Kouraklis et al, 1996; Lopez et al, 1991; Nagorney et al, 1984a; Powell et al, 1981). Technically, excision of type II bile duct cysts is similar to that of cholecystectomy. Depending on the size of the neck of the cyst at its junction with the common duct, the neck can either be closed primarily, or closure can be achieved via T-tube decompression of the common duct. Excision with Roux-en-Y hepaticojejunostomy has also been successful but has no clinical advantage over excision alone (Benhidjeb et al, 1994).

Type III Cyst (Choledochocele)

Choledochoceles are true cysts of the distal bile duct protruding into the duodenum. Patients are seen with biliary colic, cholangitis, or pancreatitis (Masetti et al, 1996). Choledochoceles are typically small (≤2 cm), and a classification scheme for them has been proposed (Sarris & Tsang 1989). Until recently, transduodenal cyst excision with or without sphincterotomy was the treatment of choice (Flanigan, 1975; Powell et al, 1981; Venu et al, 1984), but endoscopic sphincterotomy and cyst unroofing have now become the preferred treatment (Ladas et al, 1995; Martin et al, 1992; Masetti et al, 1996). The excellent long-term results with endoscopic treatment coupled with the diagnostic advantage of ERCP in defining the terminal pancreatic biliary anatomy clearly favor the endoscopic approach. Although transduodenal excision eliminates the risk of malignancy, the fact that only three cases of carcinoma in choledochoceles have been documented confirms that the risk of cancer alone is sufficiently low to justify endoscopic treatment as an alternative to surgery (Masetti et al, 1996).

Damage to the major pancreatic duct is the major source of operative morbidity and mortality. Identification of the duct of Wirsung is paramount before transduodenal cyst excision or sphincteroplasty because of numerous pancreatic biliary ductal variations (Komi et al, 1989, 1992). The pancreatic duct of Wirsung may enter the posterior wall of the choledochocele, or it may enter normally into the duodenum at the inferior aspect of the major papilla adjacent to the choledochocele (Sarris & Tsang, 1989). Before cyst excision or sphincteroplasty, the pancreatic duct orifice must be identified at the papilla to avoid damage to the duct. If the major pancreatic duct empties normally into the duodenum, it should be left in situ and not transected during choledochocele excision. If the pancreatic duct enters into the posterior wall of the cyst, the distal common bile duct and the duct of Wirsung should be implanted separately into the duodenal mucosa after cyst excision (Powell et al, 1981).

Type IV Cyst

The treatment of choice for type IV bile duct cysts is excision of the extrahepatic cyst and Roux-en-Y hepaticojejunostomy (Mercadier et al, 1984; Nagorney et al, 1984a; Todani et al, 1984a). The extrahepatic component of type IVA and IVB cysts is approached as a type I bile duct cyst. Transduodenal sphincteroplasty and Roux-en-Y hepaticojejunostomy complete the treatment of type IVB cysts, which have a choledochocele component. Type IVA cysts require more selective management because of the wide range of problems associated with the intrahepatic component of these cysts (Ando et al, 1997; Chijiiwa & Tanaka, 1994; Nagorney et al, 1984a; Todani et al, 1984a; Uno et al, 1996). When type IVA cysts are not complicated by hilar or intrahepatic ductal strictures, intrahepatic stones, intrahepatic abscess, or malignancy, bilioenteric continuity should be restored by a wide Roux-en-Y hepaticojejunostomy at the bile duct confluence (Todani et al, 1988, 1998). In addition, the hepaticojejunostomy must take into account anomalous ductal anatomy. In patients with stones sequestered within the intrahepatic cysts, refractory ductal strictures distal to the intrahepatic cysts, or intrahepatic abscess due to chronic cholangitis, the abnormal hepatic segment should be resected. Bile flow is restored by Roux-en-Y hepaticojejunostomy, and lobar hepatic resection is usually required to eliminate the complicated unilobar intrahepatic cystic component. In addition to the hepaticojejunostomy at the hilus, Roux-en-Y cholangiojejunostomy incorporating the segmental bile duct of the resected segment may further optimize intrahepatic bile drainage. In patients with type IVA cysts and an intrahepatic component involving both lobes of the liver or complicated by cirrhosis, transhepatic tubes can be added to the Roux-en-Y hepaticojejunostomy for access to the biliary tree for diagnosis and treatment.

The results of the treatment of type IVA cysts have been reviewed by several centers (Gigot et al, 1996; Todani et al, 1998; Uno et al, 1996; Ando et al, 1997). Although treatment varies widely because of the spectrum of pathology associated with these cysts, the results of cyst drainage alone without excision of either the intrahepatic or extrahepatic cystic components were considered satisfactory or good in fewer than 50% of patients (Todani et al, 1984a). In contrast, 90% of patients who had excision of the extrahepatic component of the type IVA cyst had good results, whether or not the intrahepatic component was resected. Although these findings suggest that adequate treatment of the extrahepatic component in these patients may provide effective prophylaxis for progression of the problems associated with intrahepatic cystic disease, the results of some studies (Ando et al, 1997; Todani et al, 1998) emphasize the importance of addressing the presence of variant ductal anatomy and stenoses at the hilum. If intrahepatic ductal stenosis or aberrant ducts are not recognized and addressed during extrahepatic cyst excision, subsequent reoperation will often be necessary. Both membranous or bridgelike stenoses should be

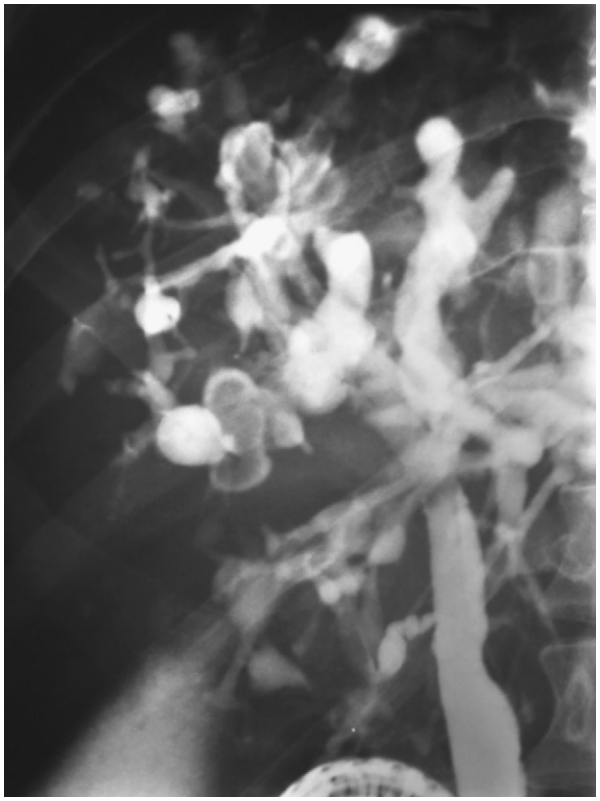


FIGURE 46.10. Endoscopic retrograde cholangiogram of Caroli disease and multiple saccular cysts of only the intrahepatic bile duct with intrahepatic stones.

excised circumferentially to their base. The long-term results of the treatment of type IVB cysts in adults are similar to those of type I choledochal cysts. Although patients with type IVA cysts and portal hypertension may be approached by proximal splenorenal shunts before cyst drainage, liver transplantation may provide a more durable solution. Resection of intrahepatic cysts in cirrhotic patients is associated with an increase in morbidity and mortality rates and is generally contraindicated.

Caroli Disease

The treatment of Caroli disease depends on the extent of the intrahepatic bile duct cysts and the presence of congenital hepatic fibrosis, secondary biliary cirrhosis, or carcinoma. Caroli disease in adults may present in a localized form, limited to one hepatic lobe or segment, or a diffuse form, involving the entire intrahepatic biliary tree (Fig. 46.10) (Barros et al, 1979; Dayton et al, 1983; Mercadier et al, 1984; Witlin et al, 1982). Most adults with Caroli disease have a unilobar fusiform dilation of the intrahepatic ducts, most commonly involving the left ductal system (Mercadier et al, 1984; Ramond et al, 1984). Hepatic resection, with or without Roux-en-Y cholangiojejunostomy, remains the treatment of choice in patients with Caroli disease limited to one lobe of the liver without the presence of concurrent cirrhosis or hepatic fibrosis. Cyst removal by hepatic resection provides the simplest solution to the recurrent problems of cholangitis, stone formation, and intrahepatic cancer (Mercadier et al, 1984; Todani et al, 1984a). Resection is always preferable to drainage if the liver parenchyma surrounding the cyst is atrophic. Indeed, segmental fibrosis and atrophy from complications of the underlying cyst are irreparable with drainage, which mandates segmental resection. Morbidity and mortality associated with hepatic resection for localized Caroli disease have been minimal, and functional results have been good, although follow-up has been limited (Bockhorn et al, 2006; Mercadier et al, 1984; Ramond et al, 1984). Alternative approaches to localized intrahepatic Caroli disease have included external T-tube biliary decompression or internal drainage via choledochoduodenostomy, Roux-en-Y choledochojejunostomy, or Roux-en-Y hepaticojejunostomy. These alternatives are often ineffective because ductal drainage is distal to the intrahepatic cysts (Witlin et al, 1982). In general, recurrent cholangitis, hepatic abscess formation, intrahepatic stone formation, and carcinoma eventually complicate these approaches. If resection in patients with localized Caroli disease is not feasible, Roux-en-Y intrahepatic cholangiojejunostomy to the intrahepatic cyst is preferable (Mercadier et al, 1984).

The results of the treatment of Caroli disease involving both lobes of the liver, or associated with portal hypertension from congenital hepatic fibrosis or secondary biliary cirrhosis, remain poor (Barros et al, 1979; Dayton et al, 1983; Mercadier et al, 1984). Most patients with diffuse Caroli disease have chronic recurrent cholangitis and portal hypertension with variceal bleeding, and their deaths are secondary to liver failure or carcinoma. Long-term medical therapy including antibiotics, analgesics, and litholytic agents may improve symptoms, but it does not permanently eliminate them. In selected patients with diffuse intrahepatic Caroli disease but with dominant unilobar disease, extended hepatic resection has been advocated, although long-term benefit remains unproven (Mercadier et al, 1984). Long-term transhepatic decompression using bilobar silicone tubes has been successful in the management of recurrent cholangitis (Witlin et al, 1982); however, to date, the treatment of diffuse Caroli disease remains disappointing.

In light of the natural history of Caroli disease—cirrhosis, variceal bleeding, and liver failure—hepatic transplantation offers the best chance of success. Orthotopic liver transplantation has been successfully used for Caroli disease (see Chapter 97A; De Kerckhove et al, 2006; Habib et al, 2006; Scharschmidt, 1984). If the diagnosis of bilobar Caroli disease is made, nonoperative medical treatment should be used until the patient is considered a transplant candidate. Avoidance of numerous ineffective operative procedures will reduce the technical risk of transplantation.

LAPAROSCOPIC ADVANCES IN SURGICAL MANAGEMENT

Minimally invasive approaches are increasingly used in most visceral procedures, and outcomes consistently suggest patient advantages over conventional approaches with regard to pain, wound complications, length of hospital stay, and recovery time. A laparoscopic approach in the management of bile duct cysts was first described in 1995 in a pediatric patient with a type I choledochal cyst (Farello et al, 1995), and several case reports and small series have been reported since (Abbas et al, 2006; Chokshi et al, 2009; Laje et al, 2007; Sun et al, 2009). Although feasibility has been demonstrated, the small numbers of patients in these reports has limited the assessment of outcomes, and comparisons with open procedures are needed. Only four contemporary series include more than 12 patients

Table 46.2

Laparoscopic Management of Bile Duct Cysts

	Palanivelu et al, 2008	Hong et al, 2008	Li et al, 2004	Lee et al, 2009	Jang et al, 2006
Patients (n)	35	31	35	37	13
Pediatric (%)*	54	100	100	100	0
Cyst type					
I†	27 (77)	31 (100)	33 (94)	35	9
II	0	0	0	0	0
III	0	0	0	0	0
IV	8 (23)	0	0	2	4
Conversion to open	3 (9)	4 (13)	0	4 (10.8)	1 (8)
Mean cyst size (cm^2)	51	3	4‡	2.8	ND
Complete cyst excision, n (%)	28 (80)	ND	35 (100)	ND	ND
Mean operating time (min)	295	312	258	439	228
Perioperative morbidity, n (%)	5 (14)	4 (13)	1 (3)	15 (40.5)	2 (15)
Mean hospital stay (days)	6.5	8.6	4.5		5.8

*Defined as <16 years of age
†Numbers in parentheses refer to type I cysts as a percentage of total number.
‡For type I cysts
ND, no data available

(Table 46.2), three of which included only pediatric cases. Palanivelu and colleagues (2008) recently reported the largest series to date of laparoscopic treatment of bile duct cysts. In this series of 35 patients, 16 were adults. Conversion to laparotomy was performed in three patients for suspicion of malignancy, and complete cyst excision was performed in 28; in five patients, an incomplete resection was performed as a result of extension of the cyst proximal to the hepatic duct confluence. Postoperative complications occurred in 14%, with no perioperative mortality.

One of the major advantages of the laparoscopic approach in choledochal cyst surgery is the superior visualization of the structures around the cyst and within the hepatic hilum. The magnification conferred by the laparoscope helps assess neovascularity around the cyst, separation of the posterior cyst wall from the portal vein, and dissection and anastomosis in the hilar area. It also may aid dissection and identification of the narrow intrapancreatic bile duct close to the anomalous pancreatobiliary junction because of the magnified laparoscopic view. However, it must be emphasized that laparoscopic excision of choledochal cysts is technically challenging and requires experience in both complex biliary operations and advanced laparoscopic surgery.

Recent large series have established the feasibility of laparoscopic cyst excision with hepaticojejunostomy. Although the outcomes appear favorable, a formal comparison has not been made to open approaches, and the expected advantages of minimally invasive approaches—reduced pain, fewer wound complications, shorter hospital stay, and faster recovery—have not been confirmed.

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SECTION II Neoplastic

A. General

CHAPTER 47

Tumors of the biliary tree: pathologic features

David S. Klimstra and N. Volkan Adsay

OVERVIEW

The biliary tract is lined by simple columnar epithelial cells of foregut origin (Fig. 47.1; Frierson, 1989; 1997). Most biliary neoplasms are related to this cell type and hence show major similarities to other foregut tumors, particularly those of pancreatic ductal origin. By far the most common neoplasm of the biliary tract is adenocarcinoma, which is referred to collectively with pancreatic ductal adenocarcinoma as a *pancreatobiliary-type* adenocarcinoma (Figs. 47.2 through 47.5), reflecting the similarities between these two neoplasms.

Tumors arising from the gallbladder and the different segments of the bile ducts have overlapping histologic characteristics; therefore their pathologic classification is also very similar (Adsay, 2004; Albores-Saavedra et al, 2000a, 2010; Lack, 2003). On the other hand, the risk factors, clinical findings, and biologic behavior may vary (see Chapters 49, 50A, and 50B). For instance, although gallstones are the main risk factor for gallbladder adenocarcinoma, adenocarcinomas of proximal bile ducts have a much stronger association with primary sclerosing cholangitis (PSC) (see Chapter 41) or anomalous pancreatobiliary duct junction (see Chapter 46). This variability also is partially reflected in the molecular alterations, which although not specific for the histologic subtype of the tumor, may affect the management and prognosis (see Chapter 8B). The different presentations of biliary adenocarcinoma also influence the mode by which a specimen is obtained for pathologic examination. For example, many gallbladder adenocarcinomas are currently identified in "routine" cholecystectomy specimens in primary care facilities, performed with a preoperative diagnosis of chronic cholecystitis or cholelithiasis, whereas extrahepatic bile duct lesions are seldom resected without a strong preoperative suspicion of carcinoma, and this is usually performed in tertiary care facilities.

This chapter discusses the pathologic aspects of biliary tract neoplasia, with special emphasis on adenocarcinomas. The tumor types are discussed by viewing the biliary system as a whole; site-specific characteristics are mentioned only when pertinent to pathologic classification. For the details of clinical findings, risk factors, and site-specific management, the reader is referred to other chapters of this book (see Chapters 49, 50A, and 50B).

INVASIVE CARCINOMAS OF THE BILIARY TRACT

Most "biliary tract cancers" are conventional adenocarcinomas (pancreatobiliary type), which are morphologically very similar to pancreatic ductal adenocarcinoma (Adsay, 2004; Albores-Saavedra et al, 2000a, 2010; Lack, 2003). This tumor is referred to as *gallbladder adenocarcinoma* in the gallbladder, *cholangiocarcinoma* in the intrahepatic biliary tract, and *adenocarcinoma of the extrahepatic bile ducts* in the extrahepatic biliary tract. As in adenocarcinomas of other organs, these are usually tumors of the elderly. The association of biliary adenocarcinomas with preceding chronic inflammation has been well established (Herzog & Goldblum, 1996; Sheth et al, 2000), mostly by epidemiologic data showing the high incidence of gallbladder cancer in areas with a high prevalence of gallstones and by the pathologic observation that many individual carcinomas have associated gallstones or cholecystitis (see Chapter 49). Also, the risk of adenocarcinoma is relatively high in patients with PSC and indirectly in those with ulcerative colitis (see Chapter 41). The association of biliary cancers with parasites (see Chapter 45; Carriaga & Henson, 1995) and choledochal cysts (see Chapter 46) is also presumably related to the potential for chronic inflammation from constant epithelial injury and repair that leads to neoplastic alterations (Parkin et al, 1993).

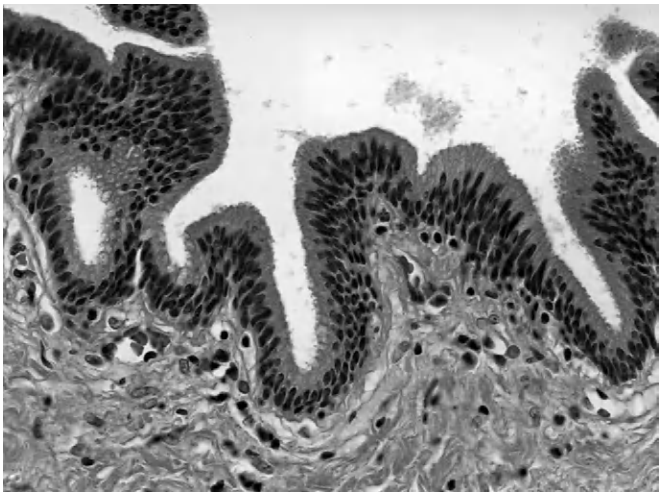


FIGURE 47.1. Benign epithelium. The biliary epithelium is composed of a layer of columnar cells with acidophilic cytoplasm.



FIGURE 47.2. Macroscopic appearance of an adenocarcinoma. The cut surfaces of adenocarcinomas of the biliary tract and gallbladder typically have a firm, white, sclerotic appearance because of the abundance of desmoplastic stroma.

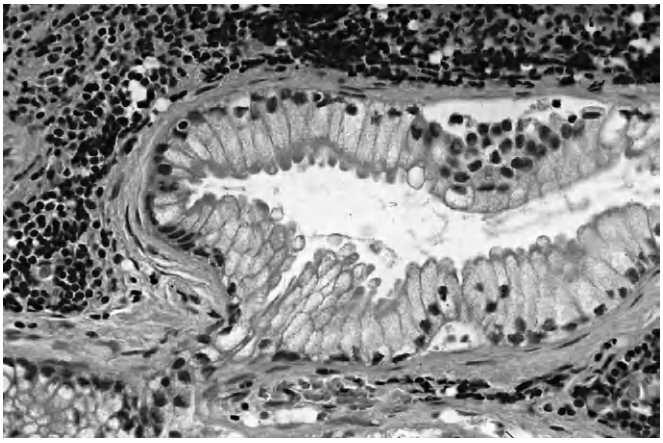


FIGURE 47.3. Well-differentiated adenocarcinoma. Most adenocarcinomas of the biliary tract are the tubular, pancreatobiliary type, characterized by simple tubular units with well-polarized, deceptively bland-appearing cells.

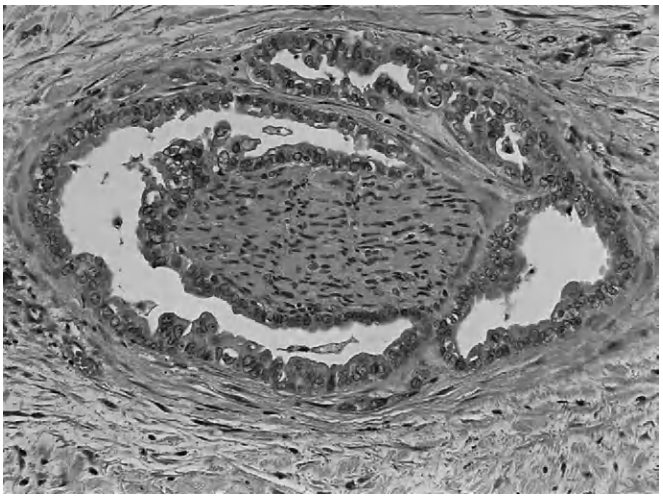


FIGURE 47.4. Adenocarcinoma with perineural invasion. Carcinoma cells wrapping around nerves is a very common finding in biliary adenocarcinomas.

Growth Patterns and Macroscopic Features

Based on their macroscopic growth pattern, biliary carcinomas have been divided into four types: 1) polypoid, 2) nodular (nodular-sclerosing), 3) schirrous-constricting, and 4) diffusely infiltrative (Albores-Saavedra et al, 2000a; Todoroki et al, 1980; Van Heerden et al, 1967; Weinbren & Mutum, 1983). Polypoid growth typically is found in carcinomas with an associated component of intraductal papillary neoplasm (IPN), previously designated *noninvasive papillary carcinoma* (Albores-Saavedra et al, 2010), which are associated with a better prognosis. The nodular and schirrous types have a propensity to infiltrate surrounding tissues and are therefore difficult to resect. The diffusely infiltrating type tends to spread linearly along the ducts. The constricting and diffusely infiltrative patterns may be difficult to differentiate from chronic inflammatory conditions, especially PSC and autoimmune cholangitis (Corvera et al, 2005). Significant histologic overlaps occur among these different growth patterns, so their utility in tumor classification is limited.

On cut sections, the intraluminal components of biliary carcinomas, especially those with a polypoid gross appearance,

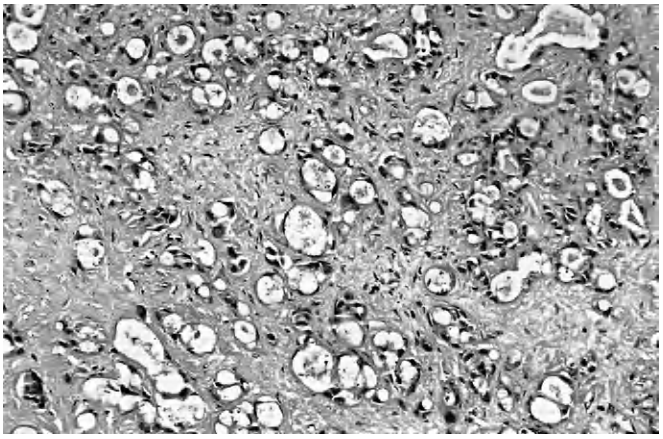


FIGURE 47.5. Adenocarcinoma with mucin. Intracytoplasmic and intraluminal mucin often are present in biliary adenocarcinomas. In this example, the granular material in the lumina represents mucin admixed with necrotic debris.

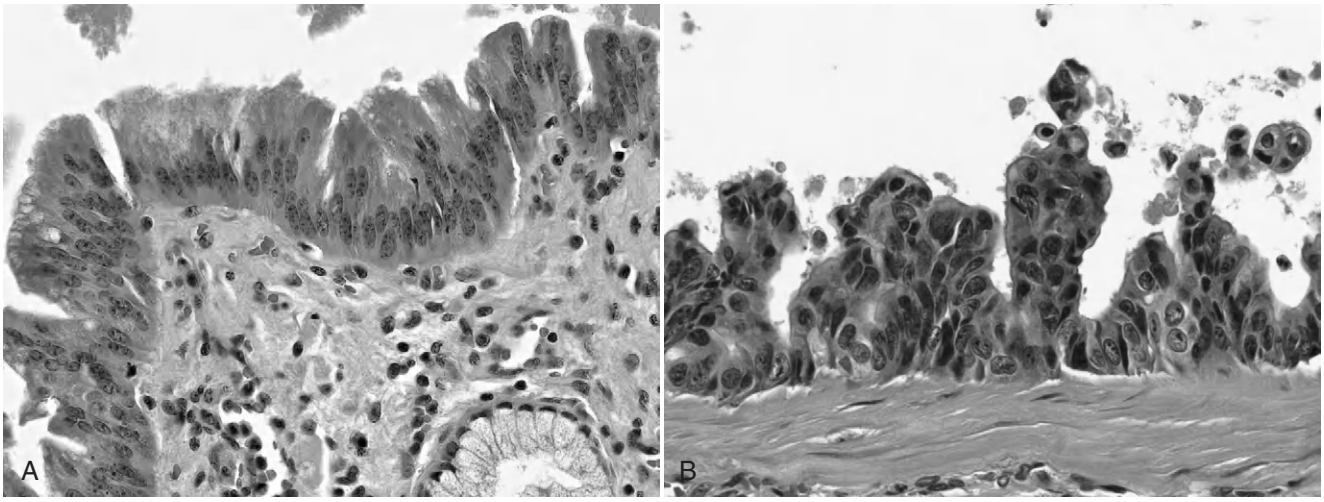


FIGURE 47.6. Dysplasia (biliary intraepithelial neoplasia). Loss of polarity of the cells is associated with nuclear atypia, including enlargement, hyperchromatism, and pleomorphism. **A,** Low-grade dysplasia. **B,** High-grade dysplasia.

may appear more friable, soft, and tan; this reflects the presence of intraductal papillary neoplasm elements growing into the lumen, and ulceration and necrosis may be evident in larger tumors. The infiltrating components of adenocarcinomas are more schirrous (scarlike) with a firm, white, gritty appearance (see Fig. 47.2) because of the abundance of desmoplasia, a fibrotic tissue reaction associated with infiltrating carcinoma. Necrosis may also be evident.

When adenocarcinoma invades into the adjacent liver, the growth pattern often becomes more expansile, and the liver-carcinoma interface appears deceptively well demarcated. This allows easier detection of the boundaries of these carcinomas in hepatic resections. In contrast, the boundaries of carcinomas invading the hilar soft tissue are typically poorly defined and difficult to appreciate. Gallbladder carcinomas are often associated with gallstones. In patients with porcelain gallbladder (Stephen & Berger, 2001), the wall of the gallbladder may be entirely calcified.

Microscopic Features

Most adenocarcinomas of gallbladder and bile ducts show the characteristic features of a pancreatobiliary-type adenocarcinoma (see Figs. 47.3 to 47.5): both simple and complex, irregularly shaped glands mixed with small clusters of cells, often with associated stromal desmoplasia (Adsay, 2004; Albores-Saavedra et al, 2000a, 2010; Lack, 2003). The glands often are well formed, lined by cuboidal cells, and show dilated lumina. Often the nuclear grade is unexpectedly high for the degree of glandular differentiation, and marked variation in nuclear size, shape, and intracellular location occurs between different cells within the individual glands. The cytoplasm may be acidophilic and granular in some cases and pale or clear in others. Variable amounts of intracytoplasmic and intraluminal mucin are present; in some cases, mucin is readily evident by routine histologic examination; in others, it is demonstrable by special stains.

Perineural (see Fig. 47.4) and vascular invasion are common, and carcinoma cells may have a deceptively well-differentiated appearance, even when they invade these structures. In fact, the distinction of a well-differentiated adenocarcinoma from a benign reactive process in this region is one of the more challenging differential diagnoses in surgical pathology.

Dysplasia, or biliary intraepithelial neoplasia (BilIN; Fig. 47.6), is often present in the adjacent biliary epithelium (Zen et al, 2007). Sometimes the intraepithelial component comprises a papillary neoplasm (Fig. 47.7). In such cases, the noninvasive and invasive components of the tumor should be evaluated separately, and the extent of invasion should be quantified because those with "minimal invasion" have a better prognosis (Albores-Saavedra et al, 2000b).

Tumors that infiltrate the adjacent liver may acquire a more trabecular pattern, presumably by growing along the sinusoidal backbone of the liver parenchyma. Entrapped reactive bile ductules and hepatocytes are often present within the tumor; these may create a diagnostic problem in biopsy specimens.

Anatomic Variations

For therapeutic and prognostic purposes, tumors of the extrahepatic biliary tract are separated by their anatomic distribution into *upper third* (above the cystic duct junction, including the

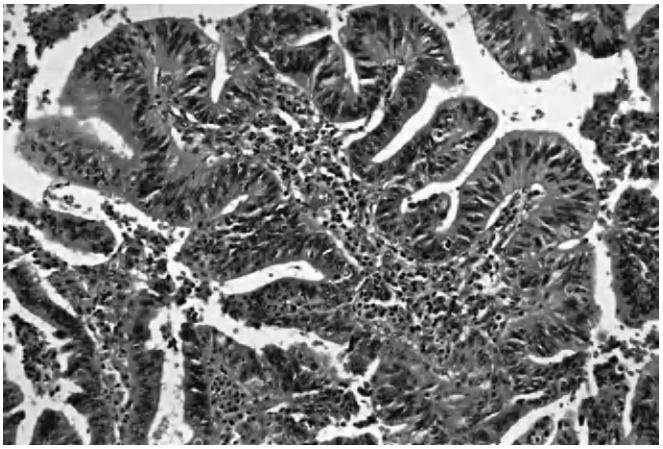


FIGURE 47.7. Intraductal papillary neoplasm. This polypoid lesion shows papillary fronds lined by neoplastic cells.

both hepatic ducts, common hepatic duct, and the cystic duct), *middle third* (upper half of the common bile duct [CBD]), and *lower third* (distal half of the CBD) (Klatskin, 1965; Tompkins et al, 1981; Van Heerden et al, 1967; Weinbren & Mutum, 1983). The distinctive clinical characteristics of adenocarcinomas occurring in different segments of the biliary tract are discussed in other chapters of this book, and only a few issues pertinent to pathologic aspects are mentioned here. Most carcinomas arise in the upper third of the bile ducts and tend to be the schirrous-constricting and diffusely infiltrative types. Recent studies have shown that many originate within 5 mm of the cystic duct junction or within the cystic duct itself. Hilar carcinoma, located at the confluence of the right and left hepatic ducts, sometimes referred to as a *Klatskin tumor* (Bosma, 1990; Klatskin, 1965), has distinctive clinical features. Klatskin tumors usually grow into the liver rather than distally toward the duodenum (see Chapter 50B; Hayashi et al, 1994), and the component that invades the liver is often well demarcated. Carcinomas in the middle third tend to be the nodular-sclerosing type—thickened along a long segment, with a narrow lumen and inflammatory changes in the surrounding tissues; hence these are difficult to differentiate from sclerosing cholangitis. They have a very high propensity for perineural invasion and involvement of radial surfaces, making curative resection difficult (Bhuiya et al, 1993). Those in the distal third have the best prognosis, partly because of their resectability by pancreatoduodenectomy and partly because many, especially those close to the ampullary region, are composed predominantly of noninvasive papillary neoplasmic elements (Adsay, 2004; Albores-Saavedra et al, 2000a; Lack, 2003).

Pathologic Differential Diagnosis

The difficulty at the clinical level of distinguishing biliary adenocarcinomas from benign inflammatory conditions, such as sclerosing cholangitis, is also problematic at the microscopic level (Ludwig, 1989; Ludwig et al, 1992). Reactive changes in the accessory biliary ductules in the wall of the bile ducts can mimic adenocarcinomas, although nonneoplastic ductules may retain a lobular configuration, and they lack the density of cellularity of a carcinoma. As also discussed in Chapter 56, pancreatobiliary adenocarcinomas can be deceptively benign appearing, composed of well-formed glandular elements lined by fairly organized, cytologically bland glandular cells (see Figs. 47.3 and 47.4). The distinction of reactive changes in the surface epithelium from dysplasia (BilIN) often proves to be even more challenging, especially because any injury to the biliary epithelium, including instrumentation and stent placement, has a tendency to induce marked cytologic atypia that mimics the appearance of high-grade dysplasia (Fig. 47.8). Marked nuclear enlargement or irregularity, hyperchromasia, loss of polarity, mitotic figures, apoptotic cells, and intraluminal necrosis are findings in favor of a neoplastic process (see Fig. 47.6); however, overlaps are common, and at times this distinction may not be possible on the basis of biopsies or frozen sections.

Biliary carcinomas that grow into the liver must be distinguished from primary hepatocellular carcinomas (see Chapter 78). The presence of true glandular elements and mucin are common findings in biliary carcinomas and typically are lacking in hepatocellular carcinomas. In contrast, hepatocellular carcinomas may have intracellular bile and generally lack significant stromal fibrosis and desmoplasia. Other distinctive features of hepatocellular carcinomas—the solid and trabecular growth pattern, centrally located nuclei with prominent nucleoli, and abundant eosinophilic cytoplasm—usually are identifiable; immunohistochemical demonstration of hepatocellular differentiation with markers such as hepatocyte-1 or glypican-3 can be used in problematic cases.

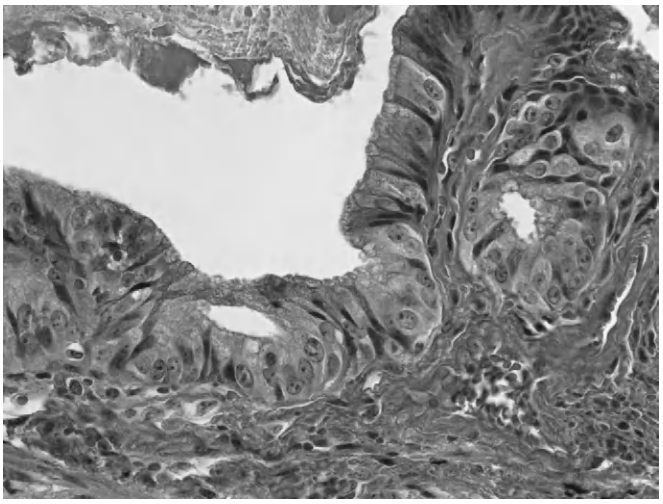


FIGURE 47.8. Reactive atypia. Injury to the bile duct epithelium—whether from a primary inflammatory process, such as sclerosing cholangitis, or to instrumentation from endoscopic retrograde cholangiopancreatography or stent placement—often induces remarkable atypia that may mimic carcinoma.

Differentiation between ampullary and duodenal neoplasms and CBD tumors can be difficult because carcinomas of these sites often infiltrate neighboring structures in close proximity. In such cases, the correct classification of the tumor greatly depends on determining where it is centered, which often can be achieved only by close correlation of the radiographic and macroscopic findings. In addition, any dysplasia or other preinvasive features may be an important clue to the site of origin. In this complex region, the origin of the tumor (by site) should be evaluated separately from the type of the carcinoma, such as ampullary carcinomas of the pancreatobiliary type. Intestinal-type carcinomas in this region are more likely to be of either ampullary or duodenal origin.

Biliary carcinomas metastatic to other sites may mimic the primary tumors of those organs. In particular, metastases to the ovary often become cystic and are mistaken for primary ovarian mucinous cystic neoplasms (Young & Hart, 1989), and lung metastases can resemble mucinous bronchioloalveolar carcinomas. Metastases to the peripheral liver from biliary carcinomas can be nearly impossible to distinguish from metastatic pancreatic ductal adenocarcinoma.

Immunohistochemical and Molecular Characteristics

By immunohistochemistry, biliary adenocarcinomas typically express CK7, CK19, CA19-9, CEA , MUC1 (Fig. 47.9), and MUC5AC (Adsay, 2004; Albores-Saavedra et al, 2000a; Lack, 2003). On occasion, these markers can be helpful in distinguishing certain other carcinomas that do not express these markers, such as hepatocellular carcinoma. However, none of

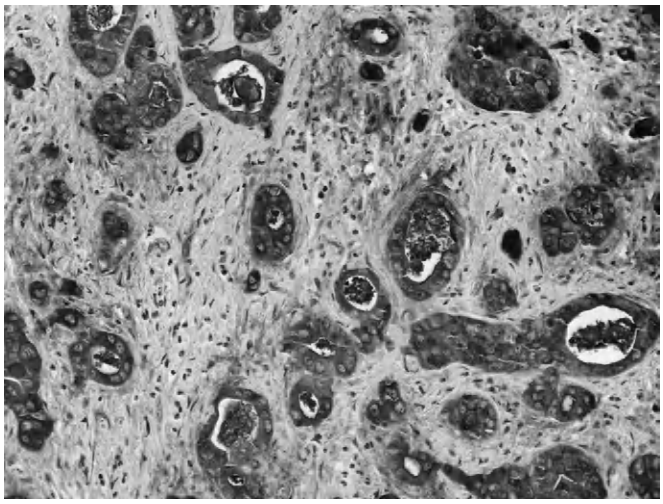


FIGURE 47.9. MUC1 in adenocarcinoma. Immunohistochemical studies may be useful in the differential diagnosis of biliary neoplasia. In this example, carcinoma cells show expression of MUC1, which often is negative in intestinal-type adenocarcinomas.

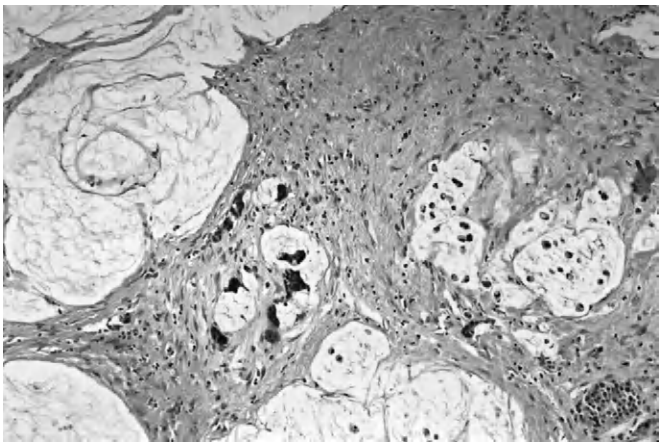


FIGURE 47.10. Mucinous carcinoma. Rarely, a biliary adenocarcinoma may be associated with abundant stromal mucin deposition. In this example, scant carcinoma cells are floating within the mucin pools.

these markers is specific enough to prove biliary origin for an adenocarcinoma when a metastasis from another organ is under consideration. Biliary adenocarcinomas generally lack expression of CK20 and CDX2 typically found in intestinal adenocarcinomas; TTF1 and napsin, found in pulmonary primaries; and hormone receptors. Mutations at codon 12 of the *KRAS* oncogene, seen in more than 90% of pancreatic ductal adenocarcinomas, are much less common in biliary adenocarcinomas (Rashid et al, 2002); the frequency of *KRAS* mutation appears to decrease from distal to proximal along the biliary tree. Similarly, loss of *SMAD4* is also less common in biliary than pancreatic adenocarcinomas (Argani et al, 2001). More than half of the cases have abnormal expression of TP53 and loss of heterozygosity at 8p, 9q, and 18q; amplification of *ERBB2* is also reported in more than half.

Other Types of Carcinomas in the Biliary Tract

Other carcinomas of glandular epithelial origin, in the gallbladder and biliary tract are classified separately from pancreatobiliary adenocarcinomas (Adsay, 2004; Albores-Saavedra et al, 1996, 2000a, 2010; Lack, 2003). *Intestinal-type adenocarcinomas* (Albores-Saavedra et al, 1986) are morphologically similar to their counterparts in the gastrointestinal tract. *Signet ring cell carcinomas* are characterized by a diffusely infiltrative pattern of individual cells, often with signet ring morphology because of intracellular mucin; a cordlike growth pattern may also occur in the biliary tract but is exceedingly uncommon. *Mucinous adenocarcinomas* may be seen in some cases, with extensive mucin production associated with stromal mucin deposition (Fig. 47.10), usually mixed with conventional adenocarcinomas; this subtype can occur with intraductal papillary neoplasms. Some studies suggest that the prognosis of mucinous adenocarcinomas may be more favorable than that of conventional pancreatobiliary-type adenocarcinoma (Bosma, 1990). *Adenosquamous carcinomas* (Nishihara et al, 1994) are rare tumors in which a mixture of glandular and squamous differentiation is seen in variable amounts. *Clear-cell carcinomas* (Vardaman & Albores-Saavedra, 1995) are described, in which the morphologic features resemble those of renal cell carcinoma.

Some patterns of biliary carcinoma lack gland, mucin, or papilla formation. *Undifferentiated* (Fig. 47.11) and *sarcomatoid* carcinomas (Appelman & Coopersmith, 1970; Nishihara & Tsuneyoshi, 1993; Suster et al, 1987) probably represent the least differentiated end of the spectrum of adenocarcinomas, in which glandular differentiation is no longer detectable; these patterns can coexist with conventional adenocarcinomas, pointing to the close relationship of these tumor types. In sarcomatoid carcinomas the cells acquire mesenchymal characteristics, including a spindle shape; in some cases "heterologous" elements, such as bone and cartilage, occur. In the absence of a more epithelioid or glandular component or preinvasive neoplasia within the bile ducts, these tumors may be difficult to distinguish from true sarcomas. Some examples of undifferentiated carcinomas are associated with abundant osteoclast-like giant cells and are referred to as *undifferentiated carcinoma osteoclastic-like giant cells* (Haratake et al, 1992; Husek, 1990; Ito et al, 1992). It has been well documented that these giant cells are in

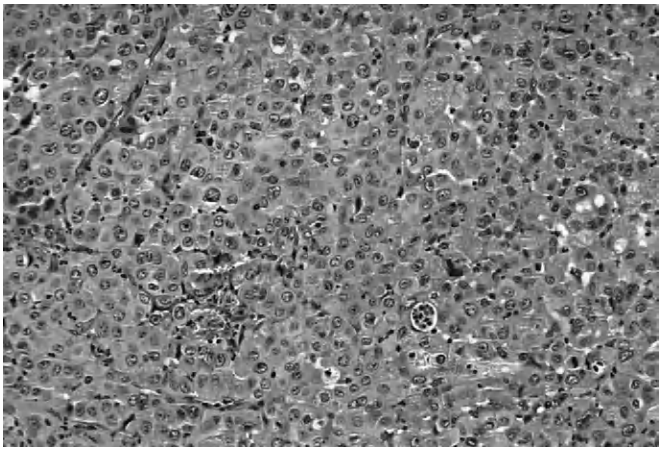


FIGURE 47.11. Undifferentiated carcinoma. This carcinoma is characterized by a diffuse, sheetlike growth pattern of large cells with prominent nucleoli.

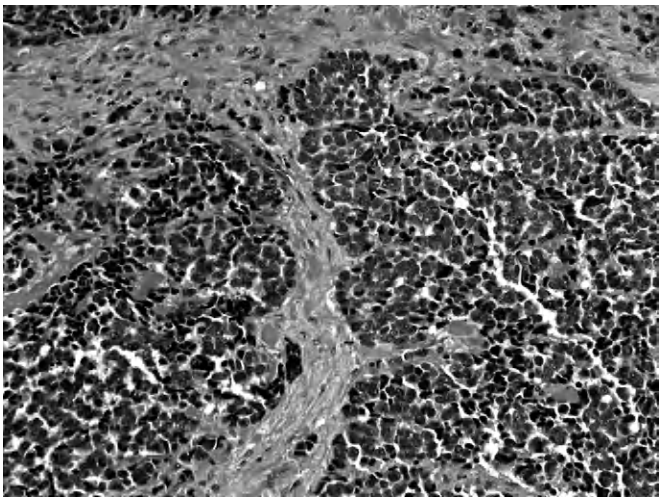


FIGURE 47.12. Small-cell carcinoma. The cells have very high nucleus/cytoplasm ratio with only minimal cytoplasm. Molding of nuclei is apparent, and the chromatin pattern is finely granular.

fact of histiocytic origin, and the malignant cells in this tumor are the mononuclear cells in the background.

Small-cell carcinoma (Komminoth et al, 2010; Maitra et al, 2001; van derWal et al, 1990) also occurs in the region of biliary tree, predominantly in the gallbladder or distal CBD. Small-cell carcinomas (Fig. 47.12) are defined by the same histologic criteria applied to their counterparts in the lung, including high nucleus/cytoplasm ratio, molding of nuclei, diffuse chromatin pattern, and absence of nucleoli. Small-cell carcinomas are high-grade neuroendocrine carcinomas; therefore neuroendocrine markers such as chromogranin, synaptophysin, and CD56 are often detectable by immunohistochemistry. *Large-cell neuroendocrine carcinomas* may also occur in this region (Komminoth et al, 2010; Papotti et al, 2000).

Pathologic Evaluation of Biliary Specimens with Carcinomas

Clinically Relevant Pathologic Parameters in Biliary Carcinomas

TUMOR TYPE. Whether the tumor is a conventional pancreatobiliary invasive adenocarcinoma or another type of neoplasm is important (Bivins et al, 1975). For instance, intraductal papillary neoplasms with focal microinvasion have a significantly better prognosis, and undifferentiated carcinoma has a worse outcome.

INVASIVE VERSUS NONINVASIVE COMPONENTS. For carcinomas with predominantly intraluminal growth (intraductal papillary neoplasms are discussed later), the extent of the noninvasive and invasive components should be considered separately. In fact, cases of biliary adenocarcinomas associated with an unusually protracted clinical course are often predominantly intraductal papillary neoplasms.

PATHOLOGIC STAGE. The size and depth of the tumor are the most important aspects of pathologic staging of biliary carcinomas (Choi et al, 2010; Greene et al, 2002; Hong et al, 2007). There are, however, pitfalls in establishing the depth of the tumor in some parts of the biliary tract, where unlike other sites, such as the gastrointestinal tract, the layers that constitute the duct walls are not well defined. In particular, in parts of the CBD the interface of the mucosa with the muscular layer and the interface of the muscle with the perimuscular tissue are highly irregular, which hinders the accurate evaluation of tumor depth. Similarly, in the intrapancreatic segment of the common bile duct, the demarcation of the common bile duct from pancreatic lobules is highly variable, and how to evaluate invasion into the pancreas is controversial (Hong et al, 2005).

GRADING. The grading scheme advocated by the World Health Organization (WHO) (Albores-Saavedra et al, 2000c) is based on the percent of the tumor showing glandular differentiation, specifically, tubule formation. If more than 95% of the tumor is composed of tubules, it is well differentiated; 40% to 95% is moderately differentiated, and 5% to 39% is poorly differentiated. Those without any glandular differentiation are regarded as undifferentiated.

PERINEURAL AND VASCULAR INVASION. Although the prognostic significance of perineural and vascular invasion has not been fully established, these are nevertheless regarded as components of the pathologic evaluation, especially in resection specimens.

ASSESSMENT OF SURGICAL MARGINS. Proper orientation of the specimen with identification of the margins by the surgical team using sutures or dyes often proves very helpful for accurate evaluation of the surgical margins, especially in complex specimens. The status of the resection margins is an important factor predictive of recurrence (Weber et al, 2001). Bile duct margins typically are amputated from the specimen and submitted *en face,* whereas hepatic and soft tissue margins are inked and sections are submitted perpendicular to the margin.

NONINVASIVE EPITHELIAL NEOPLASIA

Dysplasia (Biliary Intraepithelial Neoplasia)

Dysplasia, also called *biliary intraepithelial neoplasia* (BilIN; see Fig. 47.6), can be seen in mucosa adjacent to invasive biliary carcinomas and, on occasion, as an incidental finding in specimens obtained for other reasons (Albores-Saavedra et al, 1980; Laitio, 1983; Ojeda et al, 1985; Suzuki et al, 1989; Yamagiwa, 1989; Zen et al, 2007). In general, it is a radiographically and grossly occult process characterized by cytoarchitectural atypia of the biliary epithelium, including nuclear enlargement, irregularities, loss of polarity, and mitotic activity. Based on the degree of atypia, dysplasia is graded as *low, intermediate,* or *high grade* or *BilIN1, BilIN2,* and *BilIN3,* respectively (Zen et al, 2007); the high-grade category has been historically referred to as *carcinoma in situ*. Among biliary organs, dysplasia is most common and best studied in the gallbladder, where high-grade dysplasia has been reported in up to 3.5% of routine cholecystectomy specimens (Chan, 1988; Ojeda et al, 1985); this figure is reported to be higher in geographic regions with a higher prevalence of gallbladder carcinoma. The incidence of dysplasia in surgical specimens in the remainder of the biliary tract appears to be much lower. However, when hepatic explants for cirrhosis resulting from alcohol abuse or hepatitis C are systematically evaluated, dysplasia—particularly the low to intermediate grade—is found in more than half of the cases (Wu et al, 2009).

However, the diagnostic criteria for dysplasia are highly subjective, and reactive atypia in the biliary epithelium as a result of inflammation or stenting is very difficult to distinguish from dysplasia, rendering the intraoperative frozen section evaluation of bile duct margins challenging. On the other hand, in patients with invasive carcinoma, dysplasia may be difficult to distinguish from retrograde mucosal involvement by invasive carcinoma, a phenomenon referred to as *colonization* of the surface epithelium. For these reasons, the true frequency of dysplasia in the biliary tract is difficult to determine. It should also be noted that the concept of BilIN, proposed in analogy to pancreatic intraepithelial neoplasia (PanIN) in the pancreas (Zen et al, 2007), is thus far largely based purely on morphologic findings in the biliary epithelium. Molecular alterations supporting the neoplastic nature of all these lesions, analogous to the frequent clonal mutations in the *KRAS* oncogene found in PanINs, have yet to be documented.

In the gallbladder, dysplasia associated with invasive carcinomas appears to have no bearing on the prognosis. Cases of gallbladder dysplasia detected incidentally in the absence of invasive carcinoma appear to be clinically silent and have no documented clinical consequences, provided that the gallbladder has been extensively examined histologically to exclude occult foci of invasive carcinoma. However, data from the Surveillance Epidemiology and End Results (SEER) program of the National Cancer Institute show that one third of the patients with high-grade dysplasia (carcinoma in situ) of the gallbladder died of carcinoma in 10 years, although all were alive at 5 years, suggesting that either a small invasive carcinoma was missed or the patients developed a second malignant neoplasm elsewhere in the biliary system (Albores-Saavedra et al, 2000a). Extrapolating from these observations, a "field effect" phenomenon may occur in some cases, and patients with high-grade gallbladder dysplasia, especially if it is extensive, probably should have some surveillance to screen for subsequent invasive biliary carcinoma. In the bile ducts, high-grade dysplasia rarely is detected in the absence of invasive carcinoma, so the clinical significance of isolated dysplasia is unclear. Such patients would presumably also have an increased risk of developing invasive bile duct carcinomas, and careful examination of the biliary tree to exclude a synchronous, discontinuous focus of invasive carcinoma would seem prudent.

Mass-Forming Intraepithelial Neoplasms

Exophytic, mass-forming neoplasms that project into the lumina of the gallbladder or bile ducts include a family of related entities that have been designated by different terms depending on the location of the tumor, its architecture, and the cell types it comprises. Most of these neoplasms are predominantly formed of papillary structures or tubular glands and some cases have a mixture of both. In the gallbladder, the term *adenoma* is used for localized, generally small tumors that may be tubular, papillary, or tubulopapillary and are further subdivided into pyloric gland, intestinal, foveolar, and biliary types based on the morphology of the epithelium (O'Shea et al, 2002). Pyloric gland adenoma (tubular adenoma, pyloric gland type) is by far the most common type and typically is found as an incidental polyp less than 1 cm composed of tightly packed, cytologically bland pyloric-type cells in routine cholecystectomy specimens (Albores-Saavedra et al, 2010). Exophytic gallbladder neoplasms composed of complex biliary-type epithelium with more marked atypia, a predominantly papillary architecture, and more diffuse involvement of the gallbladder mucosa are regarded as *intracystic papillary neoplasms* (Albores-Saavedra et al, 2010). Most have high-grade dysplasia, which should be graded on the basis of the most severe focus. These tumors have also been designated *noninvasive papillary carcinoma* when high-grade dysplasia is present (Albores-Saavedra et al, 2000a).

Adenomas are uncommon in the bile ducts, and most exophytic bile duct tumors are collectively designated *intraductal papillary neoplasms*, including cases previously reported as *papillomatosis* (Albores-Saavedra et al, 2010; Gouma et al, 1984; Sagar et al, 1993; Taguchi et al, 1993). Most intraductal papillary neoplasms of the bile ducts have high-grade dysplasia (see Fig. 47.7) and were previously designated *noninvasive papillary carcinoma* (Albores-Saavedra et al, 2000b). In contrast to dysplasia or BilIN, intraductal papillary neoplasms can be identified grossly as soft, polypoid tumors within the bile duct lumen. Most are relatively localized within a segment of the bile duct, although multicentric or diffuse involvement can occur, as in so-called *papillomatosis* (Gouma et al, 1984; Sagar et al, 1993; Taguchi et al, 1993). Cystic dilation of the bile ducts may occur (Zen et al, 2006), and some cases exhibit mucin hypersecretion (Shibahara et al, 2004). The epithelial cell types in intraductal papillary neoplasms include pancreatobiliary, gastric, intestinal, and oncocytic (Albores-Saavedra et al, 2010; Ji et al, 2008; Martin et al, 2002; Shibahara et al, 2004; Tanaka et al, 2009), similar to the spectrum of intraductal papillary mucinous neoplasms (IPMNs) of the pancreas. Some authors have referred to these tumors as *biliary IPMNs* (Abraham et al, 2003; Chen et al, 2001; Kim et al, 2000; Shibahara et al, 2004; Tamada et al, 2002). However, differences in the frequency and types of associated invasive carcinoma, as well as the morphology and staining, are significant (Klimstra, 2002). Accumulating data suggest regional geographic differences in the proportion of intraductal papillary neoplasms with the different cell types, perhaps related to varying etiologic factors in different parts of the world (Shibahara et al, 2004). In Asian patients, for example, an association of intraductal papillary neoplasms with *Clonorchis* infection has been reported (see Chapter 45; Jang et al, 2008).

Exophytic intraepithelial neoplasms of the biliary tree are biologically benign when no invasive carcinoma is present, so the detection of a component of invasive carcinoma is key to the pathologic evaluation of these tumors. Small gallbladder adenomas may display high-grade dysplasia, but invasive carcinomas are very rare. In contrast, intracystic papillary neoplasms of the gallbladder and intraductal papillary neoplasms of the bile ducts have associated invasive carcinomas in more than half of all cases (Choi et al, 2010; Paik et al, 2008; Shipov & Aizikov, 1992). Conversely, in some patients with invasive adenocarcinomas, a focal, residual, intraductal papillary neoplasm component is identifiable; in fact, many adenocarcinomas with a polypoid gross appearance represent this latter group. Intraductal/intracystic papillary neoplasms have an excellent prognosis if they can be completely resected, and patients with minimally invasive carcinoma also have a favorable prognosis (Albores-Saavedra et al, 2000b). Once there is a significant amount of invasive carcinoma, however, the prognosis approaches that of biliary adenocarcinomas that do not arise from papillary precursors. Most invasive carcinomas arising in intraductal papillary neoplasms are conventional tubular adenocarcinomas, similar to other bile duct carcinomas. Some cases have a mucinous

(colloid) pattern, usually when the intraductal neoplasm is of the intestinal type. Undifferentiated carcinoma and high-grade neuroendocrine carcinoma have also been reported (Albores-Saavedra et al, 2010).

One lesion to be distinguished from intraductal papillary neoplasms of the bile ducts is biliary mucinous cystic neoplasm, also know as *hepatobiliary cystadenoma* (Albores-Saavedra et al, 2010; Devaney et al, 1994; Wheeler & Edmondson, 1985). Biliary mucinous cystic neoplasms are analogous to mucinous cystic neoplasms of the pancreas and are also regarded as a type of mass-forming preinvasive neoplasm. They form multilocular cystic lesions that occur predominantly in adult women and exhibit pathognomonic hormone receptor–expressing ovarian-type subepithelial stroma (Grayson et al, 1996). The lining epithelium is composed of cuboidal to columnar cells, sometimes with abundant apical mucin. Papillary projections may be identified in the cyst lumen. Although most biliary mucinous cystic neoplasms show benign cytoarchitectural features, some may harbor foci of high-grade dysplasia or invasive carcinoma. Carcinoma can be focal; for this reason, thorough histologic examination is warranted.

NEUROENDOCRINE NEOPLASMS

Carcinoid tumors (Fig. 47.13), also known as *well-differentiated neuroendocrine tumors,* may occur in any part of the biliary tract but tend to be more common in the gallbladder and CBD (Barron-Rodriguez et al, 1991; Ferrone et al, 2007; Kommi-noth et al, 2010; Maitra et al, 2000; Modlin & Sandor, 1997). They are seen predominantly in young or middle-aged adults. Most cases are nonfunctioning and patients present with signs and symptoms of biliary obstruction. Rare examples may be associated with von Hippel–Lindau syndrome (Sinkre et al, 2001). Grossly, carcinoid tumors form relatively well-demarcated nodules and may be polypoid and mucosa covered. They are fleshy, firm, and homogeneous on cut sections. Microscopically, carcinoid tumors are characterized by distinct nests separated by a fibrovascular stroma and strands of cells with round, uniform nuclei, coarsely granular chromatin, and abundant cytoplasm. Rarely, the cytoplasm may exhibit clear-cell, oncocytic, or signet ring–like changes, and a goblet cell variant has also been described. In general, carcinoid tumors are low-grade malignancies with an indolent clinical course. Rare carcinoid tumors mixed with adenocarcinoma (composite adenocarcinoma-carcinoid; Olinici & Vasiu, 1991) behave more like standard adenocarcinomas.

Focal neuroendocrine differentiation and carcinoid-like patterns may be seen in other neoplasms of the biliary tract that should *not* be classified as carcinoids. Rarely, paraganglioma (Caceres et al, 2001), a tumor that also displays neuroendocrine differentiation, may occur in the biliary tract.

OTHER TUMORS

Mesenchymal Tumors

Among the extremely rare mesenchymal tumors of the biliary tree (Adsay, 2004; Albores-Saavedra et al, 2000a, 2010; Lack, 2003), the one that warrants specific attention is *embryonal (botyroid) rhabdomyosarcoma* (Davis et al, 1969; Lack et al, 1981) because it is relatively more common and well characterized in this region. These are predominantly seen in children 3 to 4 years old and constitute 1% of all rhabdomyosarcomas. The tumor consists of a conglomerate of soft, mucosa-covered polyps filling the lumen. Sizes range from 3 to 14 cm, and the most common site is the CBD. Beneath the surface layer of flattened biliary epithelium is a dense zone of primitive spindle cells, representing the cambium layer. Cytoplasmic cross-striations may be seen, and skeletal muscle differentiation is demonstrable by immunohistochemical staining for actin, desmin, or myoD1. Although the prognosis is poor, multimodal therapy has resulted in long-term survival in some cases. Metastases occur in 40% of cases, but death usually is caused by the local effects of the tumor.

Granular cell tumor (Fig. 47.14) is another mesenchymal tumor that occurs in this region (Eisen et al, 1991), predominantly in the CBD. It is characterized by cells containing abundant acidophilic granular cytoplasm with occasional larger

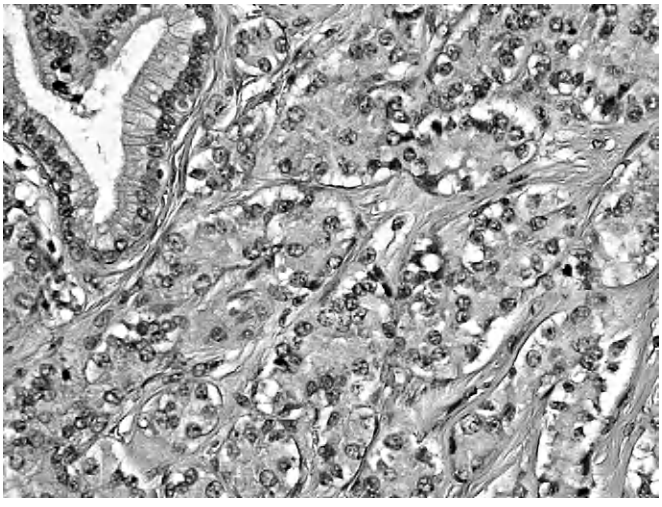


FIGURE 47.13. Carcinoid tumor (well-differentiated neuroendocrine tumor). Carcinoid tumors are characterized by relatively uniform cells with round nuclei and abundant cytoplasm, usually arranged in nests separated by prominent, delicate vasculature.

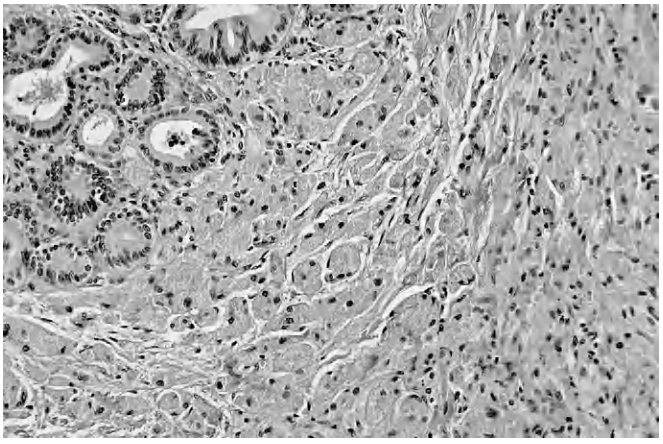


FIGURE 47.14. Granular cell tumor. The cells have small nuclei; abundant granular cytoplasm, occasionally with larger globules; and no nuclear atypia, necrosis, or mitoses.

globules. This tumor is of uncertain origin, but most evidence, including expression of S-100 protein, points toward a relationship to Schwann cells. Although it has an infiltrative appearance, it is a benign tumor with only minimal recurrence potential, even when incompletely excised.

A variety of other mesenchymal tumors have been documented in the biliary tree, both benign (neurofibroma, hemangioma, lipoma, lymphangioma, leiomyoma, ganglioneuroma, myofibroblastic tumors) and malignant (peripheral nerve sheath tumor, leiomyosarcoma, Kaposi sarcoma, angiosarcoma, fibrous histiocytoma, etc.), mostly as case reports (Adsay, 2004; Albores-Saavedra et al, 2000a, 2010; Lack, 2003). Before a case is classified as sarcoma, the possibility of a sarcomatoid carcinoma must be carefully considered.

Secondary Tumors

The biliary tree may be involved by a variety of carcinomas originating in other organs—especially the pancreas, stomach, colon, kidney, and breast—either by metastasis or direct invasion (Adsay, 2004; Albores-Saavedra et al, 2000a, 2010; Lack, 2003). Among these, metastatic renal cell carcinoma is notorious for mimicking a primary tumor because it may form a polypoid lesion, and the history of the primary tumor may be too remote to be appreciated in the preoperative clinical evaluation. Similarly, melanomas (Fig. 47.15) may also form polypoid lesions and mimic primary tumors, and often the history of melanoma may not be apparent. Metastases from primary colorectal cancer to the biliary epithelium have also been described (Povoski et al, 2000).

Hematopoietic Malignancies

The biliary tree may be involved by hematopoietic malignancies (lymphoma, myeloma, or leukemia) as a part of systemic disease; rarely, this may be the initial presentation (Adsay, 2004; Albores-Saavedra et al, 2000a, 2010; Lack, 2003). Primary tumors of the mucosa-associated lymphoid tissue type also have been reported.

TUMORLIKE LESIONS

In addition to sclerosing cholangitis, a few other nonneoplastic conditions of the biliary tract may present as tumors (see Chapters 42 and 48). Rarely, heterotopic tissue, especially pancreatic tissue (Inceoglu et al, 1993), may form a mass. Traumatic, or "amputation," neuroma (Sano et al, 1985), which is an exuberant regenerative proliferation of transected nerves, may form a tumor-like nodule, typically in the cystic duct stump, that may mimic a carcinoma. These are very rare and may be seen with obstruction-related signs and symptoms, sometimes several years after the intervention.

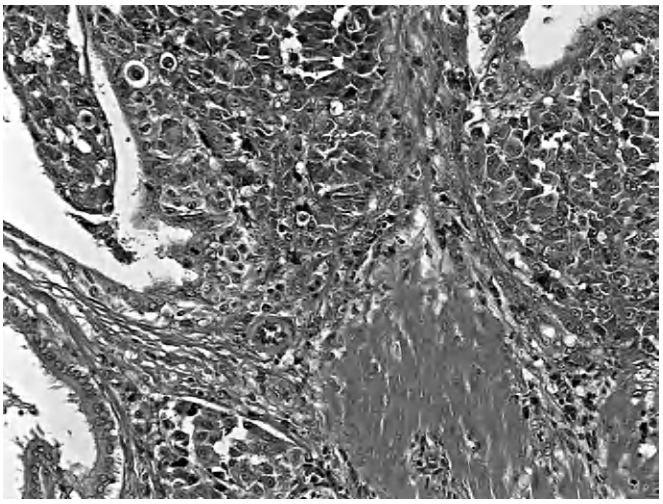


FIGURE 47.15. Melanoma. Metastatic melanomas may mimic primary carcinomas in the gallbladder and biliary tract, sometimes even forming polypoid tumors.

Certain types of tumorlike lesions occur rather frequently in the gallbladder but not often in the remainder of the biliary tree. Nonneoplastic polyps of various kinds may be seen, including cholesterolosis, lymphoid polyps, inflammatory (fibrous, granulation tissue) polyps, and hamartomatous polyps (Albores-Saavedra et al, 1993). Cystic change in Rokitansky-Aschoff sinuses and adenomyomas (Levesque et al, 1964) also commonly form pseudotumors in the gallbladder; however, these are not seen in the bile ducts.

Autoimmune sclerosing disorders related to autoimmune pancreatitis may affect the bile ducts and gallbladder. As in the pancreas, these are characterized by a dense, subepithelial lymphoplasmacytic inflammatory infiltrate; dense fibrosis, often with a storiform pattern; and obliterative venulitis. There is an association with elevated levels of immunoglobulin G4 in the serum, and immunoglobulin G4–expressing plasma cells can be found in large numbers within the lesions by immunohistochemistry (Kamisawa & Okamoto, 2008). These processes form a tumorlike mass that can be mistaken for carcinoma on imaging studies (Corvera et al, 2005). Some cases are associated with autoimmune pancreatitis (Wang et al, 2009), whereas others present with disease limited to the gallbladder or bile ducts, sometimes called *autoimmune cholangitis* (Deshpande et al, 2009).

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CHAPTER 48

Benign tumors and pseudotumors of the biliary tract

Adeel S. Khan and David C. Linehan

OVERVIEW

Painless jaundice is most frequently caused by obstruction of the extrahepatic bile duct by malignant periampullary neoplasms, but benign tumors and pseudotumors of the biliary tract, although rare, should be included in the differential diagnosis. Benign biliary tumors are clinical rarities that in the past have been the subject of infrequent case reports, usually combined with a review of the literature. In previous series, benign bile duct tumors have been reported in 0.1% of all biliary tract operations and have constituted only 6% of all extrahepatic bile duct neoplasms (Burhans & Myers, 1971). To date, fewer than 300 cases of benign bile duct tumors have been reported in the English literature. As shown in Table 48.1, benign neoplasms are derived from the epithelia or from nonepithelial structures that make up the normal bile duct (Levy et al, 2002). Similarly, pseudotumors or tumorlike lesions of the bile duct or other periampullary tissues can cause biliary tract obstruction and jaundice. When pseudotumors or nontraumatic inflammatory strictures of the extrahepatic bile duct are included, the incidence increases, with some surgical series reporting up to a 10% to 25% incidence of benign biliary pseudotumors (Corvera et al, 2005; Koea et al, 2004). Importantly, these series demonstrate that with current preoperative staging tools, it is often impossible to distinguish between benign and malignant etiologies for biliary obstruction, so preoperative tissue confirmation does not often alter management in resectable patients.

As a result of their rarity, benign tumors of the bile ducts are seldom considered in the differential diagnosis of obstructive jaundice. Symptoms may be present for a few days to several years, whereas the clinical presentation may mimic cholecystitis; biliary calculi; or ampullary, pancreatic, or bile duct cancer, all of which are much more common. In addition, true benign bile duct neoplasms must be differentiated from a number of inflammatory conditions they mimic, not only in presentation but in cholangiographic features and even appearance at laparotomy. Indeed, preoperative diagnostic and laboratory studies often cannot distinguish malignant from benign etiologies of bile duct obstruction, so preoperative biopsy in resectable patients usually is not indicated.

This chapter, after a discussion of biliary tract anatomy and embryology, addresses the clincial presentation and diagnostic workup of patients with benign tumors and pseudotumors of the biliary tract. Biliary lesions resulting from benign neoplasms or other benign conditions presenting as localized masses and causing biliary obstruction are classified in the following general categories: 1) papilloma and adenoma, 2) granular cell tumor, 3) neural tumors, 4) leiomyoma, 5) neuroendocrine tumors, and 6) pseudotumors (idiopathic benign biliary stricture or heterotopic tissue).

Biliary cystadenoma is not covered in this chapter because the lesion usually presents as an intrahepatic cystic neoplasm, which is difficult to differentiate from cystadenocarcinoma (see Chapter 79B). Indeed, benign and malignant epithelium frequently coexist, and histologic diagnosis is extremely difficult (Ishak et al, 1977; Marsh et al, 1974; Moore et al, 1984; Woods, 1981).

EMBRYOLOGIC AND ANATOMIC FACTORS

Benign tumors of a variety of histologic types have been observed in the extrahepatic ductal system. The embryology and anatomy of the region account for this to a large degree (see Chapter 1A). Embryologically, the extrahepatic biliary tree develops in close relationship to the liver, arising from a thickened area of endoderm on the ventral surface of the primitive gastrointestinal (GI) tract at the junction of the foregut and hindgut in the 3-mm human embryo during the fifth week of intrauterine life. This small outpouching is the anlage of the liver, extrahepatic biliary ducts, gallbladder, and the ventral bud of the pancreas.

Table 48.1

Benign Tumors and Pseudotumors that Can Cause Bile Duct Obstruction

Epithelial Tumors

Adenoma
Papilloma
Cystadenoma (intrahepatic)

Nonepithelial Tumors

Leiomyoma
Lipoma
Hemangioma
Lymphangioma
Granular cell tumor
Osteoma

Neural Tumors

Neurofibroma
Schwannoma
Neuroendocrine tumors

Pseudotumors

Idiopathic benign focal stricture
Lymphoplasmacytic sclerosing pancreatitis
Sclerosing cholangitis
Heterotopic tissue

Modified from Levy AD, et al, 2002: Benign tumors and tumor-like lesions of the gallbladder and extra-hepatic bile ducts: radiologic–pathologic correlation. Radiographics 22:387-413.

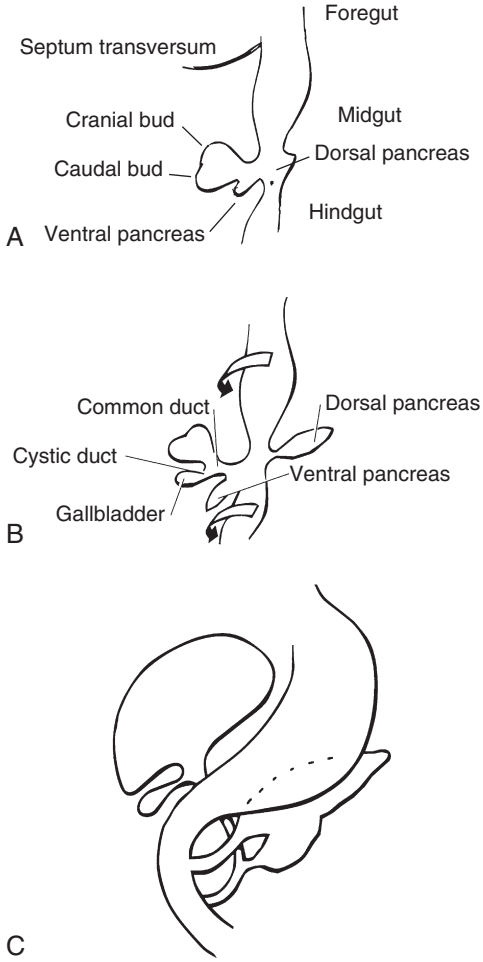


FIGURE 48.1. A, At approximately the fifth week of intrauterine life, a diverticulum evolves near the junction of the midgut and hindgut and grows into the ventral mesogastrium. The ventral pancreatic bud develops from the superior surface as the cranial sacculation and pushes cephalad into the septum transversum. **B,** The gallbladder and extrahepatic ducts develop from the caudal bud, and the liver develops from the cranial bud. The ventral pancreas evolves in close relationship to the developing common bile duct. **C,** At the 7-mm stage, left-to-right rotation occurs, resulting in subsequent fusion of the pancreas, gallbladder, duodenum, and extrahepatic bile ducts in their normal anatomic relationship.

A diverticulum evolves from this thickened area, which divides into a superior and inferior bud as it grows into the ventral mesogastrium (Fig. 48.1A). The ventral pancreatic bud develops from the superior surface of the diverticulum, proximal to the enlarging terminal sacculations. The cranial sacculation, the larger of the two, pushes ventrally and cranially into the septum transversum, which separates the thoracic from the celomic cavity. Composed of a solid mass of endodermal cells, it spreads out into the substance of the septum transversum, eventually forming the right and left lobes of the liver. Cephalad growth and extension of the cranial sacculation results in stretching of the endodermal cell mass from the duodenum to the liver, which eventually evolves into the extrahepatic biliary tree. At approximately the seventh week of intrauterine life, vacuolization takes place within the solid mass of cells of the primitive extrahepatic biliary tree and results in the development of a ductal lumen.

Before the 7-mm stage, the common bile duct (CBD) is attached to the ventral surface of the duodenum close to the ventral pancreatic bud. At the 7-mm stage, left-to-right rotation of the ventral pancreas and duodenum takes place so that the CBD eventually enters on the posteromedial surface of the duodenum (Fig. 48.1B and C). The gallbladder and cystic duct develop concurrently from the caudal portion of the primitive hepatic diverticulum during the same period (Lindner & Green, 1964).

The CBD lies in the right border of the hepatoduodenal ligament between serosal surfaces. The ductal wall is composed of mucosa, fibrous tissue, and serosa. Rare smooth muscle fibers may be found in the duct wall, but muscular tissue is not a prominent component. Thickness of the duct wall varies from 0.8 to 1.5 mm, with an average of approximately 1.1 mm (Mahour et al, 1967). The terminal end of the duct is invested with muscle fibers, as elegantly described by Boyden (1957). At this point the CBD usually joins with the major pancreatic duct, but they may fail to unite and enter the duodenum separately (Dowdy et al, 1961).

The mucosa lining the extrahepatic biliary tree consists of a single layer of columnar epithelium and a tunica propria containing mucous glands. Scattered chromogranin-positive cells can be formed in glands of the normal gallbladder neck, and rare cells immunoreactive for somatostatin have been found between the lining epithelium of the hepatic duct in patients with biliary disease (Dancygier et al, 1984). It has been observed that chronic inflammation of the biliary tract may result in intestinal metaplasia of the mucosa, which seems to result in an increase in the number of argentaffin cells (Kulchitsky cells). Barron-Rodriguez and colleagues (1991) have suggested that these changes may be the basis for the development of carcinoid tumors of the biliary tree. The epithelial surface of the duct is

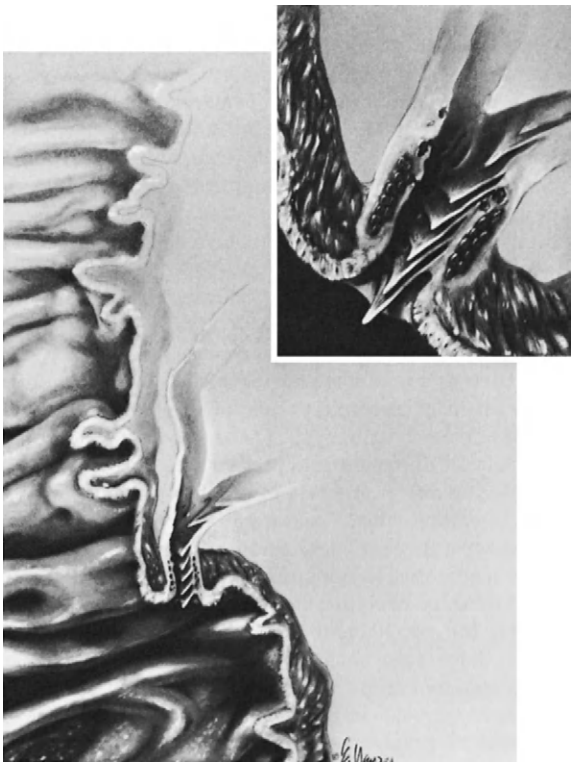


FIGURE 48.2. Artist's representation of the macroscopic anatomy of the choledochoduodenal junction, depicting the transverse valvules described by Brown and Echenberg (1964), which probably serve to prevent reflux from the duodenum.

generally flat except for tiny pits in the mucosa known as *sacculi of Beale,* which are luminal openings for the intramural mucous glands. As the duct penetrates the wall of the duodenum, the mucosa appears to become thickened and the surface roughened by longitudinal folds of mucosa, or *valvules,* particularly at the terminal end of the duct. According to Boyden (1936), the valvules were first described in the *Fabrica of Vesalius* (1543), followed later by a more detailed description by Santorini (1724). Brown and Echenberg (1964) described a more frequent occurrence of transversally oriented flaps or valvules that face the duodenal lumen and probably function to prevent reflux of duodenal contents into the biliary tree and pancreatic ducts (Fig. 48.2). Baggenstoss (1983) has also reported that free folds of ductal epithelia in the form of papillary processes may extend 2 to 3 mm beyond the Vaterian orifice.

Microscopically, a definite transition exists between the mucosa of the duct within the ampulla and the surrounding duodenal mucosa. The ductal mucosa exhibits numerous papillary processes much larger than the adjacent duodenal villi.

CLINICAL PRESENTATIONS AND DIAGNOSIS

Patients with benign biliary tract tumors, and often those with inflammatory masses masquerading as neoplasms, invariably present with clinical manifestations of jaundice. The onset of icterus may be insidious or intermittent, with few other symptoms. On the other hand, the presentation may be sudden and associated with colicky epigastric pain, referred to the back or shoulder, along with nausea and vomiting. There is seldom any significant weight loss, unlike patients with pancreas cancer or cholangiocarcinoma, who frequently present with jaundice, poor appetite, and weight loss (see Chapters 50B and 58B). Because these tumors are relatively slow growing, some of the clinical symptoms may be intermittent or gradually progressive over an extended period only to culminate with obstructive jaundice. No clinical symptoms are apparent that can help the physician differentiate a benign biliary tract tumor from other, more common causes of biliary tract obstruction.

Physical findings are likewise nonspecific: liver enlargement, a palpable gallbladder, tenderness to palpation in the right hypochondrium, and jaundice. Indeed, because of the lack of characteristic symptoms and physical findings, benign biliary tumors usually are not diagnosed preoperatively or antemortem (Chu, 1950).

Reports since the early 1970s have emphasized the usefulness of percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiopancreatography (ERCP) in the establishment of a preoperative diagnosis of extrahepatic obstruction and in distinguishing between calculus and tumor as a cause (see Chapter 18; Kittredge & Baer, 1975). Noninvasive imaging of the biliary tree with magnetic resonance cholangiopancreatography (MRCP) and high-quality computed tomography (CT) also now play a significant role in the diagnosis of these lesions. In their report of a patient with granular cell myoblastoma, Jain and colleagues (1979) suggested that an eccentric, short stenosis might be associated with a benign biliary tumor. However, obstructive changes identical to those seen in malignant neoplasms are not uncommon and indeed may be produced by inflammatory masses (Hadjis et al, 1985; Stamatakis et al, 1979). Although PTC and ERCP cannot distinguish between a benign tumor and a malignant process, adequate visualization of the ductal system can provide vital information concerning tumor location, extension, and size as well as the status of the intrahepatic ductal system. However, no preoperative diagnostic study is capable of reliably distinguishing benign from malignant tumorous obstruction of the biliary ducts. Endobiliary brush cytology has a high positive predictive value but, unfortunately, the negative predictive value is too low for clinical usefulness, particularly in the setting of a resectable tumor. Similarly, molecular study of cytology specimens, such as K-ras mutational analysis, has not shown improved diagnostic accuracy (Sturm et al, 1999). Newer minimally invasive tissue-acquisition techniques that include endoscopic, ultrasound-guided methods may improve diagnostic accuracy, although negative biopsy results still offer no assurances because of the suboptimal negative predictive value. Therefore these tests often do not often alter clinical management in the resectable patient (Byrne et al, 2004; Eloubeidi et al, 2004).

PAPILLOMA AND ADENOMA

The most common variety of benign tumor of the extrahepatic biliary tree is that arising from the glandular epithelium lining the ducts. Roughly two thirds of the benign neoplasms reported fall into the category of either *polyp, adenomatous papilloma,* or *adenoma.* Chu (1950), in his classic review of benign biliary neoplasms, found that 26 out of 30 cases studied were either papillomas or adenomas. A similar observation was made by Dowdy and colleagues (1962), when 36 of the 43 reviewed cases were noted to be either papillomas or adenomas. Since

1962, 58 additional patients have been added to the English literature (Bahuth & Winkley, 1966; Short et al, 1971; Sull & Brown, 1972; Archie & Murray, 1978; Lukes et al, 1979; Bergdahl & Andersson, 1980; Austin et al, 1981; Gouma et al, 1984; Van Steenbergen et al, 1984; Thomsen et al, 1984; Byrne et al, 1989; Loh et al, 1994; Chae et al, 1999; Fletcher et al, 2004; Kunisaki et al, 2005; Boraschi et al, 2007; Akaydin et al, 2009). Presently, we have traced a total of 120 patients reported in the English literature with benign polyps, adenoma, or cystadenoma.

A slight female predominance (1.3:1) in the incidence of these lesions has been noted, and although the average age at diagnosis is 58 years, the youngest recorded occurrence was in a 3-year-old child (Wardell, 1969). Leriche (1934) reported a massive papillomatous tumor weighing 750 grams, arising from the CBD of a 4-year-old child.

The anatomic distribution of papillomas or adenomatous lesions reported to date appears in Figure 48.3. The majority are found either in the ampulla or in close proximity to the Vaterian system (47%), and the CBD (27%) is the second most frequent site.

The onset of symptoms may vary from a few weeks to 35 years. Jaundice, a presenting symptom in more than 90% of patients (McIntyre & Pay-Zen, 1968), occurs intermittently in approximately 40% of patients. Most patients complain of right upper quadrant pain associated with the jaundice. Wright (1958) reported a patient with relapsing pancreatitis who was cured by excision of a CBD polyp that had prolapsed into the ampulla of Vater. Gallstones or biliary calculi are reported in only 20% of patients found to have benign extrahepatic ductal tumors. Cattell and Pyrtek (1950) suggest that recurrence of symptoms following cholecystectomy should suggest the possibility of a tumor in the ampullary area rather than biliary dyskinesia.

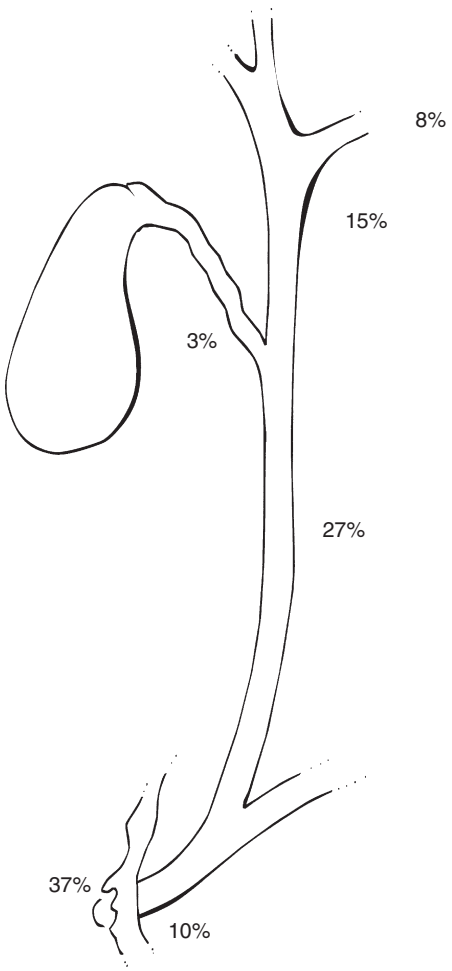


FIGURE 48.3. Location and frequency of papillomas and adenomas reported between the hepatic duct confluence and the ampulla of Vater.

A benign adenomatous tumor should be included on the differential list in all secondary operations performed for obstruction of the biliary tree. Interestingly, Kunisaki and colleagues (2005) described the case of a 54-year-old man who showed up with abdominal pain and jaundice 3 years after a cholecystectomy for cholecystitis and choledocholithiasis. ERCP revealed impingement of the common hepatic duct (CHD) at the level of the cystic duct, without filling of the cystic duct remnant. Reexploration for a presumed diagnosis of retained cystic duct stone revealed a 2-cm papillary adenoma of the cystic duct remnant, compressing the CBD (Mirizzi syndrome; see Chapter 42B) and causing symptoms. These lesions are generally soft, difficult to palpate, and present little or no resistance to exploring ductal probes; thus they are difficult to detect at operation and are more frequently detected by intraoperative cholangiography, ultrasonography, or choledochoscopy (see Chapter 21).

The radiographic features of extrahepatic bile duct adenomas are often difficult to distinguish from cholangiocarcinomas and even ampullary cancers (see Chapters 50B and 59; Figs. 50B.2 and 50B.8). Ultrasound typically reveals a nonshadowing intraluminal mass, sometimes with a visible pedicle or stalk but more often with a sessile architecture. ERCP will show a lobulated intraluminal filling defect that is often obscured by mucin accumulation in mucin-producing adenomas. Lesions developing in the lower CBD near the ampulla may actually protrude through the papilla and be visible endoscopically, and we have seen such a case. In contrast, malignant lesions developing in the ampullary area tend to be infiltrative and are usually larger, firmer, and more likely to be ulcerated at presentation. Initial symptoms related to bleeding in association with benign adenomatous polyps of the bile ducts are exceedingly rare, although Teter (1954) recorded a death due to massive hemorrhage secondary to such a lesion.

Kozuka and colleagues (1984) suggested that most polypoid or papillary cancers of the extrahepatic duct arise from preexisting adenomas (see Chapter 50B). In a review of 43 carcinomas of the extrahepatic tree, they identified an adenomatous residue in nine (21.4%). Gouma and colleagues (1984) reported a case of intrahepatic bile duct papillomata associated with changes of nuclear atypia and reviewed the literature, suggesting that it is reasonable to regard these lesions as having low-grade malignant potential. Pathologic review of the specimens often show foci of carcinoma in situ, atypia, or dysplasia; these may point to a premalignant nature, but the rarity of such lesions makes definitive conclusions difficult.

Although it has been suggested that biliary adenomas may be the result of a focal reactive process to injury, the exact etiology remains uncertain. Miyano and colleagues (1989) demonstrated that these lesions could be produced experimentally by performing a choledochopancreatostomy in puppies, a model for anomalous choledochopancreatic ductal junction. After

several years, mucosal hyperplasia was observed in 100% of the dogs, and almost half had bile duct adenomas.

Austin and colleagues (1981) reported two patients who presented with obstructive jaundice and solitary, nonparasitic liver cysts. At reoperation, the first was found to have a papillary adenoma in the CHD, which was excised; the second had an obstructing polypoid cystadenoma of the left hepatic duct compressing the right biliary system.

A possible association was proposed between solitary, nonparasitic liver cysts and adenomas of the ductal system (Austin et al, 1981), and the clinical course of these two underscores the difficulty in detection of soft adenomatous tumors obstructing the extrahepatic biliary tree. An association between nonparasitic cystic biliary disease and the development of cholangiocarcinoma has also been described in the literature (Schiewe et al, 1968; Jones & Shreeve, 1970; Gallagher et al, 1972; Dayton et al, 1983; Nasu et al, 1971; Leroy et al, 1979). However, any association between these overt malignancies and the presence of preexisting adenoma or papilloma within biliary cysts is difficult to prove.

TREATMENT

In 1962, Dowdy and others reviewed the literature and detailed the operative procedures for 37 patients with papillomas or adenomas. They reported that four out of the five recognized tumor recurrences were in patients who had had local tumor excision as primary therapy. Since that time, 41 additional patients have been reported in whom both the operative procedure and follow-up data are available: 15 underwent local excision, presumably including the stalk and/or base of the polyp, and two of these (13%) had recurrences that necessitated reoperation. Also, 14 patients with lesions in or near the ampulla had local excision by way of transduodenal papillotomy without a recorded tumor recurrence, and in three other patients, curettage of a polypoid tumor was accomplished without recurrence. In addition, 4 patients had local resection of the duct, one had local resection of the duct wall without recurrence, and four underwent pancreaticoduodenectomy for a low-lying tumor initially thought to be malignant.

Based upon reported experience, it appears that the choice of operative procedure is dependent upon the patient's age, medical condition, and the location of the tumor; any procedure should include total resection of the lesion, preferably with some duct wall. Lesions arising in the ampulla can successfully be managed by wide local excision in most instances.

MULTIPLE BILIARY PAPILLOMATOSIS

Multiple biliary papillomatosis (MBP) is a rare disease characterized by the presence of numerous mucin-secreting papillary adenomas within the extrahepatic and/or intrahepatic biliary tree. It is generally considered a low-grade malignancy with a propensity for local recurrence after resection. Histologically, these papillomas consist of fibrovascular stalk covered by a single layer of epithelial cells with apical mucin and minimal pleomorphism (Tsui et al, 2000). The etiology and pathogenesis of MBP remain unclear. One hypothesis includes induction of mucosal metaplasia or hyperplasia in response to chronic biliary inflammation by stones, infection, or pancreatic juice. Terada (1991) and Cheng (1999) suggested a relationship between MBP and Caroli disease that may indicate a congenital etiology. Most of the reported cases are from Asia, which may reflect a racial or geographic predeliction, but such an association has not yet been established.

Most patients with intrahepatic papillomatosis are initially seen with obstructive jaundice that is frequently intermittent and often complicated by cholangitis. This complication is a result of partial and intermittent obstruction of the bile duct by tumor fragments, mucus plugs, or blood clots. In some patients, however, the only symptom has been abdominal pain. The history may extend for more than 20 years and may be associated with anemia as a result of bleeding. In only two cases have associated cholelithiasis and choledocholithiasis been reported. If left untreated, the disease ultimately results in death from sepsis or liver failure.

Preoperative diagnosis is made radiologically and may be made more frequently now, since the advent of widespread availability of endoscopic retrograde cholangiography (ERC), MRCP, and direct cholangioscopy. The endoscopic examination of the papilla of Vater often shows a widely open orifice with mucin drainage. Direct or noninvasive cholangiography shows multiple intraluminal filling defects that typically do not move with vigorous catheter irrigation and hence can be differentiated from mucin or stones. The lesions can be intrahepatic, extrahepatic, or both (D'Abrigeon, 1997). Tompkins and colleagues (1976) have emphasized the value of intraoperative endoscopy in the evaluation of the biliary tree for multiple lesions. Several studies have suggested that endoscopic ultrasound (EUS) can be at least as accurate as ERCP in diagnosing MBP, with the additional advantage of visualizing invasion of the duct wall or adjacent vessels and metastasis to locoregional lymph nodes in the presence of malignancy (Mukai, 1995; Ma, 2000; Lai, 2002).

Caroli and colleagues (1959) first reported the occurrence of diffuse papillomatosis in both the intrahepatic and extrahepatic ducts of a 42-year-old male. Although the presenting symptoms were of abdominal pain and jaundice, the patient was also noted to be anemic secondary to hemobilia. A T-tube was placed in the biliary tree, through which 10 L of mucoid secretions were drained in the first 24 hours following surgery. The patient died 48 hours later. It was noted that the biliary secretions had a high potassium content, which the authors postulated might be analogous to the mucoid diarrhea and hypokalemia associated with villous adenoma of the colon. In the same report, a second patient presented with cholangitis and was reported to be cured following a left hepatectomy for papillomatosis confined to the left intrahepatic ducts.

Since Caroli's first report in 1959, an additional 87 cases of MBP have been reported in the English literature. A review of 78 cases by Yeung and colleagues (2003) showed a male/female ratio of approximately 2:1, with a mean age at presentation of 63 years (range, 6 to 83 years). The most common symptoms at the initial visit were abdominal pain and jaundice. Almost half of the patients (42%) had diffuse intrahepatic and extrahepatic disease, and 27% had only intrahepatic disease; another 27% had only extrahepatic disease, and two patients had involvement of the gallbladder. Malignant transformation was seen in 42% of the patients at the time of presentation. Only 55% of the patients were candidates for a curative resection, and the remainder were palliated in various ways, including choledochoscopic laser ablation, iridium-192 intraluminal therapy, percutaneous cholangioscopic electrocoagulation, and

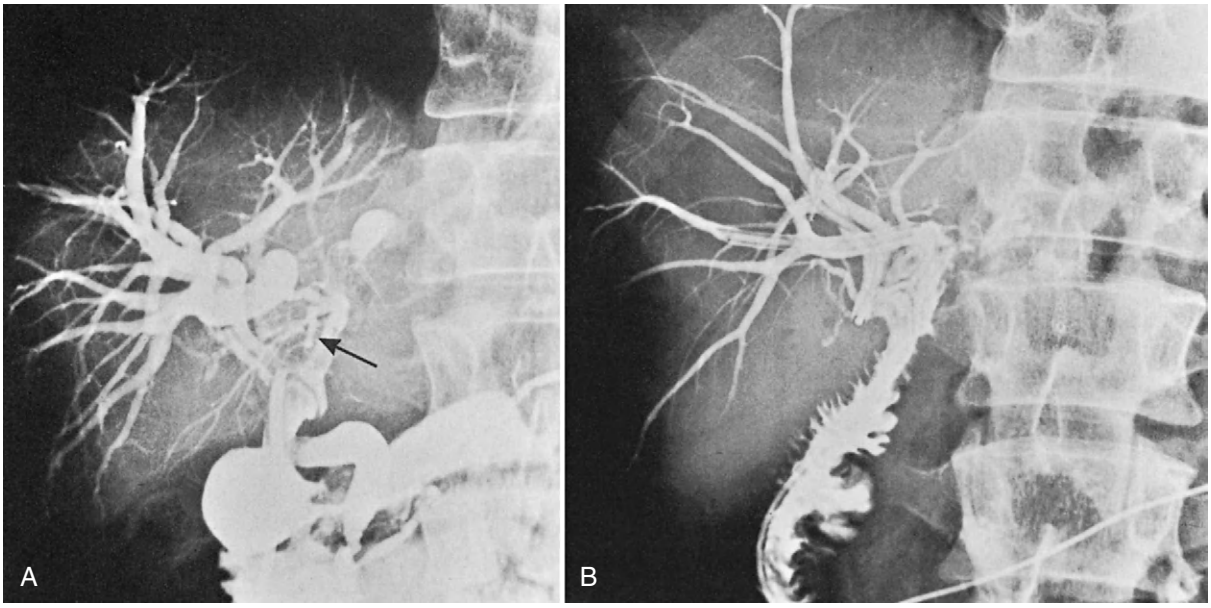


FIGURE 48.4. A, T-tube cholangiogram obtained after initial choledochotomy in a patient who presented with intermittent attacks of jaundice. At operation, loose tumor particles were found in the common bile duct and proved to be fragments of papilloma. The T-tube enters the main right hepatic duct, and a residual filling defect is seen in the left ducts (*arrow*). **B,** Tube cholangiogram following subsequent left hepatic lobectomy and reconstruction by hepaticojejunostomy Roux-en-Y. The anastomosis is widely patent. The tube was removed, and the patient was alive and well 4 years later. *(Reproduced with permission from Gouma DJ, et al, 1984: Intrahepatic biliary papillomatosus. Br J Surg 71:72-74.)*

combined cholangioscopic laser ablation and external beam radiotherapy.

The low-grade malignant potential of MBP has been the subject of many studies. Cattell and colleagues (1962) suggested that these lesions had a low-grade malignant potential after reporting recurrence of obstructive jaundice in a patient within a year of undergoing successful placement of a T-tube. Indeed, risk of malignant transformation with nuclear atypia or carcinoma in situ is significant, and it is commonly observed in papillary lesions. Ohta and others have reported point mutations of the *KRAS* gene in benign papillary lesions (Ohta et al, 1993). Padfield and colleagues (1988) documented basement membrane discontinuities in three patients consistent with patterns accompanying malignant tumors; they cautioned that papillary neoplasms, although histologically benign, should be considered premalignant. Gouma and others (1984) reported a similar case, in which intrahepatic bile duct papillomata (Fig. 48.4A) were associated with changes of nuclear atypia. The patient was treated by left hepatic resection that included the base of the papillomatous lesions, and biliary-enteric continuity was established by hepaticojejunostomy to the residual right liver (Fig. 48.4B). The patient was symptom-free and without recurrence 4 years after surgery.

The authors concur with Cattell's view that it is reasonable to regard these lesions as having low-grade malignant potential. A further patient has been reported who lived approximately 5 years before dying of cholangitis (Madden & Smith, 1974). Treatment had included partial hepatic resection, choledochoduodenostomy, and weekly courses of carmustine (BCNU). Some decrease in the amount of tumor was observed following therapy, and although cellular atypia was reported, no malignant changes could be documented at autopsy. Of the two recently reported patients, an 80-year-old male died after choledochoduodenostomy because of variceal bleeding, but the second, reported by Gertsch and colleagues (1990), was reported alive and well 15 months after curettage (Hubens et al, 1991).

The extent, distribution, and secondary obstructive changes induced by these soft lesions present management challenges. If the lesions are limited and confined to one liver lobe, liver resection should be strongly considered, although attempted radical surgery by means of hepatic lobectomy has been reported in only five cases: One of these was alive and well at 4 years (Gouma et al, 1984). One further case was reported alive 6 months after surgery with no evidence of recurrence, and one died 6 years after resection with diffuse malignant tumors in the right lobe of the liver after initial left hepatic lobectomy. The remaining two patients had multiple papillomatoses, apparently localized to the left hepatic duct at operation; both had recurrence in the common and right hepatic duct 6 months and 3 years after lobectomy and died 5 and 6 years, respectively, after the first operation. It seems clear, therefore, that even major resectional surgery for this lesion has a high recurrence rate; Gouma and colleagues (1984) were able to trace 12 patients for whom adequate follow-up figures were available and found mean survival to be 28 months. It should be noted, however, that although no patient survived more than 6 years, the only 5-year survivals were in three cases submitted to radical surgery.

A report by Helling and Strobach (1996) documents a 67-year-old female patient with papillomatosis and high-grade dysplasia occluding the left hepatic duct who was successfully managed by a left hepatic lobectomy. The patient was disease free 20 months following resection. The authors reviewed the literature and commented on three important features of this lesion: 1) a high recurrence rate, with approximately 50% of patients requiring reoperation; 2) copious mucin production

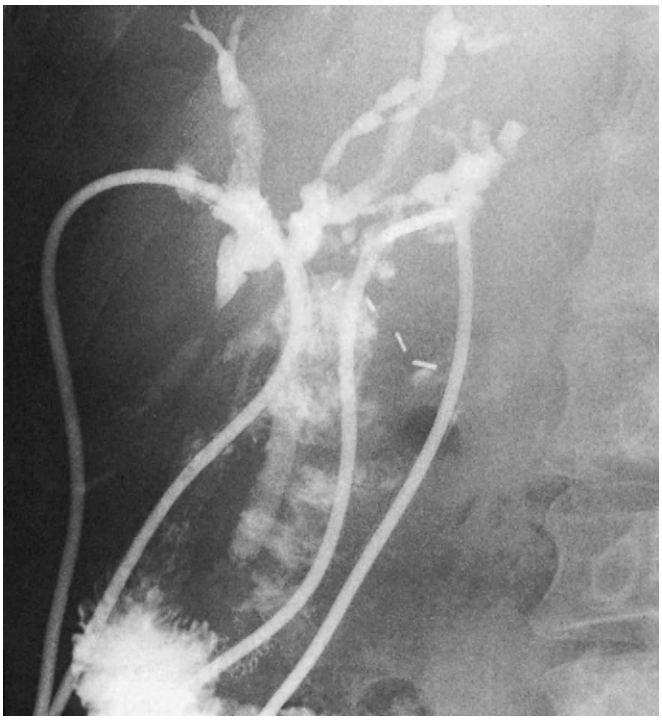


FIGURE 48.5. Bilateral U-tubes placed through hepaticojejunostomy to the right and left hepatic ducts in a patient with multiple intrahepatic biliary papillomatoses. The patient, a middle-aged woman, presented with chronic iron deficiency anemia followed by the onset of jaundice. At initial operation, papillomata at the orifice of the right and left hepatic ducts were curettaged, and bilateral U-tubes were placed. Satisfactory palliation of jaundice was obtained for 18 months, but malignancy supervened; the patient died of recurrent biliary obstruction and liver failure.

that may lead to fluid electrolyte imbalances, and 3) malignant transformation, which is observed in a significant percentage of patients (Helling & Strobach, 1996). Since this report, five additional extrahepatic benign papillary lesions have been recorded (Loh et al, 1994; Lam et al, 1996; Meng et al, 1996; Khan et al, 1998; Yeung et al, 2003).

An intubational approach to papillomatosis affecting the entire biliary tree has been described (Fig. 48.5). Employment of the approach described by Hutson and colleagues (1984) and by Barker and Winkler (1984) seems reasonable: a Roux-en-Y hepaticodochojejunostomy is fashioned in such a manner as to allow a jejunal fistula for access to the biliary tree postoperatively and permit repeated curettage or intubation. Meng and colleagues (1996) reported on the use of holmium: YAG laser therapy via choledochoscopy and successful ablation after curettage; after four sessions of choledochoscopy and laser therapy, all tumor was ablated, and there were no signs of tumor recurrence at 6 months. Lastly, consideration might be given to chemotherapy, especially with agents excreted by the liver. Recently Beavers and colleagues (2001) reported the case of a 59-year-old patient with recurrent cholangitis from diffuse biliary papillomatosis that persisted even after a left hepatectomy and hepaticojejunostomy. Because of deteriorating liver function, she was placed on the list for liver transplantation and underwent successful orthotopic liver transplantation (OLT) with a Roux-en-Y hepaticojejunostomy. She was alive and asymptomatic 9 months following the surgery. Similarly, Dumortier and colleagues (2001) reported their results for a 61-year-old patient with recurrent symptoms from diffuse MBP who underwent an OLT and pancreatoduodenectomy. Her final pathology revealed three foci of invasive carcinoma limited to the biliary wall. After 22 months of follow-up, the patient remained asymptomatic, without evidence of tumor recurrence or metastasis.

In summary, a reasonable approach to this rare condition includes preoperative and operative cholangiographic diagnosis, early choledochotomy, and assessment of the intrahepatic biliary tree by choledochoscopy. If the tumor is bulky, curettage is performed to identify the sites of origin within the bile duct. Care must be taken to perform choledochoscopy of as many intrahepatic ducts as possible. When the papillomatosis appears to be confined to one lobe, it is reasonable to perform a radical resection consisting of partial hepatectomy that includes excision of all involved ducts. Although this does not guarantee freedom from recurrence, it offers good palliation and carries the best possibility of long-term cure. In cases of papillomatosis involving both the right and left ductal system, radical surgery is not applicable. It seems best to avoid long-term external drainage as a preliminary palliative procedure, and curettage or internal bypass is indicated. Some form of hepaticojejunostomy may be helpful, as it allows percutaneous access to the biliary tract. Recent results with OLT seem promising and should be considered in patients with diffuse disease who are not candidates for any other curative procedures. The prognosis should be regarded as poor if complete removal of the tumor is not possible.

GRANULAR CELL TUMORS

Granular cell tumor (GCT) is a very rare benign tumor of uncertain etiology occasionally encountered in the extrahepatic biliary tree. First desribed in 1926 as *granular cell myoblastoma,* recent debate has ensued about the cell of origin. Levy and colleagues (2002) suggest that, rather than myoblasts, the tumor may originate fom Schwann cells, evidenced by its immunohistochemical staining with antibodies to S-100 protein normally found in the central nervous system or in Schwann cells in the peripheral nervous system. Honjo and colleagues (2003) recently reported a case of extrahepatic biliary Schwannoma, basing this diagnosis on S-100 positivity on immunohistochemistry. Similarly, Altavilla and colleagues (2004) described reactivity to S-100 and neuron-specific enolase antibodies in GCT of the intrapancreatic portion of the CBD.

GCTs constitute less than 10% of all benign tumors of the extrahepatic biliary tree (Dursi et al, 1975). Although reported in anatomic locations as varied as the pituitary and appendix, the lesions are most commonly encountered in the tongue, breast, and subcutaneous tissues, with less than 1% of GCTs occurring in the extrahepatic biliary tree (Paskin et al, 1972; Dursi et al, 1975). The most frequent sites of occurrence of extrahepatic biliary GCTs are the CBD, cystic duct, and gallbladder. The average age of patients with this tumor is 34.5 years. More than 80% of documented cases have occurred in females, 66% of whom are black, and 15% of patients have multiple lesions (Vance & Hudson, 1969).

Since Coggins' original autopsy report in 1952, 67 additional patients have been reported with GCTs of the

extrahepatic biliary tree; 33 had lesions arising from the common hepatic or CBD, 19 from the cystic duct, 5 from the cystic duct and CHD, and 4 from the hepatic duct (Kittredge & Baer, 1975; Mauro & Jacques, 1981; Cheslyn-Curtis et al, 1986; Lewis et al, 1993; MacKenzie et al, 1994; Yazdanpanah et al, 1993; Ferri Romero et al, 1994; Foulner, 1994; Karakozis et al, 2000; Pongtippan et al, 2000; te Boekhorst et al, 2000; Altavilla et al, 2004; Lochan et al, 2006). In addition, one patient had lesions involving the cystic duct and the hepatic duct (Sanchez & Nauta, 1991); two had lesions involving the cystic duct, gallbladder, and CBD (Aisner et al, 1982; Martin et al, 2000); and two had cystic duct, CHD, and CBD lesions (Balart et al, 1983; Butler & Brown, 1998). GCT arising from the ampulla of Vater has only been reported once (Khalid et al, 2005).

The fact that extrahepatic ductal granular cell myoblastomas are found more commonly in black females is attested to in the literature: 38 of 54 females recorded are black, 10 are Caucasian, 3 are Asian, and 5 are of unspecified racial origin. Three black males and a single male child of unspecified race have been reported. Multiple tumors within the extrahepatic biliary tree have been reported in seven patients (Kittredge & Baer, 1975; Mauro & Jacques, 1981; Aisner et al, 1982; Sanchez & Nauta, 1991; Cheslyn-Curtis et al, 1986; MacKenzie et al, 1994; Martin et al, 2000). Multifocal tumors have been noted in seven patients with bile duct lesions, two patients with separate gastric tumors, four with synchronous skin lesions, in one individual with lesions in the mesentery and trachea, and in one patient with simultaneous lesions in the trachea and CHD (Mulhollan et al, 1992; LiVolsi et al, 1973; Whisnant et al, 1974; Assor, 1979; Manstein et al, 1981; Orenstein et al, 1984; Yang & Ortiz, 1993). Clinical symptoms associated with granular cell myoblastoma arising in extrahepatic bile ducts tend to be those of painless jaundice, and a presentation of upper abdominal pain and colic is more commonly associated with lesions arising in the cystic duct. Other described symptoms include anorexia, weight loss, nausea, and vomiting. Granular cell myoblastoma might be included in the differential diagnosis of obstructive jaundice seen in a black female, especially if she has a tumor nodule in the tongue, breast, or subcutaneous tissue, but such a clinical presentation would be extraordinarily rare.

The majority of tumors have been described as firm to palpation, localized, confined to the wall of the CBD or cystic duct, and generally less than 3 cm in diameter. Because granular cell tumors are typically small, they may not be visible on US or CT scan, and only intrahepatic and extrahepatic biliary dilation are seen. ERCP often reveals a short, focal, annular stricture, and MRCP may show similar findings. Usually these tumors do not invade surrounding structures, and the mucosa overlying the tumor has generally been intact and histologically normal. On cut section, granular cell myoblastoma is yellowish white, and microscopically it consists of fibrous tissue diffusely infiltrated by large, elongated polygonal cells or cells containing small, dark nuclei and an abundant eosinophilic granular cytoplasm on a hematoxylin and eosin stain. The cytoplasmic granules are markedly positive with the periodic acid-Schiff reaction (Fig. 48.6), and frozen-section diagnosis has been shown to be adequate for delineating these lesions. Although this tumor usually does not metastasize, local recurrence may occur, especially if excision is incomplete.

The histogenesis is uncertain and is marked by controversy. The tumor was initially termed *granular cell myoblastoma,*

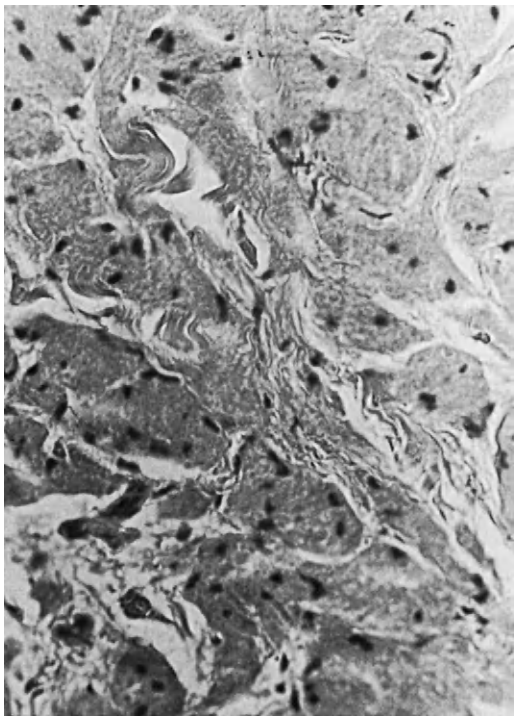


FIGURE 48.6. Granular cell myoblastoma excised from the common bile duct showing large polygonal cells with indistinct cell borders. Also typically demonstrated are uniform, small, round nuclei surrounded by finely granular, eosinophilic cytoplasma. (Hematoxylin and eosin, ×120.)

because it was thought to be derived from "myoid cells." Indeed, characteristics of the cells in tissue culture suggest a myogenic origin (Murray, 1951). Moreover, it is now generally regarded that granular cell tumors arise from the Schwann cell in that the tumor cells react to antibodies with S-100 protein, normally found in the central nervous system and in peripheral Schwann cells (Armin et al, 1983). Treatment should consist of total excision of the bile duct segment containing the lesion with reconstruction by Roux-en-Y choledochojejunostomy or hepaticojejunostomy for lesions arising in the CHD (Manstein et al, 1981; MacKenzie et al, 1994). Altavilla and colleagues (2004), Karakozis and colleagues (2000), Chandrasoma and Fitzgibbons (1984), Manstein and colleagues (1981), and Raia and colleagues (1978) have reported successful management of lesions occurring in the intrapancreatic bile duct by pancreaticoduodenectomy. Two local recurrences were documented, and three patients required second procedures because of incomplete local excision (Dursi et al, 1975; Manstein et al, 1981; Butler & Brown, 1998; Khalid et al, 2005). To date, malignancy has not been observed in any reported extrahepatic glandular cell tumor.

NEUROENDOCRINE TUMORS

Endocrine tumors of the extrahepatic bile ducts are exceedingly rare. The only endocrine cells that have been normally demonstrated in the extrahepatic ducts are somatostatin-containing D cells (Dancygier et al, 1984). However, it has been postulated that metaplastic changes in the biliary epithelium, perhaps resulting from inflammation, may lead to the development and appearance of argyrophile cells (Barron-Rodriguez et al, 1991).

Because the biliary system is derived embryologically from the foregut, it is not surprising that cells immunoreactive for gastrin, serotonin, and somatostatin have been demonstrated in the biliary tree (Angeles-Angeles et al, 1991). Only a handful of cases have been reported, most of which have been hormonally nonfunctional. Reported tumors fall into one of three categories: carcinoid, gastrinoma, or somatostatinoma. A clinical picture of obstructive jaundice is the usual presentation, although a carcinoid was found incidentally in the unobstructed CBD of an explanted cirrhotic liver following OLT (Hao et al, 1996). To date only one patient has been recorded as having a functioning endocrine tumor, a 52-year-old female with a 2-year history of recurrent duodenal ulcer whose peptic disease was cured when her gastrinoma was excised from the CBD (Mandujano-Vera et al, 1995).

Since Davies' original report in 1959, an additional 61 documented cases of carcinoid tumors arising in the extrahepatic bile ducts have been reported in the literature (Felekouras et al, 2009). In the cases reviewed, jaundice was the most common presenting symptom (two thirds of patients), and a third had right upper quadrant abdominal pain. Other symptoms included back pain, weight loss, nausea, and vomiting. Analysis also indicates an increased incidence of extrahepatic carcinoid tumors in younger people along with a slight female predominance (1.9:1). There have been 35 reported cases of biliary carcinoids arising in the CBD, 14 of tumors originating in the hilum, 7 in the cystic duct, and 5 arising in the CHD (Davies, 1959; Bumin et al, 1990; El Rassi et al, 2004; Nesi et al, 2006; Felekouras et al, 2009). A recent report from Memorial Sloan–Kettering Cancer Center (MSKCC) documented a case of isolated carcinoid arising from the right hepatic duct (Ferrone et al, 2007; Fig. 48.7A and B). The clinical course is indolent, and endoscopic or percutaneous biopsy or brush cytology tends to be notoriously nondiagnostic, which makes preoperative diagnosis difficult. Most small neuroendocrine tumors of the CBD are found incidentally during biliary tract operations performed for other indications, and the final diagnosis is made postoperatively, after histologic and immunohistochemical examination. Although some patients with carcinoid tumors of the extrahepatic bile ducts may have slightly elevated levels of urinary 5-hydroxyindoleacetic acid, none of the published cases have reported carcinoid syndrome. Biliary neuroendocrine tumors have an indolent biologic behavior and exhibit limited propensity for metastatic disease, which has been reported only in a third of the patients at presentation. Most patients are candidates for curative resection, with excellent long-term results.

The choice of operation depends on the location of the tumor and the extent of disease. Hilar, CHD, and proximal CBD neoplasms can be treated with regional lymphadenectomy, Roux-en-Y hepaticojejunostomy (Jutte et al, 1986; Bumin et al, 1990), and en bloc resection of the tumor and adjacent bile ducts. In the uncommon situation of carcinoid tumors arising at or above the biliary confluence, distinguishing this diagnosis from cholangiocarcinoma prior to operation is nearly impossible; an approach to resection that includes en bloc partial hepatectomy is required for cholangiocarcinoma (see Chapter 50B; Ferrone et al, 2007; see Fig. 48.7A and B). Patients seen initially with tumors of the distal bile duct are generally managed with pancreatoduodenectomy, or Whipple procedure (Vitaux et al, 1981; Nesi et al, 2006). There have been three reported cases of patients with cystic duct tumors treated with a simple cholecystectomy (Goodman et al, 1984; Hermina et al, 1999; Nahas et al, 1998). Long-term disease-free survival up to 20 years has been reported, even in the presence of distant metastases (Davies, 1959; Little et al, 1968; Hao et al, 1996; El Rassi et al, 2004).

No absolute histologic criteria are available by which to judge the malignant potential of biliary endocrine tumors. Larger tumors are thought to be more aggressive with respect to metastatic potential; however, metastases with very small carcinoid tumors of the cystic duct have been reported (Hermina et al, 1999). Ki-67 cell index greater than 5% also does not

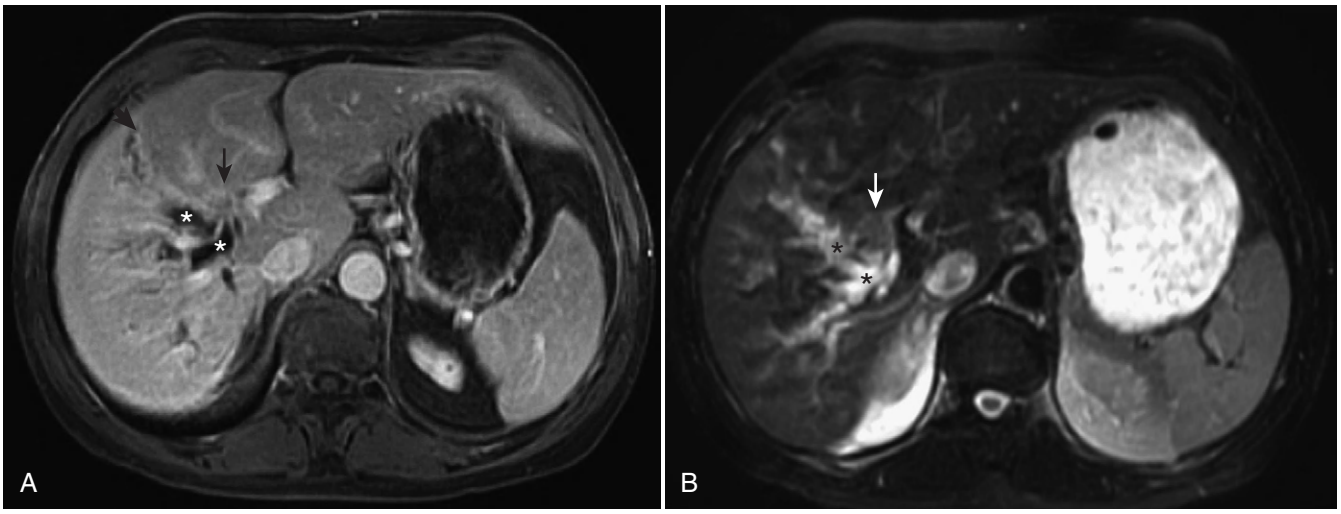


FIGURE 48.7. Magnetic resonance cholangiopancreatogram (MRCP) showing a carcinoid tumor arising from the right hepatic duct. **A,** Contrast-enhanced axial T1 sequence. The tumor (*arrow*) is located at the confluence of the right anterior and posterior sectoral ducts, which are dilated (*asterisks*). Despite the absence of vascular inflow involvement by tumor, a notable difference in perfusion was found between the right and left hemilivers (*arrowhead*) with hypertophy of the left side, the apparent result of long-standing biliary obstruction. **B,** Axial MRCP image of the same patient. The tumor (*arrow*) at the confluence of the dilated right and left anterior sectoral ducts (*asterisks*), which appear white in this sequence.

necessarily predict aggressive behavior (Ligato et al, 2005). Given the good long-term results with surgical resection, it is generally agreed that curative surgical resection is the most relevant prognostic factor in management of endocrine tumors of the extrahepatic biliary ducts.

NEURAL TUMORS

The incidence of neural tumors would appear to be lower than expected, when the abundant network of neural tissue that normally surrounds the extrahepatic bile ducts is considered. In 1955, Oden reported the occurrence of a neuroma in a 40-year-old woman who presented with jaundice and mild epigastric discomfort. At operation, a cystic tumor was found displacing the CBD medially. The cyst was extirpated, but the wall contiguous to the CBD was left in situ. Several common duct stones were also removed.

Neurofibromas of the bile duct are extremely uncommon, although they have been reported in patients with type 1 neurofibromatosis (NF). Because GI involvement occurs in approximately 25% of patients with NF, biliary involvement is more commonly secondary to obstructing duodenal or periampullary neurofibromas (Mendes, 2000). Although bleeding, perforation, and obstruction as a result of intussusception, volvulus, and stenosis have been reported, only one other instance of obstructive jaundice secondary to visceral neurofibromatosis has been recorded in the literature. Curry and Gray (1972) reported the autopsy finding of a submucosal nodular tumor 25 mm in diameter protruding into the duodenum around the ampullary opening.

Sarma and colleagues (1980) reported a hilar tumor arising in the left hepatic duct and surrounding the right hepatic duct that was deemed unresectable. The biopsy submitted at that time was interpreted as poorly differentiated carcinoma. A tube was placed through the lesion, and the patient was readmitted with cholangitis several times over the next 7 years. A second exploration revealed total obstruction of the left hepatic duct, partial obstruction of the right hepatic duct, and cystic degeneration of the left lobe of the liver. Another tube was placed through the tumor into the right hepatic duct, and the cystic left liver lobe was drained by a Roux-en-Y jejunal loop. Review of the fresh biopsies and the original material were each interpreted as paraganglioma. Although these tumors commonly arise in the adrenal gland as pheochromocytoma, extraadrenal lesions are more commonly found in the neck, the mediastinum, and around the aorta. Paragangliomas have been observed in the gallbladder, GI tract, and the genitourinary tract; this appears to be the first lesion reported in the extrahepatic biliary tree.

LEIOMYOMA

Leiomyomas are the most common benign tumors of the esophagus, stomach, and small intestine; in the extrahepatic biliary tree, they are among the least common. The scanty presence of muscle fibers in the normal CBD probably accounts for the fact that only seven such lesions have been reported. Each of these patients presented with progressive jaundice, itching, nausea, vomiting, and weight loss. The first case was reported in a 31-year-old female with a 2-cm tumor confined to the intrapancreatic segment of the CBD, which was locally excised, along with some of the overlying pancreatic tissue; the duct of Santorini was also ligated, and the proximal bile duct was anastomosed to the jejunum. This patient was reported well 3 years following surgery (Archambault & Archambault, 1952). Fernandez and Gonzales-Bueno (1974) recorded a leiomyoma occuring at the ampulla of Vater. A third patient, reported by Kune and Polgar (1976), was a 49-year-old male treated by pancreatoduodenectomy for a 4-cm tumor in the intrapancreatic segment of the CBD, which was assumed to be a pancreatic carcinoma at surgery. Microscopically, the lesion was observed to arise from the bile duct wall, and the patient was well 28 months after operation. The fourth patient died of septicemia following ERCP demonstration of a tumor obstructing the lower part of the CBD, seemingly as a result of external compression. Autopsy examination revealed an angioleiomyoma of the CBD; the mucosa overlying the tumor was observed to be intact (Ponka et al, 1983). Mandeville and Stawski (1991) reported a fifth patient in whom a leiomyoma of the hepatic duct bifurcation was treated with excision and hepaticojejunostomy. Yamaoka and colleagues (1993) described the case of a 49-year-old male with distal common bile duct leiomyoma who was treated with pancreatoduodenectomy. Recently, Goo and colleagues (2006) described a seventh case of biliary leiomyoma in a 39-year-old woman who underwent a pylorus-preserving pancreatoduodenectomy for a distal CBD stricture. Final pathology disclosed leiomyoma of the CBD accompanying severe fibrosis.

PSEUDOTUMORS

Nonmalignant lesions may cause obstruction of the extrahepatic biliary ductal system and closely resemble neoplasms at investigation and even at laparotomy; they occur frequently enough to be seriously considered in the differential diagnosis of any lesion suspected to be a bile duct tumor. In a recent large series of 132 consecutive patients undergoing resection for a suspicious hilar lesion, 20 (15%) had a histopathologically proven benign tumor diagnosed as chronic fibrosing or erosive inflammation, sclerosing cholangitis, or a granular cell tumor (Gerhards et al, 2001). Similarly, the incidence of benign pseudotumors is approximately 10% to 20% in several recently published large series of surgically treated patients with proximal biliary obstruction (Corvera et al, 2005; Koea et al, 2004; Binkley et al, 2002). Interestingly, all of these published series show that preoperative diagnosis is difficult, and resection remains the only reliable way to rule out malignancy. In a more recent study of 171 patients with a presumptive diagnosis of hilar cholangiocarcinoma, benign strictures were ultimately identified in nine (5.3%; Are et al, 2006). In this study, the combination of vascular involvement and lobar atrophy were much more common in patients with cholangiocarcinoma (38%) than in those with other diagnoses (3.3%, $P < .001$; see Chapter 50).

The possibility of a benign diagnosis, although uncommon, must always be kept in mind. Lesions should not be assumed to be neoplastic without histologic proof, and certainly a presumed diagnosis of neoplasm should not be the signal for incomplete drainage procedures carried out surgically, percutaneously, or endoscopically. Such maneuvers are inevitably followed by infection that necessitates stent exchange, and they are likely to complicate subsequent curative surgery.

Primary sclerosing cholangitis (PSC) should be strongly suspected in a patient with biliary stricture in the setting of ulcerative colitis; the prevalence may be as high as 90% when routine

rectal and sigmoid biopsies are obtained (Tung et al, 1996; see Chapter 41). Diagnosis can be established by demonstration of characteristic multifocal stricturing and dilation of the intrahepatic or extrahepatic biliary tree on cholangiography (Lee & Kaplan, 1995). Untreated disease almost always leads to complications of hepatic failure and cholestasis, and liver transplantation is the treatment of choice for patients with advanced disease. Five-year survival rates as high as 85% have been described after liver transplantation for patients with PSC (Langnas et al, 1990; Graziadei et al, 1999).

INFLAMMATORY TUMORS

Stamatakis and colleagues (1979) reported the occurrence of a benign inflammatory mass of the CBD in a 13-year-old girl who presented with obstructive jaundice and abdominal pain. PTC demonstrated complete obstruction of the CHD with intraluminal shouldering, suggesting a tumor. At operation, a 3-cm spherical mass was found to be closely applied to the porta hepatis, necessitating excision of the confluence, CHD, and CBD with reconstruction by Roux-en-Y hepaticojejunostomy. Pathologic examination demonstrated nearly complete obstruction of the CHD and CBD by an encapsulated yellowish-brown mass. Microscopically, the encased bile duct exhibited loss of muscular coat, loss of ductal epithelium, and replacement by collagenous fibrous tissue. Scattered throughout the fibrous tissue were foci of acute inflammatory cells. These authors concluded that the mass represented an excessive inflammatory reaction to some local chemical or infective irritant and further speculated that the lesion might represent a form of localized sclerosing cholangitis. The child was reported fit and active 1 year after treatment.

Haith and colleagues (1964) reported a somewhat similar clinical occurrence in a 6-year-old boy with a lesion located in the distal CBD, treated successfully by pancreatoduodenectomy. A similar case was reported by Golematis and colleagues (1982) of a 23-year-old man who presented with obstructive jaundice and a lesion at the confluence of the hepatic ducts. The lesion was successfully resected and histologically appeared to represent a localized area of sclerosing cholangitis. One other such case has been reported by Heuser and Polk (1983).

Standfield and colleagues (1989) reported an interesting group of 12 patients with localized strictures of the extrahepatic biliary system. No patient had a history of trauma, gallbladder stones, or antecedent diseases generally associated with sclerosing cholangitis. All patients were found to have histologic evidence of chronic inflammation, fibrosis, and epithelial ulceration. These authors felt that this entity was distinct from sclerosing cholangitis in that the mucosa remains intact in sclerosing cholangitis.

At the Hammersmith Hospital, London, Hadjis and colleagues (1985) showed eight out of 104 patients submitted to surgery with a clinical diagnosis of malignant obstruction at the confluence of the bile ducts to have benign disease. The benign nature of the lesion was not certain in 6 of these patients even at the time of laparotomy. Comprehensive investigation had failed to give an accurate preoperative diagnosis, although biliary obstruction was accurately shown in all patients, and preoperative assessment using cholangiographic and angiographic data indicated that all were potentially resectable. For this reason, and in light of the safety of local excisional surgery and excellent quality of life obtained (Beazley et al, 1984; Blumgart et al, 1984), palliation by intubational methods was not attempted. In all patients, the obstructing lesion was removed, biliary reconstruction was by means of Roux-en-Y hepaticojejunostomy, and liver biopsy was obtained.

Microscopic examination of the biopsies taken from the bile ducts of these patients showed an extensive increase of fibrous tissue in all instances. Subepithelial mucous glandular proliferation was evident in all patients, but not in every specimen, and the glandular cells were always well differentiated with elongated to round nuclei showing normal polarity. Most glands were surrounded but not replaced by fibrous tissue. In some instances, glands appeared to be distorted by fibrous tissue coursing between acini. Striking nerve trunks were observed in four of the patients but not in all the specimens, some of which were very small. Accumulations of lymphocytes were present in most specimens and were sometimes perivascular, sometimes perineural, but not diffusely infiltrating the wall of the bile duct, with little adventitial inflammation. Sections of associated lymph nodes and of the gallbladder were unremarkable, and no vascular changes were identified. In no specimen was evidence of dysplastic, neoplastic, or preneoplastic cytologic change found. Nuclei were normal, no single epithelial cells were encountered within connective tissue, and no pools of mucin were found. Similar changes were reported by Ikei and colleagues (1989).

One patient with overt signs of peritonitis following previous laparotomy underwent emergency exploration and was found to have a loculated intraabdominal bile collection and a subhepatic abscess, which was drained; renal function was impaired at the time of laparotomy, and the patient subsequently died of multiple system failure. No tumor was found at the hilum of the liver, but a sclerotic lesion was confirmed together with proximal large duct obstruction.

No operative deaths were recorded in the eight patients submitted to elective surgery, and seven were alive and asymptomatic from 16 to 46 months after operation. One patient required reoperation for a further stricture and remained reasonably well for 2 years, at which time she developed recurrent episodes of cholangitis with cholangiographic evidence of progression of intrahepatic sclerosing cholangitic lesions; she died 30 months after a second operation.

Although the cholangiographic picture of diffuse sclerosing cholangitis is usually characteristic (see Chapter 41), this is not necessarily true of the localized form of the disease. The diagnostic difficulty is compounded in that cholangiocarcinoma has been described in association with, or as a complication of, PSC. It is important to emphasize that in the presence of a localized high bile duct stricture, and in the absence of angiographic involvement, it is impossible, without specific biopsy or cytology, to make a definitive diagnosis in this situation. The marked desmoplastic reaction that even small hilar cholangiocarcinoma often excites, together with the ductal and glandular hyperplastic changes consequent of long-standing obstruction and severe secondary cholangitic changes, comprise the main pathologic factors responsible for histologic difficulty in differentiating benign from malignant disease (Weinbren & Mutum, 1983). Indeed, some believe that cases of sclerosing cholangitis localized at the hilum may be instances of slow-growing sclerosing carcinoma, and that it is only a matter of time before such a lesion declares its malignant potential. However, extensive studies at the Royal Postgraduate Medical School have demonstrated characteristic features of malignant biliary disease (see

Table 48.2

Malignant Masquerade Tumors of the Extrahepatic Biliary Tree Reported Since 1987

Reference	Number	Location	Etiology	Treatment
Schroyens et al (1987)	1	CBD	Sclerosing cholangitis	Liver transplant
	1	CBD	Sclerosing cholangitis	Autopsy
Standfield et al (1989)	12		Nontraumatic inflammatory strictures	Excision Roux-en-Y (7)
				Hepaticojejunostomy (3)
				Intubation (2)
Wetter et al (1990)	2		Mirizzi syndrome	
	3		Granuloma	
	3		Focal stenosis	
Tsunoda et al (1991)	1	Confluence	Sclerosing cholangitis	Partial hepatectomy
Oren et al (1991)	1	CHD	Sclerosing cholangitis	Stent and liver transplant
Gerhards et al (2001)	20	Hilus	Fibrosis, granular cell tumor	
				Resection
Binkley et al (2002)	4	Hilus	Fibrosis	Resection
Koea et al (2004)	12	Hilus	Idiopathic benign biliary stricture (10)	Resection
			Stone disease (2)	
Corvera (2005)	22	Hilus	Lymphocytic sclerosing cholangitis (2)	Resection
			PSC (3)	
			Granulomatous process (3)	
			Idiopathic benign biliary stricture (8)	
			Stone disease (6)	

For data prior to 1987, see text.
CBD, common bile duct; CHD, common hepatic duct; PSC, primary sclerosing cholangitis

Chapter 47; Weinbren & Mutum, 1983), and these were found to be absent in all cases in the series reported by Hadjis and colleagues (1985). Six patients remained symptom free with normal liver function at a mean follow-up period of 28.3 months.

In a more recent series, Koea and colleagues (2004) presented a New Zealand experience of 49 consecutive patients who presented with obstructive jaundice as a result of a stenosing lesion at the hepatic hilus. The final tissue diagnosis in 12 of these patients was benign (idiopathic benign biliary stricture in ten and stone disease in two). MRI, US, CT scan, and cholangiography were performed in all patients. At least half of the benign lesions had radiologic features suggestive of malignancy. Routine measurement of serum CEA and CA19-9 was also performed. Marked elevation of CA19-9 was shown to have a high positive predictive value, but five of 32 patients with malignancy had a normal CA19-9, and CEA was not found to be useful. The authors concluded that current diagnostic modalities do not reliably distinguish malignant and benign disease, and therefore definitive resection should remain the gold standard. Interestingly, Koea and others point out that frozen section performed intraoperatively did not guarantee an accurate tissue diagnosis, as these were negative in two patients with subsequently confirmed cholangiocarcinoma.

Gerhards and colleagues (2001) reported 20 cases of suspicious hilar lesions that ultimately proved to be benign. Interestingly, of the 16 patients who had ERCP, 13 were considered to have radiographic characteristics suspicious for malignancy (irregular eccentric stenosis or blunt ending). Brush cytology revealed no malignant cells in nine patients, atypical cells in four, and carcinoma in a single patient, again attesting to the poor accuracy of this test.

Similarly, in the report by Corvera and colleagues (2005), 22 of 275 patients treated at MSKCC for proximal biliary obstruction had a final histologic diagnosis of benign fibroinflammatory stricture despite preoperative radiologic assessment suggestive of malignancy, a feature termed "malignant masquerade" by the authors. The etiology of obstruction in these cases is listed in Table 48.2. No preoperative clinical or diagnostic features were identified in this series that could reliably distinguish between benign and malignant causes of bile duct stricture, leading the authors to conclude that the treatment approach should continue to be resection for presumed malignancy.

Lymphoplasmacytic sclerosing pancreatitis and cholangitis (LPSPC) is a rare inflammatory cause of pancreatitis that can be indistinguishable from pancreatic cancer and may result in biliary obstruction (see Chapter 55). The hallmark of this diagnosis is an exuberant inflammatory process characterized histologically by fibrosis and a large population of plasma cells, and in many patients it is associated with elevated serum IgG4 levels (Yoshida et al, 1995). Patients usually are seen with painless jaundice and a pancreatic mass. Radiographic studies show biliary obstruction due to the pancreatic mass, which shows characteristics indistinguishable from pancreatic cancer (see Chapter 58b). Weber and colleagues (2003) published a series of patients presumed to have pancreas adenocarcinoma who were subsequently determined to have LPSCP. The pathologic characteristics of this inflammatory tumor includes 1) lymphoplasmacytic infiltration of the pancreas, 2) interstitial fibrosis, 3) periductal inflammation, and 4) periphlebitis. Some have reported on the effectiveness of pancreatoduodenctomy in the treatment of this disease (Weber et al, 2003; Hardacre et al, 2003), but others have argued that preoperative diagnosis by

evaluating serum IgG4 levels may avoid unnecessary pancreatic resection in these patients, who can often be successfully treated with systemic corticosteroids (Hughes et al, 2004).

It is now recognized that a similar process may involve the biliary tract without concomitant pancreatic disease (Ghazale et al, 2008). Such cases of IgG4-associated cholangitis are extremely difficult to distinguish from sclerosing cholangitis. In a recent report of 10 patients with this diagnosis, compared with 17 with PSC, the former had higher portal and lobular inflammatory scores (Deshpande et al, 2009).

As termed by Hadjis and colleagues in their original report in 1985, *malignant masquerade* has since been observed by many others. Table 48.2 records the reports in the literature since 1987 related to benign inflammatory lesions occurring in the extrahepatic biliary tree. The authors draw attention to the fact that these lesions should not be allowed to masquerade in the guise of malignant tumors, but it is equally important that bile duct malignancies are not mistaken for benign tumors.

HETEROTOPIC TISSUE

Symptomatic heterotopic tissue arising in the biliary tree is exceedingly rare. In 1967, Whittaker and colleagues first observed heterotopic gastric mucosa in a cystic duct that had obstructed the gallbladder. Welling and colleagues (1970) have since recorded a similar mucosal mass obstructing the CBD at the level of the cystic duct. Kalman and colleagues (1981) reported a 1-cm papillary tumor arising in the CHD, which on microscopic examination demonstrated gastric fundal mucosa replacing the full thickness of the bile duct wall.

Heterotopic gastric mucosa occurring at the ampulla of Vater was observed to be the basis for biliary tract obstruction by Blundell and colleagues (1982). Although occurrence elsewhere in the GI tract is well documented, this appears to be the first documented ampullary obstruction secondary to heterotopic gastric mucosa. A more recent report documented a case of heterotopic gastric tissue causing biliary tract obstruction that was clinically indistinguishable from cholangiocarcinoma (Quispel et al, 2005).

Kalman and colleagues (1981) cite two hypotheses for the etiology of heterotopia: First, metaplasia with heterotopic differentiation is suggested. Several authors have described metaplastic gastric replacement of the gallbladder mucosa in cases of chronic cholecystitis; usually the metaplastic glands resemble pyloric and Brunner glands, whereas specialized chief and parietal cells are absent. A second, perhaps more tenable theory is one based upon the observation that embryologically, the epithelial lining of the foregut together with parenchyma of the liver and pancreas all arise from the same primitive endoderm, as discussed previously. Kalman states that because of the "common origin of these structures lined by multipotential cells capable of differentiation along several cell lines, it is not unreasonable to conclude that the heterotopic gastric replacement may have resulted from congenitally replaced tissue."

Heterotopic pancreatic tissue has been observed to occur from the stomach to the ileum, as well as in the omentum, spleen, gallbladder, and CBD. Seven cases have been reported in which heterotopic pancreatic tissue was found in the CBD or ampulla of Vater (Barbosa et al, 1946; Weber et al, 1968; Sabini et al, 1970; Laughlin et al, 1983). Al-Shraim and colleagues (2010) recently reported a case of ectopic pancreatic tissue in the gallbladder associated with chronic cholecystitis.

References are available at expertconsult.com.

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CHAPTER 49

Cancer of the gallbladder

T. Peter Kingham and Michael I. D'Angelica

OVERVIEW

Gallbladder cancer is rare and traditionally has been considered an incurable disease with an extremely poor prognosis. The pessimism and nihilism that historically have been associated with gallbladder cancer stem from its commonly late presentation, often with disseminated disease, its overall dismal prognosis, and lack of effective therapy. The quote that sums up this sentiment best comes from Blalock, who stated in 1924, "In malignancy of the gallbladder, when a diagnosis can be made without exploration, no operation should be performed, inasmuch as it only shortens the patient's life." Although it is clear that gallbladder cancer has a tendency to spread early via lymphatic, hematogenous, and peritoneal metastases, it also has the unique ability to implant along biopsy tracts and wounds. Gallbladder cancer is often discovered incidentally after cholecystectomy performed for presumed benign disease; unfortunately, this operation is incomplete except for the earliest stage of disease.

Pessimistic attitudes about gallbladder cancer have persisted from its original description in 1778 (Kato et al, 1994) to more recent times and are supported by reports of overall 5-year survival of 5% and median survivals of less than 6 months. For advanced, untreated gallbladder cancer, the median survival is generally 2 to 5 months, and long-term survival is exceedingly rare (Perpetuo et al, 1978; Piehler & Crichlow, 1978). Systemic chemotherapy remains limited in its effectiveness, but with major improvements in systemic chemotherapy in other diseases, these benefits may begin to extend to patients with gallbladder cancer. The role of definitive resection, however, has now been shown to be effective in properly selected patients. Complete surgical removal of gallbladder cancer is the only potentially curative therapy. With improvements in imaging, staging, and hepatic and biliary resection, there is now hope for patients with nonmetastatic gallbladder cancer. Effective adjuvant therapy is lacking, however, and this represents a significant limitation of current treatment options.

All surgeons who treat gallbladder disease must understand the natural history, biology, imaging, staging, and proper surgical treatment of gallbladder tumors. It is crucial to make proper treatment decisions early rather than after an incomplete, noncurative cholecystectomy. For surgeons whose specialty includes gallbladder cancer, it is important to understand the outcome and limitations of surgical resection so that a complete understanding of the risks and benefits can be analyzed and presented to the patient and result in a rational treatment strategy.

EPIDEMIOLOGY

The incidence of gallbladder cancer varies by racial group, and it has been reported that internationally, incidence varies 20-fold based on geographic region (Randi et al, 2006). The highest incidence of gallbladder cancer is found in women living in India (21.5 cases per 100,000 population annually), Pakistan (13.8 per 100,000), and Ecuador (12.9 per 100,000). Approximately 9760 cases of gallbladder and other biliary cancers are diagnosed annually in the United States, with 3320 deaths annually (Jemal et al, 2010). In North America, high incidence rates are found among Native Americans and Hispanic women (Barakat et al, 2006). The annual incidence of gallbladder cancer in the United States is approximately 2 per 100,000 women and 1 per 100,000 men. In North America and Western Europe, urban areas and areas of lower socioeconomic status harbor higher rates of gallbladder cancer (Diehl, 1980; Zatonski et al, 1993). In these areas, limited access to health care delays and decreases the rate of cholecystectomy for gallstone disease (see Chapter 30) may lead to higher rates of gallbladder cancer (Serra et al, 1996). In the United States overall, gallbladder cancer is the most common cancer of the biliary tract and the fifth most common gastrointestinal cancer (Carriaga & Henson, 1995).

Across all populations that have been studied, women are approximately three times more likely to develop gallbladder cancer than are men (Lazcano-Ponce et al, 2001). This ratio is as high as 5:1 in countries such as Pakistan and Colombia (Randi et al, 2006). Although rare, reports of children (<21 years old) developing gallbladder cancer do exist (Rudolph & Cohen, 1972; De Aretxabala et al, 1994); it is generally a disease of advancing age, with the incidence steadily increasing to a

plateau after age 60 years (Nakayama, 1991). Rare reports of familial gallbladder cancer exist but probably account for only a small percentage of cases (Trajber et al, 1982; Fernandez et al, 1994). Throughout the world, no consistent trend in the incidence of gallbladder cancer has been found, with decreases and increases reported in different countries. From 1978 to 1997, the incidence generally stabilized or declined in North America and Western Europe, but in Japan and South America, the incidence increased (Randi et al, 2006).

Obesity is now associated with increased death rates from many cancers. In a prospective cohort study of 900,000 U.S. adults, the relative risk of death from gallbladder cancer in women with a body mass index (BMI) of 30 to 34.9 was 2.13 compared with women with a BMI of 18.5 to 24.9. In men, the relative risk of death from gallbladder cancer with an elevated BMI was also significant at 1.76 (Calle et al, 2003). Other rare associations with gallbladder cancer include inflammatory bowel disease, primary sclerosing cholangitis (Lewis et al, 2007), and polyposis coli (Willson et al, 1987).

ETIOLOGY

The most consistently implicated etiologic factor in the development of gallbladder cancer is cholelithiasis and chronic inflammation. Of gallbladder cancer cases, 75% to 90% occur in the setting of cholelithiasis (Lazcano-Ponce et al, 2001; Serra & Diehl, 2002; Wanebo & Vezeridis, 1994). In one case-control study, the relative risk of gallbladder cancer was 10.1 in patients with stones larger than 3 cm (Diehl, 1983). Similar results were reported in another case-control study that compared gallstones in patients with gallbladder cancer with gallstones in patients with benign gallbladder disease (Roa et al, 2006). There were significantly more stones, heavier stones, and increased stone volume in the patients who had gallbladder cancer. The epidemiology of gallstones often parallels that of gallbladder cancer (Zatonski et al, 1997; Shrikhande et al, 2010); however, most patients with gallstones never have cancer develop, and a definitive cause-and-effect relationship has not been established. It is possible that stones and cancer share similar risk factors (see Chapter 8B), or stones may simply prompt a radiologic workup or cholecystectomy, increasing recognition in this group of patients.

There appears to be an association between cholesterol metabolism gene polymorphisms and a combined risk of gallbladder cancer and stones (Xu et al, 2010). Although nearly 90% of gallbladder cancer specimens contain stones, the incidence of gallbladder cancer in the population of patients with stones is 0.3% to 3%, which is low when considering this as the only risk factor. The other epidemiologic associations such as biliary-enteric fistulae, typhoid infection, and pancreaticobiliary maljunction also represent conditions in which the mucosa of the gallbladder is exposed to the effects of chronic inflammation. Although a true cause-and-effect relationship has never been proven, most epidemiologic data point to a significant relationship between chronic inflammation of the gallbladder and the development of neoplasia.

The presence of calcification in the wall of the gallbladder, otherwise known as *porcelain gallbladder,* is also a condition associated with a higher risk of gallbladder cancer. The calcification is probably the result of long-standing inflammation. The risk of malignancy within a porcelain gallbladder was previously reported to be extremely high (10% to 50%); modern series, however, have shown a much lower incidence (<10%) (Berk et al, 1973; Kim et al, 2009; Kwon et al, 2004; Stephen & Berger, 2001). The type of calcification seems to be associated with the degree of risk, with stippled calcification of the mucosa apparently representing a higher risk than diffuse intramural calcification.

Chronic inflammatory conditions of the gallbladder, such as cholecystoenteric fistula and chronic infection with typhoid bacillus, also have been associated with a risk for gallbladder cancer (Welton et al, 1979). Because bacterial colonization often accompanies chronic cholecystitis, bacteria has been proposed to play an important role in carcinogenesis. The argument against this etiology is that gallbladder cancer occurs in the setting of bacterial infection without stones and commonly occurs in the setting of stones without infection. The presence of an anomalous pancreaticobiliary junction with a long common channel between the pancreatic and bile duct also has been associated independently with gallbladder cancer risk and may be related to chronic inflammation (Chijiiwa et al, 1993). It has been difficult in experimental models, however, to induce gallbladder carcinoma with chronic inflammation. Fortner and Randall (1961) placed gallstones from patients with and without gallbladder carcinoma into the gallbladders of 126 cats. After 4 to 5 years, they found carcinoma in three cats, one of whose stones came from a patient without carcinoma. Despite these data, it is likely that chronic inflammation, regardless of cause, at the least predisposes to gallbladder carcinoma.

In patients with chronic inflammation as a predisposing factor, one hypothesis is that one or more carcinogenic exposures are required for carcinoma to develop. In numerous animal experiments, rates of gallbladder cancer were dramatically higher when inflammation was combined with known carcinogenic agents compared with exposure to the carcinogen alone (Enomoto et al, 1974; Kowalewski & Todd, 1971; Piehler & Crichlow, 1978). The composition of bile in patients with gallbladder cancer has been studied in attempts to identify carcinogenic agents. Higher concentrations of free radical oxidation products (Shukla et al, 1994) and secondary bile acids (Shukla et al, 1993) were found in gallbladders harboring cancer compared with gallbladders with gallstones alone. Some chemicals have been implicated in gallbladder carcinogenesis, including methyldopa (Broden & Bengtsson, 1980), oral contraceptives (Broden & Bengtsson, 1980), isoniazid (Lowenfels & Norman, 1978), and occupational exposure in the rubber industry (Mancuso & Brennan, 1970). None of these associations has been definitively proved (Pandey, 2006).

There is some suggestion of an adenoma-carcinoma progression in the development of gallbladder cancer. Severe dysplasia and carcinoma in situ are often adjacent to gallbladder carcinomas (Lazcano-Ponce et al, 2001). Unlike colorectal cancer, however, the association of polypoid gallbladder tumors and gallbladder cancer is rare. In fact, in patients with multiple gallbladder polyps, no increased risk of malignancy was found (Ito et al, 2009; Zielinski et al, 2009). Kubota and colleagues (1995) found that 11% of cholecystectomy specimens with gallbladder polyps had malignancies, and 88% of these polyps were larger than 1 cm. Yang and colleagues (1992) reported similar results with an 8% incidence of gallbladder cancer in gallbladder specimens with polyps, all more than 1 cm in size. Based on these studies, current practice recommendations are to perform cholecystectomy for gallbladder polyps larger than 1 cm.

ANATOMIC CONSIDERATIONS

It is important to understand the anatomy of the gallbladder, biliary tree, liver, and hepatic hilum to manage tumors of the gallbladder properly. The anatomy of the gallbladder is reviewed in Chapter 1, but a few specific comments are worthy of review. The gallbladder is a partially intraperitoneal structure that lies attached to the undersurface of the liver on segments IVb and V. On the side of the gallbladder that is attached to the liver, there is no peritoneal covering; a fibrous lining known as the *cystic plate* occupies this space. When a simple cholecystectomy is performed, the plane between the muscularis of the gallbladder and the cystic plate is dissected, which is an inadequate resection for a malignancy involving this portion of the gallbladder. This fact makes a simple cholecystectomy inadequate for most gallbladder cancers. Because the body and fundus of the gallbladder generally lie at a distance from the major inflow structures to the liver, a limited segmental resection (segment IVb/V) is adequate to resect most tumors arising from this area of the gallbladder. The infundibulum and cystic duct encroach into the porta hepatis, however, and tumors of this area often involve the porta. The surgeon must be prepared to perform bile duct resections or major hepatic resections for tumors of the lower part of the gallbladder because major inflow structures are commonly involved.

The lymphatic drainage of the gallbladder has been extensively studied (Shirai et al, 1992c); it is crucial to understand this drainage when radiologically or surgically staging patients with gallbladder cancer. The principal lymphatic drainage of the gallbladder as studied by dye injections is shown in Figure 49.1. When injected into the lymphatics of the gallbladder, the dye never ascends into the proximal porta hepatis lymphatics. The channels lead to the cystic and choledochal nodes first. From these nodes, the primary drainage areas are the retroportal and posterior-superior pancreaticoduodenal nodes. Progressing from these lower portal areas, the lymphatics course to the celiac, superior mesenteric, and interaortocaval nodes. An important finding was that some lymphatic material seemed to drain directly from the pericholedochal nodes to the interaortocaval nodes in the retropancreatic space. These connections may offer an explanation for the often advanced nature of gallbladder cancer at diagnosis and highlight the importance of analyzing the retropancreatic area radiologically and with a full Kocher maneuver at operation to stage patients with gallbladder cancer properly.

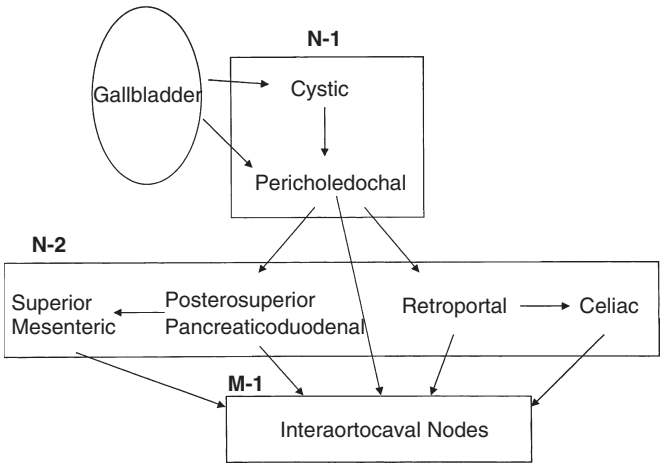


FIGURE 49.1. Schematic representation of lymphatic drainage routes for gallbladder cancer as reported by Shirai and colleagues (1992c). Note the direct route from N-1 pericholedochal lymph nodes to M-1 interaortocaval nodes.

PATHOLOGY

Preneoplastic Lesions

Similar to many gastrointestinal malignancies, progression from dysplasia to carcinoma in situ to frank invasive carcinoma is seen in gallbladder epithelium (Albores-Saavedra et al, 1986; Kozuka et al, 1982). When surrounding mucosa is sectioned in cases of gallbladder cancer, more than 90% of the cases harbor high-grade dysplasia or carcinoma in situ. Although chronic inflammation of the gallbladder can cause cellular atypia, it is generally easy to differentiate this from dysplasia and carcinoma in situ (Fig. 49.2). Carcinoma in situ may appear in the Rokitansky-Aschoff sinuses and may be mistaken for invasive carcinoma. Although it is impossible to know definitively the time course between dysplastic changes and invasive carcinoma, estimations have been made. In one series, the rate of progression of precursor lesions to invasive carcinoma was estimated to be approximately 15 years based on the mean ages of patients at each stage (Roa et al, 1996). Another study found a 5-year difference between the mean ages of patients with dysplasia and those with carcinoma in situ, and a 10-year difference was found between the mean ages of patients with carcinoma in situ and those with invasive carcinoma (Albores-Saavedra et al, 1986).

The precancerous nature of gallbladder polyps is more controversial; however, it provides some evidence that an adenoma-adenocarcinoma progression exists. Gallbladder polyps have been noted in 3% to 6% of patients undergoing ultrasonography (US). Most are cholesterol polyps with no malignant potential (Choi et al, 2008; Zielinski et al, 2009). The incidence of carcinoma in nonadenomatous polyps—cholesterol polyps, inflammatory polyps, and hyperplastic polyps—is close to zero

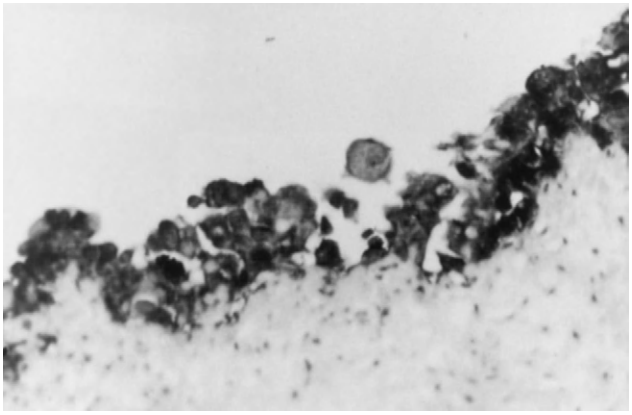


FIGURE 49.2. Light micrograph of gallbladder carcinoma in situ after peroxide antiperoxidase and carcinoembryonic antigen antibody staining. *(From Albores-Saavedra J, Henson DE, 1986: Tumors of the gallbladder and extrahepatic bile ducts. In Atlas of Tumor Pathology, Second Series. Bethesda, MD, Armed Forces Institute of Pathology.)*

(Canturk et al, 2007; Choi et al, 2008; Ito et al, 2009). Approximately 1% of cholecystectomy specimens contain adenomatous polyps (Aldridge & Bismuth, 1990; Fong & Malhotra, 2001). In another series of 123 gallbladder polyps, 21 (17%) were found to be adenomatous, and seven (6%) were found to harbor malignancy. Risk of malignancy was associated with increasing age, size greater than 1 cm, and the presence of a single polyp (Yeh et al, 2001). Ito and colleagues (2009) reviewed 417 patients with gallbladder polyps found on US. Only 7% of patients had polyps larger than 1 cm. Among the 80 patients who underwent cholecystectomy, neoplastic (adenomatous) polyps were found in 10%, and one patient had a carcinoma in situ (in a 14-mm polyp). No patient was found to harbor an invasive malignancy.

Kozuka and colleagues (1982) described seven adenomas showing histologic progression into malignancy and showed that 19% of invasive carcinomas had adenomatous components. In a series of 182 resected gallbladder polyps, 13 (7%) were found to harbor a malignancy, which was related to the size of the polyp (Yang et al, 1992). One report described a higher incidence of malignancy in gallbladder polyps arising in the face of primary sclerosing cholangitis (Buckles et al, 2002).

Benign adenomatous polyps do not have the same association with cholelithiasis that invasive carcinomas do, and it is unlikely that most gallbladder cancers arise from adenomatous polyps. It may be that some tumors arise in this manner, although the specific percentages would be difficult to estimate.

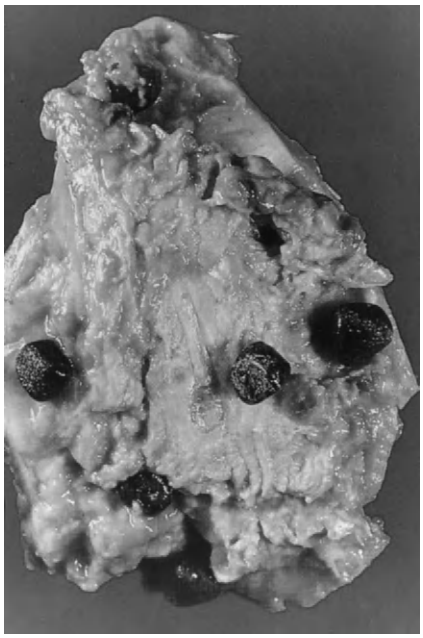


FIGURE 49.3. Giant cell adenocarcinoma of the gallbladder. This tumor has an infiltrative nature, but it fills most of the lumen of the gallbladder. *(From Albores-Saavedra J, Henson DE, 1986: Tumors of the gallbladder and extrahepatic bile ducts. In Atlas of Tumor Pathology, Second Series. Bethesda, MD, Armed Forces Institute of Pathology.)*

Gross Morphology

Early-stage gallbladder cancers are difficult to distinguish from the findings typical of chronic cholecystitis because they both often present as a thickened gallbladder wall in the face of inflammation. This similar presentation accounts for the frequent discovery of gallbladder cancer incidentally in a cholecystectomy specimen. The overall incidence of gallbladder cancer discovered during cholecystectomy for presumed benign disease is less than 1% (Bazoua et al, 2007). As gallbladder tumors progress, they can present in numerous ways. The gallbladder may become distended with tumor, or it may become contracted and collapsed. Approximately 60% of tumors originate from the fundus, 30% from the body, and 10% from the neck of the gallbladder (Albores-Saavedra et al, 1986; Daines et al, 2004; Rajagopalan et al, 2004). Tumors in the lower end of the gallbladder may obstruct the neck or cystic duct, leading to hydrops. Advanced tumors of the neck, infundibulum, or cystic duct may infiltrate the porta hepatis and result in major vascular invasion, jaundice, and even hepatic atrophy. This presentation is often indistinguishable from a hilar cholangiocarcinoma.

Gross descriptions of gallbladder cancer have been grouped into infiltrative, nodular, combined nodular-infiltrative, papillary, and combined papillary-infiltrative forms (Albores-Saavedra et al, 2005; Sumiyoshi et al, 1991). Most tumors have an infiltrative pattern as part of their presentation, which causes thickening and induration of the gallbladder wall (Fig 49.3). These types of tumors seem to spread in a subserosal plane and can invade the whole gallbladder wall and even invade into the porta hepatis, causing jaundice from diffuse biliary involvement. These types of tumor can also diffusely invade the liver. Nodular types of tumors tend to grow as a more circumscribed mass. Despite invasion into the liver, these lesions are more easily resected because they are less diffuse in their invasive pattern. Papillary tumors of the gallbladder are polypoid lesions with frondlike extensions that give a cauliflower-like appearance (Fig. 49.4). Despite the fact that papillary tumors can grow quite large, they tend to have a better prognosis than the other gross types; this is likely related to the less invasive nature of these tumors. Even at large sizes, papillary gallbladder tumors may have minimal invasion into the gallbladder wall (Albores-Saavedra et al, 2005).

HISTOLOGY (SEE CHAPTER 47)

Table 49.1 shows the classification of malignant gallbladder tumors, and Table 49.2 summarizes the relative incidence of the various histologic types of gallbladder cancer. Over a 10-year period at Memorial Sloan-Kettering Cancer Center (MSKCC), 391 (90%) of the 435 patients with gallbladder cancer had adenocarcinomas. Additional diagnoses were squamous/adenosquamous carcinoma (4%), neuroendocrine carcinoma (3%), sarcoma/adenosarcoma (1.6%), unspecified carcinoma (1.1%), and melanoma (<1%) (Duffy et al, 2008). Most gallbladder tumors can be characterized histologically, but more than one histologic pattern is commonly found in each tumor. The only histologic subtype that seems to have prognostic significance is the papillary tumor. Papillary adenocarcinomas of the gallbladder tend to have a better prognosis than the other subtypes (Albores-Saavedra et al, 2005; Carriaga & Henson, 1995). This improved prognosis is likely related to the tendency of this tumor to be noninvasive or minimally invasive. When this tumor becomes invasive, however, it can metastasize and have a prognosis typical of the pathologic stage (Albores-Saavedra et al, 2005).



FIGURE 49.4. Papillary adenocarcinoma of the gallbladder: this tumor has a cauliflower-like appearance and protrudes into the lumen with minimal invasion of the gallbladder wall. These tumors have the best prognosis. *(From Albores-Saavedra J, Henson DE, 1986: Tumors of the gallbladder and extrahepatic bile ducts. In Atlas of Tumor Pathology, Second Series. Bethesda, MD, Armed Forces Institute of Pathology.)*

Table 49.1

Classification of Malignant Tumors of the Gallbladder

Epithelial Tumors

Adenocarcinoma
- Well differentiated
- Papillary
- Intestinal type
- Pleomorphic giant cell
- Poorly differentiated
- Small cell
- Signet ring cell
- Clear cell
- Colloid
- Choriocarcinoma-like

Squamous cell
Adenosquamous cell

Mesenchymal Tumors

Embryonal rhabdomyosarcoma
Leiomyosarcoma
Malignant fibrous histiocytoma
Angiosarcoma

Other Tumors

Melanoma
Carcinoid

Modfied from Albores-Saavedra J, Henson DE, 1986: Tumors of the gallbladder and extrahepatic bile ducts. In Atlas of Tumor Pathology, Second Series. Bethesda, MD, Armed Forces Institute of Pathology.

Throughout the medical literature are many case reports and small case series of other rare gallbladder cancers. Primary sarcomas of the gallbladder—including embryonal rhabdomyosarcoma, leiomyosarcoma, malignant fibrous histiocytoma, angiosarcoma, and Kaposi sarcoma—have been reported and

Table 49.2

Relative Incidence of Gallbladder Cancer by Histologic Type

	RELATIVE INCIDENCE (%)	
Histologic Type	Carriaga & Henson, 1995	Duffy et al, 2008
Carcinoma	99	94
Adenocarcinoma	89.4	90
Papillary	5.7	—
Mucinous and mucin producing	5.3	—
Squamous cell	1.8	4
Other and unspecified	7.8	1.4
Sarcoma	0.2	1.6
Neuroendocrine	—	3

From Carriaga MT, Henson DE, 1995: Liver, gallbladder, extrahepatic bile ducts, and pancreas. Cancer 75(Suppl 1):171-190; and Duffy A, et al, 2008: Gallbladder cancer (GBC): 10-year experience at Memorial Sloan-Kettering Cancer Center (MSKCC). J Surg Oncol 98(7):485-489.

are extremely rare. Other reported uncommon gallbladder cancers include carcinosarcoma, carcinoid, lymphoma, melanoma, and metastatic tumors to the gallbladder. Although reports have suggested a poorer outcome for oat-cell carcinomas (Henson et al, 1992) and adenosquamous carcinomas (Yamaguchi & Enjoji, 1988), these conclusions are based on small numbers, and comparisons of such rare tumors are impossible.

Gallbladder cancers also have been grouped into metaplastic and nonmetaplastic types based on metaplastic changes in the tumors; this is similar to the classification of gastric cancers into intestinal and diffuse types. The two predominant types of metaplasia that are precursors to malignancy in the gallbladder mucosa are *pseudopyloric* and *intestinal* (Duarte et al, 1993). The intestinal type has a higher rate of carcinoma. The progression from metaplasia to carcinoma in situ to carcinoma is evident in that patients with invasive cancer are 15 and 5 years older than patients with dysplasia and carcinoma in situ, respectively (Roa et al, 1996).

Histologically, gallbladder cancers are graded into four categories that range from well differentiated to poorly differentiated. This differentiation does not have a significant impact on prognosis except for the observation that most papillary tumors are well differentiated, which may account for the better prognosis seen in these types of tumors. Most gallbladder cancers are poorly differentiated at presentation. DNA ploidy has been studied in gallbladder tumors and corresponds to the histologic grade but does not correlate with prognosis (Baretton et al, 1994). Although it is clear that gallbladder cancers can be differentiated based on histologic type and grade, the most important prognostic factor is the stage at presentation, making grade and type prognostically unimportant.

Molecular Biology (See Chapter 8B)

The precise pathway linking different genetic mutations responsible for gallbladder cancer is not clear; however, multiple genetic defects are known to be associated with gallbladder cancer (Lazcano-Ponce et al, 2001; Rashid, 2002; Sasatomi

Table 49.3

Genetic Mutation in Gallbladder Cancer

Gene	Gene Type	Mutation	Expression in Gallbladder Cancer (%)	Comments
Oncogenes	*KRAS* (Ajiki et al, 1996a)	Activation	40-50	Higher percent with anomalous pancreaticobiliary duct
	CDKN1A (Puhalla et al, 2007)	Activation	28	Survival lower when coexpressed with *TP27* and *TP53*
	ERBB2 (Kim et al, 2001)	Activation	10-46.5	Survival lower if mutation present
Tumor suppressor	*TP53* (Ajiki et al, 1996b)	Inactivation	27-70	Present at high stage of disease
	CDKN2A (Quan et al, 2001)	Inactivation	50	Survival worse with mutation
	FHIT (Koda et al, 2003)	Inactivation	100	Potentially involved in early initiating events
PG pathway	*COX2* (Asano et al, 2002)	Increased expression	70	Survival worse with mutation
Angiogenesis	*VEGFA* (Tian et al, 2006)	Increased expression	Unknown	Increased expression with higher stages
Inflammatory mediator	*NOS2* (Zhang et al, 2003)	Increased expression	71	Common with chronic gallbladder inflammation
Telomerase subunit	*hTERT* (Itoi et al, 2000)	Increased expression	93	Expressed in premalignant tumors
Adhesion molecules	Cadherins (Choi et al, 2004), catenins (Yanagisawa et al, 2001)	Decreased expression	14-40	Present early in tumor progression and with metastases
	MSI (Yanagisawa et al, 2001)	Presence	10	Found in 83% of dysplastic lesions
	DNA methylation (Roa et al, 2006)	Presence	Unknown	Prognosis worse when some genes (*FHIT, TP73*) are methylated

et al, 2000). Tumor suppressor genes, oncogenes, microsatellite instability, and DNA repair genes all participate in the initiation of gallbladder cancer (Table 49.3) (Goldin & Roa, 2009). Several of these genetic mutations have been identified in case-control studies and have been combined into risk scores. For example, Srivastava and colleagues (2010) compared genetic variations in three DNA repair genes—*ERCC2, MSH2,* and *OGG1*—among 230 patients with gallbladder cancer and 230 control subjects. They found that patients with more than six of the variant alleles that were studied had a fourfold increased risk for developing gallbladder cancer.

Serologic biomarkers can potentially be useful to identify groups of patients at increased risk for gallbladder cancer. When used together, polymorphisms CA242 and CA125 have been associated with high sensitivity and specificity for differentiating between cholelithiasis and gallbladder cancer (Shukla et al, 2006). Several other serum markers may identify patients at high risk for developing gallbladder cancer, regardless of the presence of cholelithiasis. These markers include the NAT2 slow acetylator phenotype, the X(+), D haplotype of apolipoprotein B, and the D allele of lipoprotein receptor–associated protein (LRPAP1) insertion/deletion polymorphism (Pandey, 2006; Pandey et al, 2007a, 2007b).

Pattern of Spread

Gallbladder cancer spreads via lymphatics, hematogenously, and notoriously into the peritoneal cavity or along biopsy or surgical wound tracts. Cancers of the gallbladder seem to invade and metastasize relatively early, which may be attributable to the anatomy of the gallbladder; the wall is thin, contains a narrow lamina propria, and is only a single muscular layer with no serosal covering between it and the liver. Tumors invade into the liver at such a thickness that a second muscular layer would be encountered in many organs, and the thin wall of the gallbladder may be conducive to early hematogenous and lymphatic spread. Gallbladder tumors, once through the muscular layer, have access to major lymphatic and vascular channels, providing these tumors with early opportunities for dissemination.

An autopsy study showed a 94% incidence of lymphatic metastases and a 65% incidence of hematogenous dissemination (Kimura et al, 1989); however, autopsy studies represent the end stage of disease, with sufficient time for extensive metastases to develop. It has been postulated that hematogenous metastases originate from small veins extending directly from the gallbladder into the portal venous system of the gallbladder fossa. These connections can lead to segments IV and V of the liver or via larger veins to the portal venous branches of segments V and VIII (Boerma, 1994). A review of the incidence of regional invasion and metastases at the time of diagnosis and treatment is summarized in Table 49.4.

It is also important to understand the patterns of spread after complete resection because these facts can help guide approaches to adjuvant therapy. Autopsy studies have shown widely disseminated disease, including liver metastases, in greater than 90%; abdominal lymph node metastases in greater than 80%; and peritoneal metastases in 60% of patients (Perpetuo et al, 1978). The only common extraabdominal site of distant metastases is the lung, but lung metastases are rarely seen in the absence of advanced intraabdominal disease. In an attempt to define sites of first recurrence after complete resection, Jarnagin and colleagues (2003) found that only 15% of patients had locoregional recurrence as the only site of

Table 49.4

Incidence of Regional Invasion and Metastasis at the Time of Diagnosis and Treatment Based on a Literature Review

Pathologic Finding	Relative Incidence (%)
Confined to gallbladder wall	10
Liver invasion	59
Common bile duct infiltration	35
Lymphatic invasion and regional lymphatic metastases	45
Gallbladder vein infiltration	39
Portal vein or hepatic artery invasion	15
Adjacent organ invasion (excluding liver)	40
Perineural invasion	42
Liver metastasis	34
Distant metastasis (excluding liver)	20

Data from Boerma EJ, 1994: Towards an oncological resection of gall bladder cancer. Eur J Surg Oncol 20(5):537-544.

recurrence, and most (85%) had recurrence involving a distant site. This finding shows the minimal potential utility of adjuvant locoregional strategies and underscores the importance of effective adjuvant systemic therapies.

CLINICAL PRESENTATION

Three clinical scenarios are common for gallbladder cancer: 1) final pathology after routine cholecystectomy identifies gallbladder cancer; 2) gallbladder cancer is discovered intraoperatively; and 3) gallbladder cancer is suspected before surgery (Miller & Jarnagin, 2008). The clinical presentation varies depending on geographic location, rates of gallbladder cancer, and referral patterns. In a study of 435 patients with gallbladder cancer treated at MSKCC during a 10-year period, 47% had cancers discovered incidentally at the time of routine laparoscopic cholecystectomy (Duffy et al, 2008), and 53% were initially seen with advanced (16%) or disseminated (37%) disease. Given the high percentage of patients diagnosed with gallbladder cancer after routine cholecystectomy for presumed benign gallbladder disease, it is appropriate for the surgeon to inspect the gallbladder mucosa at the completion of the resection if there are any concerns. Frozen-section analysis should be used to examine any suspicious areas.

Gallbladder cancer is notorious for being asymptomatic in its early stages. When symptoms do occur, however, gallbladder cancer tends to present in a similar manner to biliary colic or chronic cholecystitis. Careful history taking often shows a history of constant right upper quadrant pain rather than the typical episodic crampy pain of biliary colic. The diagnosis of gallbladder cancer should be considered in an elderly patient with constant right upper quadrant pain with weight loss, anorexia, or both because weight loss, anorexia, and jaundice in particular are signs of advanced disease (Duffy et al, 2008). The presence of a palpable mass is also an ominous finding that predicts a high rate of unresectability and advanced disease (Thorbjarnarson & Glenn, 1959). The presence of jaundice is an especially ominous finding. In a report by Hawkins and colleagues (2004), 82 (34%) of 240 patients presented with jaundice. Of these 82 patients, only six (7%) were resectable, and all had recurrence or died of disease within 2 years. The median survival in jaundiced patients was 6 months compared with 16 months in patients presenting without jaundice.

The incidence of symptoms and signs at presentation is summarized in Table 49.5. A report from New York Hospital reviewed their experience with gallbladder cancer from 1915 through 2000 (Grobmyer et al, 2004). Throughout the years, the presentation was remarkably similar in that most patients had advanced disease at presentation. Over time, however, a decrease was reported in the percentage of patients who presented in the more recent era with weight loss (95% vs. 42%), palpable mass (50% vs. 9%), and nausea/vomiting (97% vs. 70%). The percentage of patients presenting with abdominal pain and jaundice was similar (approximate 85% and 50%, respectively).

Laboratory examination generally is not helpful except to identify the typical signs of advanced disease, such as anemia, hypoalbuminemia, leukocytosis, and elevated alkaline phosphatase or bilirubin levels (Grobmyer et al, 2004; Thorbjarnarson & Glenn, 1959). The only tumor markers studied that are of any potential value are carcinoembryonic antigen (CEA) and carbonin anhydrase 19-9 (CA19-9). An elevated CEA tends to be specific for gallbladder cancer (90%), but it lacks sensitivity (50%) when used as a screening test in cancer patients compared with patients who have benign gallbladder diseases (Strom et al, 1990). CA19-9 is more consistent as a marker for gallbladder cancer, with sensitivities and specificities of approximately 75% at a level greater than 20 U/mL (Ritts et al, 1994). Overall, serum tumor markers are of minimal clinical value compared with clinical awareness, a heightened level of suspicion in appropriate cases, and good-quality imaging studies. As is typical of the utility of serum tumor markers, they can be helpful in following a patient for recurrence, if they are elevated before treatment and normalize after treatment.

Table 49.5

Summary of Symptoms and Signs from Four Large Reviews

Symptoms and Signs	Grobmyer et al, 2004	North et al, 1998	Chao & Greager, 1991	Perpetuo et al, 1978
Abdominal pain	85%	62%	54%	97%
Jaundice	43%	13%	46%	44%
Weight loss	42%	7%	28%	77%
Anemia	NR	NR	8%	NR

NR, not reported

RADIOLOGIC INVESTIGATION

In the era before the availability of routine real-time US and computed tomography (CT), gallbladder cancer was rarely diagnosed preoperatively. With the development of rapid and more widely available imaging modalities, patients who have suspected or incidentally diagnosed gallbladder cancer should have high-resolution cross-sectional imaging for adequate staging. Because most patients present with advanced disease, it is important to try to establish the diagnosis and extent of disease with imaging to minimize the number of patients who have to undergo a nontherapeutic surgical exploration. Except for the earliest stage of disease, this should now be possible in most patients. In addition to the modalities available for examining the gallbladder and liver, chest radiographs or CT scan should be obtained during the complete staging workup to rule out pulmonary metastases. It is rare, however, to find pulmonary metastases without locally advanced or intraabdominal metastatic disease (Lee et al, 2010).

US is an excellent imaging modality for the gallbladder. Findings such as discontinuous mucosa, echogenic mucosa, and submucosal echolucency are more common in early malignancy compared with benign gallbladder disease. Doppler assessment of blood flow through areas of mucosal abnormalities can help to differentiate early malignancy from benign disease, and newer contrast-enhanced US techniques may improve detection confidence even further (Sato et al, 2001). In one study, a polypoid mass was present in 27% of cases, and a gallbladder-replacing or invasive mass was present 50% of the time (Wibbenmeyer et al, 1995). US is a good modality for evaluating the direct extension of gallbladder cancer. One retrospective study reported that in 203 patients with gallbladder cancer, a mass was identified in 177 patients (87%) on preoperative US (Pandey et al, 2000). US was limited, however, in identifying lymph node metastases in pericholedocal and peripancreatic nodes. Because most cases are advanced, the most typical findings in gallbladder cancer are an inhomogeneous mass replacing all or part of the gallbladder (Bach et al, 1998; Franquet et al, 1991). Diffuse thickening of the gallbladder wall also is a common finding on cross-sectional imaging and on US, but it can be difficult to differentiate from benign inflammatory changes.

Cross-sectional imaging with CT or magnetic resonance imaging (MRI) is an important part of the preoperative assessment of gallbladder cancer (see Chapters 16 and 17). These techniques provide crucial information about the local extent of disease and show whether distant metastases are present. The most common finding on CT is a mass involving all or part of the gallbladder. Extension into local organs, particularly the liver, usually can be discerned. In one study of patients with gallbladder masses, asymmetric wall thickening was found in 45% of patients, a mass replacing the gallbladder was found in 35%, and an intraluminal mass was found in 20% (Fig. 49.5) (Kalra et al, 2006). Assessment of regional and distant lymph nodes is important and can be done with CT. With criteria of size greater than 1 cm and a ringlike heterogenous enhancement, accuracy rates greater than 80% have been reported (Ohtani et al, 1993). Although large lymph nodes replaced with tumor are relatively easy to identify with CT, false-negative examination results continue to be a problem because many involved lymph nodes can be small, with minimal tumor. CT is 71% to 84% accurate in staging

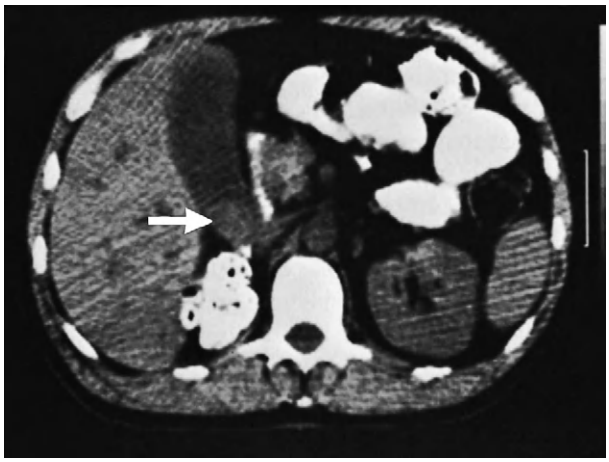


FIGURE 49.5. Computed tomography scan showing a filling defect in the neck of the gallbladder (*arrow*) representing an early carcinoma.

gallbladder cancer. In one study of 118 patients with gallbladder cancer, CT was 79% accurate for differentiating T1 versus T2 tumors, 93% accurate for differentiating T2 versus T3 tumors, and 100% accurate for differentiating T3 versus T4 tumors (Kim et al, 2008). The overall accuracy improved from 72% to 85% when multiplanar reconstructions were added to conventional axial imaging.

The utility of MRI for evaluating patients with gallbladder cancer has increased in recent years. Improvements in MRI technology over the last 2 decades has been dramatic, with wider availability of MRI cholangiography and angiography. Invasive diagnostic cholangiography has largely been replaced by MRI cholangiography in most high-volume centers (Schwartz et al, 2002). Likewise, the use of diagnostic angiography has been replaced by CT/MRI angiography, and such modern equipment can provide detailed imaging of the related vessels at the hepatic hilum. Analyses of MRI for the assessment of gallbladder cancer have shown sensitivities of 70% to 100% for hepatic invasion and 60% to 75% for lymph node metastases (Kim et al, 2002; Schwartz et al, 2002). It is unclear whether MRI adds to the results obtained from CT scan. In one study of 25 patients with gallbladder cancer, MRI/MRCP did not change the preoperative stage as determined by CT scan (Rao et al, 2005).

The development and use of fluorodeoxyglucose (FDG) positron-emission tomography (PET) has resulted in superior staging and diagnosis of many tumors. Most gallbladder cancers are visible on PET scan; theoretically, PET imaging could help differentiate between benign and malignant tumors and can help diagnose extrahepatic spread (Petrowsky et al, 2006). PET, however, is limited in differentiating between benign inflammatory states, such as postcholecystectomy, and malignancy (Corvera et al, 2008). PET appears to be more accurate in diagnosing metastatic disease than is CT scan. In a study of 61 patients with biliary tract malignancies, PET/CT had a sensitivity of 100% compared with 25% for CT alone ($P < .001$), and PET alone changed surgical management in 17% of cases (Petrowsky et al, 2006). PET is more useful for evaluating primary gallbladder cancer than it is for evaluating recurrent disease. In 41 patients with gallbladder cancer at MSKCC, PET results altered surgical management in 23%

Table 49.6

Imaging Modalities Used to Diagnose Gallbladder Cancer

Imaging	Accuracy	Pros	Cons
US*	87%	Cost effective Better than CT for diagnosing cholelithiasis Detailed view of gallbladder wall, polyps No radiation exposure	Difficult to evaluate regional nodes and CBD Operator dependent
CT	Overall: 71% to 84%†‡ T1 vs. T2: 79%‡ T2 vs. T3: 93%‡ T3 vs. T4: 100%‡	Cost effective Evaluation of regional nodes Diagnosis of extrahepatic disease More anatomic information vs. US	Difficult to differentiate between inflammation and malignancy Low sensitivity for diagnosing peritoneal implants
MRI	Hepatic invasion: 67% sensitivity, 89% specificity§ Vascular invasion: 100% sensitivity, 87% specificity§ CBD invasion: 100% sensitivity, 89% specificity§ Nodal involvement: 56% specificity, 89% sensitivity	Detailed images of CBD and vascular involvement No radiation MRA and MRCP images provide more detail than CT scan	Expensive Low sensitivity for diagnosing peritoneal disease
PET	Sensitivity: 75% to 86‖ Specificity: 78% to 87%‖ Management changed in 17% to 23% of cases‖	Clarifies suspicious findings on CT or MRI Diagnosis of extrahepatic disease	Expensive Difficult to differentiate between inflammation and malignancy Not proven to enhance CT or MRI findings

*In patients with biopsy-proven gallbladder cancer, US demonstrated mass in 87% of patients (Rodriguez-Fernandez et al, 2006).
†CT is 71% to 84% accurate in diagnosing gallbladder cancer T stage (Kalra et al, 2006; Kim et al, 2008).
‡Sensitivity for differentiating different stages of biopsy-proven gallbladder cancer (Kalra et al, 2006).
§Sensitivity and specificity of MRI for diagnosing T stage of gallbladder cancer (Kim et al, 2002).
‖Sensitivity and specificity of preoperative PET scan in diagnosing gallbladder cancer (Koh et al, 2003; Corvera et al, 2008).
US, ultrasound; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; CBD, common bile duct; MRA, magnetic resonance angiography; MRCP, magnetic resonance cholangiopancreatography

during preoperative staging (for either the initial operation or reresection after an incidental finding of cancer after cholecystectomy) compared with 10% in patients evaluated for recurrent disease (Corvera et al, 2008). In one study from Japan, 16 patients with mass lesions of the gallbladder were evaluated with PET. Eight of the tumors were histologically proven to be malignant, and PET had a sensitivity and specificity of 75% and 88%, respectively. The false-positive case was in a patient with xanthogranulomatous cholecystitis (Koh et al, 2003).

The usual first test for gallbladder symptoms is US, and it is crucial always to consider the diagnosis of gallbladder cancer when abnormalities are found in the wall of the gallbladder. Duplex US adds information in terms of vascular tumors and helps assess local hepatic vasculature. When gallbladder carcinoma is proven or suspected preoperatively, good-quality cross-sectional imaging with CT or MRI should provide adequate data on local extent of tumor to help assess for metastases. PET can also be a valuable adjunct in searching for metastatic disease or when CT or MRI provides limited information about the primary tumor (Table 49.6).

Gallbladder cancer presenting with jaundice is relatively common; this diagnosis must be in the differential diagnosis for any malignant-appearing, mid–bile duct stricture. Gallbladder cancer must also be considered when the diagnosis of Mirizzi syndrome has been made (Redaelli et al, 1997). To help plan therapeutic procedures, the level of obstruction can be assessed by CT or MRI cholangiography with reasonable accuracy. Stricturing, distortion, or nonfilling of the segment V or VI bile ducts can be caused by gallbladder tumors without effect on the rest of the biliary tree (Fig. 49.6) (Collier et al, 1984). Invasive cholangiography is indicated only when a therapeutic intervention, such as stenting, is anticipated. According to the level of obstruction, a judgment can be made regarding the best approach for biliary stenting (endoscopic retrograde vs. transhepatic cholangiography). As discussed later in this chapter, this can be a crucial part of the palliation of advanced gallbladder cancer.

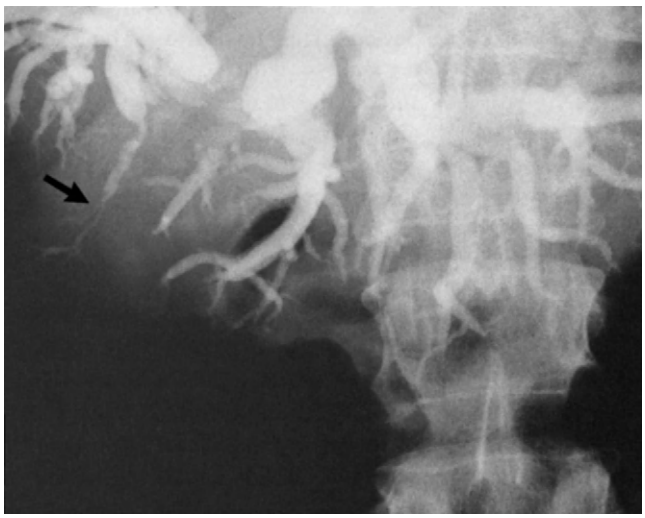


FIGURE 49.6. Percutaneous transhepatic cholangiogram showing malignant obstruction of the bile duct confluence and stricturing and distortion of the duct draining the segment V area of the liver (*arrow*). This is due to a gallbladder cancer directly invading segment V.

PREOPERATIVE PATHOLOGIC DIAGNOSIS

If gallbladder cancer is suspected on clinical and radiologic grounds, preoperative histologic diagnosis is unnecessary in

patients who are potentially resectable. Gallbladder cancer has a tendency to seed the peritoneum, biopsy tracts, and surgical wounds (Fong et al, 1993; Hu et al, 2008; Merz et al, 1993), and unnecessary biopsies simply increase this risk. Although a positive biopsy result may make the surgeon feel more justified in the operative approach, a negative biopsy result cannot be trusted because of significant false-negative rates. If the diagnosis is suspected, the surgeon and patient must be prepared for a definitive operation. If concern for gallbladder cancer is significant, it is unwise to perform a cholecystectomy to make the diagnosis because the same risk of tumor spillage applies. The surgeon and patient also must be prepared for the possibility of performing a liver resection for benign disease. In experienced hands, a limited liver resection should be safe, and the risk of this procedure should be less than the risk of multiple biopsies or noncurative operations. For a patient with unresectable or metastatic disease, a percutaneous biopsy has an accuracy of nearly 90%, and the false-positive rate is negligible (Akosa et al, 1995).

Bile cytology has been proposed as a less risky way of making the diagnosis of gallbladder cancer without risking peritoneal seeding. Although it is reasonable to check bile cytology if the patient needs to undergo endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC), for the reasons stated earlier, a deliberate attempt to make the diagnosis this way is unwarranted. Sensitivity of bile cytology has been reported to be approximately 75% (Akosa et al, 1995; Arora et al, 2005; Mohandas et al, 1994; Naito et al, 2009).

STAGING

Over the years, a variety of staging systems for gallbladder cancer have been proposed based on prognostic clinical and pathologic factors. Historically, the American Joint Committee on Cancer (AJCC) system, the Japanese Biliary Surgical Society system (Onoyama et al, 1995), the Nevin system (Nevin et al, 1976), and the modified Nevin systems (Donohue et al, 1990) were all used. These staging systems are summarized in Table 49.7. The AJCC tumor-node-metastasis (TNM) staging of gallbladder cancer was adopted in 2002 as the standard reporting mechanism for gallbladder cancer studies in the literature, and it is the preferred staging system clinically (Table 49.8).

The AJCC uses tumor depth (T), nodal status (N), and the presence of metastases (M) to place patients into four stages according to pathologic and radiographic findings. The sixth edition of the AJCC system divided T1 tumors into two groups: T1a tumors invade the lamina propria of the gallbladder, and T1b tumors invade the muscular layers; T2 tumors spread through the muscular layers into, but not beyond, the connective tissue layers. Anatomically, this translates to spread into the gallbladder serosa or cystic plate but not into the liver parenchyma. T3 lesions spread through the gallbladder serosa and invade the liver, extrahepatic bile ducts, or perihepatic organs. T4 lesions invade multiple extrahepatic organs and/or major vessels and generally reflect locally unresectable disease. The seventh edition of the AJCC system includes the cystic duct in the classification scheme and reclassifies locally unresectable T4 tumors as stage IV.

The N stage is either N0 (no nodal metastases) or N1 (positive regional nodal disease) in the AJCC sixth edition. Regional nodal metastases can be found in the porta hepatis, retroduodenal nodes, and the gastrohepatic region. Disease outside this area, for example in aortic or celiac nodes, is considered M1 disease. The AJCC seventh edition now distinguishes between hilar nodes (N1) and regional nodes (N2). The T, N, and M scores are then arranged into stages. Stage I includes node-negative T1 (stage Ia) and T2 (Ib). Stage II includes node-negative T3 (IIa) and node-positive T1 through T3 (IIb). Stage III includes any T4 lesions with no metastatic disease, and stage IV consists of any T or N score with metastatic disease. The AJCC seventh edition has changed so that N1 disease is now stage IIIb, and N2 disease is now stage IVb.

The seventh edition was issued in 2010 with stage groupings that were changed to correlate with resectability and patient outcome. Locally unresectable T4 tumors were classified as stage IV, and the N classification was changed. N1 nodes are lymph nodes adjacent to the cystic duct, bile duct, hepatic artery, and portal vein. Regional nodes are celiac, periduodenal, and peripancreatic nodes. Lymph node metastasis is now classified as stage IIIb (N1) or stage IVb (N2) disease.

Fong and colleagues analyzed the sixth edition AJCC scoring system in more than 7000 patients in the United States National Cancer Database (NCDB). They reported that stage III should be segregated into IIa from the T3N0M0 patients and that IIIb would consist of T1 through T3N1M0 patients. The justification for this change was the belief that nodal metastases indicate a different cancer biology, and the presence of nodal metastases may call for other therapies, such as radiotherapy. Stage IVa and

Table 49.7

Summary of Staging Systems

Stage	Modified Nevin	Japanese	AJCC/TNM*	AJCC/TNM†
I	In situ carcinoma	Confined to gallbladder capsule	Mucosal or muscular invasion; T1, N0, M0	Mucosal or muscular invasion; T1, N0, M0
II	Mucosal or muscular invasion	N1 LN, minimal liver or bile duct invasion	Transmural invasion; T2, N0, M0	Transmural invasion; T2, N0, M0
III	Transmural direct liver invasion	N2 LN, marked liver or bile duct invasion	Local invasion of other organs, lymph node positive; T3, T4, any N, M0	Local invasion of nearby organ; T1-T3, N0-N1, M0
IV	Lymph node metastasis	Distant metastases	Distant metastases; any T, any N, M1	Major vascular invasion or invasion of ≥2 nearby organs; T4, N0-N1, M0; Any T, N2, M0-M1
V	Distant metastases			

*Sixth edition
†Seventh edition
LN, lymph nodes; AJCC, American Joint Committee on Cancer; TNM, tumor-node-metastasis

Table 49.8

AJCC Staging System for Gallbladder Cancer

Sixth Edition		Seventh Edition
Tis = Carcinoma in situ T1 = Tumor invades lamina propria (T1a) or muscle layer (T1b) T2 = Tumor invades perimuscular connective tissue T3 = Tumor perforates serosa and/or invades the liver or adjacent organs T4 = Tumor invades main portal vein or hepatic artery, or multiple extrahepatic organs	T Stage	Tis = Carcinoma in situ T1 = Tumor invades lamina propria (T1a) or muscle layer (T1b) T2 = Tumor invades perimuscular connective tissue T3 = Tumor perforates serosa and/or invades the liver and/or one adjacent organ T4 = Tumor invades main portal vein or hepatic artery or multiple extrahepatic organs
N0 = No regional nodal metastases N1 = Positive regional nodal metastases*	N Stage	N0 = No regional nodal metastases N1 = Metastases to nodes along cystic duct, hepatic artery, common bile duct, and/or portal vein N2 = Metastases to pericaval, periaortic, superior mesenteric artery, and/or celiac artery nodes
M0 = No distant metastases M1 = Distant metastases	M Stage	M0 = No distant metastases M1 = Distant metastases

* Regional nodes are found in the porta hepatis, gastrohepatic ligament, and retroduodenual space. Positive nodes outside these areas are considered M1 disease.
AJCC, American Joint Committee on Cancer

Staging Groups*

Stage			
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1-3	N1	M0
III	T4	N0, N1	M0
IV	Any T	Any N	M1

*Sixth edition of the AJCC manual
The seventh edition has reclassified locally unresectable T4 tumors as stage IV. In addition, lymph node metastases are now classified as stage IIIb (N1) or stage IV (N2).

IVb were also regrouped to T4N0M0 for stage IVa and IVb and included anyone with nodal metastases.

SURGICAL MANAGEMENT

Benign Polyps

Benign polypoid lesions of the gallbladder are common and are best assessed by US, although definitive diagnosis is often difficult. The only polypoid lesions that have malignant potential and are associated with a significant rate of harboring malignancy are adenomatous polyps. Other benign lesions—fibromas, lipomas, hemangiomas, cholesterol polyps, inflammatory polyps, and adenomyomas—are not known to be associated with malignant potential. *Adenomyomatosis,* defined as extension of Rokitansky-Aschoff sinuses through the muscular wall, is common and often diagnosed by US criteria (Stunell et al, 2008). Cholesterol polyps are the most common gallbladder polyp, but they are not easily differentiated from other lesions of the gallbladder wall without pathologic analysis. The relevant clinical question is which lesions mandate a cholecystectomy in an asymptomatic patient.

Numerous clinical reviews have identified factors associated with malignancy in gallbladder polyps. The most consistent predictors are single polyps, size greater than 1 cm, and age older than 50 years (Shinkai et al, 1998; Yeh et al, 2001). Although some clinicians have recommended cholecystectomy for any patient with fewer than three polyps (Shinkai et al, 1998), we generally recommend cholecystectomy for any polyp greater than 1 cm because the risk of malignancy for smaller polyps, regardless of their number, is exceedingly low. In a study from MSKCC of 417 patients with polypoid lesions of the gallbladder discovered on US, 10% had neoplastic/adenomatous polyps (Ito et al, 2009). Polyp growth was found in only 6% of patients on follow-up. Eighty patients underwent cholecystectomy, and a single patient had carcinoma in situ with a 13-mm gallbladder polyp. The exception to this recommendation of resection only for polyps larger than 1 cm is for those arising in the setting of primary sclerosing cholangitis. These polyps are more likely to be neoplastic, and the threshold for cholecystectomy probably should be lower in this patient population (Buckles et al, 2002).

US is the diagnostic modality of choice to measure and characterize gallbladder polyps (see Chapter 13), but if there is any suspicion of malignancy, cross-sectional imaging with contrast-enhanced CT or MRI is essential. For gallbladder polyps found in the context of abdominal symptoms, another cause of the pain should be sought. Most polyps are asymptomatic, and if no other cause is found to explain the abdominal symptoms, a cholecystectomy should be performed. Patients with polyps smaller than 1 cm who are asymptomatic should be followed up with serial US to rule out the possibility of a growing adenomatous polyp. Long-term follow-up of stable polyps does not seem warranted according to a multiinstitutional registry of approximately 70,000 patients who had gallbladder US. A prevalence

of gallbladder cancer with polypoid lesions of the gallbadder equal to 0.08% was reported in white patients (Aldouri et al, 2009). Conversely, Kubota and colleagues (1995) reported that on periodic US 4 to 12 months after the original US, polyps grew 1.4 to 4 times larger. Thus our recommendation is for US follow-up at 6- to 12-month intervals for 2 years; if polyp size is stable, routine surveillance can be stopped. Additional studies should only be performed in the setting of new clinical findings or symptoms.

For polyps mandating cholecystectomy (>1 cm) without obvious evidence of malignancy on imaging, whether an open or laparoscopic cholecystectomy should be performed has been considered controversial. Our practice originally was to perform an open cholecystectomy for 1-cm polyps. More recently we have adopted a policy of laparoscopic cholecystectomy when there is no obvious US concern for malignancy, with the caveat that all such lesions must be examined by frozen-section histology, the threshold to convert to an open procedure should be low, and definitive resection must be performed if invasive cancer is suspected. The reasons for this policy are due to the overall low risk of malignancy, the fact that simple cholecystectomy is curative for T1a tumors, and that laparoscopically resected early-stage tumors do not seem to have a dramatically worse outcome if a definitive resection is ultimately performed and the gallbladder is not perforated. Laparoscopic US may be helpful to locate the tumor, and every patient undergoing a cholecystectomy for polyps should be carefully counseled regarding the risk of malignancy and the possibility of needing a liver resection and lymph node dissection at the same sitting.

Incidentally Discovered Gallbladder Carcinoma During or After Routine Cholecystectomy

Gallbladder cancer is found in 0.27% to 2.1% of all laparoscopic cholecystectomies (Darmas et al, 2007; Frauenschuh et al, 2000; Kwon et al, 2008). If the diagnosis of gallbladder cancer is made by frozen-section analysis in the operating room, the operating surgeon should prepare for a curative resection with possible liver and bile duct resection. If the surgeon is not comfortable with this extent of surgical resection, no further dissection should be performed and the patient should be transferred to an experienced hepatobiliary surgeon. This strategy does not appear to affect outcomes; a retrospective study at MSKCC reported that outcomes after prior noncurative resection were similar to outcomes from primary curative resections (Fong et al, 2000). However, these findings are subject to selection bias because the majority of patients diagnosed with gallbladder cancer after routine cholecystectomy have early-stage tumors. Ouchi and colleagues (2002) reported on 498 patients diagnosed with gallbladder cancer after laparoscopic cholecystectomy. They found that 34% had T1a, 14% had T1b, 41% had T2, 8% had T3, and 2% had T4 tumors.

Once the diagnosis is made, all patients should undergo a complete staging workup, as previously described. If patients have resectable disease with no contraindications to additional surgery, a second operation should be considered. With T1a tumors, if margins are negative, standard cholecystectomy cures 85% to 100% of patients (Shirai et al, 1992; Yamaguchi & Tsuneyoshi, 1992); thus no additional resection or treatment is indicated. For tumors staged as T2 and above, additional resection is indicated. Controversy surrounds treatment of T1b tumors. Principe and colleagues (2006) demonstrated a 50% 1-year survival in patients with T1b gallbladder cancers after simple cholecystectomy (Shirai et al, 1992a). Other series, however, report cure rates for T1b tumors that are 90% to 100% at 5 years (Kang et al, 2007b). A multiinstitutional study of 115 patients reported residual disease at any site in the abdomen during re-resection for 38% of T1, 57% of T2, and 77% of T3 tumors (Pawlik et al, 2007). Residual invasion of the liver parenchyma in the gallbladder bed was found in 0% of T1, 10% of T2, and 36% of T3 tumors.

When a patient who has undergone noncurative cholecystectomy is referred, careful workup is required. Reviewing the precholecystectomy US and any other imaging is prudent to try to pinpoint the location of the tumor. It is also wise to personally discuss the case with the operating surgeon to assess the specific intraoperative findings, and the specimen should be carefully re-reviewed pathologically to assess T stage and margins.

Given the results discussed above, re-resection is recommended for all patients who are medically fit with T1b or greater level of invasion. Although the role of re-resection in patients with T1b tumors has been the subject of some controversy, data from several centers now support reoperation and definitive resection in this setting. If the cystic duct stump is positive or the margin is a specific concern, a bile duct resection and reconstruction are generally required. In highly selected cases, a re-resection of the cystic duct stump with frozen-section assessment can be considered. Routine resection of the bile duct has not been globally associated with improvements in survival in all patients, but it is generally required for a complete resection in cases with a positive cystic duct stump margin (Pawlik et al, 2007; Sakamoto et al, 2006).

Staging Laparoscopy

Staging laparoscopy is an important consideration when operating on intraabdominal malignancy. Because most gallbladder cancer patients do not require palliative operations, and because incidence of occult metastatic disease is high, staging laparoscopy makes sense for this disease. The benefits of discovering occult metastases at laparoscopy compared with laparotomy are obvious and include less pain, less morbidity, quicker hospital discharge, more rapid resumption of normal activity, and earlier start of other therapies. The yield for staging laparoscopy in gallbladder cancer is high, and this examination should be routinely used. Of 44 cases in which staging laparoscopy was used, Weber and colleagues (2002) reported a 48% yield, and these patients all were spared a laparotomy. Despite this high yield, the examination still missed an additional 15 malignancies, suggesting room for further improvement. Even in patients who have had a prior noncurative cholecystectomy, the yield is still generally approximately 20% and is justified in this patient group.

Extent of Resection by Stage

An early description of a rational approach to the surgical treatment of gallbladder cancer was provided by Glenn and Hays in 1954. They recommended a wedge resection of the gallbladder bed and regional lymphadenectomy of the hepatoduodenal ligament. The late presentation and generally poor prognosis, compounded by the rarity of the disease, have resulted in significant controversy and confusion about the best surgical approach to gallbladder cancer since that time. For the same

stage of disease, surgeons have recommended varying operations, from a simple cholecystectomy to combined hepatectomy, bile duct resection, and pancreatoduodenectomy. A survey of gastrointestinal surgeons from the early 1990s showed that 49% recommended lymph node dissection and 64% recommended some form of liver resection for stage T2 through T4 disease (Gagner & Rossi, 1991). No such consensus was reached on the optimal extent of resection. In recent years, however, much has been learned and consistent radical approaches have been met with some success. Despite the lack of definitive evidence, a rational approach to gallbladder cancer can be devised and should depend on the stage of the disease, location of the tumor, margin status (if previous cholecystectomy), and whether a prior, noncurative cholecystectomy has been performed. When considering extensive operations, the morbidity must be weighed carefully against the long-term outcome data.

Despite the confusion about the extent of resection for gallbladder cancer, strong evidence supports the use of liver resection and regional lymphadenectomy for T2 and T3 tumors without distant metastases. The modest improvements in survival over time probably reflect the better surgical resections applied to this overall minority of patients (Grobmyer et al, 2004). In a study from Toronto, two separate periods were analyzed and showed improved survival in completely resected patients; median survival increased from 9 to 17 months. In the second period, liver resection and regional lymphadenectomy were used more often, and the authors attributed the improved survival to this strategy (Dixon et al, 2005). In general, we recommend the following principles based on the literature and our own data. T1a tumors can be treated with a simple cholecystectomy. T1b tumors, although associated with good long-term survival after simple cholecystectomy, are associated with a higher locoregional recurrence rate and, in most patients, liver resection and lymph node dissection should be performed. A negative cystic duct margin must be ensured, and a bile duct resection to obtain a negative margin for a T1 tumor is recommended. In general, for T2 and T3 tumors, a complete resection of the tumor en bloc with segments IVb and V of the liver should be carried out to ensure complete clearance. If the tumor extent is such that invasion of hepatic inflow vascular structures is documented or suspected, an extended right hepatectomy may be necessary to clear all tumor; this is appropriate in a healthy patient with no evidence of distant disease. A negative margin at the cystic duct should be assessed and, if necessary, a bile duct resection should be performed. A lymph node dissection of the hepatoduodenal ligament also should be carried out. It is important to stage the patient carefully at operation, and major resections should be abandoned if distant nodal (retropancreatic or celiac) or other metastases are found. A diagrammatic representation of the extent of operation in a typical extended cholecystectomy is shown in Figure 49.7.

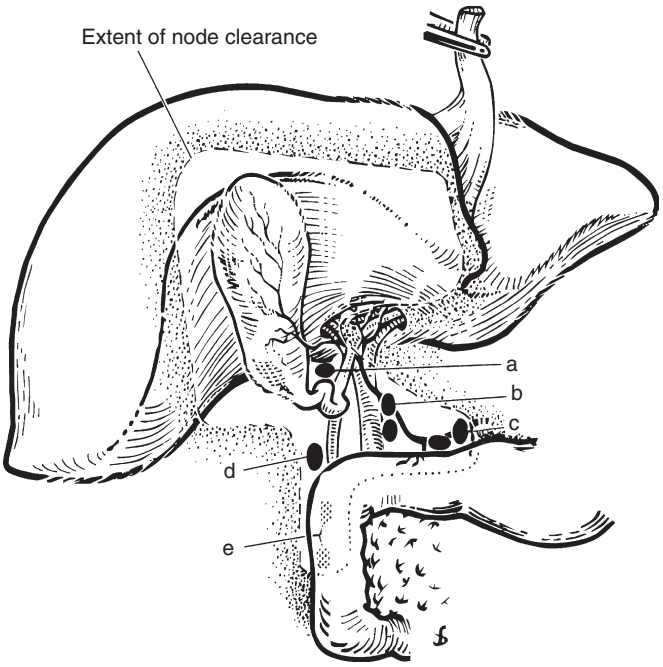


FIGURE 49.7. Diagrammatic representation of the extent of dissection in an extended cholecystectomy. *a-e*, lymph node field.

Liver Resection (See Chapter 90B)

It is now accepted that some degree of liver resection is appropriate to treat gallbladder cancers beyond the very early T1a stage. Recommendations have ranged from a limited 2-cm wedge resection of the gallbladder bed to a routine extended right hepatectomy. The goal of the liver resection is to ensure a margin of resection of approximately 1 to 2 cm because there is no serosal surface on the liver side of the gallbladder. Although a wedge resection may be sufficient for a clear margin, it is a nonanatomic approach that may compromise the safety of the operation related to bleeding or bile leakage or both. It also may result in a closer margin than anticipated. We generally recommend an anatomic resection of segments IVb and V. Intraoperative US can be helpful in delineating vascular anatomy and guiding the resection. The inflow pedicles to segments IVb and V generally are taken within the liver substance, but the segment IVb pedicles can be dissected in the umbilical fissure and divided before parenchymal dissection. Major bleeding can occur from the distal branches of the middle hepatic vein, and these must be carefully controlled. Care must be taken to avoid injury to the main right anterior sectoral pedicle and the segment VIII pedicles.

If a segment IVb/V resection would result in an inadequate margin, an extended right hepatectomy may be required. This may be the case for large tumors invading the right portal pedicle or tumors of the lower end of the gallbladder encroaching on the porta hepatis. In the latter situation, a bile duct resection is usually required. Isolated invasion of local organs (stomach, duodenum, colon) in the absence of distant metastases requires a local resection, which is reasonable to perform to ensure tumor clearance. In patients who have had a prior noncurative cholecystectomy, the preoperative US should be reviewed to find the tumor; this can guide the resection. The cystic duct margin also should be reanalyzed. Typically, a segment IVb/V resection is adequate if no obvious tumor is present and the tumor was present in the body or fundus. It often is impossible to differentiate scar from tumor in the porta hepatis at the time of operation, forcing the surgeon to perform a bile duct resection and extended right hepatectomy; this is appropriate in well-selected patients. Reddy and colleagues (2007) described 11 patients with stage I and II gallbladder cancer who underwent extended hepatectomy for either large

tumors, positive cystic duct margins, preoperative jaundice and biliary obstruction, known node-positive disease, or significant inflammation in the triangle of Calot. Morbidity and survival were similar when compared with historic controls treated with extended cholecystectomy (Reddy et al, 2007). In a series of 104 patients from MSKCC, however, morbidity and mortality increased with more extensive resections without any improvement in survival (D'Angelica et al, 2009). In this series, 20% of patients had direct invasion of other organs and concurrent en bloc resections. The principal finding of this analysis was that the stage of the tumor, rather than the extent of resection (given a margin-negative resection), was the overwhelming determinant of long-term survival. Thus current practice is to perform only the extent of hepatic resection necessary to achieve tumor clearance.

Lymph Node Dissection

Studies of the lymphatic drainage of the gallbladder have been performed and were reviewed earlier in this chapter (Shirai et al, 1992c). As in the extent of liver resection, there has been wide variability in the recommendation for the extent of lymphadenectomy, ranging from excision of the cystic duct node to a complete portal clearance combined with pancreatoduodenectomy (Matsumoto et al, 1992). Groups from Japan have reported some success for the treatment of extensive gallbladder cancer with hepatopancreatoduodenectomy even in the face of extensive nodal metastases (Sasaki et al, 2002). The recommendation for these extensive procedures is based on the fact that early lymph node metastases to the retropancreatic and interaortocaval nodes are common, and a pancreatic resection presumably improves the ability to clear these nodes. The more important question is whether the increased risk of such an approach is justified by the outcome. In general, the outcome for patients with nodal disease, in particular in patients with distant nodal disease, is so poor that this approach is not generally recommended. Given the importance of identifying lymph node metastases outside the "extended cholecystectomy" field, the first maneuver in the operating room is mobilization of the duodenum to assess the aortocaval and retropancreatic lymph nodes. The celiac lymph nodes should also be assessed early on; suspicious nodes are sent for frozen-section analysis and, if positive, the procedure is terminated.

Whether lymph node dissection improves outcome is unknown; given the rarity of this disease, this question will probably never be tested in a randomized trial. Lymph node dissection does provide important diagnostic information, however, and it may provide further regional control. Regional lymphadenectomy for gallbladder cancer includes removal of nodes in the porta hepatis, gastrohepatic ligament, and retroduodenal space (all N1 nodes). In patients with T1b or greater tumors, regional lymphadenectomy is associated with improved survival in retrospective studies when compared with extended cholecystectomy alone (Frauenschuh et al, 2000; Kwon et al, 2008). The rate of positive nodes with T1b to T3 tumors in these studies ranges from 16% to 30%. Despite these data, a study that used the epidemiology and Surveillance and Epidemiology End Results (SEER) database to track gallbladder treatment trends found that an adequate lymphadenectomy (three or more nodes) was only reported in 5.3% of patients treated surgically for gallbladder cancer (Coburn et al, 2008). The year of resection (after 1988, hazard ratio [HR] = 1.20; 95% confidence interval [CI] 1.14 to 1.26) and T1 stage (compared with T2, HR = 0.48; 95% CI, 0.27 to 0.83) were associated with adequate lymphadenectomy. Only 6% of patients with T2 or T3 tumors underwent lymphadenectomy. In addition, the majority of T3 tumors (75%) were treated with inadequate lymphadenectomies (up to two nodes). Although this study suggests that the majority of patients with gallbladder cancer did not receive appropriate surgical treatment, the limitations of the SEER database may be responsible for overestimating this trend.

Controversy surrounds the question of whether a routine bile duct resection is necessary for an adequate lymph node dissection. Although there is no question that excising the extrahepatic bile duct can make a lymph node dissection easier, it also increases the morbidity of the operation (Bartlett et al, 1996). However, no differences are reported in the numbers of lymph nodes harvested in regional lymphadenectomy with or without a bile duct resection (Sakamoto et al, 2006; Pawlik et al, 2007; D'Angelica et al, 2009). In general, a bile duct resection should not be necessary unless there is suspicion of infiltration into the porta hepatis. One study from Japan reported on patients with T2 or T3 tumors who underwent routine bile duct resection (Shimizu et al, 2004). Histologic spread of tumor in 30 of 50 specimens into the hepatoduodenal ligament was documented; some represented direct spread of tumor, and others represented lymph node metastases. It is unknown whether this resection would have any impact on outcome, especially in patients with lymph node metastases. In a study from MSKCC of 109 patients undergoing surgical resection for gallbladder cancer (D'Angelica et al, 2009), 68 patients (65%) had common bile duct resections, with 36 the result of clinical involvement and 32 with empirical resections. Bile duct resection was not associated with clinical or pathologic variables. The 5-year survival of patients without bile duct involvement was 49%, which was significantly higher than for those with bile duct involvement (20%). This study, combined with the data from Sakamoto and others, reinforces the point that stage of disease, not extent of surgery (assuming an R0 resection), determines survival in patients who undergo resection of gallbladder cancer.

Bile duct resection combined with regional lymphadenectomy requires a Kocher maneuver, division of the bile duct at the level of the duodenum, and complete dissection of all the associated soft tissue. This tissue should be swept superiorly, skeletonizing the porta hepatis vasculature. Reconstruction is with a Roux-en-Y hepaticojejunostomy (see Chapter 50B). Malignant invasion of the bile duct with jaundice would necessitate a bile duct resection, but the surgeon must consider the overwhelmingly poor prognosis in these patients and the low likelihood of a complete resection (Hawkins et al, 2004); a palliative approach may be best in this patient population.

PORT SITE RECURRENCES

There is a theoretical risk of port site seeding after laparoscopic cholecystectomy for what is eventually diagnosed as gallbladder cancer. This problem may be exacerbated by spillage of bile or stones inside the peritoneal cavity (Winston et al, 1999). One study looked at 409 patients who underwent laparoscopic cholecystectomy for presumed benign gallbladder disease but were diagnosed with gallbladder cancer on final pathology (Paolucci et al, 1999). Seventeen percent of patients at a median of 180 days were diagnosed with laparoscopic port site recurrences. As

a result of this high percentage, some surgeons recommend port site excision during reoperation for gallbladder cancer. It is important to note, however, that it is rare for port site recurrences to occur as the sole site of disease (Povoski et al, 2004; Shoup & Fong, 2002). Given that it is more a marker of aggressive disease than a single site of resectable disease, our general practice does not include empirically resecting prior port sites during reexploration for gallbladder cancer.

RESULTS

The overall picture of gallbladder cancer is slowly improving but is still a dismal one. Historically, more than two thirds of patients are initially seen with disease beyond the scope of surgery; even including patients who are lucky enough to make it to resection, the overall survival is poor. The overall 5-year survival is consistently less than 5%, with a median survival of 5 to 8 months. Older large reviews (Perpetuo et al, 1978; Piehler & Crichlow, 1978) documented a 5-year survival of 4% to 5% and a median survival of 5 months. One-year survival was 12%. Approximately 25% of the patients were resected for cure, and in this select group, 5-year survival was only 17%. Studies published in Europe and Australia in the 1990s report overall median survivals of approximately 3 months and 5-year survivals of approximately 5% (Carty & Johnson, 1991; Cubertafond et al, 1994; Wilkinson, 1995). Survival results from MSKCC for patients treated from 1995 to 2005 show some improvements compared with older studies (Duffy et al, 2008). Of the 435 patients studied, 36.6% presented with AJCC stage IV disease. Median overall survival for the entire patient cohort was 10.3 months (95% CI, 8.8 to 11.8 months) with a median follow-up of 26.6 months. For patients with stage Ia through stage III disease, median survival was 12.9 months (95% CI, 11.7 to 15.8 months) compared with 5.8 months (95% CI, 4.5 to 6.7 months) for those with stage IV disease. Median survival for patients who had an incidental diagnosis of gallbladder carcinoma after laparoscopic cholecystectomy was 15.7 months (95% CI, 12.4 to 18.4 months). Of this subset of patients, those who were reexplored had a median survival of 72 months (95% CI, 34/not reached); for patients with no pathologic evidence of residual disease, median survival was 19 months (95% CI, 12.9 to 28 months) if an R0 resection was done and 12.7 months (95% CI, 8.2 to 15.7 months) for an R1 or R2 resection ($P < .0001$). Of these patients, 104 were analyzed in a separate study (D'Angelica et al, 2009) that showed T and N stage to be strong independent predictors of outcome along with histologic differentiation and bile duct involvement.

Refinements in hepatobiliary surgery have made safe and rational approaches to malignancy more broadly applicable. As presented below, there is now mounting evidence that in selected patients without distant disease, an aggressive surgical approach can provide the potential for long-term survival. Given the rarity of this disease, prospective data are lacking and decision making relies on the analysis of imperfect retrospective analyses. Because most operable gallbladder cancer is incidental, and surgical decisions are based on T stage from a resected gallbladder or from imaging, the approach to the three potentially resectable T stages and their outcomes are outlined.

T1 Tumors: Confined to the Muscular Coat

T1 tumors are typically diagnosed incidentally in cholecystectomy specimens because they are usually not obvious on imaging studies. By definition, they do not penetrate the muscular layer, and because a simple cholecystectomy dissects the perimuscular layer, this operation theoretically should be curative. These tumors are rarely associated with lymph node metastases. In the uncommon circumstance that a T1 tumor is detected intraoperatively, the surgeon should palpate lymph nodes and sample any that are suspicious. It is crucial to obtain negative margins, and the cystic duct margin always should be reviewed to ensure this. It is sometimes necessary to resect the common bile duct to obtain this negative margin. Overall, the cure rate is 85% to 100% with a simple cholecystectomy (Table 49.9). Of the small number of patients with T1 gallbladder cancer that recurs, they are commonly found to have submucosal spread involving the cystic duct margin (Shirai et al, 1992b). T1b tumors also seem to be at a higher risk of recurrence, as previously described; because of this, an extended cholecystectomy is recommended in patients with T1b tumors who can tolerate the procedure.

T2 Tumors: Invading into the Subserosal Layer

T2 tumors are most likely to benefit from an extended resection of the lymph nodes near the liver and porta hepatis. Results from modern series are listed in Table 49.10. Because these tumors are difficult to diagnose preoperatively, they also are

Table 49.9

Actuarial Survival After Resection of T1 Gallbladder Cancer

Reference	Patients	Treatment	3-Year Survival (%)	5-Year Survival (%)
Ogura et al, 1991*	366	NS	87	78
Shirai et al, 1992b	56	SC	100	100
	38	EC	100	100
De Aretxabala et al, 1994	32	SC (69%) EC (31%)	94	94
Ouchi et al, 2002*	234	SC (82%)	NR	97
Toyonaga et al, 2003	22	SC	100	100
Kang et al, 2007a	24	SC	NR	95

*Multiinstitutional study

EC, extended cholecystectomy; NR, not reported; NS, not specified; SC, simple cholecystectomy

Table 49.10

Actuarial Survival After Resection of T2 Gallbladder Cancer Stratified by Extent of Resection

Reference	Patients	Procedure	5-Year OS (%)
Shirai et al, 1992b	10	EC	90
Yamaguchi & Tsuneyoshi, 1992	25	SC	36
Fong et al, 2000	16	SC	19†
	37	EC	61†
Ouchi et al, 2002*	48	SC	70 for all patients‡
	153	EC	
Toyonaga et al, 2003	25	SC	65†
	18	EC	38†
Suzuki et al, 2004	20	EC	77
Foster et al, 2007	10	SC	38†
	9	EC	78†
Kang et al, 2007a	19	SC	56†
	33	EC	75†
Goetze & Paolucci, 2010*	161	SC	25†
	139	EC	41†

*Multi-institutional series
†$P < .05$
‡Trend toward improved overall survival with EC ($P = .051$)
EC, extended cholecystectomy; NR, not reported; NS, not specified; OS, overall survival; SC, simple cholecystectomy

commonly diagnosed incidentally at cholecystectomy. The dissection plane of a simple cholecystectomy in the subserosal plane is often involved with tumor, resulting in a positive margin for many T2 tumors (Yamaguchi et al, 1992). In addition, approximately one third of patients with T2 tumors have nodal metastases, reinforcing the need for a regional lymphadenectomy for diagnostic and potentially therapeutic purposes (Chijiiwa et al, 2001). Although based on multiple retrospective reviews, the data indicate that survival is significantly improved in patients undergoing an extended cholecystectomy compared with patients undergoing a simple cholecystectomy. What is striking from these series is that long-term survival generally is achieved in 60% to 100% of patients undergoing an extended resection, depending on the stage, compared with less than 50% with simple cholecystectomy.

T3 and T4 Tumors: Locally Advanced

The most controversial aspect of the surgical treatment of gallbladder cancer involves patients with nonmetastatic locally advanced tumors (T3 and T4 tumors). Table 49.11 summarizes representative studies in this patient group. Historically, these patients were documented to have extremely poor survival, and surgical extirpation was thought to be futile. Since the 1990s, however, numerous small series have documented that with varying levels of extended resections, long-term survival is possible in highly selected patients. In a series from MSKCC, 15% to 20% of patients with locally advanced disease were long-term survivors (Fig. 49.8) (D'Angelica et al, 2009).

Numerous series from Japan, in particular, have shown the possibility of long-term survival in these patients. Japanese surgeons liberally use extensive surgical procedures, including

Table 49.11

Actuarial Survival After Extended Resection for T3 and T4 Nonmetastatic Gallbladder Cancer

Reference	Patients	Stage	3-Year OS (%)	5-Year OS (%)
Ogura et al, 1991*	453	IV	18	8
Matsumoto et al, 1992	8	III	38	NR
	27	IV	25	
Onoyama et al, 1995	12	III	44‡	44‡
	14	IV	8‡	8‡
Bartlett et al, 1996	8	III	63‡	63‡
	7	IV	25‡	25‡
Fong et al, 2000	58	III/IV	28	28
Kondo et al, 2002	29	IV	24	17
Ouchi et al, 2002†	40	III	NR	20‡
	11	IV		0‡
Wakabayashi et al, 2004	8	III	83‡	83‡
	13	IV	46‡	46‡
Foster et al, 2007	26	III	NR	15
Kang et al, 2007a	26	III	NR	15
D'Angelica et al, 2009	63	III/IV	NR	25
Goetze & Paolucci, 2010	46	III	NR	17

*Multiinstitutional series
†$P < .05$
‡All patients diagnosed after laparoscopic cholecystectomy
NR, not reported; OS, overall survival

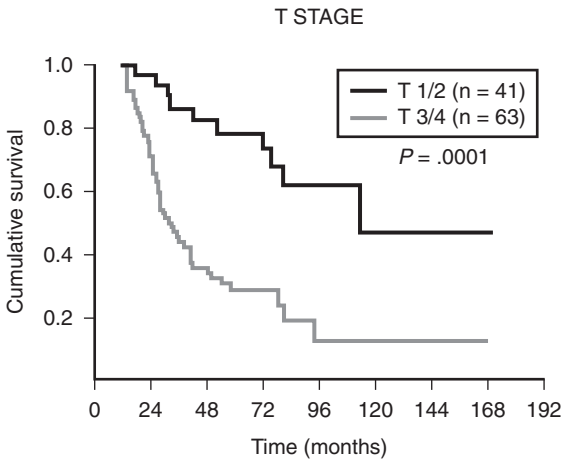


FIGURE 49.8. Disease-specific survival for 104 patients with gallbladder cancer stratified by T stage. *(From D'Angelica M, et al, 2009: Analysis of the extent of resection for adenocarcinoma of the gallbladder. Ann Surg Oncol 16[4]:806-816.)*

vascular resection, bile duct resection, extended hepatectomy, and hepatopancreatoduodenectomy (Nakamura et al, 1989; Onoyama et al, 1995; Shirai et al, 1992b). In general, extensive lymph node dissections are routinely performed, and survival results may be a reflection of stage migration and better staging. Western series also have begun to show similar results with an aggressive surgical approach (Gall et al, 1991). These data must be interpreted in the proper context, however; overall, most patients with locally advanced disease have metastatic disease, and resection is often impossible. The most important associated prognostic factor in every series is the status of lymph nodes. Long-term survival rarely accompanies distant lymph node disease, and it is uncommon with hepatoduodenal lymph node metastases. The uncommon patient with a locally advanced tumor and no lymph node metastases probably benefits the most from an extensive operation. Patients with locally advanced gallbladder tumors should be carefully evaluated to rule out distant metastases. In general, patients with lymph node metastases outside the hepatoduodenal ligament should not undergo resection. In carefully selected patients, however, extended radical resection provides the only chance for long-term survival.

Regional Lymph Node Positivity

Nodal status was found to be an independent predictor of outcome in multiple studies. Although the number and location of positive nodes can affect survival, the presence of any nodal disease is associated with poor survival. In a study of 104 patients with gallbladder cancer at MSKCC, for example, the 34 patients with N1 disease had a significantly worse 5-year survival (17%) compared with patients with N0 disease (51%; P = .0002) (D'Angelica et al, 2009). Endo and colleagues (2006) reported a similar difference in survival, with 5-year survival rates of 77% with node-negative disease and 33% with one positive lymph node. These findings also apply to patients who had gallbladder cancer discovered incidentally after cholecystectomy. Pawlik and colleagues (2007) examined nodal status in patients diagnosed after surgical resection and found a 5-year survival of 73% with node-negative disease compared with a 5-year survival of 27% in patients with node-positive disease (Endo et al, 2006). The number of positive nodes has also been described as a predictor of outcome. Patients with a single lymph node metastasis had a higher 5-year survival rate (33%) compared with patients who had two or more lymph node metastases (0%; $P < .05$) (Endo et al, 2006).

Gallbladder Cancer Discovered Incidentally After Laparoscopic Cholecystectomy

The surgical approaches to patients who have undergone a prior noncurative cholecystectomy have been previously outlined. When a patient is seen after a noncurative cholecystectomy with no evidence of disseminated disease, a repeat resection is warranted in most cases. For patients who undergo definitive operation, the outcome seems to be similar to that of patients who undergo primary resection; this seems to be true stage for stage (Fong et al, 2000).

Significance of Jaundice on Presentation

The presence of jaundice is a troubling sign; it suggests porta hepatis involvement with tumor. In 240 patients at MSKCC who presented with gallbladder cancer, 82 (34%) were jaundiced and were more likely to have advanced stage disease; only six patients underwent resection with curative intent, and only four had an R0 resection (Hawkins et al, 2004). The median disease-specific survival of patients with jaundice was 6 months, significantly worse than those without jaundice (16-month disease-specific survival; $P < .0001$), and none from the jaundiced group survived 2 years. A retrospective study by Varma and colleagues (2009) reported that although jaundice was associated with a higher stage at presentation, it did not preclude resection. Half of those patients who presented with jaundice underwent R0 resections. Survival differences, however, were not reported between jaundiced and nonjaundiced patients. Thus curative resection can be attempted in select patients with gallbladder cancer and jaundice, but the expectations of the surgical team and patient should be tempered.

ADJUVANT THERAPY

The rarity of gallbladder cancer has traditionally precluded large randomized trials, and the literature abounds with small case series and retrospective comparisons that attempt to address whether adjuvant chemotherapy and/or radiation therapy are beneficial after complete resection. In a study from MSKCC, 85% of recurrences included distant sites as part of the recurrence pattern (Jarnagin et al, 2003), highlighting the importance of systemic therapies. Reports of small series with fewer than 10 patients from the 1970s and 1980s suggested a small benefit to adjuvant chemotherapy compared with historic controls (Morrow et al, 1983; Oswalt & Cruz, 1977). Chao and Greager (1991) reported on 15 patients who received some form of chemotherapy or radiation or both after resection and found no difference compared with patients who had not received adjuvant therapy. Similarly, studies of adjuvant radiation therapy over the last few decades have suggested modest benefits (Bosset et al, 1989; Hanna & Rider, 1978; Todoroki et al, 1991).

A recent retrospective review of 123 patients who underwent resection of gallbladder cancer with adjuvant therapy (n = 24; 66% of patients with chemoradiation, 34% of patients with chemotherapy alone) or without (n = 99) showed no difference in

overall survival between the groups; however, patients treated with adjuvant therapy had a higher rate of incomplete resections, higher stage of disease, and more positive lymph nodes (Duffy et al, 2008). A recent SEER database analysis of 4000 patients with gallbladder cancer found a survival benefit with adjuvant radiotherapy in patients with positive nodal disease or T2 or greater tumors (15 months vs. 8 months). This difference was significant on multivariate analysis (HR = 1.46; 95% CI, 1.07 to 1.98; $P = .014$) (Wang et al, 2008).

Three randomized, controlled trials have included patients with gallbladder cancer. Takada and colleagues (2002) reported a phase III multiinstitutional trial of adjuvant chemotherapy performed in Japan. This trial included 508 patients with biliary and pancreatic cancers. On subset analysis, this study included 140 gallbladder cancer patients who were randomized to receive surgical resection alone or resection plus adjuvant mitomycin C and 5-fluorouracil (5-FU). When considering the gallbladder cancer patients only, the actuarial 5-year disease-free survival favored the adjuvant chemotherapy group (20.3%) compared with the surgery-alone group (11.6%, $P = .02$). Data regarding the extent of surgical resection and histologic staging were lacking, making the results difficult to interpret. More recently, gemcitabine-based regimens, often combined with a platinum agent, have become the drug of choice for treating gallbladder cancer. Much of the data for the adjuvant setting has been extrapolated from the metastatic setting. A recently published randomized, phase III study of palliative gemcitabine compared with gemcitabine and cisplatin for metastatic biliary cancers offers information that may be useful in the adjuvant setting (Valle et al, 2010). With overall survival as the primary end point, 410 patients with locally advanced or metastatic gallbladder cancer, cholangiocarcinoma, or ampullary cancers were randomized; 149 patients had gallbladder cancer. After a median follow-up of 8.2 months for all patients in the trial, a significant difference in overall survival was reported, with an HR of 0.61 (CI, 0.42 to 0.89) favoring the gemcitabine-cisplatin combination. There were, however, more neutropenic events in the gemcitabine-cisplatin group. It remains to be seen whether this new trial will change clinical practice in the adjuvant setting, but it continues to reinforce gemcitabine-based regimens as the standard chemotherapy for gallbladder cancer. Another smaller randomized, controlled trial of gemcitabine combined with oxaliplatin (GEMOX) showed a similar benefit when the gemcitibine regimen was compared with 5-FU or best supportive care in patients with unresectable or metastatic gallbladder cancer (Sharma et al, 2010). Median overall survival was 9.5 months in the GEMOX group (n = 27), compared with 4.6 months in the 5-FU group (n = 28; $P = .039$).

In light of the available data, it is reasonable to consider patients with high-risk lesions (T4 tumors, at least one positive lymph node, R1 resection) for adjuvant therapy and to offer consultation with an oncologist to discuss treatment options. However, it must be emphasized that treatment efficacy in the palliative setting may not translate into better disease control when used as an adjuvant to resection.

PALLIATIVE MANAGEMENT

Most treatment options in patients with gallbladder cancer are palliative because most patients are unresectable by the time they come to medical attention. The most common symptoms to palliate include pain, jaundice, and bowel obstruction.

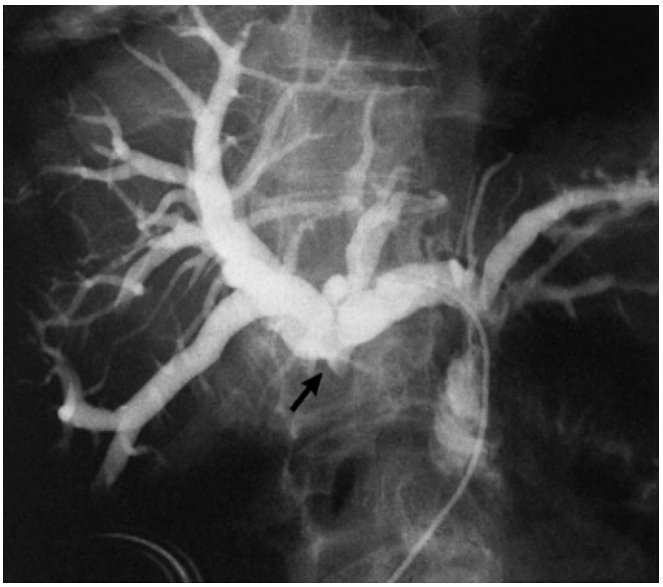


FIGURE 49.9. Tubogram showing a segment III hepaticojejunostomy. The anastomosis is well away from the malignant obstructing lesion in the liver hilus (*arrow*).

Palliation of jaundice in gallbladder cancer can be complex and depends on the location and extent of biliary obstruction. The outcome for these patients is poor, and chemotherapy often offers little in terms of prolongation of life. In the past, operative approaches provided the most effective relief of obstruction in well-selected patients. Operations such as the segment III bypass (Fig. 49.9) (Bismuth & Corlette, 1975; Kapoor et al, 1996) and the Longmire operation (Longmire et al, 1973) have become less common with the development of interventional percutaneous stenting techniques. In patients who have symptoms from obstructive jaundice, endoscopic or percutaneous interventions are the preferred approach for palliation and minimalization of morbidity (Lung et al, 2009; Naitoh et al, 2009; Togawa et al, 2008).

In general, patients in need of palliative procedures for symptomatic gallbladder cancer have high complication rates after such procedures. A prospective study from MSKCC included 109 patients undergoing percutaneous biliary drainage for malignant biliary obstruction. A 58% rate of major complication and two procedure-related deaths were reported, and the 8-week postprocedure mortality rate was 28%. These palliative procedures were successful in alleviating pruritus, but no improvement was reported in measures of quality of life (Robson et al, 2010). The high risk of morbidity and mortality precludes recommending these treatments in the absence of symptoms or a specific reason to treat jaundice, such as to allow the administration of chemotherapy. Saluja and colleagues (2008) randomized 44 patients with gallbladder cancer and obstructive jaundice to percutaneous or endoscopic stenting. They found that successful stenting occurred in 89% of patients in the percutaneous group compared with 41% in the endoscopic group ($P < .001$). Cholangitis was also significantly higher (48%) in the endoscopic stent group compared with the percutaneous group (11%; $P = .002$). The mortality rates were similar between the two groups, but percutaneous stenting in this trial offered better palliation than endoscopic stenting. The

Table 49.12

Treatment Recommendations for Gallbladder Cancer Diagnosed After Cholecystectomy

T Stage	Recommended Surgical Procedure	Notes
Ia	Simple cholecystectomy	85% to 100% of patients cured
Ib, II	Extended cholecystectomy with resection of segments IVb and V with en bloc regional lymph node dissection Bile duct resection if bile duct margin positive	
III	Hepatic resection (segments IVb, V) with major hepatectomy as necessary	More commonly involves bile duct and right-sided vascular structures, requiring major liver resection
IV	Same as stage III if resectable	Often unresectable because of hilar vascular invasion

choice between endoscopic and percutaneous interventions often depends on local resources and personnel. Intestinal bypass can also be performed in patients with symptomatic bowel obstructions. Percutaneous feeding tubes or drains and endoscopic stents are favored over surgical bypass because of the extremely poor prognosis.

Chemotherapy has been used to palliate unresectable disease but often offers little benefit. Historically, regimens have included 5-FU, leucovorin, mitomycin C, doxorubicin, and methotrexate. Response rates in these studies generally range from 10% to 20% (Hejna & Zielinski, 2001). More recently, however, phase II trials with gemcitabine and oxaliplatin have showed improved response rates ranging from 40% to 50% (Andre et al, 2008; Harder et al, 2006; Verderame et al, 2006). Radiation therapy may be an effective palliative therapy for locally advanced disease; it is generally well tolerated, may have an impact on local symptoms, and is usually combined with chemotherapy (Lin et al, 2005; Valle et al, 2010).

SUMMARY

Although the overall picture of gallbladder cancer is a dismal one, we have come a long way since Alfred Blalock's quote in 1924, which summarized the nihilism of the day. Localized gallbladder cancer can be cured with an extended resection, and although most patients who are cured had early-stage disease, there is some hope for patients with locally advanced tumors. Perhaps the most important lesson is to recognize abnormalities of the gallbladder wall as possibly malignant at an early stage because primary resection remains the best chance of a good outcome. General surgeons who treat gallbladder disease should critically review the results of preoperative imaging in patients with presumed benign gallstone disease, particularly the US findings, and the possibility of a malignant process must always be considered when abnormalities of the gallbladder wall are reported.

Cancers incidentally discovered at cholecystectomy are common, and this is sufficient treatment for most T1 cancers (Table 49.12). Exceptions are patients with positive cystic duct margins, who should undergo a definitive complete resection, and patients with T1b tumors, who should also be considered for reoperation and definitive resection. For T2 through T4 tumors, patients should undergo reexcision as described throughout this chapter. In general, patients with distant nodal metastases are not able to be cured and probably do not benefit from reoperation. Preoperative imaging and surgical staging are crucial because of the high incidence of metastatic disease. Tumors recognized before cholecystectomy should be resected with an en bloc liver resection and portal lymphadenectomy as described. Even large, locally advanced tumors are potentially curable, albeit the likelihood of such is low. In well-selected, otherwise healthy patients, an aggressive approach is warranted in the absence of distant metastases, including distant nodal disease. For the rare patient with a locally advanced, node-negative tumor, complete resection offers a significant chance for long-term survival. This is probably also true for patients with limited nodal disease in the hepatoduodenal ligament.

The proper operation to treat gallbladder cancer has been extensively discussed and involves a liver resection to encompass the tumor and achieve a negative margin. This is generally a resection of segments IVb and V, but if invasion of inflow structures to the liver mandate it, an extended hepatectomy is warranted. Bile duct resection is indicated to obtain negative margins if necessary, but it should not be routine; however, a complete lymphadenectomy of the hepatoduodenal ligament is an important part of the treatment. Extensive operations to clear distant nodal disease, including a pancreatoduodenectomy, have been described but cannot be advocated in most patients because the risk generally outweighs the benefit. Despite this relative optimism, the overwhelmingly more common issue is the treatment of advanced, metastatic, or recurrent disease. New randomized trials have helped reinforce gemcitabine-based chemotherapy regimens as the most effective, but the development of additional effective systemic agents is crucial.

The surgeon's role is often to facilitate palliative treatments to improve the quality of life for patients with advanced gallbladder cancer. In the past few decades, surgeons have proven that resection for localized gallbladder cancers can be performed safely. Because of the often advanced nature of gallbladder cancer at presentation, efforts should be focused on diagnosing biliary malignancies earlier and developing more effective systemic agents. It is not reasonable to screen an entire population for gallbladder cancer given its rarity; however, gallbladder cancer may be detected at earlier stages with better education to raise awareness so physicians will consider the diagnosis in patients who present with signs or symptoms of gallbladder disease.

References are available at expertconsult.com.

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CHAPTER 50A

Cancer of the bile ducts: intrahepatic cholangiocarcinoma

Jonathan Koea

OVERVIEW

Intrahepatic cholangiocarcinoma is a primary adenocarcinoma of the liver. Like other primary adenocarcinomas of the upper gastrointestinal (GI) tract, these tumors often present with symptoms resulting from advanced local or metastatic disease. They are biologically aggressive, and when possible, surgery is the only known potentially curative therapy, although a few active systemic therapies are available.

Intrahepatic cholangiocarcinoma is also known as *peripheral cholangiocarcinoma*, *cholangiolar cancer,* or *cholangiocellular carcinoma,* terms that have previously been used interchangeably. Cholangiocellular carcinoma was first used by Steiner and Higginson (1959) to describe a subtype of cholangiocarcinoma in which the glands are small and regular and resemble proliferating cholangioles with inconspicuous lumens. Current nomenclature uses the term *intrahepatic cholangiocarcinoma* (IHCC) to define tumors arising from biliary epithelium in intrahepatic bile ducts above the level of the left main and right main ducts (Liver Cancer Study Group of Japan, 1990). These tumors constitute 10% of primary hepatic malignancies, and although much is known about extrahepatic cholangiocarcinoma, IHCC is less well understood.

Hepatic resection for IHCC was infrequently described until recently. Foster and Berman (1977) describe only 13 cases in their summary of hepatic surgery in the United States, although they present 112 resections for hepatocellular carcinoma (HCC) and 47 cases of hepatoblastoma. This low number of resections may represent the frequency with which advanced disease was diagnosed at presentation and also reflects that recognition of IHCCs as a discrete primary liver tumor was slow to occur and that many were historically diagnosed as metastatic adenocarcinoma from unknown primary sites.

EPIDEMIOLOGY AND DEMOGRAPHICS

The incidence of cholangiocarcinoma is rising worldwide and is now the second most common primary cancer of the liver behind HCC (Olnes & Erlich, 2004). Approximately 5000 new cases are diagnosed annually in the United States (Vauthey & Blumgart, 1994), and more than 1000 cases are diagnosed annually in the United Kingdom (Khan et al, 2008). However, overall, cholangiocarcinoma is rare and makes up only 3% of all GI tract cancers (Lazaridis & Gores, 2005). This means that it is infrequently seen by general surgeons or gastroenterologists, and its rarity has frustrated attempts to design therapeutic trials to treat it.

More detailed analysis of epidemiologic data shows that the incidence and mortality rates of IHCC are increasing and those of extrahepatic cholangiocarcinoma are decreasing (see Chapter 50B; Endo et al, 2008; Khan et al, 2002; Patel, 2001, 2002), suggesting that the tumors may have different etiologic factors but similar microscopic morphology. These findings must be interpreted with caution. IHCC may occur as solitary or multiple liver lesions and, in the past, many were probably diagnosed as metastatic tumors and not further investigated. In addition, analysis of the Surveillance, Epidemiology, and End Results (SEER) database has shown that more than 90% of hilar tumors were wrongly classified as IHCCs, and extrahepatic lesions were often classified as gallbladder cancers (Shaib & El-Serag, 2004). Indeed, even when these classification issues are addressed, the mortality rate of IHCC is still increasing worldwide (Fig. 50A.1; Shaib et al, 2005).

IHCC currently has an incidence of 0.85 per 100,000 population in the United States (Shaib et al, 2004; Shaib & El-Serag, 2004); the highest incidence in the world is recorded in northeast Thailand (96 per 100,000) (Khan et al, 2008). Patients most commonly are seen in the seventh decade, and IHCCs are more common in men (Khan et al, 2002; Shaib et al, 2005).

ETIOLOGY AND RISK FACTORS

The majority of patients presenting with IHCC have no known risk factors. However, a number of specific risk factors are recognized, many of which result in chronic inflammation of the biliary epithelia. Most of these risk factors are recognized to contribute to the development of both intrahepatic and extrahepatic cholangiocarcinoma.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) (see Chapter 41) is the most common risk factor for cholangiocarcinoma in the West (Farrant et al, 1991). The cumulative annual risk of cholangiocarcinoma in patients with PSC is 1.5% per year (Farrant et al, 1991), and the prevalence of cholangiocarcinoma in these patients is between 8% and 40% (Pitt et al, 1995; Rosen et al, 1991). The risk of developing cholangiocarcinoma is increased in those with associated inflammatory bowel disease, in whom the 10- and 20-year rates for cholangiocarcinoma are 14% and 31% versus 2% and 2% in patients without inflammatory bowel disease, respectively (Claessen et al, 2009).

Cholangiocarcinoma often develops 2 to 3 decades earlier in patients with PSC than in those with sporadic tumors (30 to 50 years vs. 60 to 70 years of age, respectively) (Bergquist & Broome, 2001; Farrant et al, 1991). In addition, PSC-associated tumors often present later with advanced-stage disease because of difficulties in detecting malignant change in inflammatory

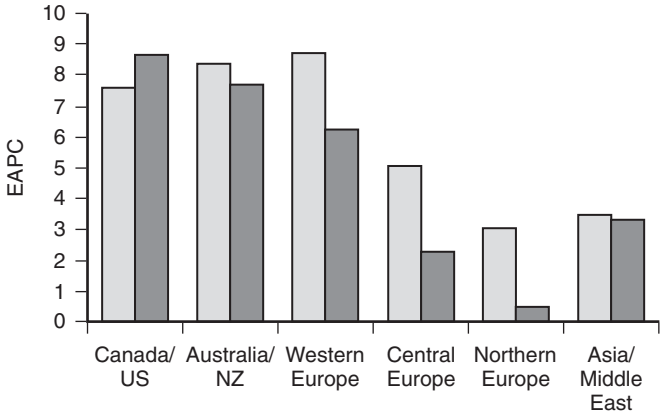


FIGURE 50A.1. Estimated annual percent change (EAPC) in age-adjusted mortality rate for intrahepatic cholangiocarcinoma by geographical region for males and females. *(Modified from Patel T, 2002: Worldwide trends in mortality from biliary tract malignancies. BMC Cancer 2:1-5.)*

strictures. Surgical treatment can be difficult in the presence of chronic liver disease, and such patients are often ineligible for orthotropic liver transplantation. Consequently. they have a poor prognosis (Kaya et al, 2001). Factors suggestive of cholangiocarcinoma in patients with PSC are the sudden development of jaundice, weight loss, marked biliary dilation proximal to a dominant stricture, a sudden rise in carbohydrate antigen 19-9 (CA19-9), the presence of a hypovascular mass with late contrast enhancement on radiologic imaging, and cytologic evidence of dysplasia or malignancy obtained on brushings of the bile ducts (Harewood, 2008).

Parasitic Infections (See Chapter 45)

Chronic infection with liver flukes (*Opisthorchis viverrini* and *Clinorchis sinensis*) is closely related to increased risk of developing cholangiocarcinoma, especially in Southeast Asia (Hasweel-Elkins et al, 2008; Jang et al, 2008; Sripa & Pairojkul, 2008; Watanapa, 1996; Watanapa & Watanapa, 2002). The mechanism of carcinogenesis is unclear; however, mechanical irritation, excreted metabolic products, and the actions of pro-inflammatory cytokines, particularly those that stimulate the release of nitric oxide from activated white cells, may all play a role (Sripa et al, 2007).

A further parasitic hepatic infection is caused by the trematodes *Fasciola hepatica* and *F. gigantica*. These parasites are widely spread throughout Asia, Africa, the Americas, and Oceania. They migrate into the liver from the duodenum and cause hepatic fibrosis, but no evidence is available to support the theory that fascioliasis increases the risk of cholangiocarcinoma. In addition, the fibrotic pathologic changes accompanying an infection can be difficult to distinguish from carcinoma (Kim et al, 2005; Marcos et al, 2008).

Hepatolithiasis (See Chapters 39 and 44)

Recurrent pyogenic cholangiohepatitis (RPC) is characterized by recurrent episodes of ascending cholangitis, hepatolithiasis, biliary stricturing, and dilation. The syndrome is present in one fifth of the population of Southeast Asia, and up to 10% of these patients develop IHCC (Chen et al, 1993; Kubo et al, 1995; Lesurtel et al, 2002; Su et al, 1997). Patients are seen with recurrent episodes of cholangitis and, on investigation, have significant hepatolithiasis and associated inflammatory biliary strictures (Chu et al, 1997). Infection with liver flukes may also be present, but RPC appears to be a separate condition and can develop in the absence of parasitic infection (Kim et al, 2003).

Congenital Biliary Cystic Disease (See Chapter 46)

Untreated choledochal cysts carry an increased risk of developing malignant change. The incidence of cholangiocarcinoma is estimated at between 10% and 20% if the cyst is not resected by the age of 20 years (Lipsett et al, 1994; Ohtsuka et al, 2001). Correspondingly, patients who have had their cysts resected have a very low incidence of cholangiocarcinoma (Hewitt et al, 1995), although the subsequent development of cholangiocarcinoma has been recorded after cyst excision (Goto et al, 2001). The mechanism of malignant transformation is not well understood, but many patients with choledochal disease have an abnormally high union of the pancreatic and bile ducts, suggesting that biliary stasis and chronic reflux of pancreatic secretions may contribute to the development of chronic inflammation of biliary epithelium (Chapman, 1999).

Hepatic Cirrhosis and Viral Infections (See Chapter 64)

The risk of developing cholangiocarcinoma is increased in patients with cirrhosis (10.7% vs. 0.7% in the general population) (Shaib & El-Serag, 2004; Sorensen et al, 1998). In addition, the incidence of cholangiocarcinoma is increased in patients with hepatitis C viral infection (0.8% vs. 0.2% in the general population) (Donato et al, 2001; Shaib et al, 2005) and in patients with chronic hepatitis B viral infection (11.5% vs. 5.5% in the general population) (Donato et al, 2001). It has been suggested the increasing incidence of cholangiocarcinoma in Western populations is related to the increasing prevalence of chronic liver disease and chronic viral infection (Shaib et al, 2005; Shaib & El-Serag, 2004).

Human immunodeficiency virus (HIV) does not cause cirrhosis, but cholangiocarcinomas have been found in up to 0.5% of patients infected with the virus compared with 0.1% in control subjects, suggesting that HIV is also associated with an increased risk of biliary carcinogenesis (Shaib et al, 2005).

Benign Biliary Tumors (See Chapter 79B)

The development of biliary cystadenocarcinomas from biliary cystadenomas is rare; in general, it occurs if a cystadenoma is untreated for many years. Patients are first seen with cystadenocarcinomas in the sixth or seventh decades of life, although cystadenomas present at an earlier age (Buetow et al, 1995). Intrahepatic cholangiocarcinoma has also been reported to develop in patients with biliary papilliomas (Cox et al, 2005; Galluoglu et al, 2007).

Chemical Agents

Thorotrast (thorium dioxide) was used as a radiologic contrast agent between 1928 and 1950. It is an α-emitter with a biologic half-life of 400 years. It accumulates in the reticuloendothelial cells in the liver and spleen and increases the risk of developing

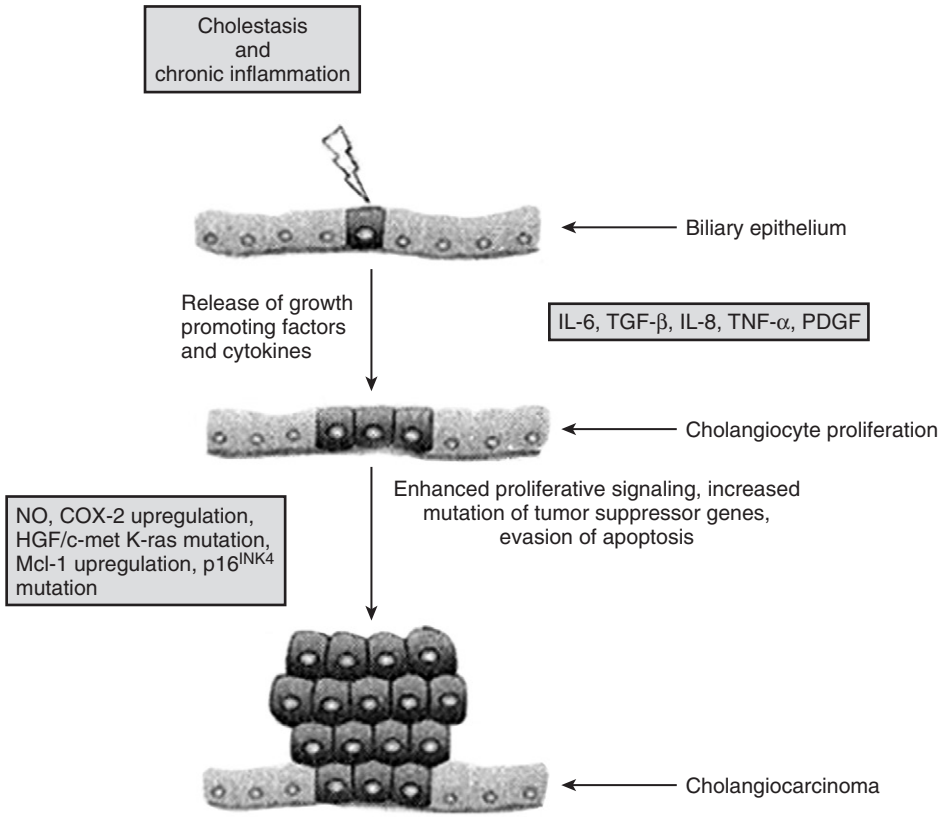


FIGURE 50A.2. Summary of possible mechanisms involved in biliary carcinogenesis. HGF, human growth factor; IL, interleukin; NO, nitric oxide; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α. *(Modified from Wise C, et al, 2008: Mechanisms of biliary carcinogenesis and growth. World J Gastroenterol 14:2986-2989.)*

cholangiocarcinoma by 300 times compared with the general population (Lipshutz et al, 2002; Rubel & Ishak, 1982). It is now no longer in use, although the latency period of 16 to 45 years means that patients who received this agent during childhood radiologic examinations will still occasionally come to medical attention (Massachusetts General Hospital, 1981).

A number of other agents have been implicated in the development of cholangiocarcinoma. Associations have been shown for asbestos (Szendroi et al, 1983), vinyl chloride (Wong et al, 1991), nitrosamines (Mitacek et al, 1999), the antituberculosis agent isoniazid (Lowenfels & Norman, 1978), and first-generation oral contraceptives (Yen et al, 1987).

General Risk Factors

Diabetes and obesity are associated with an increased risk of cholangiocarcinoma (Malhi & Gores, 2006; Oh et al, 2005). Similarly, surgical biliary-enteric bypass and surgical sphincteroplasty may also increase the risk (Hakamada et al, 1997). Smoking tobacco is a significant risk factor for the development of cholangiocarcinoma in patients with PSC (Bergquist et al, 1998), although the relationship is less marked in the general population (Shaib et al, 2005).

PATHOGENESIS

Cholangiocarcinoma develops from the malignant transformation of cholangiocytes. These cells line the intrahepatic bile ducts and canaliculi. Their physiologic functions center around the modification of bile at the canalicular surface and the detoxification of xenobiotics (Alpini et al, 2001). Normal growth and renewal of cholangiocytes is important in the maintenance of biliary mass, as well as hepatic secretory and detoxification functions, and is achieved by careful regulation of proliferation and apoptosis; however, when this process becomes uncontrolled, cholangiocarcinogenesis can occur (Wise et al, 2008).

Chronic inflammation is the most common and important feature of many of the risk factors associated with malignant transformation of cholangiocytes (see Chapter 6). Chronic inflammation can result in biliary obstruction, injury to the biliary epithelium, and increased cholangiocyte turnover (Jaiswal et al, 2000). Chronic inflammation also causes DNA damage, activates local tissue repair, stimulates cellular proliferation, and results in a local environment that promotes neoplastic transformation (Fig. 50A.2) (Schottenfeld & Beebe-Dimmer, 2004). Cholangiocytes exert significant paracrine and autocrine effects and stimulate secretion of cytokines, such as interleukin-6 (IL-6), IL-8, transforming growth factor-β (TGF-β), tumor necrosis factor-α (TNF-α), and platelet-derived growth factor (PDGF) (see Chapter 10; Berthiaume & Wands, 2004).

These cytokines activate nitric oxide synthase in cholangiocytes and result in the generation of nitric oxide, which reacts with other active oxygen species such as superoxide, all of which can damage DNA and downregulate DNA repair mechanisms (Jaiswal et al, 2000). This damage can lead to expression of oncogenes and reduced expression of tumor suppressor genes. Overexpression of the epidermal growth-factor receptor (EGFR), erb-2, K-ras, BRAF, and hepatocyte growth factor

c-Met have been reported in cholangiocarcinoma (Endo et al, 2002; Lai et al, 2005). The protooncogene *Erbb2* is activated in cholangiocarcinoma, and tumor suppressor genes *CDKN2A, P53, APC,* and *SMAD4* are underexpressed (Rashid, 2002; Taniai et al, 2002). Cytokines may also assist cholangiocytes in evading apoptosis. IL-6 is secreted by cholangiocytes and activates the prosurvival p38 mitogen-activated protein kinase (see Chapter 8B; Ishimura et al, 2004; Park et al, 1999).

PATHOLOGIC SUBTYPES AND MODE OF SPREAD

Macroscopically, IHCCs are firm, white, sclerotic tumors often with associated satellite lesions nearby. However, the variability in gross morphologic appearance has led to a number of pathologic subclassifications. Nakanuma and colleagues (1985) initially classified IHCCs into two types: mass forming and periductal. *Mass-forming tumors* were described as tumors with clear borders between malignant and nonmalignant tissues; *periductal tumors* were described as more infiltrative and extended along peri–bile duct tissues without forming a discrete nodular mass. This classification was widely adopted in Japan (Fujita, 1990) and was further modified by Ohashi and colleagues (1994), who added a specula-forming lesion present when a nodular tumor has poorly defined and irregular borders. Yamamoto and colleagues (1998) emphasized that all three morphologic types appear to have different proliferative activity and different biologic behavior. According to their research, the distinctive feature of the mass-forming type is its tendency to develop intrahepatic metastases as a result of localized vascular invasion, and the infiltrative type is distinguished by infiltrative spread via the Glisson capsule and hilar lymph node metastases. On the basis of these observations, these researchers recommended hepatectomy as the procedure of choice for the mass-forming subtype; hepatectomy with extrahepatic ductal resection and hilar lymphadenectomy is the procedure of choice for the infiltrating subtype. They also added a fourth subtype, the *intraductal variant,* characterized by papillary or granular growth within the lumen. They also were able to show that the frequency of lymph node metastases was higher in the mass-forming and periductal types compared with the intraductal subtype. A single report of a Western hepatobiliary unit used this classification and was unable to show any difference in overall survival or the frequency of lymph node metastases (Weber et al, 2001), although the intraductal subtype may carry a more favorable prognosis, as it does in the extrahepatic bile duct (Jarnagin et al, 2005). Although the subclassification of IHCC is intriguing and may have implications for surgical therapy, one significant weakness of this approach is that many tumors exhibit features of a number of the described subtypes (Shirabe et al, 2002).

Other less common histologic variants of IHCC have been reported, including mucin-hypersecreting lesions, which are similar to intraductal papillary mucinous neoplasms of the pancreas and are characterized by large mucin-filled cystic spaces (see Chapter 57; Chow et al, 1997; Kim et al, 2000; Suh et al, 2000) and intraductal oncocytic papillary carcinoma. These lesions have a distinctive appearance defined by the presence of oncocytes but appear to behave in a favorable manner, similar to the papillary type (Sudo et al, 2001; Wolf et al, 1992).

Intraabdominal lymph nodes are the most common site of metastatic spread for IHCCs and are present in up to 75% of cases at presentation (Shirabe et al, 2002). In addition, up to two thirds of patients may have evidence of remote organ metastases, most commonly lung and bone, at presentation (Endo et al, 2008; Shirabe et al, 2002). The common sites of lymphatic metastases are at the hepatic hilus, around the pancreas, in the retroperitoneum, around the aorta, and in the mediastinum (Nakajima et al, 1988). Nozaki and colleagues (1998) showed significant differences in lymphatic spread between left lobar and right lobar tumors. Patients with right lobar tumors always had lymph node metastases in the hepatoduodenal ligament, whereas in patients with left lobar tumors, 50% of nodal metastases were found distant from the hepatoduodenal ligament in the cardia and around the lesser curvature of the stomach. Furthermore, no lymph node metastases were present in the hepatoduodenal ligament in these patients.

CLINICAL PRESENTATION

In contrast to extrahepatic cholangiocarcinoma, which usually presents with jaundice and symptoms of biliary obstruction, IHCC often presents as asymptomatic hepatic masses detected during physical examination or on cross-sectional imaging. In patients with symptoms, abdominal pain is most common (Martin & Jarnagin, 2003). A significant proportion of patients may present with nonspecific constitutional symptoms, such as weight loss and decreased energy and appetite (Weber et al, 2001). Jaundice can be present in centrally placed lesions that compress or invade the biliary confluence, although extensive replacement of hepatic parenchyma by tumor, along with portal vein compromise, intrabiliary tumor invasion, or mucobilia, can also cause symptoms of biliary obstruction. An increase in liver enzymes, most commonly alkaline phosphatase or γ-glutamyl transferase, may be the only presenting feature to prompt further investigations, including physical examination and cross-sectional imaging. Roayaie and colleagues (1998) have shown that jaundice as a presenting symptom is predictive of unresectable disease because of significant involvement of inflow structures bilaterally or because of massive parenchymal replacement.

DIAGNOSIS AND EVALUATION

Resection is currently the only potentially curative therapy for IHCC. Evaluation of patients with IHCC should be focused on establishing the correct diagnosis and distinguishing it from metastatic adenocarcinoma or another primary tumor because this has significant implications on potentially available systemic therapies and in the assessment of the suitability of the patient and the tumor for operation. Thorough evaluation should include a detailed history, physical examination, assessment of comorbid conditions, assessment of hepatic function, measurement of tumor markers, and radiologic imaging to assess the extent of disease.

History and examination may reveal presenting symptoms, a liver mass, signs of jaundice, and sometimes metastatic disease. Liver function should be assessed with measurement of platelet count, serum levels of bilirubin, γ-glutamyl transferase, aspartate transaminase, alkaline phosphatase, albumin, total protein, and prothrombin time (PT) or international normalized ratio (INR). Any abnormality in hepatic function, particularly signs of underlying chronic liver disease, should be investigated in more detail.

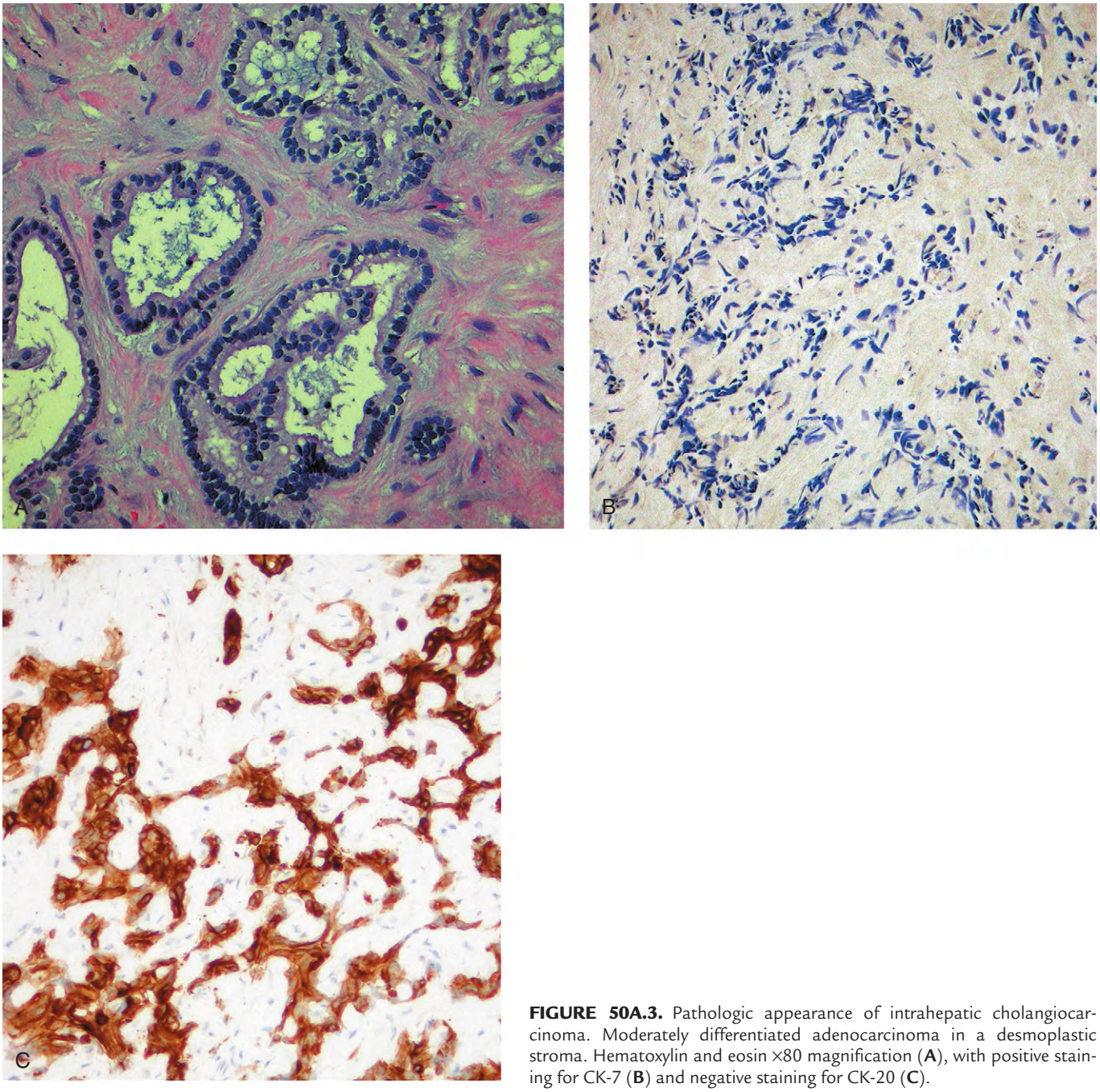


FIGURE 50A.3. Pathologic appearance of intrahepatic cholangiocarcinoma. Moderately differentiated adenocarcinoma in a desmoplastic stroma. Hematoxylin and eosin ×80 magnification (**A**), with positive staining for CK-7 (**B**) and negative staining for CK-20 (**C**).

In clinical practice, the diagnosis of IHCC is established with the typical finding of a hypovascular mass present on cross-sectional imaging (see Chapters 16 and 17). GI metastases are excluded by performing upper and lower GI endoscopies without the finding of a primary tumor and in the absence of other primary malignancies (pancreas, kidney, lung) on a staging computed tomography (CT) scan of the chest, abdomen, and pelvis. Women should have had a recent mammogram and gynecologic examination. Routine tumor biopsy is often unnecessary, particularly in patients who will undergo resection, and it is not recommended because of the small risk of tumor dissemination (Metcalfe et al, 2004; Ohlsson et al, 1994). In general, biopsy is indicated only to establish the presence of irresectable disease. Final pathologic confirmation of cholangiocarcinoma is defined by a specimen showing an adenocarcinoma that stains positively for CK-7 and CK8/18 but is negative for CK-20 (Fig. 50A.3). Staging laparoscopy is also useful in the evaluation of IHCC to exclude peritoneal disease, nodal disease, or abdominal wall invasion, which may preclude an attempt at resection (D'Angelica et al, 2003).

Table 50A.1

Serum and Bile Biomarkers Proposed for the Diagnosis of Cholangiocarcinoma

Biomarker	Sensitivity (%)	Specificity (%)	Reference
Serum			
CA19-9	53-92	50-98	Blechacz & Gores, 2008a, 2008b; Characharoenwitthaya et al, 2008; Patel & Singh, 2007; Schulick, 2008; Yachimski & Pratt, 2008
CEA	33-68	79-100	Blechacz & Gores, 2008a, 2008b; Characharoenwitthaya et al, 2008; Morris-Stiff et al, 2008; Ong et al, 2008; Patel & Singh, 2007; Schulick, 2008; Yachimski & Pratt, 2008
IL-6	73	70-100	Cheon et al, 2007
Trypsinogen 2	AUC = 0.804		Lempinen et al, 2007
MUC5AC	71	90	Bamrungphon et al, 2007
CYFRA 21-1	75	92	Uenishi et al, 2008
TRR + CA19-9	98	100	Liu et al, 2009
Bile			
CA19-9	46-61	60-70	Blechacz & Gores, 2008a, 2008b; Characharoenwitthaya et al, 2008; Morris-Stiff et al, 2008; Ong et al, 2008; Patel & Singh, 2007; Schulick, 2008; Yachimski & Pratt, 2008
CEA	67-84	33-80	Blechacz & Gores, 2008a, 2008b; Characharoenwitthaya et al, 2008; Morris-Stiff et al, 2008; Patel & Singh, 2007; Schulick, 2008; Yachimski & Pratt, 2008
IGF 1	100	100	Alvaro et al, 2007
Pancreatic elastase/amylase	82	89	Chen et al, 2008
Mcm5	62	92	Ayaru et al, 2008
Mac-2BP	69	67	Bonney et al, 2008

CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; AUC, area under the receiver operating characteristic curve; IL-6, interleukin-6; *MUC5AC,* mucin 5AC; CYFRA 21-1, soluble fragment of cytokeratin 19; TTR, transthyretin; *MCM5,* minichromosome maintenance replication protein; Mac-2BP, tumor antigen 90K–binding protein

From Alvaro D, 2009: Serum and bile biomarkers for cholangiosarcoma. Curr Opin Gastroenterol 25:279-284.

Serum Markers for Cholangiocarcinoma

Serum tumor markers are an attractive method for diagnosing and monitoring treatment response in cholangiocarcinoma because of the ease of obtaining samples and their relatively low cost. To be effective a marker must be accurate in detecting the presence of malignancy (sensitivity) and in defining the presence of benign disease (specificity). Most of the research on tumor markers in cholangiocarcinoma has been directed at diagnosis of extrahepatic tumors, particularly in the context of PSC; however, much of this is applicable to peripheral cholangiocarcinoma. The data on tumor markers that have been applied to cholangiocarcinoma are summarized in Table 50A.1.

Carcinoembryonic antigen (CEA) is widely used because of its availability but is elevated in only one third of patients with cholangiocarcinoma (Blechacz & Gores, 2008a, 2008b; Patel & Singh, 2007; Yachimski & Pratt, 2008). CA19-9 is also widely used in the diagnosis of cancers of the upper GI tract and is elevated in gastric cancer, pancreatic cancer, biliary, and gallbladder cancers as well as in smokers, during cholangitis, and in conditions causing cholestasis. In addition, it is not present in 7% of the population who are Lewis^a-antigen negative (Alvaro, 2009). In a retrospective investigation of patients with suspected biliary malignancies, of whom 10% were later found to have benign disease, CA19-9 was elevated in all patients and was decreased after biliary decompression. Elevated bilirubin was identified as the most important predictor of raised CA19-9 (Ong et al, 2008).

Other biomarkers investigated have included IL-6 either alone or in conjunction with CA19-9. Serum levels of IL-6 correlate with tumor burden in cholangiocarcinoma, but this marker is also elevated in hepatocellular carcinoma, metastatic disease, and benign biliary lesions (Cheon et al, 2007). Smith and colleagues (2008) recently proposed that an elevated preoperative platelet/lymphocyte ratio (PLR) may be a prognostic marker for resected ampullary cancer, but this ratio is also elevated in conditions associated with systemic inflammation. Serum trypsinogen-2 has also been evaluated in patients with cholangiocarcinoma and was found to be accurate in differentiating between patients with PSC and benign stricture and those who had cholangiocarcinoma develop (Lempinen et al, 2007). In addition, no correlation between serum trypsinogen-2 and bilirubin levels was found, indicating that this marker is unaffected by the presence of biliary obstruction or cholangitis (Lempinen et al, 2007). Abnormal expression of mucin 5AC (*MUC5AC*) is observed in mucin-producing adenocarcinomas, such as cholangiocarcinoma, and is detectable in 70% of patients with cholangiocarcinoma. Its presence is associated with poorer prognosis (Bamrungphon et al, 2007).

Bile Markers for Cholangiocarcinoma

Bile markers of cholangiocarcinoma have been investigated for their use in the diagnosis of biliary obstruction, and they may play a significant role in the evaluation of extrahepatic biliary obstruction because they can be easily obtained during ERCP. It is much less common for IHCC to be seen initially with biliary obstruction, however, and the use of bile markers in this tumor is limited. However, in the future they may play a role in the diagnosis of central lesions related to the hilus or intrahepatic lesions developing in patients with PSC. Bile markers

that have been suggested for use in the diagnosis and management of cholangiocarcinoma are summarized in Table 50A.1.

Imaging

IHCCs often present with vague and nonspecific symptoms. Accurate cross-sectional imaging is required to diagnose and stage the tumors as well as to plan resection or other possible treatments. Most patients will be imaged with a number of modalities.

Transabdominal Ultrasound (See Chapter 13)

Ultrasound is often used as a screening examination by primary health care practitioners investigating patients with right upper quadrant pain, a palpable mass, or unexplained jaundice. IHCC has a nonspecific appearance as a hypoechoic hepatic mass (Bloom et al, 1999; Slattery & Sahani, 2006). Satellite lesions and capsular retraction may be seen, and the tumors are hypovascular and usually have minimal Doppler evidence of internal blood flow. Ultrasound is useful for defining associated biliary dilatation, portal venous invasion, hepatic venous invasion and, rarely, portal lymphadenopathy (Bach et al, 1996; Hann et al, 1997).

Computed Tomography

Triple-phase CT scan (see Chapter 16) is widely available and is the single most effective investigation in diagnosing and staging IHCC, which is seen as hypodense lesions with irregular, infiltrative margins and a variable degree of delayed enhancement in the portal venous phase (Fig. 50A.4) (Bach et al, 1996). CT scan will also demonstrate the presence of biliary dilatation, portal or hepatic venous involvement (Asayama et al, 2006), lobar atrophy as a result of long-standing biliary obstruction, or portal venous involvement (Kim et al, 2002). CT scan is also useful in detecting metastatic disease affecting regional lymph nodes, peritoneum, or lung fields. Digital Imaging and Communications in Medicine data from newer, multiphase, fast-acquisition scanners can also be used to construct three-dimensional representations of hepatic and tumor anatomy for use in the planning of resections and in obtaining accurate measurement of hepatic volumetry, particularly in relation to remnant volume and risk of postoperative liver failure (see Chapter 93A). This is an emerging area of hepatic imaging but is particularly relevant in the management of large central tumors (Wigmore et al, 2001).

Magnetic Resonance Imaging

IHCC appears as hypointense on T1-weighted images and hyperintense on T2-weighted images with pooling of contrast within the lesions on delayed images (6 to 8 minutes after contrast injection) (Manfredi et al, 2004). Magnetic resonance imaging (MRI) is also useful in defining venous and arterial involvement by tumor, and cholangiopancreatography is a noninvasive method of obtaining cholangiograms.

Positron Emission Tomography

Positron emission tomography (PET) scanning is now a commonly used modality for staging GI malignancy, and the integration of PET and CT now provides the opportunity to obtain anatomic and functional information in a single scan (Iglehart, 2006; Slattery & Sahani, 2006). IHCCs are present as glucose-avid lesions within the liver. PET CT is also useful in detecting intraabdominal lymph node metastases (sensitivity, 42%; specificity, 80%) and distant metastases (sensitivity, 56%; specificity, 88%) (Iglehart, 2006). However, PET is limited by false-positive results in patients with biliary inflammation (Petrowsky et al, 2006), and patients with mucinous tumors can have false-negative scan findings (Fritscher-Ravens et al, 2001).

STAGING

IHCCs are classified as primary cancers of the liver by the American Joint Committee on Cancer (AJCC). Western hepatobiliary centers commonly use the AJCC systems to stage tumors. The sixth edition of the AJCC staging manual proposes a single staging system for primary cancers of the liver and applies this to both HCCs and IHCCs (Greene et al, 2002). The seventh edition of the staging manual (Edge et al, 2009), which entered clinical use in January 2010, includes a number of changes (Table 50A.2) and incorporates the staging system of Nathan and colleagues (2009), who used data from the SEER database to develop a new staging system for IHCC. They found that the sixth edition of the AJCC staging system failed to stratify T2 and T3 cohorts into distinct groups. Survival in the T3 group exceeded that of the T2 group (43% vs. 31%). In addition, these investigators found that the presence of multiple tumors at presentation and vascular invasion had an adverse effect on outcome, but tumor size at presentation was not predictive of outcome. Lymph node metastases and extrahepatic extension were also associated with poorer outcome.

Two other staging systems have been proposed from Japan, one by Okabayashi and colleagues (2001) and one by Yamasaki (2003), with that of Yamasaki being adopted by the Liver Cancer Study Group of Japan as its preferred staging system for IHCC (Table 50A.3).

TREATMENT

Because of its rarity, treatment protocols for IHCC are in their infancy compared with other intrahepatic tumors such as HCC. Nevertheless, there is a clear role for hepatic resection when feasible and in patients with disease confined to the liver. Orthotopic liver transplantation has been studied in some detail but is currently not used routinely for IHCC (see Chapter 97E). The roles of neoadjuvant and adjuvant chemotherapy, both systemic and regional; conformal radiation therapy; and ablative therapies have yet to be fully clarified.

Surgical

Hepatic Resection

Surgical therapy for intrahepatic cholangiocarcinoma is based on the principles applied to resections for HCC and metastatic tumors. Criteria for irresectability of IHCC are 1) locally advanced solitary tumors involving either inflow or outflow bilaterally, 2) multiple intrahepatic tumors, and 3) metastatic disease to distant sites. Regional lymph node metastases are an indicator of poor outcome but are not necessarily an absolute contraindication to surgery (Endo et al, 2008). An R0 resection must be performed for a potential survival benefit to be achieved. Hepatic resection is undertaken with the aim of obtaining a clear margin of 1 cm or greater, leaving a well-vascularized remnant with adequate venous and biliary drainage. Resection of up to 80% of hepatic volume can be

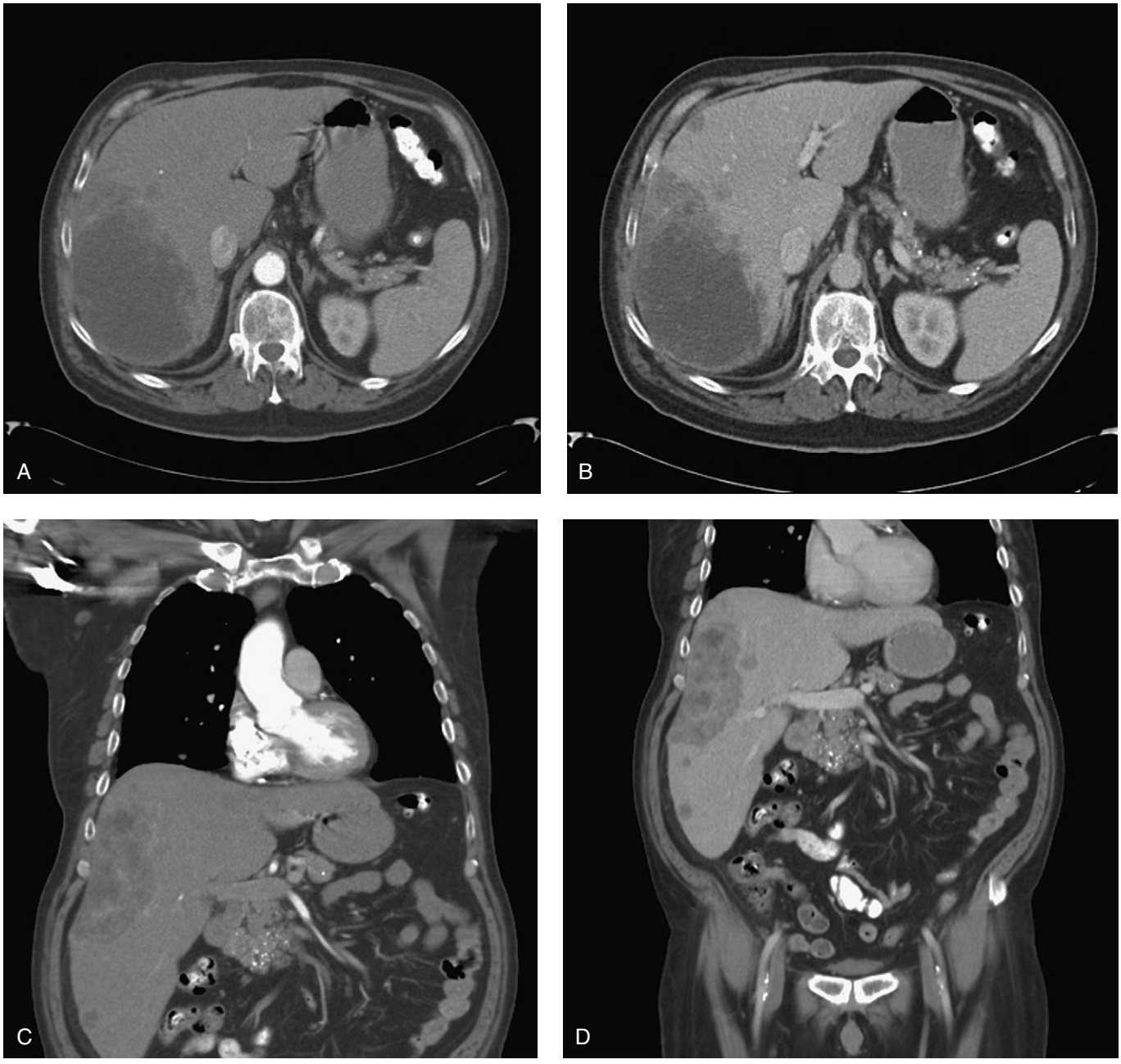


FIGURE 50A.4. Arterial (**A** and **C**) and portal venous (**B** and **D**) axial and coronal CT scans demonstrating the typical appearance of an intrahepatic cholangiocarcinoma with a large hypovascular mass involving segments VI and VII with associated satellite lesions. *(From Valle J, et al, 2010: N Engl J Med 362[14]:1273-1281.)*

Table 50A.2

AJCC Staging System (Seventh Edition) for Intrahepatic Cholangiocarcinoma

	DESCRIPTION				
Group	**Vascular Invasion**	**Multiple Tumors**	**Size**	**3-Year Survival (%)**	**5-Year Survival (%)**
sT1	No	No	Any	52	34
sT2	Overall			42	33
	Yes	No	Any	45	31
	No	Yes	Any	53	40
	Yes	Yes	Any	46	46
sT3	Extrahepatic extension			10	0

Stage 1: sT1N0M0; Stage II: sT2N0M0; Stage III: sT3N0M0 or N1M0 (any sT); Stage IV: M1 (any Ts, any N).
AJCC, American Joint Committee on Cancer

From Edge SB, et al, 2009: AJCC Cancer Staging Manual, 7th ed. New York, Springer-Verlag, pp 201-209.

Table 50A.3

Staging System for IHCC Proposed by the Liver Cancer Study Group of Japan

Stage	T	N	M
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IVa	T4	N0	M0
	or any T	N1	M0
Stage IVb	Any T	Any N	M1

T1: Meets all requirements (single nodule, tumor 2 cm or less and no portal vein, hepatic vein, and serous membrane invasion); T2: Meets two of the three requirements; T3: Meets one of the three requirements; T4: Meets none of the three requirements; N0: No lymph node metastases; N1: Metastases to any lymph nodes; M0: No distant metastases; M1: Distant metastases

IHCC, intrahepatic cholangiocarcinoma

From The Liver Cancer Study Group of Japan, 2003: General Rules for the Clinical and Pathological Study of Primary Liver Cancer, 2nd ed. Tokyo, Kanehara.

contemplated, but resections of this magnitude often need to be preceded by portal vein embolization.

Untreated patients with IHCC have a median survival of less than 12 months (Chu & Fan, 1999; Kim et al, 1999). Resection with positive margins or residual macroscopic disease is associated with median survivals of 1.8 months to 3 months (Chu & Fan, 1999; Kim et al, 1999), indicating that a cytoreductive approach is ineffective at prolonging survival.

In contrast, 5-year survival rates after complete resection range between 13% and 42%. The principal reason for the variability in survival appears to be the presence of lymph node metastases. Lieser and colleagues (1998) reported a 5-year survival of 42%, but only 13% of patients presented with lymph node metastases. In the series of Chu and Fan (1999), 50% of patients presented with nodal metastases, and none survived 5 years. Recently presented data from a number of centers in the United States, Asia, and Europe show reasonable survival after curative resection (Table 50A.4). Cherqui and colleagues (1995) report 100% survival 2 years after resection, Nakeeb and collegues (1996) report a 5-year survival of 44%, Lieser and colleagues (1998) report a 60% survival at 3 years, and Shirabe and colleagues (2002) report a 5-year survival of 32%. All these clinical series emphasize the importance of obtaining an R0 resection in achieving long-term survival.

This point was further emphasized by Lang and colleagues (2005), who reported a single-center experience with extended hepatectomy for IHCC. Twenty-seven patients underwent extended hepatectomies (19 extended right, 8 extended left), and 16 patients had en bloc resections of other structures. The median survival in this series was 46 months with a 3-year survival rate of 82%. Cherqui and others (1995) have achieved similar results with an aggressive surgical policy.

Although the importance of achieving an R0 resection is clear, the role of routine lymph node dissection is debated. The presence and extent of nodal metastatic disease is an important prognostic factor. Chu and Fan (1999) dissected portal lymph nodes in their series, and all patients with portal lymph node metastases died within 10 months of resection. A further study from Japan (Shirabe et al, 2002) confirmed that no survival benefit was evident for patients undergoing hepatectomy with portal lymphadenectomy versus hepatectomy alone. However, Nozaki and colleagues (1998) have recommended routine dissection of cardia and lesser curvature nodes for left-sided tumors and dissection of the hepatoduodenal ligament for right-sided tumors, although using this approach did not improve survival, and extended surgery was associated with a higher mortality rate (Yamamoto et al, 1999).

No clear therapeutic benefit is currently attributable to routine nodal dissection accompanying hepatectomy for IHCC. Thorough assessment of all intraabdominal nodal basins should be undertaken before hepatic resection, and sampling of suspicious nodes is indicated to stage disease accurately and assist in planning postoperative treatment. In the West, the finding of involved intraabdominal lymph nodes is a contraindication to hepatic resection.

Most surgical series confirm that the presence of lymph node metastases is the most important prognostic factor. Endo and colleagues (2008) documented a recurrence rate of 93% in node-positive patients undergoing R0 resection versus 47% in node-negative patients. These investigators also showed that a tumor greater than 5 cm in diameter and the presence of

Table 50A.4

Summary of Contemporary Results for Surgical Resection of Intrahepatic Cholangiocarcinoma

First Author	Year	Country	No. Patients	Median Survival (mo)	SURVIVAL (%)		
					1-Year	3-Year	5-Year
Cherqui	1995	France	14	27	100	–	–
Pichlmayr	1995	Germany	32	12.8	–	–	–
Casavilla	1997	United States	34	–	60	37	31
Madariaga	1998	United States	34	19	67	40	35
Chu	1999	Hong Kong	39	12.2	57.3	23.9	15.9
Kawarada	2002	Japan	37	31.5	54.1	34	23.9
Ohtsuka	2002	Japan	48	–	62	38	23
Lang	2005	Germany	16	46	94	82	
De Oliveira	2007	United States	34	28	–	–	63
Endo	2008	United States	82	36	–	–	–
Ercolani	2010	Italy	72	–	91 overall, 65 disease-free survival	62 overall, 30 disease-free survival	48 overall, 25 disease-free survival

multiple intrahepatic tumors were significant adverse prognostic factors. Other investigators have also defined lymphatic permeation, vascular invasion, and intrahepatic satellite lesions as predictors of poor survival, and two Japanese groups (Isaji et al, 1999; Shirabe et al, 2002) have also shown that the survival is higher in patients with the mass-forming tumor type than in those with the periductal infiltrating type.

After resection, the most common site of recurrence is in the liver, followed by intraabdominal sites (lymph nodes, peritoneum), lungs, and bone (Jan et al, 2005). Salvage surgery for intrahepatic recurrence or metastasectomy is usually not indicated.

Transplantation

The first significant report regarding liver transplantation for IHCC is that of Pichlmayr and colleagues (1995), who reported a median survival of 5 months in 18 patients treated with liver transplantation, with a 1-year survival rate of 13.9%. Several studies confirmed these findings (Ismail et al, 1990; O'Grady et al, 1988), although Cherqui and colleagues (1995) reported two long-term survivors and concluded that an intrahepatic tumor with no extrahepatic spread that cannot be resected for anatomic reasons may be a candidate for liver transplantation.

More recent experience has resulted in improved survival with disease-free survivals at 5 and 10 years of 27% and 23%, respectively, reported in 23 patients with IHCC treated with orthotopic liver transplantation (Robles et al, 2004). Most of these patients were deemed irresectable but showed no evidence of extrahepatic spread, and the authors concluded that transplantation could be considered in this group because the results achieved are better than palliative treatment. However, the role of transplantation in peripheral cholangiocarcinoma will continue to be limited by the lack of an effective adjuvant systemic treatment regimen. This is in contrast to the emerging protocol of neoadjuvant chemoradiation before transplantation for hilar cholangiocarcinoma (Schwartz et al, 2009).

Tumor Ablation

The role of ablative therapies in peripheral cholangiocarcinoma is currently limited but subject to significant investigation. Cryotherapy and radiofrequency ablation (RFA) are widely used in the treatment of metastatic colorectal cancer, either in addition to hepatectomy or as a primary therapy. Unfortunately, in IHCC neither of these approaches can be used; the primary tumors are hard, and percutaneous or operative ablation can be difficult to achieve. Because many of the lesions are large at presentation, their size often precludes effective ablation, and smaller lesions can be resected. Likewise, the use of ablation to treat intrahepatic metastases is ill advised because these are indicative of vascular invasion. However, Rai and colleagues (2005) reported a case of recurrent tumor after transplantation that was treated with RFA and controlled for 12 months, and others have used this technique to manage small cholangiocarcinomas that are unsuitable for resection (Zgodzinzki & Espat, 2005).

Both cryotherapy (Cuschieri et al, 1995; Sheen et al, 2002) and selective internal radiation therapy (Dubel & Soares, 2008) have been used in heterogeneous series of hepatic tumors treated with ablative therapies. Both treatments are reported to be safe, although no long-term follow-up data are available.

A number of publications have reported on the use of transarterial chemoembolization (TACE) of unresectable IHCC (Gusani et al, 2008; Herber et al, 2007; Kim et al, 2008) with gemcitabine in combination with cisplatin, oxaliplatin, or mitomycin C. Repeated treatments are usually undertaken at 8-week intervals, with median survivals reported between 12 (Kim et al, 2008) and 21 months (Herber et al, 2007). Overall combination therapy appears to be more effective than single-agent therapy (Gusani et al, 2008), with large tumor size, tumor hypovascularity, and Child-Pugh class B being adverse prognostic factors (Kim et al, 2008).

Chemotherapy

Systemic

Unfortunately, no effective adjuvant chemotherapy protocols are currently available for IHCC. This reflects the aggressive nature of the tumor as well as its rarity. Much of the information on the effectiveness of chemotherapy in this tumor has been derived from Phase II trials rather than Phase III trials. In addition, most of these trials have been carried out in groups of patients with tumors of biliary epithelia and include patients with intrahepatic and extrahepatic cholangiocarcinoma, gallbladder cancer, and pancreatic cancer. Many postoperative therapy regimens have been based on 5-fluorouracil (5-FU) and have included irinotecan, mitomycin C, and gemcitabine. None has been effective, and routine use of adjuvant chemotherapy after an R0 resection is not current practice. A recent randomized trial established the superiority of combined gemcitabine and cisplatin compared with gemcitabine alone in patients with locally advanced or metastatic biliary cancer (Valle et al, 2010); however, this study included the full range of biliary tract adenocarcinoma, including ampullary cancers, and it remains to be seen whether this therapy has any impact in the adjuvant setting. Ercolani and colleagues (2010) retrospectively analyzed long-term results of resection in 72 patients with IHCC and demonstrated improved survival in those who received adjuvant gemcitabine-based chemotherapy (5-year survival 65% after chemotherapy vs. 40% with resection alone), although this observation has not been confirmed prospectively (Ercolani et al, 2010).

Systemic chemotherapy for unresectable disease is associated with partial responses in between 10% and 20% of patients and uses either 5-FU or contemporary combination therapy with gemcitabine and cisplatin or oxaliplatin. The responses are modest, but the use of newer, targeted therapies continues to stimulate investigative trials in this area (Hezel & Zhu, 2008). More recent Phase I and II investigations have used the biologic agents sunitinib (Sweeney et al, 2010), cetuximab (Chang et al, 2010), or bevacizumab and erlotinib (Lubner et al, 2010) in the treatment of patients with advanced-stage disease. Endo and colleagues (2008) described five patients with initially unresectable tumors treated with either regional fluorodeoxyuridine in combination with systemic camptothecin-11 or systemic gemcitabine-based therapy whose tumors were downstaged sufficiently to undergo resection, indicating that effective neoadjuvant therapy is a realistic future goal for this tumor.

Regional

Regionally administered chemotherapy has not been extensively investigated in peripheral cholangiocarcinoma, although sporadic reports of its effectiveness have surfaced. Shirabe and colleagues (2002) report a single case treated with intraarterial cisplatin and 5-FU achieving a complete response for

12 months. Regional chemotherapy is an attractive means to attempt to downstage large hepatic tumors for subsequent resection, although adequate pretherapy staging would need to be undertaken to exclude extrahepatic disease, and patients with underlying cirrhosis could not be treated because of the risk of treatment-related complications (Jarnagin et al, 2009).

Radiation Therapy

Cholangiocarcinoma is a radiosensitive tumor, although the doses required (60 Gy) are toxic to normal liver and adjacent structures, including the stomach, duodenum, and kidney. However, when accurately administered, radiation therapy does have an emerging role in the management of IHCC. Postoperative radiation therapy is ineffective in improving survival after R0 resections, but several studies have shown a potential benefit in postoperative radiation therapy in patients with microscopically positive margins after resection (Stein et al, 2005), suggesting that radiation in this setting may be an effective salvage therapy. Lawrence and colleagues (Ben-Josef et al, 2005; Robertson et al, 1993, 1997) have reported on the use of conformal radiation combined with intraarterial infusional chemotherapy in patients with unresectable IHCC. This treatment resulted in a median survival of 13.3 months, which was significantly better than historical controls (Ben-Josef et al, 2005), although 30% of patients developed grade 3 or 4 toxicity, and there was one treatment-related death.

Palliation

Up to 90% of patients presenting with IHCC may not be candidates for surgical resection because of patient comorbidity or extent of disease, and these will be managed palliatively (Endo et al, 2008). Unlike extrahepatic cholangiocarcinoma, jaundice is unusual except in patients with centrally placed tumors compressing the hilus; these can be treated by placement of biliary endostents radiologically or endoscopically. Other priorities for these patients are management of capsular pain and ascites and maintenance of adequate nutritional intake.

SUMMARY

IHCCs are rare primary tumors of the liver arising in intrahepatic biliary epithelium. They constitute 10% of primary hepatic tumors, and although many are sporadic, conditions leading to chronic inflammation of biliary epithelium constitute significant risk factors for their development. Cross-sectional imaging with CT scan or MRI usually demonstrates a hypovascular mass. A specific staging system has been developed, and for patients with liver disease only, R0 resection offers the chance of cure in 20% to 40%. No active adjuvant systemic therapy is currently available, and chemotherapy (both systemic and regional), radiation therapy, and ablative therapies are reserved for patients with unresectable tumors.

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SECTION I
Inflammatory, Infective, and Congenital

A. Congenital Disorders

CHAPTER 51

Congenital disorders of the pancreas: surgical considerations

Ewen M. Harrison and Rowan W. Parks

OVERVIEW

The pancreas is a glandular organ that lies on the posterior abdominal wall in the retroperitoneum. It is an exocrine gland that secretes enzymes of digestion into the duodenum; it also performs endocrine functions, producing insulin, glucagon, somatostatin, pancreatic polypeptide, and ghrelin. Congenital abnormalities of the pancreas may be so severe that they are diagnosed in utero or in the neonatal period, such as pancreatic agenesis. However, many congenital conditions go undetected until adulthood, when the patient comes to medical attention with nonspecific symptoms or an abnormality is discovered incidentally. This chapter describes the diagnosis, investigation, and treatment of the various congenital pancreatic abnormalities.

EMBRYOLOGIC DEVELOPMENT OF THE PANCREAS

The basis for the understanding of congenital abnormalities of the pancreas is the embryologic development of the organ (see Chapter 1A). The pancreas develops from two buds originating from the endodermal lining of the duodenum. The dorsal bud forms posteriorly within the mesentery, whereas the ventral bud is associated with the hepaticopancreatic duct (Fig. 51.1). During the second month of development, the stomach rotates and the duodenum becomes C-shaped. As part of this process, the ventral pancreatic bud migrates dorsally, coming to lie posteroinferiorly to the dorsal bud, forming what will become the inferior head/uncinate process of the pancreas. In the majority of individuals, the main pancreatic duct (of Wirsung) is formed by the entire ventral duct, and the distal dorsal duct and enters the duodenum at the major papilla. The persistence of the proximal part of the dorsal duct occurs in approximately 25% and results in an accessory duct (of Santorini), which enters the duodenum by the minor papilla (see Fig. 51.1) (Rösch et al, 1976). There is no known pathologic consequence of this normal variation. A failure of fusion of the ductal system occurs in roughly 10% of the normal population (Dawson & Langman, 1961; Millbourn, 1959), resulting in the entire dorsal pancreas—superior head, body, and tail—draining through the minor papilla and ventral pancreas, the inferior head and uncinate process, and finally through the major papilla (Fig. 51.2). This abnormality is termed *pancreas divisum* and is described in more detail below.

Annular pancreas is a rare congenital abnormality, the embryologic basis of which is poorly understood. A complete or incomplete ring of pancreatic tissue is found around the second part of the duodenum, and it may cause symptoms (also discussed below).

A number of studies published recently have identified mechanisms by which the pancreas is specified from the early endoderm (Kumar & Melton, 2003). Retinoic acid and bone morphogenic peptide both appear to have important roles in defining early endodermal compartments in the embryo (Stafford & Prince, 2002; Tiso et al, 2002). The origins of the signaling mechanisms involved in the specification of the dorsal and ventral pancreas are different. In the dorsal pancreas, signals arising from the notochord (Kim et al, 1997) and dorsal aorta (Lammert et al, 2001) are required; in the ventral pancreas, the lateral plate mesoderm is important (Kumar et al, 2003). The specific identity of these signals has not yet been established, although the Hedgehog family of signaling molecules appears to be significant (Kim & MacDonald, 2002).

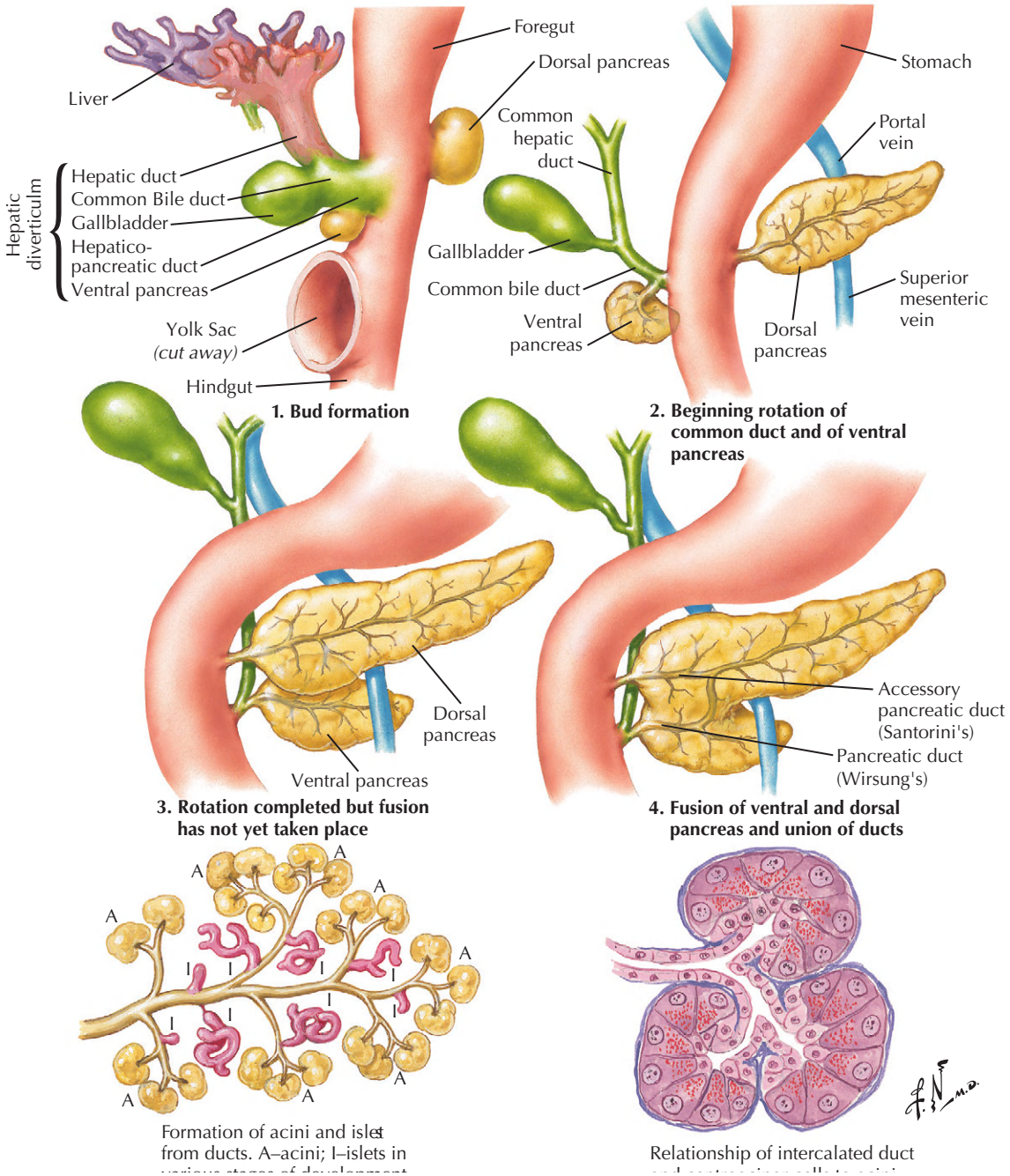


FIGURE 51.1. Embryologic development of the pancreas. *(Netter illustration from http://www.netterimages.com. Copyright Elsevier, Inc. All rights reserved.)*

PANCREAS DIVISUM

Pancreas divisum (PD) results from incomplete fusion of the dorsal and ventral pancreatic ducts toward the end of the second month of embryogenesis. The distal dorsal pancreatic duct typically fuses with the ventral pancreatic duct to drain the entire pancreas into the duodenum via the major papilla (see Chapter 1B). The proximal dorsal duct can persist as an accessory pancreatic duct and may drain via the minor papilla. Complete PD exists when there is no communication between the dorsal and ventral systems and the majority of the pancreas drains via the dorsal duct through the minor papilla (see Fig. 51.2). Variations exist where a small branch may connect the two ducts, termed *incomplete pancreas divisum*.

Recent investigations have suggested that PD may be explained by distinct patterns of incomplete fusion of branches of the dorsal and ventral pancreatic ducts (Kamisawa et al, 2007a), confirming theories first proposed in early anatomic studies (Dawson & Langman, 1961). The first description of PD is from 1865, attributed to Josef Hyrtl (1810-1894), professor of anatomy at the Universities of Prague and Vienna. However, as discussed by Stern (1986), a number of anatomists were aware of it much earlier than this, including Regnier de Graaf, who described the finding in 1664.

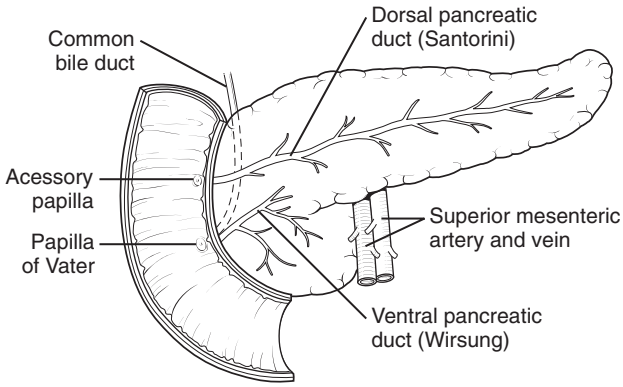


FIGURE 51.2. Pancreas divisum describes the incomplete fusion of the dorsal and ventral pancreatic ducts.

In postmortem studies performed throughout the twentieth century, the prevalence of PD is reported to be approximately 8% (range, 4% to 14.5%) (Baldwin, 1911; Berman et al, 1960; Birnstingl, 1959; Cameron, 1924; Charpy, 1898; Dawson & Langman, 1961; Fogel et al, 2007; Clairmont & Hadjipetros, 1920; Hand, 1963; Helly, 1898; Hjorth, 1947; Keyl, 1925: Kleitsch, 1955; Mehnen, 1938; Millbourn, 1959; Naatanen, 1941; Opie, 1903; Rienhoff, 1945; Schirmer, 1893; Schmieden & Sebening, 1927; Schwarz, 1926; Sigfusson et al, 1983; Smanio, 1969; Stimec et al, 1996). With the development of endoscopic retrograde pancreatography (ERCP) in the late 1960s, however, the considerable congenital variation in the ductal system of the pancreas became more widely appreciated (Cotton, 1972; McCune et al, 1968). The prevalence of PD is lower in published ERCP series than in anatomic series for reasons that are not clear, although it may be due to referral bias, difficulty in the interpretation of pancreatograms, or inability to cannulate the minor papilla. The reported prevalence is particularly low in Japanese series (0.3% to 0.6%) compared with Western populations (approximately 5%; Cotton, 1980).

PD is clinically relevant from three main points of view (Fogel et al, 2007). First, the small ventral duct seen in PD must be differentiated from a similar appearance seen in some cases of pancreatic cancer. Second, on cannulating the major papilla at ERCP, only the ventral portion of the pancreas may be visualized in PD, which risks missing important pathology if a pancreatogram is not performed via the minor papilla (see Chapter 18). Third, PD may be associated with disease, such as pancreatitis (see Chapter 53). With regard to the first point, it is important for those performing ERCP to be aware of the anomaly to become proficient in interpreting pancreatograms (Fig. 51.3). Other forms of imaging, such as computed tomography (CT), must be used if there is uncertainty whether a mass lesion is present and causing a ductal abnormality. In relation to the second point, it is important to become proficient at cannulation of the minor papilla, which is considerably more challenging than cannulating the major papilla (see Chapter 18). It commonly sits in a superior, more ventral position. Cannulation may be facilitated by having the duodenoscope in the "long position" and by administration of intravenous secretin (O'Connor & Lehman, 1985). The third point is discussed in detail below.

Possible Association Between Pancreas Divisum and Pancreatitis

The question of whether PD causes recurrent acute pancreatitis, chronic pancreatitis, or pancreas-related pain has been debated for many years (Table 51.1). Those proposing the theory suggest that obstruction occurs at the level of the minor papilla, the caliber of which is too narrow to drain the majority of the pancreas. This is supported by an early study reporting an elevated pressure in the dorsal duct (23.7 ± 1.3 mm Hg) compared with the ventral duct (10.8 ± 1.9 mm Hg) in six patients with PD, whereas pressures were similar when two ducts existed in patients without PD (Staritz & Meyer zum Buschenfelde, 1988). This was contradicted in a subsequent study in which no difference in duct pressures was observed between the major and minor papillae in four patients with recurrent acute pancreatitis and PD (Satterfield et al, 1988). Another early report demonstrated chronic pancreatitis confined to the dorsal pancreas in two pancreatoduodenectomy specimens from patients with PD who had resections for symptom control (Blair et al, 1984).

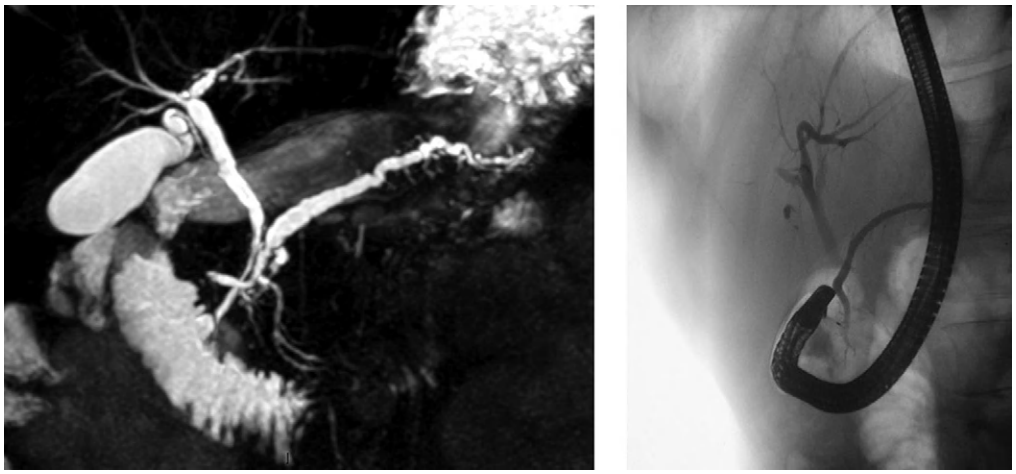


FIGURE 51.3. Imaging in pancreas divisum (PD). A magnetic resonance cholangiopancreatography image shows PD with the dorsal pancreatic duct draining through the minor papilla (*left*). Endoscopic retrograde cholangiopancreatography in PD performed through the minor papilla (*right*). Contrast can still be seen in the common bile duct after cannulation of the major papilla. *(Courtesy Dr. K. Palmer, Edinburgh.)*

Table 51.1

Early Series Reporting Pancreas Divisum

Study	Pancreatitis Relationship Supported	Study Type	N (%)	Intervention
Phillip J et al, 1974	—	ERCP series	18/911 (2.0)	—
Rösch et al, 1976	—	ERCP series	63/1850 (3.4)	—
Gregg, 1977	—	ERCP series	33/1100 (3.0)	—
Heiss & Shea, 1978	Yes	ERCP series	4	—
Mitchell et al, 1979	No	ERCP series	21/449 (4.7)	—
Cotton, 1980	Yes	ERCP series	47/810 (5.8)	—
Tulassay & Papp, 1980	Yes	ERCP series	33/2410 (1.4)	Unspecified surgery in 11; no outcomes described
Richter et al, 1981	Yes	ERCP series	519	Open sphincteroplasty to minor ampulla in 9; decreased pain: 5/6 with acute pancreatitis, 0/3 with chronic
Thompson et al, 1981	Yes	ERCP series	11/850 (1.3)	—
Cooperman et al, 1982		Case series	21/314 (6.7)	Open sphincteroplasty to minor ampulla in 5; 4 of 6 "have done well" at 28 months
Sahel et al, 1982	Yes	ERCP series	41/812 (5.0)	—
Blair et al, 1984	Yes	Case series	14	15 operative resections in 14 patients with RAP; 7/14 had no pain after surgery
Delhaye et al, 1985	No	ERCP series	304 total; 6.9% AP/CP, 5.7% no pancreatitis	—
Sugawa et al, 1987	No	ERCP series	55/1529 (3.6)	Open sphincteroplasty to minor ampulla in 3; no improvement in symptoms
Bernard et al, 1990	Yes	ERCP series	137/1825 (7.5)	—

ERCP, endoscopic retrograde cholangiopancreatography; RAP, recurrent acute pancreatitis; AP, acute pancreatitis; CP, chronic pancreatitis

Difficulty exists in demonstrating an epidemiologic relationship between PD and pancreatitis because early anatomic studies were small and confounded by different definitions, and ERCP series are skewed by selection bias (Blair et al, 1984). In the largest early series of 1850 successful major ampulla cannulations, Rösch and colleagues (1976) identified PD in 63 cases (3.4%). The indications for pancreatography were not given, but pathologic findings were seen in 13 of 63 patients with PD; changes were consistent with pancreatitis in 12 and tumor in one. In the next large series by Gregg (1977), 33 patients with PD were identified among 1100 patients referred primarily for investigation of pancreatic-type pain or pancreatitis. Documented pancreatitis was present in 15 patients, and another 11 had recurrent episodes of pain typical of pancreatitis.

These and similar studies have been used as evidence of a link between PD and pancreatitis, but the absence of a suitable control group makes the assertion weak. Mitchell and colleagues (1979) identified this problem and performed a retrospective analysis of patients who had undergone ERCP and observed that 21 (4.7%) of 449 patients had PD, whereas 4 (3.3%) of 120 patients with pancreatitis defined by clinical and/or ERCP criteria had PD. Thus in this series the prevalence of PD in patients with pancreatitis was the same as the prevalence of PD in the series as a whole. This has been supported by the largest published ERCP series of 304 patients, in which the dorsal duct was visualized in 97 patients (Delhaye et al, 1985). The frequency of PD was similar in patients with acute or chronic pancreatitis (6.9%) as in all patients in the series undergoing ERCP (5.7%).

Contrary to these findings, Cotton reported that in patients with primary biliary disease who had an incidental pancreatogram at the time of endoscopic cholangiogram, the prevalence of PD was 3.6% (Cotton, 1980). This was compared with a prevalence of 16.4% in those with chronic or recurrent acute pancreatitis. In 83 patients with idiopathic pancreatitis, recurrent pancreatitis with no clear etiology such as gallstones, alcohol, or trauma—the prevalence of PD was 25.6%.

This controversy is a good example of the difficulty in determining a causal relationship between two factors that appear to be associated. The traditional criteria used in evaluating such a relationship can be applied: 1) strength of association, 2) consistency across studies, 3) dose-response relationship, and 4) biologic plausibility. The relationship is not a strong one, and many of those in the general population who have PD (approximately 10%) never have any related symptoms, and many with pancreatitis do not have PD; fewer than 5% of individuals with PD are estimated to ever develop pancreatic symptoms. Furthermore, those with a more pronounced form of the anomaly (i.e., complete PD) do not seem to be more likely to develop pancreatitis than those with incomplete PD. The question of biologic plausibility is more interesting and is discussed further below.

Imaging in Pancreas Divisum

One of the difficulties in relating PD to pancreatitis is the inconsistency in making the diagnosis. ERCP studies of patients without pancreatitis consistently report a lower prevalence of PD when compared with MRCP or postmortem studies (Table 51.2). The use of secretin during MRCP (S-MRCP) improves the detection rate of PD (Manfredi et al, 2000), yet it is still reported to be missed on S-MRCP, possibly because of

Table 51.2

Prevalence of PD in Patients Without Pancreatitis by Method of Investigation or Imaging Modality

Investigation Type	N	% Prevalence of PD (95% CI)
Postmortem	2895	7.8 (6.8-8.8)
MRCP	505	9.3 (6.8-11.8)
S-MRCP	156	17.9 (11.9-24.0)
ERCP	16,078	4.1 (3.8-4.4)

PD, Pancreatis divisum; MRCP, magnetic resonance cholangiopancreatography; S-MRCP, secretin-enhanced MRCP; ERCP, Endoscopic retrograde cholangiopancreatography; CI, confidence interval

From Fogel EL, et al, 2007: Does endoscopic therapy favorably affect the outcome of patients who have recurrent acute pancreatitis and pancreas divisum? Pancreas 34:21-45.

suboptimal magnetic resonance techniques or inexperience in those reporting the MRCP (see Chapter 17; Carnes et al, 2008). Endoscopic ultrasound (EUS) as an alternative imaging modality has gained in popularity and is reported to be useful in the investigation of patients with acute recurrent pancreatitis of unknown etiology (see Chapter 14; Petrone et al, 2008). A recent study reported the use of portal venous phase 64 multirow detector CT. Five of 93 patients had PD diagnosed on MRCP or ERCP. Of these, one observer detected three cases and a second observer found four cases by reviewing the MDCT images (Anderson & Soto, 2009). ERCP features of the minor papilla that suggest the presence of PD include an enlarged papilla or open orifice and are believed to moderately predict the presence of PD; however, a significant number of patients with PD do not have these features (Alazmi et al, 2007; Lawrence et al, 2009).

Therapy to the Minor Papilla in Those with Pancreas Divisum and Pancreatitis

If PD is associated with obstruction at the minor papilla, which in turn contributes to the occurrence of pancreatitis and pancreatic pain, then it follows that surgical intervention to relieve this obstruction would be beneficial. As has been discussed, significant controversy exists as to whether this assumption is correct or not. A number of studies have been performed examining whether therapy to the minor papilla is beneficial in patients with acute recurrent pancreatitis, chronic pancreatitis, or pancreas-related pain; however, little in the way of randomized controlled data has been generated (Table 51.3; see Chapters 53 and 55). Interventions examined include endoscopic dilation, papillotomy, and sphincterotomy of the minor papilla, with or without stent placement, and surgical sphincteroplasty.

The first minor papilla endoscopic sphincterotomy was described by Cotton in 1978, and the majority of publications since have been small case series with short follow-up times. Lehman and colleagues (1993) described the effects of minor papilla sphincterotomy in 52 PD patients with chronic pancreatic pain (n = 24), recurrent acute pancreatitis (n = 17), or chronic pancreatitis (n = 11) with longstanding symptoms refractory to conservative management. Minor papilla sphincterotomy was performed with a needle knife over a previously placed dorsal pancreatic duct stent, with a mean follow-up of 1.7 years. When compared with the chronic pain and chronic pancreatitis groups, patients with recurrent acute pancreatitis had a significant reduction in mean symptom score (recurrent acute pancreatitis, 76.5%; chronic pancreatitis, 27.3%; chronic pain, 26.1%) and inpatient hospital stay. This reflects other published results that consistently show less benefit after minor papilla therapy in those with chronic pancreatitis or chronic

Table 51.3

Endoscopic Therapy to the Minor Papilla in Pancreas Divisum

Study	Therapy	Mean Follow-up (mo)	RAP		PAIN ONLY		CP	
			N	% Improved	N	% Improved	N	% Improved
Soehendra et al, 1986	MiES	3	2	100	0	—	4	75
Liguory et al, 1986	MiES	24	8	63	0	—	0	—
McCarthy et al, 1988	Stent	21	19	89	0	—	0	—
Lans et al, 1992	Stent	30	10	90	0	—	0	—
Lehman et al, 1993	MiES	22	17	76	23	26	11	27
Coleman et al, 1994	MiES/stent	23	9	78	5	0	20	60
Sherman et al, 1994 (RCT)	MiES	28	0	—	16	44	0	—
Kozarek et al, 1995	MiES/stent	20	15	73	5	20	19	32
Ertan, 2000	Stent	24	25	76	0	—	0	—
Heyries et al, 2002	MiES/stent	39	24	92	0	—	0	—
Linder et al, 2003a	Stent	NG (range, 3-36)	83	66	48	23	38	38
Bierig et al, 2006	MiES	19	16	94	7	43	16	38
Linder et al, 2003b	MiES	NG (range, 1-120)	38	58	12	0	4	25
Vitale et al, 2007	Stent	59.6	—	—	—	—	24*	58
Borak et al, 2009	MiES/stent	43	62	71	29	62	22	46
Total		**25**	**328**	**77**	**145**	**33**	**135**	**41**

*11 patients required open surgery.

MiES, minor papilla sphincterotomy; RCT, randomized, controlled trial; NG, not given; RAP, recurrent acute pancreatitis; CP, chronic pancreatitis

From Fogel EL, et al, 2007: Does endoscopic therapy favorably affect the outcome of patients who have recurrent acute pancreatitis and pancreas divisum? Pancreas 34:21-45.

pain compared with those with recurrent acute pancreatitis. Complications were seen in 15%, and one patient died of a pancreatic abscess after a failed cannulation. Of concern, 50% of patients evaluated at the time of stent removal had stent-induced dorsal duct changes.

In a prospective, randomized, controlled trial published by Lans and colleagues (1992), 19 patients with PD and recurrent acute pancreatitis—two or more episodes of abdominal pain associated with a rise in amylase greater than twice the upper limit of normal—and no other identified etiology were recruited. Ten patients were randomized to stent placement, and nine were randomized to no treatment, with follow-up for 1 year. In the stent group, no patients subsequently came to the hospital with pain, but five patients in the control group were admitted, and two more came in with pain. Furthermore, nine patients in the stent group rated their pain improved by 50% or more, but only one patient in the control group reported a similar improvement.

It has been pointed out that a significant period of time can exist between attacks of pancreatitis in this patient group, and this study has since been criticized on the basis of the short duration of follow-up. Sherman and colleagues (1994) have also published randomized data in abstract form in which patients with chronic abdominal pain thought to be pancreatic in origin and PD were randomized to minor papilla sphincterotomy (n = 16) or no intervention (n = 17). Mean follow-up time in the treated and untreated groups was 2.1 and 1.2 years, respectively. Although an improvement in pain was seen in 43.8% of treated patients compared with 23.5% in the control group, this trend did not reach statistical significance.

Borak and colleagues (2009) published the long-term outcomes after endoscopic minor papilla therapy in 145 patients with PD over a 6-year period. Follow-up data were available for 113 patients (78%), and the median follow-up time was 43 months. The majority of patients had a needle-knife sphincterotomy (82%) and temporary stent placement (90%). Primary success, defined as the patient being better or cured after a single ERCP session, was seen in 53.2% of patients with recurrent acute pancreatitis, 18.2% of those with chronic pancreatitis, and 41.4% of those with chronic/recurrent epigastric pain. Two or more ERCP sessions were required in 41.6%, with success in 71% of patients with recurrent acute pancreatitis, 46% of those with chronic pancreatitis, and 55% of those with chronic, recurrent epigastric pain. In a multivariate analysis that corrected for age, sex, symptom frequency/duration, and length of follow-up, chronic pancreatitis and younger age both independently predicted failure of improvement after treatment. Complications occurred in 13% after ERCP, including mild and moderate pancreatitis, mild bleeding, and anesthetic complications.

Surgical sphincteroplasty to the minor papilla, usually combined with cholecystectomy and major papilla sphincteroplasty, has been used in the treatment of recurrent acute pancreatitis, chronic pancreatitis, and chronic pancreatic-type pain associated with PD (Table 51.4). In the largest published series by Warshaw and colleagues (1990), 88 patients with recurrent acute pancreatitis (49%) or "pancreatic pain" (51%) had minor papilla sphincteroplasty with a mean follow-up of 53 months; 70% of patients were reported to show improvement, 85% if the minor papilla was stenotic at surgery, compared with 27% if it was not ($P < .01$). Of those with recurrent acute pancreatitis, 82% were reported to have improved compared with 56% in the chronic pain group ($P < .01$). Preoperative ultrasonography (US) with secretin stimulation was compared with examination of the minor papilla and had a sensitivity of 78% and a specificity of 97%. Thus preoperative US with secretin stimulation was judged to be a good predictor of surgical success (92% success if positive, 40% success if negative). Seven patients were documented to have developed a restenosis at the minor papilla, six of whom had further surgery. The study concluded that a demonstrable stenosis at the minor papilla was a necessary cofactor in the development of recurrent acute pancreatitis or pancreatic pain in patients with PD.

Surgical sphincteroplasty is not without risk, however. In a recent large series of 446 patients, complications were reported in 34.8% of patients; pancreatitis (8.8%), asymptomatic hyperamylasemia (6.0%), and wound/abdominal infection (7.1%) were the most common morbidities. One death occurred after a duodenal leak (Madura et al, 2005).

The Case Against an Association Between Pancreas Divisum and Pancreatitis

Those making the case against an association between PD and pancreatitis begin by highlighting problems with the epidemiologic studies. It is argued that in ERCP series, the true incidence of PD is underdiagnosed. This is supported by autopsy studies that demonstrate the prevalence of PD to be approximately 10%, whereas ERCP series show it to be half this. It is argued that were ERCP to accurately diagnose PD, its prevalence in control and pancreatitis groups would be the same. Patients in groups used as controls often only have cholangiography and do not undergo intentional pancreatography. Pancreatitis patients, on the other hand, have the pancreatic ducts imaged intentionally; therefore PD may be diagnosed more accurately. Furthermore, the ERCP prevalence of PD in pancreatitis patients is the same as the prevalence of PD in the general population in autopsy studies (7.6% vs. 7.8%). The argument therefore follows that if ERCP accurately diagnosed PD in the general population, no difference would exist.

An argument is also made against the theory of minor papilla obstruction. It is argued that patients with pancreatitis secondary to PD should have a dilated ductal system, but this has not been shown to be the case in the majority of studies that have assessed for it (Fogel et al, 2007). Similarly, if pancreatitis were associated with PD, only the dorsal pancreas should be affected, yet ventral duct pancreatitis is present in up to 11.8% of patients with PD and is the only duct involved in 4.2% of patients.

Cystic Fibrosis and Recurrent Pancreatitis

Cohn and colleagues (1998) and Sharer and colleagues (1998) first described the link between cystic fibrosis gene mutations and idiopathic pancreatitis. More recently, Choudari and colleagues (2004) demonstrated that mutations of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene were present in 8 (22%) of 37 patients with PD and pancreatitis compared with 0 of 20 patients with PD and no history of pancreatitis (odds ratio [OR], 11.8; confidence interval [CI], 8.9 to 14.7; $P = .02$). The authors concluded that in patients with PD, *CFTR* mutations increased the risk for pancreatitis. Furthermore, Gelrud and colleagues directly measured *CFTR* gene function in nasal epithelium in response to isoproterenol

Table 51.4

Surgical Therapy in Pancreas Divisum

			RAP		PAIN ALONE‡		CP§					
Study	Total (N)	Patients Improved (%)†	N	Patients Improved (%)	N	Patients Improved (%)	N	Patients Improved (%)	Restenosis	Major Complications	Deaths	Mean Follow-up (mo)
Warshaw et al, 1990	88	77	43	82	45	56	0	0	7/88	1/88	0	53
Brenner et al, 1990	13	54	10	70	3	0	0	0	0/13	0/13	0	18
Cooperman et al, 1982	4	75	4	75	0	0	0	0	1/4	NG	0	14
Bragg et al, 1988	4	100	3	100	1	100	0	0	0/4	NG	0	21
Rusnak et al, 1988	4	75	NG	—	NG	—	NG	—	1/4	0/4	0	~48
Madura, 1986	32	75	11	82	19	68	2	0	NG	3/32	0	31
Britt et al, 1983	5*	60	4	75	0	0	1	0	1/5	NG	0	21
Russell et al, 1984	7	71	NG	—	NG	—	NG	—	1/7	NG	0	8
Gregg et al, 1983	19	53	NG	—	NG	—	NG	—	1/19	1/19	1	NG
Keith et al, 1989	22*	86	13	100	8	75	1	0	1/22	2/22	0	53

All series used sphincteroplasty, except that by Keith et al, which performed sphincterotomy alone.
*Plus one patient who did not respond to minor papilla identification at laparotomy.
†Includes patients graded excellent, good, and fair (if more than 50% improved and off narcotics).
‡Pain suggestive of pancreatic origin (generally epigastric with back radiation) without serologic, ultrasound, computed tomographic scan, or ductographic evidence of pancreatitis.
§Some patients had a history of heavy alcohol ingestion.
RAP, recurrent acute pancreatitis; CP, chronic pancreatitis; NG, not given

From Fogel EL, et al, 2007: Does endoscopic therapy favorably affect the outcome of patients who have recurrent acute pancreatitis and pancreas divisum? Pancreas 34:21-45.

and demonstrated that those with PD and recurrent acute pancreatitis had results somewhere between those observed for healthy controls and those for classic cystic fibrosis patients. Thus CFTR dysfunction may explain why some PD patients have recurrent acute pancreatitis but others with PD do not. Moreover, of 12 patients with PD and recurrent acute pancreatitis, 10 had undergone therapy to the minor papilla, and only 2 had resolution of their symptoms.

Summary

Despite the association of pancreatitis and PD being described in the 1970s, significant controversy still exists regarding whether a causal relationship exists. Although many case series report the benefit of therapy to the minor papilla in patients with PD and pancreatitis, a lack of randomized, controlled data means interpretation of these studies must be guarded. At best, careful case selection is paramount before embarking on any such therapy: patients most likely to benefit are older, have documented recurrent acute pancreatitis, and have been exhaustively investigated for a recognized cause of pancreatitis. Those with chronic pancreatitis or pancreas-type pain are much less likely to benefit. Recurrence of symptoms is common, and repeat therapy involving the minor ampulla may be required. The *CFTR* data are interesting and may begin to explain why few patients with PD experience pancreatitis.

ANNULAR PANCREAS

Annular pancreas is a rare congenital abnormality in which the head of the pancreas completely encircles the second part of the duodenum (Fig. 51.4). It was first described in 1862 by Ecker, who reported a "ring derived from the head of the pancreas which surrounded the descending portion of the duodenum and was formed by uninterrupted glandular tissue" (Ravitch & Woods, 1950). The prevalence in autopsy studies is approximately 3 in 20,000 (Ravitch & Woods, 1950) but is higher in patients undergoing ERCP, at approximately 3 in 1000 (Fogel et al, 2006). Given the difficulty in making the diagnosis during autopsy and the highly selected patient population undergoing ERCP, the true prevalence likely lies somewhere in between.

Pathogenesis

In early development, the ventral pancreas is formed by two buds (see Chapter 1A). In mammals, the left ventral pancreatic bud is thought to regress (Lammert et al, 2001; Odgers, 1930), and the larger right ventral pancreatic bud migrates to take up the position seen in the adult. A number of hypotheses have been proposed to explain the occurrence of annular pancreas. The most persistent is that of Lecco (1910), who suggested that adherence of the right ventral pancreatic bud to the duodenum before gut rotation resulted in a partial or complete ring

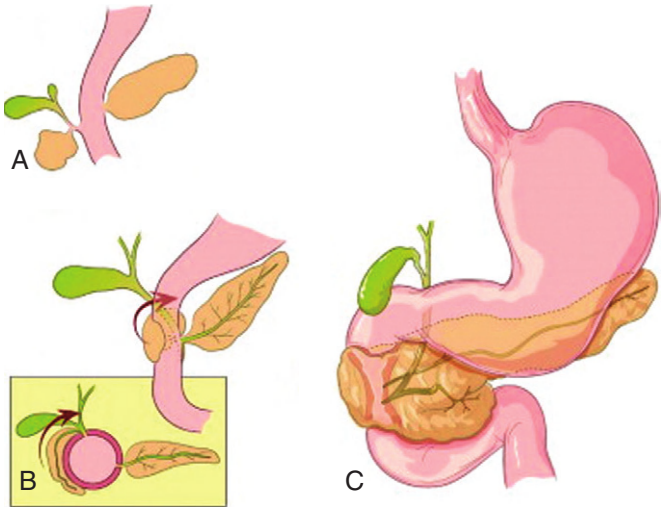


FIGURE 51.4. Development of annular pancreas. *(Modified from Zyromski, et al, 2008: Annular pancreas: dramatic differences between children and adults. J Am Coll Surg 206:1019-1025.)*

of pancreatic tissue around the duodenum. A competing hypothesis offered by Baldwin (1910) postulates that the left ventral bud persists to form the annulus. Although in most annular pancreas specimens, only one ventral lobe is apparent, reports of a bilobar ventral pancreas have surfaced that support Baldwin's theory (Nobukawa et al, 2000). Neither of these theories explains the variation in the position of the annular duct seen in various specimens, and Kamisawa and colleagues (2001) proposed a new theory that the tip of the left ventral bud adheres to the duodenum and stretches to form a ring. The exact location of this attachment in relation to the bile duct determines the final arrangement of the annular duct.

Reports of familial annular pancreas support a genetic basis for the disease. Annular pancreas has been described in siblings (Claviez et al, 1995; Lainakis et al, 2005; Montgomery et al, 1971), a mother and three of her children (Jackson & Apostolides, 1978), a mother and son (MacFadyen & Young, 1987), a mother and daughter (Hendricks & Sybert, 1991; Rogers et al, 1993), and a father and son (Mitchell et al, 1993), and a recent report describes the anomaly in monozygotic twins (Hulvat et al, 2006).

Clues as to the genetic basis of the disease are beginning to emerge. Only recently has it been shown that the cells that form the annulus are derived entirely from the ventral pancreas (Jarikji et al, 2009). In the same report, it was demonstrated that in *Xenopus* embryos, inactivation of transmembrane 4 superfamily member 3 (*TM4SF3*), a member of the tetraspanin family, inhibited fusion of the dorsal and ventral pancreatic buds. Overexpression of the same gene promoted development of annular pancreas. This would suggest that the product of this gene directly regulates the migration of ventral pancreatic bud cells, although whether it plays a role in the formation of annular pancreas in humans remains to be seen.

Another recent study has demonstrated a link between the Hedgehog signaling pathway and the development of annular pancreas. Members of the Hedgehog family of genes promote growth and differentiation of organs, and defects are associated with congenital malformations of the foregut (Litingtung et al, 1998). In 42% of mice embryos with a targeted inactivation of the Indian Hedgehog (*IHH*) gene, a member of the mammalian Hedgehog family, changes in the morphology of the ventral pancreatic bud similar to annular pancreas were seen (Hebrok et al, 2000). In most, the annulus was complete, although pancreas cells were not seen within the muscularis of the duodenum, as has been described in humans. Annular pancreas is also frequently seen after inactivation of Sonic Hedgehog (*SHH*), although the incidence of the anomaly is closely related to the background strain of the transgenic mouse, suggesting interaction with other genetic modifiers (Ramalho-Santos et al, 2000). *SHH* is not expressed in pancreatic tissue; therefore it has been suggested that a defect in duodenal Hedgehog signaling may lead to the anomaly because both *SHH* and *IHH* are expressed in the developing gut (Bitgood & McMahon, 1995; Hebrok et al, 2000). *SHH* knockout mice embryos also demonstrate a number of other abnormalities, including gut malrotation (100%), intestinal transformation of the stomach (100%), duodenal stenosis (67%), and imperforate anus (100%), strikingly similar to congenital malformations seen in humans with annular pancreas (see below).

Clinical Presentation and Diagnosis in Adults

An estimated one half to two thirds of cases of annular pancreas in adults remain asymptomatic (Sandrasegaran et al, 2009). Annular pancreas presents with equal frequency in adults and children; in a recent series of 103 patients with annular pancreas, 55 (53.4%) were seen as adults (median age, 47 years), and 48 (46.6%) were seen as children (median age, 1 day) (Zyromski et al, 2008). Of those seen as adults, 41 (75%) were seen with pain, and 12 (22%) were diagnosed with pancreatitis; only 13 (24%) had gastrointestinal symptoms that included vomiting, and 6 (11%) had obstructive jaundice and/or abnormal liver function test results. In addition, 16 patients (29%) were also found to have PD, a higher prevalence than is seen in the general population (see previous section), which may suggest that similar genetic abnormalities link the two conditions. The diagnosis of annular pancreas was made by ERCP in 26 patients (47%), by abdominal CT in 10 patients (18%), by MRCP in 9 patients (16%), and at operation in 7 patients (13%; Fig. 51.5) (Zyromski et al, 2008).

In a recent ERCP series, 26 (93%) of 28 patients with annular pancreas without previous bypass were noted to have duodenal narrowing but no retained gastric contents (Fogel et al, 2006). Pancreatography was attempted in 32 patients and was successful in 30 (94%). Improvements in imaging have led to the identification of incomplete annular pancreas, in which the annulus does not fully encircle the duodenum (Sandrasegaran et al, 2009). The presence of pancreatic tissue on cross-sectional imaging posterolateral to the second part of the duodenum has a high sensitivity (92%) and specificity (100%) for this. Three (33%) of nine patients found to have incomplete annular pancreas on imaging had gastric outlet obstruction (Sandrasegaran et al, 2009).

A number of case reports describe annular pancreatitis in association with neoplasm, most commonly periampullary or pancreatic malignancy, raising the question as to whether annular pancreas predisposes to neoplasia (Ben-David et al, 2004; Benger & Thompson, 1997; Foo et al, 2007; Kamisawa et al, 1995; Shan et al, 2002; Yasui et al, 1995). The adult population in whom annular pancreas is diagnosed is a highly select group with a variety of symptoms. The incidence of annular pancreas is too small to be certain, but it is likely that the association is a result of bias rather than pathogenesis. What should be remembered is that the symptoms of a patient diagnosed

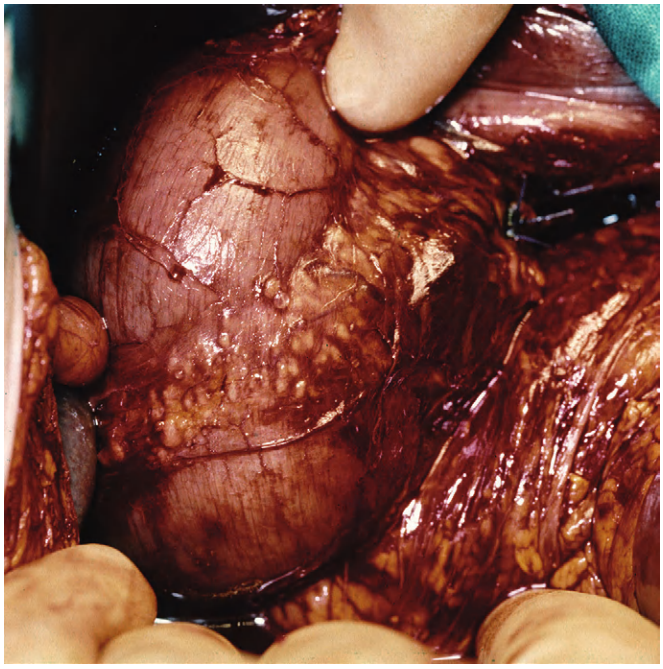


FIGURE 51.5. Annular pancreas.

with annular pancreas are not necessarily secondary to the annular pancreas; a second condition may be present. For instance, annular pancreas rarely presents with obstructive jaundice; therefore, when a patient with obstructive jaundice is found to have annular pancreas, a high index of suspicion for an underlying malignancy must be maintained.

Clinical Presentation and Diagnosis in Children

A significant difference between the adult and pediatric populations with annular pancreas is the prevalence of associated congenital abnormalities in children. The majority of children with annular pancreas show evidence of the condition in the first days after birth: in a recent series of 16 patients, 12 (75%) came to medical attention during the first week of life, one during the first month, and the remainder within the first year (Table 51.5) (Jimenez et al, 2004). If complete duodenal obstruction is present, polyhydramnios will usually be a feature; primary biliary obstruction and jaundice are not typical (Merrill & Raffensperger, 1976).

Preampullary obstruction resulting in nonbilious vomiting has been reported to be more common in annular pancreas than in other causes of duodenal obstruction (94% vs. 10%; Hays et al, 1961; Jimenez et al, 2004). In the series by Zyromski and colleagues (2008), 27 (56%) of 48 children with annular pancreas were suspected to have the condition based on prenatal US, and the remainder were seen with gastrointestinal obstruction, 37 (77%) of whom were diagnosed within the first 2 days of life; 34 (71%) of children with annular pancreas were reported to have at least one other congenital abnormality, the most common being trisomy 21 (Down syndrome), seen in 10 (21%). Gastrointestinal abnormalities included intestinal malrotation in 10 of the 48 children (21%), tracheoesophageal fistula in 4 (8.3%), and 1 each of mobile right colon, omphalocele, nonrotation, duodenal atresia, and situs inversus. In addition, 10 children (21%) had significant cardiac anomalies, and genitourinary abnormalities were seen in 5 children (10%).

Diagnosis was made in a similar way in both the Jimenez and Zyromski series; plain abdominal radiographs showed the "double-bubble" sign, or air in the stomach and first part of the duodenum, in 14 (88%) of 16 and 30 (63%) of 48 patients, respectively. Upper gastrointestinal contrast was used in 9 (56%) of 16 and 9 (19%) of 48 patients, respectively, and neonatal ultrasonography was used in 3 infants (6%) of 48 in the Zyromski series only.

Therapy for Annular Pancreas

A review of the existing literature published in 1980 concluded that "while there is no single operative procedure of choice, experience militates against any direct attack on the offending annulus" (Kiernan et al, 1980). This conclusion stands, and any attempt to divide the annulus itself risks the formation of a pancreatic fistula. Early pediatric series established duodenal bypass as the treatment of choice, although mortality rates remained high, likely related to the presence of other congenital malformations and the lack of supportive care (Hays et al, 1961; Kiesewetter & Koop, 1954; Merrill & Raffensperger, 1976). Duodenoduodenostomy has replaced duodenojejunostomy as the treatment of choice because it has a lower incidence of postoperative complications, particularly obstruction and blind-loop

Table 51.5

Annular Pancreas Case Series

Study	No.	Sex (% Male)	Neonatal Presentation (%)	Prematurity (%)	Chromosomal Abnormalities (%)	Major Congenital Abnormalities (%)	Preampullary Obstruction (%)	Complete Obstruction (%)	Survival (%)
Kiesewetter & Koop, 1954	6	67	83	NR	17	33	NR	3	17
Hays et al, 1961	7	NR	100	29	29	43	100	NR	57
Merrill & Raffensperger, 1976	24	38	96	NR	29	54	NR	54	75
Kiernan et al, 1980	6	67	100	NR	17	NR	NR	NR	67
Sencan et al, 2002	7	29	100	14	14	14	0	43	100
Current Series	16	69	81	23	31	38	94	33	100

NR, not reported.

From Jimenez JC, et al, 2004: Annular pancreas in children: a recent decade's experience. J Pediatr Surg 39:1654-1657.

syndromes (Jimenez et al, 2004). Before the procedure, care should be given to ensure adequate fluid replacement and correction of electrolyte abnormalities. A right upper quadrant incision gives excellent access, and a full examination should be performed to exclude other congenital abnormalities. An end-to-end or side-to-side duodenoduodenostomy should be performed, ensuring adequate mobilization of proximal and distal ends. Where the first part of the duodenum is distended, a tapering duodenoplasty or plication can be performed, although this may not always be required. Consideration should be given to the placement of a gastrostomy tube; however, this should be reserved for those patients who are likely to have long-term problems, such as those with complex gastrointestinal malformations or chromosomal abnormalities. An enteral feeding tube is often useful and allows early feeding to be commenced.

Outcome after surgery has improved markedly, with early mortality rates decreasing from 83% in the 1950s (Kiesewetter & Koop, 1954) to less than 10% in most recent series (Jimenez et al, 2004; Zyromski et al, 2008), largely as a result of improvements in surgical decision making and technique and advances in neonatal intensive care and anesthesia. Deaths in contemporary series are usually attributed to severe associated congenital anomalies.

In the series from Zyromski, 35 (63%) of 55 adults were reported to have had surgical therapy for symptoms related to annular pancreas. Duodenal bypass was performed in 13 adult patients (24%) compared with 100% of the children. Adults also underwent a number of other surgical procedures, including cholecystectomy, pancreatoduodenectomy, pancreatic sphincteroplasty, lateral pancreatojejunostomy, hepaticojejunostomy, and biliary sphincteroplasty. Therapeutic ERCP with sphincterotomy/stenting was performed in 37 (67%) of 55 adults.

Summary

Annular pancreas is a rare condition that is being increasingly diagnosed as a consequence of improvements in modern imaging. Children are seen at birth with gastrointestinal obstruction and often have other congenital abnormalities. Adults come to medical attention with pain or vague upper abdominal symptoms, and diagnosis can be confirmed using CT, MRCP, or ERCP. In children, duodenoduodenostomy is the treatment of choice; in adults an array of interventions may be required, often in the treatment of a coexisting pathology.

PANCREATOBILIARY MALJUNCTION

Pancreatobiliary maljunction was first described by Babbitt in 1969, and it has since been defined as "a congenital anomaly in which a junction of the pancreatic duct and biliary ducts is detected radiologically and/or anatomically outside the duodenal wall" (see Chapter 1B; Todani et al, 1994). It is often associated with congenital bile duct dilation (choledochal cyst; see Chapter 46), which is significant because it results in regurgitation of pancreatic juice into the biliary tree (pancreatobiliary reflux) and of bile into the pancreatic duct (biliopancreatic reflux). It has been associated with a number of pathologic conditions, most notably carcinoma of the biliary tree (see Chapter 50).

Pathogenesis

The anatomic relationship between the junction of the duodenum and the pancreatobiliary ducts is subject to significant variation (Suda et al, 1980, 1983). The pancreatic and bile duct may open into the duodenum in one of three configurations: 1) separately, 2) through a single opening with no common channel, or 3) through a single opening with a common channel (Fig. 51.6). Within the wall of the duodenum, the pancreatic and bile ducts are under the control of the sphincter of Oddi; proximal to this extend the sphincter choledochus (of Boyden) and the sphincter pancreaticus. A single opening with a short common channel is usual, but when the common channel extends beyond the duodenal wall, the pancreatobiliary ductal junction is not controlled by these sphincter mechanisms, allowing regurgitation to occur between the two ducts. This is termed *pancreatobiliary maljunction,* which was reported to have a prevalence of 3.1% in a recent ERCP series (Kamisawa et al, 2007b). A further 3.7% of patients were shown to have a high confluence of the pancreatobiliary ducts, and although sphincter function existed at the junction, the group was still susceptible to the same pathologic consequences as those with maljunction. The incidence of maljunction is higher in Asian compared with Western populations, although the reasons for this remain unclear.

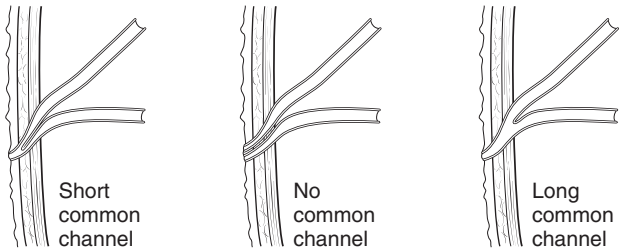


FIGURE 51.6. Normal variations in the configuration of the pancreatic and bile ducts. *(Adapted from Rizzo RJ, Szucs RA, Turner MA, 1995: Congenital abnormalities of the pancreas and biliary tree in adults. Radiographics 15:49.)*

The embryologic origins of pancreatobiliary maljunction have not been fully elucidated. Small pancreatic radicals arising from the long common channel have led to the suggestion that it originates from the ventral pancreatic duct (Matsumoto et al, 2001; Suda et al, 1991a, 1991b). In one such hypothesis, it is suggested that the persistence of the left ventral duct, usually seen to regress in normal development, associated with regression of the distal bile duct results in a long common channel (Oi, 1996). An alternative hypothesis suggests that maljunction results from a disturbance in embryologic connections of the terminal bile duct and the ductal system of the ventral pancreas (Matsumoto et al, 2001). A case report of pancreatobiliary maljunction in monozygotic twins provides strong support for a genetic basis for the disease (Yamao et al, 2004).

Diagnosis and Investigation

Maljunction is closely associated with choledochal cyst and in one series was described in all patients with type I choledochal cysts (see Chapter 46; Miyano et al, 1997). Clinical presentation in this context can be at any age and may feature a right upper quadrant mass, hepatomegaly, jaundice, abdominal pain, cholangitis, or pancreatitis. In maljunction without bile duct dilatation, patients may be asymptomatic (30%), or they may be seen with abdominal pain (24%), recurrent acute pancreatitis (18%), obstructive jaundice (18%), or acute cholangitis 9% (Matsumoto et al, 2002). When pancreatic maljunction is

suspected, the lack of effect of the sphincter muscle on the pancreatobiliary ductal junction can be confirmed radiologically, and regurgitation can be demonstrated by MRCP, ERCP, operative cholangiography, or percutaneous transhepatic cholangiography. Biliary amylase levels have also been shown to be high in this group (Ohta et al, 1990). On hepatobiliary scintigraphy, the passage time from the bile duct to the second part of the duodenum was significantly longer in maljunction patients than in controls (49 ± 13 vs. 3 ± 14 minutes) (Fujii et al, 1991).

Carcinogenesis in Pancreatobiliary Maljunction

The association of bile duct cancer and choledochal cyst is well established (Irwin & Morrison, 1944), and resection of the extrahepatic bile duct and gallbladder with biliary reconstruction is now standard treatment (Edil et al, 2009). A number of published series have described a high incidence of gallbladder cancer in patients with pancreatobiliary maljunction in the absence of a dilated bile duct (see Chapter 49; Chao et al, 1995; Chijiiwa et al, 1995; Elnemr et al, 2001; Kamisawa et al, 2006, 2007b; Kimura et al, 1985; Kinoshita et al, 1984; Mori et al, 1993; Sandoh et al, 1997; Yamauchi et al, 1987). The hydrostatic pressure in the pancreatic duct is greater than that of the bile duct (Carr-Locke & Gregg, 1981; Csendes et al, 1979), so it follows that when free communication exists between the two ducts, pancreatic juice flows from the pancreatic to the bile duct. The pathogenesis of malignant change is not fully characterized but is likely due to the effect of activated pancreatic enzymes on the biliary epithelium, together with biliary stasis. *KRAS* and *P53* mutations have been reported in noncancerous biliary epithelium of patients with maljunction, which may be important given the apparent higher incidence of carcinoma in this group (Hanada et al, 1996, 1999; Kasuya et al, 2009; Matsubara et al, 1996, 2002).

Therapy for Pancreatobiliary Maljunction Without Bile Duct Dilatation

Given the risk of malignant transformation in patients with pancreatobiliary maljunction without biliary dilation, resectional surgery is generally advocated. However, significant controversy exists as to whether a complete excision of the extrahepatic biliary tree is required or just a simple cholecystectomy. Those arguing the former cite case reports of choledochal cyst patients developing cancer in the hepatic duct above the reconstruction after bile duct resection (Thistlethwaite & Horwitz, 1967; Yamamoto et al, 1996). This, together with the *P53*/*KRAS* mutation, suggests the biliary epithelium is in a "premalignant state" (Funabiki et al, 1997; Hara et al, 2001; Ng & Lui, 1999; Toufeeq Khan & Manas, 1999; Tuech et al, 2000). Other investigators argue that cholecystectomy alone is sufficient and base this on reasonable follow-up data, albeit in small cohorts, showing no patients developed bile duct malignancy in this group (Aoki et al, 2001; Kusano et al, 2005; Ohuchida et al, 2006; Sugiyama & Atomi, 1998). It is currently impossible to confirm which strategy is correct, and any decision must be made on an individual basis.

CONGENITAL CYSTS OF THE PANCREAS

Of the cystic diseases of the pancreas (see Chapter 57), true congenital cysts are uncommon and comprise less than 1% of the total (Howard, 1989). Cysts may be solitary, but this is rare—fewer than 30 have been described in the world literature. They are usually multiple, and some are associated with a systemic disorder, such as von Hippel–Lindau syndrome or polycystic kidney disease (Boulanger et al, 2003). Enteric duplication cysts of the gastrointestinal tract are also rare (2 in 9000 fetal/neonatal autopsies) (Potter, 1962) and can lie in the pancreatic head in isolation or in communication with the pancreatic duct (Black et al, 1986). They are lined with gastrointestinal mucosa and take a layer of smooth muscle from their associated viscus. Several hypotheses on their embryologic origins exist, but no consensus has been reached (Bentley & Smith, 1960; Bishop & Koop, 1964; Bremer, 1944; Lewis & Thyng, 1908).

Congenital pancreatic cysts are most commonly seen in neonates or infants as an asymptomatic epigastric mass. It is very rare for them to present in adulthood, although case reports do exist (Casadei et al, 1996). In the case of duplication cysts, presentation with acute pancreatitis is not uncommon. This is likely to be due to the secretions of the gastrointestinal mucosa within the cyst activating pancreatic enzymes. Other modes of presentation relate to compression of other structures by the cyst and include abdominal pain, obstructive jaundice, and splenic vein thrombosis (Boulanger et al, 2003).

Diagnosis can be difficult, and most of the published cases describe extensive investigation of patients with recurrent abdominal pain or pancreatitis before the diagnosis being made. In patients with solitary congenital pancreatic cysts, US, CT, and ERCP have all been used in making the diagnosis (Casadei et al, 1996). Enteric duplication cysts involving the head of the pancreas can be differentiated from pseudocysts on US by the identification of hyperechoic muscoa and hypoechoic smooth muscle (Barr et al, 1990). Peristalsis has also been seen in these lesions (Spottswood, 1994). CT helps further characterize the lesion, and MRCP and ERCP can determine ductal relationships (Siddiqui et al, 1998).

Complete resection of solitary pancreatic cysts has been advocated, given that cystic neoplasms represent a possible differential diagnosis (Boulanger et al, 2003). Drainage procedures have been performed successfully, but multiple biopsies of the cyst wall should be taken to exclude malignancy. Drainage procedures have been performed for enteric duplication cysts but are not usually definitive because patients often return with further pain or pancreatitis. When possible, local or mucosal resection is preferable to major resection, such as pancreatoduodenectomy, which should be reserved for when malignancy cannot be excluded. The spleen should be preserved whenever possible, particularly in the pediatric population.

HETEROTOPIC PANCREAS

Heterotopic pancreas is defined as pancreatic tissue outside the boundaries of the pancreas that lacks anatomic or vascular continuity with the organ (Fig. 51.7). The first description is credited to Jean Schultz in 1729, and sporadic cases have been described since (Barbosa et al, 1946). Heterotopic pancreas is a congenital anomaly that is usually asymptomatic but can become clinically apparent when the inflamed or enlarged pancreas compresses adjacent viscera. The prevalence in the general population is difficult to determine; estimates range from 0.6% to 13.7% (Barbosa et al, 1946; Feldman & Weinberg, 1952).

The pathogenesis of heterotopic pancreas is unclear. It has been hypothesised that during embryologic development,

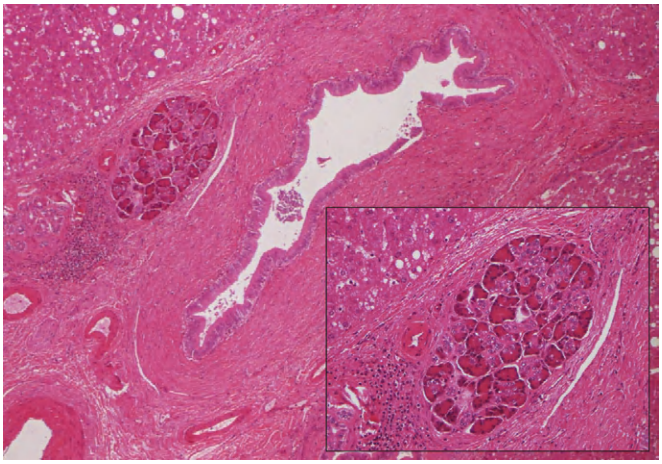


FIGURE 51.7. Heterotopic pancreas in a large portal tract in the liver found incidentally. The liver resection was for metastatic colorectal cancer. *(Courtesy Dr. Barbara Langdale-Brown, Edinburgh.)*

pancreatic tissue may become attached to the duodenum and be carried proximally or distally as the bowel elongates (Horgan, 1921). This, however, does not explain the rare instances of heterotopic pancreas at sites distant from the gastrointestinal tract, for instance, in the uterine tube (Mason & Quagliarello, 1976). As has been described, the pancreas is endodermal in origin, and contemporary studies are beginning to uncover the mechanisms by which cells destined to become pancreas are specified from surrounding tissues (Kumar & Melton, 2003). The observation that heterotopic pancreas tissue usually drains into the gastrointestinal tract via a primitive duct (Pang, 1988) suggests in situ differentiation rather than migration from elsewhere (Slack, 1995). Thus it is possible that heterotopic pancreas is the result of a process in which cells destined for other endodermal structures are anomalously diverted to a pancreatic fate.

Clinical presentation depends entirely on anatomic site. An early series of 34 patients by Armstrong and colleagues is representative: heterotopic tissue was found in stomach (24%), duodenum (32%), jejunum (29%), Meckel diverticulum (15%; Fig. 51.8), and gallbladder (3%). Occurrences have also been documented in the esophagus, bile duct, spleen, mesentery, and fallopian tubes. In the same series, heterotopic pancreas was thought to be clinically significant in 13 patients (38%) and possibly significant in four patients (12%). All gastric lesions, and four of 11 duodenal lesions, presented with epigastric pain. Two of the duodenal lesions presented with ulcer bleeding and one with chronic anemia.

Investigation and diagnosis again depend on the mode of presentation. In a contemporary series, diagnosis was made at gastroduodenoscopy in 36% and at surgery in 64% (Eisenberger et al, 2004). It was noted that definitive diagnosis was only obtained with histologic assessment. Heterotopic pancreas was the indication for surgery in 36% of cases, and in 45%, it was diagnosed incidentally during surgery. In 18% it was diagnosed on gastroduodenoscopy, and definitive surgical management was not required.

In the majority of cases found at open surgery, the lesion is resected even when thought to be asymptomatic. This is advised because the diagnosis cannot be made clinically, and the main differential is malignancy. A frozen histologic section is an alternative approach but is rarely worthwhile unless an extensive resection is required. When identified at endoscopy, initial

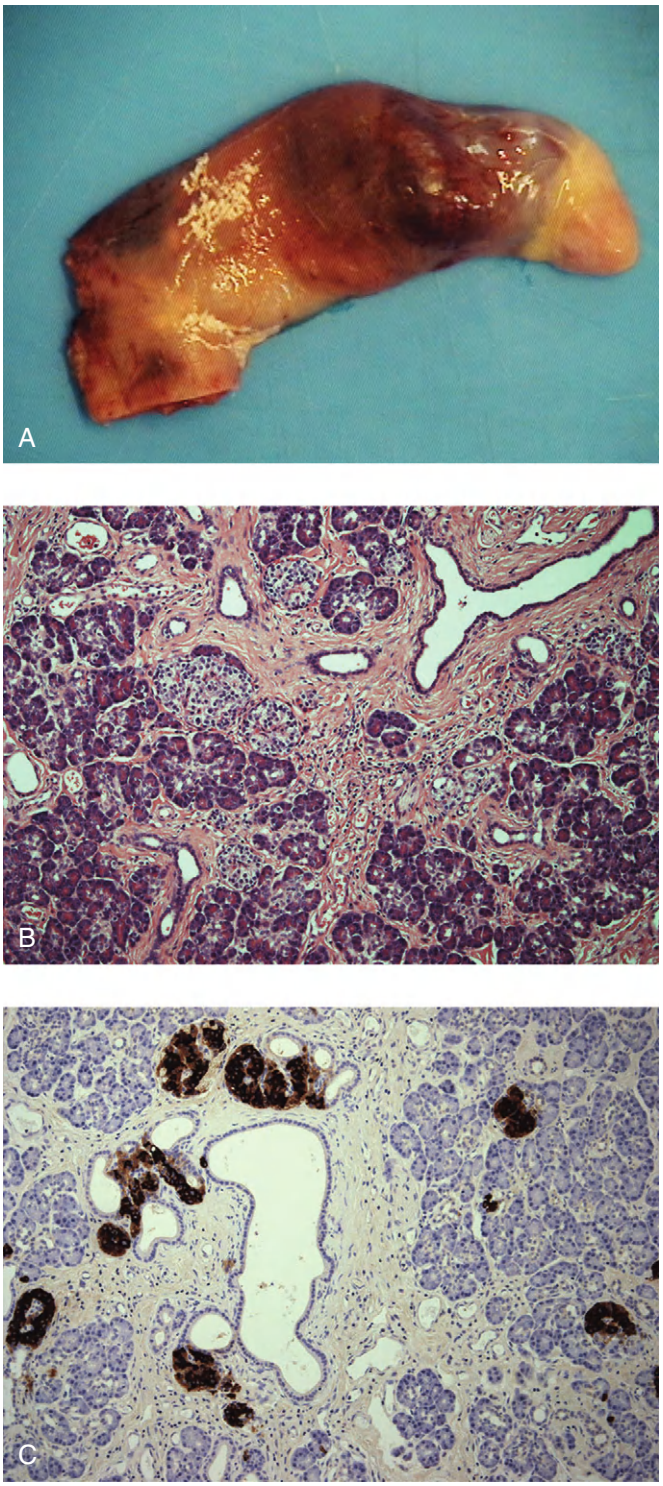


FIGURE 51.8. A, Heterotopic pancreas found in Meckel diverticulum. **B,** Hematoxylin and eosin section. **C,** Immunohistochemistry with primary antibody specific for human insulin. *(Courtesy Dr. Kathryn McKenzie, Edinburgh.)*

biopsies are often negative because the overlying mucosa may be normal. Recently, endoscopic US-guided core biopsies have been ideal. If the lesion is thought to be symptomatic, a resection can be planned, but many can be treated conservatively with no negative long-term consequences.

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CHAPTER 52

Definition and classification of pancreatitis

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OVERVIEW

Despite four international consensus meetings over 40 years, the issue of definition and classification of pancreatitis (see Chapters 53 to 55) is still under critical revision. The main reason is the difficulty, in contrast to other common inflammatory gastroenterologic diseases, to obtain pancreatic tissue specimens to define the diagnosis better during the inflammatory process. Any classification of pancreatitis must be based on clinical, morphologic, and laboratory features.

The history of the definition and classification of pancreatitis is characterized mainly by the distinction between acute and chronic pancreatitis as stated by Lagerlof in 1942. These two clinical conditions seemed to be two different and separate pathologic processes. In recent years, with the widening of clinical observation and improved accuracy of imaging studies, particularly magnetic resonance imaging (MRI) of the bile ducts and duct of Wirsung, the classic distinction between acute and chronic pancreatitis is under critical revision.

The process leading to fibrotic changes in the glandular tissue usually begins with typical acute abdominal pain with increases of serum amylase and lipase and subsequent resolution. Acute pancreatitis leads to chronic pancreatitis because of episodes of obstruction secondary to edema or inflammatory response of the sphincter of Oddi. As in other inflammatory disease, timing seems to play the main role in determining whether glandular inflammation leads to a chronic condition or self-limits with no sequelae.

The most typical natural history regarding the correlation between acute and chronic pancreatitis is so-called *recurrent pancreatitis.* It is not possible to define this condition as acute or chronic per se, and it represents the best example of the new comprehension of the pathologic process. Nevertheless, today we must keep in mind a classification of acute and chronic pancreatitis to help in developing diagnostic and therapeutic algorithms.

HISTORY OF THE DEFINITION AND CLASSIFICATION OF PANCREATITIS

Pancreatitis is an inflammation of glandular parenchyma lead to injury or destruction of acinar components. The pathologic process could result in a self-limited disease with no sequelae or in catastrophic autodigestion activity with systemic cytotoxic effects and life-threatening complications in the acute form. In the case of chronic inflammation, fibrosis and calcification are the main features of the disease.

The history of the definition and classification of pancreatitis shows the progressive awareness of experts that acute and chronic inflammation should be defined by different pathologic, clinical, and etiogenetic perspectives (Table 52.1). The different points of view correlate with each other and together provide the best comprehension of the inflammatory process. Consequently, the clinical management of an individual patient can be improved only by considering all the features of pancreatitis.

The first effort to classify and define pancreatitis by a worldwide group of experts led to the Marseille Consensus Meeting in 1963 (Sarles, 1965). The panel of pancreatologists agreed that acute and chronic pancreatitis were different diseases mainly because of different morphologic patterns. Relapsing pancreatitis was characterized by the presence of multiple episodes in a morphologic pattern of acute or chronic processes. The distinctive features of the two diseases were the pathologic benign course of acute inflammation, with biologic restitution in the acute condition, and the progressively worsening parenchymal lesions in the chronic condition (Table 52.2). The present histology-based classification does not provide clinically useful definitions, making it impossible to compare different experiences. From the clinical point of view, acute and chronic pancreatitis show a similar pattern, at least in the earlier phases.

Progress in the comprehension of pancreatitis and its classification resulted from the Cambridge meeting (Sarner & Cotton, 1984). The distinction between *acute* and *chronic*

Table 52.1

A Synopsis of Pancreatitis Classification from 1946 to 2011

Classification	Definition
Marseille, 1965	Description of morphologic characteristics and etiologic factors of the disease; no categorization according to disease severity, no imaging findings
Cambridge, 1984	Classification of disease severity based on pancreatic imaging criteria (US, CT, ERCP); discussion of etiologic factors and pancreatic function
Revised Marseille, 1985	Description and further subclassification of morphologic changes; definition of "obstructive chronic pancreatitis" as a distinct form; no discussion of the correlation between anatomic and functional changes, no inclusion of pancreatic imaging findings
Marseille-Rome, 1988	Further description of "chronic calcifying" and "chronic inflammatory" pancreatitis as distinct forms; description of etiologic factors; no further elaboration of clinical, functional, or imaging criteria
Atlanta, 1992	Description of clinical and morphologic features of pancreatitis; dynamic classification system able to characterize the individual patient and predict severity
Zurich, 1997	Description of clinical presentation and classification of the disease in "definite" and "probable" chronic pancreatitis according to imaging findings, functional testing, and histologic examination
Japan Pancreas Society, 1997	Description of clinical presentation and classification of the disease in "definite" and "probable" chronic pancreatitis according to imaging findings, functional testing, and histologic examination; definition of radiologic and laboratory features in patients lacking etiologic and pathogenetic features
TIGAR-O, 2001	Detailed categorization of etiologic risk factors and correlation between acute and chronic pancreatitis
ABC, 2002	Disease grading according to clinical criteria; limited separation of different disease severities; not all clinical presentations categorized
Manchester, 2006	Disease grading according to clinical criteria; limited separation of different disease severities
M-ANNHEIM, 2007	Categorization of patients according to etiology, clinical stage, and severity of disease; severity of pancreatic inflammation assessed using a specific scoring system

US, ultrasound; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography

pancreatitis was confirmed, and the term *relapsing pancreatitis* was avoided in the chosen terminology. The importance of the clinical impact of different severity systemic responses was emphasized (Table 52.3), and the importance of definition of a morphologic characterization of the inflammatory process was recognized, particularly for the acute pancreatitis group. The Cambridge group pointed out the relevant problem of etiology, and the role of imaging in chronic pancreatitis was addressed.

Endoscopic retrograde cholangiopancreatography (ERCP) classification (Table 52.4) is still in use in some centers. Several studies in the literature showed that ERCP findings are not pathognomonic of chronic pancreatitis but could coexist with many clinical conditions. In particular, cholelithiasis and its complications lead to demonstrable alterations in the morphology of the duct of Wirsung, as stated in the Cambridge classification (Buchler et al, 1987; Misra et al, 1990), and these morphologic changes could persist for many months. In biliary cirrhosis, Sjögren syndrome, and sclerosing cholangitis, pancreatic duct changes are commonly observed at ERCP (Bastid et al, 1990; Epstein et al, 1982; Lindstrom et al, 1991). For all these reasons, the ERCP morphology of the duct of Wirsung is not mandatory to diagnose chronic disease. In addition, increasing use of MRI of the bile ducts and duct of Wirsung provides excellent morphologic imaging of the main and side branch ducts.

The increasing attention to duct morphology and consequently to the cause-and-effect relationship of obstruction resulted in new terminology at the second Marseille meeting held in 1984 (Singer et al, 1985). In addition to the classic distinction between acute and chronic disease, a new entity was identified: *obstructive chronic pancreatitis* (Table 52.5). The role of duct obstruction in the chronic inflammatory process was recognized as a distinctive pathway to developing pancreatitis. This new concept has gained importance over the years in

Table 52.2

Marseille Classification of Pancreatitis

Feature	Acute Pancreatitis/Acute Relapsing Pancreatitis	Chronic Relapsing Pancreatitis/Chronic Pancreatitis
Clinical characteristics	Single/multiple episodes	Multiple episodes/no acute exacerbations is common
Morphologic characteristics	Not defined	Irregular sclerosis with destruction and focal segmental or diffuse loss of parenchyma with varying dilation of ductal system; strictures, intracanalicular stones (calcifications), cysts, pseudocysts; islets of Langerhans are involved much later in the course of the disease; morphologic picture is similar, independent of cause
Course	Clinical and biologic restitution if the cause is removed	Functional and morphologic lesions persist or progress after the cause is removed

Modified from Sarles H, 1965: Proposal adopted unanimously by the participants of the symposium of acute pancreatitis in Marseille, 1963. Bibl Gastroenterol 7:7-8.

Table 52.3

Cambridge Classification of Pancreatitis

Feature	Acute Pancreatitis	Chronic Pancreatitis
Clinical characteristics	Clinically defined as an acute illness owing to inflammatory pancreatic disease that typically presents with abdominal pain and usually is associated with an increase in pancreatic enzymes in blood or urine Mild pancreatitis: if no multisystem failure occurs and no complications in recovery are seen Severe pancreatitis: if multisystem failure occurs or early or late local or systemic complications occur	Defined as a continuing inflammatory disease of the pancreas; typically presents with abdominal pain or features of pancreatic insufficiency; also can remain painless Only sign of an inflammatory process may be fibrosis, indicating earlier pancreatic inflammation
Morphologic characteristics	Early: subcellular changes Later: fat necrosis or pancreatic tissue necrosis, which may be associated with hemorrhage Complications Phlegmon: an inflamatory mass in or around the pancreas Pseudocyst: a localized collection of fluid containing high concentrations of pancreatic enzymes within, adjacent to, or remote from the pancreas Abscess: pus in or around the pancreas	Not clearly defined; characterized by "irreversible morphologic changes"; classification is based on results of imaging studies
Course	Acute pancreatitis may recur	Many patients may have acute exacerbations of pain

Modified from Sarner M, Cotton PB, 1984: Classification of pancreatitis. Gut 25:756-759.

distinguishing chronic calcifying pancreatitis in alcoholics from obstructive chronic pancreatitis initially presenting as relapsing acute attacks owing to strictures resulting from different conditions, such as solid tumors, mucinous plugs typical of intraductal papillary mucinous tumors, severe pancreatitis with duct disruption, and scar and inflammation of the sphincter of Oddi of biliary origin. Regarding acute pancreatitis, another hallmark was recognized by the second Marseille meeting: The rule in mild pancreatitis is the absence of necrosis. The recognition of a dramatic and central role of necrosis in severe pancreatitis opened the doors to wide-ranging and fundamental studies on severity assessment and complication prevention; increasing use of CT scan in staging of the disease also contributed (Beger et al, 1985).

A panel of experts met in Rome in 1988 to integrate the second Marseille classification into use (Table 52.6). The main feature of the new classification (Sarles et al, 1989) was the statement about the reversibility of the lesions observed in the course of acute pancreatitis; even the severe forms responded to clinical observation in almost half of severe pancreatitis patients. In contrast, in chronic pancreatitis, some pathologic features were defined as permanent, and the condition was described as *chronic inflammatory pancreatitis*, morphologically characterized by loss of exocrine parenchyma and fibrosis with mononuclear cell infiltration. For the first time, etiology specifically was addressed, with pancreas divisum and alcohol as possible causes of acute pancreatitis.

The need for further effort to better define acute pancreatitis resulted from the observation that the terminology of the Rome meeting was conflicting and not widely applied all over the world (Lumsden & Bradley, 1990). In 1992, 40 pancreatologists met in Atlanta and developed a new, reliable classification system of acute pancreatitis (Table 52.7; Bradley, 1993). The clinical and morphologic features of pancreatitis were considered, resulting in a dynamic ongoing classification system better able to characterize the individual patient and predict disease severity.

The Zurich classification for alcoholic chronic pancreatitis (Table 52.8; Amman, 1997) specifically addresses the most common cause of the disease and gives less importance to other causes, which are sometimes difficult to diagnose, resulting in a quite complex classification system not widely adopted. In 1997, a new definition of chronic pancreatitis was published, dividing *definite* from *probable* chronic pancreatitis (Table 52.9; Homma et al, 1997). This definition provided a list of radiologic or laboratory features in chronic pancreatitis patients lacking etiologic and pathogenetic features. The TIGAR-O risk factor classification system (***t***oxic-metabolic, ***i***diopathic, ***g***enetic, ***a***utoimmune, ***r***ecurrent severe, ***o***bstructive) (Table 52.10), provides a complete overview of the risk factors for chronic pancreatitis development with special attention to the relationship between acute and chronic disease (Etemad & Whitcomb, 2001). In recent years, two main three-stage categorization systems have been mainly proposed: the ABC system (Ramesh, 2002) and the Manchester classification

Table 52.4

Grading of Chronic Pancreatitis by Endoscopic Retrograde Cholangiopancreatography

Normal	Visualization of the gland without abnormal signs
Equivocal	<3 abnormal branches
Mild	>3 abnormal branches
Moderate	Above + abnormal main duct
Marked	Above + ≥1 of: Cavity >10 mm Intraductal filling defects Calculi/pancreatic calcification Duct obstruction (stricture) Severe duct dilation or irregularity Contiguous organ invasion on ultrasound or CT

CT, Computed tomography

Modified from Sarner M, Cotton PB, 1984: Classification of pancreatitis. Gut 25:756-759.

Table 52.5

Revised Marseille Classification of Pancreatitis

Feature	Acute Pancreatitis	Chronic Pancreatitis	Special Form: Obstructive Chronic Pancreatitis
Clinical characteristics	Acute-onset abdominal pain and increase in pancreatic enzymes	Relapsing or persistent abdominal pain; occasionally painless; evidence of pancreatic insufficiency; steatorrhea or diabetes may be present	
Morphologic characteristics	Mild form: interstitial edema, pancreatic necrosis absent; possible peripancreatic fat necrosis	Irregular sclerosis with focal, segmental, or diffuse destruction and permanent loss of exocrine parenchyma; varying degrees of dilation of segments of the ductal system; protein plugs, intraductal calculi, edema, focal necrosis, inflammatory cells, cysts, and pseudocysts; islets of Langerhans are relatively well preserved The following descriptive terms can be used: *chronic pancreatitis with focal necrosis, chronic pancreatitis with segmental or diffuse fibrosis, chronic pancreatitis with or without calculi*	Dilation of the ductal system proximal to occlusion of one of the main ducts (e.g., by tumor or scar)
	Severe form: extensive peripancreatic and extrapancreatic fat necrosis, parenchymal necrosis, and hemorrhage; lesions may be either localized or diffuse		
Course	Usually benign, but severe forms may be fatal; seen as a single episode or recurrent disease; exocrine and endocrine functions impaired to a variable degree for a variable duration Restitution to normal occurs if primary cause and complications are removed; rarely, acute pancreatitis may lead to chronic pancreatitis	Progressive and permanent loss of pancreatic exocrine and endocrine function Further investigation needed about the possibility to regress after removal of primary cause	Structural and functional changes tend to improve when the obstruction is removed

From Singer MV, et al, 1985: Revised classification of pancreatitis: report of the Second International Symposium on the classification of pancreatitis in Marseille, France, March 28-30, 1984. Gastroenterology 89:683-690.

Table 52.6

Marseille-Rome Classification of Pancreatitis

Feature	Acute Pancreatitis	Chronic Pancreatitis	Chronic Inflammatory Pancreatitis
Clinical characteristics	Not defined	First stages: attacks of acute pancreatitis responsible for recurrent pain, which may be the only clinical symptom Generally, after some years, exocrine and endocrine insufficiency develop; acute attacks decrease and disappear	
Morphologic characteristics	Edema, necrosis, hemorrhagic necrosis, fatty necrosis	*Chronic calcifying pancreatitis:* irregular fibrosis, lobular spotty distribution of lesions of different density in between neighboring lobules; intraductal protein precipitates or plugs are always found and, at least in late stages, calcified precipitates (calculi) Atrophy and stenosis of duct frequent, more often than in the obstructive form; structural and functional changes may progress, even if primary cause is removed *Chronic obstructive pancreatitis:* as defined by the revised Marseille meeting (1984).	Loss of exocrine parenchyma, replaced by a dense fibrosis infiltrated by mononuclear cells —
Etiology	Extrapancreatic: gallstones, trauma, drugs, surgery, ERCP, hyperlipoproteinemia	Chronic alcohol consumption, high-protein diet, abnormally low or high-lipid diets frequently associated with disease and probably represent etiologic factors, as does hypercalcemia	—
	Intrapancreatic: tumors, chronic pancreatitis, pancreas divisum (?), alcohol (?)	Other clinical forms: *nonalcoholic, tropical, hereditary*	—
Course	Generally considered reversible; necrosis may be infected; fluid collection filled with pancreatic juice, blood, and necrotic fragments may follow; pseudocysts may form If necrosis involves a segment of the main pancreatic duct, stenosis may result, leading to obstructive chronic pancreatitis distal to necrosis	Generally progresses from painful to painless disease; may progress despite removal of cause Intrapancreatic retention cysts form when these cysts expand into peripancreatic tissues; necrotic pseudocysts form after an acute exacerbation; infected cysts or pseudocysts, called *abscesses,* form	—

ERCP, endoscopic retrograde cholangiopancreatography

Modified from Sarles H, Et Al, 1989: The classification of pancreatitis and definition of pancreatic disease. Digestion 43:234-236.

Table 52.7

Atlanta Classification

Terminology	Definition	Clinical Manifestation	Pathology
Acute pancreatitis	Acute inflammatory process with involvement of other organs	Mild with minimal organ involvement; severe disease characterized by organ failure	Interstitial edema, intrapancreatic or extrapancreatic necrosis
Acute fluid collections	Occur early, lack a wall	30% to 50% in severe pancreatitis	Absence of well-defined wall
Pancreatic necrosis	Devitalized pancreatic parenchyma	Multiorgan failure	Extensive vessel, acinar cell, islet cell, and pancreatic duct damage
Postacute pseudocysts	Nonepithelialized collection of pancreatic juice	Main symptom pain; rarely palpable	Well-defined wall with clear, often sterile contents
Pancreatic abscess	Circumscribed intraabdominal collection of pus	If present, infection	Pus confined within a wall of granulation tissue

Modified from Bradley EL 3rd, 1993: A clinically based classification system for acute pancreatitis. Arch Surg 128:586-590.

Table 52.8

Zurich Classification for Alcoholic Chronic Pancreatitis

Definite Alcoholic Chronic Pancreatitis	Probable Alcoholic Chronic Pancreatitis
In addition to a typical history or a history of excessive alcohol intake (≥80 g/day), ≥1 of the following criteria establish the diagnosis: • Calcification in the pancreas • Moderate to marked ductal lesions (Cambridge criteria) • Marked exocrine insufficiency defined as steatorrhea (>7 g fat/24 h) normalized or markedly reduced by enzyme supplementation • Typical histology of an adequate surgical specimen	In addition to a typical history or a history of excessive alcohol intake (≥80 g/day), the diagnosis of probable chronic pancreatitis is likely if any of the following criteria are present: • Mild ductal alterations (Cambridge criteria) • Recurrent or persistent pseudocysts • Pathologic secretin test • Endocrine insufficiency

Etiologic Factors*

Alcoholic chronic pancreatitis
Nonalcoholic chronic pancreatitis
Tropical (nutritional) chronic pancreatitis
Hereditary chronic pancreatitis
Metabolic (hypercalcemic, hypertriglyceridemic) chronic pancreatitis
Idiopathic (early and late onset) chronic pancreatitis
Autoimmune chronic pancreatitis
Chronic pancreatitis resulting from miscellaneous causes (e.g., radiation injury, phenacetin abuse)
Chronic pancreatitis associated with anatomic abnormalities (anatomic chronic pancreatitis—periampullary duodenal wall cysts, pancreas divisum, obstructive pancreatitis, posttraumatic pancreatic duct scars)

Clinical Staging

Early stage: recurrent attacks of clinical alcoholic acute pancreatitis (with or without local complications) without evidence of chronic pancreatitis abnormalities
Late stage: any evidence of probable or definite chronic pancreatitis

*These diagnostic definitions also may be used for nonalcoholic chronic pancreatitis.

From Amman RW, 1997: A clinically based classification system for alcoholic chronic pancreatitis: summary of an international workshop on chronic pancreatitis. Pancreas 14:215-221.

Table 52.9

Diagnostic Criteria for Chronic Pancreatitis from the Japan Pancreas Society

Definite Chronic Pancreatitis	Probable Chronic Pancreatitis
Ultrasound: pancreatic stones evidenced by intrapancreatic hyperreflective echoes with acoustic shadows behind	Ultrasound: intrapancreatic coarse hyperreflective echoes, irregular dilation of pancreatic ducts, or pancreatic deformity with irregular contour
CT: pancreatic stones evidenced by intrapancreatic calcifications	CT: pancreatic deformity with irregular contour
ERCP: irregular dilation of pancreatic duct branches of variable intensity with scattered distribution throughout the entire pancreas or irregular dilation of the main pancreatic duct and branches proximal to complete or incomplete obstruction of the main pancreatic duct (with pancreatic stones or protein plugs)	ERCP: irregular dilation of the main pancreatic duct alone; intraductal filling defects suggest noncalcified pancreatic stones or protein plugs
Secretin test: abnormally low bicarbonate concentration combined with either decreased enzyme outputs or decreased secretory volume	Secretin test: abnormally low bicarbonate concentration alone or decreased enzyme output plus decreased secretory volume; tubeless tests: simultaneous abnormalities in benzoyl-tyrosyl-p-amino benzoic acid and fecal chymotrypsin tests observed at two points several months apart
Histologic examination: irregular fibrosis with destruction and loss of exocrine parenchyma in tissue specimens obtained by biopsy, surgery, or autopsy; fibrosis with an irregular and patchy distribution in the interlobular spaces; intralobular fibrosis alone not specific for chronic pancreatitis	Histologic examination: intralobular fibrosis with one of the following findings: loss of exocrine parenchyma, isolated islets of Langerhans, or pseudocysts
Protein plugs, pancreatic stones, dilation of the pancreatic ducts, hyperplasia and metaplasia of the ductal epithelium, and cyst formation	

CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography

Modified from Homma T, et al, 1997: Diagnostic criteria for chronic pancreatitis by the Japan Pancreas Society. Pancreas 15:14-15.

Table 52.10

TIGAR-O Classification System for Chronic Pancreatitis

Toxic-Metabolic	Idiopathic	Genetic	Autoimmune	Recurrent and Severe Acute	Obstructive
Alcoholic Tobacco smoking Hypercalcemia Hyperlipidemia Chronic renal failure Medications (phenacetin abuse) Toxins (organotin compounds)	Early onset Late onset Tropical (tropical calcific and fibrocalculous pancreatic diabetes) Other	Autosomal dominant: cationic trypsinogen gene (codon 29 and 122 mutations) Autosomal recessive/modifier genes: *CFTR* mutations, *SPINK1* mutations, cationic trypsinogen (codon 16, 22, and 23 mutations), α_1-antitrypsin deficiency possible	Isolated autoimmune chronic pancreatitis Syndromic autoimmune chronic pancreatitis (Sjögren syndrome–associated, inflammatory disease–associated, primary biliary cirrhosis–associated)	Postnecrotic (severe acute pancreatitis) Recurrent acute pancreatitis Vascular disease/ischemic Radiation injury	Pancreas divisum Sphincter of Oddi disorders (controversial) Duct obstruction (e.g., tumor) Periampullary duodenal wall cysts Posttraumatic pancreatic duct scars

CFTR, cystic fibrosis transmembrane conductance regulator; *SPINK1*, serine protease inhibitor, Kazal type 1

Modified from Etemad B, Whitcomb DC, 2001: Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology 120:682-707.

(Table 52.11; Bagul & Siriwardena, 2006). The aim of these systems is to provide an accurate description of chronic pancreatitis, underlining different therapeutic approaches and prognoses depending on disease stage. The ABC system divides patients into grades depending on the presence or absence of abdominal pain, complications, and deficiency in pancreatic function. The Manchester classification uses the terms *mild*, *moderate*, and *end stage* to represent disease progression, allowing comparison between patient groups.

Table 52.11

Manchester Classification System for Chronic Pancreatitis

Mild: Five Essential Criteria

1. ERP/MRP/CT evidence of chronic pancreatitis
2. Abdominal pain
3. No regular analgesia
4. Preserved endocrine and exocrine function
5. No peripancreatic complications

Moderate: Five Essential Criteria

1. ERP/MRP/CT evidence of chronic pancreatitis
2. Abdominal pain
3. Regular (weekly) opiates
4. Evidence of impaired endocrine/exocrine function
5. No peripancreatic complications

End Stage

1. ERP/MRP/CT evidence of chronic pancreatitis
2. One or more of the following "extrapancreatic features"
   - i. Biliary stricture
   - ii. Segmental portal hypertension
   - iii. Duodenal stenosis
3. Plus one or more of the following
   - i. Diabetes
   - ii. Steatorrhea

Note that abdominal pain may or may not be present.
ERP, endoscopic retrograde pancreatography; MRP, magnetic resonance pancreatography; CT, computed tomography

Modified from Bagul A, Siriwardena AK, 2006: Evaluation of the Manchester Classification System for Chronic Pancreatitis. J Pancreas (Online) 7(4):390-396.

The most recent classification attempt is represented by the M-ANNHEIM multiple risk factor system (Table 52.12), aimed to provide a standardized method for the clinical diagnosis of chronic pancreatitis according to etiology, clinical stage, and severity of disease and to direct clinical practice (Schneider et al, 2007).

It is therefore evident how all these more recent advances in the "definition dilemma" abandoned the mere clinical purpose of a classification to better investigate different specific features of this complex disease. The classification systems will likely come full circle with the recognition of the deep but still controversial correlation between acute and chronic inflammation.

FUTURE PERSPECTIVES

The history of every patient must be carefully considered to identify risk factors that may include alcohol abuse, obstruction, genetics, and autoimmune disease. The clinical evidence of pancreas-related abdominal pain associated with alterations of serum amylase and lipase led to the term *pancreatitis*. The ongoing clinical observations obtained with imaging studies that include ultrasound, CT, and especially MRI of the bile ducts and duct of Wirsung should address the required treatment patient by patient. The early stage is the most difficult to diagnose, but it is also important to give the right medical or surgical option. Only the dynamic observation of patients with controlled follow-up enables us to classify pancreatitis and to define the disease better, assigning the definitive labels supported by the biochemical and radiologic sources well characterized by the different classification systems available. The clinician should recognize pancreatitis at an early stage but avoid assigning a definitive classification immediately, instead investigating all the factors available to determine whether a first acute attack could lead to chronic changes with fibrosis, permanent disruptions, and exocrine endocrine insufficiency.

References are available at expertconsult.com.

Table 52.12

The M-ANNHEIM Multiple Risk Factor Classification System

Multiple Risk Factor Classification	Clinical Staging of Chronic Pancreatitis
Alcohol consumption	*Asymptomatic chronic pancreatitis*
Nicotine consumption	0. Stage of subclinical chronic pancreatitis
Nutritional factors	*Symptomatic chronic pancreatitis*
Hereditary factors	I. Stage without pancreatic insufficiency
Efferent duct factors	II. Stage of partial pancreatic insufficiency
Immunologic factors	III. Stage of painful complete pancreatic insufficiency
Miscellaneous and rare metabolic factors	IV. Stage of secondary painless disease (burnout)

Diagnostic Criteria of Chronic Pancreatitis

The diagnosis requires a typical clinical history of chronic pancreatitis, such as recurrent pancreatitis or abdominal pain, except for primary painless pancreatitis. Based on these features, the three forms of chronic pancreatitis are 1) definite chronic pancreatitis, 2) probable chronic pancreatitis, and 3) borderline chronic pancreatitis.

Scoring System for the Grading of Clinical Features of Chronic Pancreatitis	Points
Patient report of pain	0-4
Pain control	0-2
Surgical intervention	0 or 4
Exocrine insufficiency	0-2
Endocrine insufficiency	0 or 4
Morphologic status on pancreatic imaging	0-4
Severe organ complications	0, 2, or 4

Severity Index of Chronic Pancreatitis

Severity Level	*Point Range*
M-Annheim A Minor	0-5 Points
M-Annheim B Increased	6-10 points
M-Annheim C Advanced	11-15 points
M-Annheim D Marked	16-20 points
M-Annheim E Exacerbated	>20 points

Modified from Schneider A, Lohr JM, Singer MV, 2007: The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system based on a review of previous classification of the disease. J Gastroenterol 42:101-119.

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CHAPTER 53

Etiology, pathogenesis, and diagnostic assessment of acute pancreatitis

Julia V. Mayerle, Colin J. McKay, Clem W. Imrie, and Markus M. Lerch

OVERVIEW

The incidence of acute pancreatitis ranges from 10 to 46 cases a year per 100,000. For 2004, per 100,000 population, 94 cases of pancreatitis were listed as the hospital discharge diagnosis, suggesting an increasing incidence in the United States. Pancreatitis was the eleventh most common cause of death from digestive diseases and the fifth most common nonmalignant cause for mortality, just after peptic ulcer disease (Everhart & Ruhl, 2009). The mortality rate of acute edematous interstitial (mild) pancreatitis is less than 1%, whereas in patients with hemorrhagic necrotizing (severe) pancreatitis, it is reported to be between 10% and 24% (see Chapter 52). Clinically acute pancreatitis thus affects a heterogeneous group of patients in whom determining the etiology, severity assessment at admission, and triage to either symptomatic or intensive care treatment remains a significant challenge.

ETIOLOGY AND PATHOGENESIS OF ACUTE PANCREATITIS

Pancreatitis is an inflammatory disorder of the exocrine pancreas caused, in most cases, by immoderate alcohol consumption or the passage of gallstones (see Chapters 30 and 35). Recent studies involving animal and isolated cell models have elucidated many of the pathophysiologic, cellular, and molecular processes involved in the disease onset. More than 100 years ago, it was proposed that pancreatitis was essentially a disease in which the pancreas falls prey to its own, prematurely activated digestive enzymes regardless of the underlying etiology (Chiari, 1896).

Etiology and Pathogenesis of Acute Biliary Pancreatitis

In roughly 30% of acute pancreatitis cases, gallstone disease is the underlying cause. The prevalence of gallstones is 18.8% (Volzke et al, 2005), which puts nearly one fifth of the population at risk of developing an acute episode of biliary pancreatitis at some point in their lifetime. Although a male/female ratio of 1:3 exists for gallstone disease, acute biliary pancreatitis is observed with a ratio of 1:1.4 to 1:1.7, suggesting that men with gallstones are at a greater risk of developing biliary pancreatitis than women with gallstones. Further studies have shown that the gender ratio changes with age. Imrie and colleagues reported a male/female ratio of 1:2.7 in younger patients with gallstone pancreatitis, whereas the ratio changed to 1:1.1 in patients older than 50 years. In the group between 60 and 70 years of age, the gender predominance was reversed; more men than women had biliary pancreatitis (Imrie & Blumgart, 1975; Imrie & Whyte, 1975).

Lankisch studied the epidemiology of acute pancreatitis and reported a worldwide predominance of alcohol-induced pancreatitis (36%) over biliary pancreatitis (28.1%). In the United Kingdom, biliary pancreatitis is more common than alcoholic pancreatitis, whereas the United States reports a steady increase in alcoholic pancreatitis, and in Sweden a shift from biliary pancreatitis to alcoholic pancreatitis over the last 50 years has also been observed. The socioeconomic impact of gallstone disease remains one of the highest in gastroenterology, in spite of the fact that the risk of developing pancreatitis remains well below 1% for gallstone carriers.

Ever since 1856, when Claude Bernard reported that bile injection into the pancreatic duct of laboratory animals leads to acute pancreatitis, the pathophysiology of gallstone pancreatitis has been a matter of dispute (Bernard, 1856; Lerch & Aghdassi, 2009). The first investigator to systematically address the issue of biliary pancreatitis was Eugene Lindsay Opie, who in 1901 published two autopsy reports, from which he concluded that two mutually exclusive triggering mechanisms exist for gallstone-induced pancreatitis (Opie, 1901a, 1901b). He tried to support his hypotheses with a series of animal studies. The first autopsy report showed that an impacted gallstone had occluded the orifice of the pancreatic duct, and the patient had died from acute pancreatitis (Opie, 1901a). When Opie simulated this finding by pancreatic duct ligation in cats, he noted the development of pancreatic tissue and fat necrosis and proposed pancreatic outflow obstruction as the triggering event for acute pancreatitis. Unfortunately, his first "impaired outflow hypothesis" was rapidly forgotten after he published his second hypothesis.

In another patient who underwent a postmortem examination, Opie found a distinctly different anatomic situation, which he regarded to be of pathophysiologic relevance. The impacted stone at the papilla of Vater had created a communication between the common bile duct and the main pancreatic duct that would have permitted the patient's bile to enter the pancreatic duct. Opie proposed the presence of infected bile in the pancreatic duct as the triggering mechanism of pancreatitis, the so-called *common channel hypothesis*. We and others have tested Opie's common channel hypothesis in the past, using the opossum model of acute necrotizing pancreatitis. This model appears ideally suited to test whether bile reflux into the pancreatic duct or blockage of pancreatic secretion triggers pancreatitis because the opossum not only possesses a gallbladder, a common bile duct, and a single pancreatic duct but also has a

long communication between the two ductal systems. If this common channel is ligated at the papilla of Vater, it creates a communication between the pancreatic and bile ducts, through which bile could potentially flow (Lerch et al, 1992).

Our experiments consistently showed that neither a common channel nor reflux of bile into the pancreas is required for the onset of acute necrotizing pancreatitis (Lerch et al, 1993), but pancreatic duct ligation is sufficient for triggering the disease. For obvious reasons, no controlled experiments in humans that would replicate the opossum data are possible; however, support comes from case observations in which unique anatomic situations allow for pathophysiologic interpretations (Lerch et al, 1994a, 1994b; Pohle et al, 2003). One of these cases is that of a young woman in whom an impacted gallstone at the papilla had caused acute pancreatitis, and a surgically inserted common bile duct T-tube had prevented any potential bile reflux into the pancreas (Lerch et al, 1994a, 1994b; Pohle et al, 2003). This case demonstrates further that therapeutic measures aimed at preventing bile reflux through a common channel will not afford protection against pancreatitis, but those aimed at preventing pancreatic duct obstruction will (Lerch et al, 1994a).

Patients in whom congenital biliopancreatic fistulas have caused a life-long flow of bile through the pancreatic duct without ever causing pancreatitis provide more arguments against Opie's common channel theory (Lerch et al, 1994b; Pohle et al, 2003). Although these studies and observations firmly put the blame for gallstone pancreatitis on the mechanisms that involve impairment of pancreatic outflow, rather than bile reflux into the pancreatic duct, there may still be a role for cholestasis in regulating its severity. Senninger and colleagues (1996) found in the opossum model that bile duct obstruction in addition to pancreatic duct ligation can aggravate pancreatitis, and two groups found independently that increased bile acid concentrations, such as those in cholestasis, can increase the susceptibility of pancreatic cells to injury (Kim et al, 2002; Perides et al, 2009; Voronina et al, 2002, 2004, 2005).

Experimental studies and reports from human case series have tried to elucidate the mechanisms through which migrating gallstones cause pancreatitis. In spite of its former popularity, Opie's common channel hypothesis of bile reflux into the pancreatic duct appears no longer valid; the *duodenal content reflux hypothesis* has also been firmly refuted in human studies (Hernandez & Lerch, 1993). The most accurate description of the pathophysiology of gallstone pancreatitis is based in Opie's original report, in which he proposes pancreatic outflow obstruction as the most critical event for the disease onset. To what extent cholestasis and circulating bile acids contribute to acinar cell injury in humans and what factors determine the ultimate disease severity must be elucidated by future investigations.

Etiology and Pathogenesis of Acute Alcoholic Pancreatitis

Alcohol abuse is a major cause of acute pancreatitis and the leading cause of chronic pancreatitis. Although the incidence of pancreatic disease increases as a function of the extent of alcohol abuse in a population, only a minority of subjects who greatly abuse alcohol develop pancreatitis. According to studies from Marseille (Levy et al, 1995), the logarithm of the relative risk of pancreatitis increases linearly as a function of the quantity of alcohol and protein consumed. Unlike the liver, no alcohol toxicity threshold has been established beyond which the pancreas is damaged. Furthermore, the type of alcoholic beverages consumed appears to be less relevant. Patients with pancreatitis and alcohol-induced liver cirrhosis do not generally differ with regard to their daily intake of alcohol. However, the duration of alcohol consumption is shorter in pancreatitis. In most studies the time between the onset of alcohol abuse and first pancreatitis symptoms ranges from 7 to 29 years. The prevalence of pancreatitis clearly correlates with the alcohol consumption in a given population (Ammann & Muellhaupt, 1994).

The mechanisms involved in alcohol-induced pancreatitis have been extensively studied in ethanol-fed laboratory animals. Although a number of biologic cell changes have been reported from these studies, their relevance to the human disease is questionable, because neither rats nor mice develop pancreatitis when fed a high-alcohol diet over an extended time. Animal studies have led to the working hypothesis that alcohol abuse sensitizes individuals to pancreatitis but does not directly cause the disease. Experimentally, ethanol can mediate its damaging effect on pancreatic acinar cells through several mechanisms. First, ethanol affects the inflammatory signaling cascade in pancreatic acini, namely the NF-κB pathway (Tando et al, 1999). Furthermore, ethanol feeding results in a decrease of in the expression and/or activity of both "initiator" and "executioner" caspases, leading to cell death (Fortunato et al, 2006).

Recent studies observing the effect of ethanol on the intracellular activation of digestive protease zymogen were rather successful in elucidating potentially disease-relevant mechanisms. Ethanol feeding enhanced the expression and activity of cathepsin B, which catalyzes 80% of the intracellular trypsinogen activation and results in active trypsin and, ultimately, cell necrosis (Fortunato et al, 2006; Halangk et al, 2000).

A number of studies found that ethanol can sensitize acinar cells to cholecystokinin (CCK)-induced procarboxypeptidase A1 processing in vitro, and it can also sensitize the pancreas to various forms of pancreatitis in vivo (Katz et al, 1996; Pandol et al, 1999; Saluja et al, 1997). Thus ethanol is believed to enhance the pathophysiologic stimuli that induce pancreatitis, and this process may explain the effects of ethanol toxicity on the pancreas.

A recent study addressed several issues relevant to zymogen activation and the effects of ethanol in isolated pancreatic acini (Gorelick, 2003). Trypsinogen and chymotrypsinogen were observed to exhibit distinct patterns of activation in response to supraphysiologic concentrations of the CCK-analogue cerulein, supraphysiologic concentrations of which are known to cause calcium-dependent intracellular protease activation and cell death; this model is regarded as *in vitro pancreatitis.* Moreover, ethanol and other alcohols were shown to sensitize acinar cells to cerulein-induced trypsin and chymotrypsin activation, and other short-chain n-aliphatic alcohols—methanol, propanol, and butanol—enhanced the effects of cerulein on the acinar cell. Ethanol alone, on the other hand, was not found to induce pancreatitis or zymogen activation in experimental models of pancreatitis (Lu et al, 2002; Ramo, 1987).

The aforementioned descriptions of the effects of alcohol on the pancreas do not take into consideration the unique metabolism of ethanol in the pancreas. The pancreas differs from the liver in that it transiently converts ethanol to fatty acid ethyl esters (FAEEs) (Gukovskaya et al, 2002; Werner et al, 1997). Recent data suggest that FAEEs cause sustained increases in the cytosolic calcium concentrations, which are closely connected

to the premature activation of zymogens, as well as mitochondrial injury, subsequently leading to necrotic cell death (Ponnappa et al, 1997).

In summary, ethanol and its metabolites have multiple effects on the pancreas that are involved in sensitizing the pancreas to pathologic stimuli. These include effects on inflammatory and cell death signaling pathway that can promote inflammation and necrosis. Mainly identified in animal models, the findings are consistent with a recent report that indicates alcohol abuse in humans is a risk factor for pancreatic necrosis during pancreatitis (Papachristou et al, 2006).

Etiology and Pathogenesis of Nonalcoholic and Nonbiliary Pancreatitis

Several other disease-causing factors have previously been elucidated. The following paragraph briefly outlines metabolic changes—such as hyperlipidemia or hypercalcemia—infectious agents, and drugs involved in the onset of acute pancreatitis. Furthermore, genetic alterations that are either closely linked or associated with an increased susceptibility to pancreatitis are discussed.

Hyperlipidemia

As with other forms of acute pancreatitis, acute hyperlipidemic pancreatitis presents clinically with varying degrees of severity. Complications typical of acute pancreatitis, such as infected necrosis and pseudocyst formation, also occur in pancreatitis triggered by hypertriglyceridemia (Toskes, 1990). According to Fortson and colleagues (1995), patients coming to medical attention with hyperlipidemic pancreatitis fit one of the following clinical scenarios: they are either patients whose diabetes mellitus is out of control; alcoholics with a lactescent serum; nondiabetic, nonalcoholic, nonobese patients with hypertriglyceridemia caused by nutrition or medication; or patients with familial hypertriglyceridemia.

The diagnosis of acute hyperlipidemic pancreatitis is made as for other etiologies of this disease. However, a few important peculiarities must be considered, such as a lipemic serum that signals hyperlipemic pancreatitis. It is also striking that in more than 50% of patients, serum and urinary amylase levels remain within the normal range (Lesser & Warshaw, 1975). The reason for this phenomenon has long been suspected to be an interference of the test assay with the plasma lipids or an unknown amylase inhibitor in plasma and urine that impairs the assay. This inhibitor has not been identified so far (Fallat et al, 1973; Warshaw et al, 1975). Although during the course of hyperlipemic pancreatitis, serum amylase levels may remain normal, renal amylase clearance increases. In the past, a higher ratio in amylase/creatinine clearance in the urine has been shown to be a diagnostic parameter of hyperlipemic pancreatitis (Fallat et al, 1973; Warshaw et al, 1975); however, this method has not entered clinical routine. Triglycerides are usually above 1000 mg/dL, and when enteral nutrition regimens cannot lower triglyceride levels below that level within 2 days, sometimes even extracorporeal lipid-lowering therapies should be considered (Iskandar & Olive, 2004).

Drug-Induced Pancreatitis

A database of the World Health Organization (WHO) lists 525 drugs that can, as an adverse reaction, induce acute pancreatitis (Table 53.1). Compared with other causes, drugs represent a relatively rare cause of pancreatitis. They should be regarded as a triggering event in patients with no other identifiable cause of the disease who take medications that have been shown to induce pancreatitis. The prevalence of drug-induced pancreatitis is still unclear because most incidences have been documented only as isolated case reports. The overall incidence probably ranges somewhere between 0.1% and 2% of pancreatitis cases.

For only very few substances, evidence from controlled trials has been obtained. Epidemiologic data suggest that the risk of pancreatitis is highest for mesalazine (hazard ratio [HR], 3.5), azathioprine (HR, 2.5), and simvastatine (HR, 1.8). Even when a definite association has been demonstrated, it is often impossible to determine whether the drug or the underlying condition for which the drug was taken has conferred the risk of pancreatitis (e.g., azathioprine and Crohn disease or pentamidine and HIV). Knowledge about the underlying pathophysiologic mechanisms and evidence for a direct causality often remains sparse. A definite causality has been established for only 31 drugs, although a cause-effect relationship is generally accepted when symptoms recur upon rechallenge. Available data from case control studies suggest that even drugs with solid evidence for an association with pancreatitis only rarely cause the disease. Even when pancreatitis is induced as an adverse drug event, the disease course is usually mild or even subclinical (Nitsche et al, 2010).

Infectious Causes

A number of viral, bacterial, parasitic, and fungal infections have been linked to acute pancreatitis (Parenti et al, 1996). As early as 1817, infection with mumps has been suspected as a cause of pancreatitis; in 1905, Lemoine described a patient whose symptoms were those typical of mumps who also had acute pancreatitis. Today, acute pancreatitis as part of an infectious disease has to be distinguished from an infectious complication of acute pancreatitis that occurs regardless of the underlying etiology. The incidence of acute pancreatitis in connection with infectious diseases is difficult to determine, as there are hardly any prospective studies, but an incidence of less than 2% is generally assumed. In many cases, somewhat increased amylase and lipase levels are described in the course of an infectious disease, and the patient is often prematurely diagnosed with pancreatitis; however, often no other evidence for pancreatitis is present, either clinically or on imaging studies (Parenti et al, 1996).

The most frequent association of a viral infection with acute pancreatitis is mumps. The incidence of pancreatitis associated with mumps (parvovirus B19) is 0.3% to 14% according to the relevant literature (Kaplan et al, 1988; Witte & Schanzer, 1968). Acute pancreatitis mainly occurs after the swelling of the parotid gland has subsided, usually 8 to 14 days after the initial onset of the disease. Every now and then, acute pancreatitis occurs up to 1 week prior to parotitis. In rare individual cases, acute pancreatitis has been reported as the only manifestation of a mumps infection (Kaplan et al, 1988; Witte & Schanzer, 1968). Acute pancreatitis associated with mumps is usually mild, with symptoms that normally persist only 3 to 7 days. For a laboratory-based diagnosis of acute pancreatitis, lipase activity should be measured. Amylase measurements may result in an incorrect diagnosis because increased activity may be due to amylase from affected salivary glands and may not necessarily reflect acute pancreatitis. There is no specific therapy for either mumps infection or for acute pancreatitis associated with mumps (Kaplan et al, 1988; Witte & Schanzer, 1968).

Table 53.1

Drugs with a Probable or Definite Association to Pancreatitis as Reported in Case Report Summaries

		TRIVEDI & PITCHUMONI (2005)		ELAND ET AL (1999)		ANDERSEN ET AL (2001)		LANKISCH ET AL (1995)	
Causality	Medication	No. of Cases	Reexposure	No. of Cases	Reexposure	No. of Cases	Reexposure	No. of Cases	Reexposure
Definite	Acetaminophen	13	1						
	Asparaginase	177	2						
	Azathioprine	86	16	4	2	5	2	6	2
	Cimetidine			1	1				
	Cisplatin	11	1						
	Cytarabine	26	4						
	Didanosine	883	9						
	Enalapril	12	2						
	Erythromycin	11	1						
	Estrogens	42	11						
	Furosemide	21	3						
	Hydrochlorothiazide	12	1						
	Interferon-α2b	12	2	1	1				
	Lamivudine	19	1						
	Mercaptopurine	69	10						
	Mesalazine/ molsalazine	59	12	1	1	9	3	5	1
	Methyldopa			2	2				
	Metronidazole			1	1				
	Octreotide	16	4						
	Opiates	42	5						
	Oxyphenbutazone			1	1				
	Pentamidine	79	2						
	Pentavalent antimonials	80	14						
	Phenformin	13	1						
	Simvastatin					1	1		
	Steroids	25	1						
	Sulfasalazine	23	5						
	Sulfmethoxazole/ trimethoprim	24	1						
	Sulindac	21	8						
	Tetracycline	34	2						
	Valproic acid	80	11						
Probable	Carbamazepine	14	0						
	Cyclopenthiazide	11	0						
	Didanosine							1	0
	Doxycycline			1	0				
	Enalapril			1	0				
	Estrogens							1	0
	Famotidine			1	0				
	Furosemide							1	0
	Hydrochlorothiazide							1	0
	Maprotiline			1	0				
	Mesalazine			3	0				
	Rifampin	25	0					1	0
	Sulindac			1	0				

The second most common viral infection associated with pancreatitis is coxsackievirus B. During a coxsackievirus type B5 aseptic meningitis epidemic in Japan, 31% of patients showed an increase in amylase activity in serum or urine (Nakao et al, 1964). During an epidemic of coxsackievirus type B4 infection in Australia, acute pancreatitis could be confirmed in 3% of the patients (Murphy & Simmul, 1964). In prospective and retrospective serologic studies, coxsackie virus infections were found in 0% to 11% of patients with positive titers for acute pancreatitis (Parenti et al, 1996). In mouse experiments, acute pancreatitis has successfully been induced with coxsackie viruses; a direct infection of acinar and islet cells with the virus led to an inflammatory reaction and necrosis.

An acute infection with hepatitis virus A, B, or C may result in a secondary infection of the pancreas (Achord, 1968). When a mild form of acute hepatitis occurs, an increase in amylase activity can be detected in up to 30% of patients. When the course of acute hepatitis was severe and ultimately lethal, acute pancreatitis was confirmed on autopsy in up to 44% of patients.

Autopsy studies have detected pathologic changes of the pancreas in up to 50% of patients who died from AIDS. Similarly, 50% of HIV patients showed elevated amylase levels and clinical signs of acute pancreatitis (Cappell & Hassan, 1993; Pezzilli et al, 1992). However, a number of factors could have caused hyperamylasemia and acute pancreatitis in patients with HIV. Apart from damage caused by the virus itself, a nonspecific amylase elevation as a result of renal insufficiency or amylase elevations may be caused by extrapancreatic factors, such as damage to the salivary glands; an infection of the pancreas through opportunistic infections; a medication-induced etiology, especially didanosine (ddI); or a pancreatic neoplasm (Cappell & Hassan, 1993).

Individual case reports have been published on acute pancreatitis in association with infections with Epstein-Barr virus, rubella, adenovirus, rubeola, herpes simplex virus, rotavirus, and after mumps vaccinations (Parenti et al, 1996).

Several bacterial infections have been found in association with acute pancreatitis, such as *Yersinia enterocolitica* and *Y. pseudotuberculosis, Salmonella enteritis* and *S. typhimurium, Campylobacter jejuni,* and *Mycoplasma pneumoniae*. Of those with yersiniosis, 2% to 14% were diagnosed with secondary acute pancreatitis. In these patients, serotypes 3 and 9 (*Y. enterocolitica*) and IA (*Y. pseudotuberculosis*) were isolated. The majority of these patients also had gastroenteritis, and the course of pancreatitis was mild in all cases (Leino et al, 1987; Saebo & Lassen, 1991). Elevated serum amylase and lipase levels in serum were diagnosed in 43% of the patients with confirmed *S. typhimurium* and in 71% of the patients with *S. enteritidis* infection. In approximately half of these patients, signs of acute pancreatitis were detected by ultrasound examination (Hermans et al, 1991). Acute pancreatitis induced by a *Campylobacter* infection is a rare event, with reports on approximately 20 cases in the literature. Amylase and lipase levels elevated three to six times above normal were reported, but the course of the acute pancreatitis was again mild in all cases (Hermans et al, 1991).

Parasites are known to be a relevant cause of acute pancreatitis, mainly on the Indian, African, and Asian continents (see Chapter 45). The incidence of ascariasis differs from region to region worldwide but is the most common type of helminthic infection in humans. An endemic manifestation is found mainly in tropical and subtropical countries. In India, for example, ascariasis is the second most common cause of acute pancreatitis, next to gallstone pathogenesis (Parenti et al, 1996). The worms can travel from the intestines to either the biliary or pancreatic ducts, where they lead to obstruction. The obstruction of the flow from the pancreatic duct then triggers pancreatitis as proposed by Opie's first hypothesis. In addition to examining the stool for worm eggs, the disease can be diagnosed by sonography or endoscopic retrograde cholangiopancreatography (ERCP). The appropriate treatment is a combination of standard therapy for acute pancreatitis and antihelminthic therapy (Lim & Ko, 1990).

The Chinese liver fluke *Clonorchis sinensis* can lodge in the biliary tract and often does not cause symptoms for years (see Chapter 45). The endemic form of the disease is found mainly in Asia (Lim & Ko, 1990; Parenti et al, 1996). An obstruction of the biliary or pancreatic ducts is rarely caused by the presence of the worm alone. Via adenomatous proliferation and squamous metaplasia, infection by *C. sinensis* causes periductal fibrosis, which then leads to further obstruction that can result in acute pancreatitis.

Post-ERCP Pancreatitis

ERCP is an important technique in gastroenterology, used for the diagnosis and treatment of pathologic conditions in the biliary tract and the pancreatic ducts (see Chapters 27 and 28). The most common complication of this intervention is procedure-related acute pancreatitis, which occurs in 2% to 9% of ERCPs in unselected prospective studies (Freeman, 2004). The severity of post-ERCP pancreatitis can range from mild disease with full recovery to critical illness with pancreatic necrosis, multiorgan failure, prolonged hospitalization, and even death (see Chapter 52). Of all cases of post-ERCP pancreatitis, approximately 10% are severe, and up to 1% take a fatal course (Freeman, 2001). Increasing pressure in the pancreatic duct, as well as chemical injury from the injection of contrast media, may play a role in the initiation of the protease activation cascade and inflammatory response that ultimately results in procedure-related pancreatitis. Very recently a low pH of 6.9 in contrast media used for ERCP was identified as contributing to the development of post-ERCP pancreatitis via activation of the α-cation channel expressed on C and Aδ fibers of primary sensory neurons called *transient receptor potential vanilloid 1* (TRPV1) neurons (Noble et al, 2008).

GENETIC CHANGES ASSOCIATED WITH RECURRENT ATTACKS OF ACUTE PANCREATITIS

Patients without identifiable risk factors for pancreatitis are classified as having idiopathic pancreatitis. This group has been diminishing since Comfort and Steinberg reported in 1946 on an inherited form of chronic pancreatitis that follows an autosomal dominant inheritance pattern (Comfort et al, 1946). Hereditary pancreatitis represents a genetic disorder closely associated with mutations in the cationic trypsinogen gene and presents with a disease penetrance of approximately 80% (Whitcomb et al, 1996). Patients with hereditary pancreatitis develop recurrent bouts of acute pancreatitis that usually begin in early childhood and progress to chronic pancreatitis (see Chapter 55). In rare cases the disease onset can be as late as the

sixth decade of life. The severity of the acute attacks in hereditary pancreatitis ranges from mild abdominal discomfort to severe disease complicated by pancreatic necrosis, organ failure, and eventually death, although the latter course is exceedingly rare. Compared with the general population, the risk of developing pancreatic carcinoma is 50 to 60 times greater in patients with hereditary pancreatitis (Schneider et al, 2003; see Chapter 55).

Because hereditary pancreatitis represents an autosomal dominant disorder, it was suspected that the disease results from a single genetic defect that disrupts a critical component that protects pancreatic function in unaffected individuals. In 1996, Whitcomb and colleagues identified a single point mutation in the third exon of the cationic trypsinogen gene on chromosome 7 (7q35) that associates with the phenotype of hereditary pancreatitis. This guanine (G) to arginine (A) transition results in an A-R-CGC to histidine (H)-CAC substitution, referred to as *R122H*. It was predicted to eliminate a failsafe trypsin hydrolysis site that is necessary to initiate the self-destruction of activated trypsin. Since 1996, more than 20 mutations in the trypsinogen gene have been reported, but the *R122H* mutation is still the most common (Whitcomb et al, 1996).

As far as the role of premature zymogen activation is concerned, the available data from hereditary pancreatitis are inconclusive. Because trypsin activation is an event known to occur in pancreatitis, and because trypsin can activate many other digestive proteases of the pancreas in vitro, previous attempts to interpret the functional consequences of trypsinogen mutations have focused on features that would either allow for premature intracellular activation of trypsinogen or permit an extended intracellular activity of trypsin. Other studies have suggested that trypsin activity may be a critical factor for the degradation of other, much more destructive digestive proteases.

The idea of digestive protease activation dates back a century, when the pathologist Hans Chiari suggested that the pancreas of a patient who had died during an episode of acute necrotizing pancreatitis "had succumbed to its own digestive properties," and he postulated pancreatic "autodigestion" as the underlying pathophysiologic mechanism of the disease (Chiari, 1896). Although the importance of digestive proteases in the onset of pancreatitis is now undisputed, the roles of individual serine proteases in that cascade-like event, and those of the different isoforms of trypsin in particular, are still a matter of intense research and debate. Other serine proteases, such as chymotrypsin C, have been found to be associated with chronic pancreatitis but do not follow an autosomal dominant inheritance pattern (Rosendahl et al, 2008).

Shortly after the identification of mutations in the trypsinogen gene associated with chronic pancreatitis, another important observation was made by Witt and colleagues (2000), who described mutations in the *SPINK1* gene, encoding the pancreatic secretory trypsin inhibitor (PSTI) associated with idiopathic chronic pancreatitis in children. *SPINK1* mutations can often be detected in patients who do not present with a family history of pancreatitis and are devoid of any classic risk factors for chronic pancreatitis (Weiss et al, 2003). *SPINK1* is believed to form a first line of defense in inhibiting trypsin in the pancreas. The discovery of *SPINK1* mutations therefore provides additional evidence for the role of protease activation in the development of pancreatitis (Bhatia et al, 2002).

ASSESSMENT OF ACUTE PANCREATITIS

Diagnostic Assessment of Acute Pancreatitis (See Chapters 52 and 54)

The diagnosis of acute pancreatitis can be made when a patient presents with threefold elevated serum levels of amylase or lipase, abdominal pain, and vomiting. If the patient presents within 24 hours after the onset of pain, the elevated serum pancreatic enzymes predict pancreatitis with a sensitivity of 98%. Sensitivity will then steadily decline over the next 5 to 7 days; serum levels will eventually be normal or below reference levels, even in the presence of acute necrotizing pancreatitis. The specificity of amylase and lipase measurements is in the range of 90%, but upper gastrointestinal perforation, mesenteric infarction, and retroperitoneal hemorrhage can present with similar clinical symptoms and elevated pancreatic serum enzymes (Farinon et al, 1987).

Clinical Assessment of Acute Pancreatitis

A prediction of the course and outcome of the disease is needed most when a patient comes in to the emergency room, but it is often rather difficult to make such a prediction. For example, although enzymatic activity of serum amylase and lipase are used to diagnose pancreatitis, they are not helpful in determining disease severity.

Although in 75% to 80% of cases, acute pancreatitis is a mild disease without associated mortality, it is important to identify the 20% to 25% of patients who are likely to develop severe disease associated with major complications and who would benefit from early intensive care monitoring and treatment. In addition to an initial clinical assessment by an experienced gastroenterologist or surgeon, several prognostic markers and scoring systems are available that help to distinguish severe from mild disease. Severity scoring systems have been used since the 1970s, the first being the widely used Ranson criteria, closely followed by the Imrie or Glasgow severity scoring system (Imrie, 2003; Imrie & Blumgart, 1975; Ranson et al, 1974).

Mortality from acute pancreatitis has a biphasic distribution. Early death is related to the development of severe and irreversible multiorgan dysfunction, whereas late death occurs in the second phase of illness, where organ failure is associated with peripancreatic sepsis and its sequelae. Several organ dysfunction scores have been developed for use in critically ill patients. Those most commonly used in the setting of acute pancreatitis are the Multiple Organ Dysfunction Score (MODS) and the Sequential Organ Failure Assessment (SOFA; Marshall et al, 1995; Vincent et al, 1996, 2000). The main difference between MODS and SOFA lies in the evaluation of cardiovascular function. In addition to the severity of organ dysfunction and the number of organ systems involved, the dynamic nature of organ impairment has been increasingly recognized as an important variable in predicting and determining mortality from acute pancreatitis. Several authors have described the prognostic significance of distinguishing transient and persistent organ failure for predicting mortality from severe acute pancreatitis. Persistent or deteriorating multiorgan dysfunction in the first 7 days after admission is the most significant predictor of death (Buter et al, 2002; Johnson & Abu-Hilal, 2004; Mayer et al, 2000; Mofidi et al, 2006, 2009a). In addition, multiorgan dysfunction during the first week of admission is closely related to the

development of local complications of severe acute pancreatitis, such as infected necrosis, which also contributes to the biphasic distribution in mortality.

From a practical point of view, if a patient has three or more laboratory signs of organ failure, such as a fall in Po_2 or a rise in creatinine levels; if an overt extrapancreatic complication develops, such as respiratory or renal insufficiency; or if pancreatic necrosis is diagnosed by contrast-enhanced CT, the course of the disease is more likely to be severe (Balthazar et al, 1994; Mofidi et al, 2009b; Mortele et al, 2004).

Laboratory Assessment of Acute Pancreatitis

C-Reactive Protein

As a stand-alone prognostic marker, an elevated C-reactive protein (CRP) concentration of greater than 130 mg/L predicts a complicated course with a sensitivity of 85% in the first 72 hours after the onset of symptoms. Although detection of elevated CRP levels is sensitive for the severity of acute pancreatitis, it is not specific for the disease; other causes of inflammation, such as cholangitis and pneumonia, need to be ruled out before severity assessment by measurement of CRP is undertaken (Buchler et al, 1986).

Trypsinogen and Trypsinogen Activation Peptide

In an attempt to use the extent of pancreatic zymogen activation to determine the severity of disease, trypsinogen activation peptide (TAP) levels have been evaluated (Neoptolemos et al, 2000). Urinary TAP concentrations have been shown to correlate well with the severity of acute pancreatitis at admission, but its measurement by a manual enzyme immunoassay combined with the limited stability of the TAP assay restricts its use as an emergency room test. By using a similar principle, a Finnish group developed a dipstick test for urinary trypsinogen-2 (Lempinen et al, 2001). They were able to show a higher positive likelihood ratio for the urinary trypsinogen-2 test strip than for CRP at 24 hours after admission, which was confirmed in a multicenter trial led by Glasgow (Johnson et al, 2004). Unfortunately, the TAP test kit is not commercially available, and therefore the TAP measurement is not a routine clinical measurement.

Hematocrit

The use of hematocrit as a prognostic marker for the severity of acute pancreatitis is an exciting development that emphasizes the pathophysiologic role of fluid loss on the severity of pancreatitis and the role of vigorous fluid replacement on the course of the disease. A hematocrit of more than 44% on admission or the absence of a fall in hematocrit during the first 24 hours after admission indicate pancreatic necrosis with a positive predictive value (PPV) of 96% and multiorgan failure with a PPV of 97% (Brown et al, 2000). A retrospective data analysis from Germany could not entirely reproduce these data, but it confirmed that a normal hematocrit predicted the absence of pancreatic necrosis with a high negative predictive value (Lankisch et al, 2001). Interestingly, Banks and colleagues provided evidence that the early hemoconcentration was associated with increased mortality only in a group of transferred cases (odds ratio [OR], 7.4; 95% confidence interval [CI], 1.6 to 35.4), pointing to the fact that hemoconcentration and its adverse effects are reversible if adequately treated on initial admission (Wu et al, 2009).

Procalcitonin

Another marker that has been evaluated as a prognostic indicator for pancreatitis is procalcitonin (PCT), which is encoded by the *CALCA* gene. Proinflammatory cytokines and bacterial lipopolysaccharides strongly induce the synthesis and release of PCT in inflammation. Although numerous attempts have been made to unravel the biologic function of PCT, its physiologic role in inflammation and sepsis is far from being understood. Nevertheless, a remarkable number of clinical studies have demonstrated the pivotal role of this parameter in the host response to microbial and fungal infections, and these have shown a strong correlation to disease severity. In addition, high serum levels of PCT implicate the synthesis of the calcitonin gene–related peptide by alternative splicing of the CALCA RNA, which directly induces peripheral vasodilation and extravasation of fluid. As a consequence, hypovolemia can occur, and this is causally related to multiorgan failure.

For the diagnosis of acute pancreatitis, it remains controversial whether high PCT levels should be regarded as a valuable marker for the prediction of either infected necrosis in pancreatitis or a severe disease course. A meta-analysis that included 24 of 59 available studies published last year reports a sensitivity and specificity of PCT for development of severe acute pancreatitis of 72% and 86%, respectively (area under the curve [AUC], 0.87; 95% CI, 5.6 to 39.8), albeit with a significant degree of heterogeneity ($Q = 28.56$; $P < .01$). The sensitivity and specificity of PCT for prediction of infected pancreatic necrosis were 80% and 91%, respectively (AUC, 0.91; OR, 28.3; 95% CI, 13.8 to 58.3) with no significant heterogeneity ($Q = 7.83$; $P = .18$). Serum measurements of PCT may therefore be valuable in predicting the severity of acute pancreatitis and the risk of developing infected pancreatic necrosis (Mofidi et al, 2009b; Rau et al, 2007).

Imaging Assessment of Acute Pancreatitis

CT and MRI (See Chapters 16 and 17)

Dynamic contrast-enhanced CT scan (DCT) is the imaging modality of choice for staging acute pancreatitis and for detecting complications. Most importantly, DCT has been shown to detect pancreatic parenchymal necrosis with a diagnostic sensitivity of 87% and an overall detection rate of 90% (Arvanitakis et al, 2004; Balthazar, 2002; Balthazar et al, 1990, 1994; Mortele et al, 2004). DCT therefore has two major roles in the evaluation of patients with known or suspected acute pancreatitis. First, DCT is used for the initial staging of the severity of the inflammatory process. Second, DCT is used for the early detection of intrapancreatic and extrapancreatic complications. Although the application of contrast media has been found to aggravate acute pancreatitis in certain animal models, an extensive analysis by Uhl and colleagues (2002) showed that no negative effect of contrast-enhanced CT is to be expected in humans, and the benefits of a CT diagnosis far outweighs the risks in pancreatitis patients. On the other hand, a CT scan of the pancreas without intravenous contrast enhancement is of little use in the context of pancreatitis.

The morphologic severity of acute pancreatitis can be determined using a CT severity index (CTSI) that was developed by Balthazar and colleagues and then simplified and extended to monitor organ failure by Silverman and colleagues in 2004 (Balthazar, 2002; Balthazar et al, 1994, 1990; Mortele et al, 2004). Comparison of the original CTSI with mortality showed

Table 53.2

Modified CT Grading System of Silverman and Colleagues

Evaluation of Pancreatic Morphology Without Considering the Extent of Pancreatic Necrosis	
0 Points, grade A	Normal pancreas consistent with mild pancreatitis
2 Points, grade B/C	Focal or diffuse enlargement of the gland, including contour irregularities and inhomogeneous attenuation with or without peripancreatic inflammation
4 Points, grade D/E	Pancreatic or peripancreatic fluid collection or peripancreatic fat necrosis
Additional 2 points	Extrapancreatic complications (one or more of the following: pleural effusion, ascites, vascular complications, parenchymal complications, or gastrointestinal tract involvement)
Scoring Pancreatic Necrosis	
0 Points	No pancreatic necrosis
2 Points	≤30% pancreatic necrosis
4 Points	>30% pancreatic necrosis

CT, computed tomography

From Balthazar EJ, Freeny PC, vanSonnenberg E, 1994: Imaging and intervention in acute pancreatitis. Radiology 193:297-306; Balthazar EJ, et al, 1990: Acute pancreatitis: value of CT in establishing prognosis. Radiology 174:331-336; and Mortele KJ, et al, 2004: A modified CT severity index for evaluating acute pancreatitis: improved correlation with patient outcome. Am J Roentgenol 183:1261-1265.

a good correlation between higher CTSI values and mortality and morbidity rates (Table 53.2), which holds true for the modified CTSI. Furthermore, the modified CTSI correlates well with the length of hospital stay and the development of organ failure (Balthazar, 2002; Balthazar et al, 1994, 1990; Mortele et al, 2004).

Although contrast-enhanced, multislice CT remains the gold standard in imaging acute pancreatitis, MRI has been investigated in several studies for utility in imaging acute pancreatitis. MRI not only avoids the administration of radiation and nephrotoxic contrast media, it is also highly suited to the detection of vascular complications, such as pseudoaneurysms and venous thromboses. A recent study reported that, compared with the Ranson score as a gold standard, MRI detected severe acute pancreatitis with 83% sensitivity (95% CI, 58% to 96%) and 91% specificity (95% CI, 68% to 98%), whereas the sensitivity for CT was 78% (95% CI, 52% to 93%), and its specificity was 86% (95% CI, 63% to 96%). Unfortunately, MRI is not universally available, it is unsuitable for patients with ferromagnetic implants, and it is rather expensive. For this reason, current guidelines recommend DCT as the imaging procedure of choice and regard it as mandatory for patients with persistent organ failure, for those who develop systemic inflammatory response syndrome or sepsis, for those who do not improve within 6 to 10 days into the disease course, and for those with probable infected pancreatic necrosis (evidence-based medicine recommendation grade B) (Working Party of the British Society of Gastroenterology et al, 2005).

Diagnostic Assessment of Biliary Pancreatitis (See Chapter 30)

An accurate diagnosis of the cause of pancreatitis modifies the therapeutic strategy: during the acute phase in a patient with prognostically severe pancreatitis, early endoscopic intervention might be beneficial (Neoptolemos et al, 1988); during the convalescence phase, cholecystectomy and/or endoscopic sphincterotomy (ES) are indicated (Sharma & Howden, 1999; Vazquez-Iglesias et al, 2004); and patients with microlithiasis or cholesterolosis might benefit from ES or cholecystectomy (Venneman et al, 2005b, 2005c). To conclude that gallstone pancreatitis is the cause of belt-like abdominal pain, vomiting, tachycardia, and mild pyrexia, a patient must meet two criteria in addition to the threefold elevated plasma pancreatic enzymes: 1) detection of gallbladder or bile duct stones and 2) exclusion of other etiologic factors such as alcohol abuse, hyperlipidemia, and hypercalcemia.

Overweight women are obviously more at risk of biliary, rather than alcohol-induced, pancreatitis. However, a previous history of biliary colic is rarely reported by patients suspected to have biliary pancreatitis. In addition to clinical risk factors, several combinations of laboratory markers have been prospectively evaluated regarding their accuracy in predicting a biliary cause of pancreatitis (Tables 53.3 and 53.4). The latest study reported an accuracy of 85% if the patient was female, older

Table 53.3

Predicting Morbidity and Mortality with the CT Severity Index Combining Scores for Pancreatic Morphology and Extent of Pancreatic Necrosis

Index	Morbidity	Mortality
0-3	8%	3%
4-6	35%	6%
7-10	92%	17%

CT, computed tomography

From Balthazar EJ, Freeny PC, vanSonnenberg E, 1994: Imaging and intervention in acute pancreatitis. Radiology 193:297-306; Balthazar EJ, et al, 1990: Acute pancreatitis: value of CT in establishing prognosis. Radiology 174:331-336; and Mortele KJ, et al, 2004: A modified CT severity index for evaluating acute pancreatitis: improved correlation with patient outcome. Am J Roentgenol 183:1261-1265.

Table 53.4

Biochemical Markers for Biliary Pancreatitis: Accuracy of the Four Different Systems for Predicting Gallstones Based on Serum Values in the First 48 Hours

Predictive Analysis	System 1 (%)	System 2 (%)	System 3 (%)	System 4 (%)
Accuracy	74	76	71	85
Sensitivity	75	74	62	93
Specificity	74	78	80	89
Positive predictive value	79	82	80	88
Negative predictive value	69	70	62	72

System 1: ALT/AST> 60 IU/L
System 2: One of the following: alkaline phosphatase >225 IU/L, ALT/AST >60 IU/L, bilrubin >40 µmol/IL
System 3: Three or more of the following: female, amylase >4000 IU/L, ALT/AST >100 IU/L, alkaline phoshatase >300IU/L
System 4: All three factors: female, age >58 years, ALT >150IU/L
ALT/AST, alanine aminotransferase/aspartate aminotransferase

Table 53.5

Comparison of Transcutaneous US, ERCP, and EUS in the Detection of Choledocholithiasis in Patients with Acute Pancreatitis

			SENSITIVITY (%)			SPECIFITY (%)			OVERALL ACCURACY		
Study	N	Time of ERCP	US	ERCP	EUS	US	ERCP	EUS	US	ERCP	EUS
Chak et al, 1999	36	Within 72 h of admission	50	92	91	100	97	100	83	89	97
Liu et al, 2005b	100	Within 24 h of admission	26	97	97	100	95	98	75	96	98

According to two recently published studies by Chak et al (1999) and Liu et al (2005b); the presence of gallbladder stones was confirmed by direct inspection of the gallbladder contents whenever cholecystectomy was performed, and the presence of choledocholithiasis was assessed by comparing ERC and EUS.
US, ultrasound; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound

than 58 years, and had serum alanine aminotransferase (ALT) levels above 150 IU/L. In this study the authors used endoscopic ultrasound (EUS) as the gold standard (Liu et al, 2005a).

Previous studies suggested a correct prediction of 74% for ALT/AST (aspartate aminotransferase) greater than 60 IU/L (Mayer & McMahon, 1985) and 76% for alkaline phosphatase (AP) greater than 225 IU/L combined with ALT/AST greater than 60 IU/L plus bilirubin above 49 µmol/L (Goodman, 1985; Goodman et al, 1985). The accuracy was 71% for three or more of the following parameters: female, amylase greater than 4000 IU/L, ALT/AST greater than 100 IU/L, and AP greater than 300 IU/L (Blamey et al, 1983). No single serum marker can diagnose biliary pancreatitis with certainty, but a serum bilirubin twice above the normal range and an elevated ALT within the first 24 hours after onset of pain show a sensitivity of 73%, a specificity of 86%, and a PPV of 92% and are therefore somewhat predictive of a biliary cause (Grau et al, 1999).

In addition to laboratory markers of cholestasis, abdominal ultrasound (US) is used to confirm the diagnosis of biliary pancreatitis. Although transabdominal US has an accuracy greater than 95% for detecting gallbladder stones, this number is reduced to 70% to 80% in patients with acute pancreatitis (Ammori et al, 2003; Neoptolemos et al, 1984a; Wang et al, 1988). This is partly due to meteorism in acute pancreatitis, which prevents visualization of the gallbladder in 20% of patients; it is also partly due to the association of pancreatitis with smaller gallstones (Neoptolemos et al, 1984b; Sugiyama & Atomi, 2004) that escape US detection. The use of CT scans alone to detect gallbladder stones is obsolete (sensitivity 30% to 53%) (Wang et al, 1988; London et al, 1989). In patients with gallbladder stones, pancreatitis is most likely of biliary origin, and a risk assessment for biliary pancreatitis can be performed by US during recovery from the acute episode. If the diameter of the smallest stones is 5 mm or less, if the cystic duct diameter is 5 mm or more, and 20 or more gallbladder stones are present, pancreatitis will most likely recur (Venneman et al, 2005a, 2005c; Sugiyama & Atomi, 2004).

If biliary pancreatitis is suspected, ERCP is indicated in some patients, often combined with endoscopic sphincterotomy; this will confirm the diagnosis of biliary pancreatitis with a sensitivity of 90%, provided the stones are larger than 4 mm in diameter (Ney et al, 2005; see Chapter 18). Stones smaller than 4 mm in diameter can be detected with a sensitivity of up to 97% by EUS. If bile duct stones or stones impacted at the papilla are suspected, EUS should be used before ERCP, because EUS has fewer complications and shows a higher sensitivity for the detection of small common bile duct stones than ERCP (EBM grade Ib, recommendation grade A) (Buscarini et al, 2003; Fusaroli & Caletti, 2005a, 2005b; Liu et al, 2005a; Prat et al, 2001; Sugiyama & Atomi, 1997a, 1997b; see Chapter 14).

As biliary microlithiasis is increasingly recognized as a major cause of recurrent idiopathic pancreatitis, EUS is gaining in importance as a diagnostic tool. In 52.4% of patients with repeatedly negative transabdominal US examinations, gallstones were ultimately diagnosed by EUS, and patients subsequently underwent endoscopic papillotomy or cholecystectomy (Saraswat et al, 2004;Thorboll et al, 2004). It is noteworthy that biliary microlithiasis is present in 75% of patients with recurrent idiopathic pancreatitis (Saraswat et al, 2004). The sensitivity of MRCP for common bile duct stones varies; it can be as high as 88.9%, but it decreases to 72.7% if the bile duct is dilated to a diameter greater than 10 mm (Moon et al, 2005). This only applies for an elective setting, clarifying the etiology of an episode of acute pancreatitis. Emergency ERCP for severe acute biliary pancreatitis follows a different algorithm and is still much debated (Table 53.5).

SUMMARY

The incidence of acute pancreatitis varies considerably among geographical regions and is estimated at 5 to 80 per 100,000 worldwide. The mortality rate of acute edematous interstitial pancreatitis is less than 1%, whereas 10% to 24% of patients with severe acute pancreatitis die of the disease. The etiology of 80% of acute pancreatitis episodes is either gallstone disease or excessive alcohol consumption. Early prognostic factors for evaluating the clinical course and severity of acute pancreatitis are three or more signs of organ failure, according to the Ranson or Imrie score, as well as nonpancreatic complications or the detection of pancreatic necrosis by imaging techniques. Elevated CRP levels above 130 mg/L can also predict a severe course of acute pancreatitis with high sensitivity. An accurate diagnosis of the cause of pancreatitis modifies the therapeutic strategy, and appropriate diagnostic measures to establish biliary pancreatitis need to be undertaken.

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CHAPTER 54

Management of acute pancreatitis and complications

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OVERVIEW

The severity of acute pancreatitis (AP) varies from mild uncomplicated disease to critical disease associated with both local and systemic complications (see Chapters 52 and 53). It is important to determine the severity of acute pancreatitis in the individual patient for triage, treatment, and prognosis. Since 1992, when the International Symposium on Acute Pancreatitis in Atlanta published its consensus, it has become customary to define the severity of acute pancreatitis as either mild or severe (Bradley, 1993). Acute pancreatitis is severe when it is associated with local or systemic complications. Although the Atlanta classification was a significant advance, it is now accepted that the dichotomous approach fails to capture clinically relevant categories of patients (Petrov & Windsor, 2010). For instance, it does not allow for discrimination among patients with transient and persistent organ failure, those with sterile and infectious local complications, and those with either local or systemic complications.

A large body of evidence now demonstrates that the two key determinants of severity in acute pancreatitis are *organ failure*—absent, transient, or persistent—and *pancreatic complications*—absent, noninfectious, or infectious. Determinants-based classification of the severity of acute pancreatitis composed of four categories (Table 54.1) appears to be more useful for the clinical assessment of severity in individual patients and for comparing groups of patients (Petrov & Windsor, 2010). The distinct advantages of this new classification is that it uses widely accepted and unambiguous terms, it can be applied in both early and late phases of acute pancreatitis, it can facilitate communication between treating physicians, and it promotes standardization for management of acute pancreatitis (Petrov et al, 2010).

Although many aspects of the management of acute pancreatitis remain controversial, significant overall progress has been made during the last few decades, evidenced by a reduction in morbidity and mortality rates (Lowenfels et al, 2009; Banks & Freeman, 2006). The improved outcomes have not been due to any treatments based on specific, critical pathophysiology. A wide range of drugs has been evaluated in randomized controlled trials (RCTs) and have proved ineffective in the treatment of acute pancreatitis. These include aprotinin, atropine, calcitonin, fresh frozen plasma, glucagon, gabexate, glucocorticoids, lexipafant, nonsteroidal antiinflammataory drugs (NSAIDs), and octreotide. The overall improvement in outcome for patients with acute pancreatitis has been due to a combination of factors that include improvements in intensive care medicine, imaging techniques, severity prediction, and selection of patients for endoscopic retrograde cholangiopancreatography (ERCP) and surgery.

This chapter describes the current management of acute pancreatitis, and considerable opportunities remain for improvement. The discussion of the evidence base for current practice will highlight these points.

GENERAL MANAGEMENT

Pain Management

Pain is the cardinal symptom of acute pancreatitis, and its relief is a clinical priority. The strategy in patients with acute pancreatitis, as for all acute pain, is the staged use of analgesics. Although some debate still surrounds step-up and step-down approaches, it is best practice to use NSAIDs for the management of mild pain (Pezzilli et al, 2007). The potential risk of bleeding as a result of the antiplatelet effect of NSAIDS has not been an issue in practice. For patients with moderate and severe pain, and for those for whom NSAIDs are inadequate, the second step is to use a weak opioid; the third step is to use a strong opioid.

Although experimental findings show that morphine can induce spasm of the sphincter of Oddi and exacerbate the severity of acute pancreatitis, it is worth noting that the avoidance of morphine as an analgesic has not been supported by clinical studies (Economou & Ward-McQuaid, 1971). A comprehensive review of the literature shows that all opiates increase the pressure in the sphincter of Oddi but that physiologic effect is of marginal clinical relevance (Thompson, 2001).

In practice, patients with severe acute pancreatitis require intravenous analgesia, and patient-controlled analgesia should be considered. Epidural analgesia can be considered for patients with severe and critical acute pancreatitis who require high doses of opioids for an extended period. Oral analgesics can be introduced but are less helpful in the acute setting because of the longer onset of action and concerns about variable absorption. Because the pain in acute pancreatitis is continuous, oral analgesics should be prescribed at regular intervals that are at least equal to the half-life of the drug. Although it has been reported that analgesics can also be given transdermally or rectally, no RCTs have compared the different routes of administration of the same analgesic in patients with acute pancreatitis.

Different analgesics have been compared in patients with acute pancreatitis, and the six published RCTs are summarized in Table 54.2 (Blamey et al, 1984; Ebbehoj et al, 1985; Jakobs et al, 2000; Kahl et al, 2004; Peiro et al, 2008; Stevens et al, 2002). These trials had a different study design, evaluated different analgesics, and had small sample sizes; only three of the trials were double-blinded. From these studies it can be said that no credible clinical evidence supports avoiding the use of

Table 54.1

Determinants-Based Classification of Acute Pancreatitis

Severity Category*	Local Determinant		Systemic Determinant
Mild	No local complications	*and*	No organ failure
Moderate	Sterile pancreatic and peripancreatic complications	*or*	Transient organ failure
Severe*	Infectious pancreatic and peripancreatic complications	*or*	Persistent organ failure
Critical	Infectious pancreatic and peripancreatic complications	*and*	Persistent organ failure

*Severity is graded on the basis of more severe local or systemic complication (e.g., sterile pancreatic necrosis without organ failure has to be graded as moderate; sterile pancreatic necrosis with persistent organ failure has to be graded as severe).

Petrov MS, Windsor JA, 2010: Classification of the severity of acute pancreatitis: how many categories make sense? Am J Gastroenterol 105(1):74-76.

morphine in treating the pain associated with acute pancreatitis; however, the NSAID of choice is metamizole (2 g/8 h IV), and the opioid of choice is buprenorphine (0.3 g/4 h IV). There is no evidence to support the use of parenterally administered local anesthetics such as procaine in the management of pain associated with acute pancreatitis. However, the lack of high-quality evidence means that the choice of analgesic and the strategy for administration remain uncertain. No recent guidelines relating to the management of acute pancreatitis provide a specific recommendation regarding pain management (Loveday et al, 2010).

Fluid Resuscitation

Acute pancreatitis can be associated with substantial third-space fluid losses, and the resultant hypovolemia that impairs the microcirculation of the pancreas is a major determinant of pancreatic necrosis. The reflex splanchnic vasoconstriction in response to hypovolemia may compound pancreatic hypoperfusion and further predispose to ischemia. Fluid resuscitation is one of the most important aspects of the early management of acute pancreatitis (Gardner et al, 2008; Talukdar & Vege, 2009) and is the intervention most likely to improve outcome. No high-level evidence describes the optimal resuscitation fluid, required fluid rate, or best marker to guide resuscitation and indicate its adequacy (Banks & Freeman, 2006; Pandol et al, 2007). It is not even known whether colloids or crystalloids are more effective in improving pancreatic microcirculation and outcome. The initial goal of fluid resuscitation is to restore circulating blood volume (euvolemia), with the aim of normalizing heart rate, blood pressure, central venous pressure, and urine output, even though these do not reflect the adequacy of pancreatic and splanchnic perfusion (Flint & Windsor, 2003). In

Table 54.2

Randomized Controlled Trials of Analgesics in Patients with Acute Pancreatitis

First Author	Year	Setting	Intervention Group	Control Group	NO. PATIENTS		Allocation Concealment	Reduction of Pain Score	Other Important Findings
					Intervention Group	Control Group			
Blamey	1984	U.K.	IM buprenorphine	IM pethidine	17	15	Single blind	No difference	No difference in terms of adverse effects
Ebbehoj	1985	Denmark	Indomethacin (rectal)	Placebo (rectal)	14	16	Double blind	Significantly greater in the intervention group over the first 168 h	The number of opiate injections was significantly less in the intervention group
Jakobs	2000	Germany	IV buprenorphine	IV procaine	20	20	Open label	Significantly greater in the intervention group over the first 48 h	The number of additional analgesics was significantly less in the intervention group
Stevens	2002	U.S.	Fentanyl (transdermal)	Placebo (transdermal)	16	16	Double blind	Significantly greater in the intervention group between 36 and 60 h	A significantly reduced LOS was reported in the intervention group
Kahl	2004	Germany	IV pentazocine	IV procaine	50	51	Open label	Significantly greater in the intervention group over the first 72 h	The number of additional analgesics was significantly less in the intervention group
Peiro	2008	Spain	IV metamizole	SC morphine	8	8	Open label	Insignificantly greater in the intervention group over the first 24 h	No difference reported in terms of adverse effects

IM, intramuscular; IV, intravenous; SC, subcutaneous; LOS, length of stay

Table 54.3

Randomized Controlled Trials of Intravenous Antibiotic Prophylaxis vs. No Antibiotics in Patients with Acute Pancreatitis

First Author	Year	Setting	Intervention Group	Control Group	NO. PATIENTS		Allocation Concealment	Main Findings
					Intervention Group	Control Group		
Howes	1975	U.S.	Ampicillin	None	48	47	Open label	No significant difference in any outcome
Craig	1975	U.S.	Ampicillin	None	23	23	Open label	No significant difference in any outcome
Finch	1976	U.S.	Ampicillin	Placebo	31	27	Double blind	No significant difference in any outcome
Pederzoli	1993	Italy	Imipenem	None	41	33	Open label	Significantly lower rate of pancreatic infection in the intervention group
Sainio	1995	Finland	Cefuroxime	None	30	30	Open label	Significantly lower mortality rate, but not pancreatic infection, in the intervention group
Delcenserie	1996	France	Ceftazidime + amikacin + metronidazole	None	11	12	Open label	No significant difference in any outcome
Schwarz	1997	Germany	Ofloxacin + metronidazole	None	13	13	Open label	No significant difference in any outcome
Spicak	2003	Czech Republic	Meropenem	None	20	21	Open label	No significant difference in any outcome
Isenmann	2004	Germany	Ciprofloxacin + metronidazole	Placebo	58	56	Double blind	No significant difference in an outcome
Dellinger	2007	North America and Europe	Meropenem	Placebo	50	50	Double blind	No significant difference in any outcome
Rokke	2007	Norway	Imipenem	None	36	37	Open label	Significantly lower rate of pancreatic and extrapancreatic infection in the intervention group
Xue	2009	China	Imipenem	None	29	27	Open label	No significant difference in any outcome
Garcia-Barrasa	2009	Spain	Ciprofloxacin	Placebo	22	19	Double blind	No significant difference in any outcome

general, urine output should be restored at greater than 0.5 mL/h/kg body weight, and the central venous pressure should be restored to between 8 and 12 cm H_2O. Swan-Ganz monitoring can be helpful in hemodynamically unstable patients, and some evidence shows that as an independent risk factor of pancreatitis severity and a marker of hydrations status, hematocrit might be useful with fluid resuscitation (Pitchumoni et al, 2005; Wu et al, 2009). Adequate fluid resuscitation is likely when the hematocrit is restored to between 30% and 35%. A number of other approaches to guide resuscitation offer promise but have not become established in clinical practice. An example is the use of intramucosal pH (pHi) derived by nasogastric tonometry (Juvonen et al, 2000a; van Haren et al, 2007), which is predictive of severity and reflects the adequacy of perfusion in the splanchnic circulation.

Antibiotics

Although the use of broad-spectrum antibiotics to treat the established infection in acute pancreatitis is a well-established practice, the use of prophylactic antibiotics has been controversial for decades. Three RCTs in the 1970s failed to demonstrate a beneficial effect of antibiotic prophylaxis, probably because of a small sample size, inappropriate selection of antibiotics—such as ampicillin, which does not sufficiently penetrate the pancreas—and inclusion of patients with mild pancreatitis (Table 54.3; Craig et al, 1975; Finch et al, 1976; Howes et al, 1975). Between 1993 and 2009, several randomized, controlled, open-label trials were published evaluating the efficacy of prophylactic antibiotic treatment in patients with severe acute pancreatitis (Delcenserie et al, 1996; Pederzoli et al, 1993; Rokke et al, 2007; Sainio et al, 1995; Schwarz et al, 1997; Spicak et al, 2003; Xue et al, 2009). The results of these trials were conflicting. Although some RCTs demonstrated a significant reduction of infectious complications and mortality with the use of prophylactic antibiotics, others failed to do so (see Table 54.3). Only three double-blind, placebo-controlled RCTs were published between 2004 and 2009, and all of them were unable to show a beneficial effect of antibiotic prophylaxis regarding infectious pancreatic complications, the need for surgery, and mortality (Dellinger et al, 2007; Garcia-Barrasa et al, 2009; Isenmann et al, 2004). This is in line with the

findings of a meta-analysis that showed an inverse relationship between methodologic quality of the studies and impact of antibiotic prophylaxis on mortality (de Vries et al, 2007).

On the other hand, it is worth noting that the three double-blind RCTs mentioned were not without flaws. These include a large crossover to open-label antibiotics in the control group (i.e., a high percentage of patients in the placebo group were treated with intravenous antibiotics) and the inclusion of patients on the basis of predicted severity of acute pancreatitis rather than proven necrotizing pancreatitis. All the studies were underpowered because the power calculation was based on an infection rate of 40%, whereas the actual infection rates in the placebo groups of the trials were only 12% to 17%.

Several attempts have been made to statistically aggregate data on the use of prophylactic antibiotics in acute pancreatitis. Although only two new RCTs were published from 2006 through 2007, it is notable that seven of the 10 meta-analyses were published within this period (Petrov, 2008). Thirteen RCTs were included in these seven meta-analyses. Because of different inclusion criteria and various meta-analysis techniques used, concordance is lacking, and they provide contradictory recommendations regarding the role of prophylactic antibiotics in reducing the risk of pancreatic infectious complications. Overall, it appears that the most recent studies do not support the use of prophylactic antibiotics to reduce the frequency of pancreatic infectious complications, surgical intervention, and death in patients with acute pancreatitis. Therefore routine broad-spectrum prophylactic antibiotics in patients with severe acute pancreatitis cannot be recommended on the basis of current evidence.

Nutritional Management

Severe acute pancreatitis is associated with a cytokine-mediated systematic inflammatory response and a hypercatabolic state (Windsor & Hammodat, 2000; see Chapter 10). The adverse consequences of this include protein-calorie malnutrition, expansion of the extracellular fluid compartment, and immune suppression. A meta-analysis of RCTs showed that nutritional support, both enteral and parenteral, significantly reduced risk of mortality in patients with acute pancreatitis compared with no nutritional support (Petrov et al, 2008c). Nutritional support is thus an essential part of the management of patients with severe acute pancreatitis (Banks & Freeman, 2006; Pandol et al, 2007).

Type of Feeding

The feasibility of providing nutritional support in patients with acute pancreatitis has been known for more than 3 decades. Parenteral nutrition (PN), rather than enteral nutrition (EN), became the standard of care because of the concept of "resting" the pancreas. The rationale for this was to prevent stimulating increased secretion of pancreatic proteolytic enzymes and exacerbating pancreatitis severity. But the use of PN has decreased in the face of well-recognized problems, such as catheter-related sepsis, the high cost of treatment, electrolyte and metabolic disturbances, villous atrophy and gut barrier failure with promotion of bacterial translocation, systemic sepsis, and multiple organ failure.

A number of RCTs compared total PN and total EN in the management of predicted severe AP (Table 54.4; Casas et al, 2007; Doley et al, 2009; Eckerwall et al, 2006; Gupta et al, 2003; Kalfarentzos et al, 1997; Louie et al, 2005; Petrov et al, 2006; Wu et al, 2010). A meta-analysis of high-quality RCTs has shown a significant twofold reduction in the risk of total and pancreatic infectious complications and a 2.5-fold reduction in the risk of death in patients receiving total EN (Petrov et al, 2008f). The basis for the clinical benefits of EN over PN remain unclear, although EN may prevent or attenuate mucosal barrier failure and bacterial translocation (Windsor & Hammodat, 2000). Intestinal permeability studies are a surrogate marker for clinically relevant events and provide conflicting results. Three clinical studies showed increased intestinal permeability to both micromolecules and macromolecules in patients with severe acute pancreatitis when compared with mild acute pancreatitis

Table 54.4

Randomized Controlled Trials of Total Enteral vs. Total Parenteral Nutrition in Patients with Predicted Severe Acute Pancreatitis

			NO. OF PATIENTS		
First Author	Year	Setting*	Intervention Group†	Control Group	RI and Mortality Rate
Kalfarentzos	1997	Greece	18	20	Significantly lower RI in the intervention group
Gupta	2003	UK	8	9	Insignificantly lower RI in the intervention group
Louie	2005	Canada	10	18	Insignificantly lower RI in the intervention group
Eckerwall	2006	Sweden	23	25	No significant difference in outcomes
Petrov	2006	Russia	35	34	Significantly lower RI and mortality rate in the intervention group
Casas	2007	Spain	11	11	Insignificantly lower RI in the intervention group
Doley	2009	India	25	25	No significant difference in outcomes
Wu	2010	China	53	54	Significantly lower RI and mortality rate in the intervention group

*Allocation concealment was open-label in all studies.
†The intervention group received enteral nutrition, whereas the control group received parenteral nutrition.
RI, rate of pancreatic infection

and healthy volunteers (Ammori et al, 1999; Juvonen et al, 2000b; Nagpal et al, 2006). But an early RCT from the United Kingdom (Powell et al, 2000) in which patients with predicted severe AP were randomized to receive either EN or no artificial nutritional support showed significantly increased intestinal permeability by day 4 in patients allocated to the EN group. Similarly, a recent RCT from Sweden comparing nasogastric EN and PN in patients with predicted severe acute pancreatitis demonstrated impaired gut permeability on day 3 in the EN group (Eckerwall et al, 2006). This difference might be explained by the inclusion of a considerable number of patients with mild AP in whom intestinal permeability is unlikely to change (Petrov et al, 2008f).

Route of Enteral Feeding

Nasogastric (NG) tube insertion may be more practical than nasojejunal (NJ), as the latter often requires endoscopy or radiology expertise, the transfer of patients within the hospital, and a delay in starting feeding. However, NJ EN has been preferred to NG EN because of a fear about pancreatic stimulation. Pancreatic response to feeding was studied in human volunteers, and it was shown that all forms of EN, with the exception of NJ feeding, stimulate pancreatic secretion (O'Keefe et al, 2003). By contrast, a study in patients with acute pancreatitis showed a significantly lower rate of secretion of trypsin, amylase, and lipase in comparison with healthy subjects (O'Keefe et al, 2005). Moreover, it was shown that the greater the severity of acute pancreatitis, the greater the reduction in pancreatic enzyme secretion as a response to duodenal feeding, probably reflecting greater injury of acinar cell mass. The possible clinical implication of these findings is that NG EN may not aggravate the course of acute pancreatitis, as was previously suggested.

Two RCTs have compared NG EN with NJ EN in patients with severe acute pancreatitis (Eatock et al, 2005; Kumar et al, 2006). These studies demonstrated the feasibility, safety, and tolerance of NG EN, but a meta-analysis did not demonstrate a statistically significant reduction in risk of death (Petrov et al, 2008b). Before NG EN can be considered the standard of care in the nutritional support of patients with AP, a well-designed and adequately powered RCT comparing mortality and morbidity of NG EN and NJ EN is required. A practical compromise is to start EN through an NG tube after the patient has been resuscitated and for the tube to be advanced when endoscopic or radiologic assistance is available.

Type of Enteral Feeding

The concept of "pancreatic rest" has also influenced decisions about the type and content of enteral feeding. The preferred formulations, elemental and semi-elemental formulas (Roberts, 2001; Petrov, 2007), did not require pancreatic enzymes for digestion and absorption. However, the major disadvantage of elemental and semi-elemental formulas is the cost, which is reportedly threefold to sevenfold higher than that of polymeric formulas. A recent meta-analysis of RCTs compared these two formula types in terms of feeding intolerance, infectious complications, and mortality and found that the use of polymeric over elemental and semi-elemental feedings did not result in reduced tolerance in patients with acute pancreatitis and appeared to reduce the risk of infectious complications and death (Petrov et al, 2009a). Thus the use of elemental and semi-elemental formulas confers no apparent advantage over relatively inexpensive polymeric formulas.

Because the gastrointestinal tract is the largest immune organ, containing approximately 65% of the immune tissue in the body, it has been considered that the use of immune-enhanced enteral formulations might increase the beneficial effects of EN in acute pancreatitis (Bengmark, 1999; Schloerb, 2001). Several trials were performed in different clinical settings, which suggested that immunonutrition might have the potential to modify the inflammatory response. The results of RCTs that compared the use of immune-enhanced and standard enteral formulas were statistically aggregated in several meta-analyses (Beale et al, 1999; Heyland et al, 2001; Heys et al, 1999). The most recent and comprehensive systematic review of 2419 patients from 22 RCTs (Heyland et al, 2001) found that the effect of immune-enhancing EN may depend on the subset of the analyzed patients. In particular, no effect of immunonutrition on the risk of infectious complications or death was reported within the subgroup of critically ill patients. At the same time, administration of a formula high in arginine in a combined group of critically ill and elective surgery patients was associated with a statistically significant reduction in infectious complications and a trend toward lower mortality rates in comparison with other immune-enhancing diets. A recent meta-analysis of RCTs in patients with acute pancreatitis did not show any clinical beneficial effect of immunonutrition when compared with standard EN (Petrov et al, 2008a).

Tolerance of Enteral Feeding

Dieticians generally agree on the caloric target in patients with acute pancreatitis: 30 kcal/kg and 1.5 g/kg of protein daily based on ideal body weight (Andersson et al, 2009; Olah & Romics, 2008). To ensure tolerance of EN, it is usually commenced at a low rate of 25 to 30 mL/h and increased incrementally over a day or more, until the desired caloric intake is reached. Despite this approach, EN can be associated with feeding intolerance in some patients with acute pancreatitis. Most commonly, the intolerance manifests as abdominal distension, delayed gastric emptying, gastroesophageal reflux, and diarrhea, all of which may develop in the presence of sepsis or with a significant clinical deterioration. In general, tolerance is achieved when EN is provided without development of one of these complications (Bankhead et al, 2009; Mallampalli et al, 2000). Various strategies to improve tolerance to EN require clinical studies, which are also needed to investigate markers of gut motility, absorption, and blood flow that can be easily applied at the bedside.

Timing of Enteral Feeding

The best time to start EN in patients with acute pancreatitis has never been studied. The indirect evidence in regard to this is derived from trials of EN versus PN only. Some authors have demonstrated clinical benefits of early enteral nutrition, but others have demonstrated the favorable effects of delayed enteral feeding (Petrov et al, 2009b). Early EN should help maintain gut integrity (enterocyte population) and function (motility) and reduce bacterial translocation and ileus. It should also help to achieve caloric targets more quickly. But early nutrition is not without risk, particularly in hemodynamically unstable patients and in those requiring inotropic support. These patients appear to be at an increased risk of nonocclusive mesenteric ischemia, and it is best to commence EN after adequate resuscitation.

Therapeutic Endoscopic Retrograde Cholangiopancreatography

Endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (ES) has been promoted as a proven intervention in patients with acute biliary pancreatitis since the early 1990s (see Chapters 18 and 27). This was based on the findings of two RCTs, from the United Kingdom and Hong Kong, of early ERCP (within 24 to 48 hours of admission) with or without ES versus conservative treatment (Neoptolemos et al, 1988; Fan et al, 1993). Both trials demonstrated that early ERCP was associated with a reduction in complications, but not in mortality, and only in patients with predicted severe acute pancreatitis.

Some evidence suggests that the duration of biliary obstruction, rather than the predicted severity of acute pancreatitis, is the most important determinant of outcome (Acosta et al, 1997, 2006). This is probably due to concomitant cholangitis secondary to the obstruction and probably best explains the usefulness of ERCP in the context of acute biliary pancreatitis (Petrov, 2009). The first multicenter RCT to examine the role of ERCP in acute pancreatitis was designed to include only patients without evidence of biliary obstruction (Folsch & Neoptolemos, 2002). This German study did not find any benefit of early ERCP (within 72 h after onset of symptoms) over conservative treatment. The most recent RCT, from Argentina, found that early ERCP in patients with biliary obstruction, defined by laboratory and radiologic criteria, and without evidence of acute cholangitis conferred no benefit (Oria et al, 2007).

Two important meta-analyses were published in 2008. The first found that compared with conservative treatment, early ERCP in patients with both predicted mild and predicted severe acute pancreatitis did not decrease the incidence of local pancreatic complications or mortality rate (Petrov et al, 2008d). The second meta-analysis was designed to negate the confounding effect of acute cholangitis and demonstrated no benefit of early ERCP over conservative treatment in terms of complications and mortality in patients with predicted mild and predicted severe acute pancreatitis (Petrov et al, 2008e). The conclusion to be drawn from these studies is that early ERCP is indicated in patients with acute pancreatitis if acute cholangitis is evident (see Chapter 43) but not for those with just cholestasis (Petrov, 2009). Although cholestasis can reflect a persisting main bile duct stone, it might also be due to edema of the ampulla secondary to stone passage to the duodenum and may thus be expected to improve over the first few days of admission. Persistent cholestasis without cholangitis may require an ERCP but not usually in the acute setting.

Cholecystectomy

Recurrent attacks of gallstone pancreatitis carry a morbidity rate of up to 40% (Banks & Freeman, 2006), and an early laparoscopic cholecystectomy is widely advocated within the same hospital admission (see Chapter 30). The optimal timing of cholecystectomy has been controversial. The U.K. guidelines for the management of acute pancreatitis recommend that all patients with biliary pancreatitis undergo definitive management of gallstones during the same hospital admission (index cholecystectomy; Working Group, 2005). However, some surgeons have concerns that early surgery may be associated with an increase in operative difficulty and hence morbidity and conversion rate; therefore they advocate cholecystectomy after a period of 4 to 6 weeks to allow resolution of the inflammatory process (interval cholecystectomy; Green, 2008; Larson et al, 2006). These two approaches have been compared in several RCTs, which demonstrated no difference in complication rates between index and interval cholecystectomy; however, index cholecystectomy resulted in a significantly shorter length of hospital stay (Siddiqui et al, 2008). It is worth mentioning that patients with acute biliary pancreatitis were excluded from these trials. An adequately powered RCT of index versus interval cholecystectomy is needed to draw a firm conclusion about the optimal timing of cholecystectomy in patients with acute biliary pancreatitis.

MANAGEMENT OF SYSTEMIC COMPLICATIONS

Most patients with acute pancreatitis have an initial sudden inflammatory respiratory syndrome response, others develop multiple organ dysfunction syndrome (MODS) in the first few days, and some develop MODS later in response to infectious complications (see Chapters 52 and 53). Patients with severe and critical acute pancreatitis are best managed in an intensive care environment to allow for optimal monitoring of fluid resuscitation and organ function and the early identification of life-threatening local or systemic complications. Systemic complications and organ failure are not an all-or-nothing phenomenon, rather a continuous spectrum exists between normal function of an organ system and its complete failure (Table 54.5; Marshall et al, 1995).

Some of the systemic complications of acute pancreatitis—coagulation abnormalities that may range from intravascular thrombosis to disseminated intravascular coagulation, metabolic disturbances (hyperlipidemia, hypocalcemia), liver failure, encephalopathy, and Purtscher retinopathy—are rare in clinical practice and beyond the scope of this chapter. In contrast,

Table 54.5

Modified Marshall Scoring System

Organ System	0	1	2	3	4
Respiratory (Pao_2/Fio_2)	>400	301-400	201-300	101-200	<101
Cardiovascular (systolic blood pressure [mm Hg])	>90	<90; fluid responsive	<90; not fluid responsive	<90; pH <7.3	<90; pH <7.2
Renal					
Serum creatinine (μmol/L)	<134	134-169	170-310	311-439	>439
Serum creatinine (mg/dL)	<1.4	1.4-1.8	1.9-3.6	3.6-4.9	>4.9

From Marshall JC, et al, 1995: Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med 23(10):1638-1652.

respiratory, cardiovascular, renal, and intestinal dysfunction are the most common systemic complications (Banks & Freeman, 2006; Pandol et al, 2007).

Respiratory failure is the most common systemic complication. The pathogenesis involves inflammatory cytokines released from the pancreas and the action of phospholipase A_2 and other pancreatic catabolic enzymes on the lung. The clinical diagnosis of incipient respiratory failure is based on tachypnea and low oxygen saturation. A chest radiograph may confirm pleural effusions, pulmonary edema, and features of acute respiratory distress syndrome. Management is supportive, with oxygen supplementation and analgesia, and some patients will ultimately require endotracheal intubation and mechanical ventilation. Lung-protective ventilation strategies should be instituted, such as adequate positive end-expiratory pressures, permissive hypercapnia, and tidal volumes of 6 mL/kg ideal body weight (Nathens et al, 2004).

Patients with severe and critical acute pancreatitis can develop hypotension (arterial pressure <90 mm Hg) secondary to vasodilation and decreased systemic vascular resistance, and sometimes as a result of cardiotoxicity. Appropriate management consists of close hemodynamic monitoring, intravenous fluid resuscitation, and inotropic medications—dopamine at 2 to 10 µg/kg/min or dobutamine at 2 to 10 µg/kg/min—if indicated (Tonsi et al, 2009).

In the setting of acute pancreatitis, acute renal failure is usually secondary to decreased renal perfusion pressure with hypovolemia and is sometimes secondary to ischemic acute tubular necrosis. The clinical diagnosis is based on acute oliguria and an acute elevation in blood urea nitrogen and serum creatinine (>0.5 mg/dL or 44 mmol/L; Nathens et al, 2004; Tonsi et al, 2009). Treatment is supportive and focused on restoring renal perfusion and providing dialysis if required.

The failure of the intestine is usually due to ischemia secondary to hypovolemia and reflex splanchnic vasoconstriction. The clinical diagnosis is based on the development of nausea and vomiting, increased NG losses, tympanic distension of the abdomen, reduced bowel sounds, and reduced tolerance to EN. Intestinal failure with the breakdown in intestinal barrier function and bacterial translocation can result in bacteremia and the infection of pancreatic necrosis.

MANAGEMENT OF LOCAL COMPLICATIONS

Because local complications can develop at any time, frequent assessment and continuous monitoring of patients is necessary. When a local complication occurs, it is necessary to make an accurate diagnosis and to decide whether intervention is required, when it is required, and what intervention is appropriate. Managing the local complications of acute pancreatitis requires a number of considerations.

Type of Complication

The first consideration is the type of local complication and its prognostic significance. Early peripancreatic fluid collections often resolve without intervention and usually have little bearing on disease course. As such, this is more a manifestation of the disease than a complication per se. Fluid collections may persist, often to the result of ductal injury and pancreatic leak; they may cause symptoms because of a mass effect (e.g., gastric outlet obstructions) and from secondary infection. Patients with pancreatic necrosis show signs of clinical deterioration: persistent abdominal discomfort, intolerance to oral feeding, and failure to thrive. The local complication in these patients is often a mature (thick-walled) collection predominantly filled with sterile necrosis. In these patients, intervention might expedite recovery. Intervention is very rarely indicated in patients with sterile necrosis but may be required in those who continue to deteriorate despite maximal supportive care. In contrast, patients with extensive infected pancreatic or peripancreatic necrosis almost always require intervention, as this complication is the most significant determinant of outcome. Although infected pancreatic necrosis has been considered an absolute indication for surgical intervention, cases successfully managed nonsurgically have been reported. Any necrotizing process, regardless of the infectious status, may cause significant hemorrhage (e.g., pseudoaneurysm) or bowel perforation (e.g., duodenum or transverse colon), both of which require urgent intervention. Thus the type of local complication has a direct bearing on the indication for treatment.

Trajectory of Patient

The second consideration is the clinical status and trajectory of the patient. If supportive measures, such as those discussed above, bring about clinical improvement—evidenced by serial clinical assessment and inflammatory markers, such as C-reactive protein (CRP)—intervention is unnecessary. If, however, the patient continues to deteriorate despite maximum intensive care support, survival will depend on effective intervention. Related to this is a consideration of the physiologic reserve of the patient. Elderly patients with significant preexistent morbidity have less physiologic reserve to withstand prolonged severe illness and invasive interventions.

Timing of Intervention

The timing of intervention is an important consideration and one of the most difficult decisions to make in the management of patients with acute pancreatitis. Early intervention of local complications is often fraught with difficulty in patients with more severe necrotizing pancreatitis because of the risk of hemorrhage when necrotic tissue is less well demarcated from viable tissue. Delaying intervention allows this demarcation and thus reduces the risks of bleeding, dissemination of infection, and collateral damage to adjacent organs as the necrotic process has stopped extending, and infected necrotic tissues become organized and "walled off." Appreciation of this has resulted in a notable trend toward delayed intervention, which is uncommonly performed before 4 weeks from the onset of symptoms.

Another emerging concept related to timing is the increasing use of percutaneous catheter drainage in patients with infected fluid collections and those with infected necrosis. Preemptive drainage with one or more catheters often produces an improvement in the patient's overall clinical status, or at least it arrests clinical deterioration. In this way drainage buys time and allows the more definitive necrosectomy to be delayed, until the patient is more stable, and the lesion is better defined. If required, repeat intervention can be undertaken on a programmed basis (e.g., every second day) or with an on-demand strategy, wherein the intervention is repeated only if and when it is clinically indicated. The former is often necessary if intervention has occurred

earlier in the disease course, when immature necrosum does not readily debride.

Type of Intervention

Another important consideration is the type of intervention. There are many different interventions, and the challenge is to select the intervention that is appropriate for the particular local complication, taking into account the anatomic location, infection status, complexity of any target lesions, the physiologic status and comorbidity of the individual patient, and the availability of expertise with the type of intervention. A review of current guidelines highlights the absence of level 1 evidence to guide decision making regarding the types of intervention (Loveday et al, 2008). Two broad philosophies are evolving in this regard. Many consider open surgical drainage with necrosectomy to be the gold standard in the management of infected pancreatic necrosis, and they reserve less invasive interventions for subsequent complications, such as percutaneous tube drainage of residual fluid complications. Such a *step-down approach* contrasts with the approach that advocates starting with less invasive interventions, such as percutaneous or endoscopic drainage, and only employing open surgical techniques later in the disease course in those who fail to respond (i.e., the *step-up approach*). These two approaches have been subjected to an RCT demonstrating that a minimally invasive step-up approach results in a reduced rate of the composite endpoint of major complications or death in patients with necrotizing pancreatitis and suspected or confirmed infected necrotic tissue (van Santvoort et al, 2010).

There are a number of variations to open surgical necrosectomy. More recently a number of less invasive approaches to treatment have been developed. The advocates for a less invasive approach argue that open surgery adds insult to injury and pushes a patient closer to or beyond their physiologic reserve; they point to the need to tailor treatment to specific lesions in individual patients and to the opportunities afforded by the development and convergence of minimally invasive technologies. Enthusiasts must be cautious not to overstate the benefits of less invasive approaches in the absence of high-level evidence. The reported improvement in outcomes with less invasive approaches might be due to a number of factors, including improvements in the early management of acute pancreatitis, such as resuscitation and EN; better intensive care to prevent and treat organ failure; more aggressive and appropriate use of percutaneous drainage; and better timing and selection of patients for intervention.

Classification of Interventions

In response to the need to standardize the description of invasive interventions to facilitate communication, comparison, and controlled trials (Windsor, 2007), progress has been made with the introduction of the VRP classification system, based on the ICD-10 approach (Loveday et al, 2011). It uses three dimensions, combining the method of *visualization* of the lesion, *route* taken to reach the lesion, and the *purpose* of the intervention (Table 54.6). Visualization includes open procedures, in which the operative site is exposed through the skin incision; endoscopic procedures, in which the operative site is

Table 54.6

VRP Classification of Invasive Procedures

V1 Radiologic	Using only radiologic modalities (e.g., fluoroscopy, CT, US, MR) to visualize and assist entering the target lesion
V2 Endoscopic	Using any white-light endoscopic instrument (e.g., flexible or rigid endoscope, urologic endoscope) to visualize the target lesion
V3 Combined	Using an endoscopic technique as the primary mode of visualization, assisted by a real-time radiologic modality
V4 Open	Using any method in which skin and any other body layers are cut to expose the site of the procedure
Vx	Insufficient information
Vz	Other visualization technique
R1 Per os transpapillary	External orifice entry point, internal route traversing papilla to enter pancreatic duct
R2 Per os transmural	External orifice entry point, internal route traversing gastrointestinal wall
R3 Percutaneous retroperitoneal	Skin external entry point, internal route traversing retroperitoneum
R4 Percutaneous transperitoneal	Skin external entry point, internal route traversing peritoneum
R5 Percutaneous transmural	Skin external entry point, internal route traversing gastrointestinal wall
Rx	Insufficient information
Rz	Other route
P1 Drainage	Letting out fluid and/or solid necrotic matter, externally out of the body or internally into the gastrointestinal tract
P2 Lavage	Flushing away solid necrotic matter with fluid to facilitate external or internal drainage
P3 Fragmentation	Breaking down solid necrotic matter by instrumental or mechanical disruption to facilitate external or internal drainage
P4 Debridement	Taking or cutting out solid necrotic matter with either sharp or blunt dissection
P5 Excision	Cutting out all or part of the pancreas, including healthy tissue, with the intention to fully remove all necrotic matter
Px	Insufficient information
Pz	Other purpose

Procedures should be classified using a single value from each component, and the highest applicable value should be selected.
CT, computed tomography; US, ultrasound; MR, magnetic resonance

Loveday BP, et al, 2011: A comprehensive classification of invasive procedures for treating the local complications of acute pancreatitis based on visualization, route, and purpose. *Pancreatology* 11:406-413.

visualized with an endoscope (gastroscope, laparoscope, or nephroscope); radiologic procedures that use computed tomography (CT), ultrasound, or fluoroscopy to visulalize lesions; and hybrid procedures that combine endoscopic and radiologic techniques. The routes taken by these interventions include the *external* route into the body, by mouth or gastrostomy tube, or the *percutaneous route,* through the skin; the *internal routes* used to reach a target lesion might pass through the gastrointestinal wall, peritoneum, or retroperitoneum.

The overall purpose of treatment is to eliminate areas of necrotic and infected tissue or fluid and inflammatory and enzyme-rich exudates. However, the way in which this is achieved varies considerably, and some procedures are much more aggressive than others. Therefore the purpose of individual treatment procedures for PN may be to effect simple drainage alone or to lavage the necrotic cavity to assist drainage of necrotic debris, fragment necrotic tissue to facilitate its drainage, debride necrotic tissue, or excise or resect the pancreas. The overall aim of intervention is to control the septic focus and preserve pancreatic function.

Open Surgical Necrosectomy

Three general variations of open necrosectomy are currently practiced: 1) open necrosectomy with open or closed packing, 2) open necrosectomy with continuous closed postoperative lavage, and 3) programmed open necrosectomy. Although these are broadly similar in terms of the necrosectomy, they differ in terms of how they provide egress routes for infected fluid, debris, and tissue. The abdomen is entered though a midline or bilateral subcostal incision. The latter is preferred, as it minimizes contamination of the greater sac and allows easy access to the extremities of the gland. The pancreas is exposed by dividing the gastrocolic omentum or gastrohepatic omentum to access the pancreas through the lesser sac. The body and tail of the pancreas (Fig. 54.1) can also be exposed by elevating the transverse colon and gaining access to the lesser sac via the transverse mesocolon (Fig. 54.2). Inflammatory adhesions may exist between the pancreas and stomach or transverse mesocolon, and great care is required during exposure. It is generally useful to take down both the hepatic and splenic flexures, if possible, as this will facilitate exposure and reduce the risk of colonic fistula secondary to drain erosion. When the process involves the head of the pancreas, access might require medial mobilization of the duodenum.

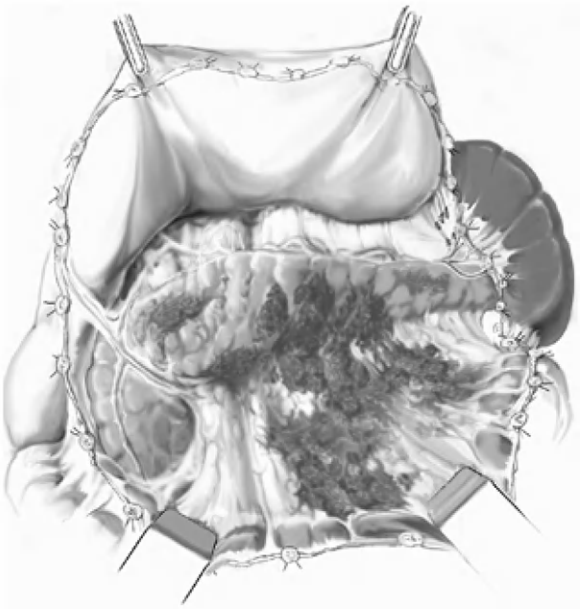


FIGURE 54.1. Access to the pancreas via the gastrocolic omentum. *(From Uhl W, et al, 2007: Necrosectomy. In Clavien P-A, et al (eds): Atlas of Upper Gastrointestinal and Hepato-Pancreato-Biliary Surgery. New York, Springer, pp 893-915.)*

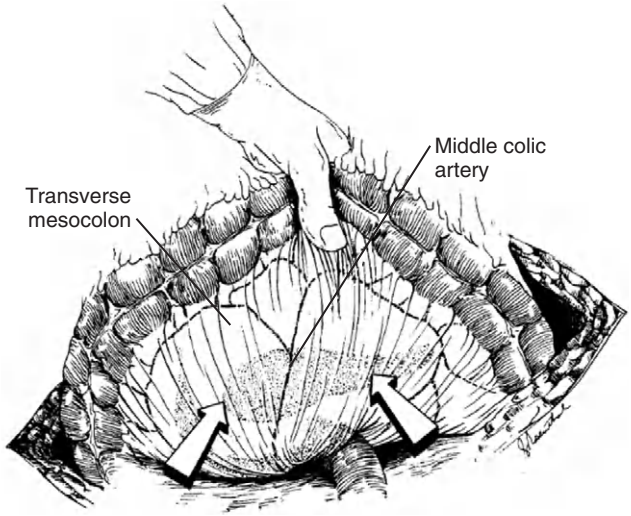


FIGURE 54.2. Access to the pancreas via the transverse mesocolon. *(From Mithofer K, et al, 1997: Interventional and surgical treatment of pancreatic abscess. World J Surg 21[2]:162-168.)*

Open Necrosectomy with Closed Packing

The goal of necrosectomy with closed packing is to perform a single operation by performing a thorough debridement and removal of necrotic and infected tissue to minimize the need for reoperation or subsequent drainage (Pezzilli et al, 2007). Primary closure of the abdomen is the intention. Once the necrotic cavity is opened, fluid collections are drained, and the exposure is enlarged to allow debridement of all areas of necrosis, including those in the perirenal and paracolic spaces. Early advocates used gauze-stuffed Penrose drains placed via separate stab incisions, but many variations are in practice with regard to the type and number of drains. Between 2 and 12 drains are placed with the intention to fill the cavity and provide some compression. Additional silicone drains (Jackson-Pratt) are placed in the pancreatic bed and lesser sac for fluid drainage. The stuffed Penrose drains are removed one every other day, starting 5 to 7 days postoperatively, allowing a slow collapse of the cavity. The silicone drains are removed later.

Open Necrosectomy with Open Packing

The difference with this approach is that the abdomen is left open after debridement and packing of the pancreatic bed, lesser sac, and retroperitoneum (Gotzinger, 2008). Drains are placed in addition to the packing. Sometimes the abdomen is closed, and the packing is accessed via separate flank incisions (Nakasaki et al, 1999). Open packing techniques have been reported to have higher incidences of fistulae, bleeding, and incisional hernias as well as a slightly higher mortality rate (Heinrich et al, 2006). However, it should be noted that no prospective trials have compared open packing with any other technique.

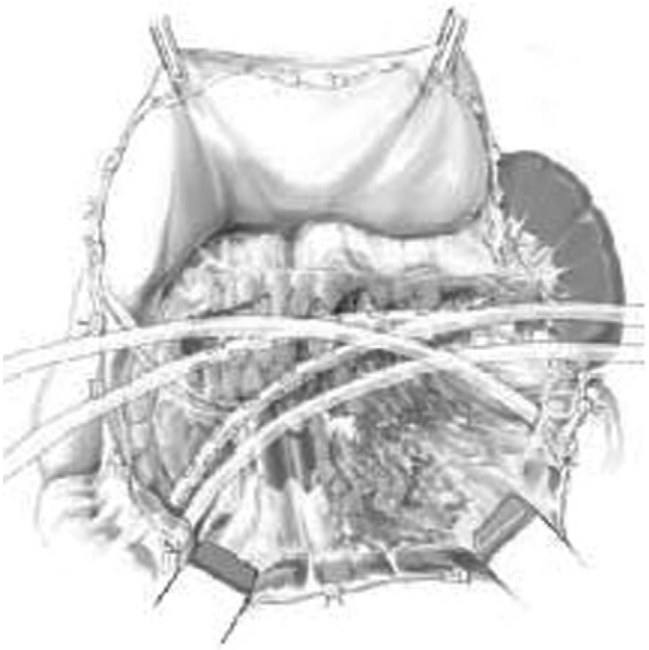


FIGURE 54.3. Open necrosectomy with continuous closed postoperative lavage. *(From Uhl W, et al, 2007: Necrosectomy. In Clavien P-A, et al (eds): Atlas of Upper Gastrointestinal and Hepato-Pancreato-Biliary Surgery. New York, Springer, pp 893-915.)*

Open Necrosectomy with Continuous Closed Postoperative Lavage

In this approach, debridement is followed by continuous peripancreatic lavage to remove infected necrotic debris, peripancreatic exudates, and extravasated pancreatic exocrine fluid (Fernandez-del Castillo et al, 1998). The large silicone drainage catheters are placed into the pancreatic bed to inflow and outflow isotonic irrigation fluid (Fig. 54.3). During closure, a closed peripancreatic compartment is made by resuturing the gastrocolic and duodenocolic ligaments. Postoperative continuous lavage is instituted at 1 to 10 L per day and should be continued until the effluent is clear and the patient shows improvement in clinical and laboratory parameters (Wig et al, 2004). No evidence is available to suggest the best irrigation fluid, the optimal number or caliber of drains, or the duration of irrigation.

Programmed Open Necrosectomy

The principle of this approach is to be more conservative with debridement, particularly if necrosum has not fully demarcated, with the intention of performing repeat procedures every 48 hours until debridement is no longer required. The pancreatic bed is drained or packed, and the abdomen is closed by suturing mesh or a zipper to the fascial edges of the wound. This allows multiple reentries and helps to prevent wound retraction, which aids in later delayed primary wound closure. In a proportion of patients, primary closure is not possible, and secondary intention healing is allowed to occur, accepting that this may require elective scar excision and repair of an incisional hernia. This procedure may be modified with the addition of intra-abdominal vacuum sealing (negative pressure 50 to 75 mm Hg) to encourage granulation of the pancreatic bed, potentially reducing the number of operations and mortality (Olejnik et al, 2008).

Several approaches to open surgical necrosectomy are possible. Comparing them has limited value in the absence of controlled trials because of variations in referral patterns, selection criteria, patient comorbidities, and the use of presurgical percutaneous management. Most techniques are associated with a 15% to 25% mortality rate, but this can be higher in patients with multiple organ failure and in those who have had early surgery. The important principles are adequate exposure guided by high-quality preoperative CT scanning, gentle debridement of demarcated dead tissue, preservation of viable pancreatic tissue, and thorough irrigation of the pancreatic bed, lesser sac, and retroperitoneum. Packing is probably best reserved to control hemorrhage, as it is associated with an increased risk of enteric fistulae. The placement of wide-bore dependent drains allows further egress of necrotic and infected material, aided by continuous irrigation, which may reduce the need for reoperation. In rare cases, when a necrosectomy is indicated within the first 2 weeks, an open approach should be considered because of the higher probability of requiring multiple procedures.

Endoscopic Techniques

In 1996, Gagner described the first true endoscopic treatment of necrotizing pancreatitis, in which the pancreas was debrided using a laparoscopic approach. Over the last decade, a wide range of endoscopic approaches for pancreatic necrosectomy have been described, including infracolic laparoscopy, transgastric laparoscopy, hand-assisted laparoscopy, retroperitoneal laparoscopy, transgastric flexible endoscopy, flexible endoscopy via a percutaneous endoscopic gastrostomy, and retroperitoneal nephroscopy (Ammori, 2002; Baron & Morgan, 1999; Charnley et al, 2006; Cuschieri et al, 1998; Horvath et al, 2001; Parekh, 2006). This array of endoscopic techniques can be classified by the type of scope that is used: laparoscope, nephroscope, or flexible endoscope (Windsor, 2007). Although some endoscopic procedures do not utilize radiologic modalities, many are hybrid procedures that incorporate fluoroscopy or endoscopic ultrasound into the procedure.

Laparoscopic Techniques

Most laparoscopic techniques are minimally invasive versions of open surgical techniques, and they use an anterior or lateral approach. In Gagner's original (1996) description of laparoscopic necrosectomy, two anterior routes—*retrogastric retrocolic* and *transgastric*—and one lateral route were described. In the retrogastric retrocolic route, a 30-degree laparoscope is introduced through the umbilical port following CO_2 insufflation (15 mm Hg). Placement of additional ports depends on the location of the necrosis. Following necrosectomy, large sump drains are placed in the necrotic beds, and continuous lavage may be established to remove peritoneal contaminants. In the transgastric route, the stomach is opened anteriorly and posteriorly. Endoluminal ports are used, which maintain the tip of the port inside the stomach. Debridement is performed internally through the posterior stomach wall, in a technique akin to an open cystogastrostomy. It is also possible to use a transduodenal route for necrosis of the pancreatic head, although this can be more difficult. No drains are left in the stomach, but a drain may be placed over the incision in the anterior gastric wall. With the retroperitoneal route, the patient is placed in the

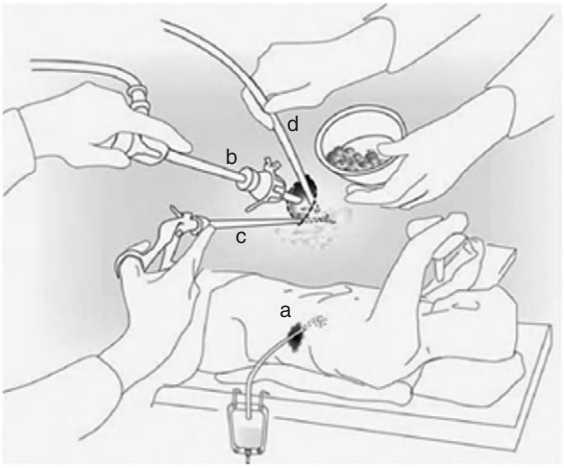


FIGURE 54.4. Videoscopic-assisted retroperitoneal debridement technique. *(From van Santvoort HC, et al, for the Dutch Acute Pancreatitis Study Group, 2007: Case-matched comparison of the retroperitoneal approach with laparotomy for necrotizing pancreatitis. World J Surg 31:1635-1642.)*

left or right lateral position, and a small flank incision made. The three muscle layers of the abdominal wall are split, and a trocar is inserted. Using a 0-degree laparoscope and CO_2 insufflation (10 to 15 mm Hg), a tract is made through to the pancreas. Once the necrotic areas have been identified, necrosectomy proceeds as when approached via a retrogastric retrocolic route.

These techniques have subsequently been modified. Of the lateral approaches, one of the most widely used laparoscopic techniques is *videoscopic-assisted retroperitoneal debridement* (VARD; Fig. 54.4), which was first described by Horvath and colleagues in 2001. The purpose of this procedure differs from those of open necrosectomy. Rather than performing complete removal of all infected and necrotic tissue, the purpose of VARD is to facilitate percutaneous drainage. In this technique, radiologic drainage of the lesion is first instituted. In the operating room, the patient is placed in a modified left lateral decubitus position, and a 4- to 5-cm incision is made in the left flank at the site of the drain. A finger is used to probe and confirm entry into the necrotic cavity. Fluid and loose necrotic debris are removed by suction, and two ports (10 to 12 mm) are inserted through the incision. The incision is sealed with wet sponges and towel clips to allow insufflation with CO_2. Debridement of necrotic tissue is performed with hydrodissection and 10 mm forceps. Drains are placed for postoperative continuous lavage: a 10-Fr red rubber drain is brought through a separate anterolateral incision, and two 1.3-cm (0.5-inch) Penrose drains are placed in the original skin incision. An ostomy bag is then positioned over the flank incision and Penrose drains, and continuous lavage is performed through the red rubber drain at 200 mL/h for 5 days or until the effluent is clear.

Variations of the anterior laparoscopic approaches are well described. In addition to the retrogastric, recolic, and transgastric routes, a transmesocolic route may be used, in which the transverse colon is elevated to expose the pancreatic lesion in the lesser sac (Cuschieri et al, 1998). Laparoscopic ultrasound may be used to confirm the position of the lesion, and the transverse mesocolon is usually opened to the left of the middle colic vessels. Following necrosectomy, two or more drains are placed in the pancreatic bed for postoperative lavage of the lesser sac. Anterior approaches may also incorporate a hand-assist device; this is termed *hand-assisted laparoscopic surgery* (HALS; Parekh, 2006). Another recent publication described single-port laparoscopic necrosectomy (Bucher et al, 2008). Port placement (12 mm) is through postlaparotomy drain tracts, allowing introduction of both a 4-mm laparoscope and 5-mm instruments. Insufflation pressures are kept to 8 mm Hg, as higher pressures may promote bacterial translocation from the cavity. Debridement is performed with both hydrodissection and atraumatic grasping forceps, hemostasis is achieved with monopolar diathermy, and a sump drain is placed for continuous postoperative lavage.

Nephroscopic Techniques

Nephroscopic techniques utilize warmed fluid to expand the necrotic cavity, irrigate turbid fluid, and maintain a clear visual field. Carter and colleagues (2000) were the first to describe the use of a nephroscope during necrosectomy, terming the procedure *percutaneous necrosectomy*. The principle underlying this procedure is the same as for an open procedure: debridement of devitalized tissue and establishment of a system for continuous postoperative lavage—with reduced physiologic stress on the patient. Percutaneous necrosectomy may only be used when the area of necrosis is accessible to percutaneous puncture, and it is contraindicated in the presence of bowel ischemia, perforated viscus, or significant preoperative hemorrhage. The first step is to insert a drainage catheter into the pancreatic lesion under CT guidance. The preferred path for drainage is between the lower pole of the spleen and the splenic flexure (Fig. 54.5), although in right-sided necrosis, a path through the gastrocolic omentum, anterior to the duodenum, may occasionally be used. The patient is then transferred to the operating room and positioned in the left lateral position, or for right-sided necrosis, in the right lateral position. A nephrolithotomy drape is used to collect irrigant fluid, and the drain tract is dilated to allow insertion of a 34-Fr Amplatz sheath. A nephroscope is inserted through the sheath into the cavity, and lavage is used to clear away debris and suppurative fluid (Fig. 54.6). Following necrosectomy, a 32-Fr soft drainage tube is left in the cavity. A smaller (8-Fr) catheter can be inserted through or alongside the larger drain to allow continuous postoperative lavage. This might be commenced at 250 mL/h with warmed dialysis fluid. Repeat procedures are often required after 2 to 10 days (Carter & Wysocki, 2008).

Flexible Endoscopic Techniques

The use of flexible endoscopy to treat patients with PN has a long history. In 1991, Prinz and Olen recognized that some areas of the abdomen were difficult to access during open necrosectomy as a result of the inflammatory process, therefore a choledochoscope was passed through the open abdomen to debride necrosis located in the lower retroperitoneum following open necrosectomy (Prinz & Olen, 1991). Since that time, the use of flexible endoscopes has developed considerably, with many different techniques currently available, as discussed below. In these procedures, the endoscope is either inserted via an external orifice, usually the mouth, or a skin incision is made.

Peroral flexible endoscopic techniques follow an internal route through either the gastric/duodenal wall or duodenal papilla, and some authors consider this to be a form of natural orifice transluminal endoscopic surgery (Friedland et al, 2009). Initial descriptions of flexible endoscopic treatment of PN used

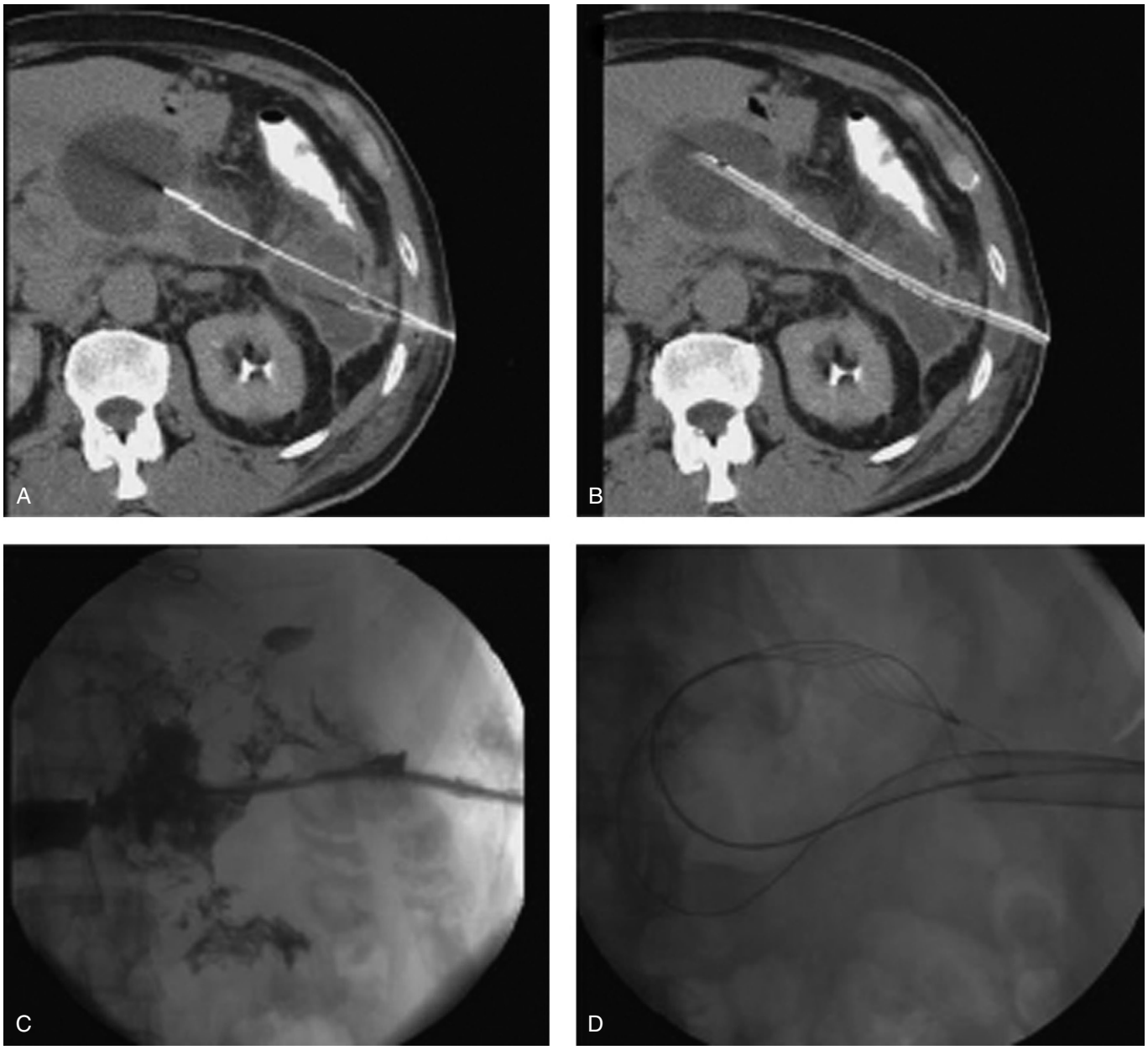


FIGURE 54.5. Insertion of a drainage catheter under CT guidance. *(From Bruennler T, et al, 2008: Percutaneous necrosectomy in patients with acute, necrotizing pancreatitis. Eur Radiol 18[8]:1604-1610.)*

lavage and drainage without instrumental debridement (Baron et al, 1996). A more aggressive approach was subsequently introduced, which demonstrated that necrotic tissue may be debrided with baskets, snares (Fig. 54.7), forceps, and suction (Seewald et al, 2005). A recent long-term multicenter study of transluminal endoscopic necrosectomy described 93 patients who underwent a mean of six interventions, starting at a mean of 43 days after the onset of severe acute pancreatitis (Seifert et al, 2009). Initial clinical success was obtained in 80% of patients but with a complication rate of 26% over 43 months of follow-up; 16% developed recurrent pancreatitis, 10% required further endoscopic procedures, 4% required surgical treatment, and the mortality rate was 7.5% at 30 days. Surgical necrosectomy was required in 12% of patients.

Endoscopic retrograde pancreatography (ERP) can be used to diagnose any communication between the duct and cavity or duct stenosis or disruption, and transpapillary stenting can be employed to decompress the duct. Puncture of the posterior gastric wall into the pancreatic lesion may be performed at the point of maximal bulging, although confirmation of the location with endoscopic ultrasound helps achieve correct placement of the perforation and avoids injury to vessels. A successful puncture is confirmed with aspiration of suppurative fluid from the cavity.

The injection of contrast with fluoroscopy can be used to determine the extent of the cavity. The gastric perforation is dilated with balloons up to 20 mm. For lavage and drainage, a 7-Fr nasocystic (lavage) and a 10-Fr pigtail drain (drainage) are

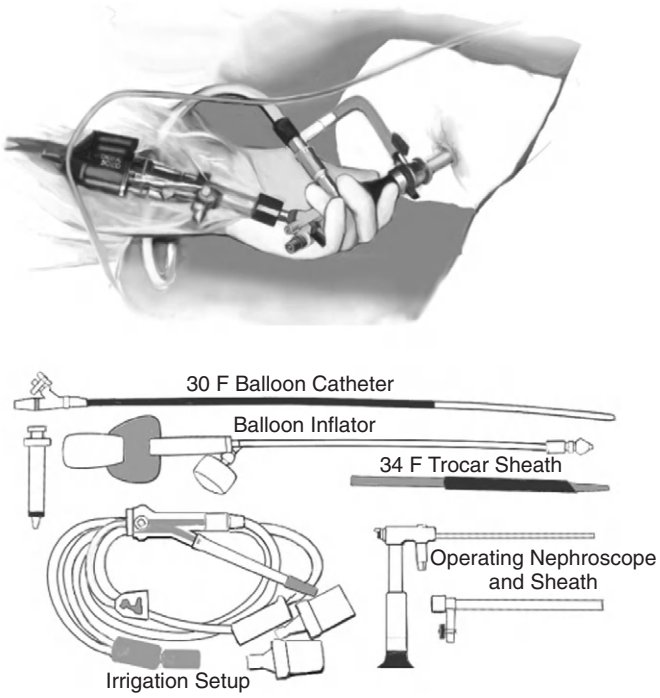


FIGURE 54.6. Percutaneous necrosectomy technique. *(From Uhl W, et al, 2007: Necrosectomy. In Clavien P-A, et al (eds): Atlas of Upper Gastrointestinal and Hepato-Pancreato-Biliary Surgery. New York, Springer, pp 893-915.)*

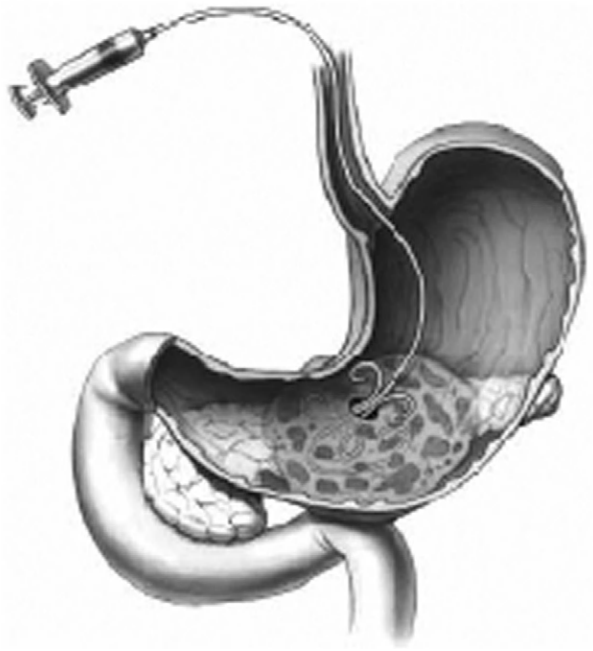


FIGURE 54.8. Transmural drainage of organized pancreatic necrosis. *(From Baron TH, et al, 2002: Outcome differences after endoscopic drainage of pancreatic necrosis, acute pancreatic pseudocysts, and chronic pancreatic pseudocysts. Gastrointest Endosc 56[1]:7-17.)*

placed in the cavity (Fig. 54.8). Continuous lavage with 1500 mL/day saline is established. Necrosectomy may be performed with endoscopic instruments, such as a Dormia basket or polypectomy snare, and introduction of a forward-viewing endoscope into the necrotic cavity can be used for better visualization during the necrosectomy. Multiple necrosectomy procedures are usually required to clear the cavity of necrotic tissue. A similar procedure may be performed with external entry into the body via a percutaneous endoscopic gastrostomy (PEG) tube (Baron & Morgan, 1999).

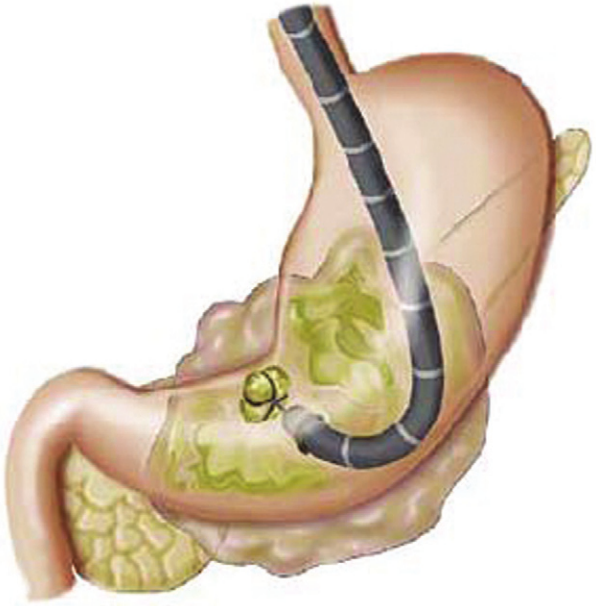


FIGURE 54.7. Pancreatic necrosis debridement with the use of flexible endoscope. *(From Seewald S, et al, 2005: Aggressive endoscopic therapy for pancreatic necrosis and pancreatic abscess: a new safe and effective treatment algorithm [videos]. Gastrointest Endosc 62[1]:92-100.)*

Several techniques using flexible endoscopy through skin incisions have been described. The first was by Prinz and Olen (1991) after open necrosectomy, as detailed above. Following percutaneous necrosectomy with a nephroscope, subsequent debridement may be undertaken using a flexible endoscope, a so-called *sinus-tract endoscopy* (Carter et al, 2000). The drain tract is dilated to 45 Fr, and a flexible endoscope is inserted into the cavity for necrosectomy. A similar technique has been described following open necrosectomy via a translumbar incision, in which a flexible endoscope is inserted into the cavity for debridement of ongoing necrosis (Jakobs et al, 2000). These endoscopic debridements were initiated 10 days after the open necrosectomy and were carried out every 3 days for 4 weeks (approximately 8 to 10 sessions).

The plethora of endoscopic approaches to necrosectomy and the absence of formal comparison make a recommendation for the optimal approach problematic. The selection of an endoscopic technique will be influenced by training, experience, and the availability of equipment, but it will also be determined by the location and complexity of the target lesion and the clinical status of the patient.

Radiologic Techniques

Interventional radiology techniques are assuming greater importance, particularly for initial sepsis control to allow definitive necrosectomy to be performed more electively (Jakobs et al, 2000). Ultrasound, fluoroscopy, or CT is used to guide the interventional radiologist into the pancreatic lesion. These

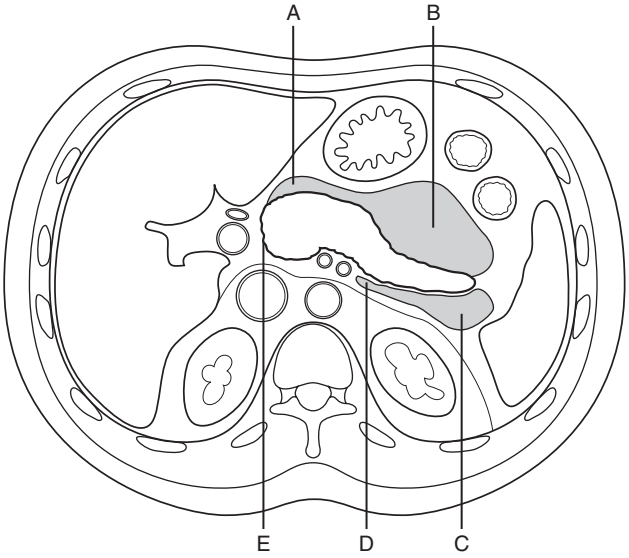


FIGURE 54.9. Common percutaneous access routes for drainage of pancreas and peripancreatic sites. **A,** Transhepatic. **B,** Transgastric. **C,** Retroperitoneal from left flank. **D,** Paravertebral. **E,** Subhepatic. *(Modified from Lee MJ, Wittich GR, Mueller PR, 1998: Percutaneous intervention in acute pancreatitis. Radiographics 18[3]:711-724.)*

radiologic modalities are also used to define the extent and composition of the lesion, visualize the instruments used, and determine the efficacy of the treatment procedure. The purpose of radiologic techniques may be to achieve either drainage, with or without lavage, or debridement.

Radiologic Drainage Techniques

Drainage techniques are most effective if target lesions have a significant fluid component. They can be located in many sites but are most often in the lesser sac, anterior and left pararenal spaces, and other parts of the retroperitoneum (Fig. 54.9; Jakobs et al, 2000). Image-guided needle puncture of the lesion may involve a retroperitoneal or transperitoneal route and may be transmural (transgastric or transduodenal), but a retroperitoneal approach is preferred to reduce the risk of contamination and possible peritonitis (Jakobs et al, 2000). A guidewire is passed down the needle, and the tract is dilated to accommodate a catheter. Because catheters readily block with necrosum and debris, it is advisable to maximize catheter diameter to improve patency. Typically, catheters should have multiple sideholes and a minimum diameter of 12 Fr (Jakobs et al, 2000). Drain tracts may be serially dilated to accommodate larger catheters (20 to 24 Fr). Often multiple catheters are required, especially for large or complex lesions. To increase the efficacy of the drainage procedure, remove toxic factors, and help maintain catheter patency, lavage should be considered (Eatock et al, 2005; Jakobs et al, 2000). Theoretical concerns have been raised that lavage may spread infection, either from infected fluid spilling over into previously sterile cavities or from the increased intracavity pressure, resulting in translocation of bacteria into surrounding tissues. However, this has not been demonstrated as a major problem clinically, most likely because the pancreatic lesion is walled off in a fibrous capsule 4 to 6 weeks after the onset of acute pancreatitis.

The efficacy of radiologic drainage procedures is reduced with more solid lesions. In patients with PN treated with percutaneous catheter drainage, approximately half will be successful and will not require surgical intervention (Jakobs et al, 2000). Indications for surgical intervention in patients who have undergone percutaneous catheter drainage include persistent systemic or local manifestations of infected PN, physiologic deterioration despite the placement of a patent drain, persistent abdominal pain, and intolerance of oral intake after the systemic inflammatory response syndrome has resolved (Jakobs et al, 2000).

Radiologic Debridement Techniques

In some specialized centers, radiologic techniques have been used to debride PN. These procedures are similar to percutaneous catheter drainage, as described above, but they also include removal of necrotic material with snares, baskets, or even by applying suction to a catheter during its removal (Economou & Ward-McQuaid, 1971; Jakobs et al, 2000; Thompson, 2001). Necrotic tissue may be fragmented with wires before attempting its extraction (Blamey et al, 1984; Jakobs et al, 2000), and lavage is recommended to flush out loosened necrotic debris.

A tailored approach to the treatment of the local complications of acute pancreatitis is required and must take into account the specific lesion, the patient's status, and the operator's expertise. Strong trends toward delayed intervention and less invasive intervention have been seen. Radiologic drainage has assumed a more important role for the definitive treatment of predominantly fluid-filled lesions and to delay definitive necrosectomy, either by minimally invasive or open methods. The convergence of technologies is apparent, and the plethora of minimally invasive techniques can now be classified to facilitate accurate description and much needed RCTs.

CONCLUSION

The management of acute pancreatitis remains a formidable challenge and continues to evolve. Although specific treatments for acute pancreatitis remain elusive, progress has been made in the management of pain, fluid resuscitation, antibiotic prophylaxis, enteral nutrition, therapeutic ERCP, and cholecystectomy. Progress has also been made in the intensive care management of systemic complications and in the development of less invasive interventions for the treatment of local complications, particularly infected pancreatic necrosis. This chapter has highlighted the need for more evidence to guide decision making, quell persisting controversies, and reduce variations in practice, particularly in patients with severe and critical acute pancreatitis.

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CHAPTER 55A

Chronic pancreatitis: etiology, pathogenesis, and diagnosis

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OVERVIEW

The most common etiology of chronic pancreatitis (CP) in adults in Western societies is long-term alcohol abuse, which accounts for 70% of cases. Although many of the etiologies of CP are well known, as are the clinical and morphologic characteristics, the pathogenic mechanisms of CP have remained elusive. Major scientific progress has been made in the understanding of the underlying genetic, cellular, and molecular aspects of CP, but ongoing debate continues regarding the initiating events of the various factors of CP. Multiple hypotheses have been proposed to explain the pathophysiology in subgroups of patients with CP, but to date no single, unifying theory exists. The best known hypotheses about the pathogenesis of CP include necrosis-fibrosis, toxic-metabolic causes, oxidative stress, plug and stone formation with duct obstruction, primary duct obstruction, and the sentinel acute pancreatitis event (SAPE).

CP is a well-defined disease on histopathologic grounds, but histology is rarely available for diagnosis; therefore the diagnosis is reached by using a combination of clinical, laboratory, and imaging criteria. The correct diagnosis of CP is easy in late stages but difficult in early stages of the disease. Several imaging methods are available for patients with known or suspected CP. In early stages of the disease, both endoscopic retrograde pancreatography (ERP; see Chapter 18) and endoscopic ultrasonography (EUS; see Chapter 14) are methods with reliable diagnostic accuracy. Initial studies have shown superiority of EUS over ERP for the diagnosis of CP in its early stages. Transabdominal ultrasonography (US) is less sensitive for diagnosis of CP and is limited only to patients with advanced disease. In patients with an early stage of disease, we believe that EUS is the method of choice. In the absence of EUS, the combination of ERP and computed tomography (CT; see Chapter 16) provides the most reliable morphologic information. Among all imaging methods, magnetic resonance imaging (MRI), includingmagnetic resonance cholangiopancreatography (MRCP), has seen the most rapid development over the last years (see Chapter 17). With further improvement of hardware and software, it is likely that these methods will be capable of visualizing even early stages of the disease in the near future. The most common pancreatic function tests do not detect mild to moderate exocrine pancreatic insufficiency with adequate accuracy, therefore functional investigation techniques of the pancreas play only a complementary role in the routine clinical evaluation of CP but are important methods used in clinical research and in specialized pancreatic disease centers.

This chapter is divided into three sections. The first part presents the known etiologies of CP; the second part is a discussion of the most important pathogenic mechanisms of CP. The etiology and pathogenesis of CP are presented based on the TIGAR-O classification (***t***oxic–metabolic, ***i***diopathic, ***g***enetic, ***a***utoimmune, ***r***ecurrent severe, ***o***bstructive) proposed by Etemad and Whitcomb (2001) and elegantly delineated by Stevens and colleagues (2004). It is inevitable that data must be provided on the pathogenesis of CP while presenting its etiology and vice versa; in this manner, the reader will have a better comprehension of the disease process. The third part of this chapter discusses an approach to the diagnosis of CP, with emphasis on the use of radiologic diagnostic methods, and a brief discussion of the most commonly used pancreatic function tests.

ETIOLOGY OF CHRONIC PANCREATITIS

The classification of CP has evolved during the last several decades, and the basis for such classification stems from three consensus conferences: Marseille in 1963, Marseille-Rome in 1986, and Cambridge in 1984 (Axon et al, 1984; Sarles, 1986, 1991; Singer et al, 1985). Subdivisions of CP are based mainly on imaging characteristics, but newer classification systems such as the TIGAR-O categorize CP based on the various known etiologic factors and mechanisms jointly considered to be risk modifiers (Chari & Singer, 1994; Etemad & Whitcomb, 2001). It is likely that these risk modifiers, as well as multiple genetic and environmental cofactors, interact to produce expression of the disease in a given individual (Bourliere et al, 1991; Cavallini et al, 1994; Cavestro et al, 2003; Cohn et al, 1998; Ichimura et al, 2002; Whitcomb, 2001). It is clear that an individual, whose genetic composition is unique, will respond or not respond to an insult of similar etiology in a different morphologic pattern (inflammation or no inflammation) giving rise to disease. Response to an insult results in presence or absence of disease and progression or regression of the disease. Progression is likely to be closely related to the individual's genetic characteristics and to ongoing environmental toxic or infectious insults. This general concept explains why individuals respond differently to the same amounts of a toxin, such as alcohol, or why less amounts of the same toxin produce disease in a susceptible individual. Furthermore, the low prevalence of CP among alcoholics would seem to suggest other cofactors at play in many with diagnosed "alcoholic" pancreatitis. In fact, the presence of multiple risk factors may be required for progression to fibrosis. The various etiologies of CP based on the TIGAR-O system (Stevens et al, 2004) provide a further advancement in the etiologic and mechanistic classification of CP, although we anticipate it will likely require revision in the future. For example, the category of "idiopathic" will tend to decrease or even disappear as other etiologies are being discovered (Jansen

Table 55A.1

Etiopathogenesis of Chronic Pancreatitis

Etiology/Mechanism of Injury	Pathogenesis	Etiology/Mechanism of Injury	Pathogenesis
Toxic-Metabolic		**Autoimmune and Immunologic**	
Alcohol i (genetic mutations) Tobacco Hypercalcemia (hyperparathyroidism) Lipoprotein lipase deficiency Apolipoprotein C-2 deficiency Chronic renal failure (uremia) Protein deficiency Trace element deficiency Dietary toxins Medicinal products (phenacetin)	Protein plug obstructive hypothesis Toxic-metabolic hypothesis Necrosis-fibrosis Oxidative stress (detoxification insufficiency)	Viral infection Hepatitis B Coxsackie Autoimmune diseases Primary AIP Associated with Sjögren syndrome, Crohn disease, ulcerative colitis, primary biliary cirrhosis	Large duct
Idiopathic		**Recurrent and Severe Acute Pancreatitis**	
Early onset Late onset Tropical form (*SPINK1* mutations) Tropical calcific pancreatitis Fibrocalculous pancreatic diabetes	Necrosis-fibrosis Protein plug	Vascular disease Ischemia Postradiation therapy	Necrosis-fibrosis
Genetic/Hereditary		**Obstructive Mechanical Causes**	
Autosomal dominant mutations, cationic trypsinogen gene (*PRSS1*) Autosomal-recessive mutations: *SPINK1*, cationic trypsinogen (codons 16, 22, 23) Cystic fibrosis transmembrane conductant regulator (*CFTR*) defects α_1-Antitripsin deficiency	Necrosis-fibrosis	PD with insufficient accessory papilla Annular pancreas Papillary stenosis Ductal scarring Malignant PD stricture (pancreatic, ampullary, or duodenal carcinoma) Duodenal obstruction (diverticulum, duodenal) Stricture of the pancreatic duct after severe acute pancreatitis or trauma Stones Sphincter of Oddi dysfunction Choledochocele	Stone and duct obstruction Protein plug

AIP, autoimmune pancreatitis; PD, pancreas divisum

et al, 2002; Mahlke et al, 2005; Teich et al, 2005; Whitcomb, 2001; Whitcomb et al, 1996a; Whitcomb & Schneider, 2002; Witt et al, 2000, 2001).

Toxic and Metabolic

Table 55A.1 shows the multiple toxic and metabolic etiologies involved in CP. The association of alcohol and CP was first described almost 60 years ago by Comfort and colleagues (1946). Alcohol is still the most common cause of CP in Western industrialized countries, but interestingly, only 5% to 10% of alcoholics develop clinically apparent CP; at autopsy, 10% to 20% of alcoholics are found to have evidence of CP (Ammann, 1997; Ammann et al, 1994; Ammann et al, 1999; Angelini et al, 1993; Bernades et al, 1983; Layer & Melle, 2004; Sarles et al, 1989). Therefore, the majority of alcohol abusers never develop CP. Most patients (60% to 90%) with CP have a history of 10 to 15 years of heavy alcohol consumption, but some individuals have drunk less during a shorter period and still develop CP. This is especially true for patients who began to drink alcohol during puberty (Layer & Melle, 2004). The critical threshold of daily alcohol intake has been estimated to be about 40 g daily for women and 80 g daily for men, regardless of the quality or type of the alcoholic beverage (Layer & Melle, 2004; Papachristou & Whitcomb, 2004). Because the tolerance limits for alcohol differ substantially among individuals, smaller amounts of alcohol may be sufficient to induce pancreatic damage in susceptible individuals.

In the past it was believed that at the time of the initial attack, most patients with alcohol-induced CP already had underlying fibrosis and calcifications of the pancreas, but the Zürich group has demonstrated that acute attacks preceded the development of chronic disease (Ammann & Muellhaupt, 1994). Because only a fraction of alcoholics develop CP, involvements of other factors are actively being investigated. Several lines of evidence have shown that in addition to the direct effects of alcohol, various predisposing factors, such as genetics, smoking, intestinal infection, high-fat diet, compromised immune function, gallstones, gender, hormonal factors, and drinking patterns, may render the pancreas more susceptible to alcohol-induced tissue injury (Angelini et al, 1993; Lankisch et al, 2002; Levy et al, 1995; Lowenfels et al, 1994; Sahel et al, 1986). Many patients thought to have CP as a result of alcohol abuse, may indeed have a higher inherited susceptibility to alcohol-induced pancreatic damage or genetic defects that cause pancreatitis independent of alcohol exposure (Malats et al, 2001; Stevens et al, 2004).

There is convincing evidence that smoking is also independently associated with increased risk for CP, with odds ratios as high as 17.3 (Talamini et al, 1996). CP induced by smoking is particularly associated with pancreatic calcifications. By mechanisms similar to alcohol, tobacco produces alterations in the secretion and composition of pancreatic juice mainly as a result of decreased pancreatic juice and bicarbonate secretion and induction of oxidative stress (Bynum et al, 1972; Cavallini et al, 1994; Crowley-Weber et al, 2003; Stevens et al, 2004). In a large study involving 146 patients with CP, 52 patients with pancreatic cancer, and 235 healthy controls, Ockenga and colleagues (2003) analyzed the genomic DNA for expression of uridine 5′-diphospho (*UDP*) glucuronosyltransferase (*UGT1A7*) genes. These proteins are vital biochemical factors for detoxification and cell defense. The incidence of this mutation was much more common in patients with CP and tobacco abuse but not in

patients with nonalcoholic CP. This study establishes the possible connection between genetic predisposition and external triggering factors. It is possible that smoking is the main factor of CP in some patients, whereas in others smoking may increase the damage induced by alcohol, and in another group it might potentiate an as yet unidentified factor or pathogen (Crowley-Weber, 2003).

Calcium plays a central role in trypsinogen secretion and trypsin stabilization. Hypercalcemia as a result of primary or secondary hyperparathyroidism results in recurrent acute pancreatitis, which progresses to CP, likely due to trypsinogen activation, which in turn results in necrosis and fibrosis of the parenchyma (Goebell, 1976; Noël-Jorand et al, 1981). Increased serum calcium concentration is believed to induce direct damage to acinar cells, and increased secretion of calcium results in intraductal stone formation. It also appears that hypercalcemia modifies pancreatic secretion and leads to protein plug formation (Goebell, 1976; Noël-Jorand et al, 1981), in turn resulting in varying degrees of pancreatic fibrosis with calcifications. This is likely due to hypercalcemia related to secondary hyperparathyroidism, but other mechanisms msy nr involved, including toxicity of uremic substances to the pancreatic parenchyma (Karanjia et al, 1992; Owyang et al, 1982).

Idiopathic

Up to 30% of patients with CP have no known risk factors; therefore the CP they have is called *idiopathic*. It is likely that many of these patients are mislabeled because of underreported alcohol abuse, an underlying genetic abnormality, or other unknown factors (Truninger et al, 2002; Witt, 2000). Pfützer and colleagues (2000) and Witt and colleagues (2000) have described mutations of the serine protease inhibitor Kazal type 1 (*SPINK1* gene) in up to 25% of patients with idiopathic CP. Based on the bimodal age of onset of the clinical symptoms, idiopathic pancreatitis is separated into two distinct entities: *Early idiopathic CP* is seen during the first 2 decades of life, with abdominal pain being the predominant clinical feature, whereas pancreatic calcifications and exocrine and endocrine pancreatic insufficiency are very rare at the time of first diagnosis (Layer et al, 1994). In contrast, the clinical presentation of *late-onset idiopathic CP* is in patients during their fifth decade of life, usually following a rather painless course but associated with significant exocrine and endocrine pancreatic insufficiency and pancreatic calcifications (Layer et al, 1994; Papachristou & Whitcomb, 2004). Histologically, many cases of idiopathic chronic pancreatitis have T-lymphocyte infiltration, ductal obstruction, acinar atrophy, and fibrosis, raising the possibility of autoimmune etiology.

Tropical or *nutritional pancreatitis* is considered a form of idiopathic CP. It is the most common form of CP in certain parts of the world, such as India, sub-Saharan Africa, and Brazil, where it is a disease of youth and young adulthood (Schneider et al, 2002). The disease is subdivided into *tropical calcific pancreatitis,* characterized by severe recurrent and chronic abdominal pain and extensive pancreatic calcifications and fibrocalculous pancreatic diabetes with significant pancreatic endocrine insufficiency. This form of CP is clearly related to mutations in the *SPINK1* gene (Chandak et al, 2002). Based on this important fact, this form of CP is likely going to be categorized as genetic. The *SPINK1* pancreatic secretory trypsin inhibitory (*PSTI*) gene, is responsible for the encoding of *SPINK1* (Chandak et al, 2002; Schneider et al, 2002). *PSTI* has the main function of inhibiting activated trypsin. *SPINK1* is the major intrapancreatic "deactivator" of activated trypsinogen (Kukor et al, 2002; Teich et al, 2005). Trypsin has a central role in the digestion of dietary proteins and in the activation of other digestive enzymes. If the trypsin inhibitory protein malfunctions or cannot bind itself to trypsin, then trypsin is not properly deactivated or destroyed, and it remains active for a longer period of time. This is called a *gain of function* of trypsin (Gorry et al, 1997; Kukor et al, 2002; Pfützer et al, 2000; Sahin-Tóth, 2000; Stevens et al, 2004; Whitcomb et al, 1996a). Other genetic alterations have been described in patients with idiopathic CP. Cohn and colleagues (1998) and Durie (1998) independently demonstrated the strong association between cystic fibrosis transmembrane regulator (*CFTR*) mutations and idiopathic CP. In patients without evidence of cystic fibrosis, the frequency of *CFTR* mutations was six times that of patients without mutations. Subsequently, Cavestro and colleagues (2003) reported that one third of all patients with idiopathic CP have *CFTR* mutations. In the future, many patients categorized under idiopathic CP will fall into the categories of the other risk factor groups, specifically in the genetic category. In fact, leading pancreatologists speculate that most CP might be a genetic disease with multifactorial triggering factors (Papachristou & Whitcomb, 2004; Stevens et al, 2004; Whitcomb et al, 1996b).

Genetic

Until a few years ago, data on the genetic basis of CP were scarce. The only well-studied hereditary form of chronic pancreatic insufficiency was cystic fibrosis (Cohn et al, 1998; Durie, 1998). Many cases of CP represent a variable part of the cystic fibrosis syndrome, which is caused by mutations in the gene coding for the cystic fibrosis transmembrane conductance regulator. Several groups have reported an increased prevalence of *CFTR* mutations in patients with chronic pancreatitis of different etiologies. Later studies demonstrated that the mutations associated with cystic fibrosis (*CFTR* mutations) were also found with increased frequency in patients with CP (Teich et al, 2005). Interestingly, this mutation was also found to be more frequent in patients with CP thought to be secondary to pancreas divisum (Gelrud et al, 2004).

Other genetic variants predispose for CP. Research has focused on the *SPINK1-N34S* gene mutation, which is also closely associated with tropical (50%), alcoholic (6%), or idiopathic (20%) CP (Schneider et al, 2002; Sahin-Tóth & Tóth, 2000). One of the major discoveries in CP was the description of the point mutation in patients with autosomal dominant hereditary pancreatitis (HP) (Gorry et al, 1997). Several variants of the mutation of the cationic trypsinogen gene exist, all of which lead to a malfunction of trypsinogen (Chandak et al, 2002; Chen et al, 2000; Kukor et al, 2002; Sahin-Tóth, 2000; Teich et al, 2004). Consequently, premature intracellular activation of trypsinogen within the pancreatic acinar cell leads to activation of other enzymes, which may ultimately result in autodigestion (Kukor et al, 2002). Genetic abnormalities have been described more commonly in HP, which present typically in a bimodal pattern of childhood and adulthood (Teich et al, 2004, 2005). Associated with trypsinogen gene mutations, HP is an autosomal dominant disease that carries an 80% penetrance (Howes et al, 2004; Keim et al, 2001; Sossenheimer et al,

1997). HP is characterized by recurrent episodes of acute pancreatitis or familiar aggregation of CP, but most patients with this genetic mutation are asymptomatic (Teich et al, 2005). The progression of CP is faster in patients with *SPINK-N34S* mutation than in patients with cationic trypsinogen mutations (Howes et al, 2004; Keim et al, 2003). Patients with HP have a more than 50-fold increased risk of pancreatic ductal cancer compared with the general population (Howes et al, 2004; Lowenfels et al, 1987). Despite great advances in the knowledge of genetics in pancreatitis, currently it is only advised to evaluate for mutations in patients with HP. The genetic-phenotyping correlation of *SPINK1* or *CFTR* mutations has not been studied well enough to allow for guidelines and recommendations to be established regarding its use in general clinical practice (Ellis et al, 2001; Teich et al, 2005).

Autoimmune

Autoimmune pancreatitis (AIP) is a rare but distinct form of CP characterized by specific histopathologic and immunologic features (Klöppel et al, 2005; Külling et al, 2003; Montefusco et al, 1984). In recent years, it has been established as a special type of CP whose morphologic hallmarks are periductal infiltration by lymphocytes and plasma cells and granulocytic epithelial lesions with consequent destruction of the duct epithelium and venulitis (Klöppel et al, 2003).

The pathogenesis of AIP involves both a cellular (CD4+ and CD8+ T cells) and humoral immune-mediated attack to the ductal cells and pancreatic ducts that results in cytokine-mediated inflammation and periductular fibrosis with subsequent obstruction of the pancreatic ducts (see *primary duct hypothesis*) (Okazaki, 2002). AIP is commonly associated with other autoimmune diseases such as Sjögren syndrome, primary sclerosing cholangitis, and inflammatory bowel disease (Külling et al, 2003; Montefusco et al, 1984). Nevertheless, more than a third of patients with AIP do not have other extrapancreatic autoimmune disorders.

AIP is clinically characterized by minimal abdominal pain and diffuse enlargement of the pancreas without calcifications or pseudocysts, and it most commonly involves the head of the pancreas and the distal bile duct. On occassion, masses have been described as *inflammatory myofibroblastic tumors* (Klöppel et al, 2005). On laboratory examination patients have hypergammaglobulinemia and autoantibodies, such as antinuclear and anti–smooth muscle antibodies (Bovo et al, 1987; Okazaki et al, 2000). Histopathologic examination of the pancreas reveals inflammatory infiltration of lymphocytes and plasma cells around the pancreatic duct, as well as fibrosis, in a pattern similar to primary sclerosing cholangitis (Montefusco et al, 1984; Okazaki et al, 2000).

In 2002, the Japan Pancreas Society was the first in the world to propose diagnostic criteria for autoimmune pancreatitis. These criteria were revised by an Asian consensus conference a few years later (Otsuki et al, 2008).

Recurrent and Severe Acute Pancreatitis

Recurrent acute pancreatitis can result in CP. This form of pancreatitis is discussed in more detail in the chapter on acute pancreatitis, but it is mentioned here as part of the TIGAR-O classification, in which the *R* is for recurrent and severe acute pancreatitis.

Obstructive

Obstruction of the main pancreatic duct is well known to result in CP. The most common etiologies causing CP as a result of obstruction of the pancreatic duct include scars of the pancreatic duct, tumors of the ampulla of Vater and head of the pancreas, and trauma (see Table 55A.1). Other disorders, such as sphincter of Oddi dysfunction and pancreas divisum, have a more tenuous connection with CP. Obstruction of the main pancreatic duct produces changes of CP within weeks in several animal models (Boerma et al, 2003; Reber et al, 1999). Main pancreatic duct obstruction may lead to stagnation and stone formation of pancreatic juice (stone and duct obstruction theory) or acute recurrent pancreatitis and periductular fibrosis (necrosis-fibrosis theory). Histopathologic characteristics of human CP as a result of obstruction include uniform distribution of interlobular and intralobular fibrosis and marked destruction of the exocrine parenchyma in the territory of obstruction, without significant protein plugs and calcifications (Suda et al, 1990). Experiments in cats with obstructive chronic pancreatitis have demonstrated impaired pancreatic blood flow in addition to elevated tissue pressure (Karanjia et al, 1992; Reber et al, 1992). In contrast to the normal hyperemic response, these cats show a decrease in blood flow after secretin injection that constitutes a form of compartment syndrome, as the normal postprandial augmentation of blood flow and oxygen supply is prevented because of decreased tissue compliance and increased interstitial pressures.

PATHOGENESIS OF CHRONIC PANCREATITIS

In the past 50 years, several hypotheses have been postulated to explain the pathogenesis of CP. Debate is ongoing as to which of these hypotheses bests explains the origins of CP, and although each proposes a specific mechanism to explain the pathophysiology, none of them explains the entire pathogenic process in all cases. Thus far, no hypothesis or theory has been able to unify the concepts of the known pathways of CP, and no reported hypothesis convincingly demonstrates the first molecular steps in the development of CP. Six major theories are described, and the reader will no doubt notice that many of the hypotheses share similarities, especially later in the disease process, once the initiating factors of each mechanism have "opened the flood gates" for the amplification and continuation of the process of CP. A close interaction is known to exist between underlying genetic predisposition, triggering factors, inflammatory processes mediated through cytokines, the immunologic process, oxidative and toxic-metabolic stress, changes in the consistency and flow of pancreatic juice, and fibrosis and obstruction of the ducts that play a role in almost every case of CP. Furthermore, every year, new information on cellular, genetic, and molecular mechanisms of pancreatic inflammation and fibrosis emerge, and it is likely that other pathogenic models or the unification of existing models will come into existence.

Necrosis-Fibrosis Hypothesis

The hypothesis originally proposed by Comfort and colleagues almost 60 years ago (Comfort et al, 1946) fits most with the understanding of the pathogenesis of chronic pancreatitis. The histologic changes and pathogenesis of CP have been

extensively studied by Klöppel and Maillet (1991, 1992). The hypothesis of necrosis-fibrosis views the development and course of CP as a consequence of acute pancreatitis, emphasizing that fibrosis is a late development resulting from repeated attacks of acute (alcoholic) pancreatitis, which initially lead to inflammation and necrosis (Demols, 2002; Klöppel & Maillet, 1991). Ongoing inflammation is replaced by fibrosis in the parenchyma and in the area around the pancreatic ducts, resulting in scarring and sacculations of the ducts, which in turn obstruct the flow of juice and facilitate the precipitation of proteins and subsequent calcification (Kennedy et al, 1987). This process in turn leads to further stasis, plugging, and stone formation, further obstruction, additional fibrosis, and, finally, atrophy of the gland (Klöppel & Maillet, 1992). The necrosis-fibrosis hypothesis has significant supporting evidence from epidemiologic and large follow-up studies that have shown CP to result from recurrent attacks of acute pancreatitis. Several histopathologic studies have demonstrated that mild perilobular fibrosis is common in resolving acute pancreatitis; marked fibrosis with ductal distortion is seen more frequently in patients with advanced CP (Ammann et al, 1984, 1994, 1996). In one study by Ammann and colleagues (1984), 245 patients were prospectively followed after their first episode of alcoholic pancreatitis, and investigators found that the higher the severity and frequency of attacks, the more rapid the progression to CP. Studies of *ERBB2* oncogene expression also support the acute pancreatitis–CP sequence (Standop et al, 2002). The recurrent attacks of acute pancreatitis in HP are also supportive of the necrosis-fibrosis hypothesis. One important aspect that partially negates this hypothesis is the fact that the type of fibrosis that follows acute attacks of pancreatitis involves short-lived collagen type III and procollagen type IV, not the long-lasting collagen types I and IV (Casini et al, 2000).

Protein-Plug (Stone/Ductal Obstruction) Hypothesis

Sarles of France has proposed and extensively studied the hypothesis that states that CP results from plugging of the pancreatic duct (Multigner et al, 1985; Sarles, 1986). These investigators proposed that the origin of CP was within the lumen of the pancreatic ductules, in contrast to the origins of acute pancreatitis, which tends to be inside the acinar cell. The investigators proposed that increased lithogenicity of pancreatic fluid leads to the formation of eosinophilic proteinaceous aggregates that precipitate and obstruct the pancreatic ductules (Guy et al, 1983). These plugs then become rich in calcium and precipitate in the ductules because of deficiency of lithostatin or pancreatic stone protein (PSP); this protein is synthesized in the acinar cell and is an important factor in avoiding calcification within the ductules (Bimmler et al, 2001; Cavallini et al, 1998; Guy et al, 1983; Sarles, 1986; Sarles et al, 1990). Indeed, several studies have proven that alcohol decreases the formation and secretion of pancreatic juice, making it more viscous; lower in bicarbonate; richer in protein, enzymes, and calcium crystals; and deficient in lithostatin (Sarles et al, 1989; Suda et al, 1990).

The mechanism by which heavy alcohol use leads to a decrease in PSP synthesis has not been fully elucidated. Alcohol has also been shown to mediate the release of gastrointestinal hormones by increasing cholecystokinin (CCK)-releasing factor, which in turn affects pancreatic juice formation and flow. The pancreatic stones and plugs are believed to produce ulceration of the ductal epithelial cells that results in inflammation, fibrosis, obstruction, stasis, and further stone formation. Parenchymal damage in the form of inflammation and fibrosis then follows and is usually worst proximal to the obstruction (Boerma et al, 2003).

Another protein believed to induce pancreatic plug formation is glycoprotein 2 (GP-2), a major component of the zymogen granule cell membranes (Fukuoka et al, 1991). The chain of events of decreased flow, decreased lithostatin production, plug formation, calcification, stone precipitation, ductal ulceration, parenchymal and periductular inflammation, stenosis, and stasis repeats itself in a constant vicious cycle (Guy et al, 1983; Reber et al, 1992). Although pancreatic stones and plugs are found in late stages of pancreatitis, it has not been proven whether their formation represents a primary event or is only part of the sequence of CP.

Oxidative Stress Theory

Braganza (1983) from England postulated that the original pathogenic mechanism of CP was a dysregulation and overactivity of the hepatic mixed-function oxidases, mechanisms leading to oxidative stress. This theory places the major area of injury by oxidative stress at the acinar cell, usually as a result of steady exposure of xenobiotics that induce the cytochrome P-450 enzymatic system and deplete glutathione (Braganza, 1998). The hepatic mixed-function oxidases are part of the hepatic detoxification system, and as a consequence of the metabolization process, several "waste products"—such as toxic epoxides, free radicals, and lipid peroxidation products—are produced and are then released into the systemic circulation and reach the pancreatic parenchyma; or they are secreted into the bile and end up refluxing into the pancreatic duct, where they induce inflammatory damage of the acinar and ductular cell. Each burst of oxidative stress affects exocytosis, resulting in fragility of the lysozomes. Pancreatitis is triggered through interference of the methionine–glutathione transulfuration pathway, resulting in diversion of free radicals into the pancreatic tissue with subsequent activation of inflammation and fibrosis of the ductules and resultant low flow of pancreatic juice, inhibition of lithostatin, and precipitation of proteins and calcium (Braganza, 1998; Wilson et al, 1990). Alcohol may also contribute to oxidative stress as a result of the depletion of scavengers such as selenium, vitamins E and C, and riboflavin; such depletion helps to induce or propagate the damage (Atten et al, 2003; De las Heras Castano et al, 2000; Wilson & Apte, 2003).

Toxic-Metabolic Theory

Bordalo and colleagues from Portugal (1977) have proposed the toxic-metabolic hypothesis of CP. They described how alcohol and its toxic metabolites cause accumulation of intracellular lipids and fatty acid ethyl esters, which damage the acinar cell. The alterations of intracellular lipid metabolism lead to fatty degeneration, apoptosis, and scarring of the pancreatic parenchyma with impairment of the pancreatic microcirculation. In a landmark study, biopsies from 42 chronic alcoholics with and without established CP were evaluated by histology and electron microscopy (Bordalo et al, 1977). Even though many of these patients did not have CP, many changes were found to be due to cellular damage, such as cytoplasmic fat droplets of the acinar cells, decreased zymogen granules, and increased mitochondrial size.

Several studies in animals, as well as in human pancreatic tissue, have demonstrated that the toxic or metabolic insult to the fat cells (Kupffer cells) plays an important role in the pathogenesis of pancreas fibrosis in a similar fashion as Ito cells do in the liver (Jaskiewicz et al, 2003; Luttenberger et al, 2000; McCarroll et al, 2003; Phillips et al, 2003). It was demonstrated that these fat cells exist in the human pancreas; they can migrate into the periacinar spaces, and they are activated by alcohol and acetylaldehyde, transforming into scar-producing cells (Vogelmann et al, 2001; Xie et al, 2001; Yokota et al, 2002). As demonstrated in immunohistochemical analysis of pancreatic tissue, a clear correlation exists between the expression of activated Kupffer cells and the degree of fibrosis. These cells have been shown to deposit collagen very early in the process of CP (Haber et al, 1999); therefore an analogy with cirrhosis of the liver can be made when talking about macronodular and micronodular fibrosis in CP.

Primary Duct Hypothesis

Cavallini (1993) from Italy proposed that CP represents a primary autoimmune or inflammatory condition beginning in the pancreatic duct and suggests that the primary pathogenic factor leading to CP is an outflow obstruction, likely the result of duct inflammation, destruction, and fibrosis; these are likely the result of an immunologic attack to a specific genetic, structural, or acquired antigen of the periductular epithelium. The target of this attack may be some specific genetic or acquired antigen on the duct epithelium. Cavallini proposes that the immune-type mechanism occurs via two channels; one is due to aberrant expression of major histocompatibility antigens by the ductal epithelium, the other to infiltration of activated lymphocytes that produce a periductular cytotoxic response. Several reports have shown a defect of ductal epithelial aberrant expression, which leads to periductular lymphocyte infiltration (Bedossa et al, 1990; Bovo, 1987; Jaskiewicz et al, 2003). Therefore, it appears that CP is an autoimmune or "duct-destroying" disease, analogous to primary sclerosing cholangitis (PSC). This is supported by several observations: the radiologic and histologic similarity of chronic PC and PSC, the activation of cytotoxic T lymphocytes in the periductular areas of the pancreas in patients with alcoholic CP, and the occasional association of CP and PSC (Külling et al, 2003; Montefusco et al, 1984; Okazaki, 2001).

Sentinel Acute Pancreatitis Event Hypothesis

Introduced by Whitcomb (1999), the sentinel acute pancreatitis event (SAPE) hypothesis is fascinating because it incorporates much of the knowledge about the molecular and cellular mechanisms of CP pathogenesis in an effort to put previous hypotheses together. The SAPE hypothesis tries to provide a "final common pathway" for the many etiologies for pancreatitis. According to Whitcomb, a SAPE is essential to initiate the inflammatory and immunologic process of CP. In addition, it is necessary for multiple risk factors or insults—agents, toxins, and infections—to propagate CP through membrane and mitochondrial injury as well as through the release of inflammatory cytokines. Susceptibility is essential, either genetic or through some other mechanism, such as ongoing injury (i.e., alcohol toxicity). Then the critical sentinel event appears, triggers the process, and causes acute pancreatitis and CP. Further activation of the immunologic system and the stellate cells propagates CP, and the end result is fibrosis and calcification. Most studies demonstrate that an acute attack of pancreatitis tends to be self-limited; other studies have also demonstrated that the continued oxidative stress cannot cause pancreatitis under normal conditions. Even patients with genetic mutations (susceptibility) known to be associated with CP do not develop the disease spontaneously. Nevertheless, this hypothesis has the merits of placing several of the previous theories under one umbrella.

DIAGNOSIS OF CHRONIC PANCREATITIS

Diagnosis of CP is made by imaging studies. For many years, the gold standard for diagnosing CP has been ERP. In advanced stages, the diagnosis is easy, but diagnosis is challenging in the early stages. In a clinical setting, diagnosis of CP is based on a thorough history and physical examination, laboratory data, and imaging study evaluation, which will reflect the imaging abnormalities as well as functional impairments of the pancreas. The most exact method for diagnosing CP is histologic evaluation of the gland, but this method is rarely used in clinical practice, given the gland's retroperitoneal location and the risks involved in the procedure. Because alcohol is the most common etiology of CP, most studies have based their data on the clinical presentation of alcohol-related CP. Abdominal pain is the most common initial symptom, but it may be absent in up to 15% of patients with alcohol-related CP and in up to 23% of patients with nonalcoholic CP. Steatorrhea is a later symptom because 90% of exocrine function must be lost before steatorrhea develops. Patients can have symptoms of bloating discomfort, abdominal pain, or a change in bowel habits when 60% to 90% of pancreatic function is lost.

CP is a dynamic disease characterized by a progressive loss of pancreatic parenchyma caused by inflammation and tissue destruction and subsequent synthesis of fibrotic tissue (Braganza et al, 1982; DiMagno et al, 1973; Lankisch, 1993; Malfertheiner & Büchler, 1989). According to Amman, the course of the disease can be classified in three distinct stages (Table 55A.2). *Stage A* is the early stage, characterized by recurrent acute attacks, without any or with only mild impairment of pancreatic function. *Stage B* comes later in the course of the disease, when complications are seen—pseudocysts, cholestasis, segmental portal hypertension—along with increasing intensity of pain, more frequent acute painful attacks, and significantly impaired pancreatic function. *Stage C* represents end-stage disease, characterized by less frequent episodes and less intense pain but with marked impairment of endocrine and exocrine pancreatic function ("burnout").

In all stages of the disease, clinical symptoms, such as pain, weight loss, steatorrhea, diabetes mellitus, and local complications, can be observed in various combinations and degrees. Abdominal pain is usually located in the epigastrium and radiates to the back. Weight loss is due to two factors: at first, patients fear eating because of the accompanying pain, whereas later in the disease process, weight loss occurs as a result malabsorption related to pancreatic insufficiency (Mahlke et al, 2005). Close correlation between morphologic changes and impairment of pancreatic function is demonstrated in late stages of the disease, but in the early course of CP, no correlation is seen between morphologic changes and pancreatic function (Antman et al, 1994). In various stages of the disease,

Table 55A.2

Stages of Chronic Pancreatitis: Typical Clinical and Morphologic Pictures, Pancreatic Function, and Recommended Diagnostic Procedures

	CLINICAL PICTURE				
Stage	**Pain**	**Complications**	**Morphology**	**Pancreatic Function**	**Diagnostics**
Early	Recurrent acute attacks	No complications	Morphologic changes detectable with imaging procedures directed to pancreatic parenchyma and ductal system	Normal pancreatic endocrine and exocrine function	EUS, ERP/MRP, CT, secretin
Moderate	Increasing number of attacks and increased intensity	Pseudocysts, cholestasis, segmental portal hypertension	Progredient morphologic changes detectable in several imaging procedures	Impairment of pancreatic function in several degrees, but rarely steatorrhea	Transabdominal US, ERP/MRP, EUS, CT, fasting blood glucose, oral glucose tolerance test
Advanced	Decreasing pain ("burnout" of the pancreas)	Pseudocysts, cholestasis, segmental portal hypertension	Calculi	Marked impairment of pancreatic function, more often steatorrhea than in other stages; diabetes mellitus	Transabdominal US, ERP/MRP, CT, FE-1, fasting blood glucose, oral glucose tolerance test

CT, computed tomography; ERP, endoscopic retrograde pancreatography; EUS, endoscopic ultrasound; FE-1, fecal elastase-1; MRP, magnetic resonance pancreatography

different morphologic examinations and function tests are necessary to establish the diagnosis of CP (Glasbrenner et al, 1997). In all cases, a complete staging of the disease is only possible by the assessment of the clinical setting and evaluation of morphologic changes and functional impairment. For patients presenting with advanced CP after lifelong alcohol abuse, staging is not difficult; most patients are initially seen in earlier stages of the disease, and the diagnosis of CP in these cases is challenging. Idiopathic CP is diagnosed by exclusion of known causes of CP, including nutritional or hereditary causes, hypercalcemia, trauma with residual duct injury, hyperlipidemia, autoimmunity, pancreas divisum, ampullary and duodenal diseases that cause obstructive CP, and primary pancreatic tumors that cause obstructive pancreatitis.

Two scoring systems are widely used for aiding in the diagnosis of CP: the Luneburg and Mayo Clinic scores. The Luneburg score appears to provide a more complete evaluation than the Mayo score, because it includes more aspects, such as US, EUS, CT, and indirect pancreatic function tests (Mahlke et al, 2005).

Imaging Methods

Noninvasive imaging methods are preferred for diagnosing CP in most cases (Malfertheiner & Büchler, 1989). Sensitivity and specificity of different imaging methods vary significantly, depending on the imaging modality used, the stage of the disease, and the experience of the investigator. ERP is still the gold standard among all imaging methods, but in the future, it may be replaced by other methods, such as EUS (see Chapter 14), or after a further significant refinement by magnetic resonance cholangiography (MRC; see Chapter 17).

Plain Abdominal Radiographs

Although plain abdominal radiographs cannot exclude the diagnosis, the presence of focal or diffuse pancreatic calcification, seen in 30% to 40% of cases, makes the diagnosis of advanced CP almost certain and in most cases obviates the need for additional testing. However, calcification is not always found in early CP. In addition, the clinician must be certain that the calcifications are within the pancreas, that they do not simply represent vascular calcifications, and that they are not associated with neoplasms.

Transabdominal Ultrasonography (See Chapter 13)

Transabdominal ultrasonography (US) is an essential tool to visualize the entire pancreas. It is useful for the detection of calcifications and pseudocysts (Figs. 55A.1 to 55A.4). It is inexpensive, simple, noninvasive, widely distributed, well tolerated, and therefore often the first imaging method in patients with abdominal complaints. The sensitivity of US to detect CP is low: it varies from 48% to 96% and increases in advanced stages of CP; the specificity is described between 75% and 90% (Bolondi et al, 1987, 1989b; Freeny & Lawson, 1982; Hessel et al, 1982; Table 55A.3). If US detects changes of CP,

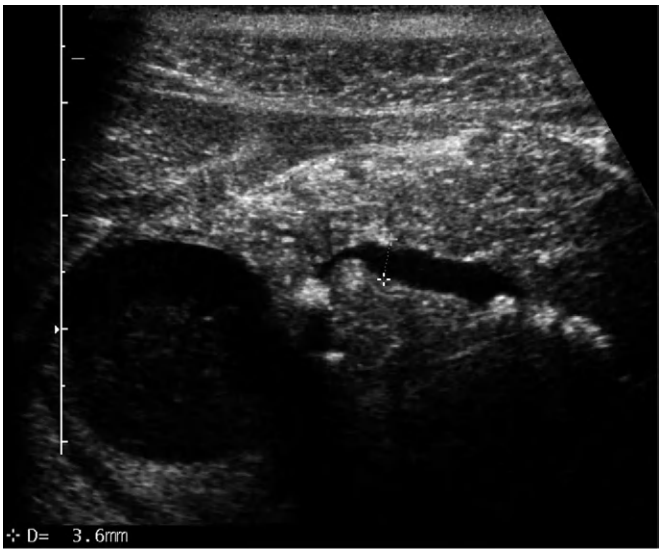


FIGURE 55A.1. Transabdominal ultrasound showing typical changes of chronic pancreatitis. Note the multiple intrapancreatic calcifications and the dilated pancreatic duct. A large pseudocyst is also present in the region of the head of the pancreas.

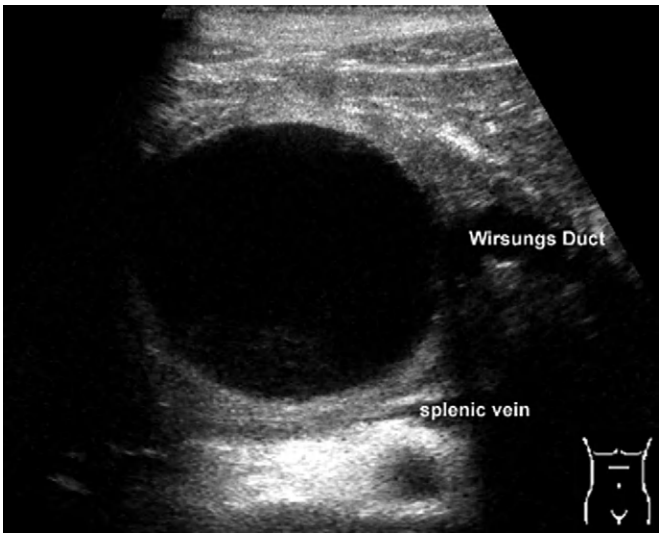


FIGURE 55A.2. Ultrasound showing a large solitary pancreatic pseudocyst complicating chronic pancreatitis.

diagnosis is certain (high specificity), but if the pancreas is not completely visualized or appears normal, further examinations are necessary (low sensitivity). US is the easiest method to detect complications of CP and to follow up patients with CP. The major disadvantage of US is the difficult examination based on poor visualization of the pancreas, mainly because of overlying gas-filled bowel loops and technical and operator-dependent factors, such as experience of the operator and the stage of disease. Reliance on US for the diagnosis of CP is therefore limited to advanced stages (see Fig. 55A.2). Diagnostic criteria for the diagnosis of CP by transabdominal US are 1) irregular contour (lobulation), 2) pancreatic duct dilation and irregularity of the main pancreatic duct, 3) loss or reduction of pancreatic parenchyma echogenicity (echo-poor or echo-rich areas), 4) cysts or cavities, and 5) calcifications (Alpern et al, 1985; Niederau & Grendell, 1985).



FIGURE 55A.3. Ultrasound of a cystlike structure in the pancreas in a 56-year-old woman with chronic pancreatitis and sudden anemia without evidence of gastrointestinal blood loss. This pseudoaneurysm is one of the most dreadful complications of chronic pancreatitis.

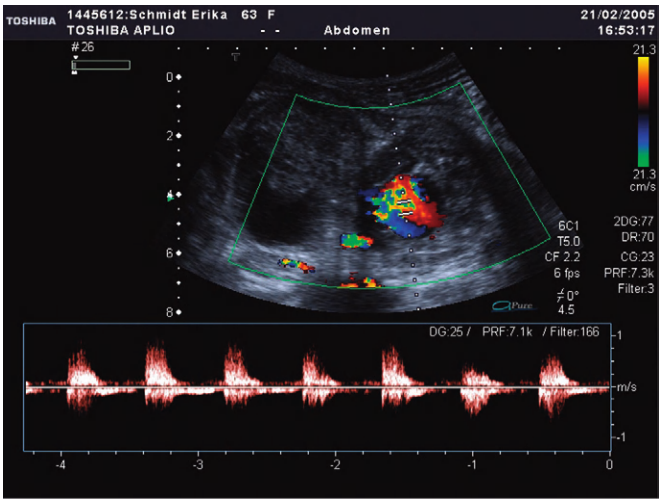


FIGURE 55A.4. Ultrasound with Doppler flow studies demonstrating blood flow inside a pseudocyst-like structure. This study confirmed the presence of a pseudoaneurysm. The patient underwent percutaneous angiographic therapy with release of an endocoil, which completely obliterated blood flow to the aneurysm, therefore averting its rupture.

Computed Tomography (See Chapter 16)

CT findings of CP include pancreatic duct dilatation, calcifications, and cystic lesions (Fig. 55A.5). Other significant findings include heterogeneous density of the pancreatic gland with atrophy or enlargement. CT is as specific as US but is more sensitive (80%). Early parenchymal changes and effects on small pancreatic ducts cannot be detected by CT, but advanced stages and complications of the disease can be evaluated with high reliability. After oral and intravenous administration of contrast medium, the pancreas can be completely visualized with spiral CT and an optimal scanning technique using a slice thickness of 5 mm (Lieb & Dragonov, 2008). In this technical setting, CT is the most sensitive method to detect calculi. Dilation of the main pancreatic duct is visualized with high sensitivity, whereas side branches are only detectable in advanced stages of the disease. CT is an excellent method to detect advanced stages, but discrete changes of the early stages of CP can be easily missed. In summary, CT shows a sensitivity of 56% to 95% with a specificity of 85% to 100% (Robinson & Sheridan, 2000; Lieb & Dragonov, 2008) (see Table 55A.3).

Endoscopic Retrograde Pancreatography (See Chapter 18)

Endoscopic retrograde pancreatography (ERP) is the gold standard among all imaging methods for diagnosis and staging of CP, because it has 90% sensitivity and 100% specificity in

Table 55A.3

Sensitivity and Specificity of Imaging Methods

	Sensitivity (%)	Specificity (%)
Transabdominal ultrasound	48-96	75-90
Computed tomography	56-95	85-100
Endoscopic retrograde pancreatography	68-100	89-100
Endoscopic ultrasound	85-100	85-100



FIGURE 55A.5. Computed tomography of the mid-abdomen showing pancreatic calcifications. This patient also has a stenosis of the distal common bile duct as a result of fibrosis and calcification in the head of the pancreas (also see Fig. 55A.6).



FIGURE 55A.6. Endoscopic retrograde cholangiopancreatography in a patient with chronic pancreatitis demonstrates calcification in the region of the pancreatic head and concomitant distal common bile duct stenosis.

diagnosis (Axon et al, 1984; Forsmark & Toskes, 1984). An ERP staging system based on pancreatic ductal changes has been developed for the diagnosis of CP, and international definitions are based on ERP findings published in 1984 as the Cambridge criteria (Table 55A.4; Axon et al, 1984). Nevertheless, it is important to mention that changes of early CP may not be seen on ERP, which may assess ductal changes that occur in advanced CP, such as irregularity, dilation, tortuosity, stenosis, cysts, and calculi (see Fig. 55A.5). These findings may culminate in a "chain of lakes" appearance in the main pancreatic duct with intermittent points of obstruction in a dilated pancreatic duct (Figs. 55A.6 and 55A.7). In large multicenter trials, the sensitivity of ERP was described to be 68% to 100%, with a specificity of 89% to 100% (Braganza et al, 1982; Malfertheiner & Büchler, 1989; Sica et al, 1999).

It must be kept in mind, however, that ERP is an invasive method with a low but important rate of post-ERP pancreatitis in 3% to 7% (Sherman & Lehman, 1993). For successful ERP, specially trained personnel are necessary to perform the procedure and to interpret the pancreatograms. In special cases, typical changes of CP detected by ERP are not pathognomonic for CP: in patients examined early after AP, ductal changes might be reversible; in patients older than 65 years, these changes can be obvious without having CP (Lieb & Dragonov, 2008). In general, correlation is good between the changes observed on ERP and results of a secretin stimulation test. ERP may also be useful in distinguishing CP from pancreatic cancer. A dominant stricture as opposed to ductular ectasia—with multiple stenosis, irregular branching ducts, and intraductal calculi—is highly suggestive of pancreatic cancer rahter than CP.

Abnormal pancreatograms in patients with upper abdominal pain should not always lead to a diagnosis of CP. Occasionally, patients have suffered a previous episode of acute pancreatitis that resulted in fibrotic damage to the pancreatic duct. In these patients, it is likely that the pancreatic changes are from the initial acute inflammatory episode, and they do not have CP (Mahlke et al, 2005).

In summary, the advantages of using ERP for the diagnosis of CP are standardization, evaluation of the method in multicenter trials with large patient groups, and the possibility of

Table 55A.4

Cambridge Criteria of Chronic Pancreatitis

Stage	Typical Changes
Normal	Normal appearance of side branches and main pancreatic duct
Equivocal	Dilation or obstruction of less than three side branches; normal main pancreatic duct
Mild	Dilation or obstruction of more than three side branches; normal main pancreatic duct
Moderate	Additional stenosis and dilatation of main pancreatic duct
Severe	Additional obstructions, cysts, and stenosis of main pancreatic duct; calculi

From Axon AT, et al, 1984: Pancreatography in chronic pancreatitis: international definitions. Gut 25:1107-1112.

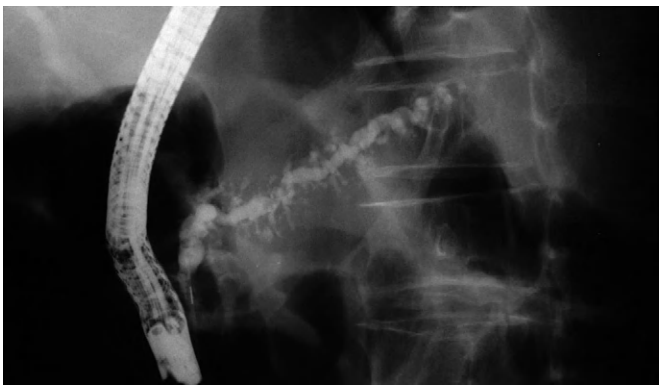


FIGURE 55A.7. Pancreatogram shows a dilated and tortuous pancreatic duct with multiple side branches.

Table 55A.5

Endoscopic Ultrasound Criteria of Chronic Pancreatitis

Parenchymal Features
Gland size, cysts
Echo-poor lesions (focal areas of reduced echogenicity)
Echo-rich lesions >3 mm in diameter
Accentuation of lobular pattern
Ductal Features
Increased duct wall echogenicity
Narrowing or dilation (main pancreatic duct, side branches)
Calculi

From Wiersema MJ, et al, 1993: Prospective evaluation of endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography in patients with chronic abdominal pain of suspected pancreatic origin. Endoscopy 25(9):555-564.

interventions. The disadvantages are complications, costs, and invasiveness.

Endoscopic Ultrasonography

Endoscopic ultrasonography (EUS) visualizes both the pancreatic ducts and the parenchyma (see Chapter 14; Nattermann et al, 1993, 1995; Tenner et al, 1997; Vazquez & Wiersema, 2000; Wiersema et al, 1993). Wiersema and colleagues (1993) described diagnostic criteria of CP detectable by EUS (Stevens & Parsi, 2011; Table 55A.5). These Milwaukee criteria were further refined with the Rosemont classification (Catalano et al, 2009). Parenchymal and ductal changes were divided into major and minor criteria, based on their importance. To diagnose CP based on the Rosemont classification criteria, a sum score consisting of different major and minor changes must be calculated. The advantage of this classification system, compared with further descriptions, is to support the endosonographer with weighted criteria.

In contrast to other imaging methods, which detect CP only in its advanced stages, EUS has the ability to detect CP in patients with early stages of the disease as well as in those with advanced CP (Wiersema et al, 1993; Mönkemüller et al, 2004). EUS features of CP include ductal and parenchymal changes,

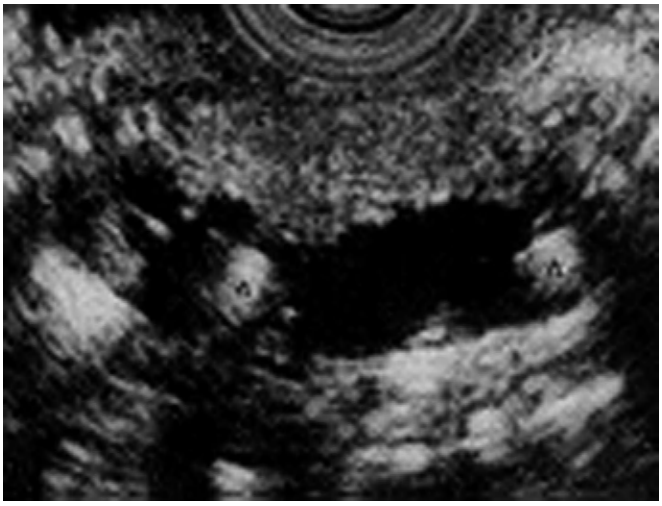


FIGURE 55A.8. Endoscopic ultrasound in 54-year-old patient with chronic pancreatitis as a result of alcohol abuse. Note the marked dilation of the pancreatic duct, with its echo-rich changes and calcifications.

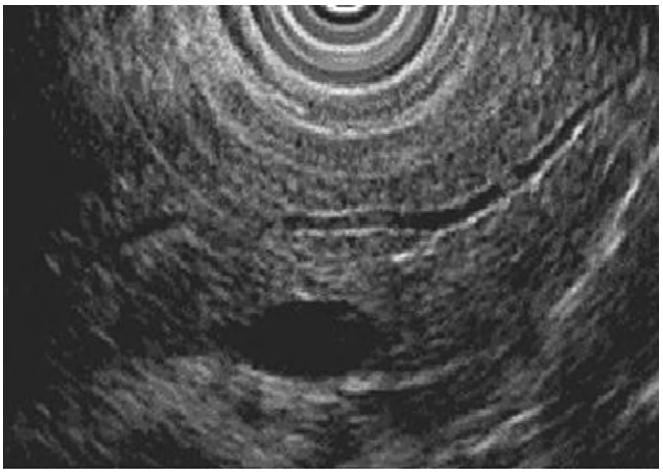


FIGURE 55A.9. EUS in a 48-year-old female with idiopathic pancreatitis. Note the echo-rich changes of the pancreatic duct, which is not pathologically dilated. This EUS is characteristic for early changes of chronic pancreatitis.

such as echotexture of the gland, calcification, lobulation, and bands of fibrosis (Figs. 55A.8 and 55A.9). A prospective evaluation comparing EUS with ERP and a secretin stimulation test in the diagnosis of CP showed good correlation in normal subjects and in patients with moderate disease, showing three or four features, or severe disease, in which more than five features are evident. The agreement was poor for mild EUS changes (one to two features) compared with ERP and a secretin stimulation test; moderate EUS criteria for CP also correlated poorly with secretin test results but had a 92% concordance with ERP in moderate disease. In summary, compared with ERP, EUS is accurate and at least as sensitive for detection of moderate to severe CP.

In early stages of CP, EUS has a number of advantages compared with other imaging modalities. In a series of patients with a history of chronic alcohol abuse and recurrent abdominal pain with normal ERP, we detected typical changes of CP by EUS. These patients were included in a follow-up program. After a median follow-up of 18 months, we detected typical changes of CP by repeat ERP in 68.8% of patients initially presenting with normal ERP but who showed typical changes of CP on EUS. Our conclusion is that EUS has a higher sensitivity to detect CP compared with ERP in a typical clinical and patient history setting (Kahl et al, 2002). The disadvantage of this method is the need for expert EUS endoscopists and a dedicated EUS unit. The advantages of EUS are the reliable visualization of the pancreatic parenchyma and ductal system without any risk for pancreatitis.

Magnetic Resonance Pancreatography (See Chapter 17)

Combining magnetic resonance tomography (MRT) and magnetic resonance pancreatography (MRP) provides an imaging method that allows visualization of the ductal and parenchymal changes of CP. Hardware and software for MRT and MRP are under ongoing, intensive development. Several possibilities of this method have been developed but have yet to be evaluated in patients with inflammatory pancreatic diseases. The major disadvantage is that changes of side branches are not visualized with the same accuracy as in ERP, therefore MRP is not sensitive enough to detect early stages of CP. The future benefit of MRP in patients with CP will depend on patient selection.

Table 55A.6

Sensitivity and Specificity of Imaging Methods and Tests of Exocrine Pancreatic Function

	Sensitivity (%)	Specificity (%)
Invasive Tests		
Spiral computed tomography	≥90-100	>90
Noninvasive Tests		
Pancreolauryl	70-85	75
Fecal elastase-1	35-85	83

Tests of Exocrine Pancreatic Function

Today, function tests play only a minor, complementary role in the diagnosis of CP. The two main reasons are that noninvasive tests of exocrine pancreatic function show high sensitivity only in advanced stages of CP (Glasbrenner et al, 1997; Lankisch, 2000; Leodolter et al, 2000) and any clinical manifestation of an exocrine pancreatic insufficiency occurs late in the course of the disease, after approximately 90% of the exocrine parenchyma has been destroyed (DiMagno et al, 1973). The two types of function tests are *direct* (invasive) and *indirect* (noninvasive) (Table 55A.6; Mahlke et al, 2005). Nevertheless, one of the most sensitive tests to detect exocrine insufficiency is an invasive test, which requires duodenal intubation and aspiration of duodenal juice after pancreatic stimulation. Only this test is able to detect functional impairment in early stages of CP (Malfertheiner & Büchler, 1989), but invasive tests are time consuming, expensive, and require additional manpower and technical equipment to provide little information that is of use in the clinical routine. Therefore such tests are only used in specialized centers or to answer scientific questions. For clinical decision making, such as that regarding enzyme supplementation, pancreatic function tests can provide important information and can allow follow-up of patients with CP (Malfertheiner & Büchler, 1989). In clinical routine today, noninvasive tests, such as the pancreolauryl test and determination of fecal elastase-1 (FE-1) play a more relevant role. With the exception of secretin cerulein test function, tests of exocrine pancreatic function do not play any role in the initial diagnosis of CP because of their decreased sensitivity to detect early functional impairment (see Table 55A.6).

Invasive Function Tests

Duodenal intubation to measure pancreatic juice production after humoral stimulation of the pancreas (secretin-cerulein test, Lundh test) is the only test able to detect functional impairment in all stages of disease (Mahlke et al, 2005). Even though this test has some limitations, it is considered the gold standard in the evaluation of exocrine pancreatic function, because of its acceptable sensitivity and specificity (75% to 95%; see Table 55A.5). The secretin stimulation test, with or without concomitant cholecystokinin (CCK 8) or cerulein administration, measures the volume of secretion and the concentration of output of bicarbonate and pancreatic enzymes via aspiration of duodenal contents in response to injection of secretin. Bicarbonate levels less than 50 mEq/L are consistent with CP; levels greater than 50 mEq/L but less than 75 mEq/L are normal. The disadvantages of this test are its invasiveness, as it requires duodenal tube insertion for collection of secretions. False-positive results may be associated with primary diabetes mellitus, Billroth II gastrectomy, celiac sprue, and cirrhosis.

Until recently, standardization of the secretin-cerulein test has not been done. Most of the investigators use a maximal stimulation of the pancreas with CCK 8 or cerulein, which leads to maximal pancreatic stimulation and output over 60 to 90 minutes (Lankisch, 1993). Direct function tests are not widely employed in clinical routine despite the fact that the costs and time involved in their performance are similar or less than imaging tests such as ERCP, MRCP, or CT (Mahlke et al, 2005).

Noninvasive Function Tests

In contrast to invasive tests, noninvasive pancreatic function tests are more applicable in clinical routine. Most indirect tests of pancreatic function measure the absorption of some compound that first requires digestion by pancreatic enzymes, thereby indirectly assessing pancreatic function. These tests have the disadvantage of a lesser sensitivity in early stages of the disease. The diagnostic accuracy increases slightly when mild to moderate disease is present.

The pancreatolauryl and bentiromide tests are only of historical interest because neither is currently available or useful for clinical practice (Malfertheiner et al, 1987a, 1987b; Dominguez-Munoz & Mlafertheiner, 1998). The only noninvasive function tests that play a potential role in the evaluation of chronic pancreatitis are stool tests, such as measurement of fat and/or pancreas elastase, and the mixed trigylceride C breath test.

Measurement of stool quantity and weight over a period of 72 hours has been considered essential for the diagnosis of CP with malabsorption, but this complicated and malaodorous process has not gained popularity in clinical routine (Mahlke et al, 2005). Stool tests for the quantification of fat (with subsequent correction after pancreatic enzyme replacement), chymotrypsin, and FE-1 have been well studied. Today, evaluation of stool fat plays no further role in the diagnosis of CP, because fat malabsorption occurs only in later stages, after more than 90% of the exocrine pancreatic parenchyma has been destroyed (DiMagno et al, 1973). Therefore only a minority of patients will have significant steatorrhea even with marked exocrine insufficiency (DiMagno et al, 1973). Two stool tests are commercially available for use in clinical routine: chymotrypsin (Immunodiagnostik AG, Bensheim, Germany), and Elastase-1 (ScheBo Biotech, Wettenberg, Germany, and BioServ Diagnostics, Rostock, Germany). Measurement of fecal chymotrypsin is still popular today, but the diagnostic accuracy of this test is not acceptable. Before performing this test, it is important to discontinue pancreatic enzyme supplement therapy. The best accuracy among all stool tests is obtained by measurement of FE-1. Besides high stability of pancreatic elastase during passage throughout the intestine, the commercial test measures only human elastase. This is of advantage in cases of therapeutic oral enzyme supplementation, because this lipase is of porcine origin. Even if FE-1 measurement is superior to other stool tests, its diagnostic value should not be overrated; sensitivity and specificity are low in early stages of the disease, with only mild to moderate exocrine insufficiency (Lankisch et al, 1998; Leodolter et al, 2000).

The ^{13}C breath tests are based on the fact that, after oral administration, the ^{13}C-marked substrates are cleaved by

specific pancreatic enzymes. Exhalation of $^{13}CO_2$ can then be measured and indirectly reveals exocrine pancreatic function. Several tests are available to detect different pancreatic enzyme systems. Lipase activity is detected by ^{13}C mixed-triglyceride breath tests or triolein breath tests, a ^{13}C-cholesteryl-octanoate breath test detects pancreatic cholesterol-esterase, and a ^{13}C-starch breath test is directed to amylase activity. All these tests are mainly used under research conditions in scientific laboratories and currently do not play any role in the clinical management of CP; they are expensive and have been neither standardized nor sufficiently evaluated. Tests able to detect specific pancreatic enzymes secreted in amounts lower than amylase or lipase would be useful in the future.

Endocrine Pancreatic Function

For clinical decision making, the differentiation between normal endocrine function, impaired oral glucose tolerance, and overt diabetes mellitus is sufficient. This differentiation succeeds with determination of fasting blood glucose level and, if normal, with an oral glucose tolerance test (Glasbrenner et al, 1997).

References are available at expertconsult.com.

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PART 6: Pancreatic Disease

SECTION II Neoplastic

A. General

CHAPTER 56

Pancreatic and periampullary tumors: classification and pathologic features

N. Volkan Adsay and David S. Klimstra

TUMORS OF THE PANCREAS

Pancreatic neoplasms are classified based on the degree to which they recapitulate one of the cellular components of the pancreas (Hruban et al, 2007; Klimstra & Adsay, 2009; Klimstra et al, 2007b). To appreciate the various tumor types that occur in the pancreas, basic functional and histomorphologic characteristics of the elements that constitute this gland, both neuroendocrine and exocrine, must be recognized. The neuroendocrine component consists of the islets of Langerhans, small nests of up to a few hundred cells, scattered throughout the pancreas, usually forming round, well-delineated units amid the exocrine elements. Islet cells synthesize hormones (i.e., insulin, glucagon, and somatostatin) and store them in neurosecretory granules; under appropriate stimuli, these hormones are released into the surrounding capillary network. Pancreatic neoplasms that recapitulate the islet cells were previously referred to as *islet cell tumors* but are now called *pancreatic neuroendocrine tumors* (PanNETs; see Chapter 61).

Pancreatic acini—which are responsible for the production of digestive enzymes such as amylase, lipase, trypsin, and others—constitute most of the organ, and acinar neoplasms are uncommon. Acinar cells are arranged in small, rosette-like clusters packed back to back to form compact lobules separated by thin, fibrous septa. To achieve their laborious secretory activity, acinar cells have abundant rough endoplasmic reticulum. The enzymes produced here are transferred to the zymogen granules concentrated in the apical cytoplasm, ready to be secreted into the ductal system.

The ductal component of the pancreas is responsible for most of the neoplasms (see Chapter 58), but it is perhaps the least sophisticated. Ducts are responsible for transporting the acinar secretions to the duodenum. The ductal system starts with the centroacinar cells, and through intralobar and interlobar ducts, the enzymatic secretions are carried to the main pancreatic duct and eventually to the duodenum through the ampulla of Vater. The larger ducts produce and secrete mucins for lubrication and protection, to aid the passage of acinar products, and to create the proper milieu for the enzymes during transportation. However, intracellular mucin is not normally detectable in cells of the interlobular or smaller ducts. Recapitulating the normal ducts, ductal neoplasms are characterized by gland, duct, or cyst formation with or without papillary structures. Production of variable amounts of mucin is also typical and ranges from focal intracellular to abundant intracystic or stromal. As in any organ of the body, supportive tissues (mesenchymal elements) and neighboring organs may also give rise to tumors in the pancreas, although these are very rare. This section reviews the general characteristics of pancreatic neoplasms.

Invasive Ductal Adenocarcinoma

Invasive ductal adenocarcinoma is the most common neoplasm of the pancreas. Its clinical characteristics are discussed in detail elsewhere in this text (see Chapter 58). Most are solid, ill-defined masses; conversely, most solid, ill-defined lesions in the pancreas also prove to be ductal adenocarcinoma. Ductal adenocarcinomas have a remarkable tendency for rapid dissemination and insidious infiltration. Typically, it spreads in the abdomen in a multinodular fashion (intraabdominal carcinomatosis) or is already widely metastatic by the time the primary tumor grows to 5 to 6 cm in size. This feature is so characteristic that a larger solitary pancreatic mass is unlikely to be ductal adenocarcinoma. Interestingly, however, despite the high frequency of distant metastases, some ductal carcinomas cause

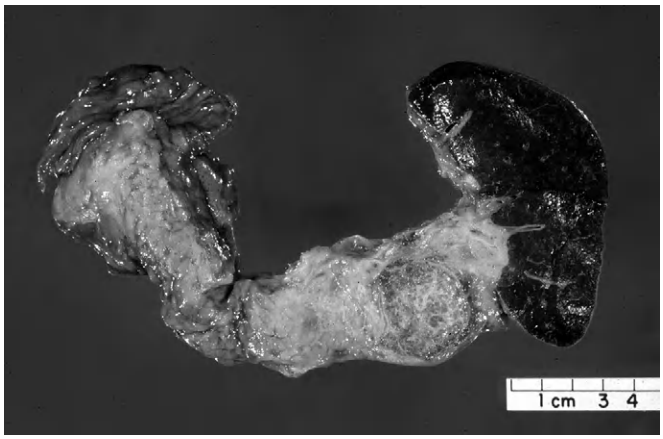


FIGURE 56.1. Ductal adenocarcinoma, gross appearance at autopsy. The solid tumor diffusely involves the pancreatic tail with extension into splenic hilar soft tissues. The periphery of the tumor is poorly defined.

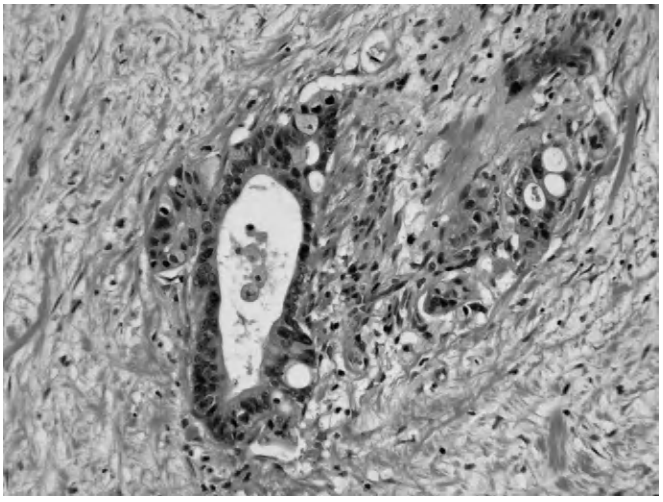


FIGURE 56.2. Infiltrating ductal adenocarcinoma. The tumor is composed of well-formed glands, individual cells, and small, solid cellular clusters. Desmoplastic stroma is abundant.

death of the patient as a result of predominantly local extension; such cases appear to be molecularly distinctive.

Macroscopically, ductal adenocarcinoma is a scirrhous (scar-forming) type of carcinoma; it is associated with abundant desmoplastic stroma, in which the neoplastic glands are widely scattered. This creates a challenge in the diagnosis of ductal adenocarcinoma, because often only a few cancer cells are present, if any, for evaluation in biopsy specimens. This is also a problem for cancer researchers, because most procured "tumor" specimens may in fact contain much more host tissue than carcinoma cells. Also, because ductal adenocarcinoma is typically very sclerotic, it can be difficult to distinguish from fibrosis of chronic pancreatitis, not only radiologically and intraoperatively but also for pathologists examining the gross specimen. The characteristics that distinguish ductal adenocarcinoma are its firm, gray, and gritty cut surface rather than the rubbery, milky white appearance of benign fibrotic lesions (Fig. 56.1).

Most ductal adenocarcinomas are located in the head of the pancreas and infiltrate the neighboring structures, especially the common bile duct, and obstructive jaundice is a common finding at presentation. For this reason, it is often difficult to distinguish pancreatic carcinoma from a carcinoma of the distal common bile duct, especially given that the two are microscopically similar. Some pancreatic ductal adenocarcinomas infiltrate and ulcerate the duodenum or ampulla of Vater and may mimic a primary duodenal or ampullary neoplasm, and the classification of such cases may have to be based on arbitrary criteria such as the epicenter of the mass.

Microscopically, ductal adenocarcinoma is characterized by infiltrating tubular glands, often widely scattered, embedded in a desmoplastic stroma of variable cellularity (Fig. 56.2). The ducts are lined by cuboidal to columnar cells, with variable amounts of intracellular mucin and nuclear atypia (Klimstra & Adsay, 2009). The columnar cells may form cords or nests, or they may grow as individual cells. Perineural invasion is present in more than 60% of cases and is often identifiable in the retroperitoneal region or around the common bile duct, even away from the grossly evident tumor (Fig. 56.3). Neoadjuvant therapy seems to cause substantial alterations in the morphology of the tumor cells. Also, residual foci of previously treated ductal adenocarcinoma may be patchy and may require more careful examination. Recently, scoring systems have been devised in an attempt to evaluate the efficacy of chemotherapy; however, the relevance of these proposals requires further study.

The difficulty in distinguishing ductal adenocarcinoma from chronic pancreatitis (see Chapter 55) also applies to the microscopic diagnosis and is regarded to be one of the most difficult distinctions in diagnostic pathology (Adsay et al, 2004a). Chronic pancreatitis may be associated with epithelial atypia, both architectural and cytologic, in pancreatic tissue; conversely, ductal adenocarcinoma is notorious for its deceptively bland appearance. Features favoring a malignant diagnosis include abnormal location of glands (adjacent to muscular arteries, within the duodenal muscularis, adjacent to adipocytes in the peripancreatic tissue, or around nerves), architectural abnormalities in the shape of the glands (cribriforming, angulation, or incomplete gland formation), and nuclear

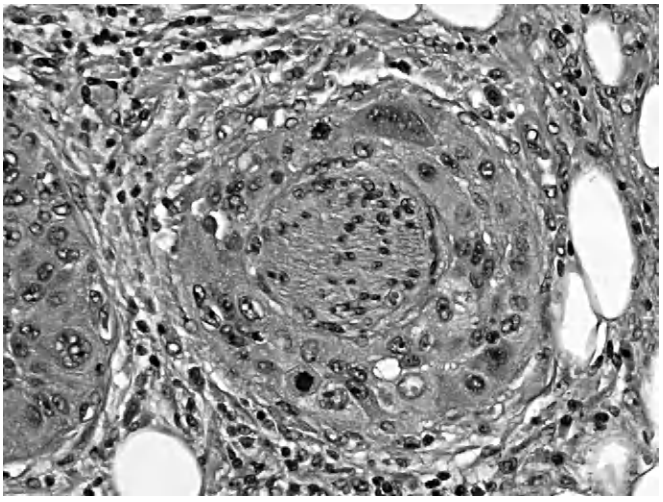


FIGURE 56.3. Infiltrating ductal adenocarcinoma with perineural invasion. The poorly differentiated adenocarcinoma cells completely encircle a small nerve.

abnormalities (variation in the shape and size of nuclei among the cells within an individual gland). A fourfold variation in nuclear volume between adjacent cells, otherwise known as the *4-to-1 rule,* is helpful to recognize carcinoma. Diagnostic difficulty also extends to the differential diagnosis of ductal adenocarcinoma in metastatic sites, because ductal adenocarcinoma often retains its well-differentiated appearance and mimics benign or low-grade neoplasms of these sites. Common pitfalls include misinterpretation of metastatic ductal adenocarcinoma in the ovary as a primary borderline ovarian cystadenoma (Young, 2007); in the lung, as bronchioloalveolar carcinoma; and in the liver, as bile duct adenoma. In the last instance, the converse—misinterpretation of bile duct adenoma as metastatic ductal adenocarcinoma—seems to be more common.

No uniformly applied pathologic grading system exists for ductal adenocarcinoma. Schemes advocated by Western and Asian experts show major philosophical differences in principle and results. The current American Joint Commission on Cancer–endorsed tumor-node-metastasis (TNM) grading system (Edge et al, 2010) is similar to the grading of other adenocarcinomas of the gastrointestinal (GI) tract: *well differentiated* means 95% or more composed of glandular structures; *moderately differentiated,* 50% to 95% glandular in pattern, the remainder occurring as solid nests or individual cells; and *poorly differentiated,* with more than 50% solid nest and individual cells. The World Health Organization (WHO) has adopted the complex grading scheme proposed by Klöppel and colleagues, which is difficult to employ and not widely used in daily practice (Fukushima, 2010). Intratumoral heterogeneity seems to be an important problem in the grading of ductal adenocarcinoma, and for this reason, a simpler, more practical, and more clinically relevant grading scheme that accounts for this heterogeneity by scoring the patterns of infiltration has been proposed (Adsay et al, 2005).

The pathologic evaluation of a pancreatectomy specimen is important both for staging and in determining the adequacy of resection (Lüttges et al, 1998; see Chapter 58). Extrapancreatic extension and involvement of neighboring organs are documented in the pathology report, and determination of tumor size is important. As stated earlier, it is often difficult to appreciate the boundaries of ductal adenocarcinomas; careful macroscopic examination and close correlation with the microscopic findings are necessary to establish the correct size of the tumor. Microscopic foci of carcinoma are often present within the pancreas distant from the main tumor (Bandyopadhyay et al, 2009). Metastasis to lymph nodes is considered one of the most important predictors of outcome in resected ductal adenocarcinomas. Generally, at least 12 lymph nodes should be identified in a simple pancreatoduodenectomy specimen (Adsay et al, 2009). Most of these lymph nodes are embedded in the surfaces of the pancreas or in the groove between the pancreas and duodenum.

Proper identification of margins and their adequate sampling also are important components in the pathologic evaluation of a pancreatoduodenectomy specimen (Ferrone et al, 2008). For pancreatic ductal adenocarcinoma, the most important margin seems to be the retroperitoneal margin, also termed the *uncinate, superior mesenteric vein,* or *vascular margin* (Staley et al, 1996; Lüttges et al, 1998). The retroperitoneal margin at the posteroinferior aspect of the head of the pancreas can be distinguished by its nodular, granular, and irregular appearance, with the vascular bed of the superior mesenteric vessels appearing as a groove to its left. Studies have shown that the retroperitoneal margin should be sampled thoroughly, because this margin is often microscopically positive for grossly undetectable disease. Common bile duct, distal pancreatic (pancreatic ductal), and GI mucosal margins also should be evaluated.

As expected, ductal adenocarcinoma shows immunohistochemical evidence of ductal differentiation. Mucin-related glycoproteins and oncoproteins, including carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), B72.3, DUPAN2, MUC1, and MUC5AC are commonly detected in ductal adenocarcinoma (Basturk et al, 2010b; Hruban et al, 2007; Klimstra, 1998). Expression of these and the differential labeling for cytokeratins (CK7 positive, CK20 variable) sometimes may help distinguish ductal adenocarcinoma from other carcinomas, although no profile of immunohistochemical markers is specific for ductal adenocarcinoma. Scattered cells with neuroendocrine differentiation may be present, and acinar enzymes typically are not expressed.

Substantial developments have occurred in understanding the molecular carcinogenesis of ductal adenocarcinoma (see Chapter 8A). Mutation in codon 12 of the *KRAS* oncogene is found in more than 90% of ductal adenocarcinoma and seems to be an early event (Hruban & Adsay, 2009). Mutation of *P16* or methylation of the promoter also is common (>80%) and represents the pathogenetic link with the familial atypical multiple mole–melanoma syndrome (Hruban et al, 2001a). Overexpression of *TP53* (Barton et al, 1991; Hameed et al, 1994) and loss of *SMAD4*/*DPC4* are detected in about half of cases (Tascilar et al, 2001). The latter appears to have a modest degree of specificity for pancreatic ductal adenocarcinoma. Immunohistochemical demonstration of these abnormalities may be useful in the diagnosis of carcinoma (Fig. 56.4). *BRCA2* and Peutz-Jeghers gene mutations have been implicated in about 5% of ductal adenocarcinoma cases (Hruban & Adsay, 2009). Fanconi anemia gene alterations also have been identified (van der Heijden et al, 2003). Abnormalities in mismatch repair proteins and microsatellite instability are uncommon, although pancreatic ductal adenocarcinomas can occur as one of the less common manifestations of Lynch syndrome.

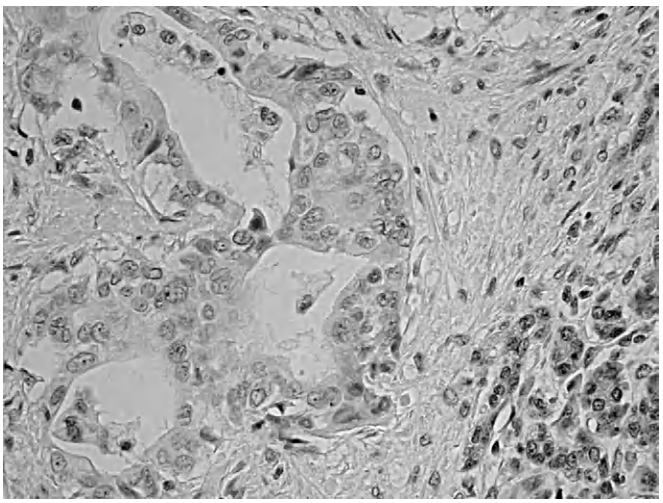


FIGURE 56.4. Infiltrating ductal adenocarcinoma immunohistochemical staining for *SMAD4*. The neoplastic cells have completely lost immunolabeling, whereas the adjacent normal cells show nuclear and cytoplasmic positivity.

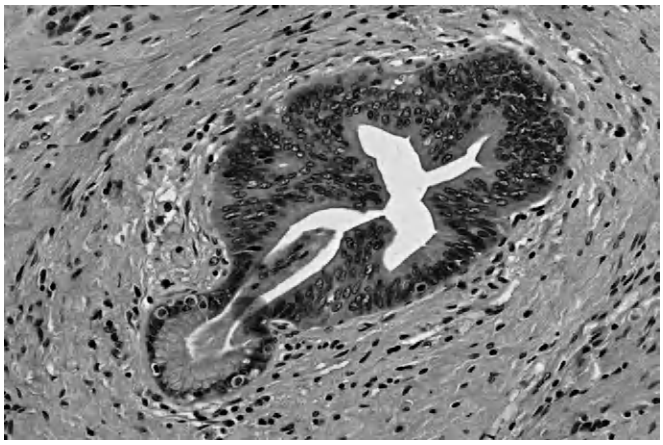


FIGURE 56.5. Pancreatic intraepithelial neoplasia. In this example (PanIN2), full-thickness nuclear pseudostratification and mild cytologic atypia are seen.

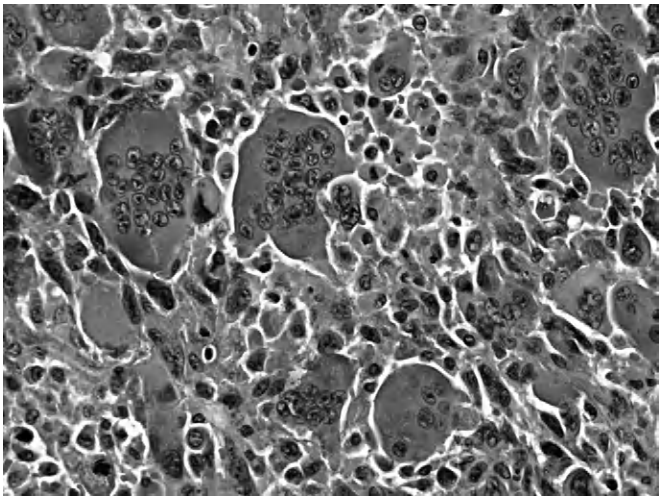


FIGURE 56.6. Undifferentiated carcinoma with osteoclast-like giant cells. Neoplastic cells are mononuclear and dyscohesive, with moderate to marked nuclear atypia. Nonneoplastic, osteoclast-like giant cells contain numerous nuclei that show more uniform cytologic features.

Pancreatic Intraepithelial Neoplasia (PanIN)

It has been speculated for decades that proliferative lesions in the ducts precede the development of invasive ductal carcinoma (Klöppel et al, 1980). These proliferations have been referred to by a plethora of terms, including *hyperplasia* and *dysplasia,* but these are now designated *pancreatic intraepithelial neoplasia* (Hruban et al, 2001b) in recognition of their neoplastic nature (Fig. 56.5). The spectrum of changes is classified in three grades (Hruban et al, 2001b). Replacement of the normal cuboidal, nonmucinous ductal epithelium with columnar cells that contain abundant apical mucin, but without architectural complexity (e.g., papilla formation) or cytologic atypia, is regarded as *PanIN1A*. Cytologically similar lesions that form papillae constitute *PanIN1B*. When a substantial pseudostratification of the cells and some degree of cytologic atypia are seen, the lesion is *PanIN2*. When irregular papillary architecture is present with tufting, cytologic atypia, necrosis, suprabasal mitoses, and loss of cell polarity, it is regarded as *PanIN3*.

A progressive accumulation of molecular alterations is reported from PanIN1 to invasive carcinoma (Hruban & Adsay, 2009). Some alterations, such as *KRAS* mutations, are early events; others, such as *TP53* overexpression, occur at the more advanced end of this spectrum. Low-grade PanINs are very common incidental findings in the normal population (Andea et al, 2003); therefore they are generally believed to not to require any further clinical attention, if encountered in isolation or at resection margins. PanIN3, on the other hand, is seldom seen in the absence of an invasive carcinoma (Andea et al, 2003), and for this reason, if PanIN3 is encountered in a pancreas, the likelihood of pancreas cancer elsewhere in the gland is very high.

Other Invasive Carcinomas Related to Ductal Adenocarcinoma

Certain types of carcinomas are closely related to, and often seen in association with, ductal adenocarcinoma (Klimstra & Adsay, 2009). *Undifferentiated carcinoma* can be regarded as the least differentiated form of ductal adenocarcinoma, in which characteristic tubule formation is no longer evident or only focal. Such tumors are rare, and their demographics do not seem to differ from ordinary ductal adenocarcinoma, except that they may have even more aggressive behavior. Undifferentiated carcinomas include sarcomatoid (spindle cell) carcinoma, anaplastic giant cell carcinoma, and carcinosarcoma. Rarely, the sarcomatoid components of these tumors may show aberrant differentiation, including bone and cartilage formation.

Also known as *osteoclastic giant cell carcinoma, undifferentiated carcinoma with osteoclast-like giant cells* is the name commonly used for a distinctive tumor type characterized by an abundance of such cells in the background of a sarcomatoid carcinoma (Fig. 56.6; Hoorens et al, 1998; Westra et al, 1998). Studies have shown that the osteoclastic giant cells are nonneoplastic histiocytic cells (Westra et al, 1998); the reasons for this chemotaxis are unknown. The true neoplastic cells in this tumor type are the sarcomatoid mononuclear cells. An adenocarcinoma component or, in some cases, high-grade PanIN or mucinous cystic neoplasm precursors may be present. Undifferentiated carcinomas with osteoclast-like giant cells often appear well demarcated and form a large solitary mass. If examined carefully, many such tumors appear to have substantial intraductal growth. These are clearly malignant neoplasms, most exhibiting an aggressive clinical course; however, some examples with minimal ductal adenocarcinoma components have a protracted clinical course.

Squamous differentiation is seen in some conventional ductal adenocarcinomas (i.e., adenosquamous carcinomas; Fig. 56.7; Kardon et al, 2001), but rare pure examples of squamous cell carcinoma without any glandular components also may be seen. They may have variable degrees of keratinization. Squamous cell carcinoma and adenosquamous carcinoma of this region are highly aggressive tumors (Kardon et al, 2001) with a prognosis that is even worse then that of ordinary ductal adenocarcinoma.

Colloid carcinoma, pure mucinous or mucinous noncystic carcinoma (Adsay et al, 2001; Hruban et al, 2007; Seidel et al, 2002), is characterized by extensive stromal mucin deposition (Fig. 56.8). Those tumors composed almost exclusively of the

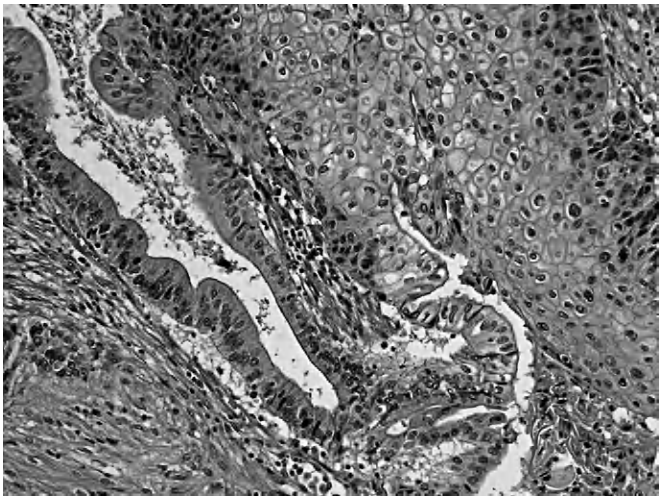


FIGURE 56.7. Adenosquamous carcinoma. Glandular differentiation and pavement-like squamous morphology are apparent.

colloid pattern—in which the mucin/epithelium ratio is very high, and most carcinoma cells are floating within the mucin (detached from the stroma)—have a different biology with an unusually protracted clinical course. Anecdotal evidence suggests that open biopsy of colloid carcinomas may contribute to dissemination, presumably owing to the adherent nature of the mucin. Colloid carcinomas also tend to be larger and better demarcated than ductal adenocarcinomas, and their molecular alterations seem to be somewhat unique. They usually are associated with intraductal papillary mucinous neoplasms (IPMNs) of the intestinal type (see Chapter 57) and also exhibit immunohistochemical evidence of intestinal differentiation (see later).

Medullary carcinomas, akin to those seen in the GI tract associated with microsatellite instability, also have been reported in the pancreas (Goggins et al, 1998; Wilentz et al, 2000). Syncytial nodules of large, poorly differentiated epithelioid cells with a pushing pattern of invasion characterize medullary carcinomas. In one study (Goggins et al, 1998), these tumors were found to have a more protracted clinical course, but further data are necessary to define the prognosis of these rare tumors.

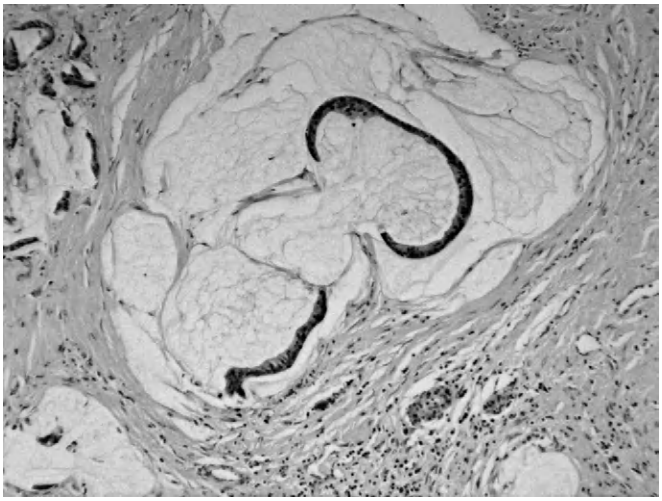


FIGURE 56.8. Colloid carcinoma. Strips of cytologically bland mucinous epithelium are suspended in large pools of extracellular mucin.

Intraductal Neoplasms

Intraductal neoplasms constitute an increasingly encountered and important category of pancreatic tumors of ductal origin, characterized by intraductal polypoid/papillary nodules that are often associated with cystic dilatation of the ducts (Basturk et al, 2009). Intraductal neoplasms constitute a wide spectrum of morphologic variants, but they are all regarded to represent precursors to invasive carcinoma; that is, they may be associated with, or may progress to, invasive carcinoma. As preinvasive neoplasms, they are similar to PanINs; but in contrast to PanINs, which are incidentally detected microscopic forms of dysplasia, intraductal tumors form clinically detectable masses (defined as >1.0 cm), conceptually similar to adenomas of the GI tract. It is estimated that about 2% of invasive adenocarcinomas in the pancreas arise from these tumor types. The neoplasms that are included under this umbrella are intraductal papillary mucinous neoplasms and intraductal tubulopapillary neoplasms.

Intraductal Papillary Mucinous Neoplasms (See Chapter 57)

Intraductal papillary mucinous neoplasms (IPMNs) arise predominantly in the head of the gland and occur more commonly in elderly men (males ≥ females; mean age, 64 years; Basturk et al, 2009). The mucin produced by these tumors may exude from the ampulla of Vater, a finding that is virtually diagnostic of an IPMN. Radiographic findings of ductal dilatation with irregularities also are often diagnostic. A history of pancreatitis is noted in some patients. An adenoma-to-carcinoma progression is seen in IPMNs, which are correspondingly classified as having low-, intermediate- or high-grade dysplasia based on the greatest degree of atypia (Hruban et al, 2007; Adsay et al, 2010); invasive carcinomas that arise in IPMNs are recognized separately and are graded and staged like other ductal-type carcinomas. IPMNs that predominantly involve the secondary ducts (branch duct type; Tanaka et al, 2006; Schnelldorfer et al, 2008; Nagai et al, 2009; Koizumi et al, 2009; Tanno et al, 2008, 2010; Terris et al, 2000) tend to be small (<3 cm) and noncomplex, and they generally prove to have low- to intermediate-grade dysplasia, with simple, gastric foveolar-type epithelium by microscopic examination. IPMNs that mostly involve the major ducts (main duct type; Fig. 56.9) (Tanaka et al, 2006) more commonly harbor high-grade dysplasia or invasive carcinoma (Salvia et al, 2004).

Distinctive pathologic subsets of IPMNs are emerging (Adsay et al, 2004b; Furukawa et al, 2005) with different histologic characteristics. In *intestinal-type IPMNs,* the papillary nodules are morphologically identical to colonic villous adenomas (Fig. 56.10), and the invasive carcinomas that develop in these tend to be of the relatively indolent colloid type (Adsay et al, 2001; Seidel et al, 2002). Intestinal-type IPMNs and colloid carcinomas typically express intestinal differentiation markers (MUC2 and CDX2) not found in ductal adenocarcinomas or in the nonintestinal subtypes of IPMNs discussed below, indicating that they represent a distinct "intestinal pathway" of carcinogenesis in the pancreas (Adsay et al, 2004b). Other IPMNs have more complex papillae that resemble papillary carcinomas of the biliary tree (Fig. 56.11). These *pancreatobiliary-type* IPMNs tend to be associated with tubular-type invasive



FIGURE 56.9. Intraductal papillary mucinous neoplasm, gross appearance. The main pancreatic duct is dilated and lined by friable, papillary excrescences. The surrounding parenchyma is diffusely fibrotic.

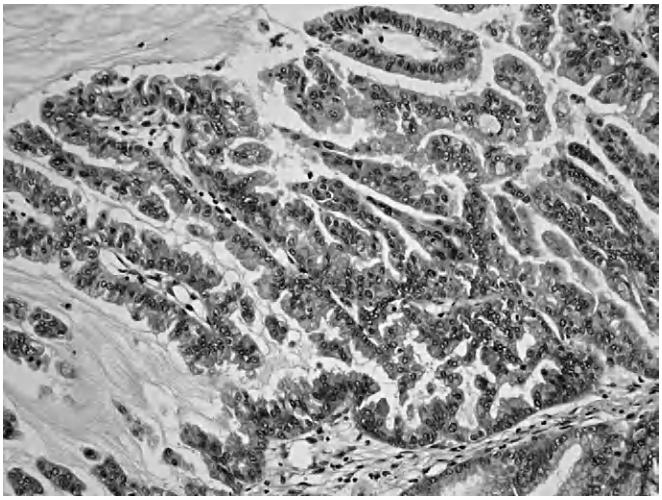


FIGURE 56.11. Intraductal papillary mucinous neoplasm, pancreatobiliary type. The papillae are markedly complex and are lined by cuboidal cells with a single layer of round nuclei, showing loss of cell polarity and moderate nuclear atypia.

carcinoma (conventional ductal adenocarcinoma) and appear to have more aggressive behavior (Sadakari et al, 2010). What is also known as *intraductal oncocytic papillary neoplasm* (Adsay et al, 1996) is now regarded as a distinct subtype of IPMN, characterized not only by the oncocytic nature of the cells but also by the complexity of the papillary nodules, which have an arborizing pattern. Oncocytic IPMNs are often large and very floridly proliferative; however, the carcinomas arising from them tend to be small, the incidence of metastasis is low, and the overall prognosis appears to be favorable. They also have different molecular changes from other IPMNs, with a much lower incidence of *KRAS* mutation and frequent expression of MUC6, suggesting a pyloropancreatic lineage distinct from the intestinal-type IPMNs (Basturk et al, 2010b).



FIGURE 56.10. Intraductal papillary mucinous neoplasm, intestinal type. The papillae resemble those of a villous adenoma of the large bowel, with pseudostratified, elongated nuclei with apical mucinous cytoplasm.

IPMNs can be multifocal in up to 40% of patients. They seem not only to be precursors but also "markers" of invasive adenocarcinoma (i.e., in some cases, invasive carcinoma is detected elsewhere in the gland, away from the IPMN; Fujii et al, 1996; Yamaguchi et al, 2002). Invasive carcinoma of either the colloid or tubular type (Adsay et al, 2004b) is present in more than one third of resected IPMNs. Colloid-type invasion occurs almost exclusively in intestinal-type IPMNs. It is generally believed that IPMNs proven devoid of high-grade dysplasia or invasive carcinoma by thorough histologic examination are innocuous, curable neoplasms. Patients with high-grade dysplasia may on occasion experience recurrences and metastases (White et al, 2007), presumably the result of undetected foci of invasive carcinoma; invasive carcinoma has a malignant clinical course, albeit often significantly more protracted than that of ordinary ductal adenocarcinoma. It should be kept in mind that most patients with IPMNs are older, often with comorbid diseases—including another malignant neoplasm in one third of patients (Eguchi et al, 2006; Sugiyama & Atomi, 1999; Adsay et al, 2002a; Adsay, 2008). The prognosis and management of IPMNs are discussed in detail elsewhere in this book (see Chapter 58).

Intraductal Tubulopapillary Neoplasms

Intraductal tubulopapillary neoplasm (Adsay et al, 2004b; Tajiri et al, 2005; Yamaguchi et al, 2009; Klimstra et al, 2007c) is a recently recognized category of mass-forming (>1.0 cm) intraductal neoplasm that is fairly similar to an IPMN, from which it is distinguished microscopically by its mucin-poor nature and distinctive tubular architecture. First reported by Tajiri and colleagues (2005) under the heading of *intraductal tubular adenocarcinoma,* the entity is now being designated *intraductal tubulopapillary neoplasm* in the new WHO classification. It is a rare tumor seen at an average age of 53 years, and it presents with nonspecific symptoms. The clinical findings are often indistinguishable from those of IPMNs. Most cases have cystic ducts

filled with tumor nodules. Intraductal tubulopapillary neoplasm occurs predominantly in the head of the pancreas but may involve any part. It is often large (mean, 7 cm; range, ≤15 cm).

The common characteristic present in all cases is intraductal nodular/polypoid growth of round, cuboidal *nonmucinous* cells in a tubular, or on occasion, tubulopapillary arrangement. Tubules are small to medium sized, typically well formed, with recognizable lumina of variable sizes, although more ill-defined, abortive tubular arrangements can be seen in some cases. The overall pattern closely mimics the intraductal variant of acinar cell carcinoma, but acinar differentiation is not evident by immunohistochemistry. Mitotic activity is often high, and a third of patients are seen with invasive carcinoma of the tubular type. Invasion, usually microscopic, is difficult to assess in these tumors because of the relative complexity of the intraductal component. The tumor cells express *MUC1* in the vast majority, and *MUC6* is present in 60% of patients, highlighting the similarities—and kinship—of this tumor type with the pancreatobiliary variant of IPMN. Limited follow-up suggests that these are indolent neoplasms with a protracted clinical course.

It should be noted that a variety of pancreatic neoplasms can show prominent intraductal growth, including acinar cell carcinomas (Basturk et al, 2007; Ban et al, 2010), pancreatic neuroendocrine tumors, osteoclastic giant-cell carcinomas (Basturk et al, 2010c), and even metastatic tumors; thus, they fall into the differential diagnosis of these intraductal neoplasms.

Mucinous Cystic Neoplasms (See Chapter 57)

Mucinous cystic neoplasms (MCNs) are seen almost exclusively in perimenopausal women (>95% female; mean age, 48 years; Tanaka et al, 2006; Thompson et al, 1999; Zamboni et al, 1999). One of the characteristic features, which essentially has become a requirement for the diagnosis, is an ovarian-type subepithelial stroma that is not only histologically similar to the ovarian cortex but that also expresses progesterone and estrogen receptors by immunohistochemistry. This distinctive mesenchyme helps distinguish MCNs from similar neoplasms, especially IPMNs (see above). MCNs typically form a thick-walled multilocular cyst in the body or tail of the pancreas (Fig. 56.12). Some examples may mimic pseudocysts, although the surrounding pancreatic tissue typically does not show evidence of chronic pancreatitis. In most cases, cysts do not communicate with the ductal system. The cyst fluid is rich in mucin-related glycoproteins and oncoproteins, such as CEA (Pitman et al, 2010; Deshpande et al, 2006), which may help distinguish these tumors from other cystic lesions. The cysts are lined by mucinous epithelium, which may exhibit varying degrees of cytologic and architectural atypia (Fig. 56.13), graded as low-, intermediate-, or high-grade dysplasia based on the most atypical region. Invasive carcinoma typically occurs in larger and more complex cases that show florid papillary nodules in the cysts.

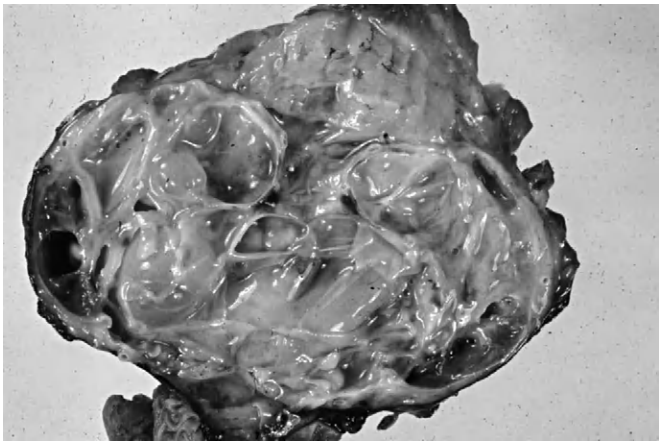


FIGURE 56.12. Mucinous cystic neoplasm, gross appearance. Multiple cystic locules are present, each measuring several centimeters. The intervening septa are thin and translucent.



FIGURE 56.13. Mucinous cystic neoplasm. A layer of hypercellular ovarian-like stroma underlie columnar mucinous epithelium that lines the cystic spaces.

Invasive carcinomas are found in 10% to 15% of MCNs (Pitman et al, 2010; Zamboni et al, 1999; Reddy et al, 2004). The carcinoma may be limited to microscopic foci within the septa of the cysts, or it may invade out of the cyst into the peripancreatic tissues. Invasive carcinomas resemble ductal adenocarcinoma histologically, including the occasional occurrence of an uncommon histologic variant such as sarcomatoid or giant-cell carcinoma. Although some studies have questioned the utility of grading MCNs, it has become clear recently that if these tumors are examined thoroughly, and the presence of invasive carcinoma is ruled out by rigorous pathologic examination, patients typically are cured by complete excision (Zamboni et al, 1999; Sakorafas & Sarr, 2005; Hruban & Zamboni, 2009). Because all MCNs have the potential to harbor invasive carcinoma, most authors agree that these tumors should be completely resected.

Serous Cystic Tumors (See Chapter 57)

Serous cystadenomas (Bassi et al, 2003; Compton, 2000) form relatively large masses (mean size, 9 cm, some 25 cm) that tend to be well demarcated, predominantly in elderly women (mean age, 63 years; female/male ratio, 3:1). Typically, serous cystadenomas are composed of thousands of small cysts, each measuring only millimeters and creating the diagnostic macroscopic appearance of a spongelike configuration, hence the synonym *microcystic adenoma* (Fig. 56.14). Rare macrocystic and solid examples of serous adenomas also have been

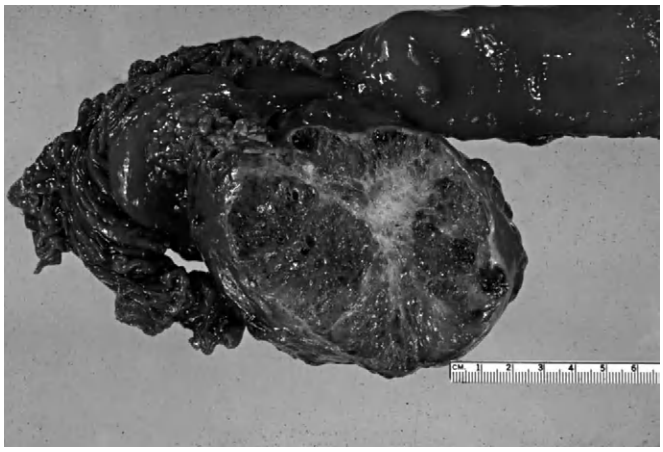


FIGURE 56.14. Microcystic serous cystadenoma, gross appearance. The tumor is well circumscribed with a central stellate fibrous scar. The cystic spaces are small, ranging from one to several millimeters.

described. Microcystic serous cystadenomas often have a central stellate scar. The defining microscopic feature is a simple, nonmucinous, cuboidal epithelium that contains intracytoplasmic glycogen, resulting in characteristic clear cytoplasm (Fig. 56.15). Serous cystic tumors are one of the few ductal neoplasms of the pancreas that do not produce mucin, possibly reflecting a recapitulation of the centroacinar cells that are nonmucinous. Along the same lines, the cyst contents are devoid of the mucin-related glycoproteins and oncoproteins that typically are found in mucinous pancreatic tumors, a feature that may help in the preoperative diagnosis (Brugge et al, 2004). Microscopically, these lesions are similar to the cysts seen in von Hippel–Lindau (VHL) disease, and some serous cystadenomas do show *VHL* gene alterations. Serous cystadenomas often are reported to coexist or "collide" with other pancreatic neoplasms and with congenital pathologic conditions (Compton, 2000).

Malignant serous tumors (serous cystadenocarcinomas) (Matsumoto et al, 2005; Shintaku et al, 2005; Strobel et al, 2003) are exceedingly rare. Only the presence of recurrence, metastases, or angioinvasive growth separates these tumors from their benign counterparts (i.e., the cytologic appearance is entirely bland). For practical purposes, serous cystadenomas limited to the pancreas are regarded as uniformly benign.

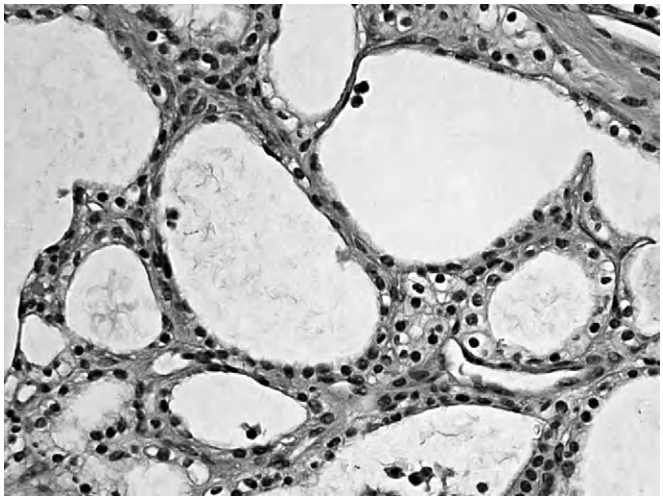


FIGURE 56.15. Microcystic serous cystadenoma. The individual cysts are lined by a flattened-to-cuboidal layer of uniform epithelial cells with clear cytoplasm and round hyperchromatic nuclei.



FIGURE 56.16. Pancreatic neuroendocrine tumor, gross appearance. This example involves the tail and consists of a relatively circumscribed, multinodular, uniform, yellow-tan mass.

Pancreatic Neuroendocrine Tumors (See Chapter 61)

Most neuroendocrine-type tumors of the pancreas are well-differentiated, low- to intermediate-grade neuroendocrine tumors, previously referred to as *islet cell tumors* and now designated as *pancreatic neuroendocrine tumors* (PanNETs) by the World Health Organization (WHO) (Klimstra et al, 2010a; Solcia et al, 1991), with low-grade malignant behavior (Hochwald et al, 2002). Grossly, PanNETs are usually solid, circumscribed, and fleshy tumors, although multinodular and sclerotic examples occur (Fig. 56.16). Rarely, cystic degeneration may be seen (Adsay & Klimstra, 2000; Deshpande & Lauwers, 2007), with a central unilocular cyst lined by a cuff of viable tumor; this occurs more often in the setting of multiple endocrine neoplasia (MEN) syndrome type I. PanNETs recapitulate the morphologic features of islet cells by forming nested, gyriform, trabecular, or rarely acinar or glandular patterns (Fig. 56.17). The cells have characteristic neuroendocrine features, including round, monotonous nuclei with a coarsely stippled chromatin pattern and moderate amounts of cytoplasm (Fig. 56.18).

Almost half of PanNETs are clinically functional, and patients come to medical attention with signs or symptoms of inappropriate production and serologic activity of one or more hormones. These functional PanNETs are named based on the hormonal syndrome: *insulinoma*, *glucagonoma*, *gastrinoma*, *somatostatinoma*, and *VIPoma* (vasoactive intestinal peptide tumor) for example. The correlation of serum hormone levels and expression of the corresponding hormone in the tumor itself by immunohistochemistry is often imperfect. Nonfunctional PanNETs (Hochwald, et al, 2001; Klimstra & Adsay, 2009; La Rosa et al, 1996) constitute an ever-enlarging proportion of PanNETs because they are being detected more commonly as incidental findings on abdominal imaging studies.

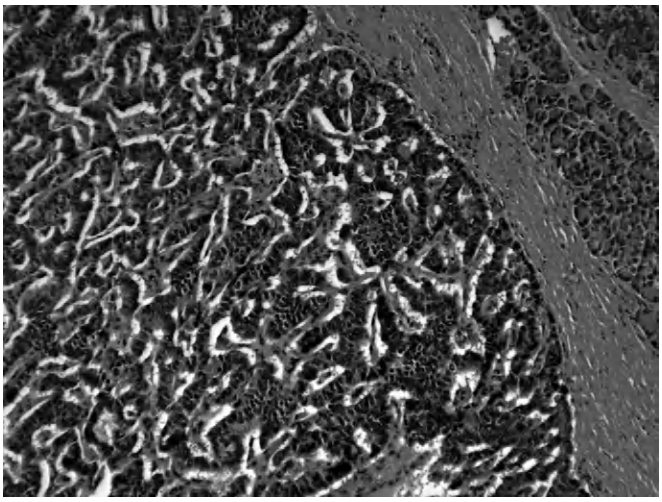


FIGURE 56.17. Pancreatic neuroendocrine tumor. The uniform cells are arranged in nests, and trabecula and are separated by a richly vascular stroma.

Most insulinomas follow a benign clinical course, likely because insulinomas typically are highly symptomatic, even when they are small, which leads to their early detection. Glucagonomas, on the other hand, tend to be large at diagnosis and have a more aggressive course. PanNETs associated with MEN type I or other syndromes tend to be multifocal and less aggressive (Anlauf et al, 2006, 2007; Klimstra & Adsay, 2009; Perigny et al, 2009). In addition to grossly evident and usually functional PanNETs, patients with MEN type I have numerous neuroendocrine microadenomas, defined as PanNETs (<0.5 cm). Most sporadically occurring functional and nonfunctional PanNETs are clinically low-grade malignancies. More than half of patients have recurrence or metastasis after resection, and many patients come to attention only after the development of metastatic disease. Nonetheless, there may be a relatively protracted clinical course even in patients with metastatic disease. It has been difficult, as in neuroendocrine tumors of other organs, to determine which PanNETs are more likely to metastasize and which metastatic cases are likely to progress most rapidly (Pelosi et al, 1996; White et al, 1994). Findings associated with more aggressive behavior include size greater than 3 cm, a functional PanNET other than insulinoma, extrapancreatic or vascular invasion, high mitotic activity, high proliferation index (based on immunohistochemical staining for Ki-67) (Jamali & Chetty, 2008; Rindi et al, 2007; Chatzipantelis et al, 2009), CK19 expression (La Rosa et al, 2007), and c-KIT expression (Zhang et al, 2009); however, some PanNETs lacking all of these features still may metastasize.

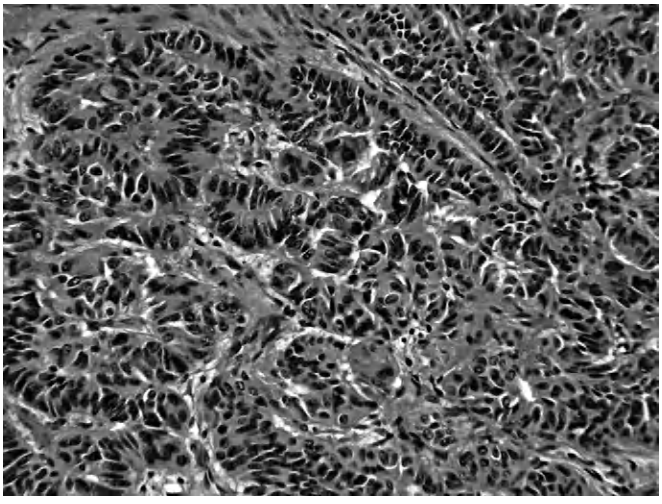


FIGURE 56.18. Pancreatic neuroendocrine tumor. Although the nuclei show some variation in size and shape, the chromatin pattern is uniformly granular with no evident mitotic figures.

The 2004 WHO classification (Heitz et al, 2004) separated *well-differentiated pancreatic neuroendocrine tumors*, those lacking metastases or gross local invasion, from *well-differentiated pancreatic neuroendocrine carcinomas,* with metastases or gross local invasion; they further predicted "benign behavior" or "uncertain behavior" in the former group based on size less than 2 cm, mitotic rate below 2/10 high-power fields (HPFs), Ki-67 labeling index below 2%, and absence of vascular or perineural invasion. However, studies have demonstrated that the patients who fall in the uncertain behavior group still experience recurrence and metastasis in long-term follow-up in up to 40% of the cases (Schmitt et al, 2007); therefore it is clear that even this group represents a low-grade malignancy.

Another more recent proposal (Ferrone et al, 2007) divides PanNETs into low-grade and intermediate-grade groups based on the mitotic rate (2 mitoses per 50 HPFs) and necrosis. The two groups exhibit a highly significant difference in prognosis, although no subset specifically is regarded to be utterly benign. Recently, a multidisciplinary group of international experts have proposed a set of parameters to be included in pathology reports (Klimstra et al, 2010a). It was emphasized that PanNETs ought to be evaluated by the approach used for any other malignancy, and accordingly, the grade and stage should be reported separately (Klimstra et al, 2010b; Klöppel et al, 2010a). For grading, in 2010 the WHO adopted the system originally devised and tested by the European Neuroendocrine Tumor Society (ENETS), which grades PanNETs based on the mitotic count and Ki-67 labeling index. *Grade 1* if the mitotic rate is less than 2/10 HPFs *and* the Ki-67 index is below 3%; *grade 2* if the mitotic rate is 2 to 20/10 HPFs *or* the Ki-67 index is 3% to 20%; and *grade 3* if *either* is above 20. For staging, the AJCC has adapted the TNM-based staging system used for adenocarcinomas, but the ENETS system is somewhat different (Klöppel et al, 2007).

On the other end of the spectrum of neuroendocrine neoplasia, very rarely, poorly differentiated neuroendocrine carcinoma, related to small cell carcinoma, may be encountered in the pancreas (Tranchida et al, 2000). Some are composed of large cells with more abundant cytoplasm (high-grade neuroendocrine carcinomas of a "large cell" type). According to WHO, high-grade neuroendocrine carcinomas are classified as *grade 3* PanNETs, although the true nature of such tumors is difficult to characterize because of their rarity, and they appear to be a distinct tumor type with morphology and behavior usually very similar to that of high-grade neuroendocrine carcinomas of the lung rather than being advanced forms of well-differentiated PanNETs. In fact, especially when the small cell morphology is present, poorly differentiated neuroendocrine carcinomas must be distinguished from metastases to the pancreas from a pulmonary primary.

Acinar Neoplasms

Although acinar tissue constitutes most of the pancreas, acinar neoplasms are rare. Acinar neoplasms are characterized by the production of pancreatic enzymes, such as trypsin, chymotrypsin, and lipase. Solid acinar cell neoplasms are carcinomas; although a benign cystic variant exists, known as *acinar cell cystadenoma*, no solid acinar cell adenoma has been defined in the pancreas.

Acinar cell carcinomas (Kitagami et al 2007; Klimstra, 2007; Wisnoski, 2008) form relatively large tumors (mean, 10 cm), usually in older men (mean age, 63 years), although some occur in children (Shorter et al, 2002). In a small percentage of cases (10%), patients experience a "lipase hypersecretion syndrome" (Klimstra & Adsay, 2001) characterized by subcutaneous fat necrosis, polyarthralgia, and peripheral eosinophilia. Serum α-fetoprotein (AFP) levels may be elevated in some cases (Cingolani et al, 2000). Half of acinar cell carcinomas have metastases at the time of diagnosis, usually in the liver and/or regional lymph nodes (Holen et al, 2002). Once believed to be almost as aggressive clinically as ductal adenocarcinomas with a 5-year survival of 10% (Holen et al, 2002), more recent studies place acinar cell carcinomas in a somewhat more indolent category (Klimstra et al, 1992) with some studies reporting a 5-year survival over 40% (Kitagami et al, 2007; Wisnoski et al, 2008). In contrast to ductal adenocarcinomas, acinar cell carcinomas are stroma-poor cellular tumors composed of sheets of cells and small glands (acini) composed of polygonal cells with prominent nucleoli (Labate et al, 1997) and cytoplasmic eosinophilia (Fig. 56.19), often with periodic acid-Schiff (PAS)-positive granules. Acinar enzymes, especially trypsin and chymotrypsin, are demonstrable by immunohistochemistry in essentially all cases (Klimstra et al, 1992). A subset of acinar cell carcinomas is characterized by prominent intraductal growth; such cases are reportedly associated with a more protracted clinical course (Basturk et al, 2007; Ban et al, 2010). Molecular genetic findings of acinar cell carcinomas markedly differ from those of ductal adenocarcinomas (Cao et al, 2005), with absence of the common alterations of ductal adenocarcinoma in genes such as *KRAS, TP53, P16,* or *SMAD4*.

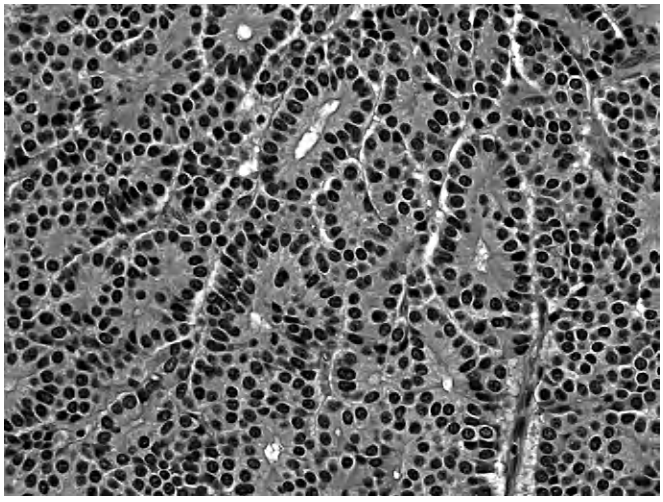


FIGURE 56.19. Acinar cell carcinoma. The cells are arranged in nests and acinar formations. The cytoplasm is eosinophilic and granular, especially in the regions surrounding the pinpoint luminal spaces.

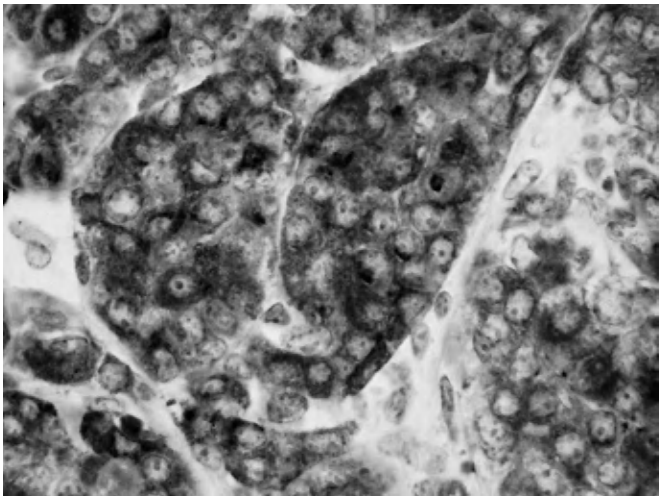


FIGURE 56.20. Mixed acinar-neuroendocrine carcinoma. Immunohistochemical labeling for trypsin and chromogranin shows participation of acinar and endocrine cells in this mixed neoplasm.

Immunohistochemistry discloses scattered neuroendocrine cells in 30% to 40% of acinar cell carcinomas. Some cases have a significant neuroendocrine component that may be evident microscopically (Klimstra et al, 1992). If the latter constitutes more than 25% of the tumor, it is classified as *mixed acinar-neuroendocrine carcinoma* (Fig. 56.20), a tumor that seems to be biologically similar to pure acinar cell carcinoma (Klimstra et al, 1994; Ohike et al, 2004). Similarly, acinar cell carcinomas with more than 25% ductal differentiation are classified as *mixed acinar-ductal carcinoma* (Stelow et al, 2010). Rarely, acinar cell carcinomas may show a grossly cystic pattern and are designated *acinar cell cystadenocarcinoma* (Cantrell et al, 1981; Stamm et al, 1987).

Acinar Cell Cystadenoma

Acinar cell cystadenoma, also referred to as *acinar cystic transformation,* is a rare entity (Albores-Saavedra, 2002; Zamboni et al, 2002). Acinar cell cystadenomas are usually small, incidental cysts lined by benign-appearing acinar cells, although some may form a mass that measures a few centimeters. Some examples have a patchy distribution that spans to a large segment of the organ. They are considered to be benign.

Pancreatoblastoma

Pancreatoblastoma is an extremely rare childhood tumor of the pancreas (mean age of 4 years, with a second small peak in the third decade) (Dhebri et al, 2004; Klimstra et al, 1995; Shorter et al, 2002). Pancreatoblastomas are usually large (7 to 18 cm). Some cases are associated with elevated serum AFP levels, and occasional cases are seen in association with Beckwith-Wiedemann syndrome (Drut & Jones, 1988; Kerr et al, 2002) or familial adenomatous polyposis (FAP) syndrome (Abraham et al, 2001). Pancreatoblastomas are malignant tumors with a 5-year survival of about 25%, although children diagnosed before the development of metastases have been cured. Pancreatoblastomas are predominantly acinar neoplasms. Microscopically, they have sheets of primitive-appearing epithelial cells and acinar formations. A characteristic and peculiar

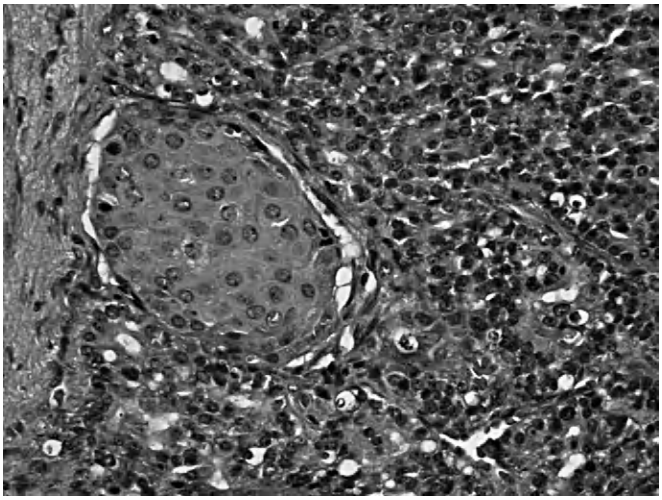


FIGURE 56.21. Pancreatoblastoma. Solid nests and small acinar formations are composed of uniform small cells. In addition, larger cells form circumscribed squamous corpuscles, and a cellular stromal component is present.

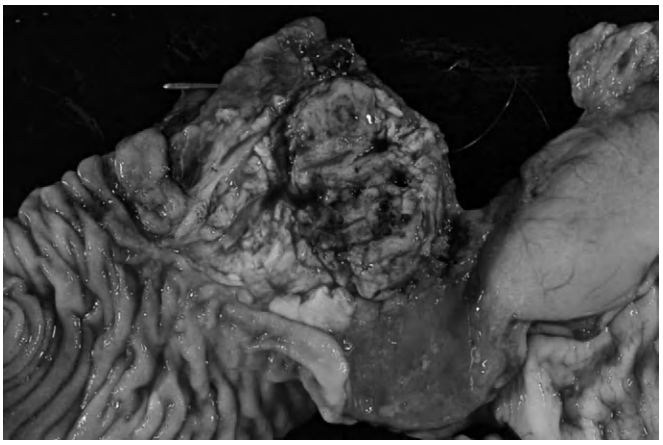


FIGURE 56.22. Solid pseudopapillary neoplasm, gross appearance. The tumor is grossly circumscribed and composed of soft, tan tissue with areas of hemorrhage. No gross cystic change is apparent in this relatively small example.

microscopic finding is the squamoid nest, which is a small morular arrangement of squamoid cells specific for this tumor type in the pancreas (Fig. 56.21). Typically, pancreatoblastomas exhibit all three lines of pancreatic differentiation—*acinar, neuroendocrine,* and *ductal*—with acinar elements being the most consistently present (Klimstra et al, 1995). Molecular genetic findings of pancreatoblastomas differ from the findings of ductal adenocarcinoma; they are associated with β-catenin pathway alterations (Cao et al, 2005). The squamoid nests (morules) are interesting in this regard because they are also often encountered in other cancer types in which this pathway is abnormal (Nakatani et al, 2004).

Solid Pseudopapillary Neoplasm

Solid pseudopapillary neoplasm is seen predominantly in young women (mean age, 25 years; >80% female) (Klimstra et al, 2000; Kosmahl et al, 2000; Papavramidis & Papavramidis, 2005; Tang et al, 2005). It is a peculiar neoplasm of unknown origin, and its obscure nature is reflected in the various descriptive names assigned to this tumor in the past, including *papillary cystic tumor, solid and papillary tumor, solid and cystic tumor,* and *Frantz tumor* (Klöppel et al 1981; Lieber et al, 1987; Pettinato et al, 1992; Stommer et al, 1991). It is an indolent malignant neoplasm for which complete resection is curative in most cases. In a small percentage (approximately 15%), metastases are noted, usually to liver or peritoneum and often at the time of diagnosis. Even patients with metastases have a protracted clinical course, and death as a result of this tumor is rare; however, a few highly aggressive solid pseudopapillary neoplasms have been reported that exhibit high-grade malignant transformation from a conventional solid pseudopapillary neoplasm (Tang et al, 2005).

Solid pseudopapillary neoplasms are relatively large tumors (mean, 8 to 10 cm). Although they are typically solid cellular neoplasms, cystic degeneration is common (Fig. 56.22). Degenerative changes combined with the preservation of the cells around the microvasculature create the pseudopapillary microscopic pattern (Fig. 56.23). The cells are round to oval and often show nuclear grooves. Intracytoplasmic hyaline globules and aggregates of foamy macrophages are characteristic findings, and calcifications may also be seen. Overall, the histologic picture may resemble closely that of PanNETs. The immunophenotype of this tumor is quite distinctive but fails to disclose the line of differentiation of the cells. The tumor typically expresses vimentin, progesterone receptors, CD10, and some of the neuroendocrine markers, CD56 and synaptophysin (Klimstra et al, 2000; Kosmahl et al, 2000; Ladanyi et al, 1987). Chromogranin, the most specific neuroendocrine marker, is negative, which is important for the differential diagnosis with PanNETs, and pancreatic enzymes are not expressed. β-Catenin and cyclin D1 expression have been found in these tumors, suggesting an alteration in the *WNT* signaling pathway. E-cadherin and n-cadherin expression are also abnormal (Abraham et al, 2002; Tiemann et al, 2007).

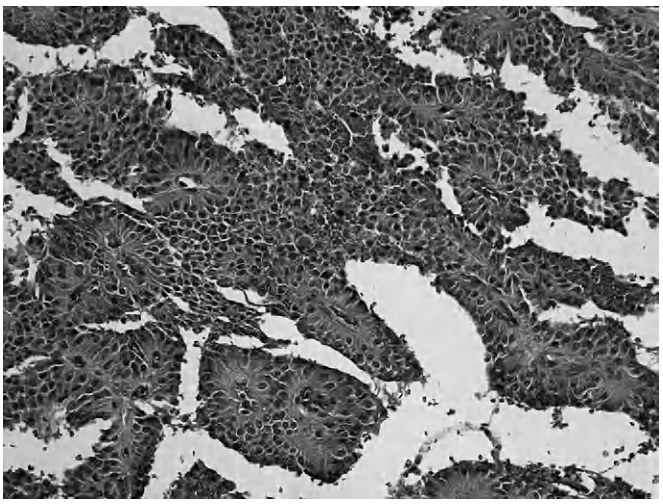


FIGURE 56.23. Solid pseudopapillary neoplasm. The pseudopapillae are formed by a cuff of cells adherent to a central small vessel. Many of the cells contain large eosinophilic globules, and the nuclei have longitudinal grooves.

Miscellaneous Cystic Pancreatic Lesions

Other uncommon cystic lesions occur in the pancreas in addition to pseudocysts, intraductal cyst-forming neoplasms, mucinous cystic neoplasms, and serous cystic tumors (Adsay et al, 2000; Kosmahl et al, 2004). Lymphoepithelial cysts (Adsay et al, 2002b) are usually peripancreatic rather than intrapancreatic, and they occur predominantly in men (mean age, 52 years; male/female ratio, 3 : 1). In contrast to their salivary gland counterparts, pancreatic lymphoepithelial cysts do not show associations with autoimmune syndromes, human immunodeficiency virus (HIV), or lymphoma. Lymphoepithelial cysts may occur in any part of the pancreas and may be unilocular or multilocular. They are characterized by variably keratinized, squamous-lined cysts immediately surrounded by a rim of lymphoid tissue, some with lymphoid follicles and a capsule (Fig. 56.24). The cyst contents may extrude into the cyst wall and cause an inflammatory reaction, including granulomas. Dermoid cysts are similar to lymphoepithelial cysts but lack the lymphoid tissue and show skin adnexal elements, including sebaceous glands. Lymphangiomas (Paal et al, 1998) are seen in young women (mean age, 29 years; male/female ratio, 1 : 3) and form endothelial-lined cysts surrounded by a rim of lymphoid tissue. Congenital cysts and intestinal duplications also may form cystic lesions in the vicinity of the pancreas and periampullary region. These may have a variable lining, including respiratory type, intestinal, squamous, or transitional.

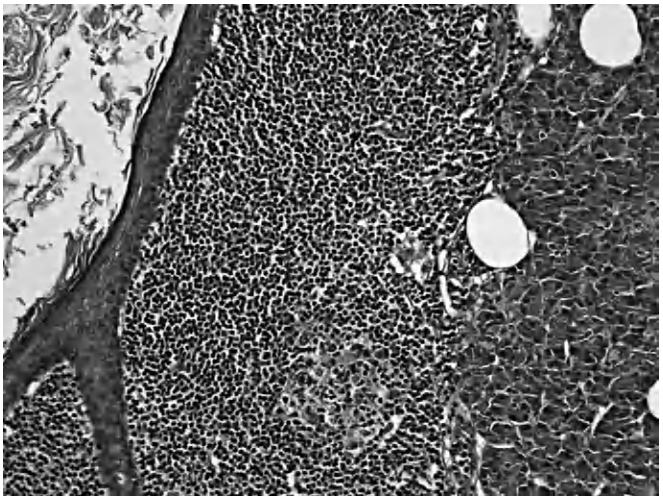


FIGURE 56.24. Lymphoepithelial cyst. The cyst is lined by stratified squamous epithelium with keratinization, and a band of lymphoid cells separates it from the pancreatic parenchyma.

Pseudotumors

As discussed in the section on ductal adenocarcinoma, benign chronic inflammatory and fibrosing conditions of the pancreas may be difficult to distinguish from carcinomas both clinically and pathologically. Chronic pancreatitis of any cause—including alcohol, obstruction, and even causes with granulomatous inflammation—may lead to segmental fibrosis and a tumorous mass (see Chapter 55; Adsay et al, 2004c; Klöppel & Maillet, 1991). However, certain subtypes of chronic pancreatitis are especially prone to form pseudotumors and mimic carcinomas, as discussed below (Adsay et al, 2004c; Klöppel, 2007; Levenick et al, 2009).

Autoimmune pancreatitis (AIP), also called *lymphoplasmacytic sclerosing pancreatitis* (Zamboni et al, 2004), is often misdiagnosed as carcinoma preoperatively (see Chapter 55). AIP typically is seen in patients in their 30s to 50s, and high serum immunoglobulin G4 (IgG4) levels are helpful in the preoperative diagnosis (Dhall et al, 2010; Morselli-Labate & Pezzilli, 2009; Sanchez-Castanon et al, 2009; Tabata et al, 2009). It may be associated with other autoimmune disorders, such as Sjögren syndrome, and with components of the multifocal fibrosclerosis syndrome: retroperitoneal and mediastinal fibrosis, Riedel thyroiditis, inflammatory pseudotumor of the orbit, and sclerosing cholangitis. Microscopically, dense periductal lymphoplasmacytic infiltrates, interstitial fibrosis with abundant myofibroblasts arranged in a storiform pattern, and obliterative venulitis are characteristic (Fig. 56.25).

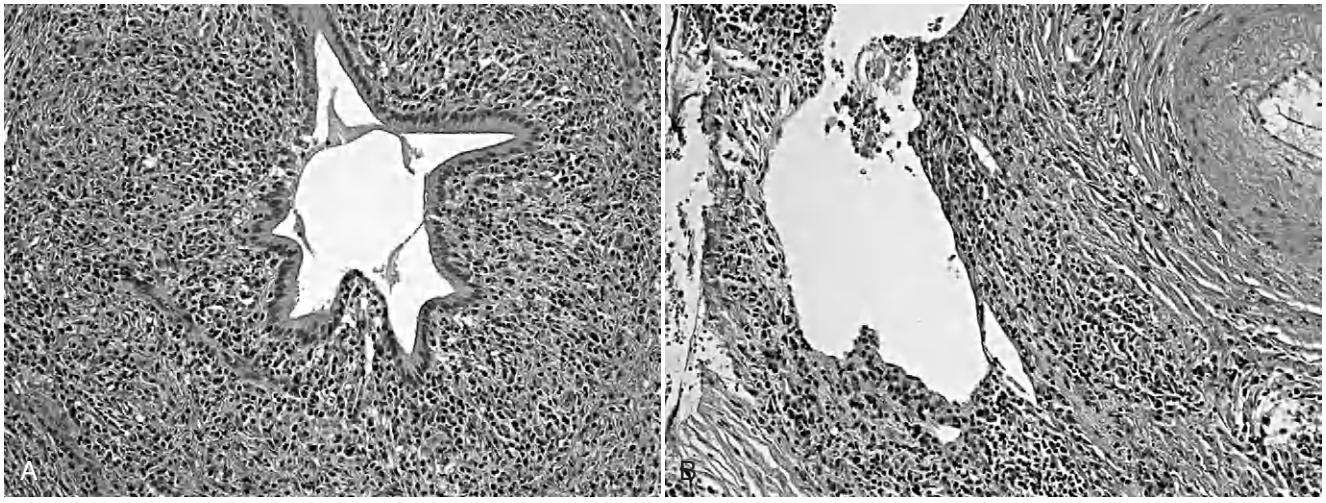


FIGURE 56.25. Autoimmune pancreatitis. **A,** Dense inflammation is evident and includes lymphocytes, plasma cells, and eosinophils arranged in a periductal pattern. **B,** The inflammatory infiltrate also involves the walls of small veins.

Recently, a variant of AIP has been recognized (Klöppel et al, 2010b) and termed variably as *type 2 autoimmune pancreatitis* or *pancreatitis with granulocytic epithelial lesions* (GELs). This type is more commonly seen in patients with ulcerative colitis and does not seem to be associated with IgG4-producing plasma cells but rather shows neutrophilic destruction of the duct epithelium (Klöppel et al, 2010b).

Paraduodenal pancreatitis (Adsay & Zamboni, 2004; Coban et al, 2009) is the name recently proposed for a distinct but poorly recognized subset of chronic pancreatitis that creates a clinical picture often indistinguishable from pancreatic or periampullary carcinoma. This entity is also known as *groove pancreatitis* (Badia Bartolome et al, 2009; Castell-Monsalve et al, 2008; Ishigami et al, 2009; Levenick et al, 2009; Triantopoulou et al, 2009) or *cystic dystrophy of heterotopic pancreas* (Casetti et al, 2009; de Madaria et al, 2009). Affected patients are predominantly men in their 50s with a history of alcohol abuse. Endoscopically, in the second portion of the duodenum, proximal to the ampulla, mucosal nodularities are present that microscopically reveal inflamed mucosa, Brunner gland hyperplasia, or myoid spindle cell proliferation in the submucosa that can also extend to the mucosa. These pseudotumors are typically centered around the minor papilla or accessory duct and thus invade into the region between the common bile duct, duodenum, and pancreas (i.e., the "groove" region) (Badia Bartolome et al, 2009; Castell-Monsalve et al, 2008; Ishigami et al, 2009; Levenick et al, 2009; Triantopoulou et al, 2009). The process often exhibits a dense myofibroblastic proliferation within which lobules of pancreatic tissue are scattered, and cystic ducts contain inspissated enzymatic secretions. In some cases, cystic change in the duodenal wall can be prominent (cystic dystrophy of the duodenum) and may become large (paraduodenal wall cyst) (Casetti et al, 2009; de Madaria et al, 2009), mimicking pseudocysts, congenital cysts, or intestinal duplication. Some of the cysts are lined by granulation tissue without any epithelium.

Some developmental abnormalities also may lead to pseudotumors. A solid and cystic hamartoma and a cellular hamartoma (Pauser et al, 2005a, 2005b) have been reported to present as pancreatic tumors in adults. *Lipomatous pseudohypertrophy* (Altinel et al, 2009) of the pancreas also may lead to a mass that could be mistaken for carcinoma. Adenomyomatous hyperplasia (Handra-Luca et al, 2003) of the ampulla—a common finding in the general population, reported in 40% of autopsies—has been implicated as a cause of biliary obstruction that mimics a periampullary carcinoma.

Mesenchymal Tumors

Primary mesenchymal tumors of the pancreas are rare (Khanani et al, 2003; Lüttges et al, 1997), but mesenchymal tumors from neighboring sites may secondarily involve the pancreas. In particular, GI stromal tumors and retroperitoneal sarcomas may appear to be centered in the pancreas. A variety of benign mesenchymal tumors, including fibromatosis (desmoid tumor), solitary fibrous tumor (Lüttges et al, 1999b), and schwannoma (Paal et al, 1998), have been reported in the pancreas. Primary sarcomas include primitive neuroectodermal tumor (Movahedi-Lankarani et al, 2002), synovial sarcoma, desmoplastic small round-cell tumor, leiomyosarcoma, and malignant fibrous histiocytoma, all of which are largely documented in single case reports.

Secondary Tumors

A widely metastatic malignant neoplasm commonly may involve the pancreas; however, most of these are clinically undetected lesions identified only at autopsy (see Chapter 60; Adsay et al, 2004d). Autopsy studies have shown that most secondary tumors involving the pancreas are of pulmonary origin, followed by GI carcinomas; however, a few metastatic tumors are prone to involve the pancreas in the absence of other metastatic foci, mimicking a primary carcinoma. Lymphomas and renal cell carcinomas (Adsay et al, 2004d; Temellini et al, 1989) seem to be the most common tumor types responsible for such cases. Renal cell carcinomas in particular are known to form polypoid ampullary nodules or even to grow within the ducts (Klimstra & Adsay, 2009).

TUMORS OF THE AMPULLA OF VATER (SEE CHAPTER 59)

Although the ampulla of Vater is anatomically a small structure, it and the surrounding periampullary duodenum give rise to a surprising number and variety of neoplasms that often present with dramatic symptoms because of the strategic location of the ampulla at the confluence of the pancreatic and biliary ducts. The ampulla itself includes several kinds of epithelia: the duodenal mucosa, covering the papilla; the pancreatic ductal epithelium and that of the distal common bile duct; and the epithelium lining the common channel—the short, if not hypothetical, union of the two ducts within the duodenal wall. The epithelia lining the ducts and the common channel are histologically similar pancreatobiliary-type epithelium, whereas the papilla is covered by intestinal-type epithelium (Klimstra et al, 2007a). Different cell types can be observed intimately admixed in the transitional region. Neoplasms arising in the ampulla may have predominantly intestinal or pancreatobiliary features, or patterns may be mixed. Most ampullary neoplasms are adenocarcinomas (Klimstra & Adsay, 2009), although some neuroendocrine tumors also affect this region. Benign neoplasms also arise in the ampulla, and techniques for local treatment, such as endoscopic polypectomy or transduodenal ampullectomy (Roggin et al, 2005) have introduced new challenges into the pathologic analysis of ampullary tumors (Klimstra & Adsay, 2009). This section reviews the pathologic features of these ampullary neoplasms.

Adenoma and Noninvasive Papillary Carcinoma

These tumors can be regarded in two categories: 1) those that arise from the duodenal surface of the ampulla, which are nearly identical to colonic-type adenomas and may occur in association with FAP syndrome (Albores-Saavedra et al, 2000; Alexander et al, 1989; Domizio et al, 1990; Klimstra & Adsay, 2009; Noda et al, 1992; Odze et al, 1994); and 2) those that arise *within* the ampulla (Fig. 56.26), which are not only of an intestinal type, similar to colonic-type adenomas, but are also of a pancreatobiliary type, referred as *noninvasive papillary carcinomas* in the WHO classification (Klimstra et al, 2010c). For the latter group, those occurring within the ampulla, the designation of *intraampullary papillary tubular neoplasm* (IAPN), akin to pancreatic IPMNs and intraductal tubulopapillary neoplasms, also has been recently proposed (Ohike et al, 2010a).

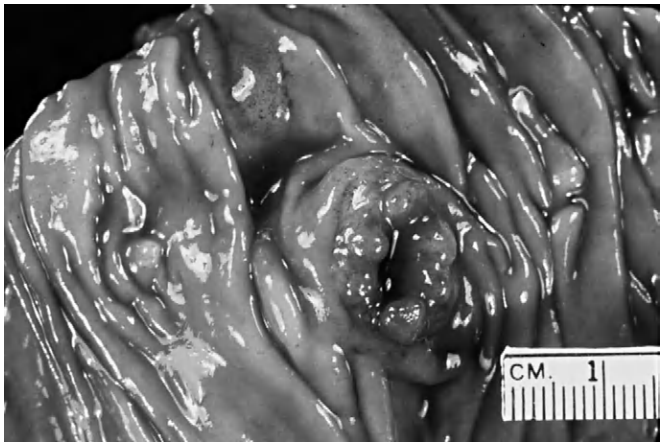


FIGURE 56.26. Intrampullary papillary tubular neoplasm, gross appearance. This predominantly intraampullary tumor produces a bulging ampulla with a nodular orifice.

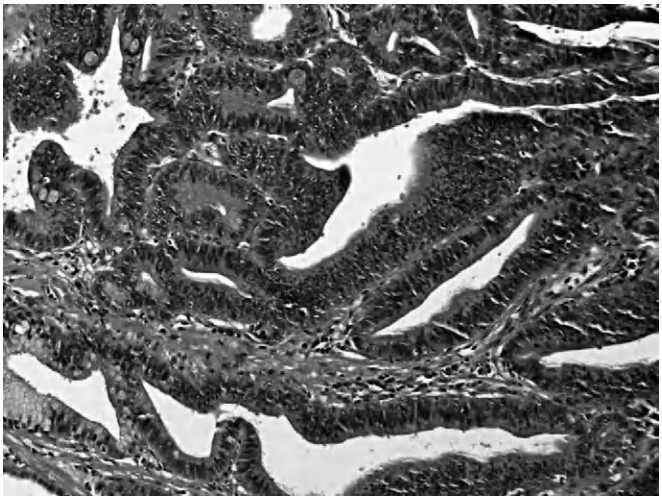


FIGURE 56.27. Ampullary adenoma. The histologic appearance resembles that of an adenoma of the large bowel, with predominantly tubular glands showing pseudostratified, elongated nuclei.

Adenomas of the Duodenal Surface of the Papilla of Vater

Adenomas of the duodenal surface of the ampulla are morphologically and genetically similar to adenomas of the large bowel. Although in most clinical studies, invasive carcinomas outnumber pure adenomas, residual adenomas are commonly found associated with invasive carcinomas. Most ampullary adenocarcinomas, especially those with an intestinal phenotype, are thought to arise from adenoma precursors. Conversely, many adenomas of the ampulla contain foci of invasive carcinoma, requiring a thorough histologic evaluation (Perzin & Bridge, 1981).

A significant percentage of adenomas of the small intestine involve the ampulla or the surrounding duodenal mucosa (Perzin & Bridge, 1981). They may occur sporadically, or they may be associated with FAP. The ampulla and periampullary duodenum are the most common sites of extracolonic adenomas in patients with FAP (Alexander et al, 1989; Domizio et al, 1990; Klimstra & Adsay, 2009; Noda et al, 1992; Odze et al, 1994). Sporadic ampullary adenomas are generally solitary, whereas those arising in patients with FAP usually are accompanied by numerous adenomas in the periampullary duodenum, sometimes forming a carpet of polyps. Ampullary adenomas in patients with FAP usually are detected at a younger age (mean, 41 years) compared with sporadic ampullary adenomas (mean, 62 years) (Albores-Saavedra et al, 2000). Symptomatic patients are generally seen initially with biliary obstruction, although ampullary and duodenal adenomas are increasingly detected in asymptomatic patients with FAP owing to endoscopic screening (Shemesh & Bat, 1985). The risk of an invasive carcinoma being found within an ampullary adenoma is proportional to the size of the adenoma, and it is greater for a given size compared to adenomas of the large bowel.

Microscopically, ampullary adenomas resemble their large bowel counterparts and may be tubular, villous, or mixed (tubulovillous) (Albores-Saavedra et al, 2000). The intestinal-type epithelium shows pseudostratification of elongated nuclei, and additional cytologic atypia and architectural complexity may be evident, depending on the degree of dysplasia (Fig. 56.27). Areas of high-grade dysplasia are characterized by complex, cribriform glands with considerable nuclear atypia and loss of epithelial polarity. Immunohistochemical stains often reveal abundant neuroendocrine cells and Paneth cells in ampullary adenomas (Fig. 56.28; Albores-Saavedra et al, 2000; Mora et al, 2004), and these two cell types may be prominent enough to be recognized in routinely stained material.

In some instances, ampullary adenomas may be treated effectively by endoscopic resection or transduodenal ampullectomy rather than pancreatoduodenectomy (see Chapters 27 and 62C; Bohra et al, 2002; Saurin et al, 2003). When this procedure is performed, it is essential for the pathologist to evaluate the lesion carefully to determine the completeness of

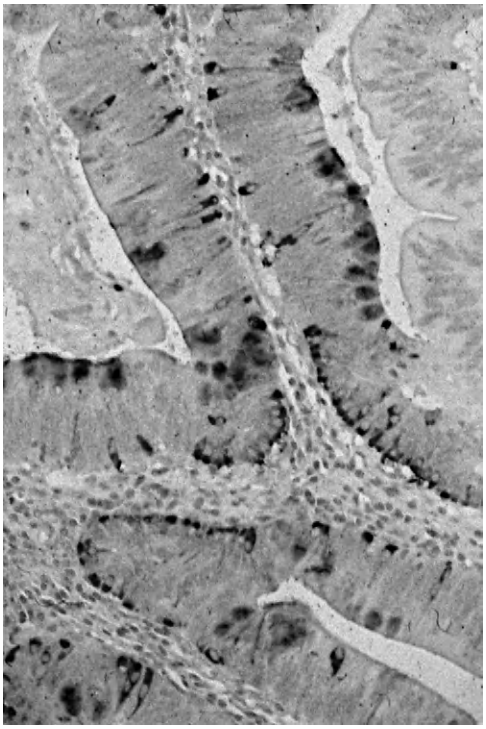


FIGURE 56.28. Ampullary adenoma. Immunohistochemical labeling for chromogranin and lysozyme shows abundant endocrine and Paneth cells.

resection and to search for subtle foci of invasive carcinoma. Sometimes this evaluation must be performed on frozen sections.

Intraampullary Papillary Tubular Neoplasms

Intestinal-type preinvasive neoplasms (adenomas), similar to those occurring on the duodenal surface, may also occur *within* the ampulla; however, in addition, *noninvasive pancreatobiliary-type neoplasms* (Klimstra et al, 2010c) may also be encountered in this region. Recently, the term *intraampullary papillary tubular neoplasm* (Ohike et al, 2010a) was proposed to unify all the tumoral intraepithelial neoplasms that arise predominantly within the ampulla—or the very terminal, intraampullary ends of the two ducts—under one category to avoid confusion and also to establish their kinship with IPMNs and intraductal tubulopapillary neoplasms of the pancreas. As in IPMNs, IAPNs occur predominantly in men at a mean age of 64 years. They form exophytic masses within the ampulla that lead to a protuberant ampulla with a widened orifice (see Fig. 56.26) through which a granular, polypoid tumor can be appreciated within the ampulla. Cut sections show friable, granular lesions with a mean size of 2.5 cm filling the ampullary lumen. Microscopically, half of the cases exhibit a mixture of papillary and tubular growth pattern, and in the remainder, one of the two patterns predominates. About three quarters of the cases have a more intestinal-type appearance, and the remainder have gastropancreatobiliary features; however, overlaps and hybrid types are common, presumably owing to the transitional nature of ampullary epithelium, which harbors different cell types. This is reflected also in the immunophenotype, which often shows discrepant and unexpected profiles using markers that are putatively lineage-specific. High-grade dysplasia is detected in the majority of the cases, and invasive carcinoma is found in more than 75%. Conversely, from the invasive carcinoma perspective, IAPNs are detected in the background of about 30% of invasive ampullary carcinomas. Invasive carcinoma often but not always follows the cell phenotype of the preinvasive component. Noninvasive carcinomas have a very good prognosis; however, they may occasionally develop recurrence in long-term follow-up. Invasive carcinomas arising from IAPNs have a malignant course but one that is significantly more protracted than that of invasive carcinomas unaccompanied by IAPNs (Ohike et al, 2010a).

Flat-Type Intraepithelial Neoplasia (Dysplasia and Carcinoma in Situ)

Much less common preinvasive neoplastic lesions of the ampulla include *flat dysplasia* (Albores-Saavedra et al, 2000), a lesion with epithelial dysplasia that does not form a grossly polypoid mass. Microscopically, a low papillary pattern may be apparent, because the epithelia of the papilla of Vater and the common channel normally have papillae. Otherwise, the dysplastic epithelium involves the native architecture of the ampulla.

Adenocarcinoma (See Chapter 59)

Adenocarcinomas are the most common malignancies of the ampulla. Their precise incidence is difficult to determine because of definitional differences. Many carcinomas arising in the common bile duct, pancreas, or duodenum secondarily invade into the ampulla and can be mistaken as a primary. If defined stringently as tumors with their epicenter at the ampulla, with more than 75% of the tumor confined to the ampulla, or with a convincing preinvasive neoplasm within the ampulla, the incidence of ampullary carcinomas becomes fairly low, typically comprising less than 20% of carcinomas in pancreatoduodenectomy specimens.

Similar to the adenomas and IAPNs from which many of them arise (Stolte & Pscherer, 1996), adenocarcinomas are more common in the ampulla than in other sites in the small bowel (Klimstra & Adsay, 2009). Also, they are prevalent in patients with FAP (Harned & Williams, 1982), generally presenting later than the large bowel carcinomas that these patients also have. The classic presentation of ampullary adenocarcinoma is considered to be biliary obstruction accompanied by a distended, palpable gallbladder (the Courvoisier sign); in truth, a palpable gallbladder is an uncommon finding. Accurate preoperative diagnosis depends on the extent of the invasive carcinoma, relative to any residual adenoma, and on the technique of endoscopic biopsy (Elek et al 2003; Rodriguez et al, 2002). The invasive components are commonly deeply situated within the adenoma, so superficial biopsy specimens may fail to reveal invasion. Especially for carcinomas located within the common channel, endoscopic papillotomy may be helpful to reach the diagnostic areas.

Ampullary adenocarcinomas are often relatively small when detected, presumably because of early symptoms. Nearly 20% are less than 1 cm, and more than 75% are less than 4 cm at diagnosis (Albores-Saavedra et al, 2000; Tajiri et al, 2009a). Because about a third of the cases arise in an adenoma or IAPN, the overall tumor size is often misleading. The gross configuration depends on the specific epithelia involved. Some ampullary carcinomas have the bulk of the lesion at the duodenal surface of the ampulla, forming a polypoid or ulcerated mass readily recognizable endoscopically, whereas other intraampullary carcinomas are covered by intact duodenal mucosa (Fig. 56.29). Larger tumors may replace the normal ampullary structures completely, making it difficult to determine precisely where the tumor arose. A subset of ampullary carcinomas forms schirrous, constrictive lesions in the wall of the distal tips of the ducts, in particular the common bile duct, without causing an overt exophytic mass in the ampulla or on the duodenal surface.

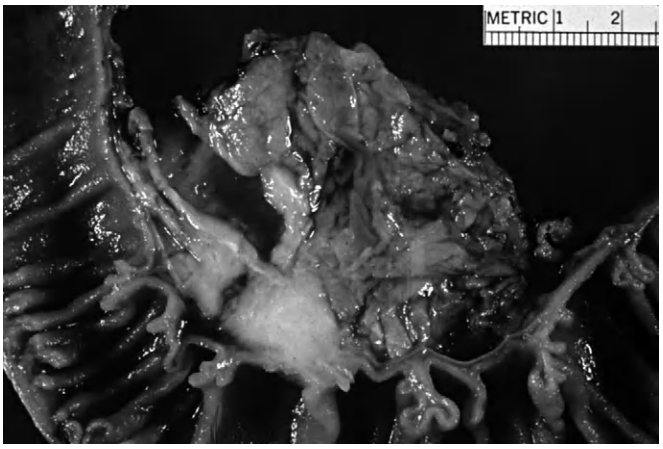


FIGURE 56.29. Ampullary adenocarcinoma, gross appearance. This intraampullary carcinoma forms a sclerotic, infiltrative mass situated in the wall of the duodenum, with associated dilation of the common bile duct and invasion into the head of the pancreas.

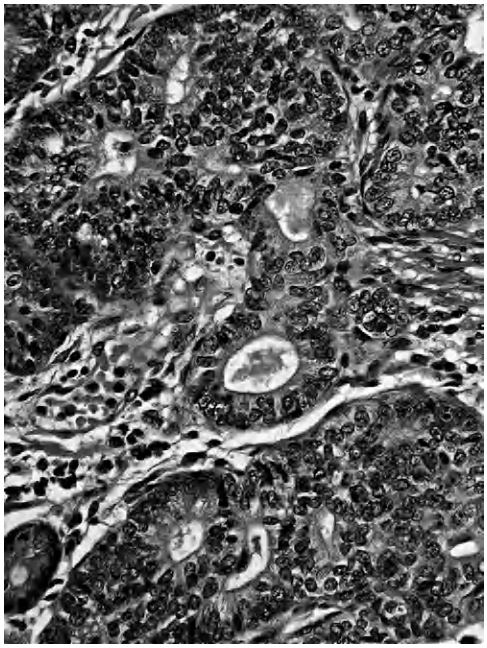


FIGURE 56.30. Ampullary adenocarcinoma, intestinal type. This invasive carcinoma is formed of cribriform, tubular glands with pseudostratified nuclei, resembling a carcinoma of the large intestine.

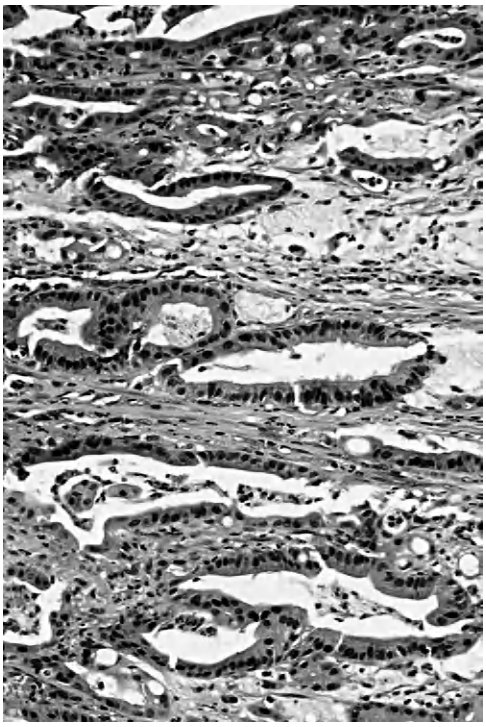


FIGURE 56.31. Ampullary adenocarcinoma, pancreatobiliary type. The glands are arranged individually, with a single layer of round nuclei and mucinous cytoplasm. Abundant desmoplastic stroma is present, resembling a primary ductal adenocarcinoma of the pancreas.

Microscopically, some ampullary adenocarcinomas resemble carcinomas of the large bowel and are referred to as *intestinal type* (Albores-Saavedra et al, 2000; Kimura et al, 1994). They are composed of individual, complex, cribriform glands with pseudostratified, elongated nuclei, commonly exhibiting extensive luminal necrosis (Fig. 56.30). Another subset of ampullary adenocarcinomas resembles ductal adenocarcinoma of the pancreas or common bile duct; these are referred to as a *pancreatobiliary type,* which show simple and relatively small glands with a single layer of cells with round nuclei and abundant stromal desmoplastic cells (Fig. 56.31). Most commonly, intestinal-type ampullary adenocarcinomas arise in association with a preinvasive neoplasm, although many pancreatobiliary-type adenocarcinomas appear to arise without a recognizable preinvasive lesion (Albores-Saavedra et al, 2000). Recent sudies have shown different biologic behavior for intestinal versus pancreatobiliary adenocarcinomas; however, it is also clear that a substantial portion of the cases has either hybrid or unclassifiable patterns, making this distinction highly subjective (Balci et al, 2010). Small, infiltrative clusters at the advancing edge of the tumor, so-called *tumor budding,* is seen quite commonly in ampullary adenocarcinomas when examined carefully and has been found to be an indicator of aggressive behavior (Ohike et al, 2010b). Perineural invasion is less common than it is in pancreatic cancer and may also be an indicator of adverse behavior (Lowe et al, 2009).

Ampullary adenocarcinomas typically invade into the muscularis of the sphincter of Oddi, extend through the duodenal submucosa and muscularis propria, and invade the pancreatic parenchyma or peripancreatic soft tissues. However, it is often difficult to determine the precise extent of the tumor at the three-dimensional level because of the anatomic complexity of this region. This may be partly responsible for the better survival recorded for stage pT2 cases compared with pT1 cases in the data from the National Cancer Database of American College of Surgeons (Edge et al, 2010). Furthermore, even relatively small invasive carcinomas can extend to the peripancreatic soft tissues, which creates problems in staging such cases (Tajiri et al, 2009a). Lymph node metastases may be found even in superficially invasive carcinomas and are detected in about 40% of patients, far less than the 75% associated with pancreatic ductal adenocarcinomas.

Numerous histologic variants of ampullary adenocarcinoma have been described, including adenosquamous carcinoma, clear cell carcinoma, mucinous adenocarcinoma, signet ring cell carcinoma, and micropapillary carcinoma, often associated with tumor infiltrating neutrophils (Albores-Saavedra et al, 2000; Hara et al, 2002; Khayyata et al, 2005; Ueno et al, 2002). Although the morphologic features of each of these subtypes are distinctive, specific clinical or genetic differences from the more common histologic types have yet to be described. Unusual carcinoma types, such as acinar, medullary, and osteoclastic giant cell, can also occur in the ampulla (see the discussion on other invasive carcinomas related to ductal adenocarcinoma).

The molecular genetic changes involved in the development of ampullary adenocarinomas roughly parallel those that occur in colorectal carcinomas: mutations in the *KRAS* oncogene are found in approximately 40% and include mutations in codon 12 and codon 13 (Scarpa et al, 1993). More than half of cases have mutations in *TP53* (Albores-Saavedra et al, 2000; Howe et al, 1997; Kubota et al, 2003; Matsubayashi et al, 1999; Takashima et al, 2000; Younes et al, 1995), and loss of *SMAD4* has been shown (McCarthy et al, 2003). However, abnormalities of DNA mismatch repair genes are uncommon in ampullary carcinomas (Park et al, 2003).

Ampullary carcinomas have a relatively favorable survival compared with ductal carcinomas of the pancreas; patients with localized disease have a 5-year survival of 50%, and patients with lymph node metastases have a 5-year survival of 28% (Albores-Saavedra et al, 2000; Howe et al, 1998; Tajiri et al, 2009b). Although some authors have questioned whether this outcome reflects a different biology for ampullary carcinoma, as opposed to simple detection at an earlier stage because of earlier onset of symptoms, even ampullary carcinoma patients with positive lymph nodes have a better survival than any group of pancreatic carcinoma patients (Howe et al, 1998).

High-Grade Neuroendocrine Carcinoma

Although high-grade neuroendocrine carcinomas of the ampulla are rare, they are more common in this location than in the pancreas (see Chapter 61). The clinical findings are the same as those of ampullary adenocarcinomas; hormonal symptoms are uncommon (Nassar et al, 2005). Many high-grade neuroendocrine carcinomas arise in association with an adenoma, and some contain mixed components of adenocarcinoma. Two histologic types occur, including *small cell carcinoma* (Zamboni et al, 1990) and *large cell neuroendocrine carcinoma* (Albores-Saavedra et al, 2000; Nassar et al, 2005). Small cell carcinomas have fusiform small cells with minimal cytoplasm, finely granular chromatin, and nuclear molding (Fig. 56.32). Large cell neuroendocrine carcinomas have moderate amounts of cytoplasm and round nuclei with prominent nucleoli. Both are distinguished from well-differentiated neuroendocrine tumors by their high mitotic rate (>20 per 10 HPFs) and abundant necrosis. Immunohistochemical evidence of neuroendocrine differentiation is generally identifiable and is required for the diagnosis of the large cell type, but staining for chromogranin and synaptophysin is less widespread than in carcinoid tumors (Fig. 56.33). Some of the molecular genetic abnormalities are different from those of ampullary adenocarcinomas, including frequent loss of retinoblastoma gene product expression (Nassar et al, 2005). High-grade neuroendocrine carcinomas are highly aggressive. Most patients are seen initially with lymph node involvement and suffer early recurrence and death from the tumor.

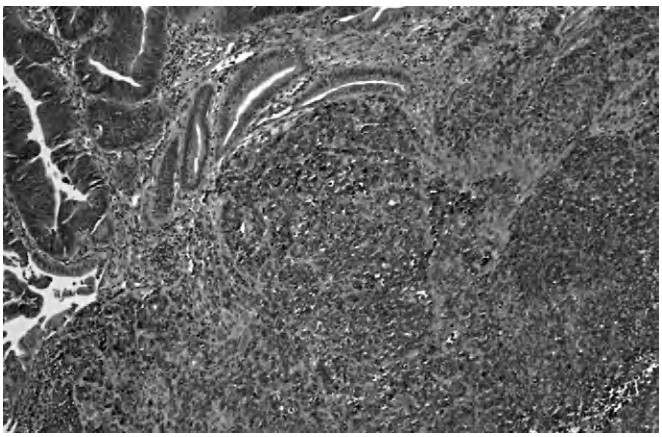


FIGURE 56.32. Small cell carcinoma of the ampulla. The invasive carcinoma is composed of diffuse sheets of small cells. The overlying epithelium contains a tubulovillous adenoma.

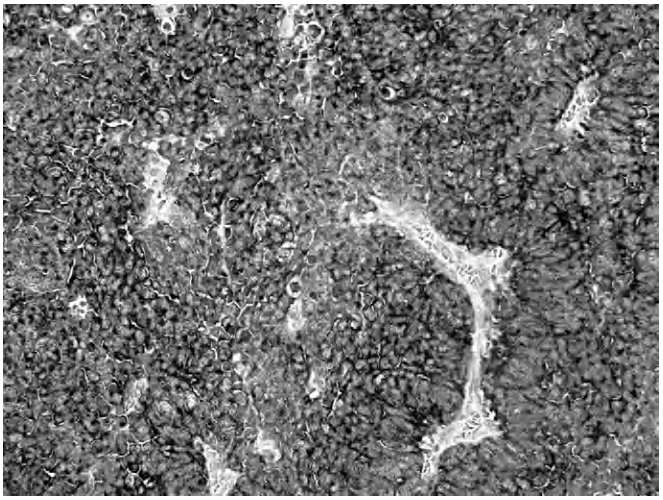


FIGURE 56.33. Large cell neuroendocrine carcinoma of the ampulla. Immunohistochemical labeling for synaptophysin confirms the endocrine nature of this carcinoma.

Well-Differentiated Neuroendocrine Neoplasms

Carcinoid Tumors

A family of well-differentiated neuroendocrine tumors occurs in and around the ampulla of Vater. Most of these have also been designated *carcinoid tumors,* although *neuroendocrine tumor* (NET) is now the preferred term (Burke et al, 1989; Hartel et al, 2005; Hatzitheoklitos et al, 1994; Niido et al, 2005). Ampullary NETs are distinguished from high-grade neuroendocrine carcinomas by their strikingly organoid growth pattern, with nests and ribbons of cells; their low mitotic rate (<20 mitoses per 10 HPFs); and their relative paucity of necrosis. They predominantly involve the submucosa and muscularis of the duodenum and ampulla, although extension into the mucosa is generally present, and endoscopic mucosal biopsy specimens usually yield diagnostic tissue (Bornstein-Quevedo & Gamboa-Dominguez, 2001). Most periampullary NETs are relatively small, ranging from a few millimeters to several centimeters. Tumors that directly involve the ampulla of Vater manifest early with biliary obstruction, whereas tumors situated in the surrounding duodenum are often asymptomatic unless associated with a neuroendocrine paraneoplastic syndrome. Periampullary NETs are associated with several hereditary genetic syndromes, including neurofibromatosis type 1 and MEN type I (Burke et al, 1989). Some NETs arising in these patients have distinctive clinical or morphologic features, representing either gastrinomas or so-called *glandular duodenal carcinoid tumors.* Most periampullary NETs are not associated with a clinical syndrome or distinctive morphology, however, and they only rarely give rise to the carcinoid syndrome, generally after the development of hepatic metastases. These NETs, not otherwise specified, resemble NETs of the stomach and upper GI tract, with a predominately solid, nested architecture; cytologic uniformity; coarsely granular chromatin pattern; and moderate amounts of amphophilic cytoplasm (Fig. 56.34; Makhlouf et al, 1999). By immunohistochemistry, the tumors strongly express the general neuroendocrine markers chromogranin and synaptophysin, and most express keratin as well (Albores-Saavedra et al, 2000; Burke et al, 1989). The low proliferative rate correlates with a low rate of immunolabeling for

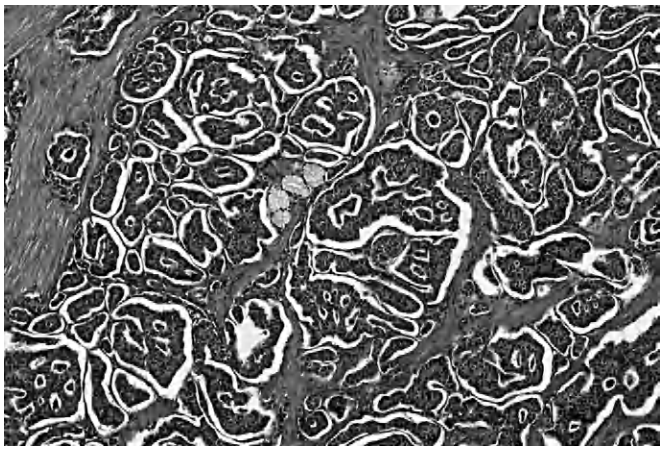


FIGURE 56.34. Well-differentiated neuroendocrine tumor of the ampulla. This neoplasm is composed of nests of uniform epithelial cells predominantly involving the submucosa and muscularis propria.

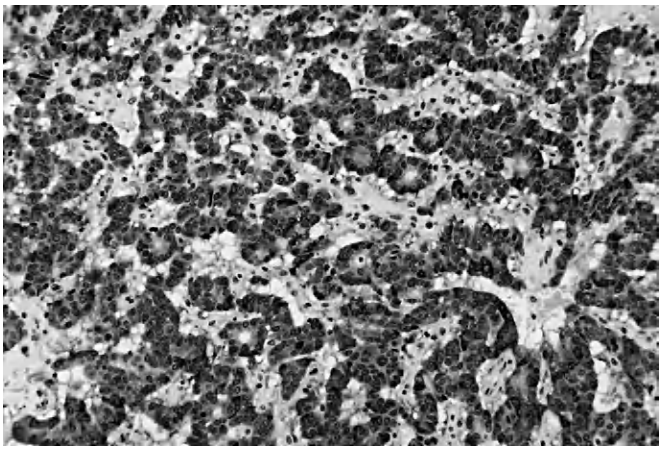


FIGURE 56.35. Gastrinoma of the ampulla. Immunohistochemical staining for gastrin shows positivity in the neoplastic cells that otherwise have characteristic features of a neuroendocrine tumor.

Ki-67, defined to be less than 20% and usually less than 5%. Small NETs (<1 cm) limited to the mucosa and submucosa generally lack lymph node metastases, and some may be treated effectively by local excision (Pyun et al, 2004); however, the lesion often proves to be more advanced than originally appreciated, and even small tumors may on occasion have metastases, thus these tumors can require pancreatoduodenectomy. As the size increases, the risk for nodal metastases also increases. Patients with nodal or hepatic metastases are difficult to cure, but the disease has a protracted clinical course, and survival for many years in the presence of liver metastases is not unusual.

Gastrinomas of the periampullary region are NETs associated with hypersecretion of gastrin, resulting in peptic ulceration (Zollinger-Ellison syndrome). Periampullary gastrinomas are particularly prevalent in patients with MEN type I, and they outnumber pancreatic gastrinomas as the source of Zollinger-Ellison syndrome (Donow et al, 1991). In contrast to the pancreatic primaries, periampullary gastrinomas are often small (<1 cm), and regional lymph node metastases from these tumors may be larger than the primaries; and in some cases, the primary tumor is difficult to identify (Anlauf et al, 2008). For this reason, some authors advocate pancreatoduodenectomy for patients with gastrinoma syndrome with an unidentified primary to remove the most plausible culprit region, the "gastrinoma triangle." Processing of such specimens in the pathology laboratory may require special protocols (Anlauf et al, 2008). Histologically, gastrinomas are indistinguishable from nonfunctioning NETs, but gastrin production is usually demonstrable by immunohistochemistry (Fig. 56.35). Although regional lymph node metastases are commonly present, periampullary gastrinomas have a better long-term prognosis than pancreatic gastrinomas, which are usually considerably larger at the time of diagnosis.

Glandular duodenal carcinoid tumors, also known as *ampullary somatostatinomas* or *psammomatous somatostatinomas,* are well-differentiated NETs with an exquisitely glandular growth pattern (Thirabanjasak et al, 2008). These tumors are highly characteristic of the periampullary region and are closely associated with neurofibromatosis type 1, although sporadic examples occur (Burke et al, 1990). Many of these tumors produce somatostatin (Dayal et al, 1983), and they almost never cause the somatostatinoma syndrome, in contrast to pancreatic somatostatinomas. In addition to their gland-forming architecture, glandular duodenal carcinoid tumors often exhibit psammoma bodies (Fig. 56.36; Albores-Saavedra et al, 2000; Dayal et al, 1983). By immunohistochemistry, expression of general neuroendocrine markers, such as chromogranin and synaptophysin, is consistent, and somatostatin is usually detectable. Although the nuclear features are those of a well-differentiated NET, the glandular architecture of glandular duodenal carcinoid tumors may cause confusion for adenocarcinoma. Also, abundant, lightly eosinophilic cytoplasm causes resemblance of the neoplastic glands to submucosal Brunner glands of the duodenum on endoscopic biopsy specimens. Glandular duodenal carcinoid tumors are relatively aggressive in their spread and are frequently associated with lymph node and hepatic metastases; however, limited data in the literature indicate that they may still be indolent neoplasms like other ampullary-region NETs (Thirabanjasak et al, 2008).

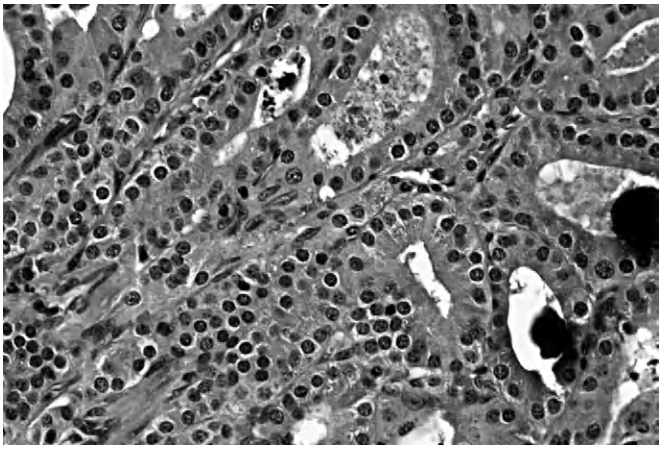


FIGURE 56.36. Glandular duodenal carcinoid of the ampulla. The uniform endocrine cells are arranged in well-formed glands with granular eosinophilic cytoplasm. Calcified psammoma bodies are a characteristic feature.

Gangliocytic Paraganglioma

A pathologically distinctive tumor that is essentially limited to the ampullary region, gangliocytic paraganglioma contains a variety of different cell types that have defied a logical histogenetic explanation. Most patients are adults who present with minimal symptoms, unless the tumor is close enough to the ampulla to cause biliary obstruction. Some cases are associated with neurofibromatosis type 1 (Burke & Helwig, 1989; Castoldi et al, 2001), but the association is less strong than for glandular duodenal carcinoid tumors. Gangliocytic paragangliomas are situated in the submucosa, similar to NETs, and some are polypoid or pedunculated and usually measure 1 to 3 cm. Microscopically, three different cellular components vary in proportion from case to case (Fig. 56.37; Albores-Saavedra et al, 2000; Burke & Helwig, 1989). Nests of epithelioid neuroendocrine cells are usually predominant. Individual ganglionic cells have abundant cytoplasm and large, round nuclei with prominent nucleoli. Finally, a spindle cell component represents Schwann cells. The neuroendocrine cells stain for chromogranin and synaptophysin and variably express keratin (Collina et al, 1991); this last finding establishes a relationship with NETs and distinguishes them from true paragangliomas. The ganglion cells express synaptophysin and neurofilaments, and the schwannian component stains for S100 protein. Most gangliocytic paragangliomas also produce pancreatic polypeptide (Altavilla et al, 2001). The origin of these tumors has been debated, because they contain endodermally derived (NET-like elements) and neural crest–derived (schwannian) components (Perrone, 1986). Most gangliocytic paragangliomas are benign, but rare metastases have been reported.

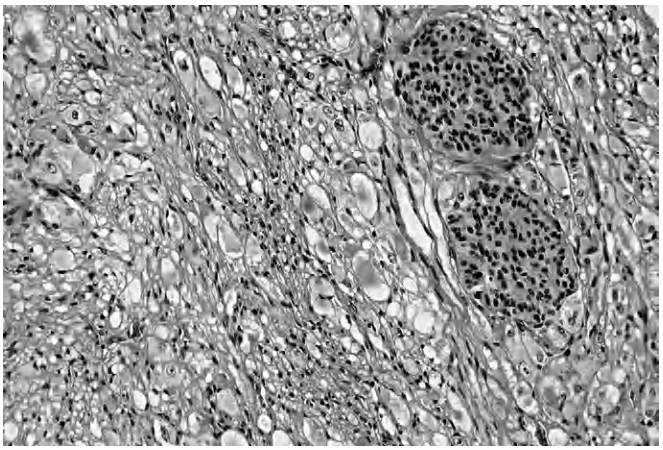


FIGURE 56.37. Gangliocytic paraganglioma of the ampulla. The neoplasm has three characteristic elements: the nested neuroendocrine tumor–like epithelial component, the large ganglion cells with abundant granular cytoplasm, and the intervening spindled Schwann cell component.

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CHAPTER 57

Cystic neoplasms of the pancreas: epidemiology, clinical features, assessment, and management

James J. Mezhir and Peter J. Allen

OVERVIEW

Cystic neoplasms of the pancreas have become a well-defined radiographic entity over the last decade. With increasing use of cross-sectional imaging, nearly 2.6 cystic lesions per 100 individuals are encountered per year (Brugge et al, 2004a; Gorin & Sackier, 1997; Kimura et al, 1995). These lesions have a broad histologic differential, which has been well characterized by Klöppel and Kosmahl (2001) and others (Table 57.1; Kosmahl et al, 2004). This differential includes benign nonneoplastic pancreatic pseudocysts and also cystic neoplasms, which comprise benign entities such as serous cystadenoma, premalignant cysts such as intraductal papillary mucinous neoplasms (IPMNs), and cystic lesions with invasive carcinoma. The ability to differentiate among neoplastic pancreatic cystic neoplasms without the need for resection continues to evolve. Serous cysts can often be differentiated from mucinous cysts by cross-sectional imaging and endoscopic ultrasound (EUS) with cyst fluid analysis (Allen et al, 2003, 2006; Allen & Brennan, 2007; Brugge et al, 2004b; Carpizo et al, 2008; Ferrone et al, 2009). However, diagnostic dilemmas continue, and the ability to predict future progression to malignancy within the premalignant group is currently limited (Lee et al, 2008).

As shown in Table 57.1, these lesions remain a diagnostic challenge. As their incidence increases, so does the differential diagnosis. With an increasing knowledge of the clinicopathologic variables predictive of malignancy and an improved understanding of the natural history of many of the common cystic lesions, management has changed to one of selective resection. Despite the improvement in diagnostic capability, there still remain a significant number of lesions that are indeterminate; in this setting the clinician must balance the risk of malignancy with the morbidity and mortality associated with pancreatic resection.

Following is a summarization of the current literature on the diagnosis and management of patients with cystic neoplasms of the pancreas.

CLINICOPATHOLOGIC VARIABLES

The majority of patients with pancreatic cysts will have nonneoplastic inflammatory pseudocysts that develop as a complication of acute pancreatitis (see Chapter 54; Brugge et al, 2004a; Cannon et al, 2009). A *pseudocyst* is a fluid collection that is devoid of an epithelial lining. Pseudocysts have been reported to develop in up to 50% of patients who have acute pancreatitis (Cannon et al, 2009; Grace & Williamson, 1993; O'Malley et al, 1985). Because of the frequency of pancreatitis, some studies have reported that pseudocysts comprise up to 85% of all cystic pancreatic lesions. Pseudocysts can be managed with observation, endoscopic drainage, or operative drainage (Cannon et al, 2009). The particulars of the management of patients with pancreatic pseudocysts are beyond the scope of this chapter.

Cystic neoplasms are a heterogeneous group of lesions carefully described by Klöppel and Kosmahl (see Table 57.1; Klöppel & Kosmahl, 2001; Kosmahl et al, 2004). They comprise approximately 10% to 15% of cystic lesions of the pancreas and are a heterogeneous group of lesions that range from benign to malignant. Despite the fact that numerous neoplasms can present as a cystic lesion, the most common cystic neoplasms encountered by surgeons include serous cystadenoma (SCA), mucinous cystic neoplasm (MCN), and intraductal papillary mucinous neoplasm (IPMN). In a study by the French Surgical Association of 372 resected cystic neoplasms from 73 institutions, these three lesions comprised 87% of all lesions (Le Borgne et al, 1999). More recent series of pancreatic cystic neoplasms are outlined in Table 57.2. The clinicopathologic

Table 57.1

Classification of Cystic Neoplasms of the Pancreas

Neoplastic	Nonneoplastic
Epithelial	**Epithelial**
Benign	Congenital cyst (in malformation syndromes) Lymphoepithelial cyst Mucinous nonneoplastic cyst Enterogeneous cyst Retention cyst Periampullary duodenal wall cyst Endometrial cyst
Serous adenoma (microcystic) Serous adenoma (oligocystic, poorly demarcated) MCN IPMN Acinar cell cystadenoma Dermoid cyst Cystic hamartoma Von Hippel–Lindau–associated cystic neoplasm	**Nonepithelial**
Borderline	Pseudocyst Parasitic cyst
MCN IPMN Solid pseudopapillary tumor	
Malignant	
MCN-associated carcinoma IPMN-associated carcinoma Ductal adenocarcinoma, cystic Serous cystadenocarcinoma Pancreatoblastoma, cystic Cystic metastatic epithelial neoplasm Neuroendocrine carcinoma, cystic	
Nonepithelial	
Benign neoplasm (i.e., lymphangioma) Malignant neoplasm (i.e., sarcoma)	

IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm

Modified from Kosmahl M, et al, 2004: Cystic neoplasms of the pancreas and tumor-like lesions with cystic features: a review of 418 cases and a classification proposal. Virchows Arch 445(2):168-178.

factors associated with the more common cystic neoplasms are shown in Table 57.3.

Serous Cystadenomas

Serous cystadenomas (SCA) were first characterized by Compagno and Oertel in 1978 as microcystic and glycogen rich, and they distinguished these lesions from mucinous cysts (MCNs and IPMNs) (Compagno & Oertel, 1978a). SCAs occur with variable size, and when large (>10 cm) may cause symptoms from local compression. Grossly, these cysts are characterized by septations and thick fibrous walls and have what appear to be innumerable small cysts containing clear, thin fluid. A classic honeycomb appearance is often present, as is a calcified central scar with or without hemorrhage (Fig. 57.1A and B). On imaging, these lesions may appear as a single, large cyst (oligocystic) (Fig. 57.1C and D); if so, they are very difficult to distinguish from mucinous lesions. Because of the fibrous nature of this lesion, a solid component is often visualized; if noted in the presence of the other characteristic findings of SCA, this should not be concerning for malignancy. Histologically these lesions are characterized by a bland, cuboidal epithelial lining without nuclear polymorphism or mitoses. Typically, no mucin is present in the epithelial lining, but glycogen may be detected in the cytoplasm or in the amorphous cellular material.

SCAs are generally considered benign lesions, and only 25 cases of serous "cystadenocarcinoma" have been reported in the world literature as of 2010 (King et al, 2009; Matsumoto et al, 2005). Many of these case reports describe the "malignant" serous cystadenoma as locally invasive, and only 9 (36%) of 25 cases had evidence of metastasis. Despite the presence of metastasis, long-term prognosis remains excellent in these patients; it appears that the true incidence of malignancy within SCA is less than 1%. The institutional database at Memorial Sloan-Kettering Cancer Center (MSKCC) includes approximately 200 patients who have had resection for SCA, and none has developed or presented with metastatic disease. The more common problem caused by these lesions is local invasion that results in symptoms such as early satiety, obstructive jaundice, and pain. It stands to reason that large lesions are more likely to produce symptoms; however, many patients with lesions greater than 10 cm in diameter will have their lesion identified incidentally; for example, with a mean diameter of 11 cm, 71% of patients had symptoms compared with a mean diameter of 5 cm, with which 53% had symptoms (Compagno & Ortel, 1978a; Tseng et al, 2005).

Mucinous Cystic Neoplasms

Mucinous cystic neoplasms (MCNs) are mucin-producing cystic tumors that lack communication with the pancreatic duct and contain mucin-producing columnar epithelium. Ovarian-like stroma surrounding the columnar epithelium is considered a pathognomonic finding and is the presumed reason that MCNs are almost exclusively found in females. The stroma is a characteristic that pancreatic MCNs share with some mucinous

Table 57.2

Single-Institution Series of Patients with Resected Cystic Neoplasms of the Pancreas

Reference	Years (Inclusive)	No. Patients	SCA N (%)	MCN N (%)	IPMN N (%)	SPT N (%)	Pseudocyst N (%)	Other N (%)	Malignancy N (%)*
Kosmahl et al, 2004	1971-2003	418	43 (10)	32 (8)	77 (18)	89 (21)	73 (.7)	42 (10)	62 (15)
Spinelli et al, 2004	1995-2002	49	10 (20)	16 (33)	5 (10)	2 (4)	00 (0)	2 (4)	14 (29)
Allen et al, 2006	1995-2005	199	76 (38)	19 (10)	30 (15)	4 (2)	11 (.5)	20 (10)	39 (20)
Ferrone et al, 2009	2004-2007	256	34 (13)	40 (16)	84 (33)	13 (5)	2 3 (1)	21 (8)	61 (24)

SCA, serous cystadenoma; MCN, mucinous cystic neoplasms; IPMN, intraductal papillary mucinous neoplasm; SPT, solid pseudopapillary tumor

*Includes ductal adenocarcinoma, serous cystadenocarcinoma, mucinous cystadenocarcinoma, neuroendocrine neoplasm, and cystic neoplasms with high-grade dysplasia.

Table 57.3

Characteristics of Common Cystic Neoplasms of the Pancreas

Cystic Neoplasm	Mean Age (Yr)	Gender (M/F)	Gross Features	Macroscopic Features	Imaging Characteristics	Cyst Fluid Characteristics	Cyst Fluid Cytology
Serous cystadenoma	61-65	7:3	Variable size, microcystic, stellate scar	Clear cytoplasm, well-defined borders, uniform nuclei, glycogen-rich cells	Microcystic, characteristic honeycomb pattern, stellate scar	Low viscosity, CEA low, amylase low	Cuboidal cells, clear glycogen-rich cytoplasm
Mucinous cystic neoplasm	45-55	>10:1	Large size, multilocular, thick walled	Tall, columnar mucin-producing epithelial; ovarian-type stroma	Macrocystic, body/tail location, does not communicate with duct, peripheral calcifications	High viscosity, CEA elevated, amylase low	Variable cellularity with columnar cells with or without atypia
Intraductal papillary mucinous neoplasm	65-75	1:1	Variable size, multilocular, involves main or branch ducts	Mucin-producing epithelium with papillae	Macrocystic ductal involvement	High viscosity, CEA elevated, amylase high	Variable cellularity with columnar cells with or without atypia
Solid pseudopapillary tumor	25	9:1	Irregular cystic cavities with hemorrhage	Solid sheets of variable cells, hyaline globules neuroendocrine features	Macrocystic areas of hemorrhage	Bloody necrotic debris	Polygonal cells, eosinophilic cytoplasm
Ductal adenocarcinoma with cystic degeneration	60-80	1:1.3	Mass with cystic degeneration	Ductal adenocarcinoma	Cyst with solid component, ductal dilation	Bloody necrotic debris	Malignant cells
Pseudocyst	Variable	1:1	Fibrous, thick-walled capsule	No epithelial lining	Unilocular, associated with pancreatitis	Low viscosity, CEA low, CA19-9 elevated, amylase elevated	Inflammatory cells, no mucin, epithelial cells

Modified from Carpizo et al, 2008: Current management of cystic neoplasms of the pancreas. Surgeon 6(5):298-307.

cysts of the ovary and the liver. Pancreatic MCNs are most commonly found in the body and tail and can range in size from small (2 cm) to large (25 cm). Despite their distal location, patients are often symptomatic (76% in a review of multiple series) at the time of diagnosis (Goh et al, 2006).

Any macrocystic lesion in the distal pancreas of a female patient should be highly suspicious for MCN. These lesions are often unilocular but may contain septa within the primary lesion (Fig. 57.2A to C). When these lesions are multilocular, they are typically macrocystic, in contrast to serous cystadenomas. These lesions may also have peripheral "eggshell" calcifications. Any evidence of mural nodularity in these lesions should be concerning for invasion (Fig. 57.2D). Upon gross inspection, these tumors are round, with a smooth surface and fibrous pseudocapsule.

Unlike serous cystadenomas, MCNs have a risk for harboring malignancy. Rates of invasive disease range from 10% to 50%, which may be an underestimate because of the fact that both benign and malignant epithelium may coexist within the same cyst. Only an extensive pathologic evaluation will detect both entities, which is critical for accurate diagnosis. Clinical factors that increase the risk for malignancy in MCNs are not well characterized, but one study found that older age was more often associated with cancer (Crippa et al, 2008). Factors on imaging associated with malignancy within MCNs include the presence of septations, larger size, and mural nodularity (Allen et al, 2006; Zamboni et al, 1999). Because these lesions are so rare, their natural history is not well defined, although the extent of invasion was demonstrated to be associated with recurrence and death from disease in one study (Allen et al, 2006; Zamboni et al, 1999). In one of the largest studies of MCNs to date, 5-year disease-specific survival for patients with malignancy was 57% (Goh et al, 2006).

Intraductal Papillary Mucinous Neoplasms

Before the first classification system published by the World Health Organization (WHO) (Klöppel et al, 1996), IPMN was described under a variety of names, including *mucinous ductal ectasia*, *papillary carcinoma*, and *villous adenoma*. In contrast to other mucinous and cystic tumors, IPMNs occur equally in men and women and are more often found in older individuals, with the peak incidence between 60 and 70 years of age (Brugge et al, 2004a). Among cystic neoplasms diagnosed in large series, IPMNs represent approximately 15% to 30% of all lesions (see Table 57.2; Allen et al, 2006; Ferrone et al, 2009; Kosmahl et al, 2004; Spinelli et al, 2004). Because of the recent evolution in the understanding of IPMNs, many early reports may include a mixture of patients with IPMNs and MCNs and should be interpreted with caution.

Current nomenclature as defined by the WHO divides IPMN into the categories of *adenoma* (low-grade dysplasia), *borderline* (moderate dysplasia), *carcinoma in situ* (high-grade dysplasia), and *carcinoma* (Furukawa et al, 2005). As clinical experience with IPMN increases, it is becoming more evident that the underlying process presents as a spectrum of neoplasia with significant variation (Schnelldorfer et al, 2008). The clinical and radiologic presentation, malignant potential, and

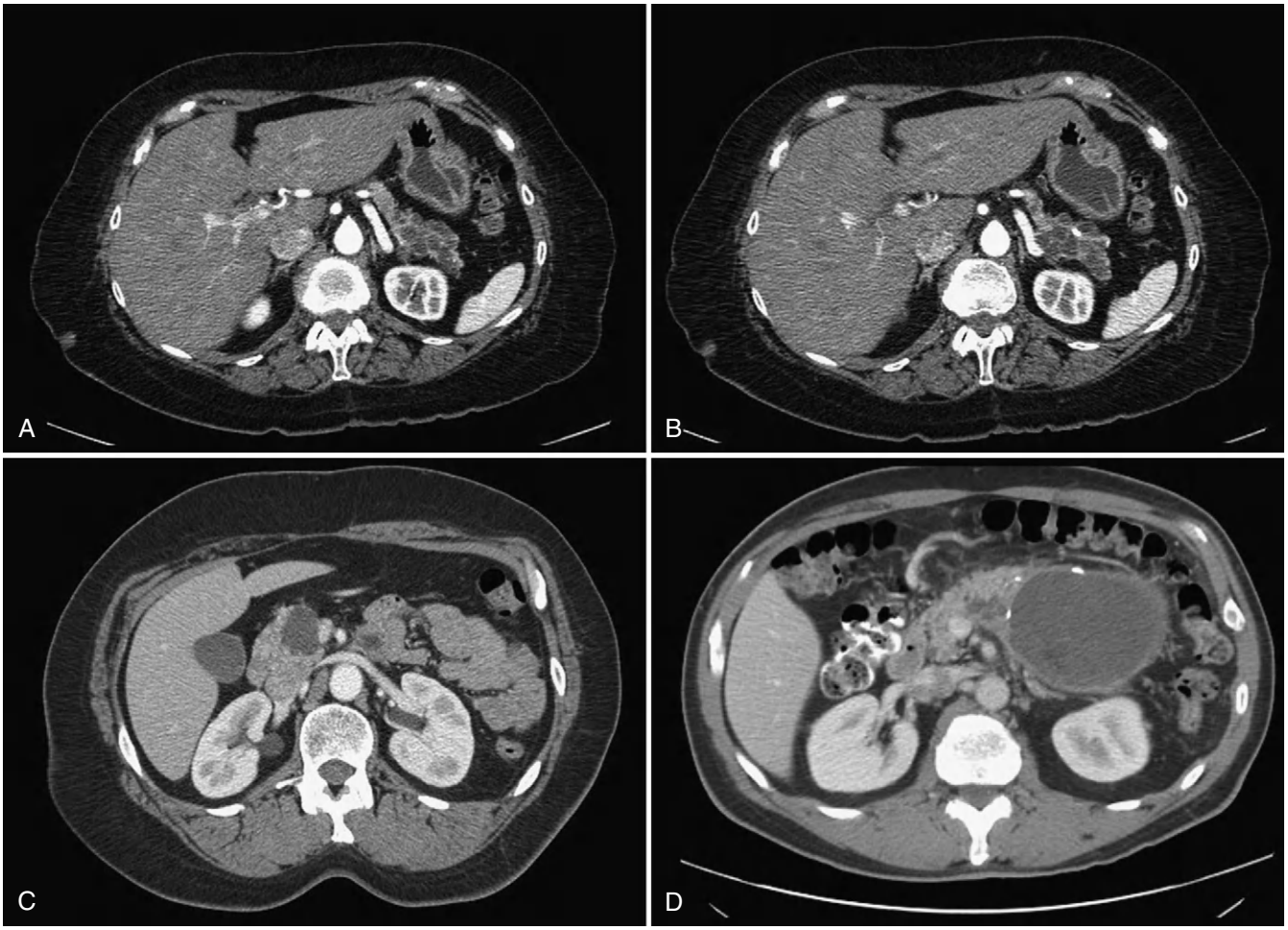


FIGURE 57.1. Imaging characteristics of serous cystadenoma. **A,** Classic honeycomb appearance. **B,** Central calcification. **C,** Oligocystic serous cystadenoma. **D,** Large cystic neoplasm with peripheral calcification, a thickened wall, and pancreatic ductal dilation. This patient underwent distal pancreatectomy and splenectomy because of the inability to exclude malignancy. Final diagnosis was serous cystadenoma.

disease-specific outcomes are highly variable. There also appears to be a progression from adenoma to intraductal carcinoma to invasive carcinoma that can be predicted based on molecular studies.

IPMN is indeed a process that involves the entire pancreas; however, radiographically detectable disease may involve the main duct alone, branch ducts alone, or both (mixed variant). The main duct variant of IPMN is typically seen with diffuse ductal dilation (Fig. 57.3). The presence of a discrete mass or solid component should be concerning for malignancy. Branch duct IPMNs, particularly when smaller than 3 cm, do not have any defining features. They may be unilocular, multilocular, and may be present without dilation of the main pancreatic duct. In the absence of septations, mural nodules, or a solid component, branch duct IPMNs may be indistinguishable from pancreatic retention cysts, MCNs, small cystic endocrine tumors, or even pancreatic pseudocysts.

IPMNs are now a well-characterized mucinous cystic tumor of the pancreas evidenced by ductal involvement and mucin production. Recently, a histopathologic consensus conference defined IPMN as a grossly visible, noninvasive, mucin-producing neoplasm arising from either the main or side branches of the pancreatic duct with variable degrees of ductal dilation (Fig. 57.4A; Furukawa et al, 2005). On histologic analysis, IMPN lesions are characterized by papillary projections of columnar lined epithelium with varying degrees of dysplasia. Mucin is typically abundant both within the cytoplasm of the lining epithelial cells as well as within the acellular fluid matrix (Fig. 57.4B).

IPMN-Associated Malignancy

Malignancy arising from IPMN is well documented, and several large series have been reported in the literature (Table 57.4; D'Angelica et al, 2004; Nara et al, 2009; Salvia et al, 2004; Schnelldorfer et al, 2008; Shin et al, 2010; Sohn et al, 2004; Woo et al, 2009). Invasive cancer is found in 20% to 50% of resected IPMN specimens, which is the reason that these lesions are typically resected. Factors shown to be associated with the presence of invasive cancer in large series include symptoms at presentation, large size, mural nodularity, main duct dilation, and elevated levels of carbohydrate antigen 19-9 (CA19-9).

The reported outcome associated with invasive cancer in patients with IPMN of 5-year survival of 43% to 60% is better than that of ductal adenocarcinoma (15%) (see Chapter 58) following resection. Poultsides and colleagues (2010) reported the Johns Hopkins experience of IPMN-associated invasive cancers and found that compared with patients with ductal

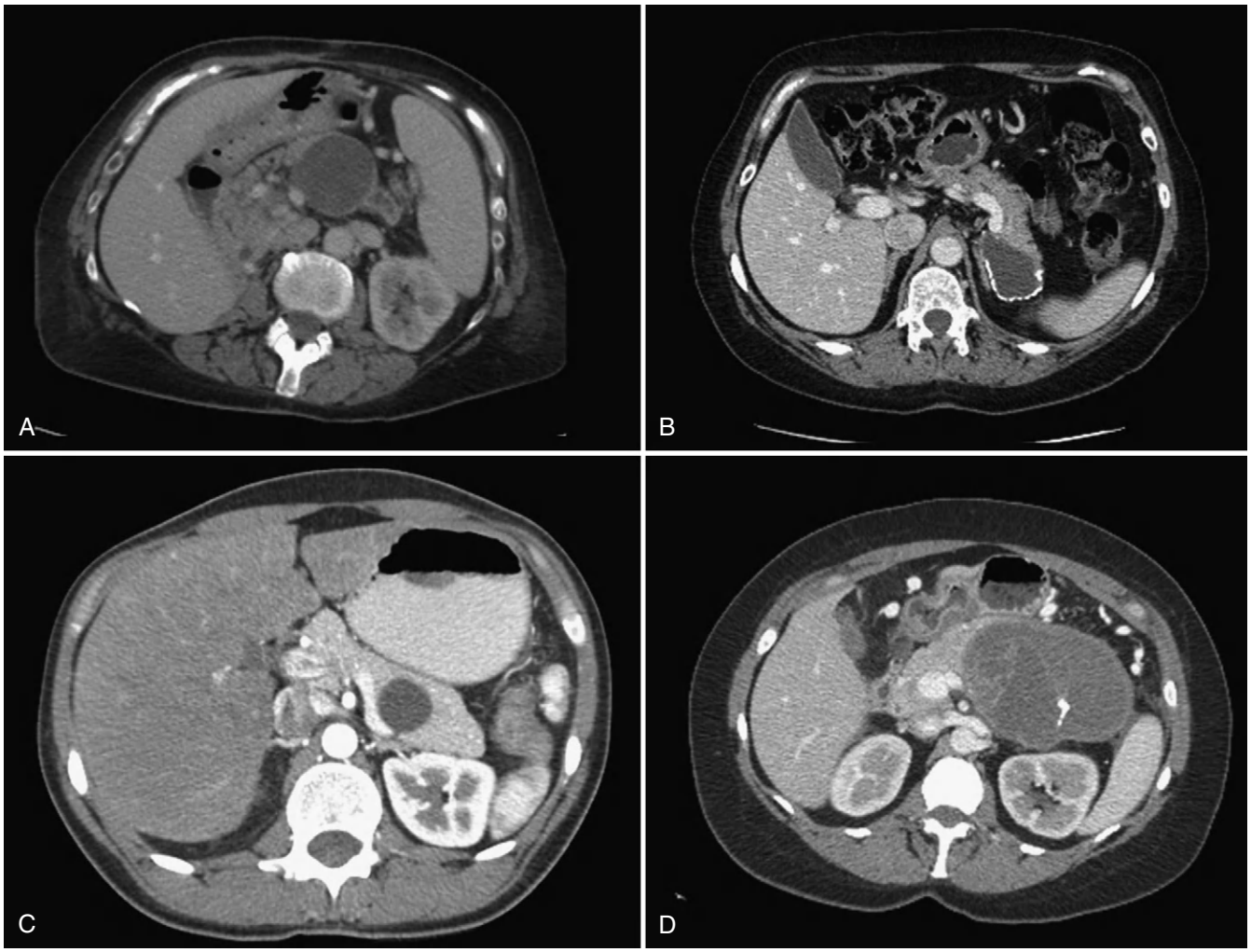


FIGURE 57.2. Imaging characteristics of mucinous cystic neoplasm. **A,** Unilocular lesion in the tail of the pancreas in a young female. **B,** Peripheral "eggshell" calcifications. **C,** Oligocystic lesion in tail of pancreas. **D,** Large macrocystic lesion with central calcification and mural nodularity.

adenocarcinoma, IMPN patients had a lower rate of advanced T stage and lymph node metastasis. Patients with ductal adenocarcinoma more often had high-grade lesions and evidence of perineural invasion, vascular invasion, and positive margins. Despite patients with IPMN-associated cancers having an overall better outcome, if any of the adverse tumor-related factors were present, outcome was similar to patients with ductal adenocarcinoma. It can be inferred from this study that the improved outcome of IPMN-associated cancers is a factor of earlier stage of disease at resection.

Variants of IPMN-associated cancer also have different prognoses. A matched controlled study from our institution demonstrated that patients with colloid-subtype invasive IPMN had significantly better survival than both matched patients with conventional pancreatic carcinoma and patients with invasive tubular IPMN. Fifty-nine patients with IPMN-associated cancer were matched one-to-one with patients with ductal adenocarcinoma with factors from the MSKCC pancreatic cancer nomogram (unpublished data). Among IPMN-associated cancers, tubular histology (compared with the colloid variant) and lymph node involvement were negative prognostic factors associated with outcome. Patients with conventional adenocarcinoma more often presented with obstructive jaundice and had more specimens with evidence of perineural/vascular invasion and regional lymph node metastasis. Survival among patients with colloid variant carcinoma (87% estimated 5-year survival) was significantly better compared with patients with tubular cancers (55%) and ductal adenocarcinoma (23%) (Fig. 57.5).

DIAGNOSTIC EVALUATION OF PANCREATIC CYSTIC NEOPLASMS

High-quality cross-sectional imaging is the key to the diagnostic evaluation of any cystic lesion of the pancreas (see Chapter 16; Sahani et al, 2005). Multidetector computed tomography (CT) allows thin-section imaging of the pancreas and is the most common method at our institution for evaluation of pancreatic cysts. A high-quality CT scan can carefully delineate and characterize the pancreatic parenchyma near a cystic lesion, which is critical in assessing for a radiographically occult malignancy causing adjacent dilation of a pancreatic duct (Allen et al, 2006). In addition, careful visualization of the cystic lesion allows evaluation of septations, mural nodules, and

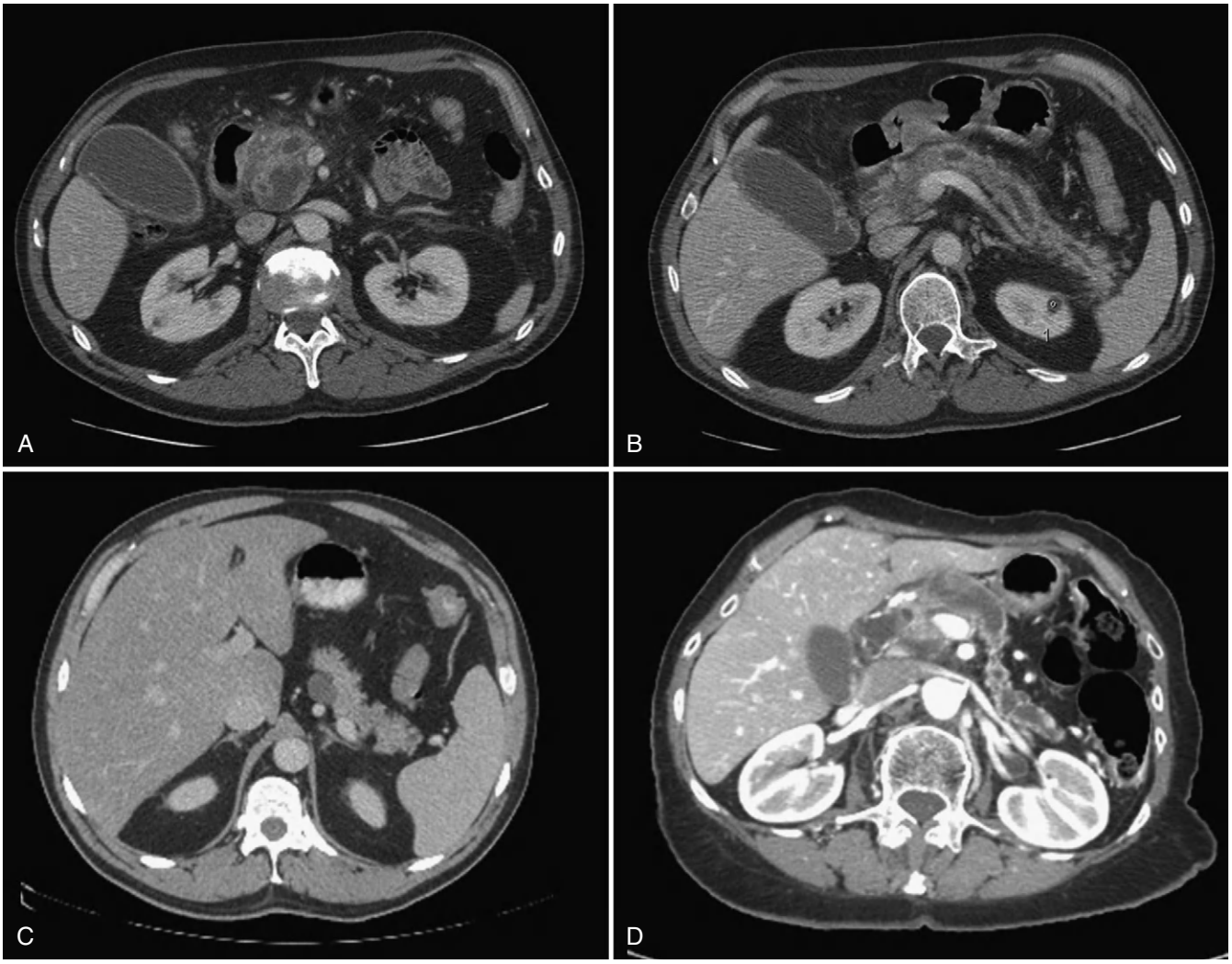


FIGURE 57.3. Imaging characteristics of intraductal papillary mucinous neoplasm (IPMN). **A** and **B,** Main duct IPMN with involvement of the entire main pancreatic duct. **C,** Branch duct IPMN. **D,** Chronic dilation of the main pancreatic duct in a patient with conventional ductal adenocarcinoma. The patient did have a component of IPMN in the resected specimen after pancreatoduodenectomy.

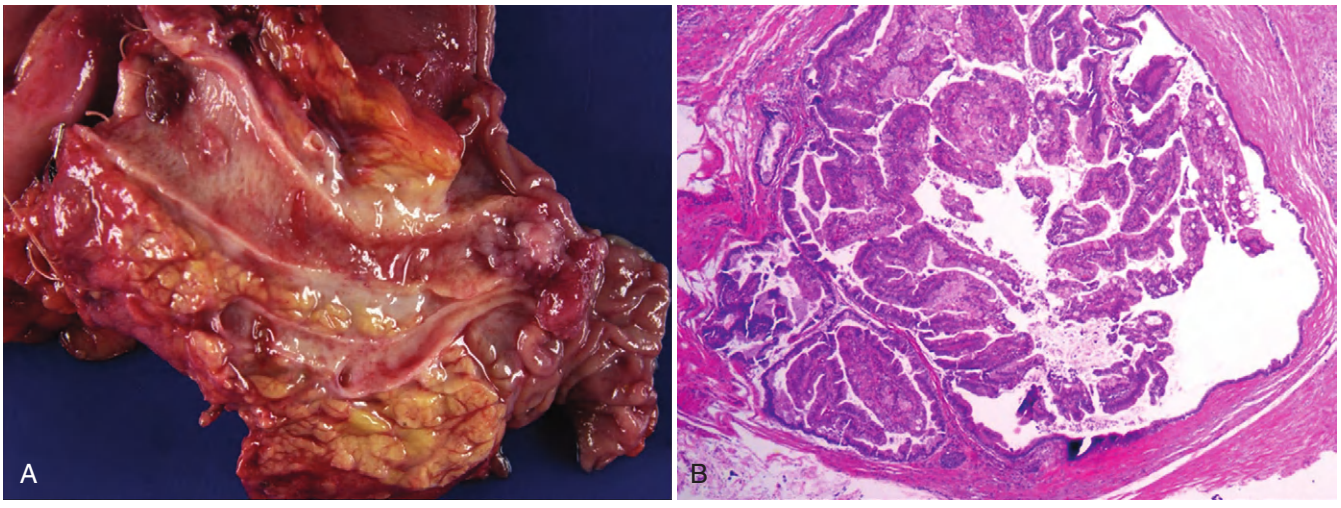


FIGURE 57.4. Gross (**A**) and microscopic (**B**) features of intraductal papillary mucinous neoplasm.

Table 57.4

Single-Institution Series of Patients with Intraductal Papillary Mucinous Neoplasms

Reference	Years Inclusive	No. Patients	Type of IPMN Resected	HGD N (%)	Invasive Cancer N (%)	5-Year OS in Patients with Invasive Cancer	Factors Associated with Malignancy
Sohn, 2004	1987-2003	136	Main duct, branch duct, and mixed	46 (34)	52 (38)	43%	Jaundice, weight loss, nausea and vomiting; main duct variant
Salvia, 2004	1990-2002	140	Main duct	25 (18)	58 (41)	60%	Older age, jaundice, diabetes
D'Angelica, 2004	1983-2000	63	Main duct and branch duct	12 (19)	30 (48)	50%	Tumor size >3 cm; main duct variant
Schnelldorfer, 2008	1992-2005	208	Main duct, branch duct, and mixed	19 (9)	63 (30)	31%	Mural nodule, jaundice, weight loss, mucin visualized on endoscopy; main duct variant
Nara, 2009	1984-2006	123	Main duct and branch duct	21 (17)	61 (50)	—	Tumor size >4 cm; main duct or mixed variant; mural nodule or thick septum
Woo, 2009	1998-2005	85	Branch duct	5 (6)	9 (11)	—	Solid component or thickened wall size ≥3 cm
Shin, 2010	1994-2007	204	Main duct, branch duct, and mixed	9 (4)	41 (20)	58%	Age >60 y, mural nodules, main duct >6 mm, history of pancreatitis, elevated CA19-9

IPMN, intraductal pancreatic mucinous neoplasm; HGD, high-grade dysplasia; OS, overall survival; DSS, disease-specific survival

calcifications. Magnetic resonance cholangiopancreatography (MRCP) can also be used to define cyst morphology and may actually be better than CT for determining a communication with the pancreatic duct and to diagnose branch duct IPMN (Koito et al, 1998; Sainani et al, 2009).

An improvement in endoscopic techniques has significantly improved the clinician's ability to evaluate pancreatic cystic neoplasms (Michael & Gress, 2002). EUS with or without cyst aspiration is a valuable diagnostic tool in the assessment of indeterminate cystic lesions (see Chapter 14). Because this procedure is operator dependent, a gastroenterologist with expertise in performing EUS is highly valuable (Ingram & Arregui, 2004). Careful evaluation with EUS can provide detailed images of the cyst wall and internal cyst architecture. Fine-needle aspiration and biopsy can be performed with EUS and may include both biopsy of the cyst and aspiration of cyst fluid for cytology and analysis for tumor markers (Linder et al, 2006).

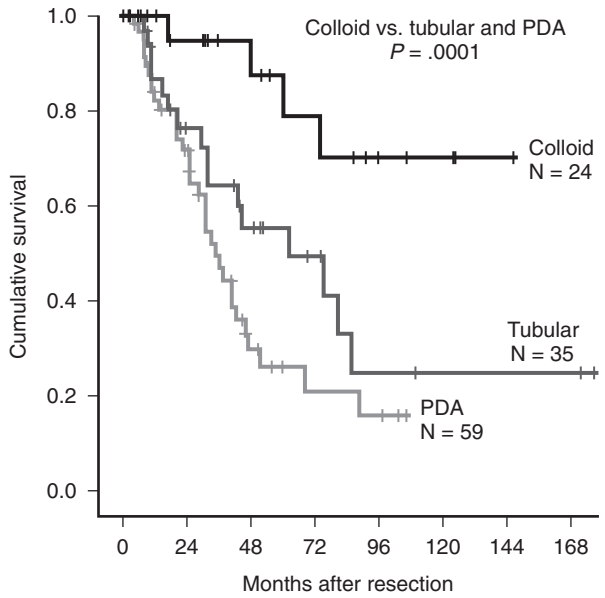


FIGURE 57.5. Outcome of intraductal papillary mucinous neoplasm–associated malignancy *(Memorial Sloan-Kettering Cancer Center, unpublished data). PDA, pancreatic ductal adenocarcinoma.*

Cyst fluid analysis has been extensively studied as a diagnostic tool in assessment of cystic lesions of the pancreas (Allen et al, 2009; Brugge et al, 2004b; Hammel et al, 1995, 1997; Sand et al, 1996). Numerous markers have been evaluated including CA19-9, CEA, CA15-3, MUC proteins, K-Ras, and amylase. In a landmark study by Brugge and colleagues (2004b), cyst fluid CEA greater than 192 ng/mL was the best predictor of a mucinous lesion, which accurately defined these lesions in 79% of patients. An elevation of cyst fluid CEA in combination with the presence of extracellular mucin has been shown to have a positive predictive value as high as 85% in some series. The ability to predict the presence of invasive disease, however, has not been demonstrated by measurement of cyst fluid CEA. SCA and pancreatic retention cysts uniformly have undetectable levels of CEA (Lewandrowski et al, 1993; van der Waaij et al, 2005).

One of the most significant diagnostic challenges is to delineate serous from mucinous cysts. Unfortunately, cyst fluid evaluation for both cytology and tumor markers is limited in this evaluation. The limitations of cyst fluid cytology stem from the very small volume of evaluable fluid and the low cellular content of aspirates. Furthermore, the samples are often contaminated with mucin and mucin-producing cells from the stomach or duodenum, where the EUS needle is passed to reach the cyst.

TREATMENT OF PANCREATIC CYSTIC NEOPLASMS

If the histopathology of a cystic neoplasm can be diagnosed by clinical and imaging criteria, treatment recommendations can be made based on the known behavior of that specific histologic

entity. In some instances, most often in patients with small cysts, the exact histopathologic diagnosis cannot be determined without formal pancreatectomy. It is under these circumstances that treatment recommendations are based on the radiographic and *inferred* histopathology, once a comprehensive diagnostic evaluation is complete.

Serous Cystadenoma

When radiographic and/or endoscopic findings are characteristic of SCA, resection should be reserved for young patients with significant growth or for those whose lesion is clearly symptomatic. As previously discussed, asymptomatic patients have a risk of malignancy of less than 1%. For these lesions the risk associated with pancreatectomy is much greater than the risk of cancer, and it is well documented that the risk of malignancy in SCA is exceedingly rare. The scenario that presents a challenge is the young asymptomatic patient because the natural growth history of SCA is not well defined.

Tseng and colleagues (2005) radiographically followed 24 patients with SCA for a median of 23 months and reported a 0.6 cm per year median growth rate for these lesions and noted that larger lesions (≥4 cm) had a higher growth rate (1.98 cm/year) compared with lesions smaller than 4 cm (0.12 cm/year). The authors recommended that all patients with SCAs larger than 4 cm be resected, regardless of symptoms. At MSKCC, we have noted a growth rate for SCA of approximately 0.5 cm per year but have not found an association between larger size and faster growth (Allen et al, 2006). It is our current practice to observe asymptomatic patients, regardless of lesion size, with the possible exception of those patients who have large lesions that are marginally resectable at presentation, where tumor growth would preclude the ability to perform resection. However, even in the latter circumstance, resection of asymptomatic SCA is difficult to justify given its benign nature.

Mucinous Cystic Neoplasms

Because of the malignant potential of MCNs, it is recommended that these lesions be resected in most cases. MCNs are more often located in the distal pancreas and therefore may be amenable to splenic preservation and laparoscopic resection, which has been demonstrated to be safe and feasible. The remnant pancreas is not known to be at risk following resection of MCN, and therefore patients do not require long-term follow-up. Patients with features concerning for malignancy should have a formal pancreatectomy. Patients with mucinous cystadenocarcinomas should undergo postoperative surveillance the same as patients with pancreatic cancer.

Intraductal Papillary Mucinous Neoplasms

Resection is reserved for selected patients with IPMNs. When radiographic or endoscopic studies identify dilation of the main pancreatic duct and/or any other concerning features, the standard approach is resection. Concerning radiographic features in the setting of branch duct IPMN include a solid component or mural nodule, septations, or size greater than 3 cm (Allen et al, 2006). Lesions in the head of the pancreas are resected with pancreatoduodenectomy, and in the tail, distal pancreatectomy with or without splenectomy is used. In centers where pancreatectomy is commonplace, central pancreatectomy may be considered for lesions in the body of the pancreas. Total pancreatectomy is reserved for fit patients with diffuse IPMN; however, this procedure should be reserved for highly selected patients, in whom surveillance of the affected remnant duct would not be feasible.

The goal of resection of IPMN is to achieve a complete resection. One of the controversies that exist is the extent of pancreatic resection (Lai & Lau, 2005). IPMN is considered a diffuse process; therefore some concern has been raised that removal of only part of the pancreas would be inadequate. The clinical significance of a glandular recurrence in a patient with invasive IPMN is small because invasive IPMN is a disease characterized more by distant recurrence, similar to that of ductal adenocarcinoma. However, patients who undergo resection of noninvasive IPMN are at risk for recurrence in the remnant pancreas. In a recent report from MSKCC, White and colleagues (2007) reviewed 78 patients who had a resection for noninvasive IPMN; at a median follow-up of 40 months, a recurrence rate in the remnant pancreas of 8% was reported. Only 2% of patients (1 in 50) with a negative margin had recurrence, but 17% of those (4 of 23) with a margin positive for IPMN had recurrence ($P = .02$). Because 92% of this cohort of patients did not have a recurrence, it would seem that the risk associated with total pancreatectomy outweighs the risk for recurrence. However, routine surveillance of these patients with cross-sectional imaging is recommended. In this study, recurrences occurred at a median of 22 months (range, 8 to 62 months) from the time of initial resection and were noninvasive. Completion pancreatectomy is indicated for treatment of any detected recurrence.

One of the challenges of managing patients with IPMN is that many patients are young and are seen with small cysts in the head of the pancreas. Our institution and others have demonstrated the exceedingly rare incidence of invasive malignancy in cysts smaller than 3 cm (Allen et al, 2006; Lee et al, 2008; Sahani et al, 2006). We have not seen invasive IPMN less than 3 cm in the setting of isolated branch duct disease without concerning radiographic features. Because of the low risk of invasive cancer in small mucinous cysts, our current approach to these lesions is selective. Resection is indicated for patients with symptoms, which are infrequently present in patients with cystic neoplasms. A second indication for resection is for cysts with concerning features, such as a solid component or increasing size (Fig. 57.6; Allen et al, 2006). If the decision is made for nonoperative management, our current surveillance protocol includes high-quality cross-sectional imaging with multidetector CT scan or magnetic resonance imaging (MRI) every 6 months for 2 years (Landa et al, 2009). After 2 years of demonstrable stability, patients can graduate to annual imaging. Indications for resection in patients undergoing surveillance include significant tumor growth or development of other features concerning for malignancy.

Solid Pseudopapillary Tumor and Other Cystic Pancreatic Neoplasms

Solid pseudopapillary tumors (SPTs) are also known as *Frantz tumors* or *Hamoudi tumors* after the pathologists who first described this unique entity (Frantz, 1959; Hamoudi et al, 1970). SPTs are rare tumors that account for up to 2.5% of resected pancreatic neoplasms. They predominate in young women and are often discovered when patients have symptoms. In a review of SPTs, Papavramidis and Papavramidis (2005) described the clinicopathologic factors of 718 patients collected from the English literature. The female/male ratio was 9.8:1,

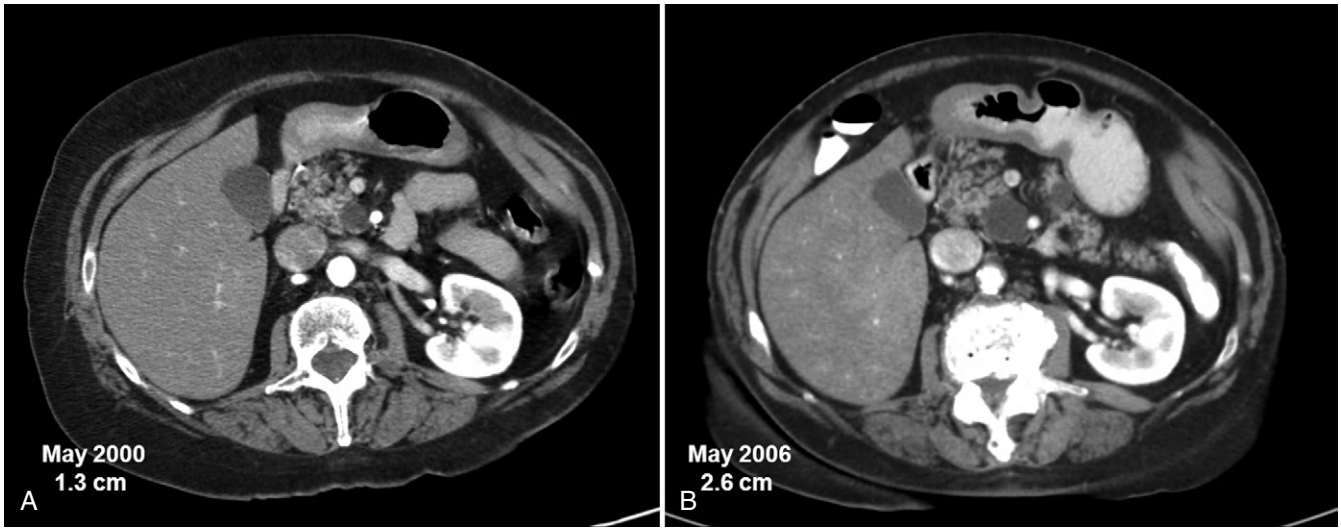


FIGURE 57.6. A, Intraductal papillary mucinous neoplasm (IPMN) in the head and uncinate process of the pancreas in a 68-year-old woman. Because the lesion was small without associated concerning features, the patient was initially only monitored. **B,** Over time, the lesion increased in size, and the patient underwent pancreatoduodenectomy. Final pathology revealed a main duct IPMN with moderate dysplasia.

and the mean age was 22 years. Only 15% of the patients in the review were asymptomatic at presentation; 47% had pain, and 35% had a mass. Tumors were often large, and 34% were greater than 10 cm in diameter. The most common location for SPT was the tail (36%) and head (34%) of the pancreas, and metastases were present in approximately 20% of patients.

Cross-sectional imaging characteristically reveals encapsulated lesions with irregular areas of hypodensity secondary to necrosis or hemorrhage (Fig. 57.7). The wall often reveals calcifications. Because of the cystic degeneration exhibited by these lesions, they are often difficult to differentiate from pseudocysts or other pancreatic cystic neoplasms. What differentiates these lesions from other cystic tumors is a combination of solid and cystic components with gradual degenerative changes resulting in pseudopapillae formation (Tang et al, 2005). SPTs are distinct from the normal pancreatic parenchyma, and like other cystic neoplasms, they rarely cause ductal dilation because of the lack of invasion.

Grossly, tumors appear tan or yellow and are well circumscribed and smooth on palpation. When opened, the tumors show irregular cystic cavities with some areas of necrosis or hemorrhage (Fig. 57.8). Most SPT can be diagnosed with routine histologic evaluation by the presence of polygonal epithelial cells arranged in a discohesive pattern; the boundaries resemble a mass effect as opposed to being invasive. Immunohistochemical staining for vimentin, keratin, neuron-specific enolase, CD10, and progesterone is common (Martin et al, 2002). These lesions rarely express chromogranin or estrogen. In contrast to ductal adenocarcinoma, abnormal β-catenin expression has been shown to be present in SPTs, but *KRAS*, *TP53*, and *SMAD4* appear to be unaltered (Abraham et al, 2002). Aggressive phenotypes of SPT have been demonstrated and histologically exhibit a high mitotic rate, nuclear atypia, spindling of tumor cells, and anaplastic giant tumor cells consistent with sarcomatoid carcinoma (Tang et al, 2005).

Clinically, SPTs are indolent and are typically cured with complete surgical extirpation. Many series have demonstrated long-term survival after resection (Lam et al, 1999; Martin et al, 2002; Reddy et al, 2009). Significant vascular invasion is the most common reason for the inability to resect these lesions, and metastatic disease has been noted to be present in up to 15% of patients. Criteria for defining SPTs as "malignant" may be locally advanced disease with vascular invasion precluding resection or lymph node or hepatic metastasis. Long-term survival is often possible despite the presence of malignant factors, such as metastatic disease, and should not preclude resection in selected cases (Lam et al, 1999; Martin et al, 2002; Reddy et al, 2009).

Indeterminate Cystic Neoplasm

The spectrum of cystic lesions discussed above represents many of the incidental lesions seen on cross-sectional imaging. However, a significant number of patients present with lesions that lack diagnostic certainty. Because of the inability to determine the exact histologic diagnosis without pancreatectomy, and because of the risk for malignancy of some cyst subtypes, some authors advocate a routine resection of pancreatic cysts (Horvath & Chabot, 1999; Ooi et al, 1998; Siech et al, 1998; Spinelli et al, 2004). Advocates of this approach argue that the clinical distinction between benign and malignant lesions is unreliable, and that there is a risk for the development of cancer; therefore all medically fit patients should undergo pancreatic resection. Despite the fact that this approach allows definitive treatment of all malignant lesions, it exposes patients with benign lesions to the risk associated with pancreatectomy without known benefit.

A selective approach to resection of pancreatic cystic neoplasms has been advocated by several reports, including those from our institution (Allen et al, 2003, 2006; Fernandez-del Castillo et al, 2003). Advocates of this approach argue that with improved knowledge of specific histologic subtypes and with the advances in diagnostics, a group of patients can be identified who are at very low risk (<1%) of harboring malignancy. Most authors who have reported their experience with this approach have recommended radiologic surveillance over resection for small, incidentally discovered cysts that lack a solid component or that have other concerning features of malignancy. Although this approach avoids the risks associated with pancreatectomy in patients with benign lesions, it does not

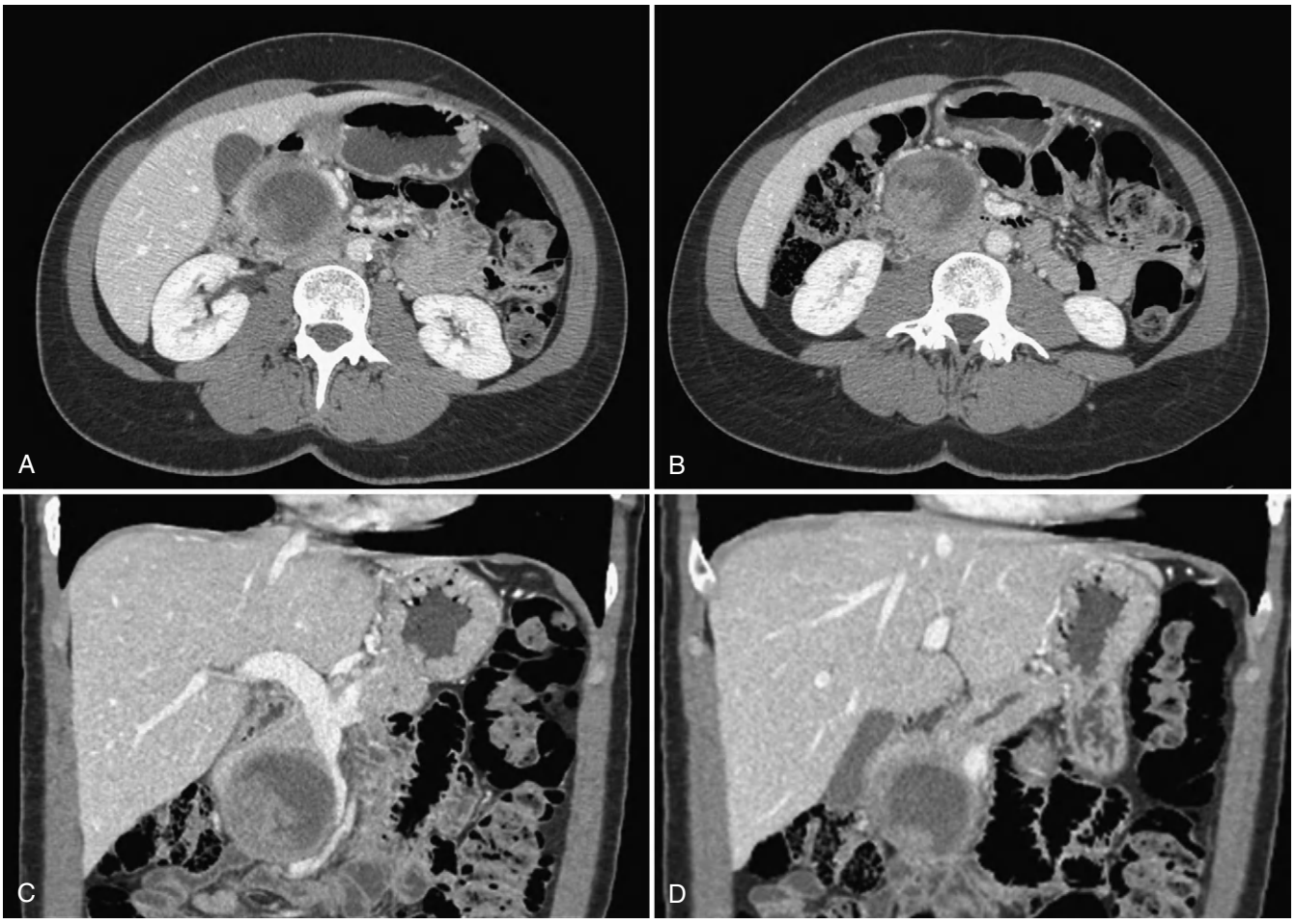


FIGURE 57.7. Imaging characteristics of solid pseudopapillary tumor (SPT) in the pancreas of a 35-year-old woman. A large lesion in the head of the pancreas was causing chronic abdominal pain; note the thickened wall and area of hemorrhage classic for SPT (**A** to **D**). This patient underwent endoscopic ultrasound to confirm SPT prior to pancreatoduodenectomy.

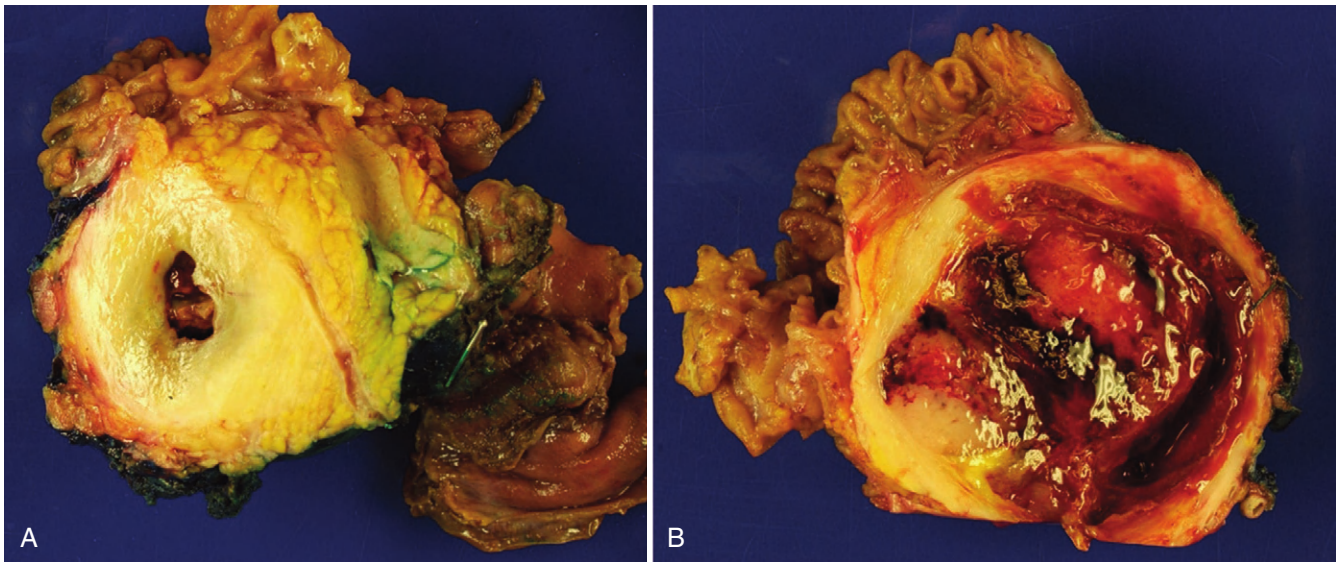


FIGURE 57.8. Gross appearance of solid pseudopapillary tumor (resected specimen from patient in Fig. 57.7).

guarantee that a cancer is being mistakenly observed. Operative morbidity following pancreatectomy is consistently as high as 45%, and mortality rates range from 2% to 10% (Büchler et al, 2000; Mezhir et al, 2009; Muscari et al, 2006; Winter et al, 2006). Published data suggest that with current imaging and endoscopic techniques, a group of patients with pancreatic cysts can be identified with a malignancy rate of less than 3% (Allen et al, 2006). It is in this select group of patients that the risk of death from pancreatectomy approaches or exceeds the risk of the lesion harboring a malignancy.

Despite the well-characterized lesions described above, many patients are seen with a cystic neoplasm that does not fit a specific diagnosis. In these patients, a nonoperative histologic diagnosis may not be made; therefore treatment recommendations for these patients are primarily based on imaging findings. The majority of patients who fit into this category have small, asymptomatic lesions, and their management is controversial. Our approach to such patients has been published in recent reports (Allen et al, 2003, 2006). Allen and colleagues (2006) reviewed 539 patients, the majority of which (369 [68%]) were followed up without operative intervention. Compared with patients treated with resection, observed patients were more likely to have small (median diameter, 2.4 cm) asymptomatic cysts without a solid component. At a median follow-up of 24 months, the average change in diameter of the observed lesions was 0.2 cm. Changes leading to resection developed in 29 patients (8% of 369 initially observed), and no patients with malignant mucinous tumors were reported in this group. Eight patients (2%) who did not undergo immediate resection developed malignancy, which is lower than the mortality rate associated with pancreatic resection, even in high-volume centers. Of note, in five of the eight patients who developed malignancy in the observed group, the cysts appeared to have represented retention cysts that developed adjacent to a radiographically undetectable malignancy. The decision-tree analysis illustrating the approach used is shown in Fig. 57.9.

As a result of our findings from this retrospective review, our current approach to patients with incidental cysts less than 2.5 cm in diameter is to initially obtain high-quality cross-sectional imaging with triphasic multidetector CT with 2-mm cuts through the pancreas or an MRCP. The imaging is reviewed at a multidisciplinary hepatopancreatobiliary conference by surgeons, gastroenterologists, and radiologists with expertise in pancreatic diseases. A detailed analysis of the cyst characteristics and the adjacent parenchyma is undertaken. Any findings concerning for malignancy—such as a solid component, mural nodules, or any pancreatic parenchymal abnormality—should result in EUS for further diagnosis or resection.

The importance of evaluating the adjacent pancreatic parenchyma cannot be overstated in that a number of patients in our series who developed adenocarcinoma in the observed group had small retention cysts adjacent to invasive cancer. Incidentally discovered cystic neoplasms smaller than 3 cm without solid component of main duct dilation are typically followed radiographically every 6 months for 2 years and then annually thereafter.

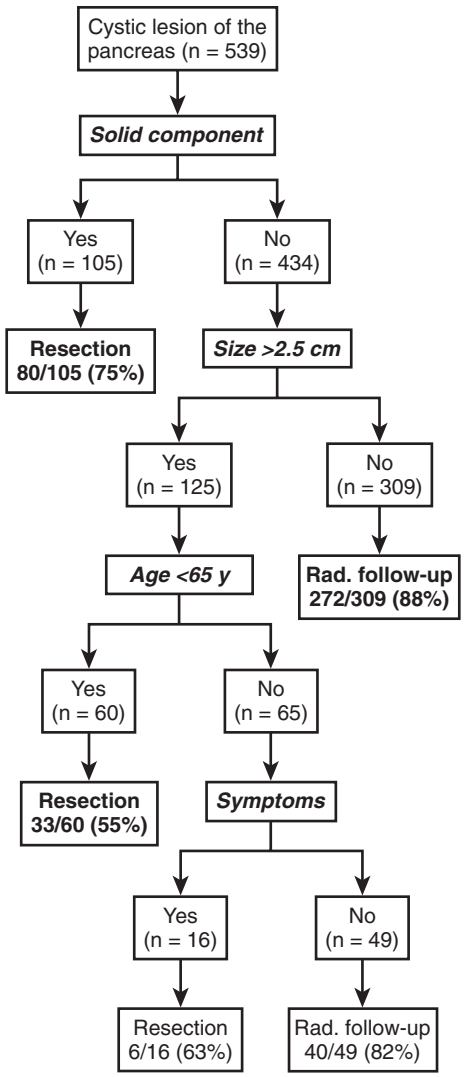


FIGURE 57.9. Selective management of cystic neoplasms of the pancreas. Rad., radiologic. *(From Allen PJ, Brennan, MF, 2007: The management of cystic lesions of the pancreas. Adv Surg 41:211-228.)*

CONCLUSIONS

The diagnosis of cystic lesions of the pancreas is increasing, and the most common lesions are SCAs, MCNs, and IPMNs. SCAs should be considered benign, and in the asymptomatic patient, they can be followed radiographically. Most patients with mucinous lesions should undergo resection, especially in the setting of concerning features such as size greater than 3 cm, solid component, and ductal dilation. The initial evaluation of a small, benign-appearing cyst should include one early interval image to ensure no occult malignancy is present that has resulted in a retention cyst.

As more clinicians are adopting a selective approach, improvements have been made in the ability to determine histopathologic subtypes without resection. High-quality cross-sectional imaging and EUS with cyst fluid analysis can help subtype many pancreatic cystic neoplasms. Advancements are also being made in the development of biomarkers from cyst fluid. Continued improvements in all of these modalities should lead to better identification of mucinous subtypes, obviating the need for resection.

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CHAPTER 58A

Epidemiology of pancreatic cancer

Theresa P. Yeo and Charles J. Yeo

OVERVIEW

Pancreatic ductal adenocarcinoma (PDA) accounts for 6% of all cancers in the United States. It is the fourth leading cause of cancer death in men, after lung, prostate, and colorectal cancer, and the fifth leading cause of cancer death in women, following lung, breast, colorectal, and ovarian cancer (Jemal et al, 2009). More than 42,000 incident cases of pancreas cancer are predicted annually, with about 35,240 deaths. Although mortality rates from pancreas cancer have improved slightly in the last decade, the diagnosis of PDA still confers an unfavorable prognosis.

Traditionally, PDA has been considered a predominantly male cancer; however, in 2009 the number of incident cases in women (21,420) exceeded the number of new cases in men (21,050) (Jemal et al, 2009). This suggests that the health consequences of increased smoking behavior by women over the last 3 decades are now becoming apparent. Pancreas cancer deaths remain higher in men (18,030) than in women (17,210), perhaps because of the presence of increased comorbidities or delayed diagnosis in men or greater genetic susceptibility to cancer, which limits treatment responsiveness in men (Jemal et al, 2009).

In the United States, the peak incidence of pancreas cancer occurs in the seventh and eighth decades of life (Horner et al, 2009). The U.S. population risk for pancreas cancer is 13.1 per 100,000 for men and 10.4 per 100,000 for women. The main risk for PDA occurs with advancing age. Between 2002 and 2006, the median age at diagnosis for cancer of the pancreas was 72 years, and the median age at death was 73 years according to Surveillance Epidemiology and End Results (SEER) data (Horner et al, 2009; SEER, 2010). Fifty-six percent of new PDA cases occur between the ages 65 and 84 years. The incidence of PDA remains highest for black Americans, with rates of 15.4 per 100,000 in men and 12.4 per 100,000 in women. The lowest risk of PDA is among Asian/Pacific Islander men and women (8.1 and 7.0 per 100,000, respectively). PDA is also a common second malignancy in both men and women who have had a prior smoking-related malignancy, such as lung or head and neck cancers (Neugut et al, 1995). The annual incidence rate worldwide for all histologic types of pancreas cancer is approximately 9 new cases per 100,000 persons (0.009), ranking it eleventh among all cancers.

In 2000, 217,000 new cases of pancreas cancer were reported globally, with 213,000 resultant deaths (Hariharan et al, 2008). The highest incidence of PDA in the world has been reported among Maoris in New Zealand, native Hawaiians, and black American populations; India and Nigeria have the lowest reported incidence (Boyle et al, 1989; Mack et al, 1985). In Europe during the same period, there were 60,139 incident cases with 64,801 deaths (Parkin et al, 2001). In Japan, PDA is the fifth leading cause of cancer death. Between 1950 and 1995, the worldwide incidence rates of PDA increased ninefold in men (1.4 to 12.5 per 100,000) and women (0.8 to 6.8 per 100,000), but rates have leveled off since 1985 (Lin et al, 1998). China reported 1619 deaths from pancreas cancer between 1991 and 2000, with rates higher in men and in urban areas compared with rural communities (Wang et al, 2003). No cases of PDA are reported in many African nations, reflecting the absence of an organized cancer registry system and an increased focus on more predominant causes of death in these nations. Incidence rates vary between 6 and 12 per 100,000 for the five Scandinavian countries, with Iceland having the lowest rates (Engholm et al, 2009).

RACE AND ETHNICITY

African Americans

Combining all types of cancer, African Americans have the highest death rate (Ward et al, 2004) at 1.4 times higher than that of white males and 1.2 times higher than that of white females. In a 2004 study, Chang and colleagues (2004) used the California Cancer Registry of the Cancer Surveillance Section of the California Department of Health Services to determine the incidence of PDA between 1988 and 1998. African Americans had a higher age-adjusted incidence rate (8.8 per 100,000) for PDA when compared with all other races and ethnicities

combined. African Americans were more likely to be seen with advanced disease and were least likely to receive surgical treatment, regardless of stage of disease (82.9% had no surgery compared with 77% of Asians, 67.8% of Hispanics, and 62.5% of non-Hispanic whites). Interestingly, serum cotinine levels, the primary metabolite of nicotine, are consistently higher in African Americans than in whites and Mexican Americans, even after adjustment for the number of cigarettes smoked per day, the number of smokers in the home, the number of hours of environmental tobacco smoke (ETS) exposure at work, the number of rooms in the home, and the region of the country where the subject lived (Caraballo et al, 1998). This suggests that genetic differences in cigarette product metabolism may influence rates of PDA.

Asians

Asian patients with PDA tend to have less aggressive tumors than do non-Asians (either black or white patients) and higher survival rates when assessed on a stage-adjusted basis (Clegg et al, 2008). To determine whether Asians develop a histologically different type of PDA than Western populations, Longnecker and colleagues (2000) conducted a population-based study using three SEER geographic areas: Hawaii, San Francisco, and Seattle. They compared PDA cases in Japanese, Chinese, Filipino, Hawaiian, black, and white patients. The study revealed that Japanese patients had the highest fraction of localized tumors with the lowest grade, and that Chinese, Filipino, and Japanese women had longer survival times than did whites, although survival time was significantly different for Japanese women only. Race-related genetic and environmental exposure factors may be involved in these survival discrepancies.

Ashkenazi Jews

Pancreatic cancer occurs in excess in Jews, particularly Jews of Ashkenazi heritage (Lynch et al, 1996). The age-standardized rates for PDA in Jews in Israel significantly exceed the rates for Israeli non-Jews (7.2 per 100,000 for all Jewish men and 5.7 per 100,000 for Jewish women vs. 4.0 per 100,000 for non-Jewish men and 2.9 per 100,000 for non-Jewish women). Approximately 5% to 10% of this discrepancy is attributed to the *BRCA2* mutation, which is associated with breast, gastric, ovarian, and bile duct cancers.

RISK FACTORS FOR PANCREATIC DUCTAL ADENOCARCINOMA

Our understanding of the risk factors for PDA continues to evolve. PDA is characterized by multiple germline and somatic genetic mutations (Hruban et al, 1998). This topic is covered extensively in Chapter 8A. It is estimated that less than 3% of pancreatic cancers are truly hereditary and due to inherited germline mutations and their respective syndromes (Wang et al, 2009). Other reported risk factors for PDA include cigarette, cigar, and pipe smoking; ETS exposure, also known as *second-hand smoke* or *passive smoke exposure*; exposure to occupational and environmental carcinogens; African American race; Ashkenazi Jewish heritage; high-fat, high-cholesterol diet; obesity; alcohol abuse; chronic pancreatitis; and long-standing diabetes (Table 58A.1; Gold et al, 1998; Everhardt et al, 1995; Silverman et al, 1994; Wynder, 1975).

Table 58A.1

Risk Factors Associated with Cancer of the Pancreas: Summary of Previous Reports

Lifestyle and Environmental Factors

Cigarette smoking (dose-response relationship)
Environmental tobacco smoke exposure, particularly early in life
Alcohol
Residential radon

Race/Ethnic Factors

African-American men and women
Native female Hawaiians
Ashkenazi Jews

Inherited Predisposition

Hereditary pancreatitis
Hereditary nonpolyposis colorectal cancer
Hereditary breast and ovarian cancer
Familial atypical multiple mole melanoma syndrome
Peutz-Jeghers syndrome
Ataxia-telangiectasia
Fanconi anemia
Cystic fibrosis

Medical Conditions

Cirrhosis
Diabetes mellitus
Chronic pancreatitis

Dietary Factors

High fat/cholesterol
Overweight and obesity
Nitrosamines in food

Occupational Exposure to Carcinogens

Asbestos, 2-naphthylamine, benzidine, gasoline products, PAHs, dry cleaning agents, DDT, radon

Selected High-Risk Occupations

Dry cleaning or chemical plant work, sawmill work, electrical equipment manufacturing work, mining and metal working occupations

Height

RR = 1.81 (CI, 1.31 to 2.52) when comparing tallest and shortest height categories for men and women

Previous Surgery

Cholecystectomy

Not all listed factors have been definitively proven to cause pancreatic cancer.
PAHs, polyaromatic hydrocarbons; CI, confidence interval; DDT, dichlorodiphenyltrichloroethane; PDABs, p-dimethylaminobenzaldehydes; RR, relative risk

Data from Ahlgren, 1996; Efthimiou et al, 2001; Ekbom et al, 1994; Garabrant et al, 1993; Gold et al, 1998; Hruban et al, 1998; Kogevinas et al, 2000; Lowenfels et al, 1997; Lynch et al, 1996; Michaud et al, 2001; Silverman et al, 1998; and Yeo et al, 2009.

Familial Pancreatic Cancer

Family history of pancreatic cancer is a strong risk factor in 5% to 10% of cases (Lowenfels et al, 2005). When a history of PDA exists in a close relative, a number of responsible genes have been identified (Wang et al, 2009). In the National Familial Pancreas Tumor Registry (NFPTR) at Johns Hopkins, prospective studies of family members of pancreas cancer kindreds found a twofold increased risk of pancreas cancer in the first-degree relatives of persons with sporadic pancreas cancer and a ninefold increased risk in first-degree relatives of those with familial pancreatic cancer (Klein et al, 2004; Wang et al, 2009). Germline mutations of *BRCA2* are found in 6% to 19% of familial pancreatic cancer patients (Murphy et al, 2002). When a more stringent definition of familial pancreas cancer is used, a 57-fold increased risk of PDA was reported in kindreds with three or more family members affected with PDA (Tersmette et al, 2001). This corresponds to an incidence rate of 301 cases per 100,000 per year compared with the SEER age-adjusted rate for the entire U.S. population of 8.8 cases per 100,000 per year. A recent report identified a germline truncating mutation of the *PALB2* gene in 3% of familial pancreas cancer patients (Jones et al, 2009; Blackford et al, 2009). Despite these many advances in the understanding of the mutations involved in the pathogenesis of PDA, no single "pancreas cancer gene" has been identified.

Table 58A.2

High-Risk Genetic Disorders Associated with Familial Pancreatic Cancer

Genetic Syndrome	Gene/Chromosomal Mutation Region	Estimated Increased Risk of PDA
Hereditary pancreatitis	*PRSS1* (7q35)	50 to 80 times
Hereditary nonpolyposis colorectal cancer (Lynch II variant)	*hMSH2, hMSH1, hPMS2, hMSH3, hPMS1, hMSH6/GTBP*	Undefined
Hereditary breast and ovarian cancer	*BRCA2* (13q12-q13)	3.5 to 10 times
FAMMM syndrome	*p16* (9p21)	20 to 34 times
Peutz-Jeghers syndrome	*STK11/LKB1* (19p13)	75 to 132 times
Ataxia-telangiectasia	*ATM* (11q22-23)	Rare

FAMMM, Familial atypical multiple mole melanoma; PDA, pancreatic ductal carcinoma

Six Genetic Syndromes Associated with Pancreatic Ductal Adenocarcinoma

Six genetic familial syndromes and their respective predisposing genes have been identified and linked to the development of PDA; these are described briefly below (see also Table 58A.2). Although individuals with these syndromes have an increased risk of developing PDA, collectively these syndromes account for less than 5% of the familial aggregation of PDA. The mean age of onset of familial PDA is similar to that of nonfamilial cases: 65.8 years versus 65.2 years (Hruban et al, 1998). Familial cases have also been noted to have a somewhat increased incidence of secondary primary cancers (23.8%) when compared with their nonfamilial counterparts (18.9%).

Hereditary Pancreatitis

Children and adolescents with hereditary pancreatitis (HP) may develop severe pancreatitis at a young age, often in childhood or adolescence, with a resultant 50-fold to 80-fold increased risk of PDA developing over their lifetime. HP results from germline or new somatic mutations in the *PRSS1* cationic trypsinogen gene (Lowenfels et al, 1997). Approximately 40% of those with HP will develop PDA when the additional risk factor of cigarette smoking is added. The risk of cancer seems to be limited to pancreatic cancers and not tumors in other organs.

Hereditary Nonpolyposis Colorectal Cancer

Hereditary nonpolyposis colorectal cancer (HNPCC) is an autosomal dominant inherited disease that predisposes affected persons to colorectal cancer and PDA (Hruban et al, 2002). It is usually caused by germline mutations in a number of DNA mismatch repair genes. Of the inherited syndromes associated with an increased risk of PDA, HNPCC is the least strongly linked to PDA.

Hereditary Breast and Ovarian Cancer

Patients with germline *BRCA2* mutations have up to a 10-fold increased risk (range, 3.5 to ×10) of PDA developing even in patients without a strong family history of breast cancer. Goggins and colleagues (1996) identified germline *BRCA2* mutations in 7% of sporadic (nonfamilial) PDA patients screened, none of whom had a family history of breast cancer or PDA.

Familial Atypical Multiple Mole and Melanoma Syndrome

Familial atypical multiple mole and melanoma (FAMMM) syndrome is rare condition associated with *p16* germline mutations, a tumor suppressor gene that may be mutated or may have its expression altered by posttranscriptional methylation. The syndrome predisposes affected individuals to melanomas, multiple nevi, atypical nevi, and PDA (Lynch et al, 1990). Those with FAMMM have a 20- to 34-fold increased risk of PDA over their lifetime.

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome is a rare autosomal dominant disease associated with alterations in the *STK11* gene, in which affected individuals develop hamartomatous polyps of the gastrointestinal tract and lip freckles referred to as *mucocutaneous melanocytic macules* (Hruban et al, 2002). Individuals with this syndrome have a roughly 100-fold increased risk of developing PDA (Giardiello et al, 2000), and they also appear to have a tendency to form intraductal papillary mucinous neoplasms (IPMNs).

Ataxia-Telangiectasia

Ataxia-telangiectasia is an autosomal recessive inherited disorder associated with *ATM* gene mutations, in which affected persons present with cerebellar ataxia, conjunctival telangiectasias, a hypofunctioning thymus gland, and oculomotor abnormalities. An association between ataxia-telangectasia and the subsequent development of PDA has been reported, but it is less well established than with the other five familial syndromes (Lynch et al, 1996).

Tobacco Exposure

Cigarette smoking is a contributing factor in approximately 20% to 25% of the cases of PDA and is the most consistently reported risk factor (Iodice et al, 2008; Jemal et al, 2009). Smoking has been associated with increased risk of PDA in at least 29 epidemiologic studies (Silverman et al, 1994), and smokers have a 70% increased risk of PDA compared with nonsmokers. Smoking habits in the 15 years preceding the diagnosis of PDA appear to be more relevant to increased risk, whereas former smokers who have quit for more than 13 years decrease their PDA risk to that of a lifetime nonsmoker (Howe et al, 1991).

Prospective and retrospective studies have found that the risk of PDA increases consistently with cigarette smoking but only inconsistently with cigar or pipe smoking (Wynder, 1975), suggesting perhaps that smoke must be deeply inhaled to exert its carcinogenic effects. A dose-response relationship between PDA and the number of cigarettes consumed has been documented in several investigations (Ahlgren, 1996; Howe et al, 1991). For current smokers who also have a family history of PDA, the relative risk of PDA has been reported to be as high as 8.23 (Schenk, 2001). Lowenfels and colleagues (1997) found that individuals with familial PDA tend to smoke more than those with sporadic PDA. These observations raise the possibility that smoking is interactive, perhaps multiplicatively, with genetic mutations known to be present in persons with familial PDA. Postmortem examinations of the pancreatic ducts of smokers have found widespread ductal hyperplasia, now called *pancreatic intraepithelial neoplasia* (PanIN), considered to be a premalignant lesion. Neugut and associates (1995)

found a relationship between cigarette smoking and the development of PDA as a second malignancy in patients with a smoking-related first malignancy, such as lung, head and neck, or bladder cancer. This relationship is likely due to overlapping smoking-related genetic mutations among these different malignancies.

The socioeconomic status (SES) gap among smokers is widening in the United States and globally. Decreases in smoking prevalence in the U.S. population as a whole have not been realized in those from a lower SES background (Gilman et al, 2003). In a 2003 study of 657 adults aged 30 to 39 years that used parental occupation, adult educational attainment, and household income as indicators of SES, those of a lower SES were more likely to start smoking and to become regular smokers and were less likely to quit smoking than their higher SES counterparts.

The carcinogenic components of cigarette smoke are usually cleared from the bloodstream and excreted into bile; they reach the pancreas from the bile duct through biliary-pancreatic reflux, or they may be carried into the pancreatic parenchyma directly by the bloodstream. Cigarette smoke contains more than 60 known carcinogens, including polycyclic aromatic hydrocarbons (PAHs), nitrosamines, benzo[a]pyrene, β-napthylamine, methylfluoranthenes, and arylamines (Hecht, 2003). These carcinogens may bind to DNA and form adducts, which increase the risk of somatic mutations and cancer if unrepaired. Nitrosamines are known to be organ specific, causing pancreatic carcinomas in hamsters that are histologically similar to the type found in humans (Wang et al, 2009). Little research has been conducted on the other carcinogens in cigarette smoke and their relationship to PDA. Another possible mechanism by which cigarette smoke leads to PDA is unrelated to the carcinogens in the smoke. Rather, higher cholesterol (lipid) levels are measured in smokers than in nonsmokers. The pathophysiologic mechanism of hypercholesterolemia may be partially due to nicotinic stimulation of circulating catecholamines, which increase serum cholesterol levels. Elevated lipid levels may be causative in the induction of PDA (Wang et al, 2009).

Mulder and colleagues (1999) developed multicountry computer-based models to estimate the impact of smoking cessation on the incidence of PDA in the European Union (EU). According to these models, the EU would reach a projected 600,000 new cases of PDA per year by 2020 if the present smoking levels were to continue. If all current smokers quit smoking, the predicted number of incident cases of PDA per year in the EU would be 175,000 by 2020. If 45% to 50% of smokers were able to successfully quit smoking, the reduction of new cases would still be a substantial 68,000 cases per year.

Environmental Tobacco Smoke

ETS is related to the development of PDA, with a possible dose-response relationship (Ahlgren, 1996; Villeneuve et al, 2004). A mildly elevated odds ratio (OR, 1.2.1; confidence interval [CI], 0.60 to 2.44) has been reported, suggesting a weak association between PDA and ETS exposure in nonsmokers who reported ETS exposure both as an adult and in childhood. The effect was more pronounced in smokers who reported ETS exposure. Recently published findings from a retrospective case-only analysis of familial and sporadic PDA indicate that nonsmokers with PDA who were exposed to ETS early in life (<21 years of age) were diagnosed with PDA at a significantly younger mean age (64.0 years) when compared with nonsmoker, non–ETS-exposed cases (66.5 years) (Yeo et al, 2009). Moreover, both cigarette smoking and ETS exposure in nonsmokers younger than 21 years is associated with a younger mean age of diagnosis in both familial, sporadic, and Ashkenazi Jewish cases of PDA.

High-Risk Occupations

The evidence linking occupational exposures to PDA is inconsistent, reflecting the difficulty of quantifying workplace exposure to carcinogens and of differentiating these exposures from other risk factors. A number of epidemiologic investigations have suggested excess risk of pancreatic cancer in certain occupations. Definitively establishing certain occupations as high risk for the development of PDA is difficult because of the problems with self-reported exposures, lack of objective quantitative monitoring data, personal comorbidities, and the presence of other confounding and modifying risk factors. The available studies are summarized in Table 58A.3.

Occupational Exposures

Studies examining occupational exposures that increase a worker's risk of developing PDA have been conducted both in the United States and in Europe, particularly in the Scandinavian countries. Occupational exposures linked to PDA are summarized in Table 58A.4. Overall the occupational etiologic fraction for PDA was estimated at 12% in a meta-analysis of 20 occupational studies conducted between 1969 and 1998 (Ojajarvi et al, 2000). A retrospective analysis of more than 22 occupational and environmental studies reported by people with PDA found that exposure to asbestos, pesticides and herbicides, residential radon, coal products, welding products, and radiation were the most commonly reported exposures (Yeo et al, 2009).

Calvert and colleagues (1989) conducted a review supported by the National Institute for Occupational Safety and Health (NIOSH) of five cohort studies reporting an association between the use of metalworking fluids (MWFs) used in industrial machining and grinding operations and the development of all types of cancer, including PDA (Acquavella et al, 1993; Hoppin et al, 2000; Porta et al, 1999; Rotimi et al, 1993; Tolbert et al, 1992). More than 1 million workers are exposed to MWFs according to NIOSH estimates (Calvert et al, 1989). Substantial evidence was found for an increased risk of cancer at several sites, including the pancreas, larynx, rectum, skin, scrotum, and bladder. MWFs contain a number of compounds suspected to be cancer initiators or promoters including long-chain aliphatics, polyaromatic hydrocarbons, nitrosamines, sulfur-containing compounds, formaldehyde-releasing biocides, and heavy metals (Tolbert et al, 1992).

Diabetes Mellitus

Two theories regarding the relationship between type 2 diabetes mellitus (DM) and PDA have been postulated; in one theory, DM is viewed as a predisposing risk factor for PDA; in the other theory, type 2 DM and its attendant altered glucose homeostasis are considered a consequence of PDA (Yalniz et al, 2005). The majority of PDA patients (80%) have either subclinical

Table 58A.3

Occupations Associated with Excess Risk of Pancreatic Cancer

Reference	Occupation	Risk Estimate	95% CI
Falk et al, 1994	Chemical processor	1.22 OR	NR
	Chemical fertilizer	1.20 OR	NR
Li et al, 1969	Chemist	10.2 MH	NR
Lin et al, 1981 Falk et al, 1990	Auto mechanic (gasoline exposure)	5.1 RR if >10 years exposure	NR
	Service station worker	1.6 SMR	NR
	Machine repairer	2.45 OR	NR
Lin & Kessler, 1981	Dry cleaner	2.1 RR	NR
Edling, 1985	Leather tanner	3.1 MH	(1.1-9.2)
Pickle et al, 1980	Oil refinery worker	2.11 OR	(0.86-5.20)
Rockette et al, 1983	Aluminum mill worker	125.2 SMR	NR
Norell et al, 1986	Floor polisher	1.3 SMR	NR
Falk et al, 1990	Electrical assembler/ installer/ repairer	2.20 OR	NR
Tolbert et al, 1992	Metalworker	2.0 SMR	(0.9-3.8)
Eisen, 1992	Manufacturing plant worker	3.0 SMR	(1.2-6.24)
Bardin et al, 1997	Assembly worker	3.0 SMR	(1.0-7.5)
Rotimi et al, 1993		3.0 SMR	(121-624)
Bu-Tian et al, 2001	Plant/system operator	6.1 OR	(1.1-33.9)
Bu-Tian et al, 2001	Pharmacist, dietician, therapist	7.1 OR	(1.8-27.5)

CI, confidence interval; NR, not reported; SMR, standardized mortality ratio; OR, odds ratio; MH, Mantel-Haenszel estimate; RR, relative risk

Table 58A.4

Occupational Exposures Linked to Pancreatic Cancer

Chemical	Exposure Route	PDA Risk Estimates
Methylene chloride (chlorinated hydrocarbons)	Spray paints	1.61 OR
	Paint strippers	1.40 OR
	Aerosol propellant	1.6 risk ratio
	Metal degreasing agent	
	Paint/paint thinners	
	Varnish	
	Solvents	
Pesticides/herbicides	Corn wet-milling	1.4 OR
DDT	Farming	4.8 RR
DDD	Flight attendants	4.3 RR
Ethylan		5.0 RR
Asbestos	Industrial	3.0 OR
Fertilizer	Farming	1.2 OR
Cotton dust	Farming	4.37 OR
Cement	Construction work (manufacturing of cement)	1.28 OR
Lead	Various	1.28 OR
Metalworking fluids	Machinist	2.0 OR

DDD, Dichlorodiphenyl-dichlorethane; OR, odds ratio; RR, relative risk

Data from references cited in Table 58A.3.

impaired glucose tolerance or type 2 DM. Many investigators regard DM as a clinical manifestation of PDA rather than a risk factor, a result of the alteration of islet cell function—specifically, the loss of β-cell mass from tumor growth—or a result of disruptions in acinar–islet cell interactions.

A meta-analysis of epidemiologic studies focused on DM and the risk of PDA found that the pooled relative risk (RR) of PDA in people diagnosed with DM 5 years or more prior to the PDA diagnosis was twice the risk (RR, 2.0; 95% CI, 1.3 to 2.2) of those without DM (Everhardt et al, 1995). In a population-based case-control study of 484 PDA cases and 2099 controls in three geographic areas of the United States, those diagnosed with DM at least 10 years prior to the development of PDA had a 50% increased risk of PDA compared with the control group (Silverman et al, 1998). Insulin treatment did not appear to alter the risk of development of PDA (OR, 1.6 with insulin and 1.5 without).

During an 18-year follow-up study of 88,802 women in the Nurses' Health Study (NHS), 180 incident cases of PDA were reported (Michaud et al, 2001). A positive association was observed between fructose intake and impaired glucose metabolism and increased PDA risk. The risk was most apparent in women with an elevated body mass index (BMI) above 30 kg/m^2 and low physical activity. A diet high in glycemic load (GL), the glucose response to each unit of carbohydrate-containing foods, may increase the risk of PDA in women with underlying insulin resistance as a result of obesity. Chronically elevated plasma glucose levels and increased PDA risk were also observed by Gapstur and colleagues (2000), further suggesting that impaired glucose tolerance, insulin resistance, and hyperinsulinemia may be involved in the etiology of PDA.

Chronic Pancreatitis

Chronic pancreatitis has been linked to the development of PDA. It is not clear whether chronic pancreatitis is a risk factor or if it represents an indolent presentation of PDA. The standardized incidence ratio of PDA in individuals with a diagnosis of chronic pancreatitis was 16.5 compared with the 1.76 expected number of cases (Lowenfels et al, 1993). Because PDA may mimic chronic pancreatitis, misdiagnosis is a possibility. A review of the records of patients with acute, chronic, or unspecified pancreatitis was conducted on all inpatient medical institutions in Sweden from 1965 to 1983. In 7956 patients with pancreatitis, 46 pancreas cancers were diagnosed compared with 21 expected cases—a standardized incidence ratio of 2.2 (CI, 1.6 to 2.9) (Ekbom et al, 1994). Although it seems reasonable to conclude that the cellular destruction and glandular dysfunction caused by pancreatitis may yield an environment favoring the initiation of tumor growth, it remains

problematic that some premalignant lesions may be initially incorrectly diagnosed as chronic pancreatitis.

Cholecystectomy

A history of cholelithiasis and/or cholecystectomy may precede the diagnosis of PDA, yet cholecystectomy per se is not believed to promote its development. Individuals who underwent cholecystectomy in the year preceding the diagnosis of PDA had an exceedingly high risk of developing PDA (OR, 57.9) in one investigation (Everhardt et al, 1995). This finding is most likely explained by the misdiagnosis of gallbladder disease, either cholelithiasis or cholecystitis, in the setting of cryptic PDA, often prompting gallbladder removal with an undetected tumor being left in place. However, when data subset analyses were performed in patients with a history of cholecystectomy 20 years or more prior to the diagnosis of PDA, a 70% excess risk of PDA was still evident.

Hormonal Factors

In recent years, a link between female reproductive factors and PDA has been hypothesized. A case-control study of 52 postmenopausal women with PDA and 233 matched controls was conducted as a component of the Canadian Enhanced Cancer Surveillance Project (Kreiger et al, 2001). A questionnaire focused on reproductive history, cigarette smoking, physical activity, diet, occupation, residential history, and sociodemographic information was mailed to eligible patients diagnosed with PDA. Multiparity, defined as three or more children, and use of oral contraceptives were associated with a decreased risk of PDA (OR, 0.22 and 0.36, respectively). Late age at birth of first child significantly increased the risk of PDA (OR, 4.05; CI, 1.50 to 10.92 for ages 25 to 29 years; for women 30 or older, OR, 3.78; CI, 1.02 to 14.06). No relationships were found between age of menarche or menopause and PDA. The inverse relationship between parity and PDA suggests that PDA may be partially an estrogen-dependent transformation, or that estrogen may act in an inhibitory manner upon pancreatic carcinogenesis.

Lifestyle Factors and Height

Michaud and associates (2001) reported on the relationship between BMI, height, physical activity, and smoking and the risk of PDA in two large, prospective cohort studies: the Health Professional Follow-up Study (HPFS) and the NHS. Activity levels and body weight were ascertained prospectively. A higher risk of PDA was found among obese men and women, as was a direct association between above-average height and risk of PDA. An additional 2.54 centimeters of height above average increased the risk of PDA by 6% in the HPFS and by 10% in the NHS. The association between height and cancer risk in general has been identified in other studies (Giovannucci et al, 1995; Smith et al, 1998). Height may serve as a proxy for calorie intake or exposure to growth factors, such as insulin or insulin-like growth factor-1, in childhood.

Furthermore, an inverse relationship between moderate physical activity and PDA was observed. Walking or hiking 1.5 hours or more per week in the overweight cohort was associated with a 50% reduction in PDA risk, but physical activity had no effect on PDA risk for participants who were not overweight. Likewise, BMI had no effect on risk if the participant was a moderate exerciser. However, individuals with a BMI of at least 30 kg/m^2 had an elevated risk of PDA (RR, 1.72; CI, 1.19 to 2.52) compared with those with a BMI of less than 23 kg/m^2. The authors speculated that the PDA risk associated with obesity might be linked to glucose intolerance, peripheral insulin resistance, and/or hyperinsulinism.

Diet

It is estimated that 30% to 50% of pancreatic cancers may be attributable to dietary factors. Both butter consumption and saturated fat intake were positively associated with PDA (hazard ratio [HR], 1.40; CI, 0.87 to 2.25; and HR, 1.60; CI, 0.96 to 2.64, respectively) in the Finnish Cancer Registry (Stolzenberg-Solomon et al, 2005). Fat entering the duodenum stimulates cholecystokinin secretion, and it is possible that chronic hypercholecystokininemia may be associated with an increased susceptibility of the pancreas to carcinogens. Other possible explanations include that the increased intake of saturated fat may lead to insulin resistance and the development of DM, or foods with a high soluble fat content may be contaminated with carcinogenic organochloride compounds from the environment.

Processed meats have been linked to the development of PDA. In a prospective study of more than 200,000 people, 482 individuals developed PDA during 7 years of follow-up (Nöthlings et al, 2007). Those who had consumed the greatest amount of processed meats had a 67% increased risk of PDA. Diets laden with pork and red meat intake were associated with a 50% increase in PDA risk, but poultry, fish, dairy product, and egg consumption conferred no additional risk. Heterocyclic amines and polycyclic aromatic hydrocarbons that form during high-temperature cooking are known to be carcinogenic and may be responsible for the increased risk of PDA observed with processed and barbecued meats. These compounds have also been linked to the development of other cancers.

Several recent investigations have focused on the relationship between *glycemic load* and *glycemic index*. Consumption of fruit juices and soda has been evaluated in six studies to date with conflicting results (Michaud et al, 2002; Mueller et al, 2010; Nöthlings et al, 2007; Silvera et al, 2005; Stolzenberg-Solomon et al, 2005). Two studies found no relationship between PDA and glycemic load, carbohydrate intake, or sugar, sucrose, or fructose intake (Johnson et al, 2005; Silvera et al, 2005). Three studies reported mixed findings (Michaud et al, 2002; Nöthlings et al, 2007; Stolzenberg-Solomon et al, 2005). In the Multiethnic Cohort Study, BMI modified the effect of high sucrose intake and the occurrence of PDA, with elevated BMI increasing the risk and normal BMI decreasing the risk (Nöthlings et al, 2007). A positive association with PDA was also observed with high fructose intake, but no association was observed with consumption of soft drinks (diet or regular).

Mueller and colleagues (2010) conducted a retrospective analysis of the Singapore Chinese Health Study regarding soft drink and fruit consumption and the risk of PDA. Among 63,257 participants, 142 incident PDA cases were identified. However, only 56.4% of the PDA cases were histologically confirmed, 5% were reported from death certificate data, and 38.8% were identified by signs and symptoms possibly related to PDA but not proven. The finding of an elevated HR for PDA

in those who drink two to three soft drinks per week is suspect in this setting and requires further evaluation.

Coffee and Alcohol Consumption

Cohort studies from the 1970s and 1980s indicating that heavy coffee and alcohol consumption led to an excess risk of PDA were often confounded by excessive smoking among the heavy coffee and alcohol drinkers (Michaud et al, 2001). Three subsequent investigations have attempted to clarify this issue while controlling for smoking (Ghadirian et al, 1991; Lagergren et al, 2002; Michaud et al, 2001). Ghadirian and colleagues (1991) conducted a case-control study of residents of greater Montreal, obtaining all information through questionnaires administered to either the patient or a proxy. The results indicated that those who consumed alcohol were, in general, at lower risk for PDA (OR, 0.65; CI, 0.30 to 1.44). This was true for beer, white wine, and hard liquor. The odds ratio for red wine drinkers was elevated at 1.57, but it did not achieve statistical significance. Likewise, coffee drinkers had a lower overall risk of developing PDA (OR, 0.55; CI, 0.19 to 1.62), regardless of whether they drank caffeinated or decaffeinated coffee. The increased risk when coffee was taken on an empty stomach or between breakfast and lunch (OR, 1.30 and 1.15, respectively) was not statistically significant.

Lagergren and colleagues (2002) hypothesized that because heavy alcohol intake often causes chronic pancreatitis, which may be a risk factor for PDA, the ideal group to examine would be those with a diagnosis of alcoholism, alcoholic chronic pancreatitis, and alcoholic liver cirrhosis. Using the Swedish National Board of Health and Welfare, data were collected on 178,688 patients over a 30-year period. A total of 305 incident cases of PDA were identified in the group, representing a 40% excess risk in observed compared with expected cases. Alcoholics with chronic pancreatitis or cirrhosis had a twofold increased risk of PDA. A major limitation of the study was the lack of information on smoking. The authors estimated that the observed excess risk of PDA in the alcoholic group "may be almost totally attributable to the confounding effect of smoking" (Lagergren et al, 2002).

Michaud and colleagues (2001) examined data on coffee and alcohol consumption and other dietary factors obtained at baseline in two large, national cohort studies. The HPFS, initiated in 1986, includes 51,529 men aged 40 to 75 years who responded to a mailed questionnaire; the NHS began in 1976 and includes 121,700 registered nurses. Follow-up information was gathered via a mailed questionnaire from both groups on age, marital status, weight, height, medical history, medication use, smoking status, physical activity, and intake of coffee and alcohol. The results regarding coffee and alcohol are compelling: during 1,907,222 person-years of follow-up, 288 incident cases of PDA were diagnosed. Data were analyzed separately for each of the cohorts and then pooled to compute overall RR estimates. The results revealed that neither coffee consumption nor alcohol consumption conferred an excess risk of PDA; a pooled RR of 0.62 was reported (95% CI, 0.27 to 1.43) for more than 3 cups of coffee per day versus no coffee, and a pooled RR of 1.00 (95% CI, 0.57 to 1.76) for more than 30 g alcohol per day versus no alcohol were found.

Most recently, Brand and colleagues examined data on 29,239 histologically confirmed cases of pancreas cancer from 350 U.S. hospitals between the years 1993 and 2003 by cigarette smoking and alcohol consumption self-reported history (Brand et al, 2009). Current smokers were diagnosed with PDA at significantly younger ages (6.3 to 8.6 years) than nonsmoking counterparts. Among nonsmokers, age at diagnosis of PDA progressed linearly according to the amount of alcohol consumed, from 6 years younger for minimal drinkers to 8.7 years younger for self-described heavy alcohol consumers.

References are available at expertconsult.com.

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CHAPTER 59

Pancreatic cancer: duodenal adenocarcinomas

Cristina R. Ferrone and Carlos Fernandez-Del Castillo

OVERVIEW

The first case of duodenal adenocarcinoma was described by Hamburger in 1746 (Hamburger, 1775). In the United States, approximately 5000 patients are diagnosed with small bowel cancer every year, and 1000 of them have duodenal adenocarcinoma (Howe et al, 1999). Duodenal adenocarcinomas are rare tumors that account for approximately 0.3% of all gastrointestinal (GI) malignancies (Spira et al, 1977). Despite the duodenum representing only about 10% of the length of the small bowel, duodenal adenocarcinomas comprise 25% to 45% of small bowel tumors (Alwmark et al, 1980; Sohn et al, 1998); up to half occur near the ampulla of Vater, which explains why some studies group them with other periampullary cancers (Joesting et al, 1981). The incidence of small bowel cancers is estimated to be 1.4 per 100,000, with duodenal adenocarcinoma in approximately 0.17 per 100,000 (DiSario et al, 1994). Other malignant tumors such as carcinoid, gastrointestinal (GI) stromal tumor, lymphoma, and sarcoma can also occur in the duodenum but are far less common there than in the rest of the small intestine.

PRESENTATION

Duodenal adenocarcinoma has a slight male predominance. The median age at presentation is in the sixth and seventh decades of life (DiSario et al, 1994; Rose et al, 1996). Approximately half of the patients with duodenal adenocarcinoma are initially seen with symptoms of abdominal pain or gastric outlet obstruction: nausea, vomiting, early satiety, and anorexia. Duodenal cancers often present as circumferential napkin-ring type lesions (Fig. 59.1). However, patients can also be seen with bleeding, melena, or jaundice. Bauer and colleagues (1994) noted a 21% incidence of a palpable mass on physical exam. A small proportion of patients are asymptomatic; the lesion is identified during the workup of an unrelated medical problem or as a result of screening for familiar adenomatous polyposis (FAP).

EVALUATION

The evaluation of any duodenal mass must assess for possible metastases and for resectability of the lesion (see Chapters 16 and 17). Depending on the patient's presenting symptoms, the initial study that identifies the lesion will vary (see Fig. 59.1). Radiologic findings highly suggestive of malignancy include central necrosis or an intraluminal exophytic mass or intramural mass with ulceration (Fig. 59.2). Patients will need either a computed tomography scan or magnetic resonance imaging to assess resectability and rule out metastatic disease. For the tumor to be considered potentially resectable, there should be no evidence of major vascular encasement, distant lymphadenopathy, or distant metastases (e.g., liver, peritoneum, lung). If patients undergo upper GI endoscopy, the lesion can be biopsied at that time. Additionally, if a segmental resection is being considered, an upper GI series is helpful, and the relationship of the tumor to the ampulla should be evaluated by endoscopy.

RISK FACTORS

The biology of duodenal adenocarcinoma is poorly understood. An adenoma-to-carcinoma sequence similar to that seen in colon cancer has been suggested. In various series of endoscopically resected adenomas, the incidence of malignancy varied from 10% to 42%, with villous adenomas being at higher risk for malignant transformation (Seifert et al, 1992; Witteman et al, 1993). Carcinoma in situ can be adequately treated with a local submucosal excision; however, it is generally impossible to know the maximal depth of invasion of the entire lesion before resection, and a more extensive procedure should be performed for any patient with invasive carcinoma (Bjork et al, 1990).

Patients with FAP are at significant risk for duodenal or ampullary adenomas, with an incidence as high as 88% (Church et al, 1992), and they have an increased relative risk of duodenal cancer of 330 compared with the general population (Offerhaus et al, 1992). Groves and colleagues (2002) prospectively followed 114 patients with FAP for 10 years, beginning at a median age of 42 years. Patients underwent upper endoscopy three times a year with a side-viewing duodenoscope. During this time three patients developed duodenal adenocarcinoma and three developed ampullary cancers. This occurred at a median of 6 years' follow-up and at a median age of 68 years. All patients were classified according to the Spigelman classification: 3 were stage 0, 15 were stage I, 44 were stage II, 41 were stage III, and 11 were stage IV. Stage progression was seen in 0, 3, 7, 5, and 4 patients, respectively. Of the patients who developed invasive carcinoma, 4 were classified as Spigelman IV, but 2 were classified as Spigelman II and III, underscoring the need for surveillance in this population. Soravia and colleagues (1997) prospectively screened 74 patients over 5 years, during which time 11 patients (15%) developed advanced polyposis, and one patient developed duodenal cancer. The patient with adenocarcinoma presented at age 66 years, and the median age for duodenal polyposis for the group was 69 years (range, 38 to 66 years). All the patients in the study who underwent local resection of duodenal polyps developed recurrent polyps at sites of previous local resection. Duodenal and ampullary carcinomas are the second most common cause of death after colon cancer

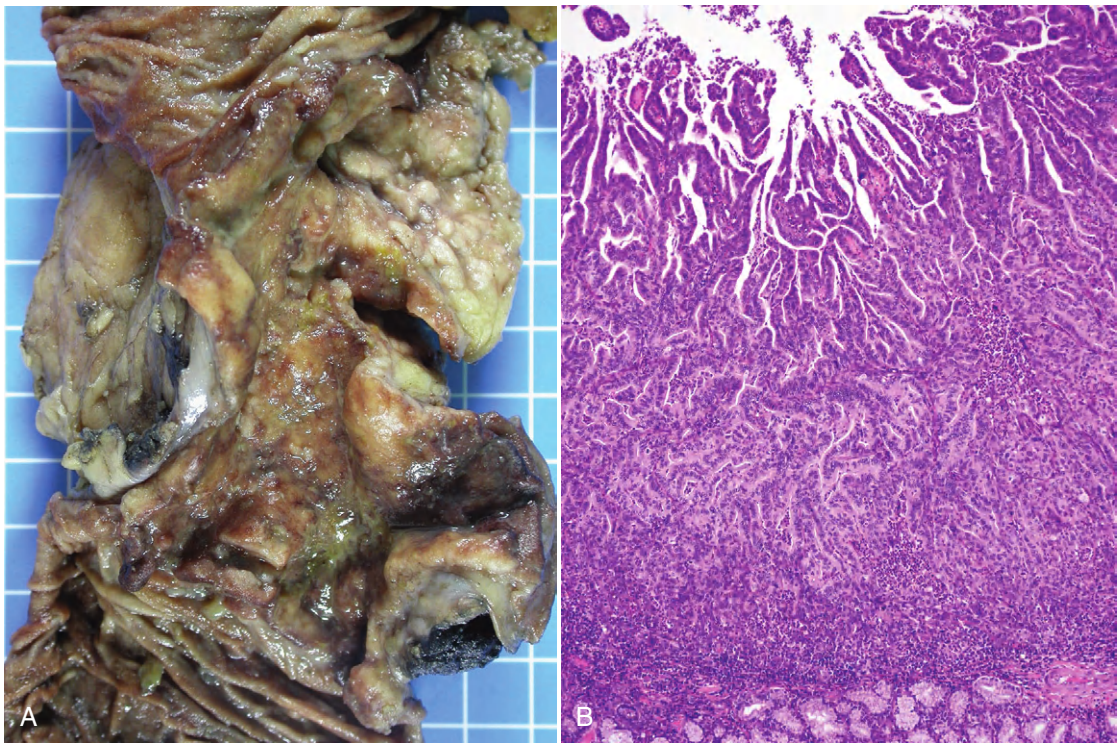


FIGURE 59.1. A, Macroscopic photograph of a resected duodenal adenocarcinoma. **B,** Microscopic image of duodenal adenocarcinoma.

in patients with FAP, underscoring the need for aggressive surveillance.

Gardner syndrome is another condition associated with a high risk for duodenal adenocarcinoma. Patients present with GI polyposis, osteomas, and soft tissue tumors. The risk of malignant degeneration in duodenal polyps is between 3% and 12%, requiring these patients to also undergo an aggressive surveillance program (Sinha & Williamson, 1988). Patients with Peutz-Jehgers syndrome are also at risk, but it is lower than that seen in patients with Gardner syndrome or FAP.

The pathogenesis of duodenal adenocarcinoma is poorly understood. It appears to have a biology similar to, yet distinct



FIGURE 59.2. A, Barium swallow demonstrating narrowing of the duodenum due to duodenal adenocarcinoma. **B,** Abdominal computed tomographic image demonstrating a duodenal mass in the second portion of the duodenum.

Table 59.1

Published Results of Patients with Resected Duodenal Adenocarcinoma

Reference	R0	Survival	Prognostic Factors	Nonprognostic Factors
Sohn et al, 1998	44/48	53% at 5 years	R1,segmental resection	Positive LNs, tumor size, adjuvant therapy
Bakaeen et al, 2000	60/101	54% at 5 years	Positive LN, AJCC stage, R1, weight loss	Segmental resection, location, size, adjuvant therapy
Ryder et al, 2000	27/31	43% at 5 years	Large tumor, transmural invasion, poor tumor grade	Segmental resection LN status, adjuvant therapy
Sarela et al, 2004	72/137	48% at 5 years	Positive LN, age	T stage
Struck et al, 2009	28/30	33% at 3 years	Positive LN, AJCC stage	Adjuvant therapy, segmental resection, T stage, surgical margins, number of LNs examined

LN, lymph node; AJCC, American Joint Commission on Cancer.

from, colon cancer and other pancreatohepatobiliary tumors. Oncogenes and tumor suppressor genes that appear to contribute to the malignant progression include *KRAS, TP53, ERBB2,* and *TGFBRII* (Achille et al, 1998; Younes et al, 1997; Zhu et al, 1996). In patients with FAP, the normal duodenal mucosa and duodenal polyps have a higher *COX-2* expression than patients with sporadic duodenal adenomas (Brosens et al, 2005). This increased expression may explain the poorer response to inhibitory COX-2 chemoprevention in these lesions.

THERAPY

Surgical

Surgical resection is the strongest predictor of long-term survival. Most series of resected duodenal carcinoma document a 5-year overall survival of more than 40%, which is twofold better than that of pancreatic ductal adenocarcinoma (Table 59.1).

The optimal extent of resection of duodenal cancers remains the subject of some debate and perhaps confusion. Superficial lesions may be amenable to endoscopic resection. In such cases, careful examination of the resected specimen is required to exclude the presence of invasive disease and the need for a more extensive operation. Transduodenal resections, even those that include the ampulla (i.e., ampullectomy), are inadequate in the face of invasive carcinoma. Such lesions generally require a pancreatoduodenectomy to achieve an R0 resection, particularly when in proximity to the ampulla. For patients in whom the entire duodenal mucosa is at risk, such as patients with FAP, a pancreatoduodenectomy should be performed.

Debate is active and ongoing as to the role of segmental resection of the duodenum in patients with duodenal adenocarcinoma not involving the ampulla. This consideration is typically germane only to lesions in the distal aspect of the duodenum. A number of clinical series from Massachusetts General Hospital (MGH), Memorial Sloan-Kettering Cancer Center, M.D. Anderson Cancer Center, and Duke University have shown no difference in survival between pancreaticoduodenectomy and a segmental resection (Cecchini et al, 2011; Rose et al, 1996). On the other hand, some series suggest that a more radical resection may improve overall survival (Alwmark et al, 1980; Dabaja et al, 2004). It is not unexpected that multiple small series of patients demonstrate no adverse effect of performing local en bloc resections for lesions in the third or fourth portions of the duodenum; because the lymphatic drainage to this area should be into the small bowel mesentery and not via the pancreatoduodenal lymphatic basins. Whether a pancreatoduodenectomy or a segmental resection is performed depends on the tumor's location with respect to the ampulla and the ability to achieve a complete resection, which ultimately is the most important prognostic factor.

Unlike many other GI tumors, metastatic disease to regional lymph nodes is not a consistent predictor of poor outcome. In the series by Joesting and colleagues (1981) and Ouriel and Adams (1984), lymph nodes did not predict an adverse outcome. More recent series from MGH and the Mayo Clinic, on the other hand, have identified that lymph node involvement was associated with an adverse outcome (Cecchini et al, 2011; Bakaeen et al, 2000). In both series, overall survival decreased from 65% to 25% in the MGH series and from 68% to 22% in the Mayo Clinic series when lymph nodes were involved. The MSKCC group evaluated lymph node status in the setting of the number of nodes evaluated. Similar to gastric cancer, resection and assessment of more than 15 lymph nodes assessed improved the disease staging and the prognostic value of finding no lymph node metastases (Sarela et al, 2004). The modern series from MGH was the first to identify perineural invasion as the most powerful independent predictor of survival (Cecchini et al, 2011). The 5-year overall survival was 56% versus 19% for patients with and without perineural invasion, respectively.

Neoadjuvant and Adjuvant Therapy

The role of neoadjuvant or adjuvant therapy for duodenal adenocarcinoma has not been studied in a Phase III prospective randomized trial. Duodenal cancers were treated in the cohort of periampullary tumors in a European Phase III adjuvant trial without any evidence of improved survival. However, a high rate of chemotherapy and radiation therapy noncompliance was reported, and the duodenal cancers were not analyzed separately; therefore the results must be interpreted with caution. The largest retrospective review from the National Cancer Database documented that only 15% of patients received adjuvant radiation therapy, and 21% received chemotherapy (Howe et al, 1999). The study from Johns Hopkins included 14 node-positive patients who underwent pancreatoduodenectomy and adjuvant chemoradiation therapy who had improved local control and median survival, but no difference was reported in 5-year overall survival (Swartz et al, 2007). Therefore no conclusive decisions can be made based on the current data in the literature regarding the role of adjuvant chemotherapy or radiation therapy.

Patterns of Recurrence

The patterns of recurrence have not been well defined in duodenal adenocarcinoma. Approximately 17% to 44% of patients will be seen with locoregional recurrences, mainly in the operative bed and retroperitoneal lymph nodes. In the MGH series, the first site of recurrence was distant in 21%, locoregional in 19%, and both in 5% at a median follow-up of 14.5 months. In the MDACC series, 17% of patients had locoregional recurrences and 33% had distant recurrences (Barnes et al, 1994). In the series from Duke, 44% of patients were seen with locoregional recurrences (Kelsey et al, 2007).

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CHAPTER 60

The pancreas as a site of metastatic cancer

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OVERVIEW

Resection has become an established part of the standard therapy for liver and lung metastases of several primary tumors (Fong et al, 1999; Quiros & Scott, 2008). Unlike liver and lung, the pancreas is an uncommon site of metastases. In autopsy series, 3% to 12% of patients with diffuse metastatic disease have pancreatic involvement (Showalter et al, 2008), and metastases account for only about 2% to 4% of malignant lesions in the pancreas (Showalter et al, 2008; Strobel et al, 2009). However, this number is increased up to 40% in patients with a pancreatic mass and a history of malignant disease (Roland & van Heerden, 1989; Z'Graggen et al, 1998).

Metastases to the pancreas may occur as isolated lesions or with additional extrapancreatic metastases that are technically resectable; isolated pancreatic metastases are very rare. Until recently the available data on resection for pancreatic metastases were based only on small series and multiple case reports. However, recent larger series and meta-analyses suggest that resection for pancreatic metastases is safe and associated with a favorable long-term outcome in appropriate patients (Reddy et al, 2008; Reddy & Wolfgang, 2009; Strobel et al, 2009; Tanis et al, 2009). This is best documented for metastastic renal cell carcinoma (RCC), the most frequent primary tumor of isolated pancreatic metastases (Sellner et al, 2006; Tanis et al, 2009). Based on these recent data, pancreatic resection can be recommended as part of an interdisciplinary treatment in metastatic disease to the pancreas.

This chapter summarizes the recent literature on surgery for pancreatic metastases and discusses the surgical approach, including diagnostic workup, patient selection, and technique of resection.

RESULTS OF SURGERY FOR PANCREATIC METASTASES

Because isolated pancreatic metastases and metastases with localized, treatable extrapancreatic disease are uncommon, the results of pancreatic resection for metastases are not as well documented as for the liver or lung (Fong et al, 1999; Internullo et al, 2008). Until recently, the available literature was based only on smaller series and multiple case reports, which inherently tend to be biased toward the report of favorable results. However, in recent years, resection for metastases to the pancreas has been used more frequently, resulting in several larger series and, most recently, meta-analyses. This change occurred for several reasons. In the last decades, morbidity and mortality rates of pancreatic surgery decreased considerably, and pancreatic surgery can now be considered a safe procedure when performed by experienced surgeons (see Chapter 62). With the development of more effective drugs and tailored chemotherapy, the prognosis of metastatic disease has largely improved for several tumor entities. Also, with standardized follow-up programs after resection for cancer and with broader use of cross-sectional imaging, pancreatic metastases are more frequently detected at a resectable stage. Finally, the decision for resection of a pancreatic metastasis is more frequently made in an interdisciplinary setting, such as by tumor boards, which are established in most centers.

Safety of Resection for Pancreatic Metastases

In a recent review of 19 series, a mortality rate of 1.2% and a morbidity rate of 38.3% were reported for resection of isolated pancreatic metastases (Reddy & Wolfgang, 2009). Resections for metastatic disease may be more difficult than resections for primary pancreatic tumors because of the necessity of extensive adhesiolysis after previous surgery in approximately 80% of patients and because of the necessity of multivisceral resections. Our series, which included 41% multivisceral resections, reported a mortality rate of 4.4% and a morbidity rate of 33% (Strobel et al, 2009). These findings are comparable to the data reported for primary pancreatic malignancies and show that resection for pancreatic metastases can be performed safely by specialized surgeons.

Oncologic Outcome of Resection for Pancreatic Metastases

The follow-up results of the largest studies of resection for pancreatic metastases are summarized in Table 60.1 and show a very favorable outcome. However, most series include several primary tumor entities, and conclusions about individual tumor types must be made with great caution. RCC is, by far, the most frequent primary tumor associated with resectable, isolated pancreatic metastases. The frequency of various primary tumors derived from surgical series is given in Table 60.2. The data for resection of RCC metastatic to the pancreas are summarized in Table 60.3; they show considerably longer survival rates compared with the mixed group of other histologies (see Table 60.1). Two systematic reviews of 236 and 311 published cases of surgery for RCC pancreatic metastases (Sellner et al, 2006; Tanis et al, 2009) report 5-year survival rates of about 75% after radical resection. However, because both reviews included case reports and smaller series, they may overestimate survival rates because of publication bias. However, RCC histology was also associated with improved outcome in several of the published series, including that of the authors (Eidt et al, 2007; Hiotis et al, 2002; Reddy et al, 2008; Strobel et al, 2009).

Table 60.1

Outcome in the Largest Series of Pancreatic Resection for Metastases (≥15)

Reference	No. Patients	Median Survival (mo)	5-Year Survival (%)
Strobel et al, 2009	44	Not reached	56.8
Reddy et al, 2008	49	35.8	36.2
Zerbi et al, 2008*	23	Not reached	88
Bahra et al, 2008	20	Not reached	63.8
Bassi et al, 2003*	17	Not reached	53
Hiotis et al, 2002	16	39.6	NR

Survival is calculated from time of resection of the metastasis.
*Exclusively RCC metastases.
NR, not reported.

Although 57% of cases in our series had extrapancreatic metastatic disease, the overall 5-year survival rate was 56.8%, and the 5-year survival rate was 67.3% after resection of RCC metastases. The 5-year survival rate after resection of isolated pancreatic metastases was as high as 75% (Strobel et al, 2009).

Efficacy of Resection for Pancreatic Metastases

Although comparison of the survival data after metastasectomy with the historic results of conservative treatment suggests a benefit of surgery, the efficacy of surgical resection and its superiority over conservative treatment alone cannot be formally proven because of the lack of controlled trials. However, for RCC, three studies observed longer survival in patients after resection compared with noncontrolled groups with irresectable disease (Sellner et al, 2006; Tanis et al, 2009; Zerbi et al, 2008). Furthermore, the survival data after pancreatic resection for RCC metastases compare very favorably to the survival reported for resection of RCC metastases in other organs (Kavolius et al, 1998). Another point supporting resection for pancreatic metastases is good local tumor control. In our series, local tumor control after 5 years was 87%, but disease-free survival was only 33% because of distant metastases (Strobel et al, 2009). This underlines the importance of interdisciplinary therapy with consideration of adjuvant treatment in these patients.

A major limitation of the literature concerning pancreatectomy for metastatic disease is the heterogeneity of patients, with most series including metastases from several different primary tumors. Except for RCC, the number of patients with other diagnoses is too small to draw reliable conclusions about the outcome and value of pancreatic resection for metastases. Thus, surgical decision making is generally based on the overall experience with resection for pancreatic metastases and on the reported outcome for each tumor type.

Table 60.2

Pathologic Diagnosis in Patients with Pancreatic Resections for Metastases

Primary Tumor Type	No. Patients	% of Total
Renal cell cancer	181	63.1
Colorectal cancer	22	7.7
Sarcoma	17	5.9
Melanoma	13	4.5
Gastric cancer	10	3.5
Lung cancer	9	3.1
Gallbladder cancer	8	2.9
Breast cancer	6	2.1
Ovarian cancer	5	1.7
Gastrointestinal stromal tumor	2	0.7
Esophageal cancer	2	0.7
Mesenteric fibromatosis	2	0.7
Schwannoma	2	0.7
Merkel cell carcinoma	1	0.3
Seminoma	1	0.3
Teratocarcinoma	1	0.3
Hemangiopericytoma	1	0.3
Urinary bladder cancer	1	0.3
Carcinoid	1	0.3
Nonpancreatic endocrine tumor	1	0.3
Hepatocellular carcinoma	1	0.3

Based on combined data from Reddy & Wolfgang, 2009, and Strobel et al, 2009.

Table 60.3

Outcome After Pancreatic Resection for Renal Cell Carcinoma Metastases

Reference	No. Patients	Median Survival	5-Year Survival (%)
Series with ≥10 Metastases			
Strobel et al, 2009	29	Not reached	67
Volk et al, 2009	14	75 months	NR
Reddy et al, 2008	21	58 months	45
Zerbi et al, 2008	23	Not reached	88
Bassi et al, 2003	17	Not reached	53
Law et al, 2003	14	Not reached	75
Hiotis et al, 2002	10	4.8 years	NR
Sohn et al, 2001	10	Not reached	75
Ghavamian et al, 2000	11	120 months	81
Reviews and Meta-Analyses Including Small Series and Case Reports			
Reddy & Wolfgang, 2009	112	105 months	66
Tanis et al, 2009	311	NR	72.6
Sweeney et al, 2009	135	70 months	65
Sellner et al, 2006	139	120 months	72

NR, not reported.

SURGICAL APPROACH IN PATIENTS WITH PANCREATIC METASTASES

Presentation of Patients with Pancreatic Metastases

Patients with pancreatic metastases can be divided into two groups: those with symptoms and those without. Patients in the first group experience typical symptoms caused by a pancreatic tumor, and the diagnostic workup reveals a pancreatic mass that

often has features atypical for primary pancreatic cancer (Palmowski et al, 2008). In the second group of patients, the lesion is found during standardized follow-up exams for the primary tumor or by imaging for other reasons. Within the past few decades, the distribution has shifted from symptomatic to asymptomatic patients, most likely as a result of standardized follow-up programs and broad use of cross-sectional imaging techniques. In studies that include patients from previous decades, 60% to 90% of patients were seen because of symptoms (Reddy et al, 2008; Sellner et al, 2006; Tanis et al, 2009); in the authors' recent series, only 18% of metastases were diagnosed because of symptoms, and 82% were detected during oncologic follow-up (Strobel et al, 2009). Patients with symptoms appear to have a worse prognosis, as has been shown for RCC metastases (Tanis et al, 2009). These findings suggest that symptoms eventually develop as local complications during progression of pancreatic metastases and present another point in favor of surgery for resectable metastatic disease.

Interestingly, pancreatic metastases frequently are identified long after resection of the primary tumor. This is best documented for RCC metastases, which are diagnosed at a median interval of 10 years after resection of the primary tumor (Sellner et al, 2006; Strobel et al, 2009). This long disease interval must be taken in account in the design of oncologic follow-up programs.

Diagnostic Workup for Suspected Pancreatic Metastases

Usually, a pancreatic mass is first detected by contrast-enhanced computed tomography or magnetic resonance imaging. Pancreatic metastases have features different from primary pancreatic malignancies (see Chapters 16 and 17). In contrast to pancreatic adenocarcinoma, most metastatic entities exhibit contrast enhancement, as shown in Figure 60.1 (Palmowski et al, 2008), particularly mestastatic RCC. Another feature of metastases is their multifocality within the pancreas: 40% in pathologic workup in our series. Perhaps because of the long interval between the primary tumor resection and the pancreatic metastases, these lesions are often misdiagnosed as primary pancreatic malignancy.

Clearly, if a pancreatic lesion is detected in a patient with a history of cancer, the serum tumor markers for the previous malignancy, if relevant, should be determined, and state-of-the-art restaging should be performed to rule out local recurrence and extrapancreatic systemic disease. The importance of a thorough workup is highlighted by the high frequency of additional, extrapancreatic lesions in patients with pancreatic metastases. If additional extrapancreatic disease is suspected, positron emission tomography is recommended to identify patients with diffuse spread who will not benefit from surgery. In contrast, preoperative tissue diagnostics are usually not needed, especially in patients with disease confined to the pancreas, because it does not alter the indication for operation, which would also be offered for a primary pancreatic malignancy without evidence of spread. Only in cases with extrapancreatic spread or features that would otherwise contraindicate resection should a tissue diagnosis be pursued because it may be helpful to rule out metastatic pancreatic cancer.

Patient Selection for Surgery

As discussed, solid data regarding the outcome of resection for pancreatic metastases are lacking for tumor types other than RCC. Decision making and selection of patients for surgery must therefore be considered on an individual basis and by using several clinical parameters, including type and history of malignant disease, pattern of metastatic spread, patient comorbidities, and operative risk. Ideally, the decision process should involve both medical oncologists and experienced pancreatic

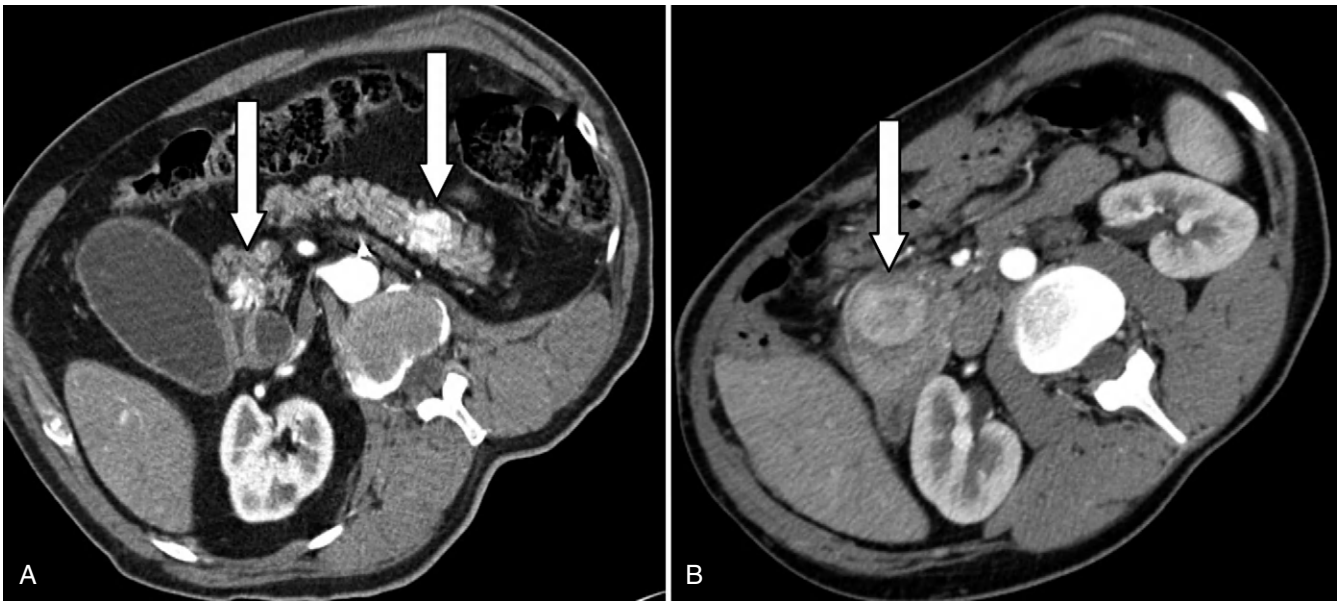


FIGURE 60.1. Typical radiologic features of pancreatic metastases. On contrast-enhanced computed tomography, pancreatic metastases typically appear as lesions with contrast enhancement in the arterial phase. **A,** Metastases of renal cell cancer to the pancreatic head and tail (*arrows*) exhibit intense contrast enhancement in the arterial phase. **B,** Metastases of soft tissue sarcoma to the pancreatic head (*arrow*) with contrast enhancement and central hypodensity.

surgeons and does not differ much from decision making for resection of other metastatic sites, such as liver and lung.

Primary Tumor Type

Clearly, the biology of the primary tumor is a key factor influencing the outcome. Patients with RCC metastases have a significantly better outcome than patients with other malignancies (Strobel et al, 2009), likely the result of a relatively slow tumor biology and, more recently, of more effective chemotherapy. Although the expected outcome in other malignancies, such as melanoma, is much worse, the decision for surgery can be based on the lack of effective nonoperative treatment in some tumor entities. Thus the decision for pancreatectomy for metastatic disease, as from other metastatic sites, can only be based on the experience with metastasectomy, per se, in each specific tumor entity.

History of the Disease

In our recent series, a prolonged interval (>36 months) between the primary tumor and the occurrence of the pancreatic metastasis was associated with improved survival. Of importance, a previous recurrence only affected disease-free but not overall survival (Strobel et al, 2009).

Pattern of Recurrent Disease

As expected, the presence of extrapancreatic disease is associated with shorter disease-free and overall survival (Strobel et al, 2009). This further highlights the importance of a thorough diagnostic workup to rule out local or extrapancreatic systemic recurrence of the primary tumor, as previously discussed. However, the survival results show that additional extrapancreatic disease should not necessarily preclude a patient from resection if the pattern is not multifocal/diffuse and if a complete resection can be expected.

Local Resectability, Patient Comorbidities, and Operative Risk

Given the lack of studies to evaluate factors that determine local resectability of pancreatic metastases, the same parameters used for primary pancreatic malignancies can be applied and typically involve assessment of mesenteric vascular and/or adjacent organ involvement (see Chapter 62A).

Of course, the same applies to patient-related factors that influence the operative risk, but consideration should also be given to the overall life expectancy related to the underlying disease and the efficacy and risk related to resection of extrapancreatic disease, if present. Clearly, medical comorbidities, functional status, and age have to be thoroughly considered.

Technique of Resection for Pancreatic Metastases (See Chapter 62A)

No studies have compared different techniques of pancreatic resection, and most larger studies only describe radical resections. However, in one report, a high rate of pancreatic recurrence was observed after limited resections (Bassi et al, 2003).



FIGURE 60.2. Pancreatic metastases of sarcoma. Cross-sections through the pancreas revealed two independent lesions located in different parts of the pancreas.

In our series, we performed standard partial resections but avoided total pancreatectomy whenever possible and observed only two pancreatic recurrences after 30 partial (6.7%) pancreatectomies (Strobel et al, 2009). Because pancreatic metastases are frequently multifocal (Fig. 60.2), a thorough exploration of the pancreatic remnant by palpation and ultrasound is mandatory whenever a partial pancreatectomy is performed (Zerbi et al, 2008). Because the two largest series showed that pancreatic metastases are associated with peripancreatic lymph node metastases in 26% to 30% of patients (Reddy et al, 2008; Strobel et al, 2009), a standard peripancreatic lymphadenectomy should be performed during pancreatic resection for metastases. To achieve curative resection, multivisceral resections should be performed if the operative risk and potential benefit are acceptable.

CONCLUSION

Rather than limited local resections, standard partial pancreatectomy combined with standard lymphadenectomy is recommended for treatment of pancreatic metastases. If complete tumor resection can be achieved with acceptable risk, total pancreatectomy and multivisceral resections may be performed in selected patients.

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CHAPTER 61

Endocrine tumors of the pancreas: clinical picture, diagnosis, and therapy

Tricia A. Moo-Young and Richard A. Prinz

OVERVIEW

Pancreatic endocrine tumors (PETs) are rare neoplasms that comprise 2% to 4% of all clinically detected pancreatic tumors (see Chapter 56). The origin of these tumors is not completely understood. Based on the most recent evidence, it has been suggested that these tumors arise from an endocrine cell–derived gastrointestinal epithelium. The pathogenesis of these tumors is not completely understood. Earlier theorists and modern geneticists have suggested that PETs arise from omnipotent endocrine stem cells present within the gastrointestinal epithelium. PETs are frequently divided into two groups based on the presence or absence of hormone function. *Nonfunctioning, or non–hormone producing, tumors* account for up to 30% or more of all neuroendocrine tumors; they express neurosecretory granules but are not associated with a clinically evident endocrinopathy, and most are discovered incidentally through the use of imaging studies done for other reasons or because of nonspecific abdominal symptoms. *Functional tumors* produce hormones that result in well-described endocrinopathies directly attributable to the hormones they secrete. The majority of PETs are sporadic, but they can be associated with hereditary syndromes, such as multiple endocrine neoplasia type 1 (MEN-1), von Hippel–Lindau (VHL) syndrome, tuberous sclerosis complex (TSC), and neurofibromatosis 1 (NF-1). The genetic predisposition for pancreatic endocrine tumors is strongest with MEN-1, which is characterized by the development of multigland parathyroid hyperplasia, pancreatic islet cell tumors, and pituitary adenomas. Almost half of all patients with MEN-1 develop symptomatic pancreatic endocrine tumors, and 100% of patients are shown to harbor small, nonfunctioning pancreatic endocrine neoplasms when the gland is examined histologically (Muscarella & Ellison, 2004).

Clinical management of PETs involves a multidisciplinary approach. Biochemical diagnosis and radiologic localization are the cornerstone of preoperative planning. Surgical resection is the only treatment that is curative, especially in an early stage of disease, but as many as 75% of patients present with advanced disease. Nonoperative therapies include chemotherapy, radiofrequency ablation (RFA), radionuclide therapy, biotherapy, and chemoembolization (see Chapters 81B and 83). These therapeutic modalities are useful for patients with unresectable or metastatic disease in whom symptomatic control of the hormonal effects and arrest of tumor progression can provide palliation and in some instances prolong survival.

CLASSIFICATION AND PROGNOSIS

Pancreatic endocrine tumors arise from the islets of Langerhans, and human islet cells display wide varieties in cellular composition and morphology. The molecular pathogenesis of PETs is poorly characterized, but they are associated with genetic syndromes such as VHL, MEN-1, NF-1, and TSC. The genetic makeup of these syndromes may help elucidate the molecular pathways from which PETs arise, although the majority of PETs are sporadic in origin. The broad heterogeneity of these tumors presents a challenge with regard to their correct classification. PETs are commonly classified by the presence or absence of a syndrome caused by hormone hypersecretion; however, neither of these classification systems offers any valuable predictive information regarding the biology or prognosis of these tumors.

The World Health Organization (WHO) developed a classification of pancreatic tumors that predicts malignant behavior based on histologic criteria (Heitz et al, 2004). This classification system assesses tumor localization, extension, proliferative capacity, and the presence of vascular or perineural invasion (Table 61.1). Some authors have challenged the clinical relevance of the WHO classification system (Schindl et al, 2000). Other studies have shown to have strong prognostic value and the ability to predict response to adjuvant treatments (Artale et al, 2005; Bajetta et al, 2005). The tumor-node-metastasis

Table 61.1

WHO Classification of Pancreatic Endocrine Tumors

Well-Differentiated Endocrine Tumor

Type 1: Benign Behavior	*Type 2: Uncertain Behavior*
Confined to the pancreas	Confined to the pancreas and *one* of the following:
<2 cm in diameter	>2 cm in diameter
<2 mitoses per high-powered field	>2 mitoses per high-powered field
<2% Ki-67–positive cells	>2% Ki-67–positive cells
No vascular or perineural invasion	Vascular or perineural invasion

Well-Differentiated Endocrine Carcinoma

Low-grade malignant
Gross local invasion
Metastases

Poorly Differentiated Carcinoma

High-grade malignant
>10 mitoses per high-powered field

(TNM) staging system for pancreatic exocrine adenocarcinoma has been applied to the staging of PETs and was recently revised to include grades relative to mitotic counts or Ki-67 index (Table 61.2). This was recently validated in a retrospective study looking at 202 foregut neuroendocrine tumors, of which 131 were PETs. This system was found to be equivalent but not superior to the WHO classification system (Pape et al, 2008).

The prognostic value of newer systems has yet to be validated in a prospective way. In a large retrospective study of PET patients from the National Cancer Database, variables predictive of outcomes included age, grade, type of resection, distant metastases, and tumor functionality. Tumor size, nodal status, and margins were not associated with survival (Bilimoria et al, 2008). The limitations of retrospective studies, usually with a small cohort size, and heterogeneity among these tumors likely explain why a standard classification system for PETs still does not exist.

Table 61.2

TNM Classification for Pancreatic Neuroendocrine Tumors

T: Primary Tumor	
T0	No evidence of cancer
Tis	Carcinoma in situ
T2	Tumor limited to the pancreas, size >2 cm
T3	Tumor extends beyond the pancreas but does not involve the celiac axis or superior mesenteric artery
T4	Tumor involves celiac axis or superior mesenteric artery (unresectable primary tumor)
N: Regional Lymph Nodes	
N0	No regional lymph nodes involved
N1	Regional lymph nodes involved
M: Distant Metastases	
M0	No distant metastases
M1	Distant metastases
Stages	
0	TisN0M0
IA	T1N0M0
IB	T2N0M0
IIA	T3N0M0
IIB	T1N1M0, T2N1M0, T3N1M0
III	T4, any N, M0
IV	Any T, any N, M1

From AJCC Cancer Staging Manual, 7th ed. Chicago, 2010, American Joint Committee on Cancer.

INSULINOMA

Insulinomas represent the most common type of functioning pancreatic endocrine tumor. They can occur sporadically or in association with the hereditary MEN-1. Patients typically are women (2 : 1) in the fifth or sixth decade of life. Among the functional PETs, insulinoma has the most favorable prognosis because the majority of these lesions are benign. Sporadic insulinomas are typically unifocal, but MEN-1 patients who develop insulinomas (approximately 10%) may present with multifocal disease.

Clinical Picture

Insulinomas are characterized clinically by fasting hypoglycemia and neuroglycopenic symptoms. Patients typically have episodic attacks of weakness, sweating, and tachycardia; however, the most notable symptoms are associated with central nervous system dysfunction. Neuroglycopenic symptoms include altered mental state, weakness, diplopia, seizures and, in late stages, coma. The stress of hypoglycemia causes a release of catecholamines responsible for the symptoms of anxiety, sweating, and palpitations. As a result, patients can be erroneously given cardiovascular, neurologic, or psychiatric diagnoses. Whipple described a triad of signs and symptoms associated with insulinomas that includes hypoglycemic symptoms after a fast or exercise, a blood glucose level less than 45 mg/dL when symptomatic, and relief of those symptoms by intravenous or oral glucose administration. The symptoms of hypoglycemia can be relieved or diminished by increasing oral intake, and appetite is stimulated by the sympathetic adrenergic surge. Because of this, patients with insulinomas often develop hyperphagia and have new-onset weight gain.

Diagnosis

The differential diagnosis of hyperinsulinemic hypoglycemia includes postprandial dumping syndromes, insulin receptor gene mutations, factitious hypoglycemia, chronic adrenal insufficiency, and hypopituitarism. In adults with symptoms of hypoglycemia, a 72-hour fast can elucidate the cause of hypoglycemia, defined as a plasma glucose level of 50 mg/dL or less. A monitored fast until symptoms of hypoglycemia develop, or until 72 hours elapse, is commonly performed, with measurement of the plasma concentrations of insulin and glucose at set intervals, especially when the patient becomes symptomatic. An insulin/glucose ratio greater than 0.4 is consistent with an insulinoma.

Insulin is synthesized in the β-cells as a larger molecule called *proinsulin*. C-peptide is cleaved from proinsulin to make the active form of insulin. Elevated levels of insulin with undetectable proinsulin and C-peptide indicate factitious hypoglycemia from the exogenous administration of insulin. Factitious hypoglycemia can also be caused by the ingestion of sulfonylureas, which cause elevated levels of all the β-cell polypeptides.

Table 61.3

Diagnostic Criteria for Insulinoma

Monitored fast for <48 hours with documented blood glucose <50 mg/dL with hypoglycemic symptoms
Relief of symptoms after oral glucose load
Elevated insulin level (>5 to 10 μU/mL)
Increased serum proinsulin level (>22 pmol)
Absence of urinary or plasma sulfonylureas
Elevated C-peptide levels

Factitious hypoglycemia often occurs in health care workers who have access to insulin or oral hypoglycemics. So, during a monitored 72-hour fast, both C-peptide and sulfonylureas should also be measured in the patient's plasma and urine. Monitored testing can detect up to 99% of insulinomas (Table 61.3; Service et al, 2000). Provocative testing with tolbutamide, glucagon, or intravenous calcium is rarely required for the diagnosis of insulinoma; furthermore, their use can cause harmful hypoglycemia with permanent neurologic damage. Autoimmune syndromes are rare causes of hypoglycemia that result from elevated levels of insulin in the presence of antiinsulin antibodies or antiinsulin receptor antibodies. Screening for these rare conditions can be done with serum measurements of the respective antibodies. Treatment is nonsurgical and sometimes warrants plasmapheresis.

Localization

Imaging for preoperative localization of insulinomas should take place only after the biochemical diagnosis has been confirmed. Most patients with insulinomas have a solitary benign adenoma (Friesen, 1982). Patients with familial syndromes, however, are more likely to have multifocal disease. Adenomas occur with equal frequency in the head, body, and tail of the pancreas. The majority of lesions are less than 1.5 cm in size and can be below the limit of detection for many conventional imaging modalities. Localization of insulinomas preoperatively remains a challenge for present-day clinicians. Traditional imaging techniques include ultrasound (US), computed tomography (CT) (see Chapter 16), and magnetic resonance imaging (MRI) (see Chapter 17). Transabdominal US, although widely available and used routinely, has low sensitivity in detecting insulinomas because of limitations from body habitus, surrounding intraabdominal organs, and the retroperitoneal depth of the pancreatic head.

Endoscopic ultrasound (EUS) (see Chapter 14) has substantially improved preoperative imaging of pancreatic neoplasms, but it is invasive. The sensitivity of EUS for localizing insulinomas has been reported to be 65% to 94%, with a mean sensitivity of 84% to 89% (Sotoudehmanesh et al, 2007). EUS visualization of the pancreatic head and uncinate process is superior to that of conventional US and provides the option of image-guided biopsy. The sensitivity of EUS is variable and depends on the location of the tumor. Sotoudehmanesh and colleagues (2007) reported sensitivity of EUS for detection of lesions in the pancreatic head, body, and tail as 92.6%, 78.9%, and 40.0%, respectively. This is understandable because of a blind spot in the distal body and tail where the stomach does not directly overly the pancreas.

Because of its wide availability, CT is usually the first localizing study performed; it can detect up to two thirds of lesions. When available, multidetector-row CT has been shown to be more sensitive for detecting small insulinomas (Liu et al, 2009). Most insulinomas are vascular and can be visualized on arterial phase imaging. One series comparing the use of CT, EUS, and the two in combination found the sensitivity of CT with EUS was superior to either modality done separately (Gouya et al, 2003). MRI alone or in combination with other imaging modalities has demonstrated higher sensitivity and rates of detection than were originally reported. More recent use of rapid triphase breath-holding imagery allows better fat suppression and reduction in motion artifact in both the arterial and venous phases (Catalano et al, 1999; Thoeni et al, 2000). At present, MRI is considered a second-line modality in the evaluation of insulinomas because of its greater expense and more limited availability.

Because only 30% of insulinomas possess somatostatin type II receptors, the value of somatostatin receptor scintigraphy (SRS) is limited in this tumor type (Kisker et al, 1997). Intraarterial calcium stimulation with hepatic venous sampling is one of the most sensitive localization modalities but also one of the most invasive (Guettier et al, 2009). It is a modification of the selective arterial secretin injection test developed by Imamura and colleagues (1993) and used to localize gastrinomas. This technique involves selective infusion of calcium into branches of the celiac axis and superior mesenteric artery with sampling of the hepatic venous effluent for insulin. It is an invasive, expensive, time-consuming, and technically difficult procedure that should be reserved for patients with persistent or recurrent disease, or when other tests are unsuccessful.

Despite these advances, preoperative localization may still not be successful in up to a third of patients. Current research suggests that future improvements will continue. A recent study showed that glucagon-like peptide-1 (GLP-1) receptor was expressed in more than 90% of insulinomas and at twice the density of somatostatin receptors (Reubi et al, 2003). Exendin-3, the analogue of GLP-1, is known to enhance insulin secretion in β-cells and has been introduced in the treatment of type 2 diabetes (Gallwitz et al, 2006). In a pilot trial of six patients, scintigraphy done with GLP-1 radioligands was able to identify all the insulinomas prior to operative exploration (Christi et al, 2009).

The extent of imaging necessary to ensure operative cure has not been clearly defined. Some institutions have suggested that preoperative localization is not necessary beyond the evaluation for metastatic disease (Hashimoto et al, 1999). This philosophy is based on the observation that the combination of surgical exploration and intraoperative US can identify more than 90% of insulinomas.

Therapy

Although the definitive treatment for patients with insulinomas is resection of the tumor, presurgical therapy to alleviate the symptoms and neurologic affects of hypoglycemia should be instituted. The medical management of insulinomas consists of dietary measures to minimize the occurrence of dangerous hypoglycemia. This involves taking small, frequent meals and closely monitoring blood glucose levels throughout the day. A number of insulin antisecretagogues can be used, such as diazoxide, verapamil, octreotide, or dilantin. Diazoxide, the most commonly prescribed drug, works by directly inhibiting the release of insulin from β-cells by stimulating their α-adrenergic receptors. Diazoxide also promotes glycogenolysis

by inhibiting cyclic adenosine monophosphate phosphodiesterase. It can offer symptom control in up to 50% to 60% of patients (Boukhman et al, 1998). Octreotide, a somatostatin analogue, has had variable results and alleviates symptoms in approximately 40% of patients (Arnold et al, 2002). Its use is limited by side effects such as bloating, malabsorption, cholelithiasis, and eventual tachyphylaxis. Dilantin and verapamil have been used alone or in combination with other drugs, but their duration of action and side effects limit their efficacy for long-term medical therapy.

Definitive treatment for an insulinoma is operative removal of the tumor. Before proceeding to surgery, it is important to exclude the presence of any familial syndromes and their other associated problems, such as pituitary tumors and hyperparathyroidism. Intraoperative glucose monitoring is done to ensure normoglycemia. Dextrose infusions should be stopped just prior to surgical resection to permit intraoperative glucose measurements as an indicator of biochemical cure. The glucose levels should be monitored frequently to be sure hypoglycemia does not persist.

Most sporadic adenomas are amenable to enucleation regardless of their location. Surgical exploration starts by gaining access to the pancreas in the lesser sac. Lesions located in the head of the pancreas should be explored via a wide kocherization of the duodenum. In experienced hands, intraoperative US in combination with palpation detects up 98% of insulinomas (Norton et al, 1988). Care must be taken not to injure the pancreatic duct when performing an enucleation or segmental resection. Intraoperative US is useful to identify the location of the pancreatic duct for lesions in the head that are being enucleated. The insulinoma can be approached anteriorly or posteriorly depending on findings from palpation and intraoperative US. After an insulinoma is fully enucleated, it is essential to inspect the area for ductal leaks. Should a leak be identified, a suture repair should be attempted if feasible, and a suction drain should be left in place; postoperative management of the drain is identical to that for any pancreatic leak. The most common complication following resection for an insulinoma is a pancreatic leak. Rates of pancreatic fistula have been reported between 18% and 38% (Espana-Gomez et al, 2009; Nikfarjam et al, 2008). Fistulas are seen more commonly among patients treated with enucleation procedures than those undergoing formal resection.

Most insulinomas are solitary, but in patients with MEN-1, multifocal lesions are typical. In MEN-1 patients—in whom multiple, subcentimeter tumors often coalesce—segmental resection rather than enucleation is preferred (see Chapter 62A). The goal of surgery in MEN-1 patients is to remove only the tumors, preserving as much normal pancreas as possible. After preoperative imaging, if the tumor cannot be identified by operative exploration with complete mobilization of the pancreas—including kocherization to allow bimanual palpation of the entire gland—or intraoperative US, blind resection is not recommended. When the lesion is not found, a pancreatic biopsy specimen should be obtained to rule out adult nesidioblastosis, which generally can be treated successfully by subtotal pancreatectomy. The biopsy specimen is obtained by removing a small portion of the most distal tail.

Numerous studies have shown that laparoscopy is a safe and feasible approach for the treatment of pancreatic insulinomas (see Chapter 62B). Solitary lesions localized preoperatively are ideally suited for this approach. In the absence of bimanual palpation, laparoscopic US assists in tumor localization. Whereas preoperative localization has an accuracy rate of 45% for laparoscopic resection alone, when combined with laparoscopic US, the accuracy rises to 96% (Luo et al, 2009). Conversion rates to an open procedure range between 7% and 44% (Ayav et al, 2005; Jaroszewski et al, 2004; Luo et al, 2009), and the most common reason for conversion is failure to localize the tumor. Limited data suggest that fistula rates are lower among patients treated by laparoscopic compared to open approaches (Cunha et al, 2007).

The rarity of malignant insulinoma limits definitive statements about therapeutic strategies and outcome. In patients with metastatic disease, surgical resection of the tumor and metastatic lesions should be considered for palliation of symptoms of hypoglycemia. Because of the often indolent nature of malignant insulinomas, extended survival is possible. Multimodal therapy that includes surgical debulking, chemoembolization, radiofrequency thermoablation, and liver transplantation has been shown to prolong survival (Begu-Le Corroller et al, 2008). Median disease-free survival has been reported to be approximately 4 years in patients who underwent curative resection for malignant disease (Danforth et al, 1984; Hirshberg et al, 2005). Chemotherapy of malignant insulinomas consists of streptozotocin in combination with other agents, including 5-fluorouracil or doxorubicin. Reports regarding the success of these agents in clinical trials are understandably scarce given the rarity of this condition.

GASTRINOMA (ZOLLINGER-ELLISON SYNDROME)

Gastrinomas are the second most common functioning islet cell tumor of the pancreas. The overall incidence of gastrinomas is 0.5 to 3 per million population per year (Jensen et al, 2006). The peak age of onset is 50 years, and there is a slight male predominance. Despite their slow-growing nature, more than 60% of gastrinomas are malignant. Because of their indolent growth pattern, even in the presence of metastases, the 10-year survival approaches 90%. Approximately two thirds of gastrinomas are sporadic, with the remainder associated with familial MEN-1. Gastrinomas in MEN-1 patients tend to be multifocal, and as many as 50% of patients have lymph node, liver, or distant metastases at the time of presentation (Andersen, 1989).

Clinical Picture

Gastrinomas are so named because they produce excess levels of the gastrointestinal hormone gastrin. This results in acid hypersecretion and the subsequent development of intractable gastrointestinal ulcers. Zollinger-Ellison syndrome (ZES) is the name given to this condition, and it includes the presence of a gastrin-producing tumor in the presence of acid hypersecretion. With the advent of effective antisecretory medications, patients may or may not have intractable ulcer disease at the time of diagnosis. ZES patients come to medical attention with symptoms of abdominal pain, heartburn, nausea, and often weight loss. Diarrhea is a common problem in ZES, occuring in close to 80% of patients (Jensen et al, 2006), and 70% of patients being seen for evaluation of ZES have a confirmed history of peptic ulcer disease. Patients with ZES are also likely to exhibit sequelae of gastric acid hypersecretion, such as esophageal stricture or prominent gastric folds, documented by endoscopic

Table 61.4

Diagnostic Criteria for Gastrinoma

Fasting gastrin level	>100 pg/mL *or* >10 times higher than upper limit of normal
Basic acid output level	>15 mEq/h
Secretin stimulation testing	Increase of >200 pg/mL
Calcium infusion provocative testing	Rise >395 pg/mL

Patients should be off antisecretory agents a minimum of 3 to 7 days.

gastroduodenoscopy (EGD). A suspicion of ZES is not appropriate for all patients who present with peptic ulcer disease (PUD). Approximately 0.2% of patients with PUD will have ZES, whereas 2% of patients with recurrent PUD will have ZES (Modlin et al, 1982). Other than recurrent ulcers, a higher suspicion of ZES should be held in patients who present with 1) PUD with diarrhea; 2) ulcers in unusual locations, including the distal duodenum and jejunum; 3) ulcers that are refractory to medical management or those associated with complications, such as bleeding and perforation; 4) disease at a young age; and 5) hyperparathyroidism, pituitary disorders, or a familial history of endocrinopathies. Given the nonspecific symptoms and relative rarity of this disorder, the mean time from the onset of symptoms to diagnosis is 5.9 years (Roy et al, 2000; Berna et al, 2006a). A high index of suspicion is necessary to diagnose these patients.

Diagnosis

The diagnosis of ZES is established by measuring a fasting serum gastrin (FSG) level and documenting the presence of acid hypersecretion (Table 61.4). Prior to testing, patients should be off all antisecretory medications at least 3 to 7 days. Proton pump inhibitors should be stopped for at least 1 week, and H_2 receptor antagonists should be stopped for 2 days prior to testing. A fasting serum gastrin (FSG) level above 100 pg/mL or 10 times greater than the upper limit of normal (ULN) is highly suggestive of ZES. However, only one third of ZES patients have an FSG level 10 times higher than the ULN, and a number of conditions that are not associated with ZES can cause an elevated FSG level (Table 61.5). To help differentiate these conditions, the presence of gastric acid hypersecretion should be documented. Excess gastric acid production is demonstrated by having a gastric pH of less than 2.1 or a basal acid output level greater than 15 mEq/h.

The magnitude of the increased FSG has been shown to correlate with certain tumor features (Berna et al, 2006a). Patients with pancreatic primary tumors are more likely than those with duodenal primary tumors to have an FSG level higher than 10 times the ULN (50% of pancreatic vs. 25% of duodenal primaries). FSG level also correlates with tumor size and extension. Patients with larger tumors (>3 cm) are more likely to have an FSG level greater than 10 times the ULN when compared with smaller tumors (40% vs. 23%, respectively). Fifty percent of patients with liver metastases will have an FSG level more than 10 times the ULN, compared with only a third of those who do not.

Two thirds of ZES patients will have equivocal FSG testing, and provocative testing should be performed. Three types of provocative tests are available for the diagnosis of ZES: 1) the secretin stimulation test, 2) the calcium infusion test, and 3) the standard meal test. The secretin stimulation test is performed by intravenously administering a 2 IU/kg bolus of secretin to the patient and serially measuring serum gastrin levels at specific time points. A serum gastrin rise of 200 pg/mL (range, >100 to 335 pg/mL) is consistent with ZES (Frucht et al, 1989b; McGuigan et al, 1980). The secretin stimulation test is highly sensitive and useful in patients who cannot tolerate being off their antisecretory medications. The calcium infusion provocative test is performed by administering an intravenous infusion of calcium gluconate 5 mg/kg/h over a 3-hour period (Deveney et al, 1977). Serial time points of gastrin and calcium are measured. A rise of more than 1.5 mEq/L of calcium is used to validate the test. A rise in serum gastrin above 395 pg/mL is considered diagnostic (range, 326 to 450 pg/mL). This test should be avoided in patients with renal disease, hypercalcemia, and cardiac disease. The standard meal test is performed by serving the patient a meal composed of 30 g protein, 20 g fat, and 35 g carbohydrate (Frucht et al, 1989a). Serum gastrin levels are again measured serially and are considered diagnostic of ZES if levels rise to either more than 50% of the zero time point level or to a maximal gastrin level greater than 500 pg/mL. This test is not performed in patients who have had a prior gastrectomy or those who cannot tolerate oral feedings.

Berna and colleagues (2006b) compared these three provocative tests for ZES and showed that the secretin test was more sensitive than the calcium infusion test (94% vs. 62%). However, 38% to 50% of patients with normal secretin test values went on to have positive calcium infusion tests. Fewer than 25% of ZES patients had an appropriate rise in their postprandial serum gastrin levels with provocative meal testing. The authors concluded that secretin stimulation should be the first-line provocative test, followed by calcium testing if the secretin test results are normal in the presence of a strong suspicion for ZES. Meal provocative testing should not be used given the high percentage of equivocal studies. Once a diagnosis of ZES is established, all patients should be screened for MEN-1 by measuring serum calcium, parathyroid hormone, and prolactin levels.

Table 61.5

Differential Diagnosis of Hypergastrinemia

High Acid Output	Normal Acid Production
Zollinger-Ellison syndrome	Atrophic gastritis
G-cell hyperplasia	Proton pump inhibitors
Retained gastric antrum	Postvagotomy syndrome
Gastric outlet obstruction	Renal failure

Localization

Once the biochemical diagnosis of ZES has been established, the next step is to localize the primary lesions and determine the presence or extent of tumor spread. The modalities for localization are similar to those used for insulinoma and include transabdominal and endoscopic US, CT, and MRI along with selective visceral angiography, selective venous sampling of the portal venous tributaries, intraarterial secretin with hepatic venous sampling for gastrin, and somatostatin receptor scintigraphy (SRS).

In contrast to insulinomas, SRS has proven effective in detecting gastrinomas. A radiolabeled form of the somatostatin

analogue octreotide can localize tumors that express high-affinity somatostatin receptors. SRS can also identify metastatic lesions elsewhere in the body. Current improvements in CT imaging have raised reported localization sensitivities from 30% to 55% through the increased use of multiphase detector CT scanning and the use of thin-slice imaging (Klose et al, 2007; Noone et al, 2005). CT imaging provides anatomic information, and it is useful for identifying metastatic disease. With MRI, gastrinomas have high signal sensitivity on T2-weighted fat-suppressed sequences. MRI can localize lesions smaller than 1 cm, but its overall sensitivity for gastrinomas is only 20% to 30% (Klose et al, 2007). Arterial angiography is now rarely used and has highly variable sensitivities because of its user-dependent variability.

As with insulinomas, EUS is extremely useful in detecting lesions within the pancreatic head but is less sensitive at identifying duodenal lesions (75% vs. 50%; Ruzzniewski et al, 1995). One promising technology being investigated for use with positron emission tomography is (68)Ga-DOTATOC, a somatostatin tracer (Hofmann et al, 2001). Preliminary studies have shown that 68 Ga-DOTATOC positron emission tomography has a higher sensitivity for detecting pancreatic endocrine tumors compared with both CT and SRS (Gabriel et al, 2007). Gastrinoma patients should first be evaluated by SRS and cross-sectional imaging (CT or MRI). If these tests fail to localize the lesions, EUS or angiography with secretin stimulation can be considered. When preoperative localization studies fail to detect the gastrinoma, surgical exploration with intraoperative palpation, US, and endoscopy with transillumination of the duodenum should be attempted, especially with sporadic gastrinomas.

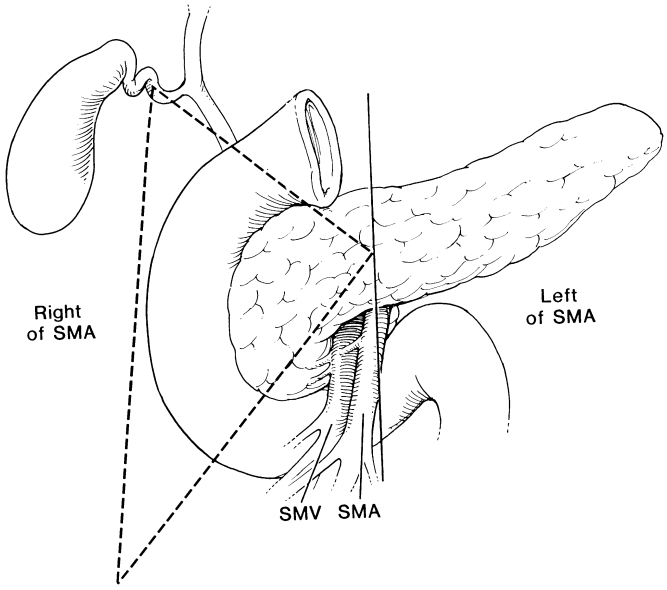


FIGURE 61.1. Gastrinoma triangle. SMA, superior mesenteric artery; SMV, superior mesenteric vein. *(From Howard TJ, et al, 1990: Anatomic distribution of pancreatic endocrine tumors. Am J Surg 159:258-264.)*

Therapy

Surgical resection is the recommended treatment for patients with sporadic, resectable disease (see Chapter 62A). As with all PETs, the only chance for cure is complete surgical resection. This is achieved in only a minority of patients (Norton et al, 1999). The majority of gastrinomas are located within the "gastrinoma triangle," as was described by Stabile and colleagues (Stabile et al, 1984; Howard et al, 1990). The *gastrinoma triangle* is defined by a line that joins the confluence of the cystic and common bile duct superiorly, the junction of the second and third portion of the duodenum inferiorly, and the junction of the neck and body of the pancreas medially (Fig. 61.1). More than 80% of gastrinomas are located within this anatomic triangle (Abood et al, 2009).

The primary goal of treatment in ZES is to control acid production, remove the primary tumor, and prevent malignant progression. Historically, ZES patients were offered total gastrectomy to control acid production, but this has become unnecessary since the development of effective pharmacologic therapies for gastric hypersecretion. Resection of the primary is undertaken by performing a complete exploration of the gastrinoma triangle, which begins with an extended Kocher maneuver to mobilize the duodenum, gaining full exposure of the pancreas in the lesser sac. Bimanual palpation with the use of intraoperative US assists in identifying small and multifocal lesions located within the pancreas. Lesions within the pancreatic head should be treated with enucleation, and those in the tail or body should be treated with spleen-preserving distal pancreatectomy or enucleation. A duodenotomy should be performed routinely in all patients undergoing operative exploration for ZES (Morrow et al, 2009). Routine duodenotomy in the exploration for ZES doubles the cure rate from 30% to 60% (Morrow et al, 2009; Norton et al, 2004, 2006). Duodenal tumors less than 5 mm can be enucleated, but larger tumors should be resected by full-thickness excision of the duodenal wall. Laparoscopy has been attempted in patients with sporadic gastrinomas. Because more than 50% of these lesions occur in the duodenum or tend to be larger than other PETs, its use is limited to patients with lesions localized to the distal pancreas or those amenable to enucleation (Fernandez Cruz et al, 2008; Pierce et al, 2007).

The operative role and appropriate procedure in MEN-1 patients with ZES is controversial. This is because more than 50% of these patients are initially seen with evidence of metastases; thus MEN-1 patients are rarely cured by surgery. The goal of surgery in MEN-1 patients is not cure but prevention of metastatic disease. Surgical resection of the primary tumor may prevent the development of liver metastases and prolong disease free-survival among patients with MEN-1 ZES (Fraker et al, 1994; Motellaro et al, 2009). The larger the tumor, the more likely the patient is to develop liver metastases. Among patients with tumors less than 1 cm, only 4% are likely to have liver metastases compared with more than 60% of patients with tumors greater than 3 cm (Bartsch et al, 2007; Weber et al, 1995a).

The main predictor of survival in MEN-1 patients is the extent of liver metastasis (Weber et al, 1995b). ZES patients with MEN-1 who have tumors smaller than 2 cm may be observed. Tumors larger than 2 cm should have resection of their primary tumors with full duodenal and pancreatic exploration for multifocal disease. The use of pancreatoduodenectomy remains controversial in the management of MEN-1 ZES. This approach is recommended for young patients or those who have large isolated pancreatic head tumors (Fendrich et al, 2007; Morrow et al, 2009).

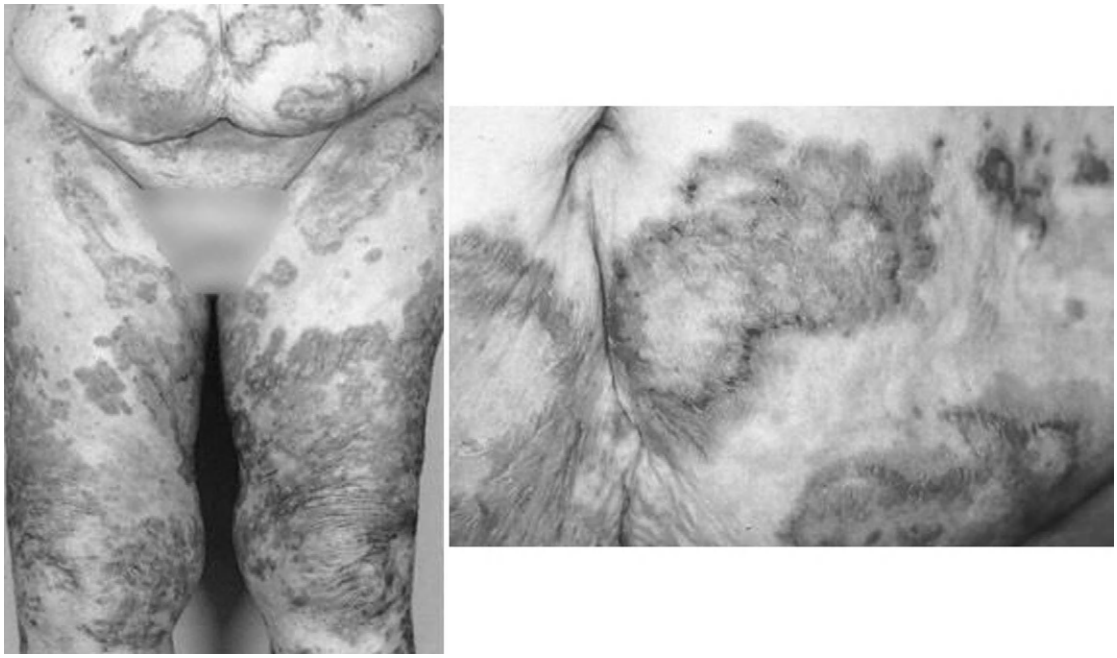


FIGURE 61.2. Necrolytic migratory erythema of glucagonoma. *(From Lebwohl MG [ed], 2002: Treatment of Skin Disease: Comprehensive Therapeutic Strategies. St. Louis, Mosby, p 416.)*

The effects of hyperparathyroidism on gastrin and acid hypersecretion should not be overlooked in MEN-1 patients. Those with both ZES and hyperparathyroidism should undergo parathyroidectomy prior to surgical treatment for their ZES.

GLUCAGONOMA

The first patient with a glucagonoma was described in 1942 by Becker and colleagues, who reported a 45-year-old woman with a diffuse, erythematous, vesicular, necrotic dermatosis in addition to diabetes mellitus, stomatitis, anemia, weight loss, and thromboembolism. Her autopsy revealed a pancreatic islet cell tumor. More than 20 years later, with the benefit of radioimmunoassay techniques, McGavran and colleagues (1966) showed elevated glucagon levels in the blood and pancreatic islet α-cell tumor tissue in a similar patient with "bullous and eczematoid dermatitis," diabetes, and anemia. Glucagonomas are rare, frequently large (>4 cm) at diagnosis, and almost always found within the pancreas. Patients typically are seen in their 40s, with an equal distribution between genders (Wermers et al, 1966). Most of the tumors (60% to 70%) are malignant, and association with MEN-1 is rare.

Clinical Picture

The clinical manifestations of a glucagonoma encompass what is sometimes referred to as the "four D syndrome," which includes ***d***iabetes mellitus type 2, ***d***ermatitis (necrolytic migratory erythema), ***d***eep vein thrombosis (30% of patients), and ***d***epression. Other symptoms can include chronic anemia, stomatitis, weight loss, and generalized weakness. Less common features include mental changes, diarrhea, arterial thrombosis, and neurologic abnormalities (Prinz et al, 1981). Necrolytic migratory erythema (NME) is present in 70% of patients (Fig. 61.2). This rash is characteristic of a glucagonoma but not definitively diagnostic. The distribution of NME is highly variable across regions of the body. It typically occurs where there is frequent friction or inadvertent trauma, such as the feet, lower legs, buttocks, or perineum, but lesions can be present anywhere. The rash is commonly confused with psoriasis, pemphigus, or eczema. To differentiate NME from these other rashes, a biopsy can be performed. Histopathology shows necrolysis, pallor of the epidermis, and mild lymphocytic and histiocytic infiltration. The biopsy should be taken from an early lesion and preferably from its edge. The reason for this is that older lesions with blisters in various stages of healing reveal nonspecific findings of dyskeratosis and acanthosis (Kovacs et al, 2006). These features make it more difficult to distinguish NME from other causes of subacute dermatitis. After resection, patients can have complete regression of NME.

Diagnosis and Localization

Laboratory findings of a glucagonoma include elevated plasma glucose level, normochromic normocytic anemia, and a generalized decrease in plasma amino acids. The diminished levels of amino acids stem from the stimulation of gluconeogenesis and amino acid oxidation by glucagon. Fasting serum glucagon levels greater than 1000 pg/mL (normal is 0 to 150 pg/mL) are virtually diagnostic. Other conditions that can cause elevated glucagon levels (usually <500 pg/mL) include fasting, sepsis, pancreatitis, abdominal surgery, Cushing syndrome, and renal or hepatic failure. Because the diagnosis is often delayed, patients with glucagonomas typically are seen with large tumors (>5 cm). CT scan with intravenous contrast administration is often sufficient for localization and has been reported to detect 86% of tumors (Wermers et al, 1966). Abdominal CT is also useful for identifying metastatic disease, which can be present in

up to 50% of patients at the time of presentation (Stacpoole, 1981). EUS is usually unnecessary for localization, but it can be useful for US-guided needle biopsy. SRS has been used more for long-term follow-up of these patients and can demonstrate metastatic disease (Lipp et al, 2000). Other imaging modalities, such as angiography and portal venous sampling, are rarely needed for localization purposes.

Therapy

Glucagonomas cause a prolonged and profound catabolic state. Preoperative nutritional status should be assessed, and the patient's metabolic deficits should be corrected before operation. Somatostatin analogues should be considered for the preoperative preparation because they can markedly diminish circulating levels of glucagon and consequently lessen or reverse its catabolic effects. The majority of tumors are located in the body or tail of the pancreas and are potentially amenable to laparoscopic spleen-preserving distal pancreatectomy, if diagnosed early. Unfortunately, most are very large at diagnosis. Glucagonomas are malignant in 60% to 70% of patients, and the likelihood of cure is small. An R0 resection is achievable in only 30% of patients (Abood et al, 2009). Nevertheless, resection of the primary and even metastatic lesions can offer substantial palliation if the tumor tissue can be removed safely. Like most islet cell carcinomas, glucagonomas frequently have an indolent course. Thus, reoperative surgery for recurrent disease is a reasonable option if the resection can be performed safely. Control of the hormonal effects through debulking procedures can help manage symptoms and prolong survival (Altimari et al, 1986). When widely metastatic disease is present and surgical debulking is not possible, medical therapy can alleviate hormonal symptoms (Nightingale et al, 1999). Somatostatin analogues such as octreotide can reduce serum glucagon levels and improve NME, diabetes, diarrhea, and neurologic symptoms. Dacarbazine and streptozotocin have been used to treat metastatic glucagonomas with some success. As with other pancreatic endocrine cell tumors, metastatic disease to the liver has been treated by resection, hepatic artery embolization, and liver transplantation (Dousset et al, 1995).

VASOACTIVE INTESTINAL PEPTIDE TUMOR

Vasoactive intestinal peptide (VIP) tumors are rare, with an annual incidence in the United States of 1 in 100,000,000 people. The majority of VIP tumors are benign and typically consist of a solitary lesion with a mean size of 3 to 5 cm. The mean age at presentation is 48 years, with a slight male predominance (Peng et al, 2004). In 1958, Verner and Morrison first described this syndrome of watery diarrhea (WD), hypokalemia (H), and achlorhydria (A) associated with a non–β-cell tumor of the pancreas (Verner & Morrison, 1958). As a result, this complex is often referred to as *WDHA syndrome* or *Verner-Morrison syndrome*, and 98% of patients are first seen with diarrhea. Hypokalemia is present in 67% to 100% of patients. The prevalence of flushing and weight loss is much more variable. The secretory diarrhea is high in volume (6 to 8 L/day) but painless and odorless; its color resembles tea, and it characteristically persists despite fasting. In VIP tumors, the diarrhea does not decrease with nasogastric fluid aspiration, whereas in ZES diarrhea will cease (Mansour & Chen, 2004). Over time, with large-volume gastrointestinal fluid losses, patients become hypokalemic and acidotic. The fluid and electrolyte deficits in VIP tumor patients can be profound and must be corrected before proceeding to surgical or other treatment.

The differential diagnosis for diarrhea is very long, so the diagnosis of a VIP tumor is typically made several months to years after the onset of symptoms. The average duration of symptoms before diagnosis is 3 years (Thomason et al, 2000). To confirm the diagnosis, a fasting serum VIP level should be greater than 200 pg/mL; average levels are close to 1000 pg/mL in patients with VIP tumors (O'Dorisio et al, 1989). The majority of pancreatic VIP tumors are located within the tail of the pancreas (72%) and thus are readily identified by conventional imaging. Radiologic examination begins with a CT scan of the abdomen and pelvis. Because of their relatively large size, sensitivity for localizing these lesions approaches 100%. Other radiographic adjuncts include MRI and SRS. Unlike insulinomas, more than 85% of VIP tumors are somatostatin receptor positive. SRS can be useful in detecting primary lesions outside the pancreas, where one third of VIP tumors are located. Compared with pancreatic tumors, extrapancreatic lesions are typically smaller, less likely to be malignant (33% vs. 64%), and less likely to present with metastases (29% vs. 56%) (Ghaferi et al, 2008).

While the diagnosis and localization of the tumor is being confirmed, electrolyte imbalances are corrected with oral or intravenous supplements when necessary. In some patients with longstanding diarrhea refractory to standard replacement strategies, it is necessary to start somatostatin therapy to reduce the amount of daily electrolyte losses. When radical resection is not possible, palliation can usually be achieved by debulking of the metastatic tumor in combination with the use of somatostatin analogues. Prognosis for these patients is largely determined by the presence or absence of metastatic disease at the time of presentation.

SOMATOSTATINOMA

Somatostatinomas are rare, representing only 1% of all pancreatic neuroendocrine tumors (O'Toole et al, 2006). In 1977, Ganda and colleagues and Larsson and colleagues independently reported the first patients with a somatostatinoma. Somatostatinoma syndrome was described by Krejs and coworkers in 1979 and includes hyperglycemia, cholelithiasis, steatorrhea, and diarrhea. The mean age of patients at diagnosis is 50 years, with an equal distribution between men and women. In most patients (>90%), the lesions are solitary and generally average between 5 and 6 cm. Extrapancreatic somatostatinomas occur in 44% of patients, most commonly within the duodenum, but they have also been reported to arise from the biliary tract or other parts of the small bowel. The inhibition of insulin secretion leads to mild hyperglycemia, and decreased gallbladder contractility from the inhibition of cholecystokinin results in the formation of gallstones. The inhibition of pancreatic enzyme and bicarbonate secretion and intestinal absorption causes diarrhea and steatorrhea. Patients also may have gastric hypochlorhydria from the inhibition of gastrin release (Jensen & Norton, 1995). These clinical manifestations are rarely present with somatostatinomas arising in the duodenum. Instead, patients with duodenal somatostatinomas are initially seen with obstructive symptoms that include abdominal pain and jaundice. Duodenal somatostatinomas often are identified as an incidental finding (Mao et al, 1995). They are malignant in

60% to 70% of patients, with nearly two thirds of patients having evidence of metastases at diagnosis (Nesi et al, 2007). Lesions greater than 2 cm are more likely to be associated with metastatic disease (Tanaka et al, 2000).

Most tumors located in the head of the pancreas are large. Localization of pancreatic somatostatinomas often can be accomplished by CT or US, whereas EUS, MRI, and SRS play a role in localization of smaller or metastatic tumors. Because many duodenal somatostatinomas are small (<1 cm), EUS can be especially useful for their localization. Surgical resection offers the only chance for cure, but many somatostatinomas have metastasized by the time they are discovered. Debulking can provide symptomatic relief, and cholecystectomy should be performed at the time of operation because of the high incidence of cholelithiasis. In unresectable disease, octreotide and interferon-alfa may improve symptoms. In patients without metastatic disease, the mean 5-year survival is 100%. Those patients with metastatic disease who undergo radical resection or debulking procedures have a mean 5-year survival of 60% (Abood et al, 2009).

NONFUNCTIONAL PANCREATIC ENDOCRINE TUMORS

Nonfunctional pancreatic neuroendocrine tumors (NF-PETs) histologically express endocrine differentiation but lack a clinical syndrome of hormone overproduction (Prinz et al, 1983). They represent more than 75% of all pancreatic endocrine tumors (Halfdanarson et al, 2008). The mean age at presentation is 45 years, and an equal distribution is found between men and women. Traditionally, NF-PETs are described as large tumors, and more than 60% to 80% are metastatic at the time of diagnosis. With the widespread use of high-resolution abdominal imaging, however, these lesions are being increasingly identified as small, asymptomatic tumors. Approximately 60% are malignant at the time of diagnosis (Ehehalt et al, 2009), and 8% of NF-PETs occur in association with MEN-1; of patients with MEN-1, approximately 55% of tumors will be NF-PETs (Thomas-Marques et al, 2006).

Clinical Picture

The diagnosis of an NF-PET is typically delayed by the lack of a clinical syndrome. These lesions are typically discovered on routine radiographic imaging done for nonspecific abdominal complaints. As these tumors grow larger and begin to compress surrounding structures, patients may develop symptoms of pain or obstruction.

Diagnosis and Localization

Although these tumors are hormonally "silent," they often release inert precursor hormones into the systemic circulation. Blood testing for such inert tumor markers include pancreatic polypeptide, neurotensin, protein S, neuron-specific enolase, and chromogranin A. Measurement of these levels prior to resection may help establish a baseline for tumor burden and provide a possible marker for follow-up for tumor recurrence. Localization of the primary tumor and establishment of the extent of metastatic disease is best achieved with a triple-phase—arterial, portal, and venous phase—CT scan (see Chapter 16). Because these tumors are typically large, EUS is only necessary for biopsy or to identify subcentimeter disease. SRS is recommended to determine receptor expression status for the postsurgical treatment with somatostatin analogues. Because a small percentage of these lesions can be associated with MEN-1, patients who have a medical or family history suggestive of MEN-1 should undergo testing for this familial syndrome's associated endocrinopathies.

Therapy

In patients with sporadic NF-PETs, resection should be geared toward cure when possible. When the lesion is limited to the pancreas, a standard oncologic resection should be performed (see Chapter 62A). In the presence of limited, synchronous hepatic metastases, concomitant liver resection should be considered if the patient is a good surgical candidate. In patients with extensive liver disease, resection of the primary tumor may be considered in conjunction with partial hepatectomy combined with locoregional ablative techniques, such as transarterial chemoembolization (TACE) and radiofrequency ablation (RFA).

In MEN-1 patients, the indications and approach to surgery remain controversial. MEN-1 patients have a field defect that makes the entire pancreas at risk of neoplastic disease, such that resection of a primary lesion does not necessarily prevent recurrence in the remnant gland. The goal of surgery for MEN-1 NF-PETs should be to resect all gross disease while also trying to preserve pancreatic function. Surveillance EUS performed in these patients often reveals small PETs of uncertain importance. The threshold for operation varies across institutions. Bartsch and colleagues (2005) advocate that patients undergo early resection at a size threshold of 10 mm, based on the observation that lesions greater than 10 mm carry a 20% risk of having locoregional metastases. Some groups advocate surgical exploration based on biochemical evidence alone, even if imaging studies fail to localize lesions (Skogseid et al, 1991). The recommended procedure includes enucleation of lesions in the pancreatic head followed by prophylactic spleen-preserving distal pancreatectomy.

METASTATIC DISEASE

Unlike exocrine pancreatic neoplasms, patients with endocrine tumors may benefit from reoperation for resectable recurrences or metastatic disease. This is likely because of the relatively indolent nature of these tumors. Observational studies have shown that many patients live for several years with untreated metastatic disease (Weber et al, 1995a). The debilitating aspects of these tumors are related to the excess hormone secretion in patients with functional PETs or to obstructive symptoms caused by large NF-PETs. The predominant site of metastatic spread is the liver. Resection, chemotherapy, and other treatment modalities may not cure the patient, but they do offer substantial palliation and may extend survival. Compared with medical management, patients treated surgically or with ablative therapy have improved overall survival (see Chapter 81B; Chamberlain et al, 2000).

Resection

With advanced metastatic disease that includes hepatic metastases, resection remains the gold standard of treatment in these patients when feasible. The biochemical response rate is 96%,

and the 5-year survival is reported as 80% (Steinmuller et al, 2008). Patients with advanced disease at initial presentation should undergo radical resection with an attempt at cure if it can be done safely. In study by Norton and colleagues (2003), in which the mean tumor size was 8 cm and 40% of patients had liver metastases, a curative resection was achieved in 75% of patients. Procedures included pancreatoduodenectomy, liver resection, nodal dissection, and total pancreatectomy. No perioperative deaths were reported, and the mean follow-up period was 19 months. During that time the actuarial overall 5-year survival rate was 80%, which supports the conclusion that patients with advanced disease at presentation may benefit from a complete resection or a debulking procedure. Musunuru and colleagues (2006) retrospectively reviewed 48 patients with neuroendocrine liver metastases only and evaluated their 3-year survival based on medical management, ablation, and surgical resection. The surgical group had a 3-year survival of 83% compared with 31% in the patients treated with medical therapy or embolization. No difference was reported in the palliation of symptoms among the three treatment groups.

Because of the limited patient population, none of these studies is likely to be validated by a prospective randomized controlled trial. Case-based studies and retrospective reviews are the basis for the current recommendations. Such studies recommend that curative resection in conjunction with an anatomic liver resection should be attempted, when it appears that at least 90% of the tumor burden can be removed based on preoperative imaging (Morrow et al, 2009).

Liver transplantation is an effective therapy for patients with hepatocellular cancer. In PET patients with isolated liver metastases, organ transplantation remains controversial. Lehnert (1998) reported 103 patients with metastatic neuroendocrine tumors who received liver transplants. The overall survival at 1 and 5 years was 61% and 30%, respectively, for the 48 patients with pancreatic islet cell tumors. Recurrence-free survival for all 103 patients was 24% at 5 years. Pretransplant treatment with a somatostatin analogue was found to be a favorable prognostic factor (Lehnert, 1998). The morbidity associated with these procedures can be high as a result of opportunistic infections, and a 10% operative mortality rate has been reported (Marin et al, 2007). There is a high risk of recurrence in the transplanted liver, and liver transplantation is generally reserved for young patients with unresectable isolated liver metastases as the single site of disease and for those who have poor symptom control on medical therapy.

Ablative Therapies for Neuroendocrine Hepatic Metastases

Although surgery remains the most effective therapy for PETs, many patients will be seen later with recurrent disease. The median time to recurrence is 21 months, with 5-year recurrence rates of 84% (Atwell et al, 2005; Sarmiento et al, 2003). At the time of recurrence, less than 10% of patients are candidates for reoperative surgery (Schurr et al, 2007). For this subset of unresectable patients, ablative cytoreductive measures have been attempted. Ablative therapies that include RFA, cryoablation, TACE, and radioembolization have been effective in reducing tumor burden in marginally resectable patients (see Chapters 83, 84A, and 85A through D; Maithel et al, 2009).

Ablative techniques are most efficacious when used for tumors smaller than 4 cm and for deep lesions, for which resection would sacrifice a great deal of normal liver parenchyma; ablative techniques are also beneficial as an adjunct in patients with bilobar disease who undergo anatomic resection of the lobe with the greatest tumor burden. The largest series on RFA therapy showed 95% symptom relief and a 5-year survival rate of 48% (Maithel et al, 2009). This was comparable to resections in which Sarmiento and colleagues (2003) showed a 5-year survival of 61% after aggressive operative removal. Hepatic artery embolization with or without direct infusion of chemotherapeutic agents has been used as an alternative therapy for patients who are not candidates for hepatic resection. Tumors of the liver receive most of their blood supply from the hepatic artery, whereas normal hepatic parenchyma can be sustained mainly from the portal venous circulation. Chemotherapeutic agents used include doxorubicin, cisplatin, mitomycin C, streptozotocin, and 5-fluorouracil (Mansour & Chen, 2004). In retrospective reviews of patients treated with TACE for unresectable liver metastases, response rates range from 66% to 100%, and 5-year survival rates of up to 83% are reported (Roche et al, 2003; Kim et al, 1999). A comparison between simple arterial embolization versus chemoinfused embolization showed no difference in symptom improvement or median overall survival between the two groups (Pitt et al, 2008).

Somatostatin Analogues and Systemic Chemotherapy

Approximately 80% of PETs express somatostatin receptors, and treatment with somatostatin analogues can alleviate symptoms associated with excessive hormone activity in patients with functional PETs. Subtypes of PETs most amenable to treatment with octreotide are glucagonomas, VIP tumors, and, to a lesser extent, gastrinomas and insulinomas. Positive SRS imaging may help predict which patients will respond to somatostatin analogue therapy (Oberg et al, 2004). The most commonly prescribed regimen starts with subcutaneous administration of 50 μg dosed three times per day. Lanreotide, a long-acting somatostatin analogue administered every 10 to 14 days, has been shown to have efficacy similar to that of octreotide (Ricci et al, 2000; Scherubl et al, 1994). Depot formulations of somatostatin analogues are also available that can be administered no more frequently than 4 to 6 weeks apart. These drugs are more difficult to titrate given their long-acting effects. It is not uncommon for patients treated with depot formulations to have "breakthrough" symptoms such that immediate, shorter acting medications must be given until a steady state is achieved.

Somatostatin analogues such as octreotide are generally well tolerated, safe, and have minimal side effects, although an increased incidence of cholelithiasis (up to 50%) is reported with continuous use of these drugs. However, the incidence of acute cholecystitis requring emergent cholecystecomy is rare (0% to 12%). Although it remains controversial, mounting evidence suggests that somatostatin analogues have cytoreductive properties in addition to their ability to control hormone symptoms (Clements et al, 1985; Imtiaz et al, 2000). An interim report at 6 months from an ongoing multiinstitutional, randomized, placebo-controlled trial has shown that 67% of patients receiving therapy had radiographic evidence of stable disease compared with 37% in the placebo group (Rinke et al, 2009). Of the patients included in this trial, 66% had undergone resection of the primary tumor, 74% were octreoscan positive, and 62% had some evidence of liver involvement.

When unresectable disease is found at laparotomy and it is likely that a somatostatin analogue will be used later, cholecystectomy should be considered.

Several trials have studied the role of interferon (IFN) in the treatment of pancreatic endocrine neoplasms. In one series, 57 patients treated with monotherapy IFN had a radiologic response of only 12% and biochemical control in 47%. IFN-alfa stimulates T-cell function and can control hormone secretion by the tumor. Oberg (2000) pooled 13 studies that examined a total of 383 patients with malignant neuroendocrine tumors; the biochemical and tumor response rates were 44% and 11%, respectively, with a disease stabilization rate of 35%. A randomized, prospective study of 80 patients with metastatic neuroendocrine gastroenteropancreatic tumors showed comparable antiproliferative effects among patients treated with somatostatin analogues, IFN-alfa, or a combination of the two (Faiss et al, 2003).

The role for systemic chemotherapy in the treatment of PETs is still undefined. Several different chemotherapeutic agents have been studied, both as single agents and in combination regimens. The most common single agents include streptozotocin, doxorubicin, capecitabine, fluorouracil, and dacarbazine. In the early trials, overall response rates for these single-agent regimens ranged from 20% to 50% (Broder et al, 1973; Moertel et al, 1982; Ramanathan et al, 2001). Combination regimens have shown even more promising outcomes, with overall response rates as high as 81% (Strosberg et al, 2011a). A newer agent, temozolomide, has been shown to have promise in Phase II trials. The combination of this drug with capecitabine in chemo-naive patients illustrated an objective radiographic response rate of 70%, with a median progression-free survival of 18 months (Strosberg et al, 2011b). The limitation of these drugs, either in combination or as single agents, is their associated toxicity. In several of these trials, patients were unable to tolerate the regimens because of complications such as lymphopenia or development of opportunistic infections.

Ki-67 is an immunohistochemical marker of high tumor proliferation. The Ki-67 index has been used to determine tumor grade and prognosis. In fact, a high Ki-67 index has been suggested as a measure to predict which patients would do better with antiproliferative or chemotherapy, even as a first-line treatment (Vilar et al, 2007).

New Drugs and Targeted Therapies

External-beam radiation has been used for the treatment of bulky hepatic metastases. The normal liver has a low tolerance for the levels of radiation needed to kill tumor cells. To minimize this, patients have been treated with targeted radiotherapy through the use of radiolabeled somatostatin analogues. These agents are conjugated to an injectable microsphere that allows high-dose intraarterial administration of the radiolabeled drug in a fashion similar to that used for TACE/transarterial embolization. Results of these studies are highly variable, but partial response rates ranging from 32% to 87% have been reported (Kennedy et al, 2008; King et al, 2008; McStay et al, 2005; Safford et al, 2004). Complete responses were seen in 5% to 18% of patients, and symptomatic improvement occurred in 49% to 61% of patients. The most common symptoms associated with toxicity were fatigue and nausea (Kennedy et al, 2008).

Novel molecular targets are also being studied for their therapeutic potential. PETs are highly vascular tumors that may be inhibited by the use of angiogenesis inhibitors such as bevacizumab, an antibody to vascular endothelial growth factor. In a Phase II trial of 44 patients with advanced carcinoid tumors, the reported progression-free surival rate over 18 weeks was 95% with bevacizumab versus 67% in those treated with IFN (Yao et al, 2008). In a Phase II study, rapamycin, a serine threonine kinase known as mTOR (mammalian target of rapamycin), was recently reported to achieve stable disease in 80% of patients treated during a 9-month period. The median progression-free survival was 17 months. As more is understood about the tumor biology of pancreatic endocrine neoplasms, it is likely more multimodal therapies will be developed.

POSTOPERATIVE SURVEILLANCE

Monitoring for recurrence after therapy is mainly based on serial measurement of tumor-specific markers and imaging. Regardless of the tumor subtype, almost all PETs express some level of chromogranin A (CgA). Every 6 months to 1 year, patients with PETs should have lab tests consisting of a CgA level and blood chemistry tests specific to their endocrine subtype. Patients with gastrinomas should be followed with serial gastrin levels and periodic SRS if their gastrin levels begin to trend upward. Insulinoma patients need only spot glucose checks; further testing should be done if glycopenic symptoms recur. Imaging is indicated when biochemical markers change during the patient's period of surveillance. This is begun by obtaining a baseline CT scan approximately 6 months after resection. Subsequent imaging is done when there is an alteration in the patient's symptom profile as it relates to the type of functional tumor for which the patient was originally treated. SRS is useful in patients with an index suspicion for metastatic disease and when receptor status is not yet known. This latter piece of information can be useful when trying to decide whether the patient is likely to benefit from somatostatin analogue therapy.

References are available at expertconsult.com.

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CHAPTER 62B

Surgery of the pancreas: minimally invasive approaches

Stefan Fritz, Markus W. Büchler, and Jens Werner

OVERVIEW

In recent years, an increasing number of laparoscopic pancreatic surgical procedures have been performed and reported from centers around the world. Even operations that were once considered impossible to perform laparoscopically, such as pancreatoduodenectomy or segmental pancreatic resection, are gaining momentum in a number of centers. With improving surgical techniques and experience, it has become crucial to reevaluate proper indications for laparoscopic pancreatic surgery. Limitations for a minimally invasive approach are often due to technical difficulties and particularly to the characteristics of pancreatic diseases.

Open pancreatic resection is commonly performed through an upper abdominal incision, whereas laparoscopic pancreatic resection is performed through four or five small abdominal incisions. The exposure during open pancreatic surgery involves the use of abdominal wall retractors and mechanical retraction of the abdominal viscera. In contrast, exposure during laparoscopic pancreatic resection is achieved with pneumoperitoneum. By reducing the length of surgical incisions and eliminating the need for mechanical retraction of the abdominal wall and viscera, operative trauma to the abdominal wall during laparoscopic pancreatic surgery can be minimized. However, the lack of direct haptic feedback, fewer degrees of freedom, a narrow working space, and a sometimes difficult orientation conspire to limit the indications for laparoscopic pancreatic surgery. Moreover, the intraabdominal surgical trauma is identical to the open technique and exceeds by far the relatively minor trauma to the abdominal wall. Within this context, the relative benefits of laparoscopic pancreatic resection must be examined critically.

Laparoscopic pancreatic surgery represents one of the most sophisticated applications for laparoscopy currently in use. Recent advances in technology and techniques have opened new gates to a wide range of applications in patients with pancreatic diseases. This chapter describes the laparoscopic techniques available today, including diagnostic laparoscopy, laparoscopic resection techniques, and new technical developments such as robotic approaches.

DIAGNOSTIC LAPAROSCOPY

Diagnostic laparoscopy is a procedure that allows the surgeon to examine directly the contents of a patient's abdomen or pelvis, including the peritoneum, small bowel, large bowel, liver, pancreas, or gallbladder (see Chapter 21). Pancreatic cancer is characterized by an aggressive, infiltrating local tumor growth and early manifestation of metastasis. Consequently, resection with curative intent can be performed in only 10% to 20% of patients with newly diagnosed pancreatic cancer.

Although staging of pancreatic cancer is critical to the planning of therapy and has improved over the past decades, especially as a result of better imaging techniques, there are still some patients in whom liver or peritoneal metastases are not detected during preoperative testing. Even with modern thin-sliced computed tomography (CT) or magnetic resonance imaging (MRI), detecting hepatic or peritoneal metastases smaller than 5 mm is difficult and often impossible. Likewise, assessing local tumor extent and the degree of infiltration into adjacent organs remains challenging. In these cases, diagnostic laparoscopy is useful for assessing whether the patient is a candidate for curative resection or radiotherapy. In addition to the possibility of obtaining peritoneal fluid for cytology, following instillation of saline into the peritoneal cavity, laparoscopic ultrasonography (US) can be performed. This technique enables the detection of locally advanced disease and intraparenchymal liver involvement and gives a good indication of vascular involvement (Menack et al, 2001). Consequently, in many cases a primarily planned surgical pancreatic resection can be aborted with minimal surgical trauma. At the same time, tissue samples for histologic evaluation can be achieved from distant metastases and from large tumors, particularly when the body or tail of the pancreas is involved.

Overall, the indications for a staging laparoscopy in pancreatic cancer are 1) large primary lesions in the neck, body, or tail of the pancreas; 2) radiographic findings suggestive of occult metastases or a possible carcinomatosis; 3) small, hypodense regions in the hepatic parenchyma suspicious for liver metastases; and 4) subtle clinical and laboratory findings suggesting more advanced disease (Pisters et al, 2001). In eliminating nontherapeutic laparotomy and redirecting treatment plans, laparoscopy contributes significantly both to the proper management of patients with pancreatic cancer and to increased efficiency of resource utilization (Warshaw et al, 1986).

HISTORY OF LAPAROSCOPIC PANCREATIC SURGERY (SEE CHAPTER 62A)

The slow progress of laparoscopy in pancreatic surgery in the past has been attributed to the retroperitoneal location of the gland, its proximity to various important vascular structures and organs, the friable nature of the gland, and the difficulty in its exposure. Similar to experiences with sigmoid colon resections, which were first performed in benign diseases such as recurrent sigma diverticulitis, laparoscopic pancreatic resections were initially performed for benign tumors. In particular, benign endocrine tumors less than 1 cm (e.g., insulinomas) or

small cystadenomas predominantly located in the distal body and tail of the pancreas were ideally suited for the laparoscopic approach. In such cases, the surgical specimen is relatively small and contrasts greatly with the size of the abdominal incision required to access this retroperitoneal gland at conventional open surgery. Furthermore, enucleation or atypical resection can often be performed to remove small pancreatic lesions without the need for an anastomosis (Ammori, 2003).

Currently, laparoscopic resection can be performed both for benign and malignant pancreatic diseases. For benign tumors, left resections or enucleations can be often performed without difficulty. On the other hand, resections that require an anastomosis or those for malignant tumors that require an adequate margin and associated lymph node dissection remain tremendously challenging. Because lymphadenectomy in pancreatic cancer is technically difficult, especially along the celiac trunk and the superior mesenteric artery, few surgeons perform laparoscopic resections for malignant disease on a routine basis. Although many reports have demonstrated technical feasibility, it must be stated that not everything that can be done should be done. Sophisticated pancreatic resections such as pancreatoduodenectomy are only performed in highly select cases by exceptionally skilled laparoscopic surgeons to achieve a satisfying postoperative outcome (Gagner & Palermo, 2009). Because the challenge in pancreatic surgery for malignant disease is to achieve an R0 resection, even in advanced cases requiring vascular and/or multivisceral resections, we feel that the potential benefit of laparoscopic resections does not outweigh the risk in patients with cancer.

LAPAROSCOPIC PANCREATIC RESECTIONS

Pancreatic Left Resection

Surgical Technique

Distal pancreatic resection has been performed for the treatment of patients with chronic pancreatitis and benign and malignant tumors in the tail or body of the pancreas. Initially, distal pancreatectomy was performed en bloc with the resection of the spleen. This technique was preferred by surgeons for technical as well as oncologic reasons. Because resection of the spleen has been reported to impair the immune system and could predispose to infective complications after distal pancreatectomy and splenectomy (Holdsworth et al, 1991), Kimura and colleagues (1996) developed a technique of preserving both the splenic artery and vein. In addition, Warshaw (1988) described a technique of distal pancreatectomy in which splenic vessels are ligated both at the level of transection of the pancreas and again at the splenic hilum, leaving the spleen to survive on blood flow through the short gastric vessels.

Over the past few years, the technique of laparoscopic pancreatic left resection has been introduced and refined. Many different methods have been described for trocar placement and surgical technique. In the technique used in Heidelberg, the patient is placed in a half-lateral position with the left side up. The surgeons stand on the right side of the patient, and the camera operator and scrub nurse stand on the opposite side. Four 10- to 12-mm trocars are inserted in the abdominal wall 3 to 4 cm above the umbilicus on the xiphoid area, subcostal on the midaxillary line, and subcostal to the midclavicular line. The first step is dissection of the splenorenal ligament; the splenic flexure of the colon is then mobilized downward. The gastrocolic omentum is widely opened along the gastroepiploic arcade up to the level of the mesenteric vessels, and the body and tail of the pancreas are then visualized (Fig. 62B.1). The inferior border of the pancreas is dissected, and the body and tail of the pancreas are completely detached from the retroperitoneum (Fig. 62B.2). This mobilization of the left pancreas allows visualization of the posterior wall of the gland, where the splenic vein is easily identified (Fig. 62B.3). The splenic vein is pushed away from the posterior pancreatic wall by gentle blunt dissection, and a tunnel is created between the splenic vein and the pancreas. The splenic artery is identified through this space by using careful blunt dissection with a curved dissector. Alternatively, the artery can be identified at the superior margin of the pancreas (Fig. 62B.4).

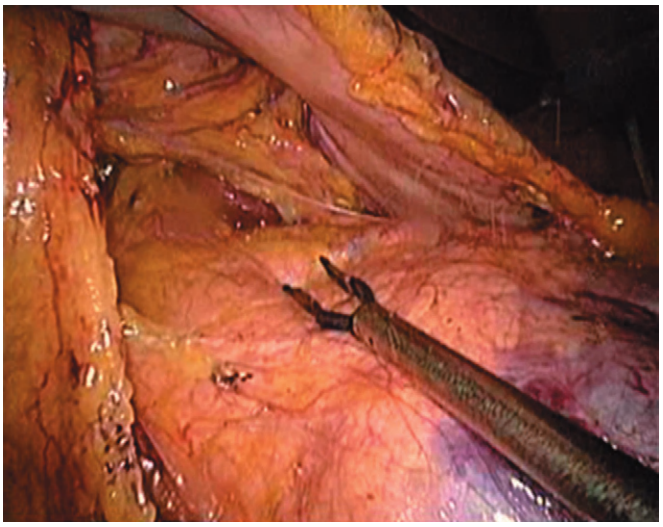


FIGURE 62B.1. Division of the gastrocolic ligament and entry into the lesser sac allows visualization of the body of the pancreas. *(Courtesy Dr. Bryce Gayet.)*

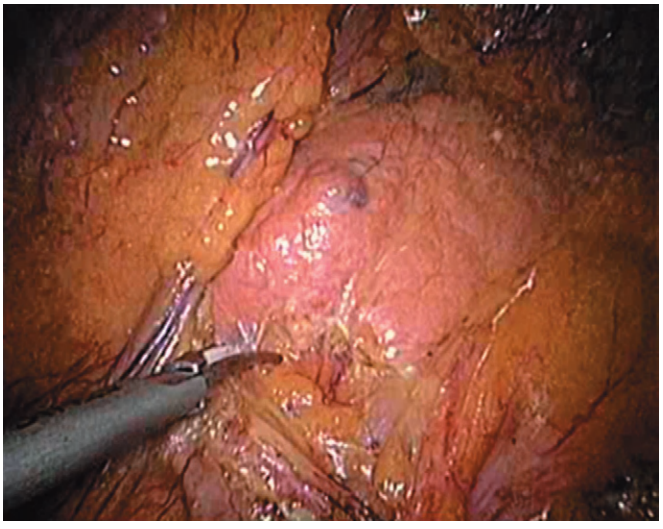


FIGURE 62B.2. Mobilization of the inferior border of the pancreas in preparation for identification of the splenic vessels. *(Courtesy Dr. Bryce Gayet.)*

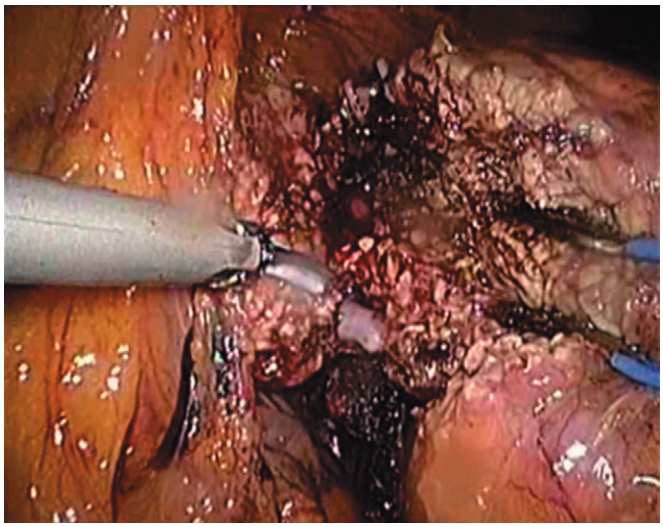


FIGURE 62B.3. Dissection of the splenic vein. In this view, the pancreas has already been divided. *(Courtesy Dr. Bryce Gayet.)*

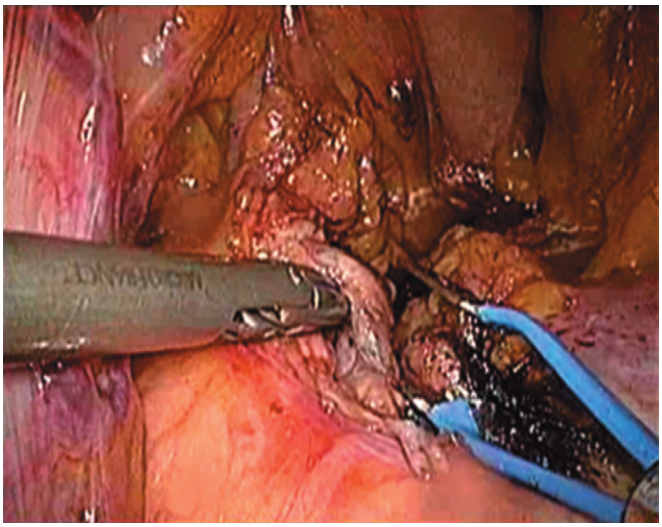


FIGURE 62B.4. The splenic artery is identified above the pancreas and is dissected in preparation for division. *(Courtesy Dr. Bryce Gayet.)*

Next, the tail of the pancreas is grasped and retracted anteriorly. Traction is applied to expose the small branches of the splenic artery and vein, which are coagulated with the LigaSure device (Covidien, Mansfield, MA). The vascular area connecting the end of the tail of the pancreas and the spleen is transected. The left pancreas is then lifted up and mobilized posteriorly with the splenic artery and vein, which are clipped and divided or transected with an Endo-GIA stapler (Covidien) as they emerge from the pancreatic tail to enter the hilum of the spleen (Fernandez-Cruz, 2006). At the end, the pancreas is transected with an endoscopic linear stapler when the pancreas is soft and not too thick. Alternatively, the pancreas may be cut with scissors or with a LigaSure, with a separate suture applied directly to pancreatic duct.

Outcome of Laparoscopic Pancreatic Left Resection

It has been convincingly shown that laparoscopic distal pancreatectomy is feasible with short- and long-term outcomes similar to open distal pancreatectomy (Kooby et al, 2010). Table 62B.1 gives an overview of recent series of more than 50 laparoscopic left pancreatic resections. In experienced hands, the laparoscopic approach has been associated with shorter operating times, early return of bowel function, minimal narcotic requirements, and early resumption of normal activities (Fernandez-Cruz et al, 2002). Sufficient experience and data confirm that laparoscopic distal pancreatectomy can be recommended as the treatment of choice for benign and noninvasive lesions in experienced hands when clinically indicated (Rosok et al, 2010); however, it is difficult to make a clear statement concerning malignant pancreatic tumors because of the lack of conclusive data (Merchant et al, 2009). An important problem leading to conversion in many studies has been the difficulty in localizing small tumors by laparoscopy or laparoscopic US.

Tumor Enucleation

Surgery is the only potentially curative treatment for pancreatic endocrine tumors amenable to resection. With the exception of gastrinomas and somatostatinomas, which are frequently localized in the head of the pancreas, neuroendocrine tumors are located predominantly in the body and tail of the pancreas. This location makes these tumors suitable for a laparoscopic surgical approach. In many cases, especially in sporadic insulinomas and if tumor size does not exceed 2 cm, laparoscopic enucleation can be performed safely (Bozbora et al, 2004). Other functioning and nonfunctioning neuroendocrine tumors should be managed with extended pancreatic resection, including peripancreatic lymph node dissection, because the malignant potential must be considered. In preoperative examination, a combination of dynamic CT and selected angiography leads to a correct diagnosis in 70% to 90% of patients (Cuschieri et al, 1996). Tumors located in the pancreatic body and tail, distant from the splenic vessels and the main pancreatic duct, are good

Table 62B.1

Published Series of More than 50 Cases of Distal Pancreatectomy

First Author	Year of Publication	No. Patients	Conversion (%)	Complications (%)	Pancreatic Fistula (%)	Length of Stay (Days)	Mortality Rate (%)
Mabrut (multicenter, Europe)	2005	82	14	31	17	7	0
Melotti	2007	58	0	53	28	9	0
Fernandez-Cruz	2007	82	7	21	8	7	0
Kooby (multicenter, US)	2008	167	13	40	11	6	0

candidates for laparoscopic enucleation if no findings of malignancy are detected on preoperative staging (Tihanyi et al, 1997).

Surgical Technique

The position of the patient and the trocar sites are the same as for distal pancreatectomy. Intraoperative US is required to confirm the location of the tumor and the absence of other lesions. If the tumor is located close to the splenic vessels, the main pancreatic duct, or the bile duct, enucleation should be abandoned in favor of a formal resection (Kano et al, 2002). For dissection of the tumor from the pancreatic parenchyma, some surgeons prefer the use of a Harmonic Scalpel (Ethicon, Somerville, NJ) or Ligasure. Because enucleations have a high risk of postoperative fistula, mainly type A fistula, a drain should be placed adjacent to the side of the enucleation.

Pancreatoduodenectomy (See Chapter 62A)

Although the first successful pancreatoduodenectomies were performed in 1912 and 1934 by Walter Kausch and Allan Whipple, respectively, the first attempt at laparoscopic pylorus-preserving pancreatoduodenectomy (PPPD) has been credited to Gagner and Pomp (1994). Today, a number of laparoscopic pancreatoduodenectomies or Whipple procedures have been performed in different centers with reasonable outcomes; therefore, no doubt remains that the Whipple procedure can be performed by laparoscopy.

Surgical Technique

The laparoscopic technique for a Whipple procedure represents a modification of the Traverso and Longmire (1978) description of the PPPD. Under general anesthesia, the patient is placed in a supine position with the legs abducted. An endoscope is inserted over a trocar at the umbilicus to examine the peritoneal cavity, liver, stomach, and mesentery vessels, and four to six more trocars are inserted under direct vision in the epigastrium and upper quadrants. The surgical dissection is performed with the usual laparoscopic devices: Harmonic Scalpel, LigaSure, bipolar cautery, and clips.

The main difficulty of the resection phase is the complete lymphadenectomy, especially along the celiac trunk and superior mesenteric artery. The major difficulty with the operation, however, is the reconstruction. The pancreatojejunostomy or pancreatogastrostomy are the most problematic anastomoses, even in the conventional open technique. The soft pancreas with a small duct is especially problematic because the haptic feedback during the anastomosis is missing in laparoscopic surgery. Thus some surgeons use a hybrid technique with a small abdominal incision for the reconstruction.

A positive correlation has been shown between postoperative mortality and morbidity and the experience of a surgeon and volume of a center (Birkmeyer et al, 2002). This is probably also true for the laparoscopic pancreatic resection; however, larger series that investigate this relationship have yet to be undertaken.

Outcome of Laparoscopic Pancreatoduodenectomy

The first laparoscopic PPPD was performed in 1992 and took at least 10 hours, even for a highly skilled endoscopic surgeon (Gagner & Pomp, 1994). The patient's postoperative course was complicated by delayed gastric emptying, resulting in a 30-day hospitalization. Cuschieri (1994) also reported two cases of PPPD with disappointing postoperative outcomes, including pancreatic fistula and delayed gastric emptying. Nevertheless, several centers with expert surgeons continued to perform this complicated procedure, and between 1994 and 2008, a total of 146 laparoscopic Whipple procedures were reported in scientific literature.

Reviewing the existing literature, Gagner and Palermo (2009) have shown that this complex surgical procedure can be performed laparoscopically with acceptable complication rates in selected patients. In the series described, the mean operating time was 439 minutes, average blood loss was 143 mL, and median hospital stay was 18 days. Postoperative complications included 2 hemorrhages, 4 bowel obstructions, 1 stress ulcer, 1 delay of gastric emptying, 4 pneumonias, and 11 leaks. Although laparoscopic pancreatoduodenectomy and laparoscopic duodenum-preserving pancreatic head resection are technically feasible, laparoscopic reconstruction after proximal pancreatectomy is not yet generally practiced because performance is limited to highly skilled endoscopic surgeons. To justify the performance of laparoscopic proximal pancreatectomy, it is mandatory to demonstrate the potential clinical benefits and safety of such a complicated procedure (Takaori & Tanigawa, 2007). Furthermore, in patients with pancreatic cancer, it yet has to be validated whether radical lymph node dissection is feasible in the same manner and extent as open surgery.

LAPAROSCOPIC PALLIATIVE PROCEDURES FOR PANCREATIC CANCER (SEE CHAPTER 63B)

Currently, endoscopic biliary stenting is the most widely performed procedure for palliation in patients with malignant biliary obstruction as a result of pancreatic cancer. However, patients with endobiliary prostheses who survive for a long time have a significant risk of stent obstruction. In patients expected to have a prolonged survival, laparoscopic biliary decompression can be performed and is a reasonable consideration. The main types of surgical palliation of malignant biliary obstruction are choledochoenterostomy and cholecystoenterostomy. With regard to outcomes and complications, choledochoenterostomy has been shown to be better than cholecystoenterostomy (Sarfeh et al, 1988). Although both procedures have been described to be feasible laparoscopically, the cholecystoenterostomy is technically easier to perform (Sussman et al, 1996). Nevertheless, because cholecystoenterostomy would never be used in conventional open surgery, this compromise should not be accepted in laparoscopic surgery either, and an inferior operation should not be performed only because it is easier.

In patients with locally advanced and inoperable pancreatic cancer, whether associated with gastric outlet obstruction or not, a retrocolic gastrojejunostomy should be added to a biliary bypass. Today, gastroenterostomy can be performed laparoscopically with acceptable outcomes (Rhodes et al, 1995). Where it is not feasible or meaningful to perform a gastroenterostomy because of extensive peritoneal disease, particularly that involving the bowel in the lower abdomen, a palliative stoma must be considered to ensure gastrointestinal patency. It has been reported that a palliative stoma done laparoscopically has significantly better outcomes in terms of postoperative morbidity and mortality compared with the open surgical procedure

(Scheidbach et al, 2009). However, laparoscopic palliation of locally advanced pancreatic cancer always demands a high level of technical expertise and should be limited to performance by experts in specialized centers (Gentileschi et al, 2002).

ROBOTIC APPROACHES FOR PANCREATIC RESECTIONS

Recently, it has been reported that laparoscopic pancreatic surgery can be performed with robotic assistance. A single-center study analyzed the charts of 134 patients who underwent robotic-assisted surgery for different pancreatic pathologies with the DaVinci system (Intuitive Surgical, Sunnyvale, CA) (Giulianotti et al, 2010). The authors showed that complication and mortality rates were comparable to those of open surgery but with the advantages of minimally invasive surgery. In another series of 17 robotic-assisted distal pancreatectomies, a shorter length of stay in robotic versus laparoscopic or open approaches has been reported. Furthermore, in this study, spleen preservation rates improved with a robotic approach at the expense of increased operative time. The authors conclude that robotic distal pancreatectomy is safe and cost effective in selected cases (Waters et al, 2010), although the indication for robotic surgery in pancreatic disease has been controversial, particularly considering the cost of robotic procedures compared with laparoscopic resection. Further experience and randomized clinical trials are clearly needed to evaluate the benefit of this surgical approach. In addition, the cost-benefit comparison needs to be assessed for this expensive method.

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CHAPTER 63A

Chemotherapy and radiotherapy for pancreatic and periampullary cancer: adjuvant, neoadjuvant, and palliative

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ADJUVANT CHEMORADIOTHERAPY

Early studies examining the role of combined external-beam radiotherapy (EBRT) with 5-fluorouracil (5-FU) as a radiosensitizing agent in advanced, unresectable pancreatic adenocarcinoma showed an increased median survival over that of solo EBRT (Douglas et al, 1979; Moertel et al, 1981). Subsequently, combination chemoradiotherapy (CRT) was used in patients who had undergone potentially curative resection for pancreatic adenocarcinoma. The Gastrointestinal Tumor Study Group trial 9173 (Kalser & Ellenberg, 1985) randomized 43 patients to either CRT (40-Gy EBRT, combined with 5-FU and follow-on 5-FU) or no adjuvant treatment after potentially curative pancreatic resection; recruitment was slow and only 43 patients were enrolled after 8 years instead of the intended 150. Median, 2-year, and 5-year survival rates were all increased in the treatment group (Table 63A.1). This trial had several problems, chief among them being poor compliance and inadequate quality assurance, with only 9% of patients completing the intended 2 years of chemotherapy; 32% had violations of the radiation therapy. To increase numbers, another 30 patients were entered into the treatment group without randomization (Douglas et al, 1987). Several subsequent studies have all shown similar advantages (Conlon et al, 1996; Neoptolemos et al, 1998; Yeo et al, 1998), although all were underpowered.

Two studies, however, have countered these results. Bakkevold and colleagues (1993) prospectively randomized 61 patients who had undergone radical pancreatic resections (including 14 patients with periampullary lesions) to adjuvant combination chemotherapy with 5-FU, adriamycin, and mitomycin-C versus observation; no postoperative EBRT was used. Although the median survival and 2-year survival were increased in the treatment groups, the overall long-term cure rate was unaffected (see Table 63A.1).

Later, on behalf of the European Organisation for Research and Treatment of Cancer (EORTC), Klinkenbijl and colleagues (1999) randomized 218 patients following potentially curative resection for pancreatic cancer to CRT (40-Gy EBRT and 5-FU, no follow-on 5-FU) or no adjuvant treatment. This included 114 patients with pancreatic head cancer and 93 with periampullary cancer. Of the patients with pancreatic head cancers, no significant increase in median survival was found between the two groups (see Table 63A.1).

These early studies set the scene for the European Study Group for Pancreatic Cancer (ESPAC) to conduct a randomized trial of adjuvant chemotherapy and chemoradiotherapy in resected pancreatic cancer. The design was as a 2×2 factorial trial in which patients were randomized twice to either chemotherapy (bolus 5-FU for six cycles) or no chemotherapy *or* to chemoradiation (fractionated 20-Gy EBRT plus an intravenous bolus of 5-FU) or no chemoradiation. This totaled 549 patients from 61 cancer centers in 11 countries, thus making it, at the time, the largest adjuvant therapy trial in pancreatic cancer ever completed. A total of 289 patients were randomized into the 2×2 factorial design, and 261 additional patients were randomized to either chemotherapy or chemoradiation versus observation outside the original design (ESPAC-1 plus).

ESPAC-1 has been criticized largely because of confusion over the 2×2 trial design; nonetheless, data from both patient datasets are relevant (Neoptolemos et al, 2001, 2004) and are suggestive of the benefit of chemotherapy (Table 63A.2 and Fig. 63A.1), evident in resection margin–positive (R1) as well as resection margin–negative (R0) patients. Two subsequent meta-analyses have confirmed this advantage, suggesting a reduction in risk of death in postresection pancreatic cancers of 25% (hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.64 to 0.90; $P = .001$) (Stocken et al, 2005) and an advantage of postresectional chemotherapy in patients with an R0 margin over those with an R1 margin (Butturini et al, 2008). Moreover, the reported that survival advantage for adjuvant chemotherapy was maintained when adjusted for quality of life over the 24-month period after resection (Carter et al, 2009).

Since the usurpation of 5-FU as the gold standard of chemotherapy for pancreas cancer, current focus has centered on the use of gemcitabine as a radiosensitizer and also on the use of biologic agents. The Radiation Therapy Oncology Group (RTOG) (Regine et al, 2006) conducted a Phase III trial, study 9704, of 538 patients (443 analyzed, with 388 having cancer in the head of the pancreas) based on chemoradiation (50.4-Gy EBRT with 5-FU) combined with either 5-FU or gemcitabine, 3 weeks before CRT and 12 weeks after. Although both the median and 3-year survival rates were increased in the group receiving gemcitabine, these increases were not significant. Analysis of the 388 patients with pancreatic head cancer suggested a 21% reduction in risk of death in the gemcitabine arm (HR, 0.79; 95% CI, 0.63 to 0.99; $P = .047$). Although this was

Table 63A.1

Summary of Findings from Major Studies Examining the Effect of Adjuvant Chemoradiotherapy

Reference	No. Patients	Regimen	Median Survival (mo)	2-Year Survival	3-Year Survival	5-Year Survival
GITSG (Kalser & Ellenberg, 1985)	21	60-Gy ERBT, 5-FU, follow-on 5-FU	20	42	—	—
	22	Observation	11	15	—	—
Douglas et al, 1987	30	60-Gy ERBT, 5-FU, follow-on 5-FU	18	46	—	—
Bakkevold et al, 1993	30	5-FU, adriamycin, mitomycin-C	23*	32	30	8
	31	Observation	11	43	27	4
EORTC (Klinkenbijl et al, 1999)	60	40-Gy ERBT, 5-FU	17.1†	37†	—	20†
	54	Observation	12.6	23	—	10

*$P = .04$
†$P = .09$
EBRT, external-beam radiation therapy; 5-FU, 5-fluorouracil; GITSG, Gastrointestinal Tumor Study Group; EORTC, European Organisation for Research and Treatment of Cancer

suggestive of the advantage of gemcitabine, a greater proportion of T3 tumors and higher toxicity were reported in this arm. In response, the EORTC 40013 Phase III trial plans to randomize 538 patients after R0 pancreatic resection to either gemcitabine or two cycles of gemcitabine followed by CRT (gemcitabine and 50.4-Gy EBRT).

A phase III trial of postoperative cisplatin, interferon alpha-2b, and 5-FU combined with external radiation treatment versus 5-FU alone for patients with resected pancreatic adenocarcinoma randomized 110 patients after pancreatectomy to either 5-FU, cisplatin, interferon-$\alpha_2\beta$, and EBRT (50.4 Gy) with two follow-on cycles of 5-FU post-CRT (arm A) or 5-FU/folinic acid (arm B). Median overall survival of patients treated in arm A was 32.1 months (95% confidence interval [CI], 22.8 to 42.2) compared with 28.5 months (95% CI, 19.5 to 38.6) for arm B. Unfortunately, this underpowered trial was not able to address satisfactorily the significance of adjuvant chemoradiation plus interferon. Further trials are required to confirm these effects.

Finally, RTOG0848 is opening a Phase III trial, recruiting 950 patients with resected adenocarcinoma of the pancreas, including intraductal papillary mucinous neoplasms (IPMNs), to either five cycles of gemcitabine or five cycles of gemcitabine with erlotinib. Patients with no progression will receive either one further cycle of chemotherapy or one cycle of chemotherapy followed by EBRT plus either 5-FU or capecitabine.

Overall, the use of chemoradiation remains controversial, but many U.S. centers continue to support adjuvant chemoradiotherapy as standard treatment (Twombly, 2008).

ADJUVANT CHEMOTHERAPY

ESPAC-1 has provided the clearest evidence to date that adjuvant chemotherapy is advantageous (see Table 63A.2) when based on regimens of biomodulated 5-FU. The advance made by ESPAC-1 has driven forward the next generation of adjuvant chemotherapy trials, notably ESPAC-3 (v2) and ESPAC-4 in addition to translational run-offs (ESPAC-T plus and ESPAC-4T).

Evidence that emerged during the 1990s showed the usefulness of gemcitabine in pancreatic cancer, initially in the setting of advanced disease (Berlin et al, 2002; Burris et al, 1997; Carmichael et al, 1996; Casper et al, 1994; Hertel et al, 1990; Huang et al, 1991; Rothenberg et al, 1996). Recently, a large, multicenter, Phase III randomized trial of 386 patients was undertaken to determine the influence of adjuvant gemcitabine

Table 63A.2

Summary of the ESPAC-1 Data (2004)

Modality	Median Survival (mo)	2-Year Survival (%)	5-Year Survival (%)
ESPAC-1 2 × 2: Final Analysis			
Chemoradiotherapy	15.9	28.5	10
No chemoradiotherapy	17.9	41.4	19.6*
Chemotherapy	20.1	39.7	21.1
No chemotherapy	15.5	30	8.4†
Observation	16.9	38.7	10.7
ESPAC-1: Individual Groups			
Chemoradiotherapy	13.9	21.7	7.3
Chemotherapy	21.6	44	29‡
Chemoradiotherapy + follow-on chemotherapy	19.9	35	13.2

*$P = .053$
†$P = .009$
‡$P = .0005$
ESPAC, European Study Group for Pancreatic Cancer

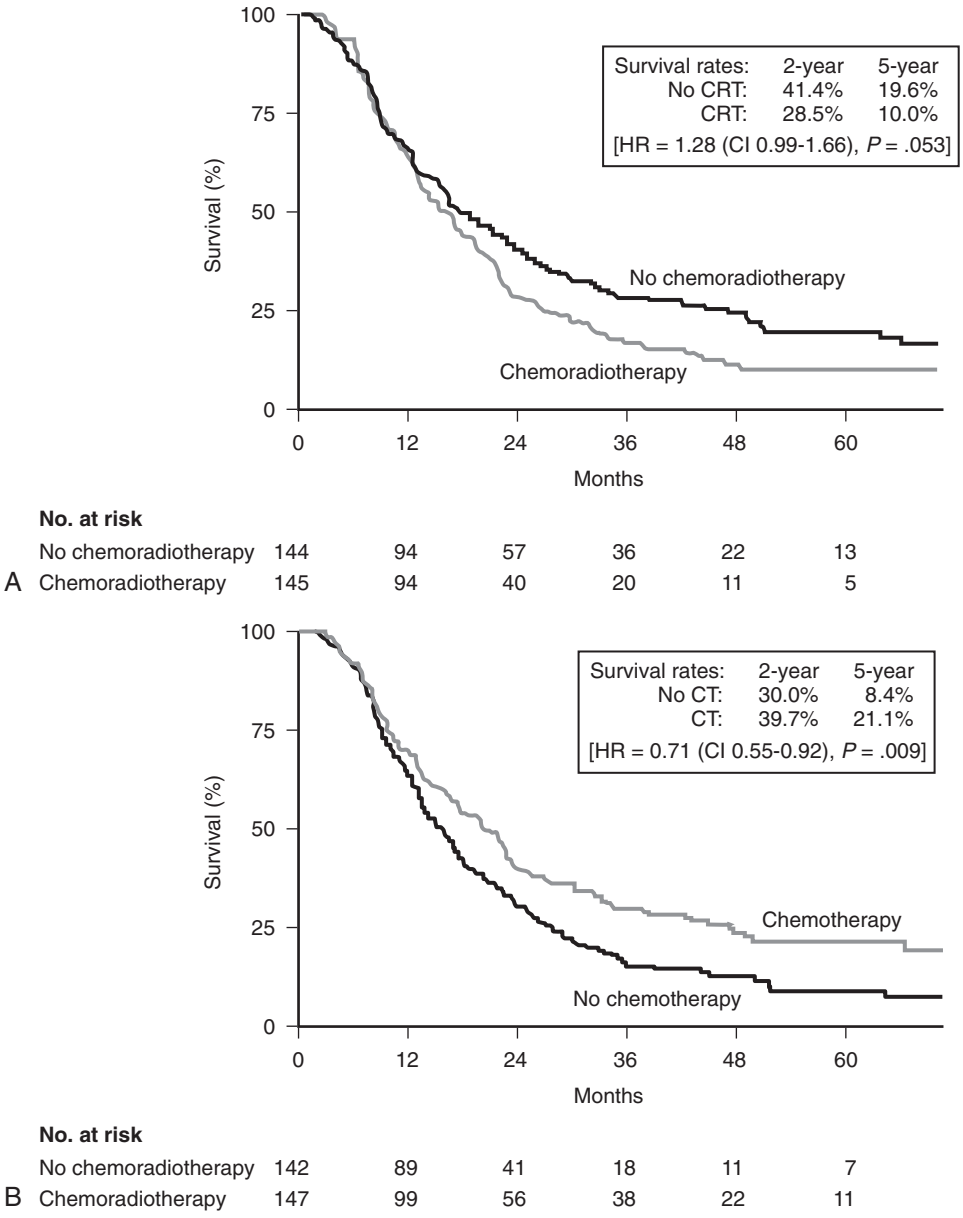


FIGURE 63A.1. Results from ESPAC-1 2 × 2 factorial design. *CRT,* chemoradiotherapy; *CT,* chemotherapy. *(Modified from Neoptolemos JP, et al, 2004: A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 350:1200-1210.)*

versus observation following resection of pancreatic cancer on disease-free survival (CONKO-001) (Oettle et al, 2007; Neuhaus et al, 2008). Median disease-free survival for the gemcitabine group was 13.4 months compared with 6.9 months for the observation arm ($P < .001$); these data are summarized in Table 63A.3. The estimated disease-free survival at 3 and 5 years was 23.5% and 16.5% in the gemcitabine group versus 7.5% and 5.5% in the observation group, respectively. In addition, a significant improvement in median overall survival of 24.2 months was reported with gemcitabine compared with observation alone (20.5 months; $P = .02$). Estimated overall survival at 3 and 5 years was 34% and 22.5% for gemcitabine patients versus 20.5% and 11.5% for observation patients, respectively. These results were suggestive of prolonged disease-free survival in patients undergoing R0 or R1 resection for pancreatic cancer. These earlier studies formed the basis for the ESPAC-3 study.

ESPAC-3 initially was designed with three arms: six cycles of 5-FU versus six cycles of gemcitabine versus observation, with a recruitment target of 330 patients. With the publication of the ESPAC-1 results, a definite survival advantage for adjuvant chemotherapy after resection of pancreatic ductal adenocarcinoma was apparent over observation alone; the trial design was therefore amended, with the observation arm being dropped. The recruitment targets for the remaining two arms were increased to 515 patients each for a total of 1030 patients with pancreatic ducal adenocarcinoma, and the trial was renamed ESPAC-3 (v2). ESPAC-1 had been underpowered to determine the role of adjuvant therapy in less common malignancies such as bile duct cancers and ampullary tumors; therefore the observation arm of ESPAC-3 was continued for these patients. The trial closed after having recruited 1583 patients, with 1088 having ductal adenocarcinoma. Overall, no difference was

Table 63A.3

Comparison of Major Trials Using Combination Chemotherapy or Solo Chemotherapy for Resected Pancreatic Cancer

Reference	No. Patients	Regimen	Median Survival (Mo)	2-Year Survival (%)	3-Year Survival (%)	5-Year Survival (%)
Bakkevold et al, 1993	30	5-FU, adriamycin, mitomycin-C	23 ($P = .04$)	32	30	8
	31	Observation	11	43	27	4
Takada et al, 2003	81	5-FU, mitomycin-C	—	—	—	11.5
	77	Observation	—	—	—	18
Kosuge et al, 2006	45	5-FU, cisplatin	12.5	—	—	26.4
	44	Observation	15.8	—	—	14.9 ($P = .94$)
Oettle et al, 2007	133	Gemcitabine	13.4*	30.5*	23.5*	16.5*
	161	Observation	6.9*	14.5*	7.5*	5.5*
Neoptolemos et al, 2009b	233	5-FU/FA†	23.2	49	—	24
	225	Observation	16.8	37	—	14

*Disease-free survival, $P < .001$

†Hazard ratio 0.70; 95% confidence interval, 0.55 to 0.88; $P = .003$

5-FU, 5-fluorouracil; FA, folinic acid

found between 5-FU/FA and gemcitabine by treatment ($P = .39$), treatment effect by R status ($P = .56$), or by progression-free survival ($P = .44$). However, significant advantages were found from the use of gemcitabine, notably its significantly reduced side effects and toxicity profiles (Neoptolemos et al, 2009a, 2009b); thus the current recommendation for adjuvant chemotherapy in pancreatic ductal adenocarcinoma is gemcitabine (see Table 63A.3).

Currently, interest lies in the use of capecitabine, a prodrug for 5-FU. It is sequentially metabolized into active 5-FU by enzymes highly expressed in both liver and tumor, notably the last enzyme in this cascade, thymidine phosphorylase. This has four potential advantages: 1) systemic side effects are reduced, 2) high concentrations are achieved in the vicinity of the tumor, 3) oral capecitabine has a pharmacokinetic profile similar to that of a continuous systemic infusion 5-FU, and 4) patients tolerate it better than 5-FU. Unfortunately, the effects of solo capecitabine seem minimal: clinical response in 24% and tumor response in 7% (Cartwright et al, 2002). Better responses have been observed when capecitabine and gemcitabine were combined. Eighty-three patients were randomized to either biweekly gemcitabine or biweekly gemcitabine and daily oral capecitabine for a duration of 6 months (Scheithauer et al, 2003). Although no increase was seen in median survival, a 33% increase in clinical benefit response was reported in the combination group.

This effect will be explored in the forthcoming ESPAC-4 study, which aims to recruit 1080 patients who have undergone curative resection for pancreatic ductal adenocarcinoma within the previous 12 weeks. Randomization will be either to six cycles of gemcitabine or to six cycles of gemcitabine plus 24 weeks of capecitabine. The primary end point is length of survival with secondary end points of toxicity, quality of life, 2-year survival, 5-year survival, and relapse-free survival.

The effects of combining chemotherapeutic agents are measured against the solo effects of the current gold standard drugs. Bakkevold and colleagues (1993) randomized patients who had undergone pancreatic resection to FAM (5-FU, adriamycin, and mitomycin-C) or observation. Although a significant increase was reported in median survival (23 vs. 11 months; $P = .04$), no increase in 3- or 5-year survivals was reported. Excessive toxicity was noted, and only 56% of the treatment group completed the six courses of chemotherapy (see Table 63A.3). Takada and colleagues (2003) enrolled 508 patients with mixed pancreatobiliary cancers (173 with pancreatic cancer) and randomized them to either surgery alone or surgery with combined mitomycin-C and 5-FU. The 5-year survival rates were 18 months and 11.5 months, respectively. Of note was the use of oral 5-FU, which has lower efficacy as a result of first-pass hepatic metabolism when compared with intravenous administration.

Kosuge and colleagues (2006) undertook a multicenter, randomized trial of surgery versus surgery and combination cisplatin and 5-FU. They concluded that although cisplatin and 5-FU were safe and well tolerated, the combination conferred no clear survival benefit over monotherapy (see Table 63A.3). As yet, no convincing evidence shows any benefit of combination chemotherapy over standard monotherapy based on either or both of these agents (Magee et al, 2002), and good evidence shows increased severity of side effects in combined regimens (Ghaneh et al, 1999).

INTRAOPERATIVE RADIOTHERAPY

The effect of EBRT on the pancreatic bed is limited by the immediacy of radiosensitive structures; the use of intraoperative radiotherapy (IORT) should reduce this effect. Studies that have explored IORT are small and have heterogenous populations, such that conclusions are hard to reach (Coquard et al, 1997; Fossati et al, 1995; Hiraoka et al, 1990; Reni et al, 2001; Shibamoto et al, 1996; Showalter et al, 2009; Zerbi et al, 1994). RTOG gave 20 Gy of IORT with EBRT (a total of 50.4 Gy) to 51 patients with advanced pancreatic cancer. Results showed a disappointing median survival of 9 months (Tepper et al, 1991). Sindelar and Kinsella (1986) similarly showed a median survival of only 12 months in patients treated with surgery or surgery and IORT. There are reports (Valentini et al, 2009), however, of long-term control and survival in operated patients receiving IORT, although such data are contaminated, with 24% of patients receiving preoperative and postoperative EBRT. Nonetheless, preoperative chemotherapy with surgery and

Table 63A.4

Summary of 5-FU–Based Neoadjuvant Chemoradiation Studies

Reference	Regimen	No. Patients Given nCRT	No. Patients Undergoing Resection	No. Patients Resected	R/LN Status	Median Survival (mo)	Long-Term Survival
Evans et al, 1992	50.4-Gy EBRT, 5-FU	28	21	17		18	
Yeung et al, 1993	50.4-Gy EBRT, 5-FU, mitomycin-C	26	26	10	All R0, 1 LN+		58% at 5 years
Hoffman et al, 1998	50.4-Gy EBRT, 5-FU, mitomycin-C	53	41	24		15.9 resected (9.7 unelected)	27% at 2 years
Pisters et al, 1998	30-Gy EBRT, 5-FU + 10- to 15-Gy IORT	35	27	20		25	23% at 3 years
Snady et al, 2000	54-Gy EBRT, 5-FU, cisplatin, streptozotocin	68	30	20		23.6	
	Adjuvant CRT in 39 (5-FU/FA + RT); adjuvant CT in 24 (5-FU/FA)			91		14	
White et al, 2001	45-Gy EBRT 5-FU (± mitomycin-C), (± cisplatin)	111	53 (PR) 58 (LA)	28 (PR) 11 (LA)	71% R0, 70% LN– 73% R0, 60% LN–		
Magnin et al, 2003	30- to 45-Gy EBRT 5-FU, cisplatin	32	19	19		30	59% at 2 years; 2-year DFS, 43.7%
Mornex et al, 2006	50-Gy EBRT, 5-FU, cisplatin	41	36	26	80% R0	9.4	20% at 2 years
Le Scodan et al, 2009	5-FU, cisplatin, 50-Gy EBRT	41	27	26	80% R0	9.4	22% at 2 years

nCRT, neoadjuvant chemoradiotherapy; ERBT, external-beam radiation therapy; R/LN, resection margin/lymph node positivity; R0, negative resection margin; R1, positive resection margin; LN–, no metastatic tumor in lymph nodes; 5-FU, 5-fluorouracil; FA, folinic acid; PR, potentially resectable; LA, locally advanced; IORT, intraoperative radiotherapy; DFS, disease-free survival

IORT gave a 5-year local control of 23.3%, although IORT is unlikely to become mainstream treatment outside specialized centers undertaking this modality because of the limited number of appropriate patients.

NEOADJUVANT CHEMORADIOTHERAPY, CHEMOTHERAPY, AND BIOLOGIC TREATMENT

Broadly speaking, medical treatments are either directed at known borderline resectable disease, with the aim of downsizing a tumor in contact with or encasing vascular structures, or to patients with staged resectable disease. The presumption of both is acceptance of the rationale for neoadjuvant chemoradiotherapy (nCRT). Early studies implied the advantage of CRT in advanced pancreatic cancer (Moertel et al, 1969, 1981), hence the extrapolation to neoadjuvant regimens. These can be categorized into studies using 5-FU (Table 63A.4) or gemcitabine (Table 63A.5) as the radiosensitizing agent.

Overall, great heterogeneity exists between studies, with mixing of preoperative and postoperative chemoradiation, lack of standardized regimens, and in some cases poor outcome data. However, a few points are worthy of discussion. First, the majority of these studies are from the United States and use multimodal therapy, which is less common in Europe. Patients are restaged after nCRT; hence, a prognostically better subgroup is the result. In addition, current histologic assessment would change the assessments of R0 resection in some of these studies. Of those receiving nCRT, the rate of tumor resection is less than 60% for those receiving 5-FU–based treatment, but it is up to 85% in those receiving gemcitabine-based therapy. Gemcitabine-based neoadjuvant therapy would appear safe and is likely to be the emerging central agent in these modalities. The addition of biologic agents would appear counterintuitive at the moment, but the literature base is currently lacking. Hence this field is in need of powered trials. A randomized, multicenter study (ESPAC-5) is being planned.

PALLIATIVE CHEMOTHERAPY

Until the landmark study by Burris and colleagues (1997), 5-FU had been considered the gold standard of palliative chemotherapy despite its poor response rates, but gemcitabine has subsequently been shown to be more beneficial than 5-FU when used as monotherapy in advanced pancreatic cancer (Carmichael et al, 1996; Casper et al, 1994; Hertel et al, 1990; Huang et al, 1991). Better response rates, longer median and 1-year survival, and enhanced clinical benefit response were achieved. The cornerstone study exploring these advantages (Burris et al, 1997) randomized patients with advanced pancreatic cancer to receive either 5-FU or gemcitabine. Those

Table 63A.5

Summary of Gemcitabine-Based Neoadjuvant Chemoradiation Studies

Reference	Regimen	No. Patients Given nCRT	Patients Undergoing Resection	Patients Resected	R/LN Status	Median Survival	Long-Term Survival
Talamonti et al, 2006	Gemcitabine, 36-Gy EBRT	20	20	17	94% R0, 65% LN–		10 patients alive at 18 months (3 with distant metastasis)
Takai et al, 2008	5-FU, cisplatin, 40-Gy EBRT		14	8			37.7% at 2 years
	Gemcitabine, 40-Gy EBRT	32	18	16		19.2	22% at 3 years
Small et al, 2008	Gemcitabine, 3D-CRT, 36-Gy EBRT	39	33	17			73% at 1 year
Evans et al, 2008	Gemcitabine, 30-Gy EBRT	86	73	64		34 resected, 22 unresected	36% at 5 years (resected); 0 (unresected)
Varadhachary et al, 2008b	Gemcitabine, cisplatin + gemcitabine, 30-Gy EBRT	90	62	52		31 resected, 10.5 unresected	
Heinrich et al, 2008	Gemcitabine, cisplatin (4 cycles)	28					
Palmer et al, 1994	Gemcitabine, cisplatin		26	18	75% R0 both groups		62% at 1 year
	Gemcitabine	50	24	9			42% at 1 year
Varadhachary et al, 2008a	Gemcitabine (6 doses), bevacizumab (3 doses), 50.4-Gy EBRT	11	9	9	All R0	Major complications (5), wound dehiscence (3), incisional hernia (1), biliary anatomoses leak (1)	

nCRT, neoadjuvant chemoradiotherapy; ERBT, external-beam radiation therapy; R/LN, resection margin/lymph node positivity; R0, negative resection margin; R1, positive resection margin; LN–, no metastatic tumor in lymph nodes

receiving gemcitabine had a modest but significant increase in median survival (5.56 vs. 4.41 months; $P = .0025$) and improved clinical benefit (23.8% vs. 4.8%; $P = .0022$). A follow-on study by the same group showed advantage for patients with advanced pancreatic cancer previously treated with 5-FU in whom there had been disease progression. The patients were subsequently given gemcitabine (Rothenberg et al, 1996), and a 27% clinical benefit response was achieved for a median of 14 weeks, with an overall median survival of 3.85 months. The Eastern Cooperative Oncology Group randomized 322 patients with advanced pancreatic cancer to receive solo gemcitabine or gemcitabine followed by 5-FU (Berlin et al, 2002). This regimen achieved a nonsignificant rise in median survival, although it did show a significantly improved progression-free survival for gemcitabine plus 5-FU ($P = .022$).

Overall, combining 5-FU with gemcitabine has little to offer over monotherapy with gemcitabine (Berlin et al, 2002; Crown et al, 1991; DeCaprio et al, 1991; Di Costanzo et al, 2005; Hansen et al, 1988; Maisey et al, 2002; Riess et al, 2005). Alternately, combining gemcitabine with platinum compounds has a better overall response rate and to some extent better median and progression-free survival (Alberts et al, 2003; Cascinu et al, 2003; Colucci et al, 2002; Heinemann et al, 2000, 2006; Philip et al, 2001; Poplin et al, 2006); however, it is associated with more toxicity side effects. The same is true for most other cytotoxic agents.

Combination of gemcitabine with capecitabine has shown promise in Phase II (Scheithauer et al, 2003) and Phase III (Herrmann et al, 2007) trials. The largest Phase III trial to date (Cunningham et al, 2009) has recently reported and is summarized in Table 63A.6. In this study, 533 patients were randomized to either gemcitabine (G) or gemcitabine and capecitabine (GC). Those receiving GC had significantly better objective response rates (19.1% GC vs. 12.4 G; $P = 0.034$) and progression-free survival (HR, 0.78; 95% CI, 0.66 to 0.93). Although not reaching significance, a trend toward increased overall survival was reported for GC. Median survival and 1-year survival for GC and G were 7.1 months versus 6.2 months and 24.3% versus 22%, respectively. This study also includes a meta-analysis of this report and directly comparable Phase II and III trials (Herrmann et al, 2007; Scheithauer et al, 2003), all of which show a significant survival benefit from gemcitabine combined with capecitabine (HR, 0.86; 95% CI 0.75 to 0.98; $P = .02$). The initial excitement regarding combining gemcitabine with biologic agents—such as erlotinib, an epidermal growth-factor receptor tyrosine kinase inhibitor, or bevacizumab, monoclonal antibody to vascular endothelial growth factor A—have not shown the expected promise in recent phase III trials and appear no better than combination gemcitabine and capeciabine (see Table 63A.6).

Several other Phase III trials of novel agents are in progress or have recently closed, notably TeloVac, RC-57, and IPC-BAYPAN. Also under development is the VIP study, a Phase II, randomized, multicenter trial comparing gemcitabine and vandetanib with solo gemcitabine in advanced pancreatic cancer.

It is vital to remember that patients with advanced pancreatic cancer are looking for improvement in quality of life, which should not be sacrificed for modest increases in survival.

Table 63A.6

Summary of Gemcitabine-Based Treatments for Advanced Pancreatic Cancer

Reference	Regimen	No. Patients	Response Rate (%)	PROGRESSION-FREE SURVIVAL		MEDIAN SURVIVAL	
				Median (mo)	1 Yr (%)	Median (mo)	1 Yr (%)
GEM CAP (Cunningham, 2009)	GC	533	19.9 ($P = .034$)	5.3*	13.9*	7.1	24.3
	G		12.4	3.8	8.4	6.2	22
PA3 Trial (Moore et al, 2007)	GE	569	8.6	3.75†	—	6.24‡	23‡
	G		8	3.55	—	5.91	17
ANITA (Van Cutsem et al, 2009)	GEB	607	13.5	4.6§	—	7.1	—
	GE		8.6	3.6	—	6	—

*HR 0.78; 95% CI 0.66 to 0.93; $P = .004$
†HR 0.77; 95% CI 0.64 to 0.92; $P = .004$
‡HR 0.82; 95% CI 0.69 to .99; $P = .038$
§HR 0.73; 95% CI 0.61 to 0.86; $P = .0002$
GC, gemcitabine plus capecitabine; G, gemcitabine; GE, gemcitabine plus erlotinib; GEB, gemcitabine, erlotinib, and bevacizumab; HR, hazard ratio; CI, confidence interval

PALLIATIVE RADIOTHERAPY

Much of the poor reputation of palliative radiotherapy may be unjustified in the modern era. This is because of a recent dramatic shift in radiotherapy delivery techniques from fractional or low doses (e.g., 2 Gy over 6 weeks with a radiation holiday of 2 weeks in the middle) to a continuous-course fraction with a higher overall dose (e.g., 50.4 Gy compared with 40 Gy in fractionated low-dose EBRT). This has the advantage of faster completion of treatment and better overall local control (Lim et al, 2003; Regine et al, 2006). Radiation field size has decreased with the use of intensity-modulated radiation therapy (IMRT), in which smaller fields are targeted by "pencil" beams to reduce the traditional scatter effect to surrounding tissues (Bai et al, 2003; Ben-Josef et al, 2004; Crane et al, 2001; Landry et al, 2002; Milano et al, 2004). This has the added advantage of potentially reducing side effects of combination agents.

Stereotactic radiotherapy (CyberKnife; Accuray, Sunnyvale, CA) uses focused radiotherapy with controlled organ movement via implanted metallic markers. Unfortunately, both Phase I (25 Gy, 15 patients) (Koong et al, 2004) and Phase II trials (45-Gy IMRT with a 25 Gy stereotactic boost, 19 patients) (Koong et al, 2005) have failed to show any great effect, with median survivals of 11 and 7.6 months, respectively. Median time to progression with sole 25-Gy stereotactic radiation was 2 months. Despite the lack of evidence for this technique, which involves a specialized setup, it is gaining some popularity as a result of recent high-profile cases.

PALLIATIVE CHEMORADIOTHERAPY

Palliative radiotherapy has been used in conjunction with chemotherapeutic agents, mainly 5-FU, which allows radiosensitization of tissues. Early work by Moertel and colleagues (1969) suggested a survival advantage for those patients given CRT (35 to 40-Gy EBRT + 5-FU) over those given only EBRT (35 to 40 Gy), with a median survival of 10.4 versus 6.3 months and a 1-year survival of 22% versus 6.3%, respectively. Several small, historic trials have addressed the role of 5-FU and EBRT and show median survival times of 10 to 15 months (Gunderson et al, 1987; Haycox et al, 1998; Ikeda et al, 2001), although these studies may be subject to patient selection bias. The larger GITSG trial (Moertel et al, 1981) randomized 194 patients with advanced pancreatic cancer to either ERBT (60 Gy), ERBT + 5-FU (40 Gy), or EBRT + 5-FU (60 Gy). Concomitant EBRT with 5-FU increased median survival from 23 to 42 weeks. Unfortunately, none of these trials had a control arm. A smaller, follow-on GITSG trial (1988) of 48 advanced pancreatic cancer patients randomized to either 5-FU plus 54-Gy EBRT with follow-on ***s***treptozotocin, ***m***itomycin-C, and 5-***F***U (SMF) versus SMF only. The combination regimen was seen to increase median survival from 32 weeks in the SMF group to 42 weeks in the combination SMF group.

Contrary to this, the Eastern Cooperative Oncology Group (Klaassen et al, 1985) randomized 91 patients to either 5-FU plus 40-Gy EBRT versus 5-FU alone and found no difference in survival in either arm. At present, there seems to be little difference between chemotherapy based on 5-FU and the radiosensitizer EBRT in the treatment of advanced pancreatic cancer (Haycox et al, 1998). A recent multicenter, randomized, Phase II trial by Wilkowski and colleagues (2009) failed to elicit any advantage of CRT regimens. In this trial, 95 patients were randomized to either 5-FU with 50-Gy EBRT (RT–5-FU arm); gemcitabine and cisplatin with 50-Gy EBRT (RT-GC arm), or gemcitabine and cisplatin with 50-Gy EBRT with follow-on gemcitabine and cisplatin (RT-GC + GC arm). Median survivals of 9.6, 9.3, and 7.3 months for RT–5-FU, RT-GC, and RT-GC + GC, respectively, with corresponding progression-free survival at 4, 5.6, and 6 months. The authors conclude that such CRT is no better than solo gemcitabine.

Overall, despite the success of gemcitabine in the adjuvant setting, there would appear to be significant side effects, especially in terms of toxicity, when combined with radiotherapy. As yet there is no clear way forward, but palliative CRT seems to have few advantages over solo chemotherapy for advanced, unresectable pancreatic carcinoma.

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PART 7: Hepatic Disease

SECTION I
Inflammatory, Infective, and Congenital

A. Hepatitis

CHAPTER 64

Chronic hepatitis: epidemiology, clinical features, and management

Christopher D. Anderson and Jeffrey S. Crippin

OVERVIEW

Surgery in the patient with chronic hepatitis can create multiple dilemmas in the preoperative, perioperative, and postoperative phases. Preoperatively, assessment of the stability of the patient's liver disease can be crucial in decisions regarding a surgical procedure. Intraoperatively, both technical and anesthesiology considerations will potentially affect the outcome. Postoperative care involves strategies to prevent or treat acute hepatic decompensation, bleeding, and infection. This chapter covers the chronic hepatitides and addresses, the issues facing the hepatologist and hepatobiliary surgeon.

CHRONIC HEPATITIS

Hepatitis, in general, means liver inflammation. Most associate the term with a viral infection; however, a number of different processes and agents can lead to an inflamed liver. Other than viral infections, other relatively common causes of hepatitis include alcohol, hepatotoxins (including medicines), autoimmune disorders, and fat (i.e., steatosis). The other important definition, for purposes of this discussion, is *chronic* versus *acute* hepatitis. Chronic hepatitis implies the presence of hepatic inflammation for longer than 6 months. Routinely, this is based on the presence of elevated transaminases: aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Although liver inflammation can certainly occur in the absence of transaminasemia, establishing the diagnosis of chronic hepatitis depends on elevations of the AST and ALT for at least 6 months. Thus the finding of elevated transaminases during an evaluation of a potential patient for surgery should lead to a careful assessment because it pertains to the clinical issues at hand. However, the presence of a single set of elevated transaminases does not necessarily imply an acute or chronic process. For example, a patient with transaminases in the range of 1000 to 1500 IU/L in the face of a common bile duct gallstone causing obstruction is distinctly different from a patient with acute cholecystitis presenting with a history of transaminasemia in the range of three to four times the upper limit of normal and an ultrasound showing fatty infiltration of the liver. Thus the clinical setting and history for any particular patient is of crucial importance when evaluating a patient for hepatobiliary surgery. Having a basic working knowledge of each of the chronic hepatitides facilitates evaluation of the patient facing surgery.

Chronic Hepatitis C

Epidemiology

Hepatitis C is an RNA virus and a member of the family *Flaviviridae* and affects approximately 1.6% of the American population, with estimates at 3 to 4 million infected (Armstrong, 2006). Most commonly, the disease is transmitted by blood-to-blood to contact. Before the availability of the hepatitis C antibody test in the early 1990s, posttransfusion hepatitis C was a common means of contraction. However, the availability of reliable assays has led to a marked decrease in the incidence of posttransfusion hepatitis C (Alter, 1997). Currently, the risk of posttransfusion hepatitis C is approximately 1 in 2 million transfusions. The much more common means of contracting hepatitis C is by intravenous drug use. Other needle-stick exposures, such as with tattoos and occupational exposure, account for a much lower percentage of cases. Sexual transmission is likewise a low risk, particularly among monogamous partners. However, the prevalence of hepatitis C is much higher at

sexually transmitted disease clinics, affecting nearly 10% of nonintravenous drug–using patients (Thomas et al, 1994), presumably related to sexual promiscuity and/or traumatic sex, with increased risk of blood to blood exposure. Inhalation of cocaine has been raised as a potential risk factor, based on the transmission via blood on straws used to snort the inhaled agent (Hepburn & Lawitz, 2004). This risk factor has been questioned, with the issue that inhaled cocaine may be associated with other high-risk behaviors that are, in fact, the modes of transmission.

Presentation

Patients with chronic hepatitis C are frequently asymptomatic, although many have nonspecific symptoms, usually related to fatigue, myalgias, arthralgias, and/or right upper quadrant discomfort. Most patients are only diagnosed when they seek medical care for other reasons or with the above symptoms and are found to have mild elevations of the transaminases. However, up to 30% of patients will have normal transaminases at any one time because transaminase levels may wax and wane over time (Piton et al, 1998). Thus a history of any of the risk factors outlined above should lead to serologic testing to rule out hepatitis C.

Diagnosis

The standard screening study for hepatitis C is an enzyme-linked immunosorbent assay (ELISA) for antibody to hepatitis C. This is the standard test used by blood banks around the country; it has a sensitivity and specificity in high-risk populations ranging from 98% to 100% (Vrielink et al, 1995). If a patient has a known risk factor and elevated transaminase levels, a positive hepatitis C antibody study by ELISA is consistent with the diagnosis of hepatitis C. The presence of hepatitis viremia is checked with a reverse transcriptase polymerase chain reaction (PCR). Unfortunately, the PCR may take days to a week to get results, depending on the frequency of testing at the local lab. Patients can have a positive antibody study without viremia if the acute infection spontaneously resolved, an event that occurs 15% to 40% of the time (Herrine, 2002). Antibody positivity frequently persists indefinitely, but it does not imply infection if viremia is absent, based on an undetectable viral load by PCR. Patients will have one of six genotypes, variants in the hepatitis C genome that mainly reflect responsiveness to antiviral therapy (McHutchison et al, 1998). If screening for hepatitis C, and background on a patient being considered for surgery is all that is needed, a genotype need not be checked. However, if antiviral therapy is being considered, a genotype will provide important information regarding the chance of a virologic response and the length of therapy. Genotype 1 is the most common genotype in the United States, accounting for 70% of cases. Genotype 2 accounts for 15% of cases, and genotype 3 accounts for another 10% (McHutchison et al, 1998). Genotype 4 is occasionally seen in the United States, although it is more commonly seen in the Middle East and northern and central Africa. Genotypes 5 and 6 are seen in the United States, although rarely; prevalence of each is higher in South Africa and Southeast Asia, respectively.

Natural History

The course of hepatitis C is quite variable and can be influenced by a number of factors. Progression of the disease is routinely measured over decades. One commonly quoted figure is that 20% of those with the disease for at least 20 years will have cirrhosis. It is important to keep in mind that this implies that 80% of those with the disease for 20 years do not have cirrhosis. Another important consideration in determining the extent of the disease at the time of surgical evaluation is knowledge of when the disease was contracted. For example, if the patient knows he or she received a blood transfusion at the time of a motor vehicle accident 35 years ago, the patient has probably had the disease for 35 years. Likewise, a patient with an extensive history of intravenous drug use as a young adult has likely had the disease for several decades by the sixth or seventh decade of life. The disease takes an accelerated course in patients who ingest excessive amounts of alcohol (Wiley et al, 1998), contract the disease at a later age, and are coinfected with HIV or hepatitis B (Ragni & Belle, 2001; Tsai et al, 1996).

Treatment

Hepatitis C treatment is centered around the use of pegylated interferon and ribavirin. Routinely, the patient with chronic hepatitis C is started on therapy for one of several reasons; without question, the presence of hepatitis C viremia is the primary consideration for therapy, but careful consideration is also given to genotype, histologic changes, and potential relative and absolute contraindications. For example, patients with genotype 1 have a 45% to 50% chance of achieving a sustained virologic response, or "cure," if they can complete a course of therapy. However, the profound fatigue and flulike symptoms commonly associated with antiviral therapy often lead to a decision to delay therapy if histologic changes are mild. For example, if a patient has genotype 1 with a high viral load, the most common demographic in American patients, a liver biopsy showing low-grade inflammation and fibrosis often leads to a period of observation that often lasts for years, or until therapeutic breakthroughs occur. If additional comorbidities associated with a poor response are added to this scenario, such as obesity (Charlton et al, 2006) and/or insulin resistance (D'Souza et al, 2005), and the patient is African American (Jeffers et al, 2004), the potential for successful treatment can drop to 20% to 25%, usually leading clinicians to delay therapy until factors that can be modified are changed. In the face of a disease that potentially may not lead to cirrhosis for 20 to 30 years, if ever, the wisdom of such an approach becomes obvious. Genotype 2 and 3 patients, however, respond in the range of 70% to 80% of the time, routinely requiring only 24 weeks of therapy versus the 48 recommended for genotype 1 patients. This higher response rate can be affected by the same cofactors outlined above.

Absolute contraindications to antiviral therapy include anemia, neutropenia, and severe thrombocytopenia. Because of a type of hemolytic anemia that can be induced by ribavirin, patients with a baseline hemoglobin less than 10 to 12 g/dL must be carefully evaluated if treatment is considered. A 2- to 3-g drop of hemoglobin is expected in the face of ribavirin; thus severe anemia is possible if the baseline hemoglobin level is low. Although reduced doses of ribavirin can be given with the hope of minimizing the anemia, reduced doses also lead to lower response rates; thus most experienced clinicians avoid dose reductions and use erythropoietin to increase hemoglobin levels. Neutropenia and thrombocytopenia are due to pegylated interferon and may improve with dose reduction, although similar lower levels of response can be expected. Granulocyte colony-stimulating factor or filgrastim can maintain neutrophil

levels and obviate the need for dose reduction. Eltrombopag, a nonpeptide thrombopoietin receptor agonist, has been approved for patients with thrombocytopenia secondary to immune thrombocytopenic purpura and is under study for the treatment of thrombocytopenia secondary to pegylated interferon treatment. This will potentially allow thrombocytopenic patients to receive antiviral therapy.

Other potential contraindications to antiviral therapy include uncontrolled psychiatric illness, renal insufficiency, severe cardiopulmonary disease, and alcohol or substance abuse. Pegylated interferon and ribavirin can induce and exacerbate depression (Renault et al, 1987); thus recent suicidal ideation is an absolute contraindication to therapy. Well-controlled psychiatric disease can be successfully treated with careful follow-up. Renal insufficiency is a relative contraindication because of renal excretion of both interferon and ribavirin (Bino et al, 1982; Glue, 1999). The ribavirin dose must be decreased to avoid severe hemolytic anemia. Unfortunately, strict guidelines are not available, so dosing is often started at a low level, then increased based on patient tolerance. The anemia induced by ribavirin can exacerbate cardiac and pulmonary disease; these patients must therefore be carefully assessed before starting therapy. For example, a patient with congestive heart failure and a left ventricular ejection fraction of 40% may decompensate in the face of a drop in hemoglobin from 14 to 7 g/dL. Finally, patients with a history of alcohol or substance abuse are usually not treated until a period of abstinence can be maintained. Studies have shown a decreased response rate in patients with ongoing alcohol abuse (Pessione et al, 1998). Whether alcohol has a direct effect on drug pharmacokinetics and/or efficacy is unclear; however, the potential effect on compliance is obvious.

Once a patient is deemed an appropriate candidate for therapy, one of two pegylated interferon products is started: pegylated interferon alfa-2a at 180 μg subcutaneously weekly or pegylated interferon alfa-2b at 1.5 μg/kg/week. Although no head-to-head studies have been performed, the agents appear to be equivalent in efficacy and side effects, although clinicians usually have a personal preference. Ribavirin is dosed at 13 mg/kg/day, given orally in divided doses. Because of the myalgias, arthralgias, fever, chills, and sweats that frequently occur after administration of pegylated interferon, patients frequently take an over-the-counter analgesic before the injection. Fatigue and flulike symptoms are usually at their worst in the 24 to 48 hours following the pegylated interferon injection, with milder symptoms for the remainder of the week, until the next scheduled injection. That said, many patients are affected by these symptoms on a nearly daily basis, but others have minimal discomfort. Most patients can maintain their usual activities with only scattered absences. However, a small percentage of patients are nearly disabled, requiring frequent absences from their usual responsibilities. Discontinuation of therapy as a result of intolerable side effects occurs in 5% to 10% of treated cases.

On treatment, laboratory work is followed at least monthly and more often if needed. Thyroid function is assessed quarterly because of the potential for development of hypothyroidism or hyperthyroidism (Marcellin et al, 1992). The addition of growth factors for cytopenias is often clinician dependent. Most clinicians start supplemental erythropoietin with a hemoglobin level less than 10 g/dL, although many clinicians start erythropoietin if a patient has severe fatigue in the face of a drop in hemoglobin of 25% to 40% (e.g., from 18 to 11 g/dL). Absolute neutrophil counts less than 500 mm^3 usually lead to supplemental filgrastim, although many clinicians start filgrastim in response to an absolute neutrophil count of less than 1000 mm^3. Drops in hemoglobin, absolute neutrophil counts, and platelet counts may lead to dose reduction of pegylated interferon and/or ribavirin, although the current standard of care is to attempt to maintain patients on standard doses unless all other measures fail.

Viral loads are monitored at 4, 12, and 24 weeks of therapy (Ghany et al, 2009). An undetectable viral load after 4 weeks of therapy is associated with an 85% to 90% response rate, if the patient can complete the course of therapy, regardless of genotype (Ferenci et al, 2005). Thus a response at 4 weeks should lead to maximal efforts to maintain a patient at standard doses and a full course of therapy. An undetectable viral load observed at 12 weeks drops the rate of a sustained virologic response to 67% to 80% (Davis et al, 2003), whereas patients with a "late" response at week 24 only respond approximately 18% to 30% of the time (Berg et al, 2006; Pearlman et al, 2007). In patients with the first undetectable viral load at 24 weeks, recent studies suggest that extending therapy for an additional 24 weeks may improve the rate of response by 20%, although patient tolerance for this extended therapy is poor (Berg et al, 2006; Pearlman et al, 2007).

If undetectable viremia is achieved during therapy, viral load is routinely checked 3 to 6 months following the end of therapy. An undetectable viral load at that point is consistent with a sustained virologic response. Long-term studies have shown this response is durable, with undetectable viral loads persisting indefinitely (Desmond et al, 2006), unless the patient is reinfected. Patients who do not respond to antiviral therapy do not benefit from another treatment trial unless specific circumstances resulted in underdosing. New classes of medicines are under study, and when used in combination with pegylated interferon and ribavirin, protease inhibitors appear to increase response rates.

Surgery in the Patient with Hepatitis C

In the noncirrhotic patient with hepatitis C undergoing hepatopancreatobiliary surgery, no special precautions need be taken. The risk of decompensation postoperatively is solely related to the presence of advanced fibrosis and is not related to the presence of the hepatitis C virus itself. If a patient is undergoing antiviral therapy at the time of surgery, the best advice is to ask a hepatologist to assess the situation. In the vast majority of cases, antiviral therapy need not be stopped in the face of surgery. Obviously, antiviral therapy can be stopped if more pressing issues require treatment. Stopping antiviral therapy for a period of weeks may necessitate starting over from the beginning.

Hepatitis B

Epidemiology

Hepatitis B is a DNA virus that represents the number one cause of chronic viral hepatitis worldwide, with more than 2 billion people infected at some point and more than 350 million infected chronically (World Health Organization, 2008). More than 45% of the world's population lives in endemic areas, particularly in Asia and sub-Saharan Africa (Mahoney, 1999).

More than 8% of the population in these areas is positive for hepatitis B surface antigen (HBsAg). The prevalence is much lower in North America, affecting less than 2% of the population overall. In the United States, approximately 73,000 new cases occur each year, with approximately 1.25 million patients infected chronically (McQuillan et al, 1999). However, because of the mobility of the world's population, the possibility of acute or chronic hepatitis B must be considered in patients who have come to the United States. These changes in patterns of immigration will likely increase the prevalence of the disease by as much as a factor of two.

Transmission

In the United States, the most common means of transmission is via percutaneous or permucosal exposure to blood or body fluids (Gust, 1996); thus sexual transmission and parenteral exposure via needle sticks account for the majority of cases. Vertical transmission is relatively rare in this country because of the identification of HBsAg-positive mothers and the administration of hepatitis B immune globulin and the hepatitis B vaccine at the time of birth. Failure to administer these agents frequently leads to chronic infection in the neonate because of the inability of an immature immune system to eradicate hepatitis B virus (Lok, 2002).

Presentation

Acute hepatitis B has a wide range of presentation, from subclinical disease to acute liver failure. The disease tends to be associated with more severe symptoms as the age of the patient increases, and malaise, arthralgias, jaundice, and anorexia may be present. Chronic hepatitis B is usually not associated with symptoms, although vague, nonspecific symptoms may be present. Differentiating fatigue, arthralgias, and myalgias from other systemic diseases may be difficult.

Diagnosis

The presence of acute or chronic hepatitis B requires the presence of HBsAg. If this test is negative, the patient does not have hepatitis B. On occasion, a patient with acute hepatitis B can present without HBsAg and without hepatitis B surface antibody (HBsAb) because the virus is being eradicated. This is referred to as the *core window.* During this phase, only the immunoglobulin M (IgM) hepatitis B core antibody (IgM HBcAb) is present, thus explaining its presence on acute hepatitis panels available through commercial laboratories. Chronic hepatitis B is only diagnosed when HBsAg is present more than 6 months following the onset of the acute infection. If HBsAg is positive, the evaluation includes assessment for the presence of the hepatitis B e-antigen (HBeAg), hepatitis B e-antibody (HBeAb), and hepatitis B viremia with a hepatitis B virus DNA level by the polymerase chain reaction. Along with the transaminases, these tests guide decisions regarding the need for antiviral therapy. Imaging studies are only required if advanced fibrosis is suspected, based on the presence of complications of end-stage liver disease, including hypoalbuminemia, a prolonged prothrombin time, and/or thrombocytopenia. Sonography is a reasonable first step, although other cross-sectional imaging studies may be indicated, depending on the sonographic findings. Similar to hepatitis C, there are different hepatitis B genotypes: eight have been found to exist, with genotypes A and C most common in the United States. Routine checks of the genotype are unnecessary with regard to screening, however, the genotype can be useful in predicting the response to antiviral agents.

Natural History

Acute hepatitis B resolves spontaneously in 90% of patients. The other 10% with persistent HBsAg require careful assessment and follow-up. Within the past decade, the natural history of chronic hepatitis B has been rewritten. Previously, patients either were "chronic carriers" or had "chronic hepatitis B," which is now defined more as a spectrum of disease that slowly evolves from one phase to another. Patients who contract hepatitis B in the perinatal period frequently maintain high levels of hepatitis B viremia with normal transaminases (Lok & Lai, 1988), which may persist for decades. This "immune tolerant" phase is characterized by the absence of liver injury, or at most only minimal injury.

Current guidelines recommend observation with regular follow-up of liver biochemistry panels, hepatitis B serology, and viral load. Spontaneous HBeAg to HBeAb seroconversion occurs at a rate of 8% to 12% of patients per year (Hoofnagle et al, 1981). An exacerbation of hepatitis B may accompany seroconversion, with marked elevations of the transaminases. Many of these patients (67% to 80%) enter the *inactive carrier state,* with absent or low-level viral replication, normal transaminases, and minimal histologic damage (Hoofnagle et al, 1981). However, 10% to 30% of HBeAb-positive patients continue to have elevated transaminases, viral replication, and histologic damage (Davis et al, 1984). Up to 20% of HBeAb-positive patients may revert back to an HBeAg-positive phase, with elevated viral loads and transaminases (Davis et al, 1984).

Treatment

Patients with acute hepatitis B are treated supportively. Because 90% of cases resolve spontaneously, antiviral therapy is not indicated, and two studies have shown no benefit to the use of lamivudine (Kumar et al, 2007; Tassopoulus et al, 1997). Cases of chronic hepatitis B must be carefully assessed to determine the appropriate treatment for the patient, and guidelines have been published by several professional societies. The key themes throughout all of the published guidelines include certain principles: 1) if transaminase levels are normal, observe, even if there is a detectable viral load; 2) consider treatment if transaminase levels are elevated or if significant histologic damage is evident; and 3) consider treatment in all patients with cirrhosis who have chronic hepatitis B.

Medical management is centered around the use of nucleoside/nucleotide analogues or pegylated interferon. The nucleoside/nucleotide analogues are relatively nontoxic and easy to take, although years of treatment may be necessary before seroconversion occurs. Entecavir, tenofovir, and telbivudine are potent suppressants of hepatitis B viral replication, although telbivudine is associated with a high rate of hepatitis B viral resistance (Lok & McMahon, 2009). Lamivudine, the mainstay of therapy for over a decade, is not considered first-line therapy because of high levels of drug resistance. Pegylated interferon offers a defined treatment length of 48 weeks; however, weekly subcutaneous injections and significant side effects make it less attractive to many. The nucleoside/nucleotide analogues lead to eradication of viral replication in approximately 80% of patients, with HBeAg seroconversion in up to

22%; pegylated interferon leads to HBeAg seroconversion in up to 34% (Lok & McMahon, 2009).

Surgery in the Patient with Chronic Hepatitis B

No special precautions are necessary in patients with chronic hepatitis B unless a patient has cirrhosis. Otherwise, surgery can proceed as scheduled. If the patient is undergoing antiviral therapy, discontinuation of the antiviral agent can lead to replicative rebound, resulting in acute hepatitis and potential liver failure. Thus antiviral agents should not be suddenly stopped until the situation can be discussed with a hepatologist. Any HBsAg-positive patient not taking an antiviral agent should be considered for prophylactic antiviral therapy if immunosuppressive therapy or chemotherapy is started (Lok & McMahon, 2009). Flares of hepatitis, even to the point of hepatic decompensation and death, have been reported in patients without evidence of viral replication (Yeo & Johnson, 2006).

Nonalcoholic Steatohepatitis

Epidemiology

Nonalcoholic steatohepatitis (NASH) is slowly becoming the most common liver disease worldwide. Nonalcoholic fatty liver disease (NAFLD) has a prevalence of 3% to 23% of the North American population (Clark et al, 2002; McCullough, 2005). The prevalence of fatty liver disease has paralleled the increase in body weight seen globally. Nearly 75% of those with obesity or type 2 diabetes mellitus have NAFLD (McCullough, 2005), and approximately 20% of obese subjects have NASH (Wanless & Lentz, 1990). The increase in body mass seen in the United States over the last 25 years suggests the prevalence will rise before it falls.

Presentation

Patients are usually without symptoms. During routine physical examinations and health screenings, abnormal transaminase levels are a frequent problem. Right upper abdominal quadrant fullness or pain is a common symptom, and patients routinely have multiple features of metabolic syndrome, including hyperlipidemia, hyperglycemia/diabetes mellitus, and hypertension. All these issues appear to be related to the development of insulin resistance (Grundy et al, 2004).

Diagnosis

The definitive diagnosis of NAFLD is made histologically; however, this does not imply that a biopsy must be obtained in all cases. The finding of elevated transaminases in an obese patient is consistent with the diagnosis, but other causes of chronic liver disease must be ruled out. Alcoholic steatohepatitis is the first consideration, although this may be limited by the honesty of the patient and whether family members are aware of the patient's alcohol consumption. If heavy alcohol use is unlikely, viral hepatitis serologies, autoimmune serologies, iron studies, and ceruloplasmin measurements should be performed. If the studies results are normal, the next step is imaging of the liver, either sonographically or with cross-sectional imaging.

Fatty infiltration of the liver is only detected if more than 30% of the parenchyma is infiltrated with fat (Saadeh et al, 2002). If fat is detected, a liver biopsy is not absolutely required. Many hepatologists proceed with biopsy if there is any suspicion of another liver disease, such as borderline autoimmune serologies or mildly elevated iron studies, or if there is some question as to the presence of moderate to severe fibrosis. The biopsy can be used to rule out other liver diseases and as a means of staging the amount of fibrotic tissue. The latter is seen as an incentive to patients to begin a dedicated weight loss program. Biopsies from patients with NASH show fat and inflammation, although distinguishing the findings from alcoholic steatohepatitis may be difficult.

Natural History

Hepatic steatosis occurs with minimal or no inflammatory changes histologically, but NASH is associated with necroinflammatory changes; both may progress to fibrosis and cirrhosis. Natural history studies are relatively few in number, because of small patient numbers and limited long-term follow-up. However, NASH progresses to cirrhosis in 15% to 20% of patients (Edmison & McCullough, 2007). Progression is obviously shorter in patients presenting with advanced fibrosis, although 30% of patients will have progression of fibrosis over 5 years (Fassio et al, 2004).

Treatment

In spite of multiple trials of medical treatments, the mainstay of therapy for NASH remains weight loss (Hickman et al, 2004). Decreased dietary intake, ideally complemented by an exercise program, will lead to weight loss, a decrease in hepatic fat, and lower transaminase levels. Weight loss in the amount of 10% to 15% of the current body weight over the course of a year is a reasonable and attainable goal for most patients. However, bariatric surgery and its frequent accelerated weight loss is not harmful and has been associated with histologic improvement (Kral et al, 2004).

Medical therapy for NASH has been the subject of multiple drug trials. Thiazolidinediones have been associated with improvement of transaminase levels and a decrease in histologic fat (Aithal et al, 2008). However, weight gain is a potential side effect; thus use of this class of medications solely to improve NASH is not standard practice. If a patient is diabetic and has NASH, pioglitazone or rosiglitazone may be considered. Agents such as vitamin E, betaine, metformin, and pentoxifylline have also been used in small trials without remarkable improvement. Thus weight loss remains the foundation of NASH treatment.

Surgery in the Patient with Nonalcoholic Steatohepatitis

Routinely, no special precautions need be taken for the operative candidate with NASH in the absence of cirrhosis. However, large hepatic resections in patients with fatty livers have been associated with decompensated liver disease postoperatively (Kooby et al, 2003; Parikh et al, 2003). Thus careful assessment of the patient being considered for hepatic resection must take all of these factors into account. A liver biopsy may provide the necessary information regarding baseline hepatic histology, the extent of fatty infiltration and fibrosis, and the presence of other lesions that may lead to postoperative decompensation.

Autoimmune Hepatitis

Epidemiology

Autoimmune hepatitis is a chronic, usually progressive liver disease with an incidence among Northern Europeans of 1.9 per 100,000 population (Boberg et al, 1998) and 1 per 200,000 in the United States (Manns et al). Although often characterized as a disease of middle-aged women, all ages can be affected,

including the very young and the elderly, but women are affected more often than men. Patients frequently have a coexistent autoimmune disease; a history of thyroid disease, rheumatoid arthritis, psoriasis, or other autoimmune disease should raise the possibility of the diagnosis in a patient who presents with elevated liver biochemistry results (Abdo et al, 2004).

Presentation

Patients present in a number of ways, ranging from relatively asymptomatic elevations of the transaminases to cirrhosis to acute liver failure, the latter two preceded by relatively nonspecific symptoms of fatigue and malaise of varying duration. Up to 40% of patients present with systemic symptoms and an acute illness with possible fever, arthralgias, myalgias, and skin rash. This can progress to acute liver failure with hepatic encephalopathy within 8 weeks of the onset of symptoms, potentially leading to death or to the need for liver transplantation. Autoimmune hepatitis historically accounts for 5% to 6% of liver transplantations done in the United States.

Diagnosis

No single test or finding leads to the diagnosis of autoimmune hepatitis. Other causes of acute and chronic liver disease must be ruled out; thus viral serologies, iron studies (hereditary hemochromatosis), serum ceruloplasmin measurements (Wilson disease), α_1 antitrypsin level, and phenotyping must be performed, and drug-induced hepatotoxicity, alcoholic liver disease, and nonalcoholic steatohepatitis must be ruled out based on historic, serologic, radiologic, and histologic data. Autoimmune serologies are helpful, particularly when present at a titer of more than 1:80. Antinuclear antibodies (ANAs) and anti–smooth muscle antibodies (ASMAs) are frequently present, although their absence does not rule out the disease. The anti–liver/kidney microsomal antibody is much less common in the United States, representing fewer than 5% of cases. Other autoimmune serologies occur even less commonly and are not routinely checked in clinical practice.

Histologic features are the foundation of the diagnosis; however, serologic and clinical findings may lead to the diagnosis, even in the absence of classic histologic findings. Characteristic histologic findings include interface hepatitis, previously known as *piecemeal necrosis,* and a portal plasma cellular infiltrate. However, other liver diseases such as Wilson disease, chronic hepatitis C, and drug-induced hepatotoxicity can have similar histologic features. Thus the issues outlined above regarding careful assessment and evaluation for other acute and chronic liver diseases cannot be forgotten. Histologic features of other autoimmune liver diseases, such as primary biliary cirrhosis, may suggest the presence of an overlap syndrome in which serologic and histologic features of both diseases are present.

Natural History

Autoimmune hepatitis is often a progressive disease, with death occurring in 40% of untreated patients. In those surviving the initial illness, another 40% progress to cirrhosis with the potential manifestations of end-stage liver disease, including ascites, portal hypertension, and hepatic encephalopathy. Not unexpectedly, severe histologic damage on the initial liver biopsy is a poor prognostic factor. Although transaminase elevations do not always correlate with the degree of liver damage or prognosis in other liver diseases, persistent transaminase elevations greater than 10 times the upper limit of normal are associated with higher early mortality rates. Patients with milder laboratory and histologic findings have a less severe course; however, cirrhosis still develops in 49% of patients over a period of 15 years (Czaja & Freese, 2002). Thus early diagnosis and treatment are key to prolonging long-term survival.

Treatment

Indications for treatment must be individualized, although in more severe cases, patients should be started on therapy immediately. Those with significant histologic changes and transaminase levels greater than 10 times the upper limit of normal should be treated. Lower level transaminase elevations in combination with bridging necrosis and/or lobular necrosis should also be treated. The potential risks and benefits of treatment should be considered in patients without the above findings; however, because of the progressive nature of the disease, most experienced hepatologists routinely treat patients with transaminase elevations and even mild histologic changes.

Immunosuppressive therapy is the key to controlling this progressive disease. Although treatment protocols vary by center and clinician, corticosteroid-based treatment is most common. A 30- to 60-mg daily dose of oral prednisone is usually started in most cases, even in patients with coexistent diseases that potentially could be affected, such as diabetes mellitus. Because of the adverse effects associated with long-term high-dose corticosteroid therapy, the dose is tapered over varying amounts of time, ranging from weeks to months. Because of the potential for disease flares as the corticosteroid dose is tapered, most patients start azathioprine at a dose of 50 mg daily along with corticosteroids, or azathioprine is started within 2 to 3 months of the initiation of treatment (Czaja & Freese, 2002). Azathioprine is usually not effective for 4 to 8 weeks after initiation; thus many clinicians start it with prednisone rather than delaying. Although 90% of adults show marked improvement in laboratory studies and symptoms within 2 weeks of starting therapy, disease remission is uncommon in less than 12 months. Thus azathioprine is continued after prednisone is tapered off. As the prednisone is tapered, elevations in transaminases can be addressed with an increase in dose; however, the long-term side effects associated with corticosteroids make this a less than ideal choice. Thus doses of azathioprine incrementally increased to a maximum dose of 2 mg/kg/day are routinely used, if the disease flares during the steroid taper.

Depending on the severity of the histologic damage seen initially, most clinicians continue the azathioprine for at least 1 to 2 years. Even with normal transaminase levels, a significant number of patients have ongoing interface hepatitis on immunosuppressive therapy. Thus any attempt to stop immunosuppressive therapy should be preceded by a liver biopsy to assess the histologic response to therapy. As a rule, more severe initial changes will take longer to correct and will lag behind biochemical improvement. Many clinicians see autoimmune hepatitis as a chronic disease that inevitably flares off therapy, although some patients go into remission and can remain off therapy without histologic progression. Patients tapered off therapy should be followed up with liver biochemistry measurements at least twice a year because relapses may occur without symptoms. Reinstitution of immunosuppressive therapy leads to improvement in most patients within 2 years and should lead to indefinite immunosuppressive therapy with azathioprine, and in some cases prednisone, based on liver biochemistries (Czaja & Freese, 2002).

The complications of long-term corticosteroid therapy are well known and need not be outlined. However, the short- and long-term consequences associated with azathioprine are less well known and worth listing. Bone marrow suppression—with anemia, leukopenia, and thrombocytopenia—is the most common laboratory abnormality. Symptomatically, nausea, vomiting, and abdominal pain may lead to cessation of therapy as a result of intolerance. Acute pancreatitis is rare, as is hepatotoxicity, typically marked by sinusoidal obstructive syndrome or cholestasis, both of which usually respond to drug cessation. Long-term treatment can result in malignancy, usually a lymphoma or leukemia (Kandiel et al, 2005). However, one series of patients with autoimmune hepatitis followed for more than 20 years showed no incidence of malignancy (Johnson et al, 1995).

Of note, allopurinol should never be used in patients taking azathioprine because it inhibits xanthine oxidase, an enzyme necessary for the breakdown of azathioprine. If this enzyme is inhibited, the half-life of azathioprine is prolonged and can lead to profound bone marrow suppression.

Other agents have been used for the treatment of autoimmune hepatitis, although the experience is predominantly anecdotal. Mycophenolate mofetil, another lymphocyte inhibitor used in solid organ transplant recipients, can be substituted for azathioprine with comparable efficacy in cases of intolerable side effects based on a relatively limited experience.

Surgery in the Patient with Autoimmune Hepatitis

No special precautions need be taken in patients with autoimmune hepatitis requiring surgery. Patients with acute autoimmune hepatitis with signs of acute liver failure or cirrhosis clearly are at risk, and indications for surgery in this setting should include only those of an emergent nature. All the risks and benefits of surgery must be carefully considered. In patients with well-controlled autoimmune hepatitis on maintenance immunosuppression, the risk of liver decompensation and/or a disease flare is small as long as patients are maintained on their medications. Stress doses of corticosteroids should be considered if a patient is taking corticosteroids or has recently been tapered off. If a patient is undergoing azathioprine monotherapy preoperatively, the dose should be restarted as soon as possible postoperatively. A prolonged absence of gut motility should lead to discussion with a hepatologist regarding the need for intravenous steroids to keep the disease in remission. Routinely, a few days off immunosuppressive therapy will not lead to a disease flare; the potential risks and benefits associated with corticosteroids therefore must be carefully considered. Patients with advanced cirrhosis routinely are not surgical candidates except in cases of emergent and/or life-threatening events requiring surgical intervention.

APPROACH TO SURGERY IN PATIENTS WITH LIVER DISEASE

Partly because of the epidemic of obesity and NAFLD, increasing numbers of patients with chronic liver disease are undergoing nonhepatic and nontransplant operations. Liver disease, especially significant fibrosis or cirrhosis, represents a significant risk factor for perioperative morbidity and mortality. Any clinically evident signs of liver dysfunction should raise concern, particularly for intraabdominal operations. Although no absolute consensus on risk quantification has been reached, the perioperative risk in patients with liver disease clearly increases with the severity of liver dysfunction (Teh et al, 2007). Perioperative risk in these patients can be quantified using the Child-Turcotte-Pugh (CTP) score and/or the Model for End-Stage Liver Disease (MELD) score (Teh et al, 2007; Muilenburg et al, 2009; del Olmo et al, 2003), which can discriminate risks to a finer degree than the CTP score and has evolved as the best predictor of 30- and 90-day operative mortality rate (Teh et al, 2007). Furthermore, perioperative mortality risk greatly increases in patients with MELD scores higher than 10 to 15 (Costa et al, 2009; Morisaki et al, 2010; Northup et al, 2005; Telem et al, 2010; Teh et al, 2007), and there also is utility in MELD-based variants in making more refined predictions regarding surgical risk (Costa et al, 2009; Telem et al, 2010).

Ultimately, the indication for surgery, whether elective or emergent, along with the patient's estimated operative risk from liver disease must be considered as the operative plan is developed. These factors should clearly influence the informed consent for the patient and family. When possible, patients should be referred to a specialty liver care center, where preoperative optimization should be carried out by a multidisciplinary team approach.

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CHAPTER 65

Hepatic steatosis, steatohepatitis, and chemotherapy-related liver injury

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OVERVIEW

Hepatic parenchymal damage from chemotherapy can be divided into two main categories: *nonalcoholic fatty liver disease* (steatosis and steatohepatitis) and *sinusoidal injury.* Both types of injuries may be caused by chemotherapy or other factors; however, hepatic injuries become relevant in the context of preoperative chemotherapy and can be a concern for the hepatic surgeon. Steatosis is linked to an increased body mass index (BMI) and to the use of chemotherapy agents, such as 5-fluorouracil (5-FU) and irinotecan. Steatohepatitis is observed in 5% to 10% of patients undergoing irinotecan-based chemotherapy, and sinusoidal injury is related to the use of oxaliplatin-containing regimens.

In patients undergoing liver resection, severe steatosis and high-grade sinusoidal injury increase the overall postoperative complication rate, and steatohepatitis can increase the 90-day posthepatectomy mortality rate, including death from postoperative liver failure. In the context of preoperative chemotherapy, preventive measures—such as limiting the duration of chemotherapy to 2 to 3 months—reduce the risk of hepatic injuries and therefore reduce surgical complication rates.

With the expansion of the indications for liver surgery in patients with hepatic malignancies, liver surgeons have become concerned with steatosis, steatohepatitis, and other liver damage from chemotherapy. Preoperative chemotherapy is widely used before resection of colorectal cancer liver metastases (see Chapters 81A and 87), and can induce different types of hepatic parenchymal injuries. Although most of these changes can be observed outside the context of preoperative chemotherapy, they have become more relevant in patients receiving preoperative chemotherapy for colorectal cancer liver metastase because they can affect perioperative outcome after hepatic resection. This chapter focuses on risk factors and prevention of chemotherapy-related liver damage as it affects liver resection.

TYPES AND ETIOLOGY OF LIVER PARENCHYMAL DAMAGE

Hepatic parenchymal damage from chemotherapy (see Chapter 87) can be divided into two main categories: *nonalcoholic fatty liver disease* (NAFLD) and *sinusoidal injury*. NAFLD describes a large spectrum of histologic liver changes unrelated to alcohol consumption. It is important to note that these lesions may also be observed in the context of alcohol abuse. Steatosis is defined by an intracellular hepatocyte lipid accumulation, and it is the hallmark of NAFLD. Histologic evidence of an inflammatory component associated with steatosis defines *steatohepatitis.* Upon operative exploration, a liver that has undergone steatotic changes is recognized by its yellow-tan color, often referred to as *yellow liver.* NAFLD is typically graded according to the scoring system of Kleiner and colleagues (2005), which considers the degree of steatosis (0 to 3 points), lobular inflammation (0 to 3 points), and hepatocellular ballooning (0 to 2 points; Fig. 65.1). A score of 5 or more indicates steatohepatitis.

Increased BMI is the main risk factor of nonalcoholic steatosis (Brouquet et al, 2009; Kooby et al, 2003; Vauthey et al, 2006). The use of chemotherapy may increase the risk of steatosis (Kooby et al, 2003), which can be detected in 30% to 47% of patients who have received systemic chemotherapy (Peppercorn et al, 1998; Sorensen et al, 1995). Although no specific chemotherapy regimen has been definitively linked to the occurrence of steatosis, it is generally attributed to the use of 5-FU or irinotecan in patients with liver metastases (Moertel et al, 1993; Sorensen et al, 1995; Vauthey et al, 2006). However, in these patients, it is difficult to ascertain whether chemotherapy directly induces steatosis or more likely aggravates preexisting NAFLD.

Steatohepatitis has long been described as a "second hit" in patients with preexisting steatosis, but the continuum between these two different types of NAFLD is uncertain. Macroscopically, no specific features distinguish the steatohepatitis from other types of NAFLD. Chemotherapy-related steatohepatitis was initially believed to be related to the use of any chemotherapy (Bilchik et al, 2005; Fong et al, 2006), but only irinotecan has been confirmed as a risk factor for steatohepatitis (Vauthey et al, 2006). The effect of an elevated BMI on the development of chemotherapy-associated steatohepatitis is additive to the risk imposed by the use of irinotecan (Vauthey et al, 2006), and this risk can rise to up to 25% in patients with a BMI of 25 kg/m^2 or more who received irinotecan-based chemotherapy (Attal et al, 1992).

Sinusoidal injury is a variant of the sinusoidal obstruction syndrome first described in association with bone marrow transplantation. In the operating room, a liver that has sustained sinusoidal injury is characterized by vascular ectasia, commonly referred as *blue liver.* The initial damage affects endothelial cells of the sinusoids, leading to a rupture of the continuity of the sinusoidal wall, which triggers a coagulation cascade and induces the deposition of coagulation factors, erythrocyte aggregates, and cytoplasmic fragments into the perisinusoidal space, ultimately leading to sinusoidal obstruction (Attal et al, 1992; Rubbia-Brandt et al, 2004).

Histologically, the severity of sinusoidal injury can be graded according to a scoring system developed by Rubbia-Brandt and colleagues (2004). This system evaluates the proportion of

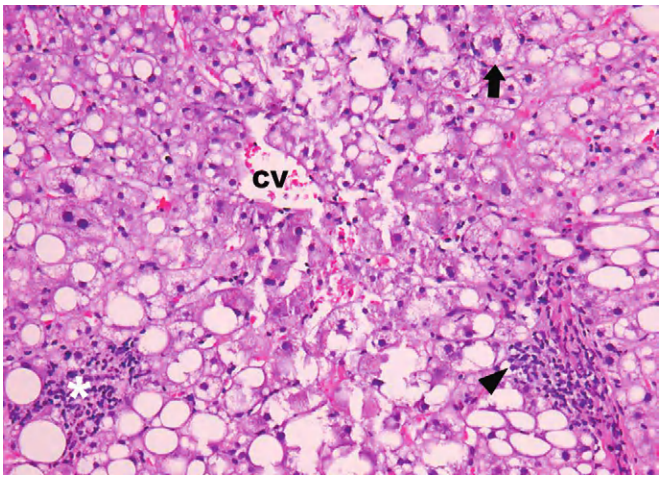


FIGURE 65.1. Steatohepatitis. Moderate steatosis (40% to 50% of hepatocytes), hepatocyte-ballooning degeneration (*arrow*), lobular inflammation (*asterisk*), and portal inflammation (*arrowhead*) can be seen in this specimen, which has a Kleiner score of 6 for nonalcoholic fatty liver disease. *CV,* central vein. Stained with hematoxylin and eosin, magnification ×200. *(From Chun YS, et al, 2009: Management of chemotherapy-associated hepatotoxicity in colorectal liver metastases. Lancet Oncol 10:278-286.)*

centrilobular involvement relative to the entire lobular surface (Fig. 65.2). A score of 0 indicates no sinusoidal dilation; 1 indicates mild sinusoidal dilation, characterized by centrilobular changes limited to one third of the lobular surface; 2 indicates moderate sinusoidal dilation, characterized by centrilobular changes extending to two thirds of the lobular surface; and 3 indicates severe sinusoidal dilation, characterized by evidence of complete lobular involvement. There is strong evidence that sinusoidal injury is caused by the use of platinum compounds, including oxaliplatin (Aloia et al, 2006; Brouquet et al, 2009; Nakano et al, 2008; Rubbia-Brandt et al, 2004; Vauthey et al, 2006), and the incidence of sinusoidal injury can range from 19% to 52% in patients who have received preoperative oxaliplatin-based chemotherapy (Aloia et al, 2006; Brouquet et al, 2009; Nakano et al, 2008; Rubbia-Brandt et al, 2004; Vauthey et al, 2006).

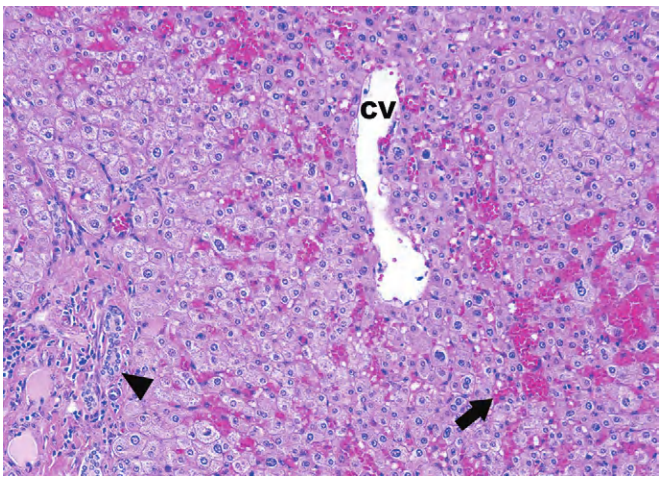


FIGURE 65.2. Severe sinusoidal injury with sinusoidal congestion and dilation (*arrow*) in hepatic metabolic zones 1 (*arrowhead*), 2, and 3. *cv,* central vein. Stained with hematoxylin and eosin, magnification ×200. *(From Chun YS, et al, 2009: Management of chemotherapy-associated hepatotoxicity in colorectal liver metastases. Lancet Oncol 10:278-286.)*

PATHOPHYSIOLOGY OF CHEMOTHERAPY-ASSOCIATED LIVER DAMAGE

Although histologically distinct, the NAFLD and sinusoidal injury pathways both involve chemical damage by reactive oxygen species (ROS) (Fig. 65.3). The initial event in the NAFLD sequence is likely drug-related damage to the mitochondrial membrane that interferes with oxidation of fatty acids and ultimately leads to the accumulation of ROS within hepatocytes (Laurent et al, 2004; Pessayre et al, 2001). Fluoro-β-alanine, a fluorouracil metabolite, is also believed to impair metabolism in hepatocytes, thus prolonging their exposure to toxic substances (Miyake et al, 2005).

The pathophysiology of sinusoidal injury also involves the accumulation of ROS. Wang and colleagues (2000) developed a rodent model of sinusoidal injury using exposure to pyrrolizidine alkaloids, which deplete the sinusoidal endothelial cells' glutathione stores, leaving them susceptible to subsequent ROS injury. Pyrrolizidine alkaloids also decrease nitric oxide concentrations, resulting in the upregulation of matrix metalloproteinase activity, which can be prevented by pretreatment with a nitric oxide donor (DeLeve et al, 2003). Damage induced by exposure to pyrrolizidine compounds can also be abrogated in a dose-dependent manner by pretreating sinusoidal endothelial cells with exogenous glutathione or N-acetyl-L-cysteine in this model (Wang et al, 2000). However, these preventive pharmacologic strategies have not yet been tested in humans.

PREOPERATIVE DETECTION OF LIVER INJURY

The definitive diagnosis of hepatic injury relies on the pathologic examination of non–tumor-bearing liver tissue after liver resection. The preoperative detection of liver injury is useful to devise the best surgical strategy in patients with severe hepatotoxicity (Fig. 65.4). Numerous modalities have been proposed to detect chemotherapy-related liver injuries preoperatively, but no consensus has been reached. Although abnormal liver function tests may suggest hepatic injury, assessment of the severity of hepatic injury is not possible based only on these laboratory values (Brouquet et al, 2009; Nakano et al, 2008). The combination of macroscopic and microscopic examinations of the liver provided by preoperative laparoscopy with intraoperative liver biopsies probably offers the best assessment of the effects of preoperative chemotherapy in patients at high risk for surgical complications (Vauthey et al, 2006). However, this is an invasive approach, which limits its routine use. Image-guided liver biopsy has also been proposed to assess liver injuries; however, the practicality of such an approach is questionable because of the heterogeneity of hepatic lesions and because of interobserver variations in the histologic identification of chemotherapy-related liver injuries.

A number of noninvasive imaging methods have been evaluated to preoperatively determine the presence and degree of liver injuries. Ultrasound (US) is ineffective in differentiating hepatic steatosis from fibrosis because it is highly operator dependent and therefore prone to interobserver variations (Mazhar et al, 2009). Computed tomography (CT) offers the

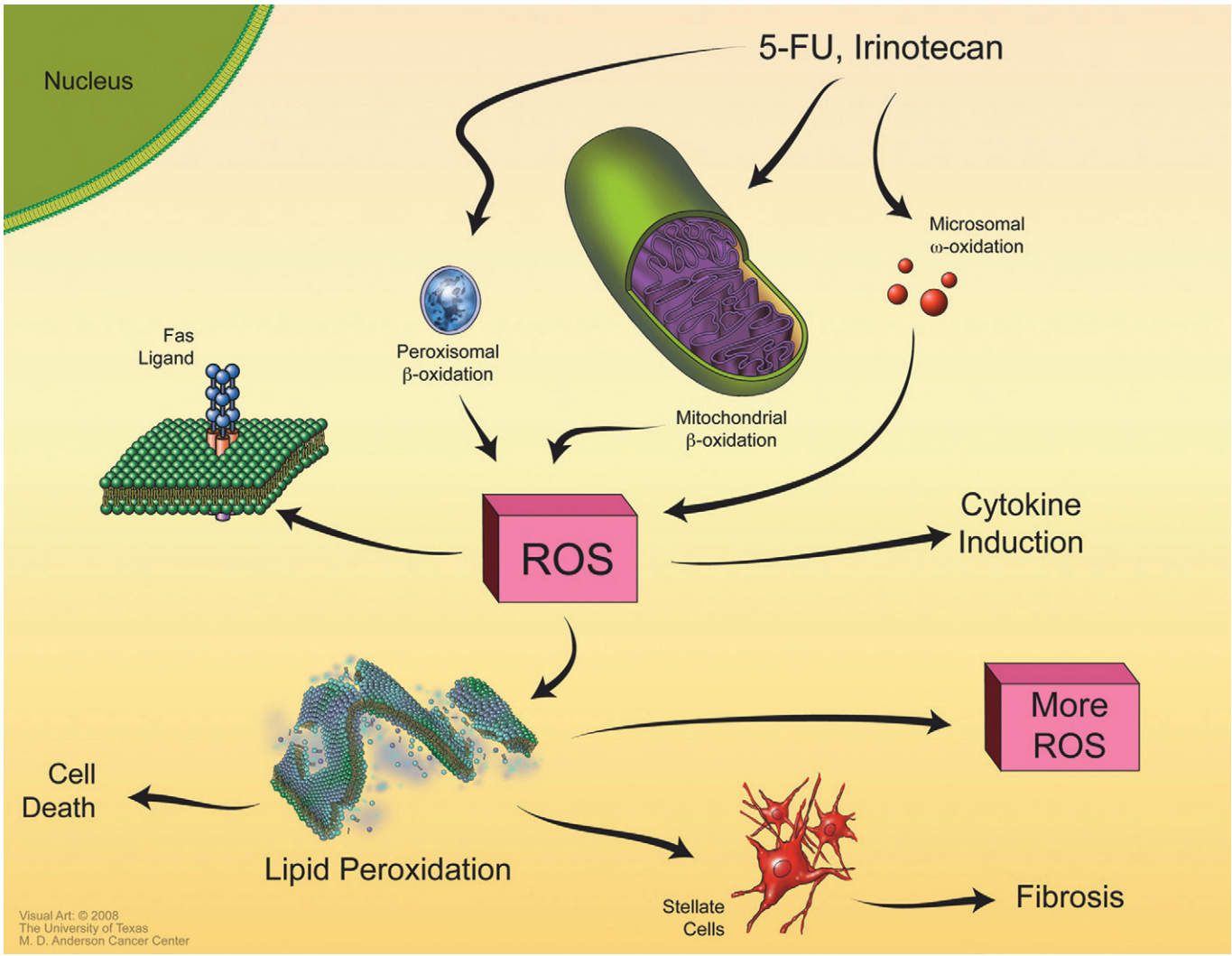


FIGURE 65.3. Cytotoxic drugs impair mitochondrial oxidation, leading to reactive oxygen species production, Fas ligand death receptor expression, and cytokine induction. Lipid peroxidation results in cell death, stellate cell activation, and fibrosis. 5-FU, 5-fluoruracil; ROS, reactive oxygen species. *(From Chun YS, et al, 2009: Management of chemotherapy-associated hepatotoxicity in colorectal liver metastases. Lancet Oncol 10:278-286.)*

advantage of being part of the preoperative workup of liver metastases, and its performance to detect steatosis has been evaluated (Kodama et al, 2007; Cho et al, 2008). Non–contrast-enhanced CT images more accurately estimate hepatic steatosis than do contrast-enhanced images. Unenhanced liver parenchyma with an attenuation value less than 40 Hounsfield units (HU) is indicative of more than 30% hepatic steatosis. However, marked steatosis cannot be excluded on non–contrast-enhanced CT (Cho et al, 2008; Kodama et al, 2007).

Magnetic resonance imaging (MRI) can also be useful for characterizing certain types of liver injuries. Super paramagnetic iron oxide (SPIO) agents are preferentially taken up in Kupffer cells (Ward et al, 2008) and can be used to increase the accuracy of MRI to detect sinusoidal injury because this lesion is associated with a change in Kupffer cell phagocytic behavior. Ward and colleagues (2008) evaluated the performance of SPIO-enhanced MRI for the assessment of sinusoidal injury and found a sensitivity of 87% and specificity of 89%; however, these MRI techniques are investigational and therefore have limited utility. Furthermore, MRI lacks specificity (63%) and is less accurate than non–contrast-enhanced CT for detecting steatosis (Cho et al, 2008). Because of these limitations and the high cost, MRI is not routinely used to detect hepatic injury.

CHEMOTHERAPY-ASSOCIATED LIVER DAMAGE AND SURGICAL RESECTION

Table 65.1 summarizes the results of several studies on the relationship between the presence of hepatic injury and the postoperative complication rate. Although the presence of steatosis does not increase 90-day postoperative mortality rates (Vauthey et al, 2006), Kooby and colleagues (2003) reported in a series of 485 patients that marked steatosis was an independent risk factor for postoperative infectious complications. In this study, the presence of marked steatosis was independently associated with preoperative chemotherapy.

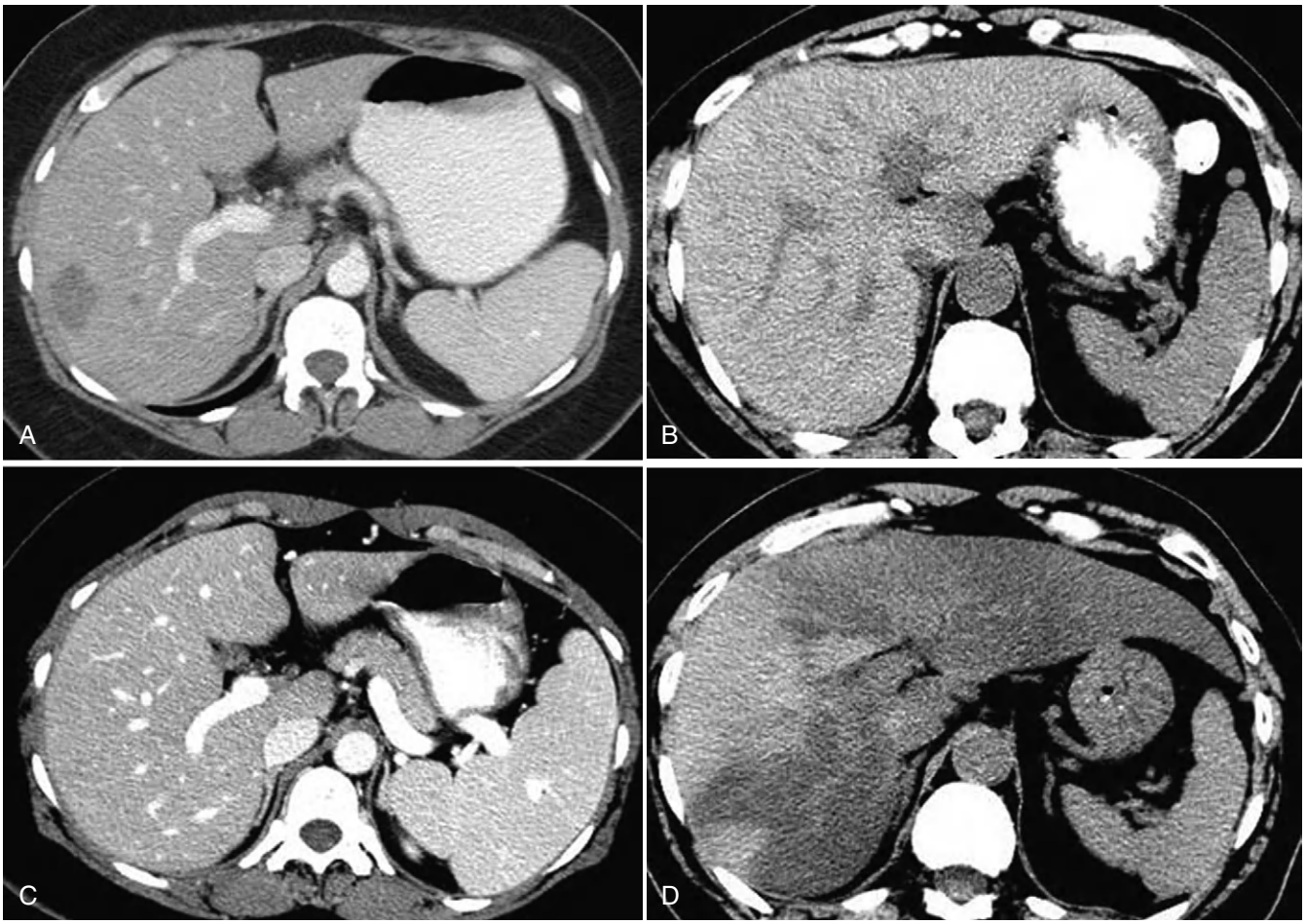


FIGURE 65.4. Radiographic manifestations of chemotherapy-related injury. Computed tomography (CT) images taken before (**A**) and after (**C**) 6 months of FOLFOX (folinic acid, fluorouracil, oxaliplatin) therapy show the resolution of colorectal cancer liver metastasis and interval development of splenomegaly. CT images taken before (**B**) and after (**D**) 2 months of FOLFIRI (folinic acid, fluorouracil, irinotecan) therapy show the interval development of contiguous areas of hepatic parenchymal steatosis.

Irinotecan-related steatohepatitis, although less frequent, is potentially more dangerous in candidates for liver resection. Vauthey and colleagues (2006) evaluated the outcomes of 406 patients who underwent liver resection for colorectal cancer liver metastases; 248 of them had received preoperative chemotherapy, and 158 had not. The presence of steatohepatitis, observed in 8.4% of patients, was associated with an increase in the 90-day postoperative mortality rate as a result of liver failure (15% in patients with steatohepatitis vs. 2% in those without; $P = .001$). The presence of severe sinusoidal injuries has been reported to be closely associated with the risk of bleeding and the requirement for blood transfusion during resection in patients who received oxaliplatin-based chemotherapy for more than 6 months (Aloia et al, 2006). Others have suggested that sinusoidal injuries increase the risk of postoperative complications after major liver resection (Nakano et al, 2008).

Overall, the effect of a sinusoidal lesion on posthepatectomy outcome is real but probably less severe than steatohepatitis, as demonstrated in the European Organisation for Research and Treatment of Cancer (EORTC) 40983 trial (Nordlinger et al, 2008). In this prospective randomized trial comparing patients treated by surgery plus perioperative FOLFOX (folinic acid, fluorouracil, oxaliplatin) versus surgery alone for resectable colorectal liver metastases, the 151 patients randomized to receive perioperative FOLFOX were more likely to develop reversible postoperative complications than the 152 patients who underwent resection without chemotherapy (25% vs. 16%, respectively; $P = .04$; Nordlinger et al, 2008). However, perioperative mortality rate was low (1%), and it was similar in the two groups.

In addition to increasing the risk for postoperative complications, chemotherapy-related liver injuries appear to impair the radiographic detection of liver metastases. Angliviel and colleagues (2009) assessed the ability of CT to detect liver metastases in patients with or without preoperative chemotherapy before planned liver resection. Preoperative CT findings were compared with intraoperative and histologic findings. In this study, preoperative chemotherapy, more than three liver metastases, and steatosis greater than 30% were independent risk factors of inaccurate CT staging.

Table 65.1

Studies Examining the Effects of Preoperative Chemotherapy and Chemotherapy-Related Liver Injury on Postoperative Morbidity and Mortality

Reference	No. Patients	Major Hepatectomy	Systemic Agent	Pathology from Non–Tumor-Bearing Liver	Morbidity	Mortality
Kooby et al (2003)	325 chemotherapy, 160 control	69% (224/325) steatosis 63% (100/160) no steatosis	Fluorouracil ± irinotecan	Steatosis	Increased*	NS
Parikh et al (2003)	61 chemotherapy, 47 control	100% (108)	Fluorouracil ± irinotecan	Steatosis	NS	NS
Fernandez et al (2005)	24 chemotherapy	54% (13/24)	Fluorouracil ± irinotecan/ oxaliplatin†	Steatohepatitis	NA	NA
Karoui et al (2006)	45 chemotherapy, 22 control	100% (67)	Fluorouracil ± irinotecan/ oxaliplatin‡	Sinusoidal injury	Increased‖	NS
Aloia et al (2006)	75 chemotherapy, 17 control	65% (60/92)	Fluorouracil ± oxaliplatin	Sinusoidal injury	NS	NS
Vauthey et al (2006)	248 chemotherapy, 158 control	68% (275/406)	Fluorouracil ± irinotecan Fluorouracil ± oxaliplatin	Steatohepatitis, sinusoidal injury	NS NS	Increased NS
D'Angelica et al (2007)	32 bevacizumab, 32 control	53% (34/64)	Bevacizumab + chemotherapy	NA	NS	NS
Pawlik et al (2007)	153 chemotherapy, 59 control	43% (91/212)	Fluorouracil + oxaliplatin Fluorouracil + irinotecan	Sinusoidal injury, steatosis, steatohepatitis	NS NS	NS NS
Reddy et al (2008)	39 bevacizumab, 57 control	69% (66/96)	Bevacizumab + chemotherapy	NA	NS	NS
Nakano et al (2008)	36 chemotherapy§	100% (36)	Fluorouracil + oxaliplatin	Sinusoidal injury	Increased	NA
Nordlinger et al (2008)	151 chemotherapy, 152 control	55% (167, ≥2 segments)	Fluorouracil + oxaliplatin	Sinusoidal injury	Increased	NS
Brouquet et al (2009)	146 chemotherapy, all within 3 months before surgery	77% (112/146)	Fluorouracil/Fluorouracil + oxaliplatin/ Fluorouracil + irinotecan	Sinusoidal injury, steatosis, steatohepatitis	Increased	NS
Kishi et al (2010)	219 chemotherapy; 157 received 1 to 8 cycles, 62 received ≥9 cycles	57% (125/219)	Fluorouracil + oxaliplatin, ± bevacizumab	Sinusoidal injury	Increased with ≥9 cycles	NS

*Overall complication rate increased, but major (grade ≥3) complications did not increase.
†Only four patients received oxaliplatin.
‡40 patients received oxaliplatin.
§36 patients who underwent major hepatectomy represent a subset of the 90 patients in the study.
‖Increases in morbidity were observed in patients who received ≥6 cycles.
NA, not available; *NS,* not significant

Modified from Chun YS, et al, 2009: Management of chemotherapy-associated hepatotoxicity in colorectal liver metastases. Lancet Oncol 10:278-286.

MINIMIZING THE RISKS AND CONSEQUENCES OF HEPATIC INJURY

A better knowledge of the determinants of chemotherapy hepatotoxicity has led to various measures proposed to minimize the incidence and consequences of hepatic injury. The duration of chemotherapy exposure and the time interval between the cessation of chemotherapy and liver resection have been recognized as risk factors of hepatic injury (Aloia et al, 2006; Karoui et al, 2006; Kishi et al, 2010; Nakano et al, 2008). In a series of 45 patients who underwent major liver resection, Karoui and colleagues (2006) showed that receiving six or more cycles of preoperative chemotherapy was a predictor of postoperative morbidity (54% vs. 19%; $P = .047$). Another study found that when compared with shorter duration treatment, preoperative chemotherapy of more than 12 cycles increased the risk of reoperation (11% vs. 0%, respectively; $P = .04$) and resulted in a longer hospital stay (11 vs. 7 days; $P = .02$) after liver resection for colorectal liver metastases (Aloia et al, 2006). In this study, hemorrhagic centrilobular necrosis was more common in patients treated with more than 12 cycles of chemotherapy than in patients with a shorter chemotherapy duration (50%, 25%, and 10%, respectively; $P = .01$). Prolonged preoperative chemotherapy has been confirmed as an independent risk factor for grade 2 and grade 3 sinusoidal injuries in a series of 90 patients who underwent liver resection for colorectal cancer liver metastases (Nakano et al, 2008). Prolonged chemotherapy is associated with an increased rate of postoperative morbidity, but it does not appear to increase the rate of major or complete pathologic response (Kishi et al, 2010); therefore it is desirable to pursue liver resection after a short course (e.g., six cycles or less) of preoperative chemotherapy and to cease chemotherapy as soon as the lesions are resectable in patients with initially unresectable liver metastases.

The time interval between cessation of chemotherapy and liver resection also influences the risk of postoperative complications and the incidence of hepatic injury (Brouquet et al, 2009; Welsh et al, 2007). Welsh and colleagues (2007) found in a series of 497 patients who underwent resection of colorectal cancer liver metastases with and without preoperative chemotherapy that an interval of 4 or fewer weeks between chemotherapy and surgery was a risk factor for the development of postoperative complications. More recently, a time interval of less than 4 weeks was identified as an independent risk factor for chemotherapy-related liver injury in a series of 146 patients who received preoperative chemotherapy for colorectal cancer liver metastases (Brouquet et al, 2009). The influence of the time interval on the severity of hepatic injury supports the current recommendation to wait at least 5 weeks between the cessation of chemotherapy and liver resection.

Other strategies to minimize liver injury have focused on the use of additional pharmacologic agents. Bevacizumab is a monoclonal antibody directed against the vascular endothelial growth factor receptor (VEGF-R); when used with 5-FU–based chemotherapy for metastatic colorectal adenocarcinoma, it is associated with improvements in both radiologic response rates and survival (Hurwitz et al, 2004). However, bevacizumab increases the risk of various tumor-related complications, including bleeding and perforation (Chen et al, 2006; Shah et al, 2005); therefore its use during the perioperative period in patients with colorectal cancer liver metastases was initially thought to be potentially deleterious. Several studies have since shown that the addition of bevacizumab to preoperative chemotherapy is safe, provided a sufficient time interval is allowed to elapse between the cessation of chemotherapy and liver resection (i.e., 6 weeks, which is two half-lives) (D'Angelica et al, 2007; Gruenberger et al, 2008; Kesmodel et al, 2008).

Ribero and colleagues (2007b) evaluated the influence of bevacizumab in a series of 105 patients who underwent liver resection for colorectal liver metastases after preoperative chemotherapy. They found that preoperative bevacizumab with oxaliplatin had higher rates of pathologic response, assessed by the proportion of patients with less than 25% viable tumor cells (45% with bevacizumab vs. 23% without bevacizumab) and a lower incidence of sinusoidal injury (any grade: 27.4% with bevacizumab vs. 53.5% without; moderate or severe: 8.1% with bevacizumab vs. 27.9% without; both $P < .01$) (Fig. 65.5). This protective effect of bevacizumab against oxaliplatin-induced sinusoidal injury has been confirmed in two other studies (Gruenberger et al, 2008; Rubbia-Brandt et al, 2010).

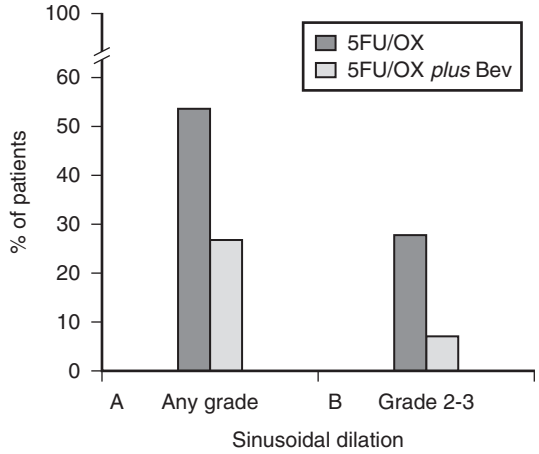


FIGURE 65.5. Frequency and grades of sinusoidal dilatation observed in non–tumor-bearing livers by type of preoperative chemotherapy regimen. *5FU/OX,* 5-fluorouracil and oxaliplatin; *Bev,* bevacizumab. *(Modified from Ribero D, et al, 2007b: Bevacizumab improves pathologic response and protects against hepatic injury in patients treated with oxaliplatin-based chemotherapy for colorectal liver metastases. Cancer 110: 2761-2767.)*

Other pharmacologic agents may also have a protective effect against liver injury. Brouquet and colleagues (2009) retrospectively explored the risk factors for chemotherapy-related

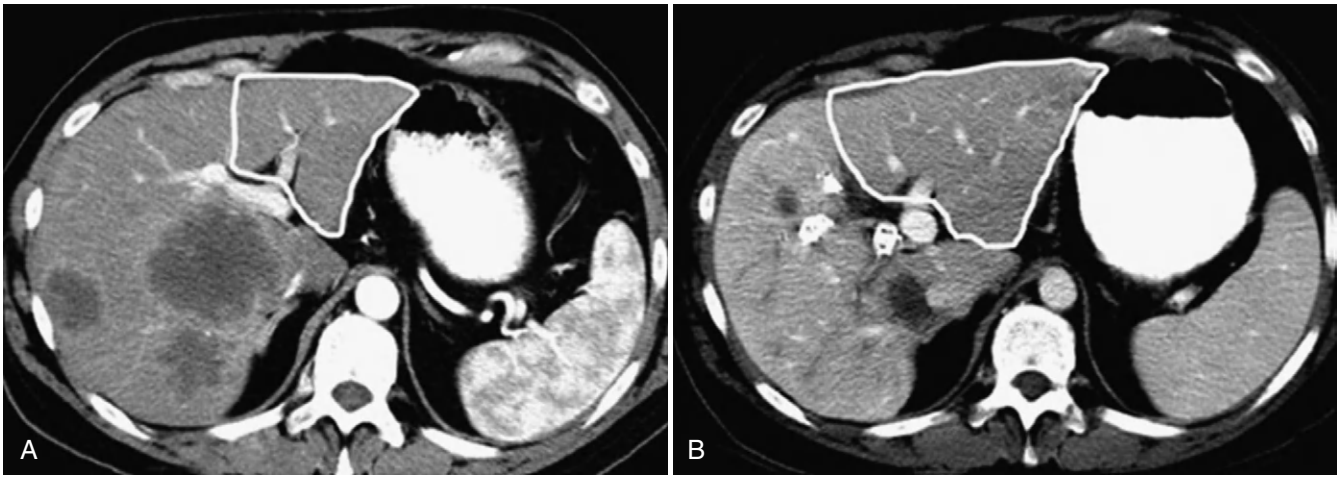


FIGURE 65.6. Computed tomography (CT) images from a patient with multiple, large metastases who required extended right hepatectomy. **A,** The measured volume of the future liver remnant (FLR; bisegments II and III, outlined in *white*) was 291 cm^3, and the standardized FLR (sFLR) was calculated as 17% of the estimated total liver volume (TLV). To downsize metastases and induce hypertrophy in the FLR before hepatectomy, chemotherapy was administered, followed by portal vein embolization. **B,** This led to an increase in the FLR volume to 510 cm^2 and in sFLR to 30% of the estimated TLV. *(From Chun YS, Vauthey JN, 2007: Extending the frontiers of resectability in advanced colorectal cancer. Eur J Surg Oncol 33[suppl 2]:S52-S58.)*

liver injuries in a group of 146 patients who had undergone resection of liver metastases within 3 months of preoperative chemotherapy and found that low, daily "cardiac prophylaxis" doses of aspirin (75 to 360 mg) may have a protective effect against sinusoidal injury and other chemotherapy-related liver injuries. This beneficial effect of aspirin has yet to be confirmed by other studies.

In patients with advanced liver disease who receive prolonged chemotherapy, hepatic injury cannot be avoided, and the objective is to minimize its consequences. Portal vein embolization (PVE) was initially proposed to increase resectability in patients who require extended resections but with an inadequate liver remnant (see Chapter 93). It can also be used to increase the hepatic reserve in patients suspected to have hepatic injury who may require extended liver resection (Fig. 65.6) (Abdalla et al, 2002; Azoulay et al, 2000; Kishi et al, 2009; Ribero et al 2007a). Hypertrophy of the liver remnant after PVE seems to not be significantly affected by the preoperative chemotherapy even if associated with bevacizumab (Goere et al, 2006; Zorzi et al, 2008). This is a test to assess the regenerative capacities of the liver because the degree of hypertrophy correlates with the postoperative mortality rate (Farges et al, 2003; Ribero et al 2007a). At the University of Texas M.D. Anderson Cancer Center, in patients who have received extended chemotherapy (>4 months) or in those with a preexisting hepatic injury, PVE is performed if the future liver volume is 30% or less of the total liver volume. A degree of hypertrophy of 5% or less after PVE is considered a contraindication to major liver resection (Ribero et al, 2007a).

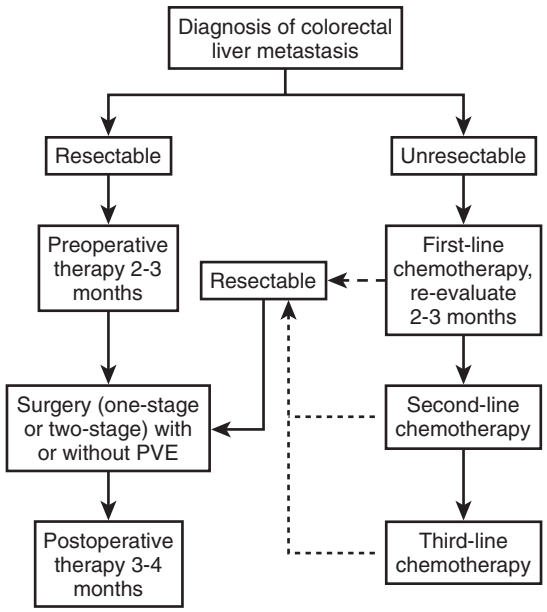


FIGURE 65.7. Treatment recommendations for colorectal cancer liver metastases when preoperative chemotherapy is used. Portal vein embolization is considered if the future liver remnant is 20% or less of the total volume in a healthy liver, 30% or less after extensive chemotherapy (>4 months), or 40% or less in patients with cirrhosis. It should be noted that not all patients with resectable disease require preoperative treatment, and proceeding directly to resection is an alternative approach. *(Modified from Kopetz S, Vauthey JN, 2008: Perioperative chemotherapy for resectable hepatic metastases. Lancet 371:963-965.)*

CONCLUSION

The increasing use of preoperative chemotherapy has led to an increased incidence of hepatic injury, including NAFLD and sinusoidal injury. Although the consequences of hepatic injury can vary widely according to its severity, it is of major concern to liver surgeons. Overall, hepatic injury rarely affects surgical outcomes if the lesions are identified preoperatively. In patients receiving preoperative chemotherapy who are at risk for developing hepatic injury, the use of simple guidelines regarding the duration of the treatment (2 to 3 months in patients with resectable metastases) and the time interval between chemotherapy and surgery (>5 weeks) should optimize surgical outcomes (Fig. 65.7).

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PART 7: Hepatic Disease

SECTION I: Inflammatory, Infective, and Congenital

B. Liver Infection and Infestation

CHAPTER 66

Pyogenic liver abscess

Oscar M. Mazza and Eduardo De Santibañes

OVERVIEW

Pyogenic liver abscess (PLA) may be defined as solitary or multiple collections of pus within the liver, the result of bacterial infection. In 1938, Ochsner and coworkers reported the first series of patients with hepatic abscesses in the modern surgical era treated by surgical drainage. This study included 47 patients and reported an overall survival of 67%. The advent of antibiotic therapy marked the basis of the contemporary treatment of liver abscesses, becoming a major part of the therapy, combined with surgical drainage. The first landmark report in minimally invasive treatment of liver abscess was that of McFadzean and colleagues in 1953. They presented a group of 14 patients who underwent percutaneous drainage for PLAs with no deaths within the group. Although potentially effective for dealing with the liver problem, such approaches present the disadvantage of overlooking the underlying abdominal pathology because of the lack of surgical exploration.

The development of clinical ultrasound (US) in the 1960s and the introduction of computed tomography (CT) in the 1970s represent the two major advances in the diagnosis and treatment of PLAs. Surgical exploration as a diagnostic tool was replaced by abdominal imaging, thus allowing minimally invasive techniques to become the first choice of treatment. Currently, percutaneous needle aspiration (PNA) and percutaneous catheter drainage (PCD) have become standard methods for both single and multiple PLAs (see Chapter 28). Surgical debridement, done either in an open or laparoscopic fashion, has a limited therapeutic role for patients in whom nonoperative treatment fails or in those requiring surgical treatment for the underlying cause of the abscess. In addition, surgical exploration may be indicated as the initial procedure when coexistence of peritonitis is suspected as result of abscess rupture into the peritoneal cavity.

ETIOLOGY

During the nineteenth century, PLAs were well known as a complication of acute appendicitis. Since then, etiology and presentation have dramatically changed. Inflammatory abdominal diseases are no longer the most common underlying conditions for PLAs, being replaced in later decades by a higher incidence of biliary causes, including malignancies, immunocompromised status, and advanced age (Branum et al, 1990). In 1996, Huang and colleagues (1996) presented a review that spanned more than 40 years in the treatment of PLAs. They analyzed and compared patterns of clinical presentation in 80 patients treated between 1952 and 1972 with a second group of 153 patients treated from 1973 to 1993. The authors concluded that the increased incidence of biliary malignancies as a cause of PLAs was due to a more aggressive approach in the treatment of this pathology, which includes more frequent instrumentation of the biliary tree (see Chapters 28 and 50D). Hilar cholangiocarcinoma was the most frequent single condition found during the second period reviewed, with the use of biliary stents and broad-spectrum antibiotics leading to the emergence of mixed bacterial and fungal infections. Biliary malignancy was an important risk factor for hospital mortality (Lok et al, 2008).

Elucidating the subjacent condition that caused a liver abscess is as important therapeutically as the correct treatment of a PLA. In a simplified schema, infection may get to the liver by five different avenues: 1) portal vein, 2) hepatic artery, 3) biliary tree, 4) adjacent organ infection, and 5) direct trauma to the liver. The term *cryptogenic PLA* applies when no underlying pathology is identified (Box 66.1).

Portal pyemia is often a consequence of intraabdominal infection, such as acute appendicitis or diverticulitis. The incidence of this mechanism as a cause of PLA has markedly decreased in the past years. However, portal vein patency must be evaluated with Doppler US or dynamic CT scan in patients with PLAs. Gastrointestinal malignancies, such as colorectal adenocarcinoma or even gastric carcinoma, may also lead to a disruption of the mucosal barrier, leading to pyemia and liver abscess in the absence of liver metastasis (Tzur et al, 2003). This phenomenon should be particularly considered in the evaluation of patients with a cryptogenic PLA (Lim & Lim, 2004). Adequate investigation of etiology after PLA treatment may lead to a diagnosis of an underlying disease previously unknown for the patient (Mohsen et al, 2002).

Box 66.1

Classification of PLA According to the Underlying Mechanism of Dissemination

Hepatobiliary

Cholelithiasis
Benign strictures
Acute cholangitis
Periampullary tumors
Gallbladder cancer

Portal

Diverticulitis
Anorectal suppuration
Pelvic suppuration
Postoperative sepsis
Intestinal perforation
Pancreatic abscess
Appendicitis
Chronic inflammatory bowel disease
Colonic cancer
Gastric cancer

Arterial

Endocarditis
Vascular sepsis
Ear, throat, nose, or dental infection

Traumatic

Open or closed abdominal trauma
Chemoembolization
Percutaneous ethanol injection or radiofrequency ablation

Adjacent Abdominal Pathology

Acute cholecystitis
Gastroduodenal perforation
Colonic perforation

Cryptogenic

PLA, pyogenic liver abscess

Hematogenous spread of infection through the hepatic artery may also cause PLA. Frequent examples are bacterial endocarditis and intravenous drug abuse, but certain immunosuppressive conditions may also be associated with this mechanism. Liver cirrhosis is often associated with immunodeficiency, and the incidence of liver abscesses in cirrhotic patients compared with the general population is increased (see Chapter 9; Molle et al, 2001). Loss of hepatic filter function, impaired immunity, and frequent abdominal infections may also be responsible factors. Immunosuppressive drug use, alcoholism, chronic pancreatitis, pyelonephritis, and acquired immune deficiency syndrome are also associated with PLA (Huang et al, 1996).

The incidence of diabetes mellitus varies among different series, but its presence is associated with a 10-fold increased risk for PLA compared with that of the general population. Diabetes mellitus was the most common comorbidity in a report of PLA from Taiwan and was present in 41 (16%) of 253 patients with PLA (Chen et al, 2008a). Biliary pathology has become the most identifiable cause of PLA in recent decades (Alvarez et al, 2001a). In this group of patients, infection may have different etiologies. Bile duct strictures, common bile duct stones, and hepatolithiasis are benign conditions that may cause PLA (see Chapters 43 and 44). Benign diseases are more commonly reported in Asia (Lok et al, 2008); in Western countries, however, biliary malignancy is a more prevalent condition. Instrumentation of bile duct obstruction by endoscopic stenting or percutaneous drainage is a frequent cause of cholangitis and PLA. Malignancy is a predictor of higher recurrence and mortality rates. The mortality rate of PLA caused by underlying malignant disease is almost twice as high as that of nonmalignant disease (Yeh et al, 1998).

Direct liver contamination by adjacent organ infection may produce a PLA, with acute cholecystitis being the most common example (see Chapter 31). However, gastric and duodenal perforation directly into the liver may also give rise to a PLA. Perforation secondary to foreign bodies, mainly from fish bones, have been also reported. In addition, liver parenchyma may become infected after direct damage. Intrahepatic biloma, hematoma, and necrotic parenchyma are favorable conditions for development of a PLA. This is a well-known consequence of blunt or penetrating liver trauma and liver resections.

In recent decades, local treatments for liver tumors have become a widespread alternative for many patients. These local techniques include ethanol injection, transarterial chemoembolization (TACE), selective internal radiation therapy, and radiofrequency ablation (RFA) (see Chapters 83 through 85), which induce tumor necrosis either by chemical or thermal tissue destruction. In all these patients, PLA is a potentially life-threatening complication that may occur up to 5 months after a successful procedure. Transarterial liver embolization may be helpful in patients with hepatocellular carcinoma or liver metastases of gastrointestinal sarcomas and neuroendocrine tumors. The incidence of liver abscess after this procedure is low. Ong and colleagues (2004) reported PLAs in 0.26% of 3878 embolizations; the mortality rate in these patients was 33%. Patients with bilioenteric anastomosis are at particular risk for this complication. The odds ratio (OR) for developing PLA in this population was 894 in a series from Philadelphia (Kim et al, 2001). Subjacent pathology is not a predisposing factor for this complication (Song et al, 2001), but RFA of liver tumors may also cause a PLA. In a multicenter study from Italy, Livraghi and coworkers (2003) reported 2320 patients with 3554 lesions, with a 0.3% incidence of PLA. This incidence was slightly higher (1.7%) in another group of patients with hepatocellular carcinoma treated by RFA (Choi et al, 2005). De Baere and colleagues (2003) reported a 100% incidence of liver abscess in patients with prior bilioenteric anastomosis who underwent RFA. A further prospective analysis showed an incidence of PLA of 50% in patients with biliary diversions, but the risk was not increased if this diversion was performed synchronously with the ablation procedure (Elias et al, 2006).

In some patients with a PLA, no underlying cause is identified; they are considered to have a cryptogenic PLA. These cases account for up to 67% in some published data (Chen et al, 2008a). Etiology and presentation are summarized in Table 66.1.

INCIDENCE

PLA is a rare disease, and actual incidence rates are poorly described in the literature. However, recent investigations demonstrated a marked increase of PLA incidence in the general population in the last few years. Huang and colleagues (1996) showed that PLA accounted for 13 per 100,000 hospital admissions in 1973, which increased to up to 20 per 100,000 only 20 years later. In a recent study from a teaching hospital in the

Table 66.1

Demographics, Origin, and Mortality Rates of PLAs in Eastern and Western Series

Reference	No. Patients	Age (Years)	Diabetes (%)	Biliary (%)	Cryptogenic (%)	Solitary (%)	Right Lobe (%)	Mortality (%)
Chen, Taiwan (2008)	253	56.4	41.9	29.6	67.2	67.6	71.5	9.1
Lok, Hong Kong (2008)	111	62.6	18.9	22.5	53	80.2	67.6	11.7
Eroles Vega, Spain (2008)	68	63	6	37	35	56		19
Seeto, United States (1996)	142	51	15	37	40	61	58	10
Alvarez, Spain (2001)	133	16-92 (range)	12	18.5	25.5	73	71.5	14

PLAs, pyogenic liver abscesses

United Kingdom, PLA had an incidence of 18.5 per 100,000 hospital admissions, with an estimated crude incidence of 2.3 cases per 100,000 the general population (Mohsen et al, 2002).

Two recent studies demonstrated this tendency in both Eastern and Western countries. In 2008, Tsai and colleagues published an analysis of PLA in the Taiwanese population from 1996 through 2004. The incidence of PLA rose from 11.15 to 17.59 cases per 100,000 inhabitants over the period of study, with more than 30,000 cases occurring in this period. Of these patients, 62% were male; the age of highest incidence in men was 80 to 84 years, and for women it was 85 to 89 years. Factors associated with PLA were diabetes, malignancy, renal disease, and pneumonia. Mortality rates, however, decreased from 12.33% in 1996 to 9.72% in 2004.

The second, a national series from Denmark (Jepsen et al, 2005), analyzed 1448 cases in a 25-year period; 54% were male. The incidence of PLA in Danish men was 6 per million in 1977 and 18 per million in 2002. In women, the incidence rose from 8 per million to 12 per million in the same period. Mortality rates in 1977 were 40% and 50% for men and women, respectively, and decreased to a global 10% in 2002.

CLINICAL PRESENTATION

Liver abscesses may have a broad array of symptoms and physical findings, which may vary according to the patient's underlying condition. Cryptogenic lesions are often found after several days of nonspecific symptoms. The most frequent clinical features include fever of more than 38° C and chills. Other symptoms that may be present are general malaise and anorexia. Patients may also have abdominal pain, nausea and vomiting, diarrhea, and weight loss. Although more often found with abscesses of biliary origin, jaundice may be an indicator of systemic sepsis response, and septic shock may be a dramatic form of the presentation. There are no significant differences in clinical presentation between single and multiple lesions, although single PLAs are more frequent in the right lobe of the liver. These symptoms may be present from several days up to several weeks before hospital admission (Chou et al, 1997; Seeto & Rockey, 1996). In another group of patients, PLA is a consequence of an underlying pathologic process that may lead to a faster diagnosis. Benign or malignant biliary disease, intraabdominal infections, and abdominal surgery are frequent causes of abscesses, and imaging studies should be systematically carried out to exclude the presence of a PLA in a septic patient.

Finally, some patients may be seen with systemic complications as a result of metastatic septic lesions that originate from a PLA. Although rare, cases of endophtalmitis; meningitis; cellulitis; lung abscess; prostate, kidney, and joint infections; pulmonary embolisms; and even cardiac tamponade due to pericardic effusion have been reported in the literature (Cahill et al, 2000; Vong et al, 2007). Infection by *Klebsiella pneumoniae* genotype K1 and an underlying condition of immunosuppression resulting from diabetes mellitus and alcoholism may be predisposing factors for these complications (Chen et al, 2006; Fang et al, 2007).

DIAGNOSIS

The most common laboratory findings are nonspecific alterations as a result of infection. In a large series from Hong Kong, low albumin levels were found in 92.8% of patients presenting with PLAs (Lok et al, 2008). Leukocytosis (74.8%), increased alkaline phosphatase (72.1%), and elevated alanine aminotransferase levels (ALT; 58.6%) were frequent laboratory abnormalities also present in these patients. Jaundice may be seen in up to 50% of patients, and alkaline phosphatase, gamma-glutamyl transferase, erythrocyte sedimentation rate, and glutamic oxaloacetic transaminase levels are usually elevated (Cosme et al, 2010). Alvarez and colleagues (2001) analyzed laboratory data obtained from patients younger than and older than 60 years. The only significant difference between these two groups was that older patients tended to present with higher blood urea nitrogen and serum creatinine levels. Hemoglobin level, serum C-reactive protein, blood urea nitrogen, creatinine levels, prothrombin time, and total bilirubin levels must be part of systematic laboratory tests in patients with PLA.

Some findings at presentation may be prognostic and associated with increased mortality rate. Chen and colleagues (2008b) presented a review of 72 patients admitted to the intensive care unit. Low levels of serum albumin, increased serum creatinine, and prolonged prothrombin time were significant risk factors for death. These authors' findings are shown in Table 66.2.

The clinical investigations used to evaluate liver abscesses have changed in recent decades. Plain radiographs may be part of the routine evaluation, but these play a minor role in PLA diagnosis. Indirect findings in chest and abdominal radiographs may include atelectasis, an elevated right hemidiaphragm, pleural effusion, enlargement of the liver shadow, and exceptionally an air-fluid level in gas-forming bacterial infections.

US imaging is usually the first diagnostic approach in these patients. Although US examination may not detect small lesions and those located on the dome, it has several advantages. It is fast, inexpensive, and provides information about biliary tract

Table 66.2

Laboratory Data of 72 Patients with PLA on the First Day of Intensive Care

Variable	Survivors (n = 52)	Nonsurvivors (n = 20)	*P* Value
WBC count (103/mm^3)	16.5 ± 18	16.4 ± 14	.99
Hemoglobin (g/dL)	11.3 ± 2	10.4 ± 3	.17
Platelet (103/mm^3)	202 ± 175	196 ± 133	.89
ALK-p (IU/L)	182 ± 134	168 ± 105	.75
AST (IU/L)	127 ± 176	562 ± 1571	.28
ALT (IU/L)	105 ± 144	234 ± 468	.09
Total bilirubin (mg/dL)	2.5 ± 2	2.6 ± 2	.89
C-reactive protein (mg/dL)	25.8 ± 10	23.8 ± 9	.61
BUN (mg/dL)	32 ± 22	38 ± 19	.29
Creatinine (mg/dL)	1.9 ± 2	2.9 ± 2	.02
Albumin (g/dL)	2.2 ± 0.6	1.9 ± 0.5	.11
Prothrombin time (s)	16 ± 5	21 ± 5	.01

Data are expressed as mean ± standard deviation.

PYA, pyogenic liver abscess; *WBC*, white blood cell; *ALK-p*, alkaline phosphatase; *AST*, aspartate aminotransferase; *ALT*, alanine aminotransferase; *BUN*, blood urea nitrogen

From Chen SC, et al, 2005b: Comparison of pyogenic liver abscesses of biliary and cryptogenic origin: an eight-year analysis in a University Hospital. Swiss Med Wkly 135:344-351.

and gallbladder pathology, the most prevalent conditions that predispose to PLA. The images obtained by this procedure vary according to different stages of evolution of the disease. Anechoic images are infrequent, with most lesions being hypoechoic; most abscesses present with a smooth wall, which thickens with chronicity. Some abscesses have inhomogeneous content, and if pus becomes thick, the lesion may be confused with liver parenchyma. Gas within an abscess is hyperechoic and casts shadows. Doppler scan should be routinely performed; this may help in differentiating solid tumors, show vessels surrounding the abscess, and, most importantly, evaluate portal vein patency.

CT has a sensitivity of more than 97% in detecting PLA and is considered the most important imaging modality. Examination should be routinely performed with intravenous contrast enhancement. During the arterial phase, parenchyma surrounding the abscess may show segmental enhancement as a result of altered portal microcirculation in the infected tissue. The typical CT image description of PLA is that of a target-like sign (see Chapter 16) that appears as a single or multiloculated mass with a central hypodense region and peripheral contrast enhancement during the portal phase of examination.

CT scan offers the advantage of detecting other intraabdominal pathology that may be the cause of the abscess, such as acute diverticulitis or appendicitis. It may also provide information about portal vein patency and may demonstrate local complications that may include pleural effusion, vascular complications, and spontaneous rupture into the peritoneal cavity, retroperitoneum, and even the pericardium (Yang et al, 2004b). Finally, CT scan is generally necessary to guide percutaneous drainage of the abscess (Fig. 66.1).

Magnetic resonance imaging (MRI) is an alternative to CT for the diagnosis of PLA. In MRI sequences, PLA appears much the same as other fluid-containing lesions: hypointense in T1-weighted and hyperintense in T2-weighted images. After contrast administration, most PLAs show a hyperintense enhancement rim, which may persist in later phases (Balci et al, 1999). Infected tumors or metastases may show the same pattern, and differentiation by MRI may be difficult, although diffusion techniques may play a role in distinguishing between benign and neoplasic lesions. MRI is not widely accepted as a first-line diagnostic approach for several reasons: examinations take more time, patient cooperation is needed, and MRI cannot be used as guidance for percutaneous treatment. Nevertheless, it has the advantage of providing data regarding the biliary tract in patients with underlying biliary pathology, findings that could change the therapeutic approach (Fig. 66.2).

Nuclear medicine has a limited role in PLA diagnosis, but in case of doubt, it may be helpful for detecting intraabdominal abscesses. This may be important, for example, in a patient with polycystic liver disease and suspected infection of a single lesion. Indium-111 leukocyte scintigraphy readily detects most hepatic abscess. Gallium-67 may also be used, but it is normally taken up by the liver, making interpretation of the results more difficult. In both cases, prior technetium-99m sulfur colloid scan provides more diagnostic accuracy (Youssef et al, 2005).

Conflicting results have been reported regarding PLA characteristics according to different origins (Chen et al, 2005). Single lesions tend to be cryptogenic, whereas multiple abscesses are more likely to have a biliary origin (Alvarez et al, 2001). Regardless of etiology, patients are most commonly seen initially with a single lesion (Chan et al, 2005). In both single and multiple forms, abscesses are more frequently located in the right hepatic lobe, followed by a left and bilateral distribution (Chen et al, 2008a; Seeto & Rockey, 1996).

A PLA less than 2 cm in diameter is described as a *microabscess*. Multiple microabscesses may present as widely scattered lesions or with a cluster pattern that tends to aggregate focally (Ralls, 2002). The diffuse miliary pattern of pyogenic microabscesses is usually staphylococcal in origin, the result of hematogenous spread of an endovascular infection. The cluster pattern is often associated with coliform and enteric organisms and may occur in cholangitic abscesses secondary to biliary obstruction. It is probable that the clustering of pyogenic microabscesses is an early stage of an evolving pyogenic abscess cavity, and the tendency of coliform microabscesses to coalesce into a larger abscess with intercommunicating cavities explains the success of single-catheter drainage of multiseptate PLAs.

MICROBIOLOGY

Although PLAs may originate from a broad spectrum of microorganisms, the underlying etiology and geographic location of PLAs are often related to specific pathogens. Identification of pathogens may be achieved by direct puncture of the abscess or by blood cultures. The positive abscess culture rates are higher than those of blood culture samples, and only up to 50% of patients with PLA have both cultures positive (Chen et al, 2005). Moreover, negative abscess cultures may be found in 20% of patients (Lok et al, 2008). Poor culture technique may be the reason in some cases, but negative cultures can also be caused by the use of broad-spectrum antibiotics before cultures are obtained. Patients with cryptogenic PLAs are more likely to have negative cultures from the blood, whereas patients with PLAs secondary to biliary tract disorders are more likely to have positive cultures from blood and aspirated pus (Seeto & Rockey, 1996).

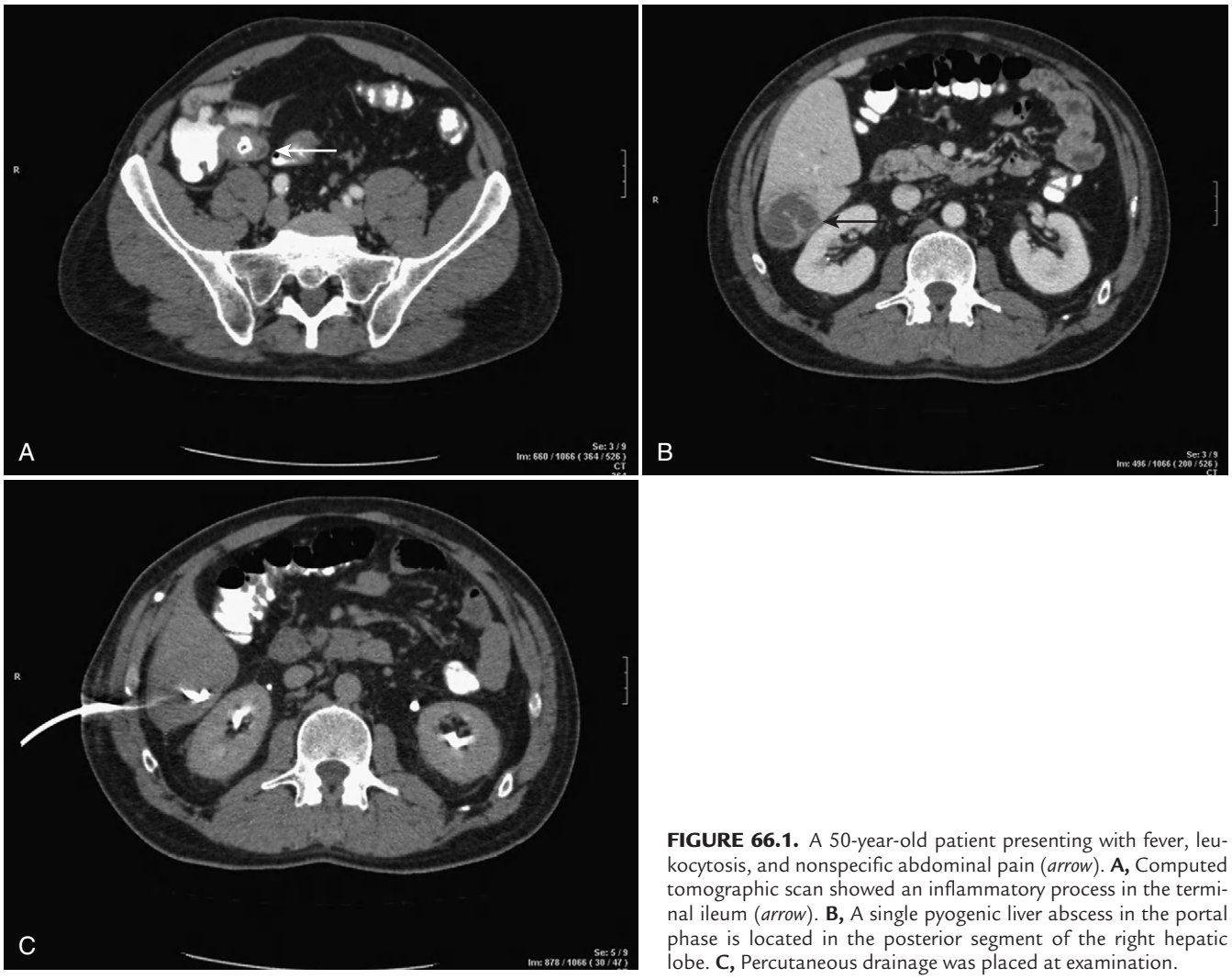


FIGURE 66.1. A 50-year-old patient presenting with fever, leukocytosis, and nonspecific abdominal pain (*arrow*). **A,** Computed tomographic scan showed an inflammatory process in the terminal ileum (*arrow*). **B,** A single pyogenic liver abscess in the portal phase is located in the posterior segment of the right hepatic lobe. **C,** Percutaneous drainage was placed at examination.

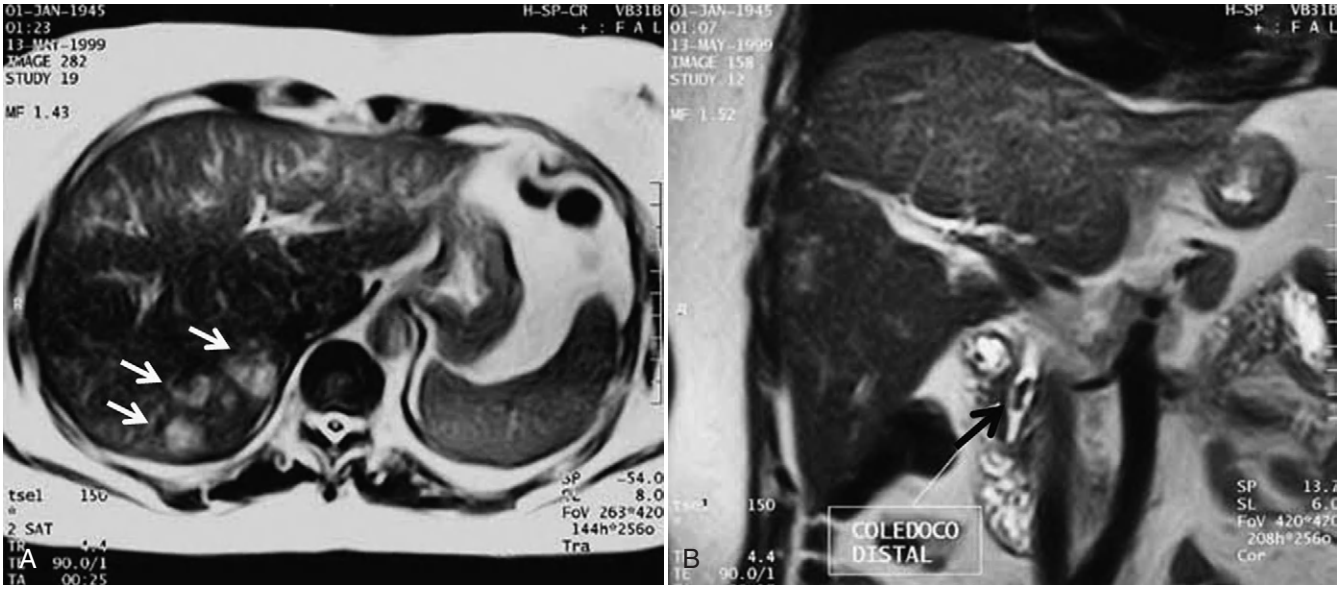


FIGURE 66.2. **A,** Magnetic resonance (MR) image of the liver showing three small pyogenic liver abscesses (PLAs) in the right posterior segment of the liver (*arrows*). **B,** MR cholangiopancreatography demonstrates a stone in the distal common bile duct originating the PLAs (*arrow*).

In Asian populations, *Klebsiella pneumoniae* is the most frequent pathogen associated with cryptogenic PLAs. The incidence of infection with *K. pneumoniae* appears to have markedly increased in this population, ranging from 50% to 88% of all cases occurring in Taiwan in the last few decades to become an endemic disease. Diabetes mellitus is suggested to be an important risk factor, but the pathogenesis is still unclear. No mutations or clonal spread strains have been found. Environmental or host factors may be responsible for the different incidence rates in Asia compared with Western series (Cheng et al, 2002). Although PLAs secondary to *K. pneumoniae* infections are associated with an increased risk of septic metastases, overall mortality, even in diabetic populations, is decreased in this group of patients (Tsai et al, 2008; Yang et al, 2004a).

Gas-forming PLAs are uncommon and often associated with compromised immunity in diabetic patients, and they present higher mortality rates than non–gas-forming PLAs. *Escherichia coli, Enterobacteriaceae,* and *K. pneumoniae* are well-known gas-forming microorganisms. The mechanisms of gas formation involves mixed acid fermentation of glucose, increased production of gas, impaired transportation of gas, and equilibrium between the gas in local tissues and that in abscesses (Lee et al, 2004).

E. coli is the most common pathogen in Western countries, in both monomicrobial and polymicrobial isolates, followed by *Streptococcus milleri.* Anaerobes may also be cultured from PLAs, and *Bacteroides* spp. are the most common isolated organism (Alvarez et al, 2001b; Mohsen et al, 2002).

An abscess secondary to biliary tract disease or originating from a gastrointestinal source is more likely to be polymicrobial with aerobic gram-negative organisms and anaerobes. PLAs that result from hematogenous spread, on the other hand, are more likely to be monomicrobial, and staphylococci and streptococci are the most frequent bacteria isolated in these patients. A summarized spectrum of possible pathogens is listed in Box 66.2.

Box 66.2

Selected Causative Microorganisms of PLAs

Gram-Negative Aerobes

Escherichia coli
Klebsiella pneumoniae
Pseudomonas aeruginosa
Proteus spp.
Enterobacter cloacae
Citrobacter freundii

Gram-Positive Aerobes

Streptococcus milleri
Staphylococcus aureus
Enterococcus spp.

Gram-Negative Anaerobes

Bacteroides spp.
Fusobacterium spp.

Gram-Positive Anaerobes

Clostridium spp.
Peptostreptococcus spp.

PLAs, pyogenic liver abscesses

TREATMENT

The basis for treatment of PLAs relies on complete drainage of pus and infected debris, initiation of adequate antibiotic therapy, and resolution of the underlying cause. Modern imaging techniques allow accurate diagnosis, localization, and assessment of dimensions and actual number of lesions. US is usually performed as the initial diagnostic approach, and CT scan should be routinely performed, either in cryptogenic suspected lesions or in secondary abscesses. The aim of CT examination is to achieve a complete evaluation of the abdominal cavity to asses any underlying condition that may need further or concomitant treatment. If a biliary origin is suspected, MR cholangiopancreatography may be useful to assess the hepatic abscess and completely evaluate the biliary tree. Abdominal imaging has replaced surgical exploration as a diagnostic tool, making possible the high success rates of the percutaneous approach.

Over the past several years, treatment of PLAs has shifted toward minimally invasive percutaneous treatment. Nevertheless, treatment options include a wide spectrum that ranges from antibiotic therapy alone to major operative interventions that could include liver debridement and/or resection. Adequate antibiotic selection is critical in the treatment of PLAs. Blood samples should be obtained before starting antibiotics, if possible, but not at the expense of treatment delay in an unstable patient. Broad-spectrum parenteral therapy must begin as soon as possible. Fine needle aspiration (FNA) or percutaneous drainage may increase the risk of bacteremia, even in stable conditions, so close monitoring of the patient during and after the procedure is always indicated.

The choice of the antimicrobial agent depends of the epidemiology, the patient's background, and the underlying disease if present, and should be adjusted according to geographic differences and local antimicrobial treatment policies. Empiric treatment of a cryptogenic abscess should be directed to cover the most commonly found organisms: gram-negative bacilli, anaerobes, and microaerophilic streptococci. A classic regimen of ampicillin, an aminoglycoside, and metronidazole may be a first therapeutic approach. Other options include combinations of third-generation cephalosporins or quinolones with metronidazole.

Patients who come to medical attention with secondary PLAs should be treated according to epidemiology and risk factors. Abscess secondary to acute cholangitis after biliary instrumentation and postoperative abscess after abdominal surgery should be treated as nosocomial infections, with a distinct epidemiology and flora compared with cryptogenic lesions. Antibiotic selection should be based primarily on the patient's clinical history and local resistance patterns. Imipenem-cilastatin, vancomycin, and piperacillin-tazobactam therapies should be considered in these cases. A sample culture, whenever possible, is mandatory, and when information regarding the organism and antibiotic sensitivity becomes available, modifications can be instituted.

PLAs must be treated with a prolonged course of antibiotics. Initially, antibiotics should be administrated parenterally. This therapy must be maintained until stabilization of the patient's condition is achieved and for at least 2 weeks thereafter. Criteria for clinical stability include subjective and objective evidence of improvement in the inflammatory response produced by the infection. The patient should be afebrile, with a white cell count

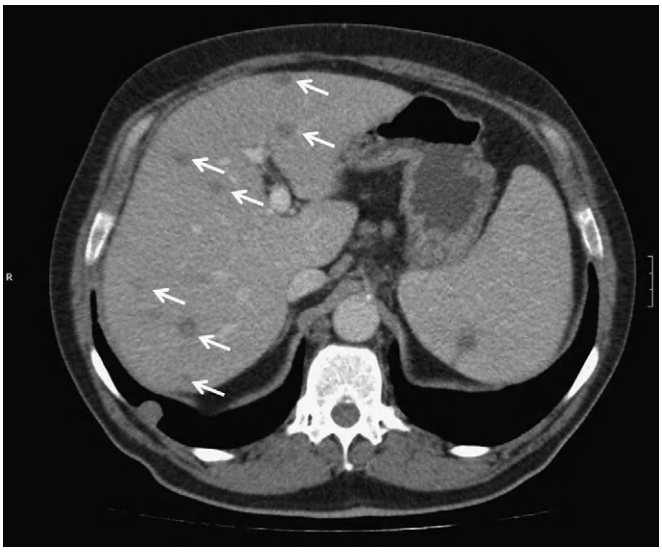


FIGURE 66.3. Multiple microabscesses (*arrows*) in a patient after left colectomy as a result of colon carcinoma. He received intravenous antibiotic therapy for 6 weeks and recovered.

trend toward normal and adequate oral intake and gastrointestinal absorption. The patient may then be switched to oral antibiotic therapy, perhaps even continued on an outpatient basis for at least 2 more weeks. This sequential modality has proven effective in the treatment of PLAs compared with continuous intravenous administration, reducing both the cost of therapy and the length of hospital stay (Ng et al, 2002).

Drainage of all lesions may not be possible in patients with multiple small abscesses. In such cases, percutaneous puncture of any of the abscess may be indicated for isolation of the causative bacteria for a rational antibiotic therapy (Fig. 66.3). If a biliary origin of these lesions is suspected, biliary decompression is mandatory, either by endoscopic, percutaneous, or surgical means (see Chapters 27 through 29). The mortality rates reported in patients with multiple liver abscesses are high, ranging from 22% to 44%. However, Giorgio and colleagues (2006) reported 0% mortality in 39 patients treated with an aggressive approach consisting of percutaneous needle aspiration of all visible lesions under sonographic guidance and antibiotic therapy.

Drainage of pus is usually necessary for an effective resolution and to shorten the duration of antibiotic therapy, especially in lesions greater than 5 cm in diameter. Drainage can be achieved by nonsurgical methods, such as percutaneous catheter drainage (PCD) or percutaneous needle aspiration (PNA). Either open drainage or laparoscopic drainage approaches can be used surgically.

PERCUTANEOUS TREATMENT

Percutaneous drainage is a safe and effective treatment for almost all PLAs (Pearce et al, 2003; see Chapter 28). This procedure can be performed under sonographic or CT guidance. The US exam provides real-time guidance of the needle, and it is fast and reliable (Fig. 66.4). Fluoroscopy control and operating theaters under aseptic conditions are recommended. The freehand technique allows dynamic changes in the needle pattern and does not have the limitations of attached needle guides. CT guidance is recommended for multiple abscess drainage, when multiple catheters may be placed or in cases of hazardous anatomic locations. Local anesthesia and minimal sedation is used for most of these procedures (Giorgio et al, 2006).

After aspiration of a PLA to obtain samples for culture and to confirm the diagnosis, the treatment options are complete aspiration of pus (PNA) or catheter drain insertion (PCD). Controversy persists regarding the optimal procedure, particularly for small abscesses. The first randomized trial conducted by Rajak and colleagues in 1998 showed 100% resolution of PLAs in the PCD group with a 60% success rate in the FNA group. Although FNA patients were given only a second chance of aspiration before placing a PCD, the thickly viscous nature of the pus was considered a major cause of failure in this group. In a subsequent randomized study conducted by Yu and colleagues in 2004 using intermittent needle aspiration, no significant differences were found between PCD and FNA, suggesting that FNA may be as effective as catheter drainage. However, a tendency toward a shorter hospitalization and lower mortality rate was found in the FNA group. Finally, a third trial randomized 60 patients to FNA or PCD (Zerem & Hadzic, 2007). The authors succeeded in all 30 patients undergoing one or two PCDs. In the FNA group, a 33% failure rate was reported after three aspiration procedures. None of the patients with multiloculated lesions was effectively treated by FNA. The authors recommended PCD as first-line treatment option but considered FNA a valid alternative in simple abscesses smaller than 50 mm in diameter. Several nonrandomized studies report experiences with both therapeutic approaches with good results. The clinical experience of the treating physicians is important in the evaluation of each patient. FNA could be considered as an alternative to routine PCD in patients with small uniloculated lesions, no viscous content, and with no communication with the biliary tree.

Placement of a PCD may cause bacteremia in spite of antibiotic administration. The most important preventive measure is to avoid excessive manipulation of infected pus. Overdistension of the abscess with contrast agents during the procedure and saline injections to wash the cavity are associated with an increased risk of bacteremia and are therefore not recommended (Thomas et al, 2006). Flushing the catheter may be useful for maintaining its patency, especially in cases of viscous pus. Furthermore, in such cases, larger catheters may be needed to drain the cavity efficiently. In some cases, after apparent successful drainage, imaging may show incomplete evacuation of the abscess cavity, and repositioning of the catheter or even placement of additional catheters may be necessary. An intercostal approach may cause pneumothorax, pleural effusion, or contamination of the pleural space, and a chest tube should be placed without removal of the abscess drain.

Failure of PCD may occur in up to 10% of patients, and the chronicity of a PLA may result in a thick, fibrous rind that will not collapse. In other cases, a cluster of abscesses may be misinterpreted as a multiloculated PLA on imaging, and the absence of communication with the main cavity results in incomplete drainage. Persistent drainage of bile through the catheter after several days or weeks is commonly seen when the abscess communicates with the biliary tree (Fig. 66.5). Endoscopic retrograde cholangiopancreatography with endoscopic sphincterotomy and transpapillary stent may help resolve this problem.

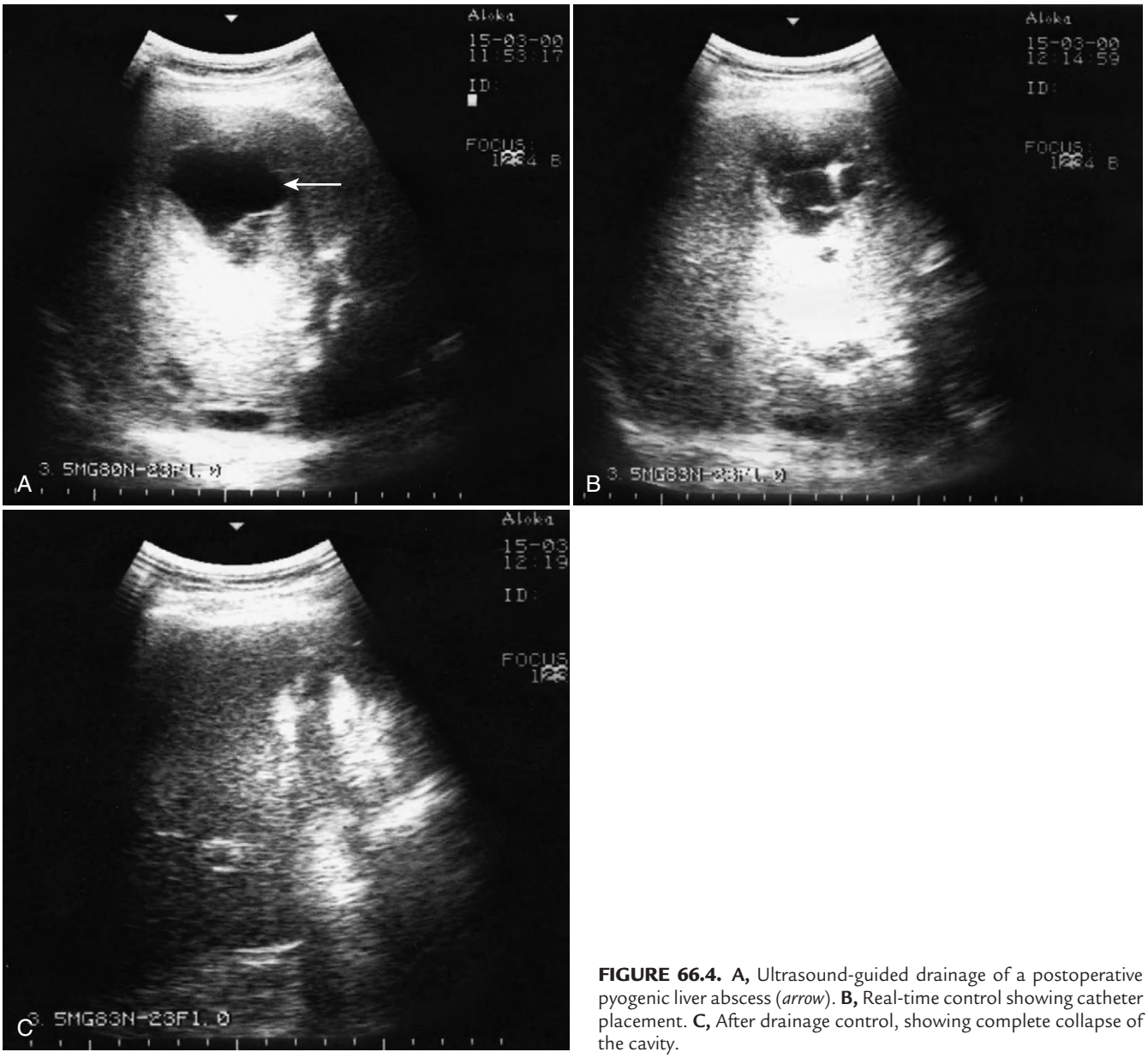


FIGURE 66.4. **A,** Ultrasound-guided drainage of a postoperative pyogenic liver abscess (*arrow*). **B,** Real-time control showing catheter placement. **C,** After drainage control, showing complete collapse of the cavity.

Sugiyama and Atomi (2002) found that in all cases of biliary communication, complete cure of abscesses after PCD required additional treatment to relieve the obstruction.

SURGICAL TREATMENT

Surgical treatment of PLAs as a first therapeutic approach is not usually indicated. Percutaneous procedures have been increasingly performed, leaving surgical drainage to salvage cases where percutaneous treatment fails (Tan et al, 2005). However, surgical treatment of PLAs may be indicated in certain specific clinical situations.

Primary surgical therapy is indicated in patients with intraperitoneal rupture, in which complete exploration and lavage of the abdomen are indicated. Laparoscopic approach combined with intraoperative US examination appears to be a minimally invasive therapeutic option for this rare condition (Siu et al, 1997). In some other patients, surgery may be indicated for the treatment of complications of the percutaneous drainage, such as bleeding or intraperitoneal leakage of pus.

Patients with an underlying pathology that needs surgical resolution can undergo treatment for the liver abscess during the same operation, such as cases of acute cholecystitis presenting with an adjacent abscess. It must be emphasized, however, that percutaneous drainage is indicated if surgery must be delayed for further stabilization of a critically ill patient.

Large, multiloculated abscesses containing thick pus are more prone to not respond to percutaneous treatment. In these patients, complete evacuation and removal of necrotic tissue and debris may be more easily achieved surgically (Hope et al, 2008). Percutaneous drainage may, on the other hand, delay effective treatment, which would increase the number

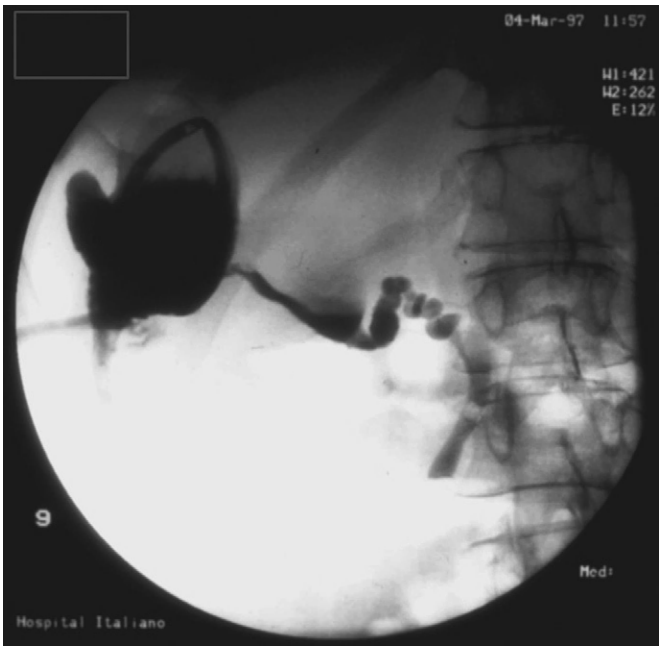


FIGURE 66.5. Percutaneous fistulogram showing a pyogenic liver abscess in communication with the gallbladder and the presence of a common bile duct stone.

of treatment failures, secondary procedures, and the length of hospital stay (Tan et al, 2005). Failure to institute appropriate surgical treatment in a timely fashion could be harmful in critically ill patients who require urgent resolution of the septic illness (Hsieh et al, 2008) and in whom salvage surgery may be associated with a mortality rate of 46% (Ng et al, 2008). However, a multidisciplinary team of surgeons and interventional radiologists is mandatory for treating patients in these complex situations. Laparoscopic drainage may play an important role in diminishing wound-related complications. With a laparoscopic approach, intraoperative US plays an important role to assess location and extension of the lesion (Yeh et al, 2007); however, it should be emphasized that an open approach should be used if there is any question regarding the adequacy of drainage achievable laparoscopically. No prospective studies compare open versus laparoscopic approach in the treatment of PLAs. Wang and colleagues (2004) presented a retrospective comparison of five patients treated with open drainage with 18 patients who underwent laparoscopic approach. Although mortality rate in the series was 0%, the laparoscopic group had shorter operating times and earlier oral intake in the postoperative period with less intraoperative blood loss and shorter hospitalization. Given the bias associated with patient selection, these results cannot be taken as evidence of the superiority of the laparoscopic approach but only as evidence that laparoscopic treatment is feasible in selected patients.

In all cases, when operating on a patient with a PLA, localization of the abscess should be assisted by means of intraoperative US for a complete examination of the liver to exclude associated lesions. In superficial lesions, the pus can be evacuated with needle aspiration to avoid peritoneal contamination, and the abscess cavity can then be opened to break up loculations and remove any debris from the cavity wall. Closed suction drainage should be considered in most cases. In lesions located deep within the liver parenchyma, an extended hepatotomy to reach the lesion may be necessary, but this maneuver may increase the risk of postoperative bile leak; for these cases, the placement of intrahepatic catheter drainage under US guidance may be an effective alternative.

Liver resection for the treatment of PLAs is rare because almost all PLAs can be cured by either percutaneous or operative drainage, but in some cases, PLAs with different physical and etiologic characteristics may need a different surgical approach. Liver atrophy and multiple abscesses may be the consequences of chronic obstruction of a segmentary bile duct branch as a result of hepatolitiasis or intrahepatic strictures (see Chapters 39, 42, and 44). Resection of the affected liver segments is the recommended treatment for these patients. Although more frequent in the left lobe, this condition may also be present in the right lobe of the liver. This aggressive approach is also indicated for multiple pyogenic abscesses with severe destruction of surrounding liver parenchyma (Chou et al, 1997). In an impressive series, Strong and colleagues (2003) reported 49 patients who underwent liver resections for PLAs over a 15-year period. Indications for surgery were failure of medical treatment or underlying hepatobiliary pathology. Two deaths (4%) occurred after intraperitoneal rupture of the PLA.

TREATMENT SUMMARY

Parenteral antibiotic therapy should be started as soon as possible in patients with PLAs. In stable patients, blood specimen samples for culture before therapy can be useful, but delaying therapy is not advisable. A combination of ampicillin, aminoglycoside, and metronidazole or a third-generation cephalosporin plus metronidazole are both effective schemes for therapy. In multiple small lesions, FNA under CT or US guidance is advised to obtain samples for culture. Solitary nonloculated cysts smaller than 50 mm can be treated by puncture and aspiration alone, but biliary tree communication must be excluded in these cases; otherwise, a PCD must be placed.

Imaging and clinical response are good indicators of treatment success. On occasion, a residual cavity may persist despite drainage. In this situation, if the patient remains asymptomatic and the lesion imaging is stable, no further procedure may be needed (Johannsen et al, 2000). After clinical stabilization, antibiotics may be switched to oral administration. A complete course of 4 weeks of antibiotics is recommended, although some authors suggest 2 weeks of treatment (Bowers et al, 1990).

Surgical debridement is indicated for the failure of nonoperative approaches for suspected intraperitoneal rupture of the abscess or in patients who need surgery to address underlying pathology. Laparoscopic drainage may be attempted in these cases. Finally, liver resection may be indicated in patients with hepatolithiasis, complex bile strictures, or liver atrophy.

OUTCOME AND PROGNOSIS

After successful treatment, recurrence of a PLA is rare; however, it is important to differentiate PLA recurrence from relapse as a result of incomplete treatment. Some patients with underlying risk factors may be at risk for recurrence. Cheng and colleagues (2008) reported 601 patients with PLAs with a median follow-up of 72 months. Recurrence rates were low in the cryptogenic (2%) and diabetes (4.4%) groups compared with those whose disease was of a biliary origin (23.8%). Except for

patients with biliary pathology, recurrences tended to be caused by the same organisms that generated the first PLA. However, the authors found no difference in recurrence rates comparing *E. coli* and *K. pneumoniae* organisms as causative agents.

PLA is a potentially life-threatening disease. Since the first report by Oschner in 1938, improvement in antibiotic therapy, new imaging techniques, and minimally invasive procedures have significantly decreased mortality. In series published in the last decades, mortality rates ranged between 6% and 20% (Chung, 2008). Although different prognostic factors have been identified in patients with PLAs, others remain controversial. Abscesses caused by *K. pneumoniae* have a higher risk of metastatic infection; however, mortality rates in these patients are lower compared with those whose PLA is caused by other organisms, even if compared with *E. coli* infections (Yang et al, 2004a). Diabetes is a well-known risk factor for PLA, but mortality rates in patients with diabetes are not increased compared with the general population in both Eastern and Western series (Alvarez et al, 2001; Tsai et al, 2008). Liver cirrhosis is a strong risk factor for developing PLA and is associated with poor prognosis and high short-term mortality rates (Molle et al, 2001). In general, the prognosis of patients with malignancy is poor, but in the absence of comorbidities, age is not associated with worse prognosis (Alvarez et al, 2001a).

Systemic response to septic injury is a major determinant of outcome. This may be indicated by the presence of septic shock, clinical jaundice, coagulopathy, leukocytosis, and hypoalbuminemia. An Acute Physiologic, Age, and Chronic Health Evaluation (APACHE II) score at admission of 15 or higher, multidrug-resistant isolates, gas-forming abscess, anaerobic infections, and a blood urea nitrogen level of 7.86 mmol/L or greater have been identified as high mortality–associated risk factors (Chen et al, 2008a).

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CHAPTER 67

Amebiasis and other parasitic infections

Hany Dabbous, Hosein Shokouh-Amiri, and Gazi Zibari

AMEBIC LIVER ABSCESS

History

The earliest report of amebiasis is probably the Sanskrit document *Brigu-samhita,* written about 3000 BCE, referring to bloody mucoid diarrhea (Vaidya & Ray, 1982). Assyrian and Babylonian texts refer to blood in the feces, suggesting the presence of amebiasis in the Tigris-Euphrates basin before the sixth century BCE (Bray, 1996), and it is possible that hepatic and perianal abscesses described in both *Epidemics* and *Aphorisms* in the *Corpus Hippocratorum* refer to amebiasis (Jones et al, 1948; Jones & Whithington, 1953). After the death of Hippocrates in 356 BCE, Alexander the Great became king of Macedonia. In Alexander's eastern campaign, he reached an area where amebiasis was endemic, and he died on the return trip at the age of 33 years, probably of an amebic liver abscess (Saville, 1964).

In 1818, Ballingall described a surgical technique to drain liver abscesses. When Ballingall practiced in Madras, India, Napoleon Bonaparte was exiled on the tropical island of St. Helena by the British after his defeat at Waterloo, where bloody diarrhea—possibly amebiasis—was common. Napoleon died in 1821 after an attack suggestive of amebic liver abscess, with symptoms of fever, diarrhea, and painful, tender swelling in the epigastrium. At the postmortem, an ulcer was found at the small curve of the stomach, communicating with the liver, suspected to be due to rupture of an amebic liver abscess of the left lobe into the stomach (Chaplin, 1913). In 1828, James Annesley gave detailed descriptions of "hepatic dysentery" (Kapoor, 1979). The connection between amebic dysentery and liver abscesses was described by the English physician William Budd (1857), but Charles Morehead, professor of Medicine and first principal of Grant Medical College, Bombay, India, was the first to report a case of hepatic abscess in 1848 (Martinez Baez, 1986).

Entamoeba histolytica was discovered by Friedrich Lösch in 1873 in Russia (Lösch, 1975). Lösch recognized amebae in the colon and terminal ileum accompanying acute dysentery (Martinez Baez, 1986). He gave descriptions of amebae, including structure, size, motility, intracytoplasmic elements, and drawings. Lösch named the amebae after his patient; *Amoeba coli* was proved later on sequencing of the genome (Tovar et al, 1999), and a calreticulin-like protein and Golgi apparatus were detected in the amebae (Gonzalez et al, 2002).

Stephanos Kartulis, a Greek physician, found amebae in intestinal ulcers in patients from Egypt in 1885 and noted that he never found amebae from nondysenteric cases (Kartulis, 1886). In 1890, Osler reported a young physician who died of amebic liver abscess (ALA) after an attack of dysentery. The report by William Thomas Councilman and Henri Lafleur, working at Johns Hopkins in 1891, represents a definitive statement about the pathology of amebiasis, amebic dysentery, and ALA at the end of the nineteenth century (Faust, 1931). Schaudinn did differentiate between harmless *Entamoeba coli* and pathogenic *E. histolytica* (Martinez Baez, 1986). In 1901, Harris produced ALAs by intrarectal infection of puppies with *E. histolytica.* Musgrave and Clegg (1904) cultivated *E. histolytica* in vitro, introducing the term *amebiasis.* In 1952, Hoare reported that *E. histolytica* had three phases. Species of amebae found in human host; *E. gingivalis, Entamoeba coli, Iodamoeba bütschlii,* and *E. hartmanni* were discovered between 1849 and 1919 (Martinez Baez, 1986).

A plant alkaloid, concessine, was found to kill *E. histolytica* (Vaidya & Ray, 1982). The first effective treatment came from Brazil in the form of ipecac; emetine was isolated from ipecac in the nineteenth century. Leonard Rogers (1912), professor of pathology at Medical College Hospital in Calcutta, India, reported successful treatment of both intestinal and hepatic amebiasis by injectable salts of emetine. The 1930s witnessed the introduction of two important hydroxyquinolines introduced by Anderson and Koch in 1931 and by a number of others. Although largely replaced by imidazoles in the 1980s, hydroxyquinolines remain useful today. In 1966, Powell and his colleagues demonstrated the effectiveness of metronidazole as an amebicidal agent in both intestinal and extraintestinal amebiasis.

Epidemiology

Approximately one tenth of the world population is believed to be infected with *E. histolytica*, with 100,000 deaths worldwide each year due to invasive amebiasis (Haque et al, 2003; Petri et al, 2000; Walsh, 1986; World Health Organization [WHO] et al, 1997b). Amebiasis is the third most common parasitic cause of death worldwide (Li & Stanley, 1996). The prevalence of *E. histolytica* could be an overestimate because it dates before the separation of *E. histolytica* from the morphologically identical, nonpathogenic *E. dispar* (Diamond & Clark, 1993) and *E. moshkovskii* (Beck et al, 2008; Fotedar et al, 2008). However, recent prevalence and morbidity data obtained through molecular techniques allow construction of more reliable map of endemic regions of amebiasis around the world, such as on the Asian subcontinent (India, Bangladesh), Africa, Asian Pacific (Thailand, Japan), and South and Central America (Mexico, Colombia) (Ximenez et al, 2009).

Disease expression varies geographically; invasive disease seen in Egypt, predominantly amebic colitis, may vary in schistosomiasis-endemic versus nonendemic areas (Mansour et al, 1997), whereas in South Africa an excessive rate of amebic liver abscess is noted. Although amebic liver abscess has been encountered in epidemic form in temperate climates, as it was

in the water-borne epidemic in Chicago in 1933 (Munoz, 1986), it is a problem chiefly of the tropics and developing countries (Sepulveda, 1982). In developed countries, it continues to be encountered sporadically in immigrants or travelers from endemic zones, low socioeconomic groups, residents of institutions, and male homosexuals (Ravdin & Stauffer, 2005).

In the United States and Europe, homosexual males are principally colonized with *E. dispar,* and patients infected with the human immunodeficiency virus (HIV) had no increased risk of either intestinal or extraintestinal amebiasis (Petri & Singh, 2006). Invasive extraintestinal amebiasis (hepatic abscesses) are more frequent in HIV-infected patients in these countries (Hung et al, 2005), whereas the same is not true elsewhere (Moran et al, 2005). *E. histolytica* remains a significant cause of morbidity and mortality in developing countries, where infection is common through flies and food handlers. The annual incidence of amebic dysentery in children is 2.2% in Bangladesh (Haque et al, 2003), and annual incidence of amebic liver abscess averaged 21 cases per 100,000 inhabitants in Hue City, Vietnam (Blessmann et al, 2002). Ingestion of *E. histolytica* occurs where poverty facilitates deficiencies in sanitation and sewage treatment. In addition, a recent report suggests that parasite genotype plays a role in determining outcome of infection by *E. histolytica* (Ali et al, 2007).

Organism

E. histolytica is a protozoan with two forms: trophozoite and cyst. Cysts constitute the infective form through fecal-oral transmission via food, water, or direct person-to-person contact. Cysts survive the acid of the stomach and travel through the small intestine, and within the terminal ileum or colon, trophozoites emerge to complete the life cycle (Guerrant, 1986). Cysts can survive for 45 minutes in feces lodged under fingernails and for 1 month in soil at 10° C. They remain infective in fresh water, seawater, and sewage but are destroyed by drying, iodine, and heat. They are not killed by chlorination used to purify drinking water (Munoz, 1986). The genus *Entamoeba* includes the pathogenic species *E. histolytica* and nonpathogenic *E. hartmanni, E. coli, E. polecki* (in swine), and *E. moshkovskii* (from sewage) (Guerrant, 1986). *E. histolytica* is morphologically similar to *E. dispar*; therefore the study of zymodemes, patterns of the electrophoretic mobility of isoenzymes; genetic differences using RNA and DNA probes; and the use of polymerase chain reaction (PCR) amplification became more reliable in their identification (Tannich et al, 1989). Encoding genes for transcription factors have been cloned for *E. histolytica* (Castanon-Sanchez et al, 2009).

Community Screening Procedures

An effective community screening protocol includes 1) microscopic examination of unfixed fecal samples, 2) Ritchie's fecal concentration, 3) staining of alcohol-fixed stools, 4) Robinson's in vitro culture, 5) screening stool antigens, 6) serology (indirect hemoagglutination test [IHAT], enzyme-linked immunosorbent assay [EIA], and immunofluorescence test [IFT]), and 7) isoenzyme electrophoresis of stool for zymodeme identification (Thomas & Garg, 2007).

Direct microscopic examination is found to be more sensitive than serology; however, the sensitivity of both is lower than Robinson's culture and zymodeme identification, the gold standards (Gatti et al, 2002). DNA-based PCR is rapid and sensitive to detect cysts in the stool (<5) and in fluids aspirated from amebic liver abscess (Rivera et al, 1998). A PCR test for *E. moshkovskii* was developed with a high sensitivity and specificity using DNA from stool samples (Fotedar et al, 2007). In 2007, Helmy used nested PCR and restriction enzyme digestion (RED) to distinguish *E. histolytica* from *E. dispar.*

Host Factors

The major reservoir for *Entamoeba* spp. is the human being. Male homosexuals transmit the infection but usually harbor nonpathogenic *E. dispar,* which is more common in females (Gatharim & Jackson, 1987). *E. histolytica* can be transmitted by heterosexual activity as well as male and female homosexual activity (Salit et al, 2009), although menstruating women are protected against invasive infection. Breastfed neonates have a low incidence as a result of the presence of immunoglobin A (IgA) and low iron content in breast milk (Thomas & Ravindra, 2000). A diet rich in iron and carbohydrates predisposes to invasive amebiasis (Gatharim & Jackson, 1987), and *HLA-DR3* gene expression is an independent risk factor for amebic liver abscess (Arellano et al, 1996).

Although immunosuppression is considered an important risk factor for invasive amebiasis in Asian Pacific countries (Hsu et al, 2008; Hung et al, 2008), others maintain there is no particular susceptibility for developing invasive forms of amebiasis in immunosuppressed individuals. Nevertheless, some HIV infections have been detected during admission of amebic liver abscess patients. On the other hand, the natural history of the disease seems to be the same as in nonimmunosuppressed patients (Kershenobish & Corona, 2008).

Pathogenesis

The disease course is determined by three virulence factors: lectin (a surface protein), amebapores (small peptides), and cysteine proteases. Trophozoite adhesion to the colonic wall is mediated by lectin, which results in persistent infection, and caspase 3 activation, which is a crucial step in cell necrosis and abscess formation (Huston et al, 2003). Amebapores are inserted by the trophozoite into the host cell, where they puncture the lipid bilayer and form a portal of entry into the host. Amebapores result in colloid osmotic lysis of the cell (Leippe et al, 1991). Cysteine proteases contribute to degradation of the extracellular matrix proteins and disruption of cell monolayers (Que & Reed, 1997).

It is anticipated that antiamebic antibodies protective against invasive infection would block lectin binding and neutralize amebapore and cysteine proteases. It has been suggested that the proteophosphoglycans (PPGs) in the amebic glycocalyx may participate in *E. histolytica* pathogenicity because the closely related, nonpathogenic *E. dispar* lacks a significant glycocalyx surface layer (Bhattacharya et al, 2000). Furthermore, antibodies that bind to PPGs neutralize liver abscess formation (Marinets, 1997). PPGs are anchored into the parasite cell membrane by a glycosylphosphatidylinositol (GPI) moiety. Synthesis of the GPI anchor requires a cascade of enzymes, including mannosyl transferase 1 (PIG-M1), whose blockage reduces GPI synthesis and PPGs in trophozoites (Weber, 2008). In addition, experimental evidence suggests that liver cell necrosis is increased when neutrophils are present along with *E. histolytica* (Aikat et al, 1979).

Normal blood flow in the portal vein is about 1.4 L/min, blood pressure is 12 to 15 mm Hg, and erythrocyte velocity is 8

to 18 cm/s. In comparison, sinusoidal blood flow is extremely low (3.4 to 0.16 mL/min), as is red blood cell velocity (0.1 mm/s; Puhl et al, 2003). Forces exerted on a parasite that adheres to the endothelium are thus much lower in the sinusoids and may partly explain why the parasite crosses the endothelium within these structures. Lack of tight junctions in liver sinusoidal endothelial cells (LSECs) can facilitate crossing by the parasite, creating a larger breach when reaching the hepatic parenchyma (Blazquez et al, 2007).

Publication of the *E. histolytica* genome (Loftus et al, 2005) facilitated transcriptome studies of the parasite. Microarrays have been used to compare virulent and avirulent trophozoites (those unable to form liver abscesses) from the same strain (Santi-Rocca et al, 2008). Overexpression of peroxiredoxin and rubrerythrin genes in virulent parasites is of interest for ALA development because inflammatory cell recruitment and subsequent inflammation are features of liver infection by *E. histolytica* (Choi et al, 2005a).

Molecular Genetics

The Institutes for Genomic Research have recognized that *E. histolytica* has a small, highly repetitive genome rich in adenosine-thymidine and densely packed sequences, but it lacks introns (Mann, 2002). Although some regions of the genome encode highly conserved proteins, other areas exhibit high degrees of polymorphism (Haghighi et al, 2002). Sequencing of the *E. histolytica* genome has revealed at least 44 genes (Clark et al, 2007). The purification of trophozoites from different organs of the same patients revealed that their tropism was linked to different genotypes (Ali et al, 2007).

Host Defense and Potential for Vaccine Development

It has not been definitively established which mechanism is responsible for invasion or recurrence (Ravdin & Guerrant, 1982). The first line of defense is the innate immunity that recognizes pathogen-associated molecular patterns (PAMPs) that trigger an inflammatory response. Natural killer T cells activated by *E. histolytica* are important in the control of amebic liver abscess (Lotter et al, 2009). Interferon (IFN)-γ initiates inflammation through macrophage production of tumor necrosis factor (TNF) and nitrous oxide (NO) synthesis by polymorphonuclear cells and macrophages. In vitro, the effects of IFN-γ can be bypassed by the recognition of PPGs of *E. histolytica* by Toll-like receptors (TLR) 2 and 4, which results in direct production of TNF and interleukins (ILs)-12 and -8 (Maldonado-Bernal, 2005). This shows the importance of early recognition of PPGs and inflammatory cell recruitment during ALA onset (Ivory & Chadee, 2007).

Complement cannot prevent invasion because it is absent from gut mucosal secretions (Braga et al, 1992), and amebic cysteine proteases degrade C3a and C5a (Reed et al, 1995). Neutrophils fail in initial host defense (Salata et al, 1989), and trophozoites can infect the human liver for months before abscesses are diagnosed. The second line of adaptive immune response constituted by activated lymphocytes and macrophages is the important effector mechanism against *E. histolytica* (Vohra et al, 2003). *E. histolytica* infection elicits mucosal IgA and serum IgG response to lectin protein shown to be protective against infection (Abd-Alla et al, 2004; Haque et al, 2002) in addition to epitope-specific antibodies that inhibit adherence to target cells (Pillai et al, 1999). The galactose/GalNAc lectin isolates from three distinct areas of the world—Bangladesh, Republic of Georgia, and Mexico—retain remarkable sequence conservation (Beck et al, 2002), and is recognized as a potential vaccine target (Thomas & Garg, 2007). Serum immunoglobulin (Ig) G response to the lectin protein does not provide protection against infection (Haque et al, 2002). Oral vaccines that use amebic antigens have been developed and tested in animals (Lotter et al, 2003; Mann et al, 1997; Snow & Stanley, 2006). A codon-optimized DNA vaccine has been tested in a murine model and was found to be useful in stimulating type 1 cellular immune response and serum antibodies (Gaucher & Chadee, 2002). Cell-mediated immunity (CMI) may be sufficient for vaccine protection from intestinal amebiasis with significant IFN-γ, interleukin (IL)-2, IL-12, IL-10, and IL-17 production with recombinant vaccines (Guo et al, 2009). Gram-negative bacteria expressing *E. histolytica* antigens may constitute a suitable oral vaccine carrier against invasive ameobiasis (Lotter et al, 2008).

Pathology

The development of ALAs is a fatal feature of infection by *E. histolytica* and is the most common extraintestinal form of invasive amoebiasis. Indeed, an estimated 100,000 people succumb to ALA each year (WHO, 1997a). Trophozoites that successfully penetrate the colonic mucosal barrier cause invasive disease, enter the portal system, and travel to the liver. Amebic colitis and amebic liver abscess rarely occur simultaneously, and the colonic lesions are usually silent; direct extension to the liver and lymphatic spread do not occur. The cecum is the most common site of amebic colitis, and the right lobe of the liver is more commonly affected because of drainage of the right portal branch from the right side of the colon. The condition usually starts as diffuse amebic hepatitis; liver cells undergo liquefactive necrosis, starting in the center and spreading peripherally to produce a cavity full of blood (Fig. 67.1) and liquefied liver tissue resembling anchovy sauce; it has no odor and is sterile. The fluid itself is free from any amebae, which may be found at the expanding edge of the abscess cavity with little inflammation. Amebae are known to lyse neutrophils, and the release of neutrophilic mediators may promote hepatocyte death and extension of the abscess. Secondary bacterial infection may occur spontaneously, altering the color, odor, and consistency of the pus. Lack of fibrotic response by the surrounding tissue with centrifugal extension results in extention of the abscess to the Glisson capsule, which is resistant to the amebae. Typically, amebic liver abscesses are solitary, large, and located in the right liver. Left lobe abscesses are less common, but because of the smaller volume of the left liver, abscesses in this location are more prone to rupture the capsule (Thomas & Ravindra, 2000). Vascular and biliary structures may traverse the abscess cavity; because of the intrahepatic covering of the Glisson capsule, such structures are resistant to the process of liquefactive necrosis. However, these structures can be mistaken for septa within the abscess cavity, and fracturing of these strands can lead to hemorrhage or biliary leak, or it can create a communication between the vascular and biliary channels and result in hemobilia and jaundice (Singh et al, 2008). The abscess wall is typically ill defined with a minimal host response of fibrous tissue, but longstanding abscesses may develop a fibrous wall and may even calcify (Rogers et al, 1980). In treated cases, complete resolution is the rule, but it may take 6 months to 2 years or longer (Thomas & Ravindra, 2000) than the usual time for pyogenic abscesses to resolve (Sudhamshu & Sharma, 2009).

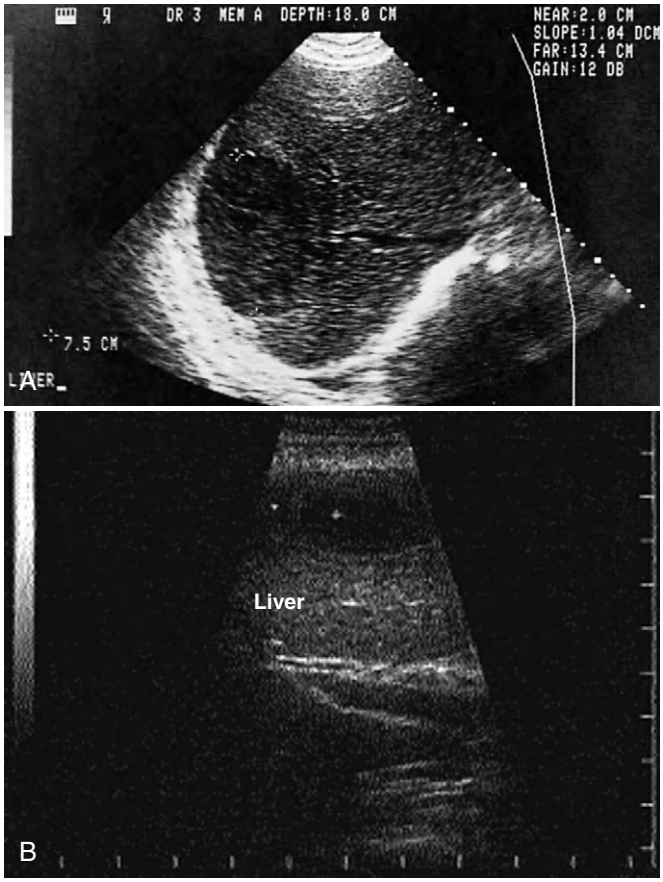


FIGURE 67.1. A, Ultrasound showing a typical liver abscess in a 36-year-old man. The abscess is peripherally located, 7.5 cm in diameter, with a poor rim, internal echoes, and distal sonic enhancement. **B,** Ultrasound showing a typical liver abscess in the left lobe. *(**A,** Courtesy Professor M.S. Khuroo, Sher-I-Kashmir Institute of Medical Sciences, Srinagar, India. **B,** Courtesy Professor A.K. El Dory, Ain Shams University, Cairo.)*

Clinical Presentation

The peak incidence of amebic liver abscess is between 20 and 60 years of age; thus it is predominantly a disease of young men. Amebic liver abscess is 10 times more common in adults than in children and is three to 10 times more common in males (Sepulveda & Manzo, 1986; Wells & Arguedas, 2004). Population groups that are not commonly affected—such as children (especially neonates), pregnant women, and women in the postpartum period—have an increased risk of severe disease and death. Treatment with steroids, malignancy, men having sex with men, advanced age, and malnutrition could be considered risk factors for severe disease (Guerrant, 1986; Li & Stanley, 1996).

Most *E. histolytica* infections are asymptomatic or present as mild, "noninvasive" disease. Asymptomatic carriers, or *cyst passers,* may excrete cysts for a short period, but the majority of these patients clear the infection within 12 months. Patients with confirmed *E. histolytica* infection, even if they are asymptomatic, should be treated to eliminate the organism and prevent further transmission (Stanley, 2003). The time between penetration of colonic mucosa and damage to hepatic parenchyma is unknown. Active diarrhea usually occurs in less than 30% of patients at any time before presentation despite intestinal infection by *E. histolytica.* In most cases, standard stool microscopy results are negative, but in research studies, cultures of stool were positive for *E. histolytica* in more than 75% of patients with amebic liver abscess (Irusen et al, 1992).

Concomitant hepatic abscess is found in only one third of patients with amebic colitis. The duration of symptoms is usually 10 days. In nonendemic regions, such as Western Europe and the United States, patients usually report travel to an endemic area in the previous 2 to 5 months (median, 3 months), although a prolonged latency may occur (Johnston et al, 2009; Wells & Arguedas, 2004). Patients with amebic liver abscess start reporting nonspecific symptoms such as anorexia, nausea, vomiting, and acute colitic illness. Abdominal pain and fever are the cardinal symptoms of the disease, seen in 90% of patients or more. Fever typically is between 38° C and 40° C and is seen in 87% to 100% of patients; rigors occur in 36% to 69%. Other signs and symptoms vary according to the site and the size of the abscess. The chief sympton is typically the abrupt onset of right hypochondrial pain radiating to the right shoulder and scapular area. The pain increases with coughing, deep breathing, and walking. If the abscess is in the left hepatic lobe, the pain may be epigastric, precordial, or retrosternal and may radiate to the left shoulder. Abscesses located on the inferior aspect of the liver may present in a manner similar to peritonitis resulting from any upper abdominal cause. On occasion, the presentation is insidious, lasting 2 or more weeks; in such patients, significant weight loss may occur (Thomas & Ravindra, 2000). One report has suggested that amebic liver abscesses can be silent and asymptomatic (Blessmann et al, 2003).

Abdominal examination usually reveals a tender, soft hepatomegaly accompanied by overlying muscle guarding and intercostal tenderness. On occasion, increased warmth and cutaneous edema may occur. Jaundice is often seen, although it was previously reported to be a prominent feature in only 5% to 8% of patients (Pitt, 1990); biliary communication of amebic liver abscess has been reported in up to 27% (Agarwal et al, 1995; Bayraktar et al, 1996). Because the right posterior-superior surface is the most common site of amebic liver abscess, it is always accompanied by right basal lung signs as a result of either pleural effusion, empyema, or lung abscess (Loulergue & Mir, 2009). On the other hand, left lobe abscess may be complicated by pericardial friction, and abscesses in this location can extend into the pericardium, a sign associated with a very high mortality rate (Wiwanitkit, 2008). Hepatic failure, ascites, and splenomegaly may occur in 15% of patients who have multiple abscesses. They present with fever, toxemia, deep jaundice, and encephalopathy; toxemia is suggestive of an added bacterial infection, leading to more severe disease. *Esherichia coli* and *Klebseilla pneumoniae* are the most commonly cultured organisms, and patients are seen with a clinical picture indistinguishable from hepatic encephalopathy as a result of acute hepatocellular failure. Hepatic encephalopathy in patients with amebic liver abscess may result from a combination of right hepatic vein occlusion, pylephlebitis, and occlusion of several portal vein radicles (Kapoor & Joshi, 1992). Clinically, the usual differential diagnosis includes acute cholecystitis, hepatitis resulting from viral or other causes, and pyogenic liver abscess. With atypical presentation, hepatocellular carcinoma, a hepatic hydatid cyst, or a simple cyst may be considered (Thomas &

Ravindra, 2000). Approximately three quarters of patients with an amebic liver abscess have leukocytosis. Leukocytosis most likely appears if symptoms are acute or complications have developed. Eosinophilia is rare, but mild anemia may occur in half of patients and is multifactorial. Hyperbilirubinemia is present in only a small proportion of cases.

In acute liver abscess, aspartate aminotransferase (AST) levels are high. In chronic liver abscess, the alkaline phosphatase level tends to be elevated, and the AST level tends to be within normal limits. Overall, the alkaline phosphatase level is elevated in about 70% of patients with amebic liver abscess. Similar complete blood count (CBC) and liver test abnormalities are found in patients with pyogenic liver abscesses and are not specific (Ravdin & Stauffer, 2005). Prolonged prothrombin time may occur. Chest radiography typically shows elevation of the right dome of the diaphragm with an anterior bulge on the lateral view (Debakey & Ochsner, 1951), atelectasis of the right lung, and pleural effusion. The liver shadow on plain abdominal radiographs is diffusely enlarged, and gas in the biliary tree or liver parenchyma is unusual unless there is communication of the hepatic abscess cavity with the lung or hollow viscus (Thomas & Garg, 2007).

Ultrasonography

Ultrasonography (US) is the preferable diagnostic test, with an accuracy of 90% (see Chapter 13; Sepulveda & Manzo, 1986). Abscesses are usually located in contact with the liver capsule (see Fig. 67.1) and are 2 to 21 cm in size, round or oval, with well-defined margins; they are hypoechoic and clearly defined from normal liver parenchyma with distal enhancement (Figs. 67.2 to 67.4; Ralls et al, 1982; Sukougj et al, 1989). In 80% of patients, the abscess is single in the right lobe; 10% in the left lobe and 6% in the caudate lobe are single, and the remaining are multiple abscesses (Ralls et al, 1979).

In early stages, amebic abscess appears as a subtle area of decreased echogenicity, and US diagnosis is not pathognomonic; complicated cysts, hematoma, metastases, and amebic abscess may mimic each other (Elzi et al, 2004; Kapoor, 1989). Only 40% of patients have typical US features of amebic liver abscess. Serial scanning tends to show no change despite adequate treatment with amebicidal drugs, complete aspiration of the abscess, or both (Ralls et al, 1979; Sukov et al, 1980). The mean resolution time is 7 months, and complete resolution may take up to 2 years. On occasion, percutaneous diagnostic aspiration may be needed to differentiate amebic from pyogenic liver abscess (Kurland & Brann, 2004). Although pyogenic liver abscesses tend to resolve earlier (within 2 to 4 months), amebic liver abscesses acquire a more echogenic and fibrous wall in 8 to 16 weeks and begin to resemble, but must be differentiated from, an encapsulated tumor. With time, resolution may be complete, or the result may be a residual cystic cavity that resembles a simple cyst of the liver (Ralls et al, 1983; Sheen et al, 1989).

Other Imaging Modalities

Computed tomography (CT) does not add to the diagnostic accuracy of US in acute stages, except in evaluation of imminent rupture of an abscess or for detection of small lesions (see Chapter 16; Kimura et al, 1997). Amebic liver abscesses usually appear on CT with contrast as rounded, well-defined lesions with complex fluid (Radin et al, 1988). The most characteristic finding is an enhancing wall with a peripheral

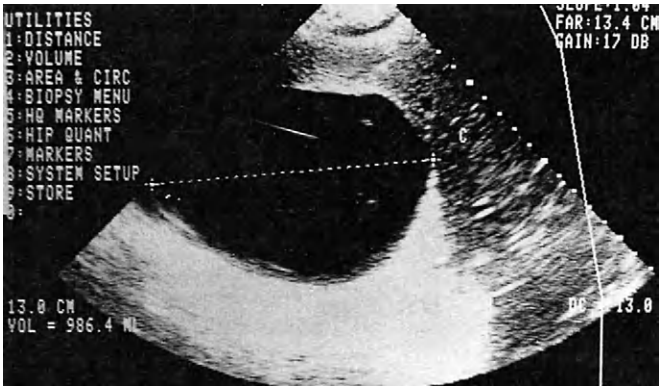


FIGURE 67.2. Ultrasound showing an abscess with more liquid contents in a 25-year-old man. The distal sonic enhancement has resulted in a "white out" of structures distal to the abscess cavity. *(Courtesy Professor M.S. Khuroo, Sher-I-Kashmir Institute of Medical Sciences, Srinagar, India.)*

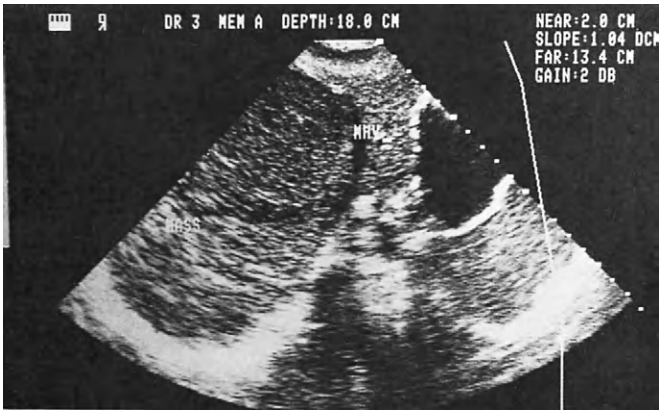


FIGURE 67.3. Ultrasound from a 50-year-old woman with a right liver mass initially mistaken for amebic liver abscess but proven on further investigation to be a tumor. There is a mixed-echo pattern with hyperechoic and medium-level echoes, no clear margin, and no distal sonic enhancement typical of an amebic abscess. *(Courtesy Professor M.S. Khuroo, Sher-I-Kashmir Institute of Medical Sciences, Srinagar, India.)*

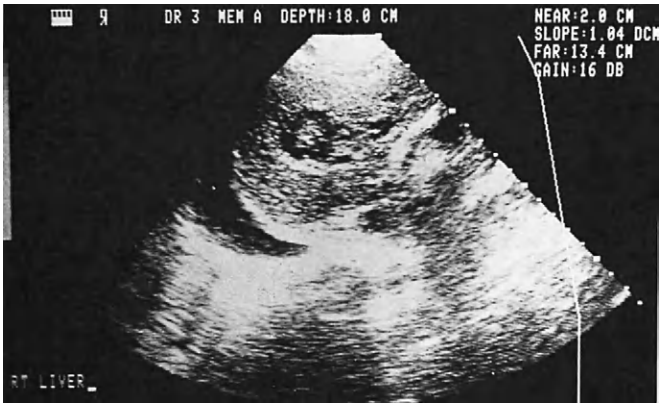


FIGURE 67.4. Ultrasound showing a typical metastatic "target" deposit in a 45-year-old woman. The central location, smaller size, and poor distal enhancement differentiate it from an amebic abscess. The presence of ascites is visible. *(Courtesy Professor M.S. Khuroo, Sher-I-Kashmir Institute of Medical Sciences, Srinagar, India.)*



FIGURE 67.5. Computed tomographic image showing a typical liver abscess with an enhancing wall and peripheral zone of edema. *(Courtesy Professor A.K. El Dory, Ain Shams University, Cairo.)*

zone of edema around the abscess (Fig. 67.5). The abscess cavity may show multiple septa (more with pyogenic abscesses), fluid and debris levels, air bubbles, or hemorrhage. CT may detect extension of amebic liver abscesses to other organs (Radin et al, 1988).

Magnetic resonance imaging (MRI; see Chapter 17) is not superior to CT in the diagnosis of amebic liver abscess, but it may be useful in differentiating it from a hepatic neoplasm. Amebic liver abscesses appear as heterogeneous cavities that are hypointense on T1-weighted images and hyperintense on T2-weighted MR images. The abscess margin may show incomplete hyperintense rings with perilesional edema on T2-weighted images. Following treatment, the abscess cavity becomes homogeneous, and complete concentric rings appear as a result of periabscess fibrosis and hemosiderin deposits (Mortelé & Ros, 2001).

Angiography is rarely required. When performed, it reveals a hypovascular or avascular mass displacing the hepatic artery and portal vein branches but may show portal vein thrombosis (Viana, 1975). Although its role is currently limited with gallium scanning, amebic liver abscesses appear as cold spots, whereas pyogenic lesions are seen as warm spots (Kapoor, 1989).

Amebic Serology

Amebic serology is highly sensitive and specific in the differentiation between pyogenic and amebic hepatic abscess. EIA is simple, rapid, inexpensive, and more sensitive, and it has now largely replaced IHAT and counterimmunoelectrophoresis (Restrepo et al, 1996). EIA detects antibodies specific for *E. histolytica* in approximately 95% of patients with extraintestinal amebiasis, 70% with active intestinal infection, and 10% who are asymptomatic cyst passers. Antibody response is related to the duration of illness and may be detectable 7 to 10 days after the onset of symptoms. Titers peak by the second and third months, decreasing to lower levels by 9 months; they revert to negative by 12 months (Munoz, 1986). Monoclonal antibody-based tests allow differentiation between invasive and noninvasive parasites (Kimura et al, 1997). Enzyme-linked immunosorbent assay (ELISA) and IHAT cannot differentiate acute from remote infection in endemic areas (Thomas & Garg, 2007).

Currently, ELISA for detection of the galactose-inhibitable adherence protein in serum and feces and IHAT appear to be the most reliable tests, with sensitivity and specificity greater than 95% (Hira et al, 2001), with a reversal rate of 82% after 1 week of treatment with metronidazole (Tanyuksel & Petri, 2003). Efforts are ongoing to identify antigens specific for acute infection (Ravdin, 1995). Rapid antigen and antibody tests are being evaluated and seem very promising (Leo et al, 2006).

Role of Aspiration

US-guided aspiration (Fig. 67.6) is often justified on the basis that the diagnosis would be "more certain," or that the abscess can be "aspirated to dryness" at the time of therapeutic aspiration. PCR may detect *E. histolytica* DNA in amebic liver abscess pus as well as in the saliva of patients (Khairnar & Parija, 2008; Khan et al, 2006). No randomized controlled trial has ever shown that aspiration is beneficial in survival, length of hospitalization, or time to become afebrile compared with treatment with antiamebic drugs alone (Chavez-Tapia et al, 2009; Sharma et al, 1989; Stanley, 2003; Van Allan et al, 1992), and aspiration may only confuse the diagnosis by revealing atypical pus or blood. The belief that aspiration hastens clinical recovery and may not involve significant procedure-related morbidity is widespread in clinical practice, however. This approach is supported by a small prospective study (Tandon et al, 1997) and continues to be advocated in reviews (Haque et al, 2002). Clinical improvement invariably occurs with antiamebic therapy alone in uncomplicated cases. When the differential diagnosis in a given case includes operable neoplasm or hydatid disease, aspiration is risky and may be contraindicated (Thomas & Garg, 2007).

Therapeutic aspiration should be reserved for the following situations (Ralls et al, 1982):

1. Serology is inconclusive and differential diagnosis is pyogenic liver abscess.
2. A therapeutic trial with antiamebic drugs is deemed inappropriate, as in pregnancy.
3. The liver abscess is secondarily infected, estimated to be true in 15% of cases (McDermott, 1995).
4. Fever and pain persist for more than 5 to 7 days after starting appropriate therapy.
5. Rupture is imminent in an extremely large abscess (>10 cm), especially if pericardial rupture from a left lobe abscess appears likely.

The following factors are predictive of the need for aspiration: 1) age 55 years or older, 2) an abscess 5 cm or more in diameter, and 3) failure of medical therapy after 7 days (Khan et al, 2008). In endemic areas, because of late presentation and existence of multiple abscesses, up to 50% of patients may require aspiration (Khanna et al, 2005). A single aspiration may be sufficient for diagnostic purposes, but it is inaccurate to recommend it because the characteristic "anchovy paste" characteristic of amebic abscess may not be found; when performed as part of therapy, it will likely be inadequate. Percutaneous catheter drainage (PCD) is better than percutaneous needle aspiration (PNA) for management of large liver abscesses (>10 cm) in

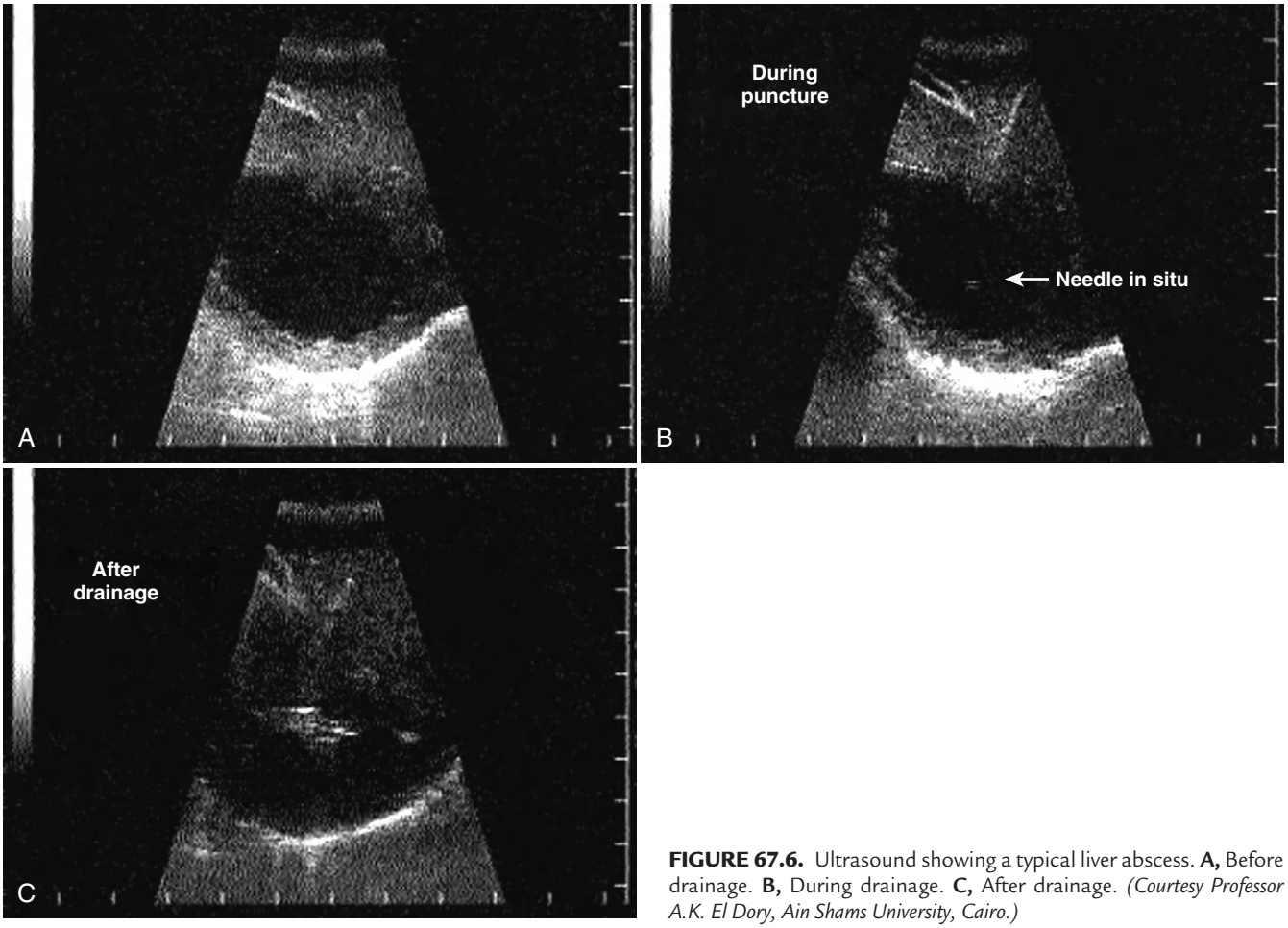


FIGURE 67.6. Ultrasound showing a typical liver abscess. **A,** Before drainage. **B,** During drainage. **C,** After drainage. *(Courtesy Professor A.K. El Dory, Ain Shams University, Cairo.)*

terms of duration to attain clinical relief and duration for which parenteral antibiotics are needed (Singh et al, 2009).

Complications

The most common complications of amebic liver abscess arise from rupture of the abscess into surrounding organs or anatomical spaces. Communication occurs into the peritoneum, viscera, and large vessels on one side of the diaphragm and the pleura, bronchi, lungs, and pericardium on the other.

Peritoneal and Visceral Involvement

Peritonitis with amebiasis is due to rupture of an amebic liver abscess in 78% of patients and perforated or necrotizing amebic colitis in the other 22% (Ken et al, 1989; Monga et al, 1976). Spontaneous rupture of amebic liver abscess may occur in 2.7% to 17% of cases (Eggleston et al, 1982; Monga et al, 1976; Sarda et al, 1989). Adherence of the liver abscess to the diaphragm, abdominal wall, omentum, or bowel tends to confine contamination and lead to rupture into hollow viscera, such as the stomach or colon (Angel et al, 2000).

A hepatogastric, hepatoduodenal, or hepatocolonic fistula and acute hepatic failure may occur. Free rupture into the peritoneal cavity is uncommon and usually only occurs in a nutritionally depleted patient (Rao et al, 2009). Patients present with abdominal pain, a palpable mass, or generalized distension. Bloody diarrhea may occur in colonic rupture, and hematemesis may occur in cases of hepatogastric fistula. Signs of peritonitis with tender hepatomegaly, intercostal tenderness, right basal lung signs, and clinical jaundice may lead to suspicion of the diagnosis, which can be confirmed on US. The diagnosis may be made only at laparotomy, with risk of bleeding from decreased prothrombin levels (Thomas & Garg, 2007). US and CT often show a perihepatic fluid collection in cases of amebic liver abscess that are reactive or with actual leaks from the abscess cavity (Radin et al, 1988). Management of abscesses that extended into the peritoneal cavity with aggressive surgical approaches were associated with increased mortality rates (Balasegaram, 1981; Eggleston et al, 1982) and have now been replaced by increasingly successful attempts at percutaneous drainage of the liver abscess and the extravasated pus (Ken et al, 1989; Sarda et al, 1989).

Absolute indications for laparotomy include a doubtful diagnosis; concomitant hollow viscus perforation with fistulization, resulting in life-threatening hemorrhage or sepsis; and failure of conservative management. At laparotomy, the liver abscess, which usually appears as a tan-colored bulge on the surface, must be handled gently. Septa running across the cavity are usually blood vessels and bile ducts traversing the abscess cavity. Hemorrhage can be difficult to control, and postoperative bile

leaks may result. Endoscopic stenting or nasobiliary drainage may be required in cases of biliary communication (Sandeep et al, 2006). Irrigation of the abscess cavity with saline is usually sufficient and may be followed by the installation for 3 to 5 minutes of a solution of 65 mg of emetine hydrochloride in 100 mL of normal saline. Tube drains are inserted and retained as necessary. Hollow viscus perforations must be dealt with on an individual basis, with exteriorization, proximal diversion, or serosal patch closure (Thomas & Garg, 2007). Postoperative intravenous metronidazole is combined with broad-spectrum antibiotics, and dehydroemetine is added if no cardiac contraindication exists. The mortality rate of viscus perforation ranges from 12% to 50% (Sarda et al, 1989).

Thoracic and Pleuropulmonary Involvement

Pulmonary complications occur in 7% to 20% of patients with amebic liver abscess (Stanley, 2003). A sympathetic right-sided effusion is the most common pulmonary complication and usually does not require treatment itself. Other thoracic complications include rupture of the abscess into the pleural cavity or into the bronchial tree. This condition manifests as dyspnea and dry cough with right basal crepitations and collapse of the right lung in addition to the abdominal signs. A pleural rub may also be found. Sudden onset of coughing with expectoration of copious quantities of chocolate-colored sputum occurs if the abscess ruptures into bronchi (Guarner, 1986). There are several routes of pulmonary infection, including direct hematogenous and inhalational amebiasis (Shamsuzzaman & Hashiguchi, 2002). Thoracocentesis is the main line of treatment. In case of aspiration and intercostal tube drainage, care is taken to go high on the right lateral side of the chest near the axilla. Ineffective early drainage of the amebic empyema is usually complicated by secondary infection that requires aggressive surgical procedures, such as pulmonary decortication, because the fibrous tissue can be dense enough to complicate thoracoscopic surgical techniques (Thomas & Garg, 2007).

Lung abscess rarely occurs, and it is walled off from the pleural and peritoneal cavities; surgical intervention is not required because postural drainage, bronchodilators, and antiamebic drugs may suffice. Metronidazole is effective, but emetine produces a rapid response and may be required in cases of metronidazole resistance (Jain et al, 1990).

Vascular and Pericardial Involvement

Some cases of vascular complications have been reported, such as Budd-Chiari syndrome (Mechai et al, 2009) and right atrial and inferior vena cava thrombosis, complicating multiple large amebic liver abscesses (Khan & Ameen, 2009; Sodhi et al, 2009). Surgical removal of the thrombus may be required.

Abscess rupture into pericardium is rare but serious, occurring in 1.3% to 2% of patients, with mortality rates from 30% to 60% (Shamsuzzaman & Hashiguchi, 2002). Abscesses of the left lobe of the liver or those more centrally located are more prone to pericardial complications that range from asymptomatic pericardial effusion to cardiac tamponade. Although left lobe abscesses resolve equally well with antiamebic drugs, as do right-sided abscesses (Thompson et al, 1985), the detection of pericardial thickening or pericardial effusion may constitute an indication for aspiration of a left-sided amebic liver abscess (Radin et al, 1988). In cardiac tamponade, pericardiocentesis must be performed, along with drainage of the liver abscess followed by antiamebic drugs, namely metronidazole. Dehydroemetine is used with caution because of its cardiotoxicity (Thomas & Garg, 2007).

Chemotherapy

Metronidazole

Metronidazole is the drug of choice for amebic liver abscess. The oral dose is 500 to 750 mg three times daily for 7 to 10 days, the same dose and duration used for intestinal amebiasis in adults, and 35 to 50 mg/kg in three divided doses for 10 days in children, with a cure rate of more than 90% (Li & Stanley, 1996). Hepatopulmonary amebiasis was found to respond equally to doses of 400 and 800 mg three times daily given over 5 days (Jain et al, 1990). The intravenous route is also highly effective at a recommended dose of 500 mg every 6 hours. Metronidazole reaches high concentrations in the liver and intestine, and it crosses the placenta and the blood-brain barrier. Its use is contraindicated in the first trimester of pregnancy and must be used cautiously in the second and third trimesters; breastfeeding should be discontinued during its use. The response of patients with amebic liver abscess to metronidazole is profound, with improvement in symptoms within 72 to 96 hours. However, a luminal agent such as paromomycin (30 mg/kg three times a day for 5 to 7 days), iodoquinol (650 mg orally three times a day for 20 days), or diloxanide furoate (500 mg orally three times a day for 10 days) should also be used to eradicate intestinal colonization (Stanley, 2003).

Medical therapy has a disulfiram-like action. The most common side effects are nausea, a metallic taste in the mouth, vomiting, and dark brown discoloration of the urine. Over 5 days, an 85% cure rate is achieved, which may increase to 95% after 10 days (Guarner, 1986). From 5% to 15% of patients with amebic liver abscess may be resistant to metronidazole (Thompson et al, 1985), but this may not be a major clinical problem (Li & Stanley, 1996); most reports of "drug resistance" reflect delayed resolution of either clinical symptoms or US findings and not a true resistance documented by drug failure. Experimental resistance may be related to inducing superoxide dismutase in vitro (Wells & Arguedas, 2004). Alternate medical therapy, percutaneous aspiration, or surgical intervention usually must be considered in patients who do not respond or show only modest improvement in 72 hours (Thompson et al, 1985). In countries where they are available, tinidazole, ornidazole, and nitazoxanide are alternative agents for the treatment of amebic liver abscess; these drugs are administered for only a few days (Lasserre et al, 1983; Quaderi et al, 1978; Vanijanonta et al, 1985). One study of a single 2-g dose of either tinidazole or ornidazole gave a success rate of 94% in both treatment arms (Lasserre et al, 1983). Other studies have shown a success rate of almost 100% for patients treated with tinidazole for 2 to 3 days (Khokhani et al, 1978; Quaderi et al, 1978; Vanijanonta et al, 1985). Tinidazole has been approved by the Food and Drug Administration (FDA) for the treatment of amebiasis, including amebic liver abscess. Secnidazole has a longer half-life, and a single daily dose of 2 g for 5 days is effective (Salles et al, 2003). Satranidazole showed lower incidence of side effects and better tolerance than metronidazole in a randomized, single-blind trial of 49 patients with amebic liver abscess (Muzaffar et al, 2006).

Other Medications

Emetine hydrochloride is effective against trophozoites and reaches amebicidal concentrations in tissues rather than

intestine. Emetine is administered by intramuscular or deep subcutaneous injection in a dose of 1 mg/kg/day (maximum 60 mg/day) for 10 days. The patient must be placed on complete bed rest. Tissue levels persist for 40 to 60 days, and readministration should be avoided for 6 weeks. Side effects include myositis at the injection site, hypotension, tachycardia, chest pain, dyspnea, and abnormalities on electrocardiogram, including T-wave inversion and prolonged Q-T interval. The drug is contraindicated in renal, cardiac, and muscular disease and is used cautiously in children and elderly patients (Thomas & Garg, 2007). Emetine or dehydroemetine is valuable in treatment of hepatopulmonary amebiasis (Guarner, 1986; Jain et al, 1990; Thompson et al, 1985).

Chloroquine phosphate is antimalarial and is effective in patients with resistance to emetine and pulmonary amebiasis (Guarner, 1986) but has no luminal amebicidal activity. Chloroquine is administered orally in a dose of 1 g (600 mg base) per day for 2 days followed by 500 mg (300 mg base) per day for 2 to 3 weeks. It is contraindicated in patients with retinopathy, but it has been used in pregnant patients (Guarner, 1986). Diloxanide is ineffective in invasive amebiasis and is used for treatment of asymptomatic carriers. The recommended dose is 500 mg three times a day for 10 days. No serious side effects are reported.

Nitazoxanide was effective in treating invasive amebiasis and eliminating colonization in intestine. Further studies are warranted in hepatic amebiasis (Rossignol et al, 2007). Trifluoromethionine is a lead compound, but a single subcutaneous or oral dose prevented the formation of amebic liver abscess in a rodent model (Sato et al, 2010).

Therapeutic Strategy

Oral metronidazole is administered as a single drug, with concomitant correction of hypoprothrombinemia, hypoproteinemia, and anemia. If dramatic improvement occurs in 48 to 72 hours, no therapy other than the complete course of metronidazole is required. A luminal agent, such as diloxanide furoate (500 mg three times a day for 10 days) or paromomycin (30 mg/kg/day in three doses for 10 days), must be administered after metronidazole therapy for eradication of intestinal infection as part of a complete treatment regimen (Irusen et al, 1992).

In patients who do not respond satisfactorily, emetine or dehydroemetine is added. Evidence of pulmonary, peritoneal, or pericardial extension is an indication for aspiration of the liver abscess with an intercostal tube or catheter drainage. Percutaneous catheter drainage is usually recommended for abscesses larger than 10 cm in diameter and for left lobe liver abscess, failure of medical treatment for 7 days, and failure to differentiate the abscess from a pyogenic abscess (Singh et al, 2009). The following are predictive of the need for aspiration: 1) age older than 55 years, 2) abscess greater than 10 cm in diameter, and 3) failure of medical therapy after 7 days (Khan et al, 2008). Late presentation with the existence of multiple abscesses may require aspiration (Khanna et al, 2005), but prompt medical care decreases the need. Laparotomy is usually reserved for patients with suspected peritonitis, fistulization, or secondary infection with sepsis after failure of above measures.

A meta-analysis of patients with amebic liver abscess showed that 4% died (Pitt, 1990). In patients treated with amebicidal drugs alone, the mortality rate was 2%. Independent risk factors for death include serum bilirubin greater than 3.5 mg/dL; encephalopathy; hypoalbuminemia, defined as less than 2 mg/dL; and multiple abscess cavities (Sharma et al, 1996) or total abscess volume greater than 500 mL (Wells & Arguedas, 2004). Rupture into the peritoneal cavity and the pericardium is responsible for most deaths. Patients treated with early and aggressive surgery as advocated by some authors (Balasegaram, 1981; Eggleston et al, 1982) did not show a remarkable improvement in mortality rate, although in Balasegaram's series, the hospital stay was probably reduced. Ruptured amebic liver abscess occurs in 2% to 17% of patients, with reported mortality rate of 6% to 50%. These patients usually constitute a major risk for surgery and anesthesia.

Prevention

In addition to regular sanitary measures that include proper washing of vegetables and fruits as well as drinking only bottled water in endemic areas, modern biologic techniques have helped characterize amebic antigens that show great promise in the development of a vaccine. No prophylactic vaccine is currently available for amebiasis, but efforts to better define antigenic candidates and wider use of animal models are encouraging. For example, a serine-rich *E. histolytica* protein (SREHP) has been expressed in avirulent vaccine strains of *Salmonella* (Stanley, 2006). *E. histolytica* galactose/N-acetyl-D-galactosamine (Gal/GalNAc) (Houpt et al, 2004) and a synthetic, enhanced, intranasal lectin-based amebiasis subunit have been extensively studied as attractive candidates for vaccine development (Abd Alla et al, 2007). In addition, Gal-inhibitable lectin shows promise in animal studies (Ivory & Chadee, 2007).

LIVER FLUKE DISEASE

Fasciola hepatica and *Clonorchis sinensis* are the primary liver flukes (see Chapter 45). They are unsegmented leaf-shaped trematodes. Although both have common features with respect to structure and life cycle, with accidental infection of humans, there are some epidemiologic differences. *C. sinensis* is endemic in East Asia, regions bordered by the South China Sea, and along the great rivers and streams of China, North Vietnam, and Korea. Disease results from eating contaminated raw freshwater fish. These areas also are endemic for viral hepatitis, and epidemiologic surveys of the population yield patients with common symptoms in whom the differential diagnosis must be made (Wang et al, 2004). *Opisthorchis viverrini* and *Opisthorchis felineus* are other liver flukes transmitted by the consumption of raw freshwater fish, but most of these cases are asymptomatic. The Western Hemisphere is free of the disease, but clinical manifestations may occur in natives of these areas several years after emigration to other countries. The first report of *C. sinensis* infection was described in a Chinese carpenter residing in Calcutta, India (McConnell, 1875).

Fascioliasis

Zoonotic disease is caused by *F. hepatica* (temperate) and *F. gigantica* (tropical), the causative agents of fascioliasis in cattle and sheep (see Chapter 45). Human infections with *F. hepatica* are found in areas where sheep and cattle are raised and where humans consume raw watercress, including Europe, the Middle East, and Asia (Thomas & Garg, 2007). Infections with *F. gigantica* have been reported in Asia, Africa, and Hawaii. Prevalence

is high in Bolivia (65% to 92%), Ecuador (24% to 53%), Egypt (2% to 17%), and Peru (10%). In hyperendemic areas of Bolivia, 68% of children are infected; 11% of Ethiopians who emigrated to Israel are also infected (Thomas & Garg, 2007). An estimated 2.4 million people are infected with liver flukes worldwide (Mas-Coma et al, 1999). The incidence in humans is estimated to be only 1%, and most patients are encountered as sporadic cases or in small community outbreaks (Ashton et al, 1970).

A distinct syndrome of fascioliasis, termed *halzoun* in Lebanon and *marrerra* in the Sudan, can result from consuming raw liver of an infected sheep, goat, or cow. The living fluke adheres to the posterior pharyngeal wall, causing severe pharyngitis and laryngeal edema. Similarly, disease can follow consumption of sashimi of bovine liver served in "yakitori" bars in Japan if the liver is contaminated with juvenile worms.

Morphology and Life Cycle

F. hepatica is a flat, leaflike, hermaphrodite trematode 15 to 30 mm long, 10 mm thick, and 3 mm wide that inhabits the bile ducts and gallbladder of the host. When the eggs in mammalian stool are deposited in tepid water (22° C to 26° C), miracidia appear, develop, and hatch in 9 to 14 days. These miracidia then invade many species of freshwater snails, in which they multiply as sporozoites and redia for 4 to 7 weeks. They leave as free-swimming cercaria that subsequently attach to watercress, water lettuce, mint, parsley, or khat. Free-swimming cercaria may remain suspended in the water and encyst over a few hours. When humans consume contaminated plants or water, larvae excyst in the duodenum, migrate through the bowel wall and peritoneal cavity, and penetrate the Glisson capsule, actions that initiate the acute larval, hepatic, and invasive stages of human infection, in which the parasites eat their way down to the bile ducts. Larvae sometimes also travel to ectopic body sites. This stage may last 3 to 4 months, during which the larvae mature and migrate through liver into large hepatic and common bile ducts. Mature flukes consume hepatocytes and duct epithelium and reside for years in the hepatic and common bile ducts and occasionally in the gallbladder; this is the chronic adult biliary stage of infection. Adult fluke worms produce eggs about 4 months (range, 3 to 18 months) after infection; these eggs traverse the sphincter of Oddi and intestine and then continue the cycle of infection. Acute and chronic stages can overlap, particularly in a high-level infection. The life cycle takes about 5 months, 3 months of which are required for the journey through the human host. The adult worms that develop in the bile ducts at the end of this period have a life span of 3 to 4 years. The parasite may invade other organs during migration, such as the urinary tract, and cause hematuria. Ectopic fascioliasis may affect the peritoneum, muscles, brain, and subcutaneous tissues (Jones et al, 1977).

Pathology

Early during infection, hepatic lesions may be white or gray nodules on the liver capsule, subcapsular tracts, and, rarely, a localized hepatic mass. Later, the worm enters the biliary system. *F. hepatica* is a relatively large parasite. In the intrahepatic ducts, the worms move to and fro, and the spinous nature of the integument causes extensive destruction of the biliary epithelium; in this way, the presence of the parasite stimulates fibrosis in the bile duct wall (Fig. 67.7). Serious infection may be associated with hepatic and biliary fibrosis, hepatic necrosis, abscess formation, cholangiohepatitis, impaired nutrition, and death. A liver biopsy may reveal a nonspecific round cell infiltration of portal tracts, and cholangiocarcinoma may occur in association with fascioliasis (Thomas & Garg, 2007).



FIGURE 67.7. Spines of *Fasciola hepatica* (*arrows*) damaging the biliary epithelium (original magnification, ×500). *(Courtesy Professor M.S. Khuroo, Sher-I-Kashmir Institute of Medical Sciences, Srinagar, India.)*

Clinical Features

Eating watercress and drinking contaminated water in an endemic area are the likely routes of infection. Clinical symptoms and signs, together with radiologic findings, are the mainstay of diagnosis. The acute phase usually lasts 4 months and is caused by the migration of the immature fluke through the hepatic parenchyma, leading to hemobilia. Patients usually develop right upper quadrant pain, hepatomegaly, fever, vomiting, diarrhea, anemia, hypergammaglobulinemia (especially IgG and IgE), and allergic reactions (Aksoy et al, 2006).

On US examination of the intrahepatic and extrahepatic bile ducts, no motile echogenic images are seen (Saba et al, 2004). The findings in the liver parenchyma are nonspecific, although suspected nodules or cavitary lesions might warrant further imaging. CT is the most useful method for diagnosis; it can show peripherally located hypodense lesions, usually on the right lobe, with peripheral enhancement on contrast scans, arranged in a track like fashion with no coalescence into a larger abscess cavity, such as is seen in pyogenic abscesses. MRI usually adds nothing and cannot show the tracklike appearance of the lesions (Oto et al, 1999). After infection of the biliary tract or gallbladder, an asymptomatic clinical phase starts during which the flukes mature into adult form. This is followed by the chronic phase, caused by the adult fluke within the biliary system, during which the symptoms persist more than 4 months, are more discrete, and reflect intermittent biliary obstruction and inflammation. The main symptoms include recurrent episodes of biliary colic, cholangitis, and cholecystitis accompanied by constitutional upset, jaundice, anemia, hypoproteinemia, and edema. The liver may be tender and enlarged with

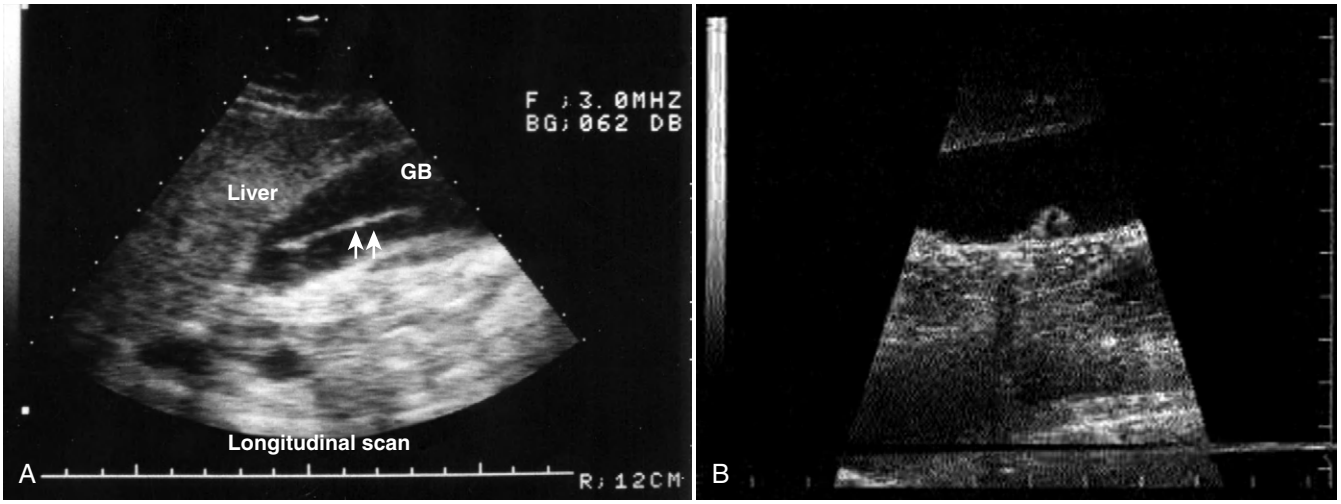


FIGURE 67.8. Ultrasound of *Fasciola hepatica* moving inside the gallbladder as an echogenic mass. **A,** Longitudinal view. **B,** Transverse view. *(Courtesy Professor A.K. El Dory, Ain Shams University, Cairo.)*

splenomegaly. Motile echogenic images with biliary mud can be seen in the gallbladder and bile ducts on US during this phase (Fig. 67.8). Real-time sonography may show the worm moving inside the gallbladder. Biliary duct dilation is common, and MRI cholangiography may show signal loss in the large bile ducts consistent with flukes or edema (LaPook et al, 2000). Diagnosis of fascioliasis by endoscopic ultrasound (EUS) (Fig. 67.9) has also been reported (Sotoudehmanesh & Yoonessi, 2003). Liver biopsy is not indicated for diagnosis and usually reveals necrotic debris, tracklike destruction of parenchyma, polymorphonuclear infiltration with abundant eosinophils, Charcot-Leyden crystals, granulomas with or without eggs, fibrosis, and bile duct proliferation (Acosta-Ferreira et al, 1979). Eosinophilia may be 50% or more of the total white blood cell count and is seen regardless of the clinical stage of infection; it may also be seen in asymptomatic contacts of the patient, who have latent infection (Saba et al, 2004; El-Shabrawi et al, 1997). It has been reported that eosinophilia could be absent in chronic cases in endemic areas (Marcos et al, 2008), and anemia is usually present (Bassiouny et al, 1991). Liver function tests show features of cholestasis. Hemoglobinuria is often present because the flukes can penetrate and lodge in the kidneys during migration through the peritoneal cavity. Adult flukes and eggs are absent from the feces and bile during the acute phase, and even in the chronic phase, so stool examination may not be diagnostic. Repeated stool analysis is required because of intermittent secretion of ova. Serologic modalities include complement fixation test (CFT), indirect fluorescent antibody test (IFAT), IHAT, and counterimmunoelectrophoresis (CIE) may be used with neither low specificity nor sensitivity (Marcos et al, 2008).

A specific serologic test to detect IgG antibodies to a crude *Fasciola* worm antigen preparation has been found to be positive in 97% to 100% of patients (Maher et al, 1999). Fas2-ELISA is more specific than Western blot and Arc II (Espinoza et al, 2005). The largest human diagnostic study has been carried out in Peru, where the Fas2-ELISA (cathepsin L1-based antibody) was validated, including 634 infected children from endemic areas. The sensitivity was 92.4% and specificity was 83.6%, with a negative predictive value of 97.2% (Espinoza et al, 2007).

The findings on imaging have already been described, and a differential diagnosis from necrotic hepatic neoplasms and liver abscesses must be made (see Chapter 66; LaPook et al, 2000). At laparoscopy or laparotomy, the characteristic features of hard, grayish white nodules on the liver surface with subcapsular channels may be seen in 55% to 75% of patients. Portal lymph nodes are often enlarged, and the common bile duct may be dilated. The diagnosis of fascioliasis should be considered in patients with a history of ingestion of raw watercress or other aquatic plants or those who have recently traveled to an endemic area and develop prostration, cholangitis, hepatosplenomegaly, anemia, and eosinophilia. The acute parenchymal phase is usually difficult to diagnose except by serologic tests for *Fasciola*. *Pseudofascioliasis* refers to the presence of eggs in the stool, which results not from an actual infection but from recent ingestion of infected liver containing eggs. This can be avoided by eating a liver-free diet several days before stool examination (Thomas & Garg, 2007).

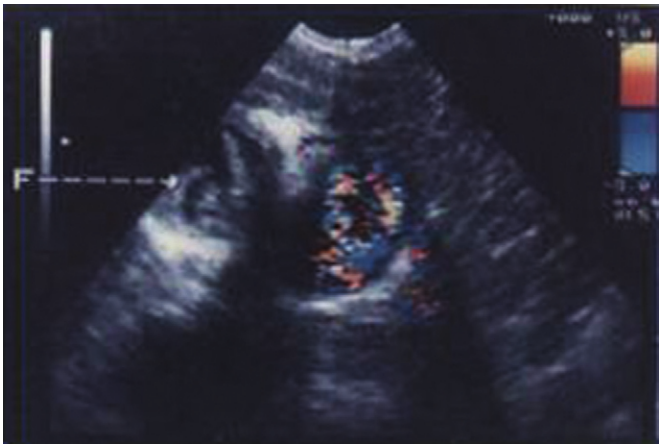


FIGURE 67.9. Endoscopic ultrasound of *Fasciola hepatica* inside the common bile duct as an echogenic mass in a transverse view. *(Courtesy Professor A.K. El Dory, Ain Shams University, Cairo.)*

Consequences of Chronicity of Infection in Fascioliasis

Recent studies have shown a strong association between fascioliasis and liver fibrosis (see Chapter 6). It seems that hepatic fibrosis may evolve in some susceptible hosts depending on the time and burden of infection. Liver cirrhosis has been reported in infected children (Marcos et al, 2005) and adults (Sanchez-Sosa et al, 2000), especially those with high-density infections (see Chapter 70). New data on the pathogenesis of hepatic involvement associated with *F. hepatica* infection have implicated cathepsin L1 and its collagenolytic function, associated with tissue invasion (Stack et al, 2007) with proteolytic activity, leading to collagen type I expression and ultimately hepatic fibrosis (Marcos, unpublished observation). On the contrary, chronic infection may also cause a persistent immunosuppressed status, suggesting that the infected host may be susceptible during chronic infection to other Th2-associated pathogens (Gironès et al, 2007).

Treatment

Emetine and chloroquine be may be successful in the short term, but recurrence is the rule because these drugs have no effect on the parasite. Fasciolae are also usually refractory to praziquantel. The drug of choice for both phases of *Fasciola* infection is triclabendazole, 10 mg/kg orally, repeated after 12 hours (El-Tantawy et al, 2007; Marcos et al, 2008), and it can be used even in the presence of biliary obstruction. Cure rates of 90% have been reported with no significant drug-related side effects. The most frequent adverse event is biliary colic caused by the passage of dead or dying parasites passing through the bile ducts. Bithionol is an alternative, available as 200-mg tablets at a daily dose of 30 mg/kg/day, to a total therapeutic dose of 150 mg/kg. The drug is administered on alternate days in three divided doses after meals. Nausea, abdominal pain, diarrhea, and photosensitivity are the most common side effects. Clinical improvement is gradual and occurs over 2 to 3 weeks (Thomas & Garg, 2007).

Surgical treatment may be indicated for diagnosis or for cholangitis (see Chapter 43). On occasion, a live worm may be found in the gallbladder or the bile duct, or the worm may find its way out through the T-tube placed at surgery (Nicholas, 1970). Endoscopic retrograde cholangiopancreatography (ERCP) may be used to relieve obstruction with removal of the worm. Rarely, percutaneous transhepatic cholangiography (PTC) may be an alternative with failed ERCP (Fig 67.10; see Chapter 18).

Proteomics and genomics have led to identification of molecules, including cathepsin L, glutathione S-transferase, leucine aminopeptidase, and fatty acid binding proteins (Dalton et al, 2003). The feasibility of inducing protective responses has been proven only in laboratory and large animals; human studies are lacking. Development of a vaccine for fasciolaisis still requires analysis of the protective effector mechanism provided by different vaccine candidates, vaccine formulations, doses, and route of administration.

Clonorchiasis

Epidemiology

C. sinensisis is endemic in northeast China, southern Korea, Japan, Taiwan, northern Vietnam, and the far eastern part of Russia (Lun et al, 2005; Rim, 2005). In general, the infection is acquired by eating raw or uncooked cyprinoid fish products in rural areas.

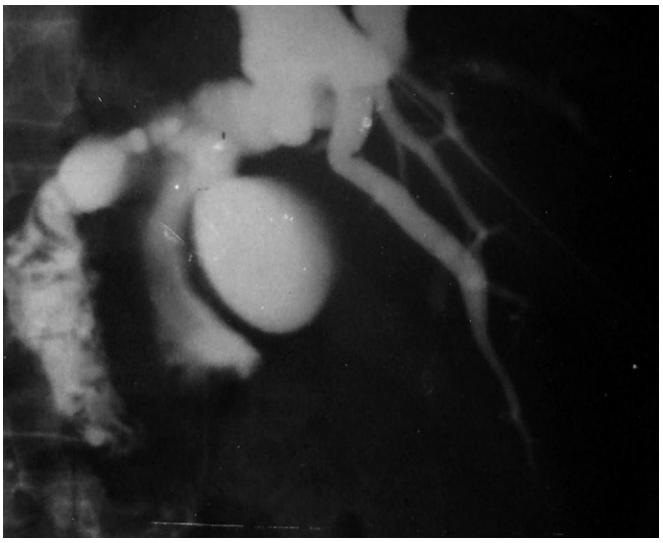


FIGURE 67.10. Percutaneous transhepatic cholangiography of *Fasciola hepatica* inside the common bile duct. *(Courtesy Professor A.K. El Dory, Ain Shams University, Cairo.)*

Morphology and Life Cycle

C. sinensis is 10 to 25 mm long, 3 to 5 mm wide, pink, and transparent when alive but hard, friable, and black when dead (Hou, 1956). Adult worms inhabit the intrahepatic ducts and may migrate down the common bile duct but tend to die in the gallbladder. In heavy infection, they may be found in the pancreatic duct. Cysts from infected fish are digested by gastric juice; larvae then migrate from the duodenum into the common bile duct upward until they lodge in a duct that is too small for further passage. Eggs laid in bile ducts reach the intestine to be excreted in feces, and the life cycle continues in fresh water in the snail, grass, or black carp, the intermediate hosts. The cercarial forms that emerge from the snail in fresh water attach to and penetrate the fish, with encysted metacercariae developing in the muscles; humans acquire the infection by ingesting the fish (Thomas & Garg, 2007).

Pathology

Irritation by the worm causes the biliary epithelium to undergo hyperplasia, which may progress to metaplasia and adenomatous hyperplasia. In the initial stages, periductal inflammation is mild, and dilation of the small- and medium-sized ducts in the periphery of the liver may occur (Choi et al, 2004; Hou, 1956). Metaplastic changes occur early in biliary epithelium, transforming normal cells into mucin-producing cells, which results in highly mucinous bile. This results in stagnation of bile with repeated cholangiohepatitis that eventually kills the worms. This may lead to ductal fibrosis and stricturing with formation of calcium bilirubinate calculi (Choi et al, 2004) and sepsis resulting from infection by *Escherichia coli* and anaerobic streptococci (Fung, 1961; Tandon, 1988). Progression to biliary cirrhosis is unusual, but there is an increased incidence of cholangiocarcinoma in patients infected with *C. sinensis* (see Chapter 50; Choi et al, 2004; Flavell, 1981; Hou, 1956). The etiology of cholangiocarcinoma is multifactorial. Carcinogens in infected individuals may be prone to malignant changes when hyperplasia of bile duct cells occurs (Flavell, 1981).

Relationship to Recurrent Pyogenic Cholangitis (See Chapter 44)

Of patients with Oriental cholangiohepatitis, 50% are infected with *C. sinensis* (Augustine et al, 1988; Tandon, 1988; Teoh, 1963). It is prudent to investigate patients with cholangitis or cholangiocarcinoma who reside in endemic areas for evidence of *Clonorchis* infection because screening for latent infection may be appropriate in relatives and close contacts of patients who test positive for *Clonorchis* (Thomas & Garg, 2007).

Clinical Features

The clinical features are independent of the severity of infestation. In an endemic area, 86% of 1091 patients screened by stool examination were found to have clonorchiasis. Only one patient had intrahepatic stones, and the 8% incidence of gallbladder stones was related more to ethnicity than to infection with *C. sinensis* (Hou et al, 1989). The classic signs associated with clonorchiasis are those of recurrent pyogenic cholangitis (Park & Son, 2008; Stunell et al, 2006). When clonorchiasis is acalculous, it is usually asymptomatic. Early symptoms include general malaise, abdominal discomfort, and diarrhea. Screening investigations may show eosinophilia with fluctuating jaundice or elevated liver enzymes (Choi et al, 2004). Clonorchiasis occurs equally in males and females, with peak incidence in the second and third decades of life (Fung, 1961). Another study showed that men are more commonly affected (Choi et al, 2004). Anemia and hypoproteinemia are common. Jaundice varies in intensity, and progression to cirrhosis results in splenomegaly. Serum bilirubin and alkaline phosphatase levels are high, and transaminase levels are slightly elevated. Evidence of pancreatitis may also be found. Plain radiographs of the abdomen may reveal gas in the biliary tree, but stones are rarely visualized. US and CT detect ductal dilation and calculi; however, contrast imaging of the biliary tract is essential to delineate the distribution of stones and strictures and to plan operative therapy. The common bile duct and hepatic ducts are usually dilated (Fung, 1961), but definite stenosis is seen in only 5%. Cholangiocarcinoma may be intrahepatic, hilar, or extrahepatic (Choi et al, 2006). The diagnosis of clonorchiasis with cholangitis depends on high index of suspicion. Elevated eosinophil counts warrant a search for the parasite, and fecal examination for eggs has been used for diagnosis of clonorchiasis (Choi et al, 2005b). Detection of specific antibodies (Kim, 1998; Lin et al, 1995) and circulating antigen by Dot-ELISA has been described (Wang et al, 2004). Other methods for diagnosis include intradermal test with diluted antigens of *C. sinensis* (Shin & Choi, 2000), radiologic studies of the liver (Choi et al, 2004), and bile examination for eggs, metacercariae, and cercariae. Of these, the intradermal test is the easiest to perform, but it has low specificity (Shin & Choi, 2000). Real-time PCR appears to be a powerful tool for both the detection and quantification of *C. sinensis* infections (Kim et al, 2009). Paramyosin (CsPmy) is a myofibrillar parasitic protein whose gene has been identified. Induction of host IgG suggests that CsPmy may be a diagnostic antigen or a vaccine for clonorchiasis (Park et al, 2009).

Treatment

Praziquantel (Biltricide) is the drug of choice. The dosage schedule is usually 25 mg/kg/day three times at 5-hour intervals in 1 day (total dose, 75 mg/kg) for 1 or 2 days, with a cure rate of 83% to 85% (Kaewpitoon et al, 2008). Antibiotics may be needed for associated pyogenic cholangitis, and interventional procedures are required in cases complicated by calculus formation and depend on the location of ductal stones and strictures. Endoscopic and minimally invasive techniques have the advantage of reduced morbidity over open surgery (Zhi et al, 2004). These procedures are usually adequate only in simple strictures, and patients referred to surgery are complicated cases in whom multiple endoscopic (ERCP) or percutaneous (PTC) procedures have failed.

Biliary Ascariasis

Epidemiology

Ascaris lumbricoides is a roundworm that commonly infects more than a quarter of the population in Asia, Africa, and Central America as well as those who have emigrated to the United States from these areas (Misra & Dwivedi, 2000). Clinical symptoms occur in individuals who have a heavy worm burden (Khuroo, 2001). When confined to the intestine, *Ascaris* infestation is usually asymptomatic, although ascariasis is an important cause of biliary disease in areas of the world where the rate of *Ascaris* infection is high. Tropical and subtropical regions with poor socioeconomic conditions and fecal contamination of the soil around dwellings and farms are main sources of infection (Khuroo et al, 1989a; Louw, 1966). Infection becomes symptomatic when the worms enter the biliary tract (Khuroo et al, 1989a, 1989b). Kamiya and colleagues (1993) reported that more than 11% of patients with gallbladder or biliary tract complications had *Ascaris* worms in their biliary tract. The incidence of gallstones in developing and developed countries is similar (Hou et al, 1989; Khuroo et al, 1989a), and it is unnecessary to consider ascariasis as an etiologic factor in all patients diagnosed with gallstone disease who hail from an endemic area.

The adult worm in humans inhabits the small intestine, mainly the jejunum, where the fertilized female lays eggs. These ova are excreted in host feces and can survive environmental conditions. In warm moist soil, the ova undergo maturation and are able to infect humans if the egg is swallowed. Mature ova hatch in the duodenum, releasing larvae that penetrate the mucosa of the proximal intestine to enter the portal venous blood, in which they are carried through the liver and via the right side of the heart to the pulmonary capillary bed. Here, larvae develop further, penetrating alveoli to travel up the trachea, enter the esophagus, and return to the intestine. In the jejunum, they mature to adults, reach 20 to 30 cm in length, and have a life span of 1 to 2 years (Thomas & Garg, 2007).

Pathology

The adult *Ascaris* reaches the duodenum either because of increased worm burden in the jejunum or as a consequence of increased intestinal motility (Khuroo, 1996). The ability of *A. lumbricoides* to enter the common bile duct, especially with heavy duodenal infection, is well known. Usually only one or two worms enter the biliary system, but massive infection may occur. The worm head moves first through the ampulla of Vater to the common bile duct, cystic duct, and intrahepatic ducts; because the length of the extrahepatic tree is only 4 to 10 cm, part of the worm may remain in the duodenum (Davies & Rode, 1982). In 2002, Kamiya and colleagues reported that 95% of the worms found in the biliary tract were located in the

hepatocholedochus, whereas only 3% were found in the gallbladder and even more rarely in the intrahepatic ducts. Migration into the biliary tract has been reported to be frequent after cholecystectomy, sphincterotomy, sphincteroplasty, choledochostomy, or biliary enteric anastomosis, presumably from increased space in the bile duct after gallbladder removal and increased release of cholecystokinin and secretin, which relaxes the sphincter of Oddi (Wani et al, 2000). Biliary migration is commonly seen in women, especially pregnant women; this is due to high levels of progesterone, which also relaxes the sphincter of Oddi (Shah et al, 2005). Children are at lower risk for biliary migration because of the small diameter of their ductal systems (Zargar & Khuroo, 1990).

The worm tends to move out of the biliary tract within 24 to 36 hours of inducing biliary or pancreatic symptoms, and the detection of live ascarids in the duodenal lumen is considered strong evidence of biliary ascariasis. The impacted worm causes spasm of the sphincter of Oddi, resulting in partial biliary obstruction and colicky pain, and cholangitis can occur after mechanical obstruction (see Chapter 43). Suppurative cholangitis may extend to intrahepatic ducts and cause multiple cholangiolitic liver abscesses. Acalculous cholecystitis, empyema of the gallbladder and, less commonly, necrosis and perforation of the bile duct may occur (Chang & Han, 1966). Dead worms cannot leave the bile duct; rather they disintegrate, providing a nidus for stones and provoking a chronic inflammatory response that leads to ductal strictures. Calculi associated with ascariasis are of the calcium bilirubinate type (Khuroo et al, 1989b; Maki, 1966), with the exception that ascarid ova or debris usually can be identified in the calculus. *Escherichia coli,* the pathogen usually identified with calcium bilirubinate stones, is frequently encountered in suppurative cholangitis (Maki, 1966). Another factor that may facilitate stone formation is the albuminoid membrane that covers most of the eggs and is not found in any other parasite. Worms reaching the intrahepatic ducts may become impacted or invade the liver parenchyma to form nests of worms (Lloyd, 1982). Unable to extricate themselves, the worms die. The resultant cholangiolitic abscess may enlarge and present on the surface or rupture into the peritoneal cavity. Extension of the abscess through the diaphragm can cause bronchopleural fistula and lung abscess, a well-known and potentially fatal complication (Chang & Han, 1966; Lloyd, 1981). The presence of dead worms in the bile duct also induces an intense eosinophilic inflammation that precipitates a fibromatous reaction. Eventually, the dead worms are surrounded by calcification, and the ongoing inflammation results in biliary stricture formation (Shah et al, 2006). Based on the aforementioned pathologic features, biliary ascariasis has been classified as *uncomplicated* and *complicated* (Thomas & Garg, 2007).

Clinical Features

Biliary ascariasis in the pediatric age group is most commonly seen in children aged 2 to 8 years. In endemic areas, adults are frequently affected, and mean age at presentation is 35 years. For unknown reasons, women are three times more likely to be affected than men; in children, a similar sex difference has not been noted. The mean duration of symptoms varies from 4 to 6 years, and 40% of patients may give a previous history of biliary surgery. In one large series, 80% of patients had undergone either cholecystectomy or endoscopic sphincterotomy (Sandouk et al, 1997a). Microscopic examination of stool and bile samples in these patients gives a positivity rate for *A. lumbricoides* of nearly 100% (Khuroo et al, 1990). Vomiting of worms is common, as well as a history of passing worms in the stool (Lloyd, 1981; Louw, 1966).

The most common presentation is usually with sudden severe upper abdominal colic with tenderness and guarding localized to the right upper quadrant or epigastrium. If present, fever is usually low grade, and jaundice, marked toxemia, and hepatomegaly are usually absent. Worms are rarely seen in the gallbladder, and the US finding of distension, wall edema, and intraluminal sludge completely resolves, usually within 2 weeks. Endoscopic examination is difficult to perform and unnecessary in the acute phase, but if done it may show duodenal or ampullary worms. ERCP has been commonly used for both diagnosis and removal of worms from the biliary tract (Fig. 67.11) and is particularly valuable when used with real-time US, with a sensitivity of 100% (Sanai & Al-Karawi, 2007).

ACUTE SUPPURATIVE CHOLANGITIS

Worms in the bile duct may block the cystic duct, leading to acute acalculous cholecystitis or empyema of the gallbladder. Biliary stasis as a result of spasm of the sphincter of Oddi coupled with intestinal contents carried by the worm into biliary tract lead to pyogenic cholangitis (Shah et al, 2006). This appears with right hypochondrial pain, fever, jaundice, tender hepatomegaly, and leukocytosis. Apathy, hypotension, metabolic acidosis, and electrolyte disturbances signify a grave prognosis. US may show worms in the biliary tree, and endoscopy may visualize pus, a tubular filling defect not suggestive of a tumor or stone on cholangiography, or a worm emerging from the ampulla (Fig. 67.12).

HEPATIC ASCARIASIS

No clinical features distinguish hepatic ascariasis from suppurative cholangitis. The diagnosis is usually made at US, and aspirated pus might yield the ova of *A. lumbricoides.* The right lobe is more commonly affected, and rupture into the peritoneal cavity is a recognized complication (Shah et al, 2006).

ACUTE PANCREATITIS

The character of the pain with acute pancreatitis varies, but an increase in serum amylase confirms diagnosis. Although encountered half as often as the purely biliary presentation (Louw, 1966), the condition was seen in only 31 of 500 patients in the series by Khuroo and colleagues (1990). Severe pancreatitis with progression to hemorrhagic pancreatitis or pancreatic fluid collections occurred in only one tenth of these cases. Sandouk and colleagues (1997a) reviewed 300 patients with pancreatic ascariasis in Syria and showed that US, along with clinical findings, was the mainstay of diagnosis, similar to another review of 14 patients (Misra & Dwivedi, 2000).

Late Complications

Late complications include intraductal calculi and biliary strictures.

Diagnosis

LABORATORY STUDIES

Stool analysis is usually the investigation of choice in the search for ascarid ova or remnants of dead worms, and results may approach 100% (Khuroo et al, 1990). Leukocytosis greater than 12,000/mm^3 usually denotes suppurative biliary and hepatic complications. The eosinophil count is seldom elevated

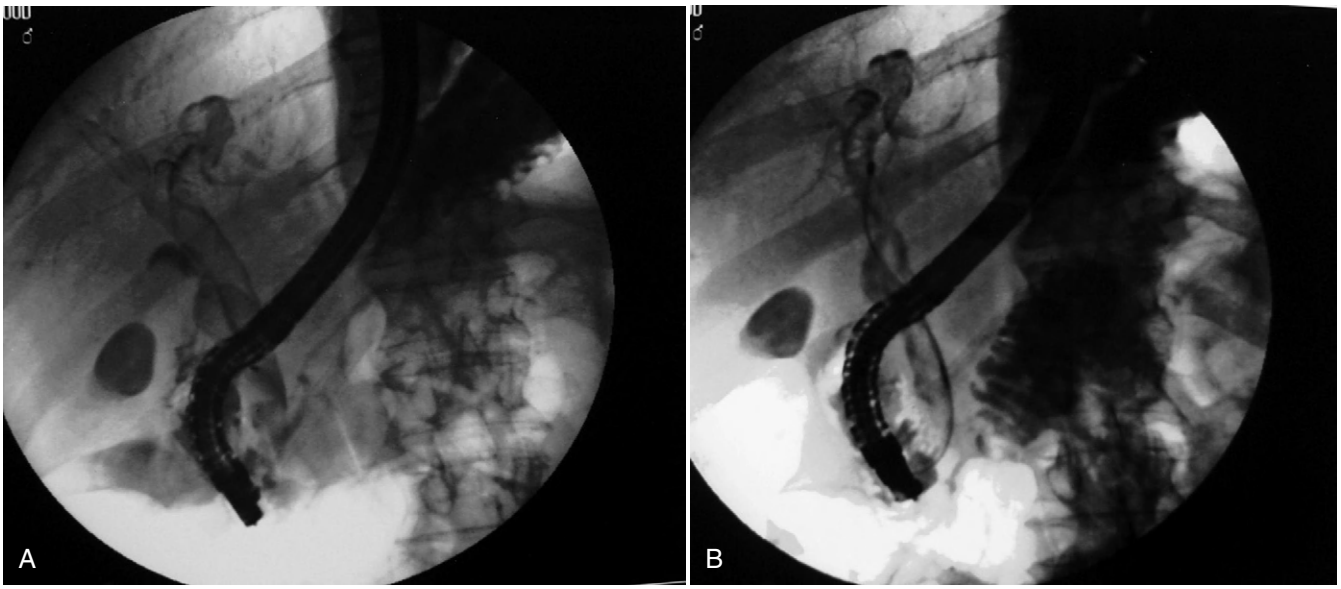


FIGURE 67.11. Endoscopic retrograde cholangiography of bilary ascariasis. **A,** Inside the common bile duct. **B,** Trial for removal using dormia basket. *(Courtesy Professor A.K. El Dory, Ain Shams University, Cairo.)*

more than 5%. Hyperbilirubinemia occurs in hepatopancreatobiliary ascariasis (Lloyd, 1982). Elevation of alkaline phosphatase and transaminases may occur when cholangitis supervenes, and pancreatitis is suggested if serum amylase is greatly elevated. Normal liver enzymes and amylase levels have been reported in a case of recurrent ascaris related pancreatitis as a result of worm migration (Lee et al, 2009). Specific serologic tests are available that can be used to monitor successful treatment (Santra et al, 2001) but are not commonly used in clinical practice.

DIAGNOSTIC IMAGING

Abdominal radiographs may confirm the presence of intestinal worms in 90% of children. On occasion, air is seen in the biliary tree or in hepatic or subphrenic abscesses (Lloyd, 1982). US is the imaging modality of choice because it shows dilated bile

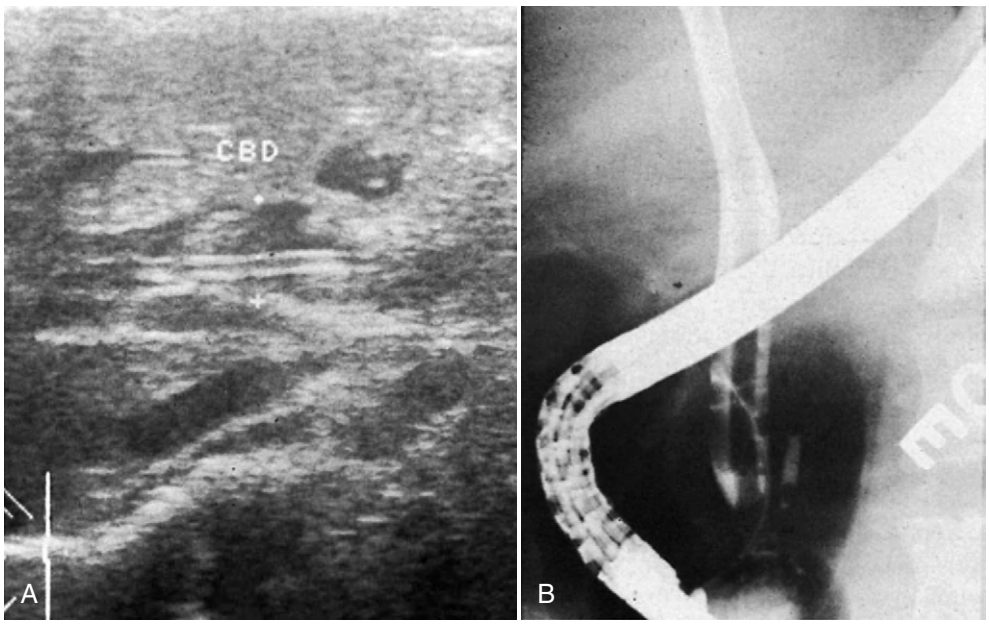


FIGURE 67.12. A, Ultrasound of a 30-year-old woman with biliary colic of 7 days' duration, showing the dilated common bile duct (*CBD*) with an echogenic tubular structure in the lumen and no distal shadowing. **B,** Endoscopic retrograde cholangiopancreatography in the same patient reveals the worm in the CBD and across the papilla. *(Courtesy Professor M.S. Khuroo, Sher-I-Kashmir Institute of Medical Sciences, Srinagar, India.)*

ducts containing linear or round areas of increased echogenicity representing worms (Desai & Tobin, 1995; Akhter et al, 2006'). Other findings were gallbladder distension with sludge inside, an edematous wall, and a mildly dilated biliary tree (Akhter et al, 2006). Real-time scanning may reveal the diagnostic movement of active worms within the biliary system. Multiple bile duct worms have a spaghetti-like appearance, with alternating echogenic and echolucent strips; if densely packed in the bile duct, they may appear as a hyperechoic pseudotumor (Shah et al, 2006). On transverse scanning, the biliary worm produces a bulls-eye appearance (Cremin, 1982). Other characteristic appearances include single or multiple long, linear echogenic strips within the bile duct without acoustic shadowing (Khuroo et al, 1987). US is useful for identifying intrahepatic worms and abscesses and for monitoring the response of lesions to therapy. Ascarid liver abscesses characteristically contain echogenic worm debris; CT does not offer significant advantage over real-time US, and it is less sensitive (Sandouk et al, 1997a). A thin line of dye is occasionally seen within the corpus of worm that has swallowed dye, and the worm is easily visualized on an unenhanced scan within the biliary tree (Sherman & Weber, 2005).

Endoscopy may reveal a worm in the duodenum, and occasionally a worm may be seen impacted in or protruding from the ampulla of Vater. ERCP has been done safely, even in the acute setting, and it shows worms in the extrahepatic and intrahepatic biliary tree, including liver abscesses (Lloyd, 1981) and cases of recurrent pancreatitis (Lee et al, 2009). Biliary strictures can be studied, and endoscopic extraction of worms and biliary decompression may succeed in aborting an attack of severe cholangitis (Khuroo et al, 1990). Magnetic resonance cholangiopancreatography (MRCP) is a useful modality in pancreaticobiliary ascariasis. The worms are described as linear, hyperintense tubular structures with a central hypointense area (Arya et al, 2005). EUS has been shown to document biliary ascariasis (Sriram et al, 2006). Percutaneous transhepatic cholangiography has been used in cases of failed ERCP to visualize and relieve obstruction in the abnormal biliary tree containing worms (Lloyd, 1982). Adult worms or debris may be identified in the aspirated bile.

Management

The management strategy for ascariasis includes conservative measures, endoscopic extraction, or surgical intervention. Without appropriate nonoperative management, worms spontaneously return to the duodenum in 98% of children (Chang & Han, 1966; Louw, 1966) and 94% of adults (Khuroo et al, 1990). Parenteral antispasmodic drugs and analgesics to relax the sphincter of Oddi and relieve biliary colic, nasogastric decompression, and intravenous fluids are recommended in the acute stage. Successful elimination of an adult *Ascaris* worm from the gallbladder 7 days after killing it with albendazole has been documented (Cha et al, 2002); however, oral antihelmintic drugs may not be helpful in the treatment of biliary ascariasis because of poor enterohepatic circulation (Khuroo, 1996). Administration of piperazine citrate through the nasobiliary catheter has been shown to be effective (Kamath et al, 1986). However, some investigators believe that this approach should not be used because it has been reported to cause paralysis or death of the worm in the bile duct, and this dead worm may act as a nidus for future stone formation (Shah et al, 2006). Albendazole (400 mg/day for 1 day) or mebendazole (100 mg twice daily for 3 days) and pyrantel pamoate (single dose of 11 mg/kg to a maximum of 1 g) are the preferred agents, and cure can be achieved in nearly 100% of cases. The safety of these drugs in pregnant women and children younger than 2 years is not established; in this situation, piperazine is safe in a single dose of 75 mg/kg (maximum 3.5 g) on 2 consecutive days. Stool examination is required to confirm eradication of the infection, and follow-up US is needed to look for intraductal worms. ERCP is recommended if symptoms or US abnormalities persist beyond 2 weeks with suspected pancreatobiliary ascariasis. To prevent reinfection in endemic areas, antihelmintic therapy must be repeated every 2 months in patients who are cured (Khuroo et al, 1990).

The problem of reinfection of the bile ducts after operative or endoscopic removal of worms has led to important modifications in the interventional approach previously advocated (Chang & Han, 1966; Louw, 1966). Preoperative eradication of intestinal worms ideally should be done before endoscopic or surgical manipulation of the common bile duct. Severe persistent pain unrespondive to antihelmintics is an indication for ERCP and endoscopic removal of intrabiliary worms. In an endemic area, multiple reinvasions of the bile ducts by worms is seen in patients who have undergone endoscopic sphincterotomy (Khuroo et al, 1990).

It would seem to be of paramount importance to preserve the sphincter of Oddi (Shah et al, 2006; Khuroo & Zargar, 1985; Khuroo et al, 1990). Failure of response to conservative management with increasing jaundice may indicate coexisting stones in the common bile duct (Khuroo & Zargar, 1985; Khuroo et al, 1990). When skilled endoscopic intervention has failed or is unavailable, PTC or surgery is recommended, a situation more likely to occur in children than in adults (Hangloo et al, 1989). Laparoscopic common bile duct exploration, with removal of the worm and a cholecystectomy, was reported by Astudillo and colleagues (2008).

Conservative management includes treatment of pain with analgesics, treatment of pyogenic cholangitis with antibiotics, and oral administration of antihelmintic drugs. The patients are subsequently allowed nothing by mouth and are given intravenous fluids. This management strategy is applied for a few days, and its success is judged by improvement in pain, fever, and jaundice with simultaneous disappearance of the worms from the bile duct. The symptoms usually resolve with this approach within 3 days in 60% to 80% of patients.

Worm extraction with biliary drainage may be lifesaving in patients with severe cholangitis, and it is successful in all patients from the papillary opening and in more than 90% of patients from the bile ducts (Shah et al, 2006). Biliary cannulation in these patients is easier to achieve because the passage of worms across the sphincter makes it patulous (Khuroo et al, 1990). Worms can be extracted across the papillary opening by using a grasping forceps or a dormia basket; polypectomy snares should be avoided because the snare may cut the worm, leaving a remnant that may lead to stone formation. The worms in the bile duct may protrude out of the papilla after injection of the contrast and thus may be extracted. If the worms are unable to come out or are dead, they can be pulled out using a dormia basket or a biliary occlusion balloon (Reddy et al, 2003). Total clearance of bile ducts may require multiple endoscopic sessions. Endoscopic papillary balloon dilation has been described in nonendemic areas to remove the worm and associated calculi (Misra & Dwivedi, 1998). When the worm cannot be reached

by conventional ERCP, Sandouk and colleagues (1997b) have suggested using the whirlpool jet technique. Early ERCP should be performed when pancreatobiliary ascariasis is suspected in cases of repeated pancreatitis following cholecystectomy and sphincterotomy, even with normal liver enzymes, because of worm migration (Lee et al, 2009).

Surgical intervention is required in patients after an unsuccessful endoscopic attempt; if the *Ascaris* organisms enter the intrahepatic ducts, leading to the formation of stones, strictures and abscesses; and when gallbladder ascariasis is present (see Chapters 39 and 44; Shah et al, 2006). Laparoscopic extraction of live worms from the bile duct has also been reported in the literature (Yoshihara et al, 2000). Overall, 20% of patients with biliary ascariasis need surgery (Wani & Chrungoo, 1992). An initial operative cholangiogram helps define the extent of the infection. Worms are removed through a longitudinal choledochotomy because compression of the liver often propels intrahepatic worms toward the common bile duct. Choledochoscopy is also valuable, especially if worms, debris, or stones are impacted in the intrahepatic ducts.

The evacuated biliary tree is irrigated with saline and closed over a large-bore T-tube. Intraoperative cholangiography through the T-tube is done to identify residual worms. The liver may contain granulomatous nodules or abscesses, and worms under the liver capsule can be extracted by incision and drainage of the abscess. Removal of all worms from the intestine via enterostomy is an important part of the operation to prevent biliary reinfestation, a serious complication that may require reoperation.

Postoperatively, a broad-spectrum antibiotic is prescribed. Worms identified in the bile duct at this point should be managed conservatively because the worm may spontaneously return to the intestine. Irrigation of the T-tube with saline may help, but antihelmintics should not be administered through the T-tube; this would kill the worm in the common bile duct and prevent spontaneous evacuation. Endoscopic extraction may be successful if the worm is impacted around the T-tube or can be removed by applying suction to a T-tube and gently withdrawing it with the worm. If these measures fail, reoperation is necessary with preoperative oral antihelmintics (Thomas & Garg, 2007).

Full recovery is the rule, with a mortality rate of 1% or less. Worm reinvasion after successful initial management is always symptomatic and may occur in 30% of those treated (Khuroo et al, 1989b, 1990). A careful search for biliary lithiasis in the intrahepatic and extrahepatic bile ducts and management of sepsis and biliary strictures should result in a good prognosis. MRCP and ERCP should always be considered in cases of repeated pancreatitis. Recurrent pyogenic cholangitis, liver abscesses, and granuloma necessitate surgery.

In endemic areas, school screening may be effective in the detection and early treatment of asymptomatic carriers. Health education, good sanitation, and early medical therapy of intestinal ascariasis are the best ways to prevent reinfection.

Biliary Opisthorchiasis (See Chapter 45)

Opisthorchiasis is caused by *Opisthorchis viverrini* and *O. felineus,* the latter of which is endemic in the Soviet Union, Kazakhstan, and Ukraine. The infection is acquired by eating raw or uncooked cyprinoid fish products in rural areas or dishes as *koi-pla* (Sayasone et al, 2007).

These small flukes migrate to the liver through the duodenum via the ampulla of Vater into the bile ducts, where they mature into adult worms in less than a month. The adult flukes reside in medium-sized and small intrahepatic bile ducts and occasionally in extrahepatic bile ducts, the gallbladder, and pancreatic duct, where they can live for many years; in the liver, they can live for decades (Marcos et al, 2008).

Clinical Features

Because *Opisthorchis* flukes do not penetrate the liver parenchyma, their disease manifestations are caused by the obstruction of the biliary tract, where they can cause prominent inflammation. Flukes can occasionally gain access to the pancreatic tract, where they can cause obstruction and pancreatitis.

OPISTHORCHIS VIVERRINI

In acute infection, only 5% to 10% of heavily infected patients have symptoms, such as right upper quadrant pain, flatulence, fatigue, and a hot sensation over the abdomen. In the chronic phase, mild hepatomegaly occurs. Jaundice and splenomegaly are rare, but intrahepatic duct stones and recurrent cholangitis are common. Whenever jaundice and ascending cholangitis are detected, fluke-related cholangiocarcinoma should be suspected (see Chapter 50B).

OPISTHORCHIS FELINEUS

In acute infection, symptoms occur 2 to 4 weeks after eating raw fish and include fever, nausea, vomiting, abdominal pain, malaise, arthralgia, lymphadenopathy, and skin rash (Tselepatiotis et al, 2003). Eosinophilia is common during the initial 2 to 6 weeks of infection, with raised liver enzyme levels. In chronic infection, eosinophilia is milder. Patients may come to medical attention with suppurative cholangitis and liver abscess because of biliary obstruction.

CONSEQUENCES OF CHRONICITY OF INFECTION IN OPISTHORCHIASIS

The higher the intensity and the higher the anti–*O. viverrini* antibody titres, the higher the risk for cholangiocarcinoma (Honjo et al, 2005). The International Agency for Research on Cancer recognizes this parasite as a category I carcinogen. The lesions that predispose to malignant changes in *O. viverrini* are dilation of subcapsular medium and large bile ducts with prominent fibrotic wall, periductal inflammatory cell infiltration, goblet cell metaplasia, epithelial and adenomatous hyperplasia, and periductal fibrosis. The pathogenesis of *O. viverrini*–mediated hepatobiliary changes may be due to mechanical irritation or its metabolic products (Sriamporn, et al, 2004). Several N-nitrosol compounds and their precursors occur at low levels in fermented food, such as preserved mud fish paste (*pla ra*), a condiment that is a ubiquitous component of the cuisine of northeastern Thailand and Laos (Sripa et al, 2007).

The study of *O. viverrini* genes should expedite molecular studies of cholangiocarcinogenesis and accelerate research focused on developing new interventions, drugs, and vaccines that might help in controlling *O. viverrini* and related flukes (Laha et al, 2007).

Diagnosis of Opisthorchiasis

Opisthorchiasis is diagnosed by detection of eggs in feces. In light infections, those with fewer than 10 adult worms in the biliary tract, a PCR detecting the DNA of the adult parasite in

stools may be helpful (Duenngai et al, 2008). Ruangsittichai and colleagues (2006) reported high sensitivity and specificity using a recombinant eggshell protein with potential for the serodiagnosis of human opisthorchiasis.

Treatment of Opisthorchiasis

Praziquantel is the drug of choice for *O. viverrini* and *O. felineus* treatment. For *O. viverrini,* a single dose (40 to 50 mg/kg) of praziquantel treatment is indicated, with a cure rate between 91% and 97% (Kaewpitoon et al, 2008).

BLOOD FLUKES

Schistosomiasis

Schistosomiasis is sometimes referred to as *bilharziasis* after Theodor Bilharz, who first identified the parasite in 1852. Schistosomiasis is caused by infection with blood flukes known as *schistosomes.* It can be associated with serious morbidity and mortality and may cause anemia, chronic pain, diarrhea, exercise intolerance, malnutrition, bladder cancer, portal hypertension, and central nervous system complications (King et al, 2005). Chronic complications usually occur in individuals who live in endemic areas and have recurrent exposure. However, schistosomiasis can also cause complications in people with even brief exposures, such as travelers (Blanchard, 2004). Three major species and two less common species produce infection in humans. Of the major species, *Schistosoma mansoni* is common in tropical and subtropical areas of sub-Saharan Africa, the Middle East, South America, and the Caribbean. *S. japonicum,* prevalent in Asia, can provoke intestinal and hepatic complications. *S. haematobium* is common in North Africa, sub-Saharan Africa, the Middle East, Turkey, and India and predominantly leads to renal and bladder sequelae, although on occasion it results in liver disease. The minor species include *S. mekongi* and *S. intercalatum,* both of which can also induce intestinal and liver disease. More than 200 million people worldwide are estimated to have schistosomiasis, a disease responsible for more than 200,000 deaths annually (Chistulo et al, 2004).

Life Cycle

The life cycle of schistosomiasis is complex and requires both intermediate and definitive hosts. The adult worms are approximately 1 to 2 cm in length with a cylindrical body, two terminal suckers, a blind digestive tract, and reproductive organs (Gryseels et al, 2006). The male schistosome forms a groove, where the female resides. Females produce hundreds to thousands of eggs per day. After contact with water, the ovum releases miracidium, which seeks an intermediate host in the snail. After 4 to 6 weeks, the miracida multiply asexually into sporocysts and later into cercariae. The cercariae leave the snail and seek a definitive host, where they develop into adult worms. As the definitive host, humans acquire schistosomiasis via contact with fresh water. Cercariae penetrate the intact skin of humans and become schistosomulae, which migrate from the skin into blood and lymph vessels and are carried to the heart and lungs. They then migrate through pulmonary capillaries into the left side of the heart and then into the arterial circulation, where they are carried to the mesenteric arteries, splanchnic arteries, and portal veins; they subsequently reach the liver, where they mature into adults over a period of 1 to 4 weeks.

Different species have a propensity to affect different organs. The adult worms migrate against portal blood flow to varying destinations: mesenteric venules of the small intestine (*S. japonicum* and *S. mekongi*), mesenteric venules of the colon (*S. mansoni* and *S. intercalatum*), and the vesical venous plexus (*S. haematobium*). Adults remain in these blood vessels for life, residing in permanent copulation and adhering to wall of blood vessels. Worms survive for 5 to 7 years but can persist up to 30 years (Arnon, 1990). Female worm begins to produce eggs, which travel hematogenously to other sites or traverse from vascular space through host tissues to the lumina of intestine or urinary bladder. The eggs are then variably excreted in the feces (*S. mansoni, S. japonicum, S. haematobium, S. intercalatum,* and *S. mekongi*) or the urine (*S. haematobium*).

Pathogenesis

Unless adult worms migrate to an unusual location, such as the spinal cord or brain, little damage occurs to the host, whereas cellular infiltrate is consistently found around the eggs (Keating et al, 2006). Eggs released into the bloodstream can invade local tissues, release toxins and enzymes, and provoke a Th-2–mediated immune response. Inflammation and granuloma formation occur around deposited eggs and lead to fibrosis of affected tissues (Cheever et al, 2000). *S. mansoni, S. japonicum, S, mekongi,* and *S. intercalatum* eggs tend to either penetrate the bowel adjacent to the mesenteric vessels or travel via the portal venous system to the liver. In the bowel, granulomatous inflammation around the invading eggs can result in intestinal schistosomiasis characterized by ulceration and scarring (Strickland, 1994).

In the liver, eggs lodge in presinusoidal radicles of the portal vein, where they elicit a granulomatous fibrosing reaction that blocks venous blood flow. Portal hypertension results, with compensatory portosystemic blood flow and late progressive liver damage. Symmers' pipestem fibrosis is pathognomonic. It is distinct from cirrhosis because there is no hepatocyte dysfunction; instead, the portal hypertension results from fibrosis within blood vessels. Eggs of *S. haematobium* usually affect urinary tract; however, this parasite may be associated with hepatic damage.

The interaction between the parasite and host immune response is complex. Immunity to infection with any schistosome species is both innate and acquired. It is the host's immune response to invading eggs that is the major cause of clinical disease. A host-mediated type 2 Th2 fibrogranulomatous inflammatory response occurs, which may result in activation of hepatic stellate cells, the mediators of fibrosis (Bartley et al, 2006).

The age-intensity curve in endemic areas characteristically shows a rise in intensity of infection during the first 2 decades of life, followed by a decline in adults, with possible acquired immunity to adult worms. The behavioral factors (e.g., walking barefoot and swimming) may play a role in the incidence of infections in children compared with adults.

Clinical Picture

Most patients are asymptomatic, and symptoms depend on the stage of disease. The different species of *Schistosoma* cause varying clinical complications. Acute symptoms may present as swimmer's itch or Katayama fever. Symptoms are also more

likely to occur in travelers and other nonimmune hosts. Lymphadenopathy, eosinophilia, and hepatosplenomegaly may be prominent findings. The diagnosis of Katayama fever relies upon appropriate epidemiology and consistent clinical findings (Gryseels et al, 2006).

Symptoms of chronic infection often begin insidiously and are progressive without treatment. Intestinal schistosomiasis may cause chronic or intermittent abdominal pain and diarrhea with iron-deficiency anemia secondary to ulceration and polyps. Acute appendicitis has also been described in one case report (Gabbi et al, 2006). Hepatic schistosomiasis can lead to hepatomegaly and severe splenomegaly in children and adolescents. Chronic hepatic schistosomiasis develops years later in young and middle-aged adults, with a long duration of intense infection, splenomegaly, and portal hypertension. However, hepatocellular function remains normal. Leading causes of morbidity and mortality include the formation of ascites and esophageal bleeding from varices. Urinary schistosomiasis may be asymptomatic or may cause hematuria, and symptoms related to anemia may be present. Squamous cell carcinoma of the bladder and nephritic syndrome may occur (Ross et al, 2002).

Schistosomiasis can sometimes be associated with serious neurologic complications. Pulmonary manifestations can also be seen in people with hepatosplenic disease as a result of heavy infections with *S. mansoni, S. japonicum,* or *S. haematobium* infection. Presinusoidal portal hypertension fosters the development of portosystemic collateral vessels that allow *Schistosoma* eggs to embolize into the pulmonary circulation, leading to granulomatous pulmonary endarteritis. Pulmonary hypertension and cor pulmonale gradually ensue with dyspnea as the principal symptom. As disease evolves, the heart enlarges and pulmonary arteries dilate to aneurysmal proportions, representing end-stage, irreversible alterations (Sarwat et al, 1986). Recurrent urinary tract infections or bacteremia as a result of *Salmonella* infection are classic complications of schistosomiasis (Elliott, 1996). It has been postulated that infection with *S. haematobium* may increase the risk of HIV infection (De Silva et al, 2006). Persons with hepatitis B or C viruses have more severe disease.

Diagnosis

Complete blood count may show anemia, leukopenia, or thrombocytopenia as a result of hypersplenism with hypercellular marrow, portal hypertension, or varices. The liver profile is usually normal except in cases of coinfection. Eggs in the stool or urine are often used as a test, and rectal snips as well as circulating antigen are specific and sensitive to detect active infection and assess treatment. Serology usually detects previous exposure, and abdominal US shows splenomegaly and periportal fibrosis.

Treatment

Praziquantel is the drug of choice for treatment of schistosomiasis. *S. haematobium, S. mansoni,* and *S. intercalatum* can be treated with 40 mg/kg in one or two doses, whereas the dosage for *S. japonicum* and *S. mekongi* is 60 mg/kg in two or three doses at least 3 hours apart. No serious side effects are reported, and treatment is efficacious in about 85% to 90% (Ross et al, 2002). In addition to antihelmintic therapy, patients with severe portal hypertension and esophageal varices may also benefit from treatment with propranolol and/or sclerotherapy band ligation or shunt procedures (see Chapter 70; Elliott, 1996).

Despite its demonstrated efficacy in decreasing recurrent variceal hemorrhage, enthusiasm for surgery has declined over the last 2 decades, due in part to the more easily administered techniques of endoscopic therapy or intervention. Orthotopic liver transplant is the only treatment that corrects the portal hypertension and also corrects the liver failure when it occurs. Endoscopic therapy or intervention and distal splenorenal shunting do not hinder transplantation but lengthen the time taken for surgery (Bismuth et al, 1995).

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CHAPTER 68

Hydatid disease of the liver

Jake Krige, Phillipus C. Bornman, and Jacques Belghiti

OVERVIEW

Hydatid disease, or echinococcosis, is a widespread zoonotic parasitic disease caused by a tapeworm that continues to be a clinical and public health problem worldwide, especially in areas where animal husbandry and subsistence farming form an integral part of community life. Hydatidosis infects a large number of wild and domestic animals and humans, and the larval stage of the disease develops into a hydatid cyst. Hydatid disease is most frequently caused by *Echinococcus granulosus*, and the liver is the most commonly involved organ in two thirds of patients, although it may affect any part of the body, either as a primary or secondary event (Shaw et al, 2006). The life cycle of *Echinococcus* requires a definitive host, which is often a dog, and an intermediate host, which is commonly sheep. Humans become accidental intermediate hosts when they become infected after ingesting ova passed in dog feces.

During the natural history of hydatid cysts in the liver, several complications may occur, the most frequent and severe of which are secondary infection of the cyst cavity, biliary fistula causing jaundice and cholangitis, and rupture of the cyst into the peritoneal or pleural cavity. The diagnosis is confirmed by noninvasive radiologic imaging. Surgery is the treatment of choice for complicated cases, but uncomplicated cysts located in anterior liver segments have been treated successfully laparoscopically. Medical treatment alone for univesicular cysts, and in conjunction with surgical and percutaneous techniques, is effective in selected patients. Percutaneous treatment techniques represent an important therapeutic advance in the treatment of hydatid disease. Increasing migration and world travel requires that clinicians, radiologists, and surgeons in developed countries have a clear understanding of the diagnosis and treatment of hydatid disease. *Echinococcus multilocularis,* which causes alveolar echinococcosis, is discussed separately.

PATHOGENESIS AND ETIOLOGY

Although 16 species and 13 subspecies were originally described in the genus *Echinococcus,* molecular epidemiologic studies have led to the recognition of only four clinically important species: *E. granulosus, E. multilocularis (E. alveolaris), E. oligarthrus,* and *E. vogeli* (Thompson, 2001). Recently, a new strain, *E. shiquicus,* has been identified on the Tibetan plateau, but to date no human infection has been described (Shaw et al, 2006). The characteristics of the four *Echinococcus* species are summarized in Table 68.1. *E. granulosus* is the most common and is the main focus of this chapter. *E. multilocularis*, a rare and aggressive form of hydatid disease, is discussed separately at the end of the chapter.

E. granulosus is a small, hermaphroditic tapeworm about 5 mm in length. The tapeworm consists of a head, or *scolex,* and a body, or *strobila,* with three or four proglottids (Fig. 68.1). The last one is the largest and bears the mature eggs. The eggs contain a hexacanth embryo that has three pairs of lancet-shaped hooklets. The life cycle of *E. granulosus* requires two hosts, a carnivore and an herbivore (Fig. 68.2). The adult tapeworm lives in the intestine of the dog, which is the most common definitive host for *E. granulosus*. Worms release large numbers of infected eggs that pass out in the dog feces and contaminate soil, water, and plants. The eggs are ingested by the intermediate host (humans are accidental intermediate hosts), the eggs hatch, and the embryo migrates through the intestinal wall into the portal system. Most embryos lodge in the liver, mainly in the right lobe because of preferential portal flow; there they develop into hydatid cysts within months to years. Embryos may escape this first filter and lodge in the capillaries of the lung, where they develop. A small percentage of embryos find their way into the systemic circulation and involve other organs, including the spleen, kidney, brain, bone, or any other site. Most patients have single organ involvement. In the liver, the parasite develops into the larval stage, the hydatid cyst, which is filled with fluid and contains hundreds of protoscolices. For the life cycle to be complete, a canine host must ingest the hydatid cyst or its contents, which commonly occurs when infected sheep are slaughtered and organs containing hydatid cysts are fed to dogs (Krige & Beckingham, 2001).

EPIDEMIOLOGY

The disease occurs principally in sheep-grazing areas, especially where dogs are allowed to stray and eat uncooked viscera. Echinococcosis is endemic in many Mediterranean countries, the Middle and Far East, South America, and South and East Africa. The incidence of disease in humans in endemic areas depends on the level of health care and veterinary control. The incidence of human hydatidosis is often established by the number of surgically treated patients. The yearly incidence of human hydatidosis per 100,000 population ranges from 0.4 in Switzerland and Wales to 196 in Turkana in the northwest of Kenya. This high incidence is due to the close relationship the Turkana people have with their dogs: they sleep with them for warmth in the desert nights, and dogs are kept as "nurses" to lick babies clean after they vomit or defecate (Richards, 1992; Watson-Jones & Macpherson, 1988). This domestic intimacy results in many of the population becoming infected when very young (Morris, 1992).

Immigrants from endemic areas have a higher incidence of hydatid disease than native residents in Western countries. Indigenous people in endemic areas are the primary high-risk group, but aid workers and tourists are also at risk for becoming infected by hydatid disease, although infection in those groups is less frequent. Human infection results from eating raw

Table 68.1

Characteristics of Echinococcus Species

	E. Granulosus	*E. Multilocularis*	*E. Oligarthus*	*E. Vogelii*
Geographic distribution	Worldwide	Limited to Northern Hemisphere	Central and South America	Central and South America
Definitive hosts	Dog, fox, wolf, dingo, jackal	Fox, dog, cat	Wild felines (e.g., jaguar, puma)	Bush dog
Intermediate hosts	Sheep, cattle, pig, goat, camel, buffalo, human	Rodent, pig, horse, human	Rodent, human	Rodent, human
Cyst structure	Typically unilocular, spherical in shape	Multivesicular	Polycystic	Polycystic
Infiltration or metastasis	No	Yes	No	No
Location of cysts	Visceral, primarily liver and lungs	Visceral, primarily liver	Peripheral, primarily muscles	Visceral, primarily liver
Number of segments in worm (range)	3 (2 to 7)	5 (2 to 6)	3	3
Total length of worm (mm)	2 to 11	1.2 to 4.5	2.2 to 2.9	3.9 to 5.5

Modified from Thompson RCA, 2001: Echinococcosis. In Gillespie S, Pearson RD (eds): Principles and Practice of Clinical Parasitology. Chichester, UK, John Wiley & Sons, pp 587-612.

vegetables infected by the feces of dogs or by direct contact with dogs, mostly through the close contact of children with their pets. Some professions are particularly exposed, especially workers in slaughterhouses, veterinary stock breeders, shepherds, tanners, and butchers.

As a result of slow growth, cysts usually become symptomatic a few years after infection, in adolescence or early adulthood. Infected adults may become symptomatic later in life. Host immunity may overcome infection, resulting in a nonviable echinococcal cyst without the person ever becoming symptomatic. Humans are accidental hosts and play little part in the transmission of the disease, making them so-called *dead-end hosts,* and the disease is not transmitted from human to human (Shaw et al, 2006).

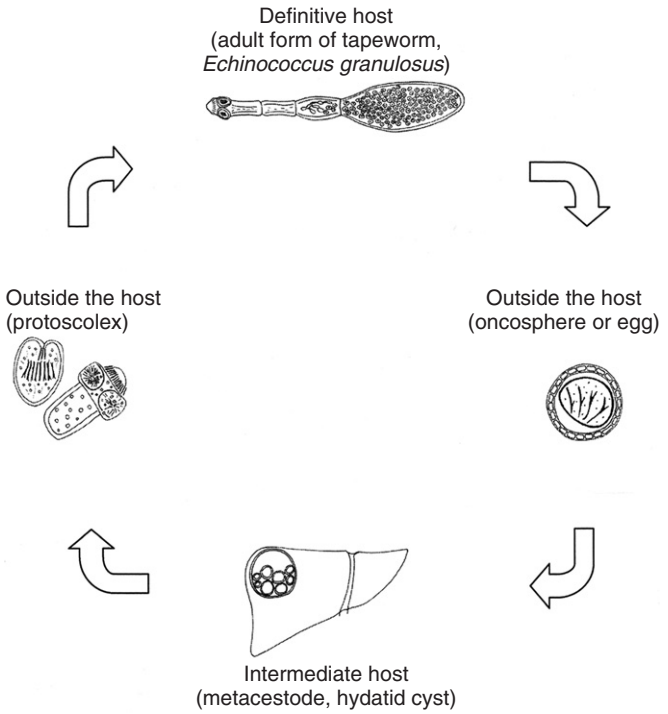


FIGURE 68.1. Life cycle of *Echinococcus granulosus.*

DEVELOPMENT OF A HYDATID CYST

When the parasite reaches the liver parenchyma, it develops into a cystic larval phase, which is visible within 3 weeks and may measure up to 3 cm in diameter after 3 months. The mature *E. granulosus* cyst consists of three layers: a *germinal layer,* a *laminated layer,* and an *ectocyst.* The inner, germinal layer surrounds the fluid-filled central hydatid cavity and in turn is surrounded by the laminated layer. These two layers together form the *endocyst.* Compression of the host tissue around the endocyst produces a fibrous layer known as the *ectocyst* or *pericyst* (Figure 68.3).

The germinal layer, also called the *germinative membrane,* is the living component of the parasite. Undifferentiated cells in the germinal layer produce invaginations into the cyst cavity, forming brood capsules that contain protoscolices, which are released into the cyst fluid. The germinal membrane secretes fluid into the cyst and is the source of daughter cysts (Fig. 68.4). The presence of daughter cysts creates multivesicular cysts, which are more common in adults than in children. Daughter cysts have a structure similar to the mother cysts, including a laminated and germinative membrane, cyst fluid, brood capsules, and protoscolices. The only difference is the absence of an adventitial layer (Krige & Beckingham, 2001).

The thin germinal layer is supported externally by a characteristic structural component of the parasite, the laminated layer, which is acellular, always separable from the pericyst, and usually 1 to 2 mm thick. Although the laminated layer is permeable to water, potassium, chloride, calcium, and urea, it protects the cyst from host enzymes, bile, and bacteria. The formation of daughter cysts is known as *endogenic vesiculation. Ectogenic vesiculation* occurs when there is a small leak or defect in the laminated membrane, and the germinal layer passes through to create a "satellite" hydatid cyst.

The ectocyst or pericyst is a fibrous capsule that develops from host tissue as an inflammatory reaction to *E. granulosus*. This thick fibrous layer is present in hydatid cysts in the liver and spleen but is absent in pulmonary and brain hydatid cysts.

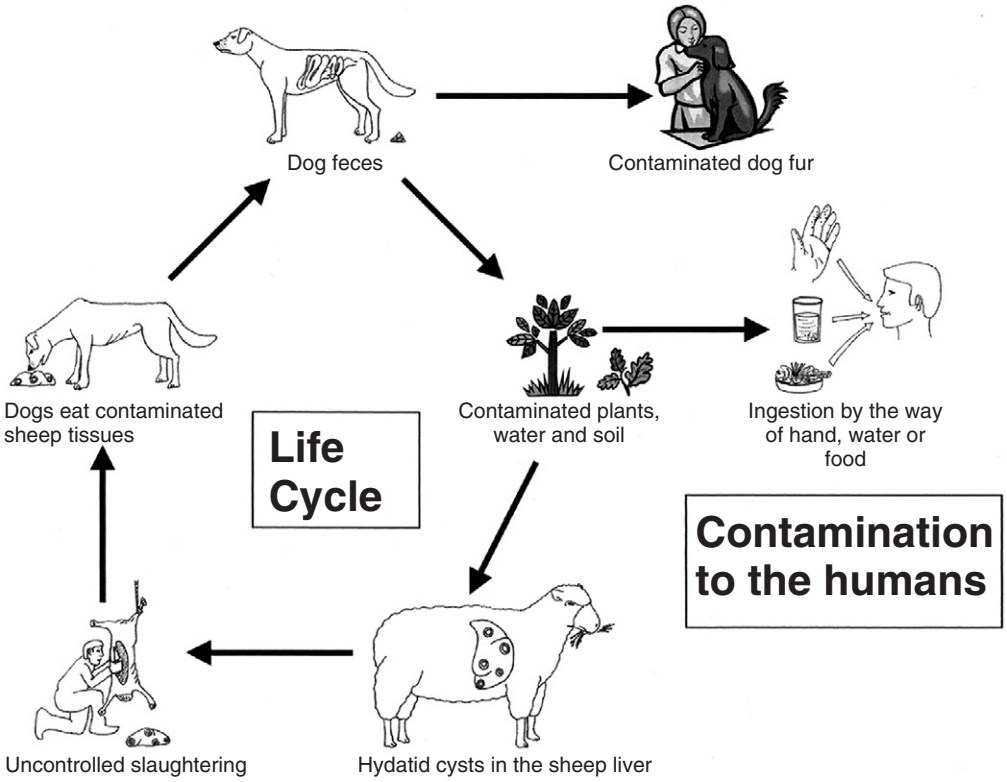


FIGURE 68.2. Usual route of *Echinococcus granulosus* and contamination of humans during the life cycle.

Vascular structures and bile ducts in the adventitial layer remain intact and patent despite enlargement of the cyst and may result in postoperative bleeding or bile leaks after partial pericystic resection. The blood supply of the adventitial layer is abundant and results in the appearance of a hypervascular rim or halo around the cystic cavity on computed tomography (CT) scans after contrast injection. No clear cleavage planes are apparent between the adventitial layer and the surrounding normal host tissue, and the cyst is not readily separable from the surrounding parenchyma. With time, the adventitial layer may calcify, either partially or totally (Krige & Beckingham, 2001).

An uncomplicated hydatid cyst typically contains a clear, colorless, odorless fluid secreted by the germinal membrane. Sodium, chloride, and bicarbonate concentrations are the same in the fluid as in the patient's plasma, whereas potassium and calcium levels are lower. In uncomplicated cysts, hydatid fluid is sterile. Bile-stained cyst fluid indicates a cystobiliary communication. When superadded infection is present, the cyst fluid appears frankly purulent; in degenerated cysts, the fluid becomes turbid. Spillage of hydatid fluid content as a result of traumatic or iatrogenic rupture produces implantation of protoscolices and secondary cysts on surrounding viscera, known as *secondary hydatidosis* (Krige & Beckingham, 2001). Although any segment

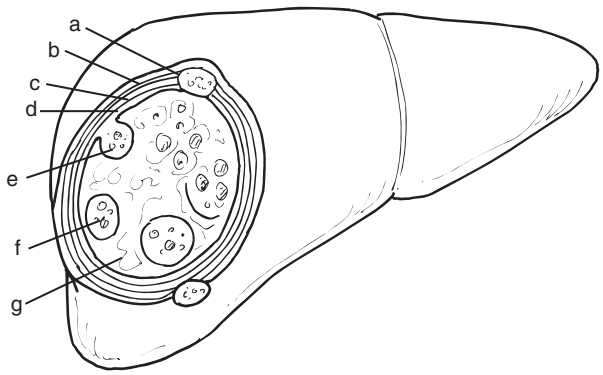


FIGURE 68.3. Structure of hydatid cyst showing exogenous daughter cyst (*a*); pericyst membrane (*b*); laminated membrane, which is acellular (*c*); germinal membrane (*d*), from which the daughter cysts are formed (*e*); daughter cyst, which is getting detached from the germinal membrane (*f*); and hydatid cyst fluid (*g*).

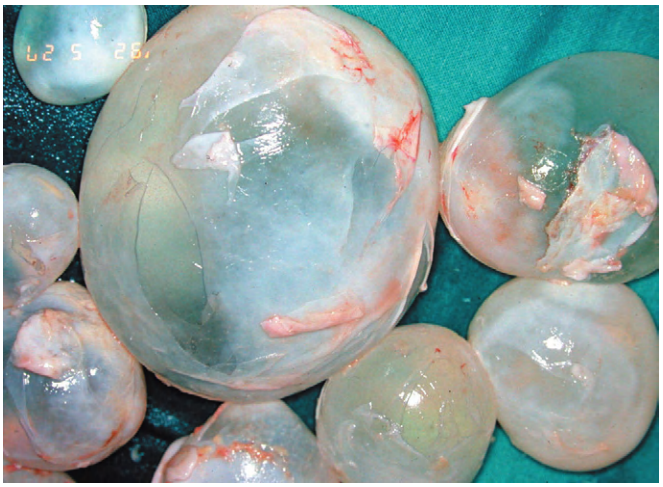


FIGURE 68.4. Hydatid daughter cysts.

of the liver can be involved, the location of liver hydatid cysts seems to be related to the respective volume of each lobe of the liver; thus a higher involvement of the right lobe is observed, especially in segments VII and VIII (Kayaalp et al, 2003).

COMPLICATIONS

Hydatid cysts in the liver may cause symptoms as a result of direct pressure, from the inflammatory reaction around the cyst, from distortion of neighboring structures or viscera, or as a result of erosion into the bile duct, pleural space, or peritoneal cavity. Rarely the cyst may communicate with the bronchial tree, pericardium, or digestive tract.

Compression

As the cyst grows, enlargement tends to occur toward the surface of the liver and Glisson's capsule, compressing the surrounding parenchyma and leading to compensatory hypertrophy of the remaining liver tissue. Sometimes an entire liver lobe can be replaced by a large cyst without any symptoms. Depending on the location, large cysts can cause compression of the adjacent bile ducts, portal or hepatic veins, or vena cava that causes obstructive jaundice, portal hypertension, or Budd-Chiari syndrome (Moreno-Gonzalez et al, 1994).

Cyst Infection

Cysts may become infected after an episode of bacteremia or via a communication with the bile ducts. Presentation is similar to a pyogenic liver abscess with right upper quadrant pain, high fever, rigors, leukocytosis, and elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Jaundice and cholangitis may occur if daughter cysts enter the bile duct. Fluid resuscitation, broad-spectrum antibiotics, and endoscopic and percutaneous drainage are the principal methods of treatment.

Rupture into the Biliary Tract

Intrabiliary rupture is the most common complication of liver hydatid cysts (Iscan & Duren, 1991; Yilmaz & Gokok, 1990). Cystobiliary communications that occur after rupture of a cyst into the bile ducts can be minor or major. Minor communications are usually asymptomatic and are revealed postoperatively by the presence of a bile leak, whereas major communications cause obstructive jaundice and cholangitis (Figure 68.5). In histologic studies of the pericyst wall, numerous biliary ducts of various sizes that communicate with the residual cavity have been demonstrated (Gahukamble et al, 2000), suggesting the existence of biliary communications in most hydatid cysts (Langer et al, 1984). The reported incidence of clinically evident cystobiliary communications rates vary from 2.6% to 28.6% (Langer et al, 1984; Ozmen et al, 1992). In a study by Kayaalp and colleagues (2003), the incidence of cystobiliary communications was 37% and the incidence of clinically apparent biliary leakage was 26%. The incidence of cystobiliary communications depends largely on the criteria used for defining the communications. Morel and colleagues (1988) showed a 36% rate of bile leaks when doing routine intraoperative cholangiography.

Preoperative and intraoperative determination of biliary communication is important. Kayaalp and colleagues (2002) found that the risk of biliary-cyst communication was higher in male patients (40.9% vs. 10.4%; $P < .01$) and in those with abnormal preoperative serum alkaline phosphatase and γ-glutamyltransferase (GGT); it was also higher in patients with multiple cysts, multilocular (23.8%) and degenerated cysts (24%) compared with unilocular cysts (12.5%); cysts near the biliary bifurcation, and in the presence of bile-stained or purulent cyst contents compared with others (61.9% vs. 2%; $P < .001$). Although the size of the cyst did not seem to be significant with regard to bile leakage in this study, Atli and colleagues (2001) found that a cyst diameter greater than 10 cm was an independent clinical predictor for the presence of intrabiliary rupture.



FIGURE 68.5. Computed tomographic scan showing a hydatid cyst biliary communication.

A *major biliary communication* has been defined as a fistula greater than 5 mm in diameter, a communication between the cyst and the main bile duct, or both (Bourgeon, 1985). The reported incidence of major biliary-cyst communications ranges from 5% to 10% (Zaouche et al, 2001). When large segmental ducts are involved, daughter cysts may enter the bile duct and cause obstructive jaundice or cholangitis or both. Ultrasound (US) and CT scans may show a detached membrane in the cyst cavity associated with dilated intrahepatic and extrahepatic bile ducts (see Fig. 68.5). Endosonography may also detect cystic material in the extrahepatic bile ducts. Endoscopic retrograde cholangiopancreatography (ERCP) is useful to confirm biliary obstruction that results from hydatid material and facilitate treatment with an endoscopic sphincterotomy and extraction of the hydatid debris with a balloon or basket (Fig. 68.6; Ozaslan & Bayraktar, 2002).

Rupture into the Bronchial Tree

A bile leak into large hydatid cysts in segments IVa, VII, and VIII of the liver with secondary infection results in inflammatory adhesions to the diaphragm and the pleurae, which may erode spontaneously into the pleural space, pulmonary parenchyma, and bronchi and lead to a bronchobiliary fistula. This classic presentation is confirmed when the patient reports coughing up "grape skins" (Krige & Beckingham, 2001).

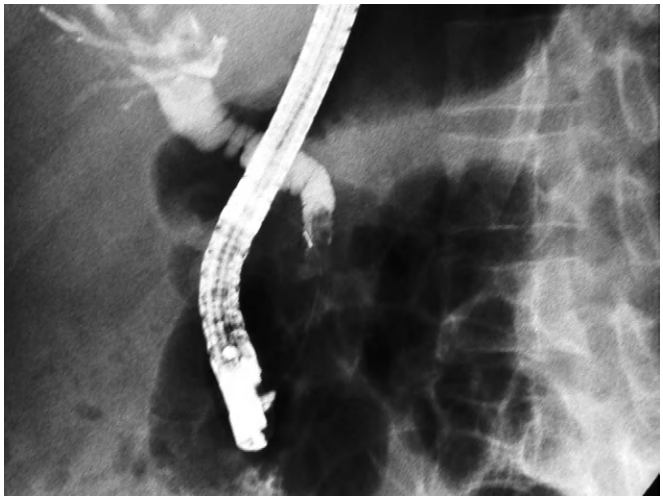


FIGURE 68.6. Endoscopic retrograde cholangiopancreatography demonstrating hydatid material within the lower common bile duct.

Rupture into the Peritoneum

Intraperitoneal rupture of a hydatid cyst is an uncommon clinical presentation, even in endemic regions, with an incidence ranging from 1% to 8% (Sozuer et al, 2002). Rupture can occur spontaneously. Although this complication may be totally silent (Abdel Hameed & Abu Aisha, 1987), abdominal pain, nausea, vomiting, and urticaria are the most common symptoms, and acute abdominal signs—such as guarding, rebound, and tenderness—are generally present. This complication should be included in the differential diagnosis of an acute abdomen in endemic areas. The release of brood cystic fluid into the peritoneal cavity leads to multiple cysts throughout the peritoneal cavity, ultimately resulting in gross abdominal distension, ascites, and intestinal obstruction. US and CT may be helpful in defining the cyst with a detached membrane and intra-abdominal fluid in patients with a ruptured hydatid cyst (Fig. 68.7).



FIGURE 68.7. Free peritoneal fluid and detached membrane, indicating perforation of a hydatid liver cyst into the peritoneal cavity.

Rupture into Other Cavities or Organs

Rupture into the gastrointestinal tract that involves the stomach and the duodenum has been reported (Diez Valladares et al, 1998). Isolated cases of rupture of liver hydatid cysts into the pericardium (Thameur et al, 2001) and into large vessels, including the inferior vena cava, have also been described (Karunajeewa et al, 2002).

DIAGNOSIS

The diagnosis of hydatid cyst is based on a careful history, imaging, and serology and a high index of suspicion in at-risk populations. The presence on cytology or histology of hydatid material or scolices in the cyst fluid confirms the diagnosis.

Symptoms

Small (<5 cm in diameter) and uncomplicated cysts usually are asymptomatic and detected incidentally during a radiologic examination of the upper abdomen or right upper quadrant. The expansion of larger cysts or the inflammatory reaction around a cyst causing irritation of the adjacent parietal peritoneum may cause moderate pain in the right upper quadrant or in the lower chest. Acute abdominal pain usually indicates an infected hydatid cyst or rupture into the peritoneal cavity. When antigenic cyst fluid is released into the circulation, especially after rupture into the peritoneal cavity, a variety of acute allergic manifestations may occur, such as urticaria, anaphylactic attacks, or episodes of asthma (Vuitton, 2004). Extrusion of cyst contents into the biliary tree may lead to absorption of the hydatid antigen in sensitized patients, resulting in similar allergic manifestations (Little, 1976). Clinical features of rupture into the biliary tree are recurrent colicky pain and jaundice, with or without resultant fevers and chills, mimicking obstructing bile duct stones. Bronchobilia resulting from a hepatobronchial fistula and ascites resulting from pressure on hepatic veins or inferior vena cava or both (Budd-Chiari syndrome) are rare clinical presentations.

Laboratory Tests

Even large hydatid cysts of the liver may not alter liver function tests, and transaminase levels are usually normal. Cholestatic enzymes, such as alkaline phosphatase and GGT, can be mildly elevated in about one third of patients, especially in patients with biliary compression (Kayaalp et al, 2002). Elevated bilirubin levels (>1 mg/dL) with elevated alkaline phosphatase and GGT levels are highly suggestive of a cystobiliary communication. White blood cell counts are elevated only if the cyst has become secondarily infected. Eosinophilia (>3%) occurs in 25% to 45% of patients with hydatid cysts in Western countries, but this is a nonspecific finding in endemic areas (Pitt et al, 1986). Serum immunoglobulin levels are elevated in 31% of patients with hydatid liver cysts (Kayaalp et al, 2002).

Radiology

Ultrasound and Computed Tomography

US and CT are standard investigations used for diagnosis, percutaneous treatment, and posttreatment follow-up of hydatid cysts. US is the preferred first-line imaging method for hydatid liver cyst visualization followed by CT, which gives more precise

Table 68.2

World Health Organization Classifications of Hydatid Cysts

Cyst Type	Status	Ultrasound Features	Remarks
CL	Active	Signs not pathognomonic, unilocular, no cyst wall	Usually early stage, not fertile; differential diagnosis necessary
CE 1	Active	Cyst wall, hydatid sand	Usually fertile
CE 2	Active	Multivesicular, cyst wall, rosette-like	Usually fertile
CE 3	Transitional	Detached laminated membrane, water-lily sign, less round, decreased intracystic pressure	Starting to degenerate, may produce daughter cysts
CE 4	Inactive	Heterogeneous hypoechogenic or hyperechogenic degenerative contents; no daughter cysts	Usually no living protoscolices; differential diagnosis necessary
CE 5	Inactive	Thick, calcified wall, calcification partial to complete; not pathognomonic, but highly suggestive of diagnosis	Usually no living protoscoleces

information regarding the morphology of the cyst, including size, location, number, and relationships to adjacent structures. CT shows exogenous daughter cysts and cysts in the rest of the peritoneal cavity and may also show evidence of complications, such as common bile duct dilation as a result of biliary obstruction in a jaundiced patient with cholangitis because of the hydatid content in the bile duct. CT is not as operator dependent as US, and it gives the surgeon an accurate roadmap of the sites of the cysts in the liver.

Hydatid cysts appear as well-defined, circumscribed cystic lesions with a clear membrane; they do not infiltrate surrounding liver tissue, and cysts are staged according to the content patterns. Staging is important for using a uniform nomenclature to allow a rational comparison of different management strategies. Although most staging protocols were based on US findings in the past, CT findings can be adapted easily to these systems. The World Health Organization (WHO) Informal Working Group on Echinococcosis (2003) described an ultrasound classification system that intended to follow the natural history of hydatid disease. Based on several studies and classifications, liver hydatid cysts can be divided into six types (Table 68.2; Beggs, 1983; Gharbi et al, 1981; McCorkel & Lewall, 1985):

1. *CL type:* a well-circumscribed liquid image with a clearly defined wall that is often difficult to differentiate from a simple biliary cyst and corresponds to an early stage of development
2. *CE 1 type:* a concentric, hyperechogenic halo around the cyst (Fig. 68.8), which may contain free-floating hyperechogenic foci called *hydatid sand.*
3. *CE 2 type:* multivesicular cysts that have the most characteristic appearance, with the "daughter" and "granddaughter" cysts identified by honeycomb, rosette, spoked-wheel, or cluster images; can also have some free cyst fluid within the main cavity or may be full of daughter cysts without any free fluid (Fig. 68.9).
4. *CE 3 type:* partial or total detachment of the laminated layer with floating and undulating hyperechogenic membranes showing the dual wall and "water lily," and "water snake" signs.
5. *CE 4 type:* cysts that contain cystic and solid components together without visible daughter cysts.
6. *CE 5 type:* cysts with a matrix or amorphous mass with a solid or semisolid appearance, often a limited amount of



FIGURE 68.8. Computed tomographic scan of a univesicular hydatid cyst shows a single cyst with clear cyst contents.



FIGURE 68.9. Computed tomographic scan of a multivesicular hydatid cyst with honeycomb or rosette appearance, containing minimal fluid and filled with daughter cysts.

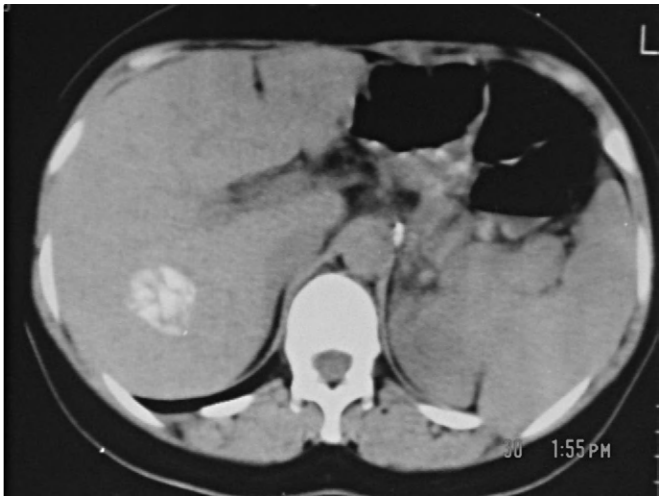


FIGURE 68.10. Computed tomographic scan of a calcified hydatid cyst.

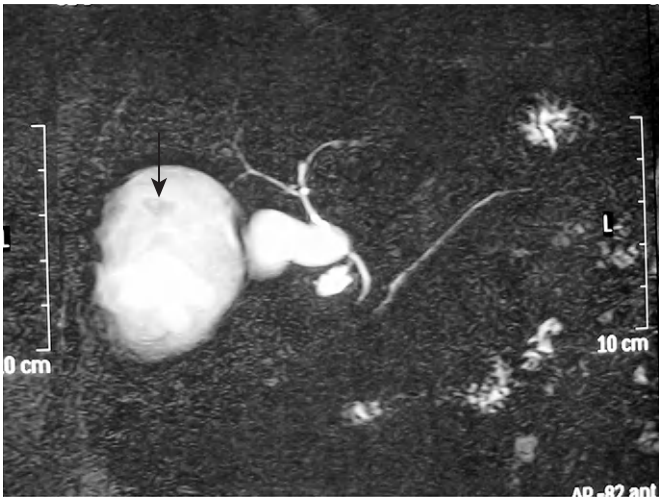


FIGURE 68.11. Magnetic resonance imaging cholangiography shows the relationship of the biliary system and the cyst along with intracystic fat density (*arrow*), suggesting cystobiliary communication.

calcification in the rim of the host adventitial tissue. This is the least typical of the cysts and may pose a diagnostic problem; they can be mistaken for a tumor, hepatic abscess, or hemangioma. Calcification in the cyst wall and hypoechogenic lacunar structures in the matrix do not indicate that the cyst is dead; a completely calcified cyst (eggshell appearance) is accepted as an effete or dead cyst (Fig. 68.10).

CL, CE 1, and CE 2 are considered active, fertile cysts. CE 3 is a transitional cyst believed to have begun degeneration. CE 4 is a degenerated cyst and CE 5 is a calcified cyst. The degree of calcification varies from partial to complete. CE 4 and CE 5 are accepted as inactive cysts (Shaw et al, 2006).

Other Imaging Studies

Plain radiography of the abdomen is of limited value in the diagnosis of hydatid liver cysts. A plain radiograph of the chest can reveal concurrent hydatid cysts of the lung. On T2-weighted magnetic resonance imaging (MRI), hydatid liver cysts may have a low signal intensity rim. This is a characteristic sign of hydatid disease that represents the outer, collagen-rich laminated membrane of the cyst. When present, daughter cysts are seen as cystic structures attached to the germinal layer that are hypointense relative to the intracystic fluid on T1-weighted images and hyperintense on T2-weighted images (Pedrosa et al, 2000). MRI is more specific than CT, especially if intracystic fat density is present, which suggests cystobiliary communication (Basaran et al, 2005). In cysts with biliary complications, MR cholangiography can provide good visualization of the intrahepatic and extrahepatic biliary tree and its relationship with the hydatid cyst and cystobiliary communications (Fig. 68.11; Little et al, 2002).

Serology

Serologic tests in hydatid disease are used for 1) the differential diagnosis of a cystic liver mass, 2) epidemiologic surveillance, and 3) posttreatment follow-up. Several serologic tests have been used in the diagnosis of human cases, and considerable differences in specificity and sensitivity are found among the various tests. Circulating *E. granulosus* antigens are small, and most are in the form of immune complexes. Detection of these antigens is less sensitive than antibody detection. At present, serologic tests usually are based on the reaction and precipitation of the test antigen and the circulating antibodies in the host. The sensitivity and specificity of the tests depend on the quality of antigens.

Immunoelectrophoresis

The diagnostic value of hydatidosis with immunoelectrophoresis ranges from 91% to 94% for hepatic cysts and 69% to 70% for pulmonary cysts (Varela-Diaz et al, 1983). Immunoelectrophoresis is not suitable for epidemiologic surveillance; rather, it is used for posttreatment follow-up.

Enzyme-Linked Immunosorbent Assay

Sensitivities for enzyme-linked immunosorbent assay (ELISA) vary from 64% to 100% depending on the antigens used (Coltorti, 1986; Iacona et al, 1980; Rickard, 1984). ELISA can also be automatized for large-scale epidemiologic studies. Selected test antibodies affect its value on posttreatment follow-up. Immunoglobulin (Ig) G assay may remain positive 4 years after successful treatment, so it is not a suitable test for posttreatment follow-up; IgM assay has been reported to be negative after 6 months of successful treatment (Zhang et al, 2003).

Blotting

Blotting allows molecular weight analysis of the antigens detected by the patient's serum. Western blotting with purified antigens has proved to be very useful in the diagnosis and postsurgical monitoring of hydatidosis patients (Doiz et al, 2001). The Arc 5 antibody test is a specific precipitation during electrophoresis of blood of hydatid cyst patients, with a specificity of 91%. Purification of antigens strongly affects the diagnostic value of the tests. Purified fractions enriched in antigens 5 and B and in glycoprotein yield a sensitivity of 95% and specificity of 100% (Sbihi et al, 1996).

TREATMENT INDICATIONS AND METHODS

Three treatment options are currently available for hydatid disease of the liver: surgery, which remains the most efficient treatment and the therapy of choice; percutaneous aspiration; and medical treatment. In general, hydatidosis is a public health problem, especially in developing countries, and the specific treatment selected may depend on social circumstances and the medical expertise available (Shaw et al, 2006).

Since the 1990s, percutaneous treatment has been increasingly used. Surgery has the advantage of removing the parasitic content of the cyst and the cyst wall and dealing with any associated complications. Although surgery may be technically demanding in patients with large and complicated hydatid cysts, advances in liver surgery have made complex operations safer and have reduced morbidity (Krige & Beckingham, 2001).

Conservative Management

Asymptomatic and small (<5 cm) CL-type cysts can be followed up with a wait-and-see policy with serial US examinations (Buttenschoen & Buttenschoen, 2003). Similarly, densely calcified hydatid cysts are accepted as dead cysts and can be monitored without any specific therapy.

Surgical Treatment

The literature on the surgical treatment of hydatid liver disease describes a variety of different techniques, ranging from simple evacuation to major liver resection. These techniques can be divided into two broad groups, *conservative* and *radical*. The conservative method involves inactivation of protoscolices and removal of the cyst contents; radical methods include total excision of the cyst and pericyst layers along with a portion of surrounding liver. Although no prospective randomized data compare radical and conservative surgery, most surgeons, especially in endemic areas, prefer conservative surgery, but some experienced liver surgeons may at times use pericystectomy or hepatectomy to deal with liver hydatid cysts. The principles of liver hydatid surgery include inactivation of protoscolices within the cyst fluid, evacuation of the cyst contents and prevention of spillage of the cyst contents, secure closure of any cystobiliary communications, and management of the residual cyst cavity (Terblanche & Krige, 1998).

Prevention of intraoperative spillage of the hydatid cyst contents is an important step during the procedure. Several methods have been described to avoid spillage. First introduced by Saidi and Nazarian (1971) and later by Aarons and Kune (1983), cone techniques allow the cyst to be entered in a safe and controlled manner with a funnel-shaped cone attached to the hydatid surface by suction or by freezing the contact area—although such an approach is not suitable for posterosuperior cysts attached to the diaphragm.

Preoperative Preparation

All patients undergoing surgery for hepatic hydatid cysts should have a detailed preoperative assessment that includes a chest radiograph to exclude pulmonary cysts (Figs. 68.12 and 68.13), an electrocardiogram, a complete blood count, international normalized ratio (INR), electrolyte and renal function tests, and liver function tests; in addition, blood should be grouped and screened. A recent CT scan of the abdomen should be reviewed before the operation to plan the surgical strategy and exclude hidden or occult pelvic, retroperitoneal, or hydatid cysts in other organs.



FIGURE 68.12. Chest radiograph showing lung hydatid cyst.

Surgical Incision

The position of the surgical incision depends on the location, size, and number of cysts in the liver and whether other extrahepatic intraabdominal cysts are present. Either a right subcostal incision with proximal midline extension or a bilateral subcostal incision will give adequate exposure to all liver hydatid cysts (Terblanche & Krige, 1998). A midline laparotomy is preferred in patients who have cysts in the left lobe of the liver and in those who have abdominal hydatidosis. Although thoracoabdominal incisions were used in the past for selected patients with large posterior liver hydatid cysts, a transthoracic approach is now used only for combined right lung and liver hydatid cysts, when a one-stage procedure can be done successfully for both cysts (Sahin et al, 2003).

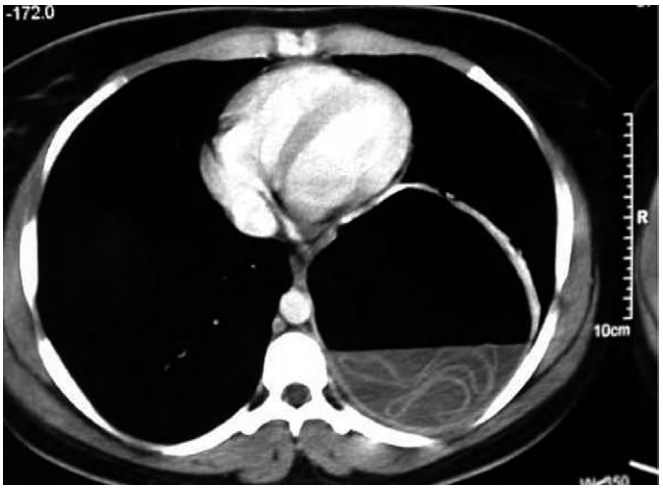


FIGURE 68.13. Chest computed tomography scan demonstrating a pulmonary hydatid cyst.

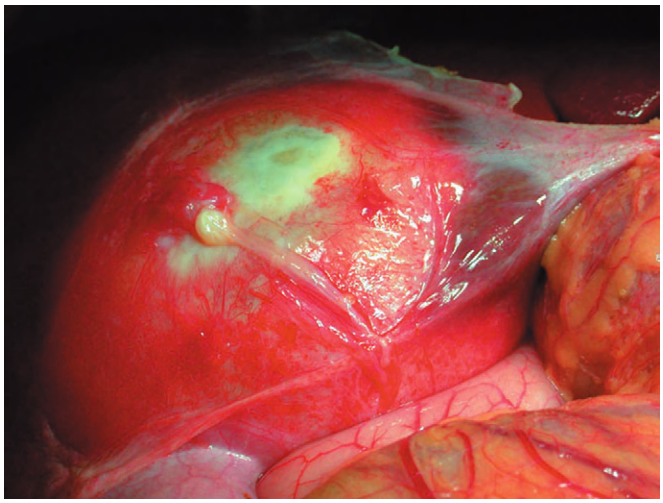


FIGURE 68.14. Shiny white appearance of the surface of a liver hydatid cyst.

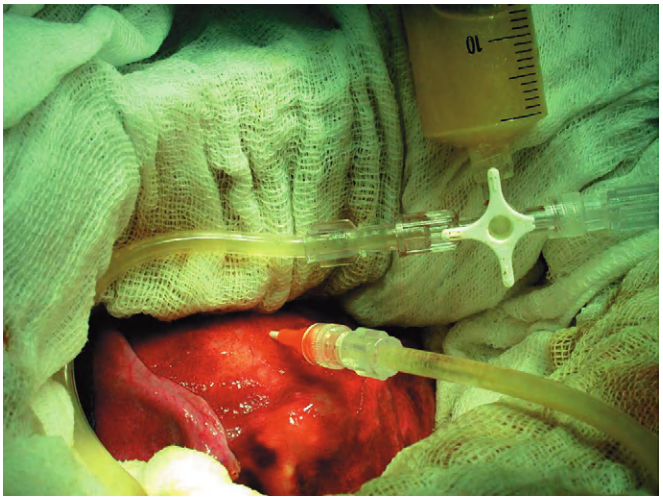


FIGURE 68.15. Aspiration of fluid from a hydatid cyst. Note the gauze packs soaked in scolicidal solution surrounding the aspiration site.

Conservative Surgery

Cystectomy is the safest and simplest surgical approach (Morris, 1992). After entering the abdomen, the skin wound is carefully protected with a plastic drape or a commercially available ring-shaped wound protector. A full laparotomy is performed, paying particular attention to potential sites of dissemination, including the omentum and pelvis (Morris, 1992). The characterisitic shiny white adventitial surface of a hydatid cyst is usually easily identified (Fig. 68.14). The position, size, and number of cysts in the liver are noted, as are the presence of complications and other extrahepatic intraabdominal cysts. It is important to assess the relationship of the cyst to the inferior vena cava, hepatic veins, and porta hepatis structures because large or multiple cysts frequently distort normal liver anatomy. For deeper cysts, palpation and intraoperative US help determine the most superficial part of the cyst suitable for aspiration and evacuation. Mobilization of the liver and the cyst should be minimal to avoid iatrogenic perforation of thin-walled cysts.

The area around the cyst is carefully isolated by gauze packs: the first layer is soaked with normal saline, and the second layer is soaked with a scolicidal solution; these act as a mechanical and a chemical barrier (Besim et al, 1998). An area 2 cm in diameter on the most prominent part of the exposed pericyst is left uncovered by the packs for insertion and evacuation. The cyst should be handled carefully because the contents of a viable cyst are usually under pressure. The point where the cyst is to be entered is identified, and the smallest possible working area is delineated by additional packing. At least two drains with powerful suction should be available, and one should have a sump cannula. The suction reservoir should have a large capacity, so that suction is not interrupted while changing reservoirs.

The cyst wall is pierced with a large-gauge needle connected to a 50-mL syringe and a three-way tap, and large-bore transparent plastic tubing is connected to a drain. The cyst is aspirated, and the volume and the color of the hydatid fluid are carefully noted (Fig. 68.15). As much fluid as possible is aspirated. If the cyst fluid is completely clear and not bile stained, turbid, or infected, scolicidal solution can be safely injected as long as the volume injected is less than what has been aspirated; the fluid is injected gently and not under pressure (Terblanche & Krige, 1998). A suction nozzle is kept at the needle puncture site at all times by the assistant to avoid any hydatid cyst fluid leaking out alongside the needle. The scolicidal fluid is left in the cavity for several minutes and then is reaspirated; this process is repeated twice. The cyst is decompressed again by aspiration; when the fluid level is sufficiently lowered, two stay sutures are placed close to the needle with upward traction on the stay sutures, which is maintained to allow the needle to be removed safely without spillage of residual cyst contents.

The objective is to remove the parasite totally, including both endocyst layers and the cyst contents. The cyst is incised between the sutures by electrocautery, a large-gauge sump suction cannula is inserted, and the contents are sucked out. The edges of the incision are grasped with Babcock tissue-holding forceps, and the stay sutures are removed. The incision is enlarged so that direct vision of the cyst cavity and its contents is obtained, and the sump suction can be moved freely around the cavity to evacuate the remaining fluid and cyst content. It is important to have a small opening of the cyst initially and to maintain constant upward traction on the edges of the incision, so that overflow or spillage does not occur. Warm saline solution is injected into the cavity intermittently to keep the suction tubing patent and to evacuate the hydatid sand.

Evaluation of the cyst content is important. The typical content of a viable cyst is clear fluid containing hydatid sand, daughter cysts, and the debris of brood capsules. Bile staining of the fluid implies a communication with the biliary tree and should warn against injection of scolicidal agents that may damage the biliary tree. Once the liquid has been drained, the laminated membrane collapses into the cavity, and the cyst contents can be evacuated. The incision is enlarged further, a kidney dish is brought close to the incision, and the evacuation of the daughter cysts begins (Fig. 68.16). Laminated membrane is best extracted with a ring forceps (Fig. 68.17), and small daughter cysts are best removed with a suction drain.

When all visible daughter cysts have been evacuated, the cavity is rinsed with warm saline, and the redundant portion of the cyst roof is excised. The adventitia and thinned-out liver are cut with electrocautery, and the cut edges are oversewn with a

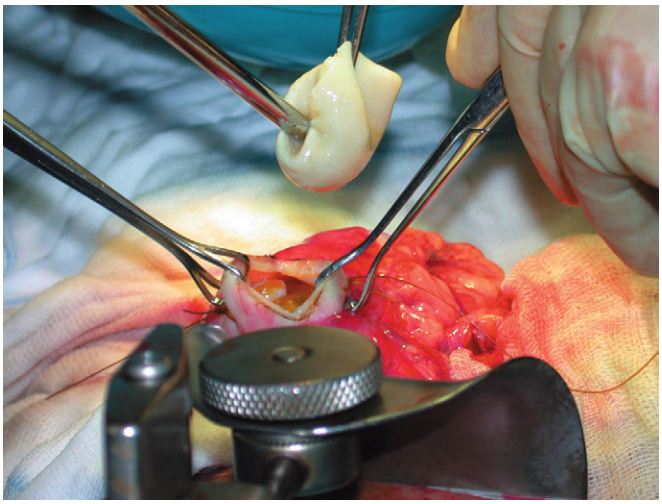


FIGURE 68.16. Removal of daughter cysts from the cyst cavity.

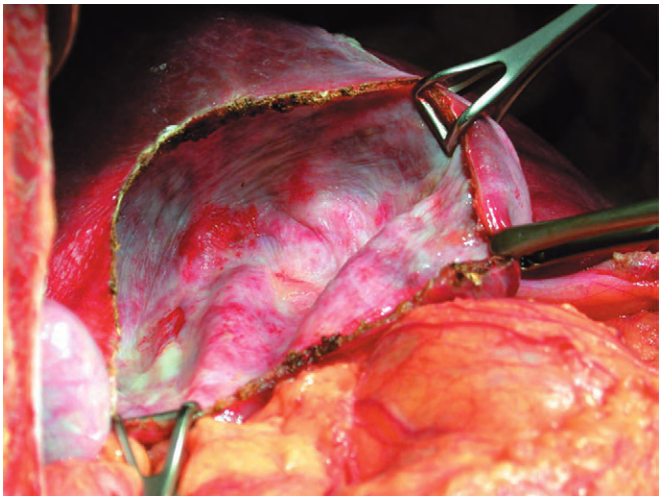


FIGURE 68.18. The residual hydatid cavity after extraction of the laminated membrane. The interior of the cyst is carefully inspected for bile leaks.

running mattress suture with an absorbable suture material; this is an important component of the operation because the cut edges contain blood vessels and small bile ducts. It is important to inspect the cavity for small daughter cysts that may be hidden in recesses of the main cavity. After removing the laminated membrane, the cavity is flushed with saline and inspected for bile leakage (Fig. 68.18). The cavity is packed with dry, white packs that are left in place for a few minutes and then removed. Bile stains are indicative of a bile communication.

If the aspirated contents are clear, scolicidal solutions are injected into the cyst, but never if the cyst has bile-stained or purulent content, which indicates a bile communication and hence the risk of causing caustic sclerosing cholangitis. Although some debate surrounds the efficacy and safety of protoscolicidal solutions injected into the cyst cavity, many consider injection of scolicidal solutions a prudent step when applying conservative surgery to reduce recurrence. Widely used scolicidal agents include hypertonic saline, fresh half-strength Eusol, 0.5% silver nitrate, and hydrogen peroxide. Hypertonic saline has been widely used in the past because of its availability and effective scolicidal properties (Kayaalp et al, 1999). Studies on different concentrations of hypertonic saline, ranging from 3% to 30%, have shown that the higher the concentration, the higher the scolicidal properties with a shorter contact time. In practice, 20% hypertonic saline is preferable, which has 100% scolicidal effect with an ideal contact time of 6 minutes (Besim et al, 1998). A danger of this practice is excessive absorption, which may result in hypernatremia, and the solution should be used with caution (Krige et al, 2002). A cetrimide (0.5%) and chlorhexidine (0.05%) combination (Savlex; Drogsan, Ankara, Turkey) used for 5 minutes is an effective scolicidal solution in laboratory and clinical studies (Besim et al, 1998). However, metabolic acidosis and methemoglobinemia have been reported as side effects (Baraka et al, 1980; Momblano et al, 1984).

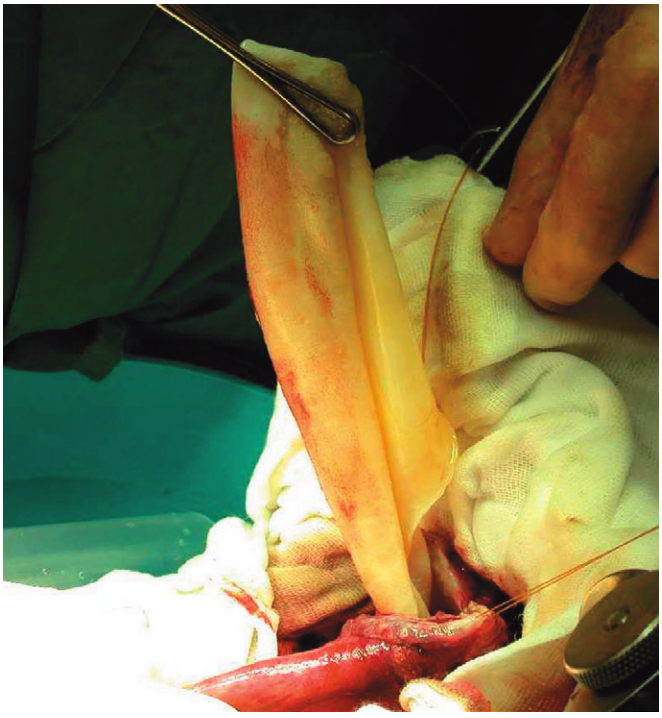


FIGURE 68.17. Removal of the laminated membrane from the cyst cavity.

Absolute alcohol has been used by interventional radiologists for the percutaneous treatment of hydatid cysts to produce sclerosis of the cyst cavity (Akhan & Ozmen, 1999), but it is not effective on protoscolices inside daughter cysts (Karayalcin et al, 1999). Disadvantages of absolute alcohol are the potential danger of caustic cholangitis and its flammable nature during surgical procedures when using electrocautery.

Povidone-iodine has been criticized because of an inappropriate animal model (Kolbakir & Erk, 1992). Gokce and colleagues (1991) reported that 1% povidone-iodine was superior to 20% saline. Landa Garcia and associates (1997) reported that 10% povidone-iodine was an effective agent for prevention of secondary hydatidosis in their in vivo study. The disadvantages of povidone–iodine are concentration dependency (Besim et al, 1998), induction of caustic cholangitis (Castellano et al, 1994), and coloring of the cyst cavity, which makes it difficult to identify the cystobiliary communications. Formalin is no longer used because of a high propensity to induce caustic sclerosing cholangitis. If a possible bile leak is suspected, the cyst is

carefully packed off and emptied by aspiration, and the contents are removed without injecting any scolicidal solutions to avoid the danger of inducing caustic sclerosing cholangitis (Shaw et al 2006).

Intraoperative Management of Biliary-Cyst Communication

Careful inspection for cyst-biliary communications should be done from a wide opening in the pericyst and should be confirmed by leaving a dry pad on the inner surface of the cyst and applying gentle pressure on the gallbladder. In cases of suspected biliary-cyst communication, intraoperative cholangiography is preferable to identify the communication site. After excision of the cyst, a methylene blue test through a transcystic duct tube is helpful in identifying small, overlooked biliary communications or leaks. Any obvious biliary orifices should be sutured to prevent postoperative biliary leakage, fistula, and cavity infections. On rare occasions, cyst communications involving a large duct may need drainage with a Roux-en-Y hepaticojejunostomy.

Management of the Residual Cavity

Although a variety of techniques have been described to prevent complications related to the residual cavity, depending on its size and shape and site, the safest way is to perform an omentoplasty. The omentum is mobilized from the transverse colon with sufficient mobility to pack the cavity and obliterate the dead space, and it is sutured to tether the omentum in place (Fig. 68.19). If the cavity has a large volume, a temporary drain is placed into the cavity alongside the omentum. Some put in two drains (Shaw et al, 2006). A closed, silastic suction drainage system is preferable; the tubes are removed as soon as drainage ceases. Omentum has a natural absorptive capacity that decreases the risk of infection and minimizes fistula formation. Older techniques, including capsulorrhaphy and capitonnage, are no longer used.

Postoperative Complications

Biliary Fistula

The incidence of biliary fistula after hydatid liver surgery varies from 1% to 10% (Abu Zeid et al, 1998; Barros, 1978). Endoscopic treatment is the main approach, and the aim of endoscopic drainage for biliary fistulas is to reduce the biliduodenal pressure difference to 0. The optimal endoscopic approach for managing external biliary fistulas resulting from hydatid liver disease has not been established. Sphincterotomy alone, stent or nasobiliary drain placement alone, and the combination of sphincterotomy and stenting or nasobiliary drainage have been used successfully for fistula healing. The overall success rate is 83.3% to 100%. Although closure time has been reported to be as short as 2 to 6 days, average duration of bile drainage after stent placement is generally 2 to 4 weeks (Ozaslan & Bayraktar, 2002; Simsek et al, 2003).

Biliary Stricture

Postoperative biliary strictures after surgical treatment of hepatic hydatid disease are uncommon. The most dramatic form is caustic sclerosing cholangitis, which is caused by the scolicidal solution entering the biliary tree from the cyst cavity (Belghiti et al, 1986). Diffuse caustic sclerosing cholangitis may result in secondary biliary cirrhosis, portal hypertension, and liver decompensation with ascites and bleeding esophageal varices, which may ultimately require liver transplantation (Loinaz et al, 2001). Minor passage of the scolicidal solution may cause a localized biliary stricture, which may be asymptomatic if the bile duct confluence is not involved (Belghiti et al, 1986). A bile duct stricture at the biliary confluence may result from a large biliary fistula treated by conservative surgery. Surgical repair is usually not feasible (Fig. 68.20), but long-term endoscopic stenting is a safe and effective method in these patients (Eickhoff et al, 2003; Yilmaz et al, 1998).

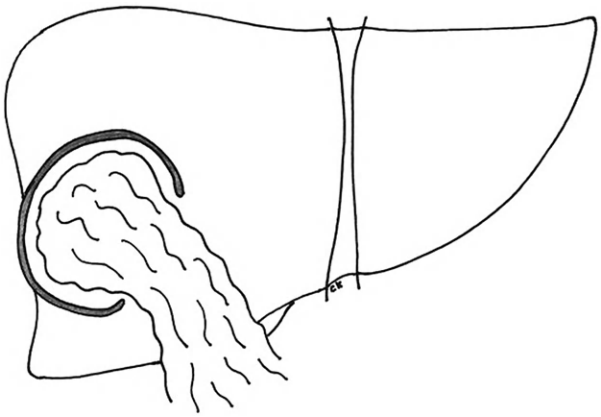


FIGURE 68.19. Omentoplasty in hydatid liver cysts.



FIGURE 68.20. Cholangiogram shows caustic cholangitis with widespread intrahepatic and extrahepatic strictures. Surgical management is often difficult in these situations.

Table 68.3

Results of Treatment of Recurrence According to the Surgical Method Used

		CONSERVATIVE SURGERY		RADICAL SURGERY	
Reference	**Follow-up (Years)**	**No. Patients**	**Recurrence (%)**	**No. Patients**	**Recurrence (%)**
Magistrelli et al (1991)	3	73	13 (18)	46	2 (4)
Karavias et al (1992)	3.5	32	3 (9)	–	–
Khuroo et al (1997)	1.4	25	0	–	–
Alfieri et al (1997)	6.9	–	–	72	1 (1.4)
Yol et al (1999)	1-7	55	0	–	–
Cirenei & Bertoldi (2001)	12.4	71	8 (11)	105	1 (1)
Yorganci & Sayek (2002)	2.7	32	8 (25)	10	NA
Nardo et al (2003)	4.4	–	–	33	0
Kayaalp (2003)	4.5	19	0	–	–
Total		307	32/307 (10.4)	266	4/256 (1.5)

Recurrence

Recurrent disease is defined as the appearance of new active cysts after therapy of intrahepatic or extrahepatic disease (Sielaff et al, 2001). Failure to achieve permanent control of the primarily treated cyst is considered local recurrence, and the appearance of new cysts in the peritoneal cavity is regarded as disseminated disease. The incidence of local recurrence is approximately 10% after conservative surgery (Table 68.3). Intraoperative spillage of cyst contents, reduced effect of protoscolicidal agents, residual cyst content, and overlooked cysts lead to recurrence. All patients initially require close follow-up at 6-month intervals. Evaluation should include radiologic and serologic studies; complement fixation test, immunoelectrophoresis, counterimmunoelectrophoresis, ELISA, and blotting are used to detect recurrences. Even with complete removal of disease, blood titers may decrease slowly over months to years; therefore a positive serologic test during follow-up is not diagnostic of recurrence, but a rising titer is (Sielaff et al, 2001).

Pericystectomy

Also called *radical cystectomy, capsulectomy, total pericystectomy,* and *cystopericystectomy,* pericystectomy involves complete removal of the hydatid cyst. By creating a surgical plane just outside the pericyst layer without opening the cyst, the parasite and the adventitial layer are excised en bloc (Fig. 68.21). No clear anatomic plane exists, although the surgical approach of this plane does not differ from a classic liver parenchymal transection. The Cavitron ultrasonic aspirator (DentSply International,York, PA) is used to isolate the vessels and biliary ducts that are deviated and compressed by the cyst, and the parenchymal transection allows the suture of these vessels and bile ducts within the liver parenchyma. The aspirator should be used away from the pericyst to avoid fracture of the cyst, which can be responsible for spillage of the cyst contents.

Pericystectomy must be avoided for a cyst impinging on the major hepatic veins, inferior vena cava, or the liver hilum. On occasion, circumstances dictate a modified approach, and the surgeon may need to use a hybrid technique that uses both cystectomy with evacuation of hydatid contents and partial pericystectomy to resect peripheral liver parenchyma.

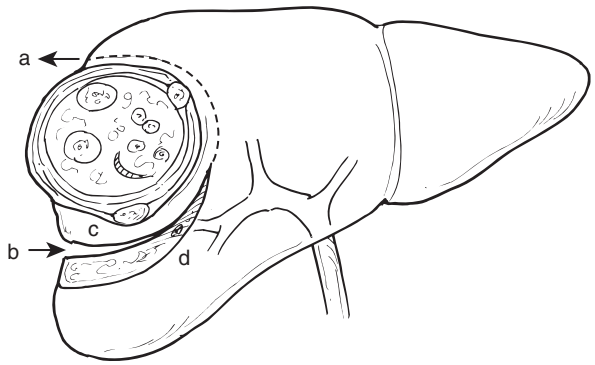


FIGURE 68.21. Closed pericystectomy. A line of parenchymal section passes close to the pericyst (*a*). A line of parenchymal section a little further from the pericyst (*b*); along the line, the liver parenchyma is shown as opened to some distance. Exogenous cyst just outside the pericyst layer (*c*). Suture of a biliary duct that communicated with the cyst (*d*).

Liver Resection

The indications for a formal hepatic resection for liver hydatid cysts are infrequent. Hepatic resection is the only surgical therapy for *E. multilocularis*, but it is inappropriately radical for *E. granulosus* (Morris, 1992). Other rare indications for liver resection are when the remaining parenchyma of a liver lobe is atrophic as a result of biliary obstruction, or when a large bile leak that cannot be safely managed with a Roux loop is present. Resection should be reserved for peripherally placed cysts, usually in the left lateral segment; for pedunculated lesions; or for extrahepatic intraabdominal cysts. Resection of small, pedunculated, and peripherally placed cysts is simple and safe, but in the majority of cases, cystectomy involves a major liver resection with its attendant increase in operative risk. Correct judgement is crucial because the operation may be complex as a result of distorted anatomy.

Radical surgery should not be standard procedure in the management of *E. granulosus* (Terblanche & Krige, 1998). In addition, a standard hepatic resection should not be done in

patients with large cysts that occupy the greater portion of the right lobe because the medial wall of such a cyst often involves the inferior vena cava and displaces the hepatic veins. Attempts to dissect outside the cyst are hazardous and unnecessary. Surgery for hydatid disease is done predominantly by general surgeons, frequently with limited resources. Surgeons who do not have extensive training and experience in liver resections should not be tempted to resect for hydatid disease. Meticulous and careful conservative surgery for this benign disease gives good results, and unnecessary operative mortality will certainly outweigh the merits of totally removing the cyst.

Laparoscopy

Although the laparoscopic approach to this disease offers some advantages, laparoscopic hydatid surgery has not gained a wide acceptance. Disadvantages of the laparoscopic approach are the limited area for manipulation, intricacy in controlling spillage during puncture, and difficulty in aspirating the thick, degenerated cyst contents. No prospective randomized clinical trials have compared laparoscopic treatment with conventional open treatment, and no reliable data are available on recurrence rates after laparoscopic treatment (Table 68.4).

Theoretically, a pneumoperitoneum can exert pressure on the hydatid cyst and increase the risk of hydatid fluid contamination during laparoscopic intervention. Bickel and colleagues (1998) examined the risk of spillage and found that laparoscopy had no disadvantages in the treatment of hydatid liver cysts. Berberoglu and colleagues (1999) used gasless laparoscopy for hydatid cyst surgery but found no significant advantage over the pneumoperitoneum method.

A supraumbilical port is the most frequent entry site for the scope, but the precise position of the trocars varies according to the position and size of the cyst. The puncture site into the cyst is protected by gauze soaked in a scolicidal solution. Several authors have developed special tools or techniques for safer and more effective evacuation of cyst contents, and some surgeons prefer puncture, aspiration, filling with a scolicidal solution, reaspiration, and evacuation of the cavity. During the procedure, the laparoscope can be introduced into the cyst cavity for magnified inspection and to ensure that no daughter cysts, laminated membranes, or bile leaks are overlooked.

Some groups have reported the use of a perforator-grinder and aspirator apparatus for insertion and evacuation (Alper et al, 1995; Saglam, 1996). An umbrella-shaped laparoscopic trocar for evacuation of the cysts has been used with a locking mechanism that enables the surgeon to suspend the cyst wall against the abdominal wall (Seven et al, 2000). Bickel and Eitan (1995) reported the use of a large, transparent cannula (12 mm) with a beveled tip for safe laparoscopic management of hydatid cysts of the liver. Suction is applied through the cannula onto the surface of the cyst, enabling oblique contact, and the cyst is aspirated through the cannula under a "vacuum." It is claimed that spillage was less with this method (Bickel & Eitan, 1995). Some investigators recommend washing the peritoneum with a scolicidal solution or creating a perihepatic scolicidal pool during laparoscopic hydatid surgery (Berberoglu et al, 1999; Palacios-Ruiz et al, 2002).

Table 68.4

Results of Laparoscopic Operation for Hydatid Liver Disease in a Series of >20 Patients

Reference	No. Patients	Conversion (%)	Morbidity (%)
Alper et al (1995)	22	6 (27)	4 (18)
Bickel et al (1998)	31	1 (3)	5 (16)
Berberoglu et al (1999)	87	0	23 (28)
Seven et al (2000)	30	7 (23)	5 (17)
Khoury et al (2000)	83	3 (3.6)	9 (11)
Ertem et al (2002)	48	2 (4)	3 (6)
TOTAL	301	19 (6.4)	49 (16.3)

Percutaneous Treatment

Percutaneous aspiration and treatment of hydatid cysts has previously been discouraged because of the risk of anaphylaxis and intraperitoneal seeding. However, unintended percutaneous aspiration in sporadic cases were not associated with the expected side effects (McCorkell, 1984). These findings encouraged interventional radiologists to aspirate and treat hydatid cysts of the liver using US guidance. Mueller and associates (1985) were the first to report successful percutaneous drainage of hydatid cysts; since then, several authors have reported successful percutaneous treatment of hydatid liver cysts. With increased experience, successful percutaneous treatment of hydatid cysts for lung, kidney, peritoneum, and orbital cavity have also been reported (Akhan & Ozmen, 1999).

It now is generally accepted that the appearance of the cyst content on US and CT examination is an important determinant for percutaneous treatment. Indications for percutaneous treatment include univesicular cysts (type CE 1), univesicular cysts with detached membrane (type CE 3), and some multiple cysts (type CE 2). Aspiration is contraindicated in cysts that are inaccessible to puncture, in cysts in which puncture may damage important vascular structures, and in peripheral cysts that do not have a sufficient layer of hepatic tissue to permit safe transhepatic puncture. Percutaneous treatment is contraindicated in liver hydatid cysts that have ruptured into the bile ducts, peritoneum, or the pleural space. Recurrent cystic collections after surgery can be diagnosed and treated by percutaneous aspiration.

Three different techniques are used in percutaneous treatment of liver hydatid cysts. The first is the PAIR technique described by Ben Amor and associates (1986). PAIR is an acronym for ***p***uncture, ***a***spiration of cyst content, ***i***njection of protoscolicidal solution, and ***r***easpiration of the fluid. Patients are given albendazole before and after the procedure for prophylaxis. Under local anesthesia, a fine needle is inserted into the cystic cavity through normal liver tissue with US or CT guidance. As much fluid as possible is aspirated and, on completion, a protoscolicidal agent is injected into the cavity. After 15 minutes, as much fluid as possible is reaspirated and the needle is withdrawn. The most characteristic sonographic signs of involution at follow-up are heterogeneous reflections of cyst content (3 months), obliteration and pseudotumor appearance (5 months), and loss of echogenicity and disappearance of the cyst (9 months) (Bret et al, 1988; Khuroo et al, 1997). Direct microscopic examination of the aspirated fluid is used to identify protoscolices (Pelaez et al, 2000).

The second technique is a catheterization technique described by Akhan and associates (1993). A catheter is placed into the cavity by the Seldinger technique and, similar to the PAIR technique, the cyst is aspirated, injected with a protoscolicidal agent, and reaspirated, but the catheter is not removed at the end of the procedure and is instead left to facilitate drainage for 24 hours. If there is no biliary fistula within 24 hours, it is accepted that there is no communication between the biliary system and the cavity, which is also confirmed by obtaining a cystogram under fluoroscopic guidance. If the amount of drainage in 24 hours is less than 10 mL and free of bile, absolute alcohol (95%) is injected into the cavity (approximately 25% to 35% of the volume); after waiting 20 minutes, all the fluid is reaspirated and the catheter is withdrawn. If the amount of drainage in 24 hours is more than 10 mL or contains bile, the catheter is kept in place until the daily amount of drainage decreases to less than 10 mL. After that, the cystogram and sclerosis are performed as already mentioned. Alcohol instillation in cysts that have biliary communications is contraindicated. Some researchers suggest that all the liver hydatid cysts suitable for percutaneous technique should be treated by the PAIR technique. Others suggest that the cysts smaller than 6 cm in diameter (volume <100 mL) should be treated by the PAIR technique, and cysts larger than 6 cm in diameter (volume >100 mL) should be treated by the catheterization technique (Akhan & Ozmen, 1999).

In the PAIR and PAIR catheterization techniques, the ruptured daughter cysts and laminated membranes remain inside the cavity; both techniques are usually recommended for uncomplicated univesicular cysts, but not for multivesicular mother and daughter cysts. Each daughter cyst must be punctured separately, which is difficult and may be dangerous for the patient.

Saremi and McNamara (1995) developed an alternative method called *percutaneous evacuation of cyst content* (PEVAC). As in the PAIR catheterization technique, the cyst is first aspirated as much as possible and the catheter is left in place for drainage. In a second session, the catheter is replaced with a 14- to 18-Fr stiff sheath. A suction catheter is introduced into the cyst cavity through the sheath, and the cyst contents are evacuated by applying suction and directing the catheter toward the daughter cysts, endocyst, and undrainable material. A special cutting instrument is used to fragment and evacuate daughter cysts and laminated membrane, while the cavity is continuously irrigated with a protoscolicidal solution. After removal of the sheath, a catheter of the same size as the sheath is placed into the cavity, similar to the PAIR catheterization technique (Schipper et al, 2002). In the absence of bile leakage or any discharge, the catheter is removed.

The effectiveness and safety of percutaneous treatment are supported by the results of more than 2500 procedures carried out in several countries by different teams, with a low morbidity (4.1%) and mortality (0.08%) (Filice et al, 1999). The major risk of percutaneous drainage of hydatid cysts is spillage of hydatid fluid during the placement of the needle. With US or CT guidance, the position of the needle can be precisely monitored, and a transhepatic approach to the cyst, rather than a direct transperitoneal approach, can be used to minimize the possibility of spillage. Urticaria, itching, and hypotension are minor complications that may occur during or several hours after the procedure; these can be treated with antihistamines. In some patients, fever (>38.5° C) may occur, but this generally resolves spontaneously. Cavity complications, such as biliary fistula and infections, have been reported in 10% of patients (Akhan & Ozmen, 1999).

Chemotherapy

Benzimidazole carbamates (mebendazole and albendazole) are antihelmintic drugs that kill the parasite by impairing its glucose uptake. The first report of the successful treatment of four patients with hydatid liver cysts was in 1977 (Bekhti et al, 1977). Mebendazole was introduced first, but albendazole became the drug of choice because of its superior absorption in the gastrointestinal tract and better clinical results (Morris, 1992; Saimot et al, 2001). Benzimidazole treatment is contraindicated for patients with chronic liver diseases and in early pregnancy (Saimot, 2001). Albendazole absorption varies from person to person, and variability may be substantial even in the same individual. In clinical practice, albendazole should be administered in a dose of 10 mg/kg twice daily with a meal; it is wise not to give albendazole with medication that reduces gastric acidity. Adverse events including headache, nausea, anorexia, vomiting, abdominal pain, and itching have been reported in 5% to 10% of patients (Schipper et al, 2000). In the first weeks of treatment, a transient increase in liver enzymes may occur, and leukopenia is rare. Complete hair loss, which is reversible when albendazole is stopped, may also occur.

Although most studies were not well designed, prospective, or randomized, it has been shown that a success rate of 74% can be expected in patients with single cysts treated for 3 to 6 months (Franchi et al, 1999). Most relapses occur within 2 years after cessation of treatment, but more prolonged monitoring has shown that a significant number of relapses occur 2 to 8 years after completing initial treatment. A controlled study of 29 patients who received albendazole (400 mg twice a day in three cycles of 6 weeks with 2 weeks between cycles) or placebo showed that 82% of the patients in the treatment group had cure or improvement compared with 14% in the placebo group (Keshmiri et al, 2001).

Factors that influence the efficacy of benzimidazoles have not been well defined, but it is known that penetration of the drug across the cyst wall depends on several factors. Young cysts without pericystic fibrosis are more sensitive to drugs than thick, calcified cysts. Chemotherapy is less effective in daughter cysts within a mother cyst and in cysts with infection or a biliary communication. Small cysts (<8 cm) and secondary cysts are mostly sensitive to chemotherapy, and chemotherapy seems to be more effective in young patients (Teggi et al, 1993; Todorov et al, 1990).

The efficacy of preoperative albendazole treatment was established by two studies. In the first study (Wen et al, 1994), cyst viability after 3 months of albendazole pretreatment was 8% at the time of surgery, significantly lower than in the control group (100%). In the other study, 1-month and 3-month preoperative courses of albendazole significantly reduced cyst viability to 28% and 6%. Although no published data are available on the efficacy of perioperative prophylaxis, it is generally advised that albendazole is given for 1 week before surgery. Similarly, postoperative treatment is recommended for 6 months in cases of intraoperative hydatid spillage.

Treatment is usually administered in three or four courses lasting 4 weeks separated by a 2-week interval. Three courses are routinely recommended, in agreement with viability data

suggesting that a maximum benefit is not reached with less than 3 months of therapy, and more than 6 months of treatment is seldom necessary (WHO Informal Working Group on Echinococcosis, 1996). This cyclical method of treatment is recommended because of the limited toxicology data available at the time of the first treatment attempts, but more recent data on uninterrupted treatment show that this approach could have better efficacy (Saimot, 2001). The use of continuous treatment has been followed without evidence of increased adverse events, but controlled comparisons with intermittent treatment have not been carried out. Preoperative treatment with a benzimidazole should begin 1 week before surgery (WHO Informal Working Group on Echinococcosis, 1996). A new albendazole formulation has shown a fivefold to tenfold enhancement of bioavailability compared with classic albendazole (Rigter et al, 2004).

There are four objectives with medical treatment: definite cure, a reduction in cyst viability, preoperative treatment, and perioperative prophylaxis. Definite cure of univesicular cysts requires a 3- to 6-month course, which can achieve an 80% success rate with a 25% relapse rate. Most relapses occur within 2 years of treatment, but lifelong follow-up is advised. A reduction in cyst viability can be achieved in multivesicular cysts and preoperatively in univesicular cysts when percutaneous or elective surgery is planned. Perioperative prophylaxis should start 1 week before the procedure. Recommendations for posttreatment prophylaxis are 3 to 8 weeks for uncomplicated cases. In complicated cases with a higher risk of spillage of cyst contents, 3 to 6 months of treatment is arbitrarily advised.

ALVEOLAR HYDATID DISEASE

All four species of *Echinococcus* are potentially zoonotic, but *E. alveolaris* and *E. multilocularis* are the most pathogenic; both represent potentially fatal, chronically progressive hepatic infections, which is unusual for a parasitic helmintic infection. The fatal outcome may occur in 95% of untreated patients within 10 years after the diagnosis. These parasites occur within a large belt between the fortieth and forty-fifth degree of northern latitude (Ammann & Eckert, 1996). Surveys in central Europe have shown an increase in the known distribution of *E. multilocularis* from four countries at the end of 1980 to at least 11 countries in 1999 (Eckert & Deplazes, 1999). There is evidence that parasites have spread from endemic areas to previously nonendemic areas in North America, Japan, and China (Deplazes & Eckert, 2001).

Control of transmission of *E. alveolaris* is difficult because the definitive and intermediate hosts involved are usually wild animals. Risk factors for alveolar hydatid disease in endemic regions are complex and include seasonal fluctuations in the size of the fox population, the susceptibility and immunity of definitive hosts, and resistance of eggs to environmental factors (McManus et al, 2003).

The life cycle of *E. alveolaris* is similar to that of *E. granulosus*. After ingestion of an infected rodent, protoscolices transform into tapeworms. Maturation of the tapeworms to adult forms takes 28 to 35 days in the jejunum of the fox, and adult tapeworms live for 6 to 12 months in the fox intestine. Eggs in the gravid proglottis are released with fox feces and contaminate the environment. Eggs may remain viable for months, even under extreme climatic conditions. When they are ingested by the intermediate host, they are released from their capsule, and an active six-hooked embryo (oncosphere) penetrates the mucosa of the small intestine. Similar to *E. granulosus*, the eggs pass via the portal vein to the liver, where cysts are formed; about 98% of primary lesions occur in the liver. The laminated layer is secreted by the germinal layer of the parasite within 7 to 14 days after the postoncosphere period.

Humans can come into contact with the eggs accidentally, such as when skinning foxes, and ingestion of the eggs results in alveolar hydatid disease. The laminated membrane of an alveolar hydatid cyst is very thin, and brood capsules and protoscolices rarely are formed in the human host (<10%). In most cases, the germinal membrane is undetectable, or it appears as an isolated, thin form. This tissue still has the potential for proliferation, however, and it produces protoscolices when inoculated into a viable intermediate host (rodent). The growth rate of the alveolar hydatid disease in the liver is usually slow; calculated median growth rate is 14.8 mL/year (Luder et al, 1985).

The parasitic mass tends to be massive, infiltrating through the parenchyma of the liver, and it proliferates and metastasizes like a malignant tumor. Satellite lesions are common, and multiple vesicles are formed. The parasitic lesion exhibits dense granulomatous infiltration and microcalcifications. The center of the cyst may become necrotic and form a spongy mass that consists of small, irregular cavities filled with a gelatinous fluid. In addition, there is a risk of metastases in advanced alveolar echinococcosis, usually resulting in secondary lesions in the lungs, brain, or both, where necrotic and cavitating masses are found.

The symptoms are similar to those of a slowly growing liver carcinoma. Clinical symptoms vary, but initially there is a long asymptomatic period that may last for 5 to 15 years. One third of patients are diagnosed in this incubation period incidentally during examination for nonspecific symptoms, such as fatigue or weight loss. One third of patients have epigastric pain or dyspepsia, and another third have cholestatic jaundice. A palpable abdominal mass and enlarged liver are the most frequent signs. Patients are usually in a good general condition, although in advanced disease, jaundice, ascites, and hepatic failure may occur.

Routine laboratory tests do not yield specific findings. ESR is elevated in most cases, and eosinophilia is usually mild or absent (Ammann & Eckert, 1996). Alkaline phosphatase and GGT levels are usually increased, especially in advanced disease. US and CT demonstrate the lesions that appear as heterogenous, hypodense masses with irregular contours (Fig. 68.22). A necrotic cavity in the center of the mass without a well-defined wall is a frequent finding. Pressure on the portal or hepatic veins, or inferior vena cava may also occur, and calcification is common and appears as irregularly distributed clusters of microcalcifications or plaquelike foci (Fig. 68.23; Czermak et al, 2001). MRI demonstrates central necrosis better than CT but is less effective in showing microcalcification and small lesions. In most cases, T1-weighted images show the margins of the lesions more clearly (Harman et al, 2003). Alveolar hydatid disease is characterized clinically by a discrepancy between the often large, tumorlike lesions of the liver and the usually well general condition of the patient, which is in contrast to advanced malignancy.

Immunodiagnosis of alveolar hydatid disease is useful, effective, and more reliable than the diagnosis of cystic hydatid disease. The sensitivity in alveolar hydatid disease is 95% to 100%, and the specificity is high if purified and specific antigens



FIGURE 68.22. Heterogenous mass with irregular contours and necrotic cavity in the center in alveolar hydatid cyst.

are used. Native Em2 antigen, alone or mixed with recombinant Em10, is highly specific for alveolar hydatid disease using ELISA, and only a few cystic hydatid disease cases are cross-reactive (Silas-Lucas & Gottstein, 2001). Immunodiagnosis has a diagnostic sensitivity of 97.1% and overall specificity of 98.9%. The reported sensitivity of the recombinant Em18-ELISA was 87% with 97% specificity (Ito et al, 2002; Sako et al, 2002). The stage of the disease is the main prognostic factor, similar to malignant tumors. The so-called *PNM system* (***parasitic mass, involvement of neighboring organs, metastasis***) is a clinical staging system for alveolar hydatid disease (Box 68.1 and Table 68.5; Pawlowski et al, 2001).

Alveolar hydatid disease is more difficult to treat than cystic hydatid disease. Early diagnosis is crucial, and new imaging and serologic techniques, advances in surgery, and the introduction of chemotherapy have improved outcome. When alveolar hydatid disease is diagnosed, the patient should undergo treatment regardless of whether symptoms are present. The two treatment options are surgery and chemotherapy.

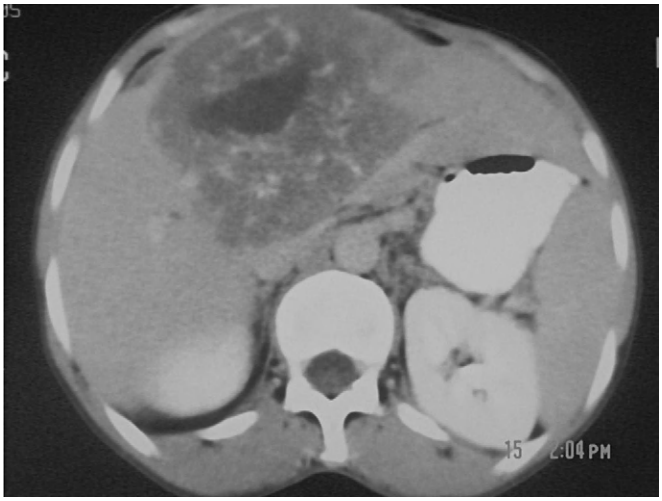


FIGURE 68.23. Plaque-like calcifications on the liver mass in an alveolar hydatid cyst.

Box 68.1

PNM Classification of Human Alveolar Echinococcosis

P: Hepatic Localization of Metacestode

PX Primary lesion unable to be assessed

P0 No detectable hepatic lesion

P1 Peripheral lesion without biliary or proximal vascular involvement

P2 Central lesions with biliary or proximal involvement of one lobe

P3 Central lesions with biliary or proximal vascular involvement of both lobes or two hepatic veins or both

P4 Any lesion with extension along the portal vein, inferior vena cava, or hepatic arteries

N: Extrahepatic Involvement of Neighboring Organs

NX Not evaluable

N0 No regional involvement

N1 Involvement of neighboring organs or tissues

M: Presence or Absence of Distant Metastasis

MX Not completely assessed

M0 No metastasis on chest radiograph and CT brain scan

M1 Metastasis present

CT, computed tomography

From Pawlowski I, et al, 2001: Echinococcosis in humans: clinical aspects, diagnosis and treatment. In Eckert J, et al (eds): WHO/OI Manual on Echinococcosis in Humans and Animals: A Public Health Problem of Global Concern. Paris, World Organisation for Animal Health, pp 20-71.

Curative liver resection is the treatment of choice for localized lesions. Because of the frequent involvement of the biliary bifurcation, liver resection often requires a biliary reconstruction using a Roux-en-Y jejunal loop. Most of the lesions occur in the right lobe of the liver; if adherent to the diaphragm, such lesions may require an associated diaphragmatic resection. Palliative resection has been proposed in patients with large bilobar involvement with extension to the portal vein or to the vena cava. This approach, combined with medical treatment, can result in long-term survival. In contrast, surgical external biliary drainage of cyst cavities is associated with poor outcome. Liver transplantation should be considered in patients who have unresectable disease, especially with massive involvement of the pedicle or coexisting chronic liver failure (Bresson-Hadni et al, 2003). The frequent extrahepatic extension of the disease—involving the hepatoduodenal ligament, vena cava, diaphragm, and pericardium—makes total hepatectomy technically difficult. In addition, hydatid disease may recur even after liver

Table 68.5

Staging of Alveolar Echinococcosis on the Basis of PNM Classification

Stage	P	N	M
I	P1	N0	M0
II	P2	N0	M0
IIIa	P3	N0	M0
IIIb	P1-3	N1	M0
IV	P4	N1	M0
	P4	N0	M0
	Any P	Any N	M1

transplantation (Bresson-Hadni et al, 1999). Adjuvant chemotherapy with albendazole should be added to posttransplant medication regimens to prevent recurrence (WHO Informal Working Group on Echinococcosis, 1996).

Albendazole (15 mg/kg/day) is probably the best drug currently available for alveolar hydatid disease. It is generally accepted that long-term albendazole therapy is primarily parasitostatic. Evidence of a parasiticidal effect of long-term albendazole has been reported, however, in a few cases (Ammann et al, 1998). More recent studies provide clear evidence that long-term chemotherapy of alveolar hydatid disease is effective. Oral albendazole resulted in an improved 10-year survival rate of 80% to 83% compared with 6% to 25% for untreated historic controls (Craig, 2003). Nitazoxanide, a broad-spectrum antihelmintic drug, has been tested for experimental alveolar hydatid disease. Nitazoxanide is better absorbed than albendazole after oral administration, and it provides an attractive potential alternative for medical treatment (Stettler et al, 2003).

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CHAPTER 69A

Simple cysts and polycystic liver disease: clinical and radiographic features

Olivier Farges and Valerie Vilgrain

OVERVIEW

The entity common to simple cysts and polycystic liver disease (PCLD) is a malformation, lined by a nontypical biliary-type epithelium that does not communicate with the biliary tree. This differentiates these diseases from hydatid cysts (see Chapter 68), cystic hepatobiliary neoplasms (Chapter 79B), and cystic dilation of the intrahepatic bile ducts (Chapter 46).

Simple cysts and PCLD differ in more than just the number of cysts; simple cysts are frequently multiple, but the extent of disease in PCLD is highly variable. PCLD is currently a well-described genetic disease that comes in two forms, with and without autosomal dominant polycystic kidney disease (ADPKD). Most of what is known about the pathogenesis of PCLD comes from the study of animal models and of patients with both liver and kidney involvement.

When present, symptoms relate either to an increase in the size of single cysts or, with PCLD, to an increase in the size of the whole liver. Apart from acute complications, the most frequent of which is intracystic bleeding, these symptoms have frequently evolved progressively for a prolonged period. It may therefore be difficult for clinicians to differentiate cyst-related symptoms from those of associated conditions. It may even occasionally take some time to understand the true severity of cyst-related symptoms, to which some patients have unconsciously become accustomed.

This chapter focuses on pathology, prevalence, manifestation, and diagnosis of PCLD. Differential diagnosis from other cystic lesions is addressed at the end of this chapter, and therapeutic management is addressed in Chapter 69B.

SIMPLE CYSTS OF THE LIVER

Simple cysts of the liver contain serous fluid and do not communicate with the intrahepatic biliary tree. Numerous terms have been used to designate such lesions; such terms include *biliary cyst, nonparasitic cyst of the liver, benign hepatic cyst, congenital hepatic cyst, unilocular cyst of the liver,* and *solitary cyst of the liver* (the last designation is inappropriate because simple cysts are often multiple, as described later in this chapter). Simple cysts frequently occur in the general population. Most simple cysts are less than 3 cm in diameter, are easily identified by ultrasound (US), and are asymptomatic. When present, symptoms occur in larger cysts, usually related to intracystic bleeding that changes the morphologic appearance of the cyst. In this circumstance differential diagnosis with other cysts, most notably cystadenoma or hydatid disease, may prove difficult.

Pathology and Pathogenesis

Macroscopically, a simple cyst of the liver has a spherical or ovoid shape. The diameter ranges from a few millimeters to 20 cm or more, and the cyst does not communicate with the intrahepatic bile ducts. Small cysts are surrounded by normal hepatic tissue. Large cysts produce atrophy of the adjacent hepatic tissue; a huge cyst may result in complete atrophy of a hepatic lobe with compensatory hypertrophy of the other lobe. Atrophy respects the large bile ducts and blood vessels, which appear to be abundant in the atrophic tissue in contact with the cyst. Large bile ducts and blood vessels that persist after atrophy may protrude and form folds over the inner surface of the cyst. No septation is apparent, the cysts are unilocular, and cystic fluid is usually clear; however, intracystic bleeding is relatively common, and the fluid may be brownish when this is the case. Even when a simple cyst is apparently unique, imaging studies disclose the presence of one or more small additional cysts in most patients. In a few cases, simple cysts are multiple, resembling the liver cysts of PCLD; criteria for distinguishing both conditions are given below.

Microscopically, the cysts appear to be bordered by a single layer of cuboid or columnar epithelial cells, resembling biliary epithelial cells (Fig. 69A.1). The cells are uniform, without any atypia. Stroma is absent in small cysts and is reduced to a thin layer of connective tissue in large cysts. Simple cysts of the liver are regarded as a congenital malformation, likely aberrant bile ducts that have lost communication with the biliary tree and

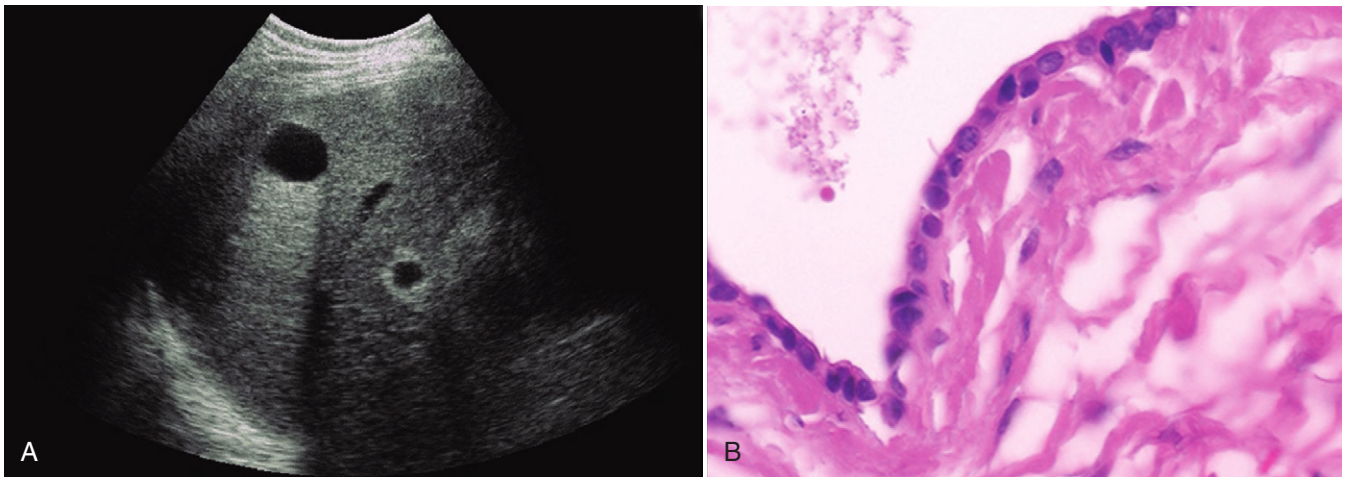


FIGURE 69A.1. A, Ultrasound of a simple cyst of the liver. **B,** Microscopic view of its epithelial lining.

dilate progressively. Liver cyst epithelial cells retain differentiated secretory function; they secrete fluid and generate a positive luminal pressure that may be greater than 30 cm H_2O, which accounts for most symptoms. The composition of the fluid, which contains water and mineral electrolytes without bile acids and bilirubin, is close to that of the normal secretion of the epithelium of the bile ducts. It is not toxic to the peritoneum, which is the rationale for cyst fenestration (see Chapter 69B).

Prevalence and Etiology

Simple cysts had been considered rare. By 1971, only 350 cases had been reported (Flagg & Robinson, 1967; Moreaux & Bloch, 1971), and early estimates from autopsy studies were less than 1% (Larsen, 1961). However, the development of imaging techniques revealed that simple cysts are much more frequent. Prevalence in ultrasound studies is 3% to 5% (Caremani et al, 1993; Gaines & Sampson, 1989); however, in a more recent spiral computed tomographic (CT) study of an adult population, prevalence was 18% (Carrim & Murchison, 2003). These discrepancies are explained by the usual small size of most cysts, which are discovered only by accurate imaging techniques. An association between simple hepatic cysts and simple renal cysts has been documented (Carrim & Murchison, 2003), but this association has not yet been explained.

The incidence of simple cysts is age and gender related. Simple cysts are uncommonly identified before age 40 years, but their incidence increases sharply thereafter. Simple cysts also are larger in adults older than 50 years (Larsen, 1961). The female/male ratio is 1.5 : 1 for all simple cysts shown at necropsy or imaging; however, this statistic jumps to 9 : 1 in symptomatic or complicated simple cysts (Moreaux & Bloch, 1971). Huge cysts affect women older than 50 years almost exclusively. Based on these observations, the diagnosis of simple cysts should be retained with caution, when a large or symptomatic cystic mass is observed in a male patient or in a young woman.

Manifestations and Diagnosis

In most cases, simple cysts—all small cysts, but also most large cysts—are asymptomatic and fortuitously shown by US or CT. Only some large cysts produce abdominal pain or discomfort. Because of the high prevalence of simple cysts in adults, the coincidence of this lesion and another hepatic or extrahepatic disease is common. The causal relationship between abdominal pain or discomfort and a simple cyst of the liver must be admitted with caution and accepted only if the cyst is large, and other possible causes of the symptoms have been excluded. At clinical examination, only large cysts can be palpated as spherical tumors. In most cases, the fluid content of the tumor can be suspected. In some cases, the cyst is so tense that it may be taken for a solid tumor. The condition of individuals with a simple cyst of the liver is generally good, and liver function tests are normal; abnormal liver function tests in a patient with a simple cyst of the liver are not related to the cyst but are caused by another liver disease, except when the cysts compress bile ducts.

US is the best imaging modality for recognizing simple cysts, which appear as a circular or oval, completely anechoic lesion with sharp, smooth borders and strong posterior wall echoes that indicate a well-defined tissue-fluid interface (Liang et al, 2005). Echoes beyond the cyst are accentuated compared with echoes at a similar depth transmitted through normal adjacent liver tissue (see Fig. 69A.1). Accentuation of the echoes beyond the cyst indicates that the lesion is filled with fluid. This so-called *acoustic posterior enhancement* is observed only when the deep tissue transmits US; it is not seen when a total reflector, such as gas or bone, lies behind the cyst or when the cyst is very posterior. Neither wall nor septation is apparent, but a false image of septation may be seen when two cysts are adjacent. In some patients, intracystic echoes or material can be detected after intracystic bleeding.

Other imaging procedures have less utility in diagnosis compared with US and are generally not required. CT confirms the presence of one or several round or oval, water-dense lesions but no septations or intracystic formations; dynamic CT shows that such lesions are avascular. In small cysts, recognition of water density may be difficult; the average density of the cyst is obscured by the density of the adjacent liver tissue, but an apparent increase in density may be observed after intravenous injection of contrast medium. On magnetic resonance imaging (MRI), the cyst is homogeneous, very hypointense on T1-weighted images, and very hyperintense on T2-weighted images, as are the gallbladder contents (Fig. 69A.2). If the

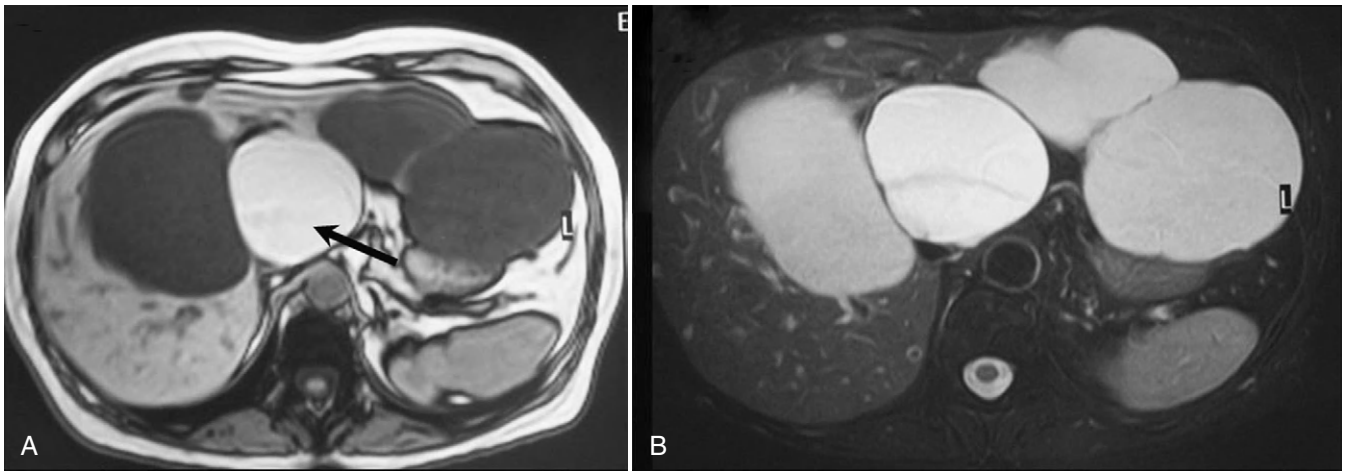


FIGURE 69A.2. Magnetic resonance image of a patient with multiple cysts. **A,** On T1-weighted images, cysts are hypointense, except for one cyst, which is hyperintense as a result of intracystic bleeding (*arrow*). **B,** All cysts are hyperintense on T2-weighted images.

patient lives or has been living in an area where hydatid disease is endemic, or when any doubt exists about a possible hydatid cyst, serologic tests for this parasitic infection should be performed, although their accuracy is fairly low. MRI should also be performed (see Chapter 68).

Course and Complications

In most cases, simple cysts are asymptomatic and remain silent; serial US studies usually show no appreciable changes over a matter of years, and surveillance is not required. In some patients, the cysts grow slowly. In a few patients, the size of the cysts increases rapidly; such a course, which may be associated with severe pain and discomfort, is observed almost exclusively in women older than 50 years.

Complications are uncommon, but intracystic bleeding is the most frequent observed (Frisell et al, 1979; Moreaux & Bloch, 1971) and is presumed to result from the erosion of an artery adjacent to the cyst. The clinical manifestations consist of sudden, severe pain and an increase in the size of the cyst. The pain resolves in a few days; in some cases, pain is mild or absent. There is no evidence of anemia, and the biologic liver tests show only a moderate elevation of γ-glutamyltransferase (GGT). On US, echoic material corresponding to clots is seen within the cyst (Fig. 69A.3); this material usually is mobile, sliding in the inferior part of the cyst. Hemorrhagic cysts also become hyperintense on T1-weighted MRI, whereas uncomplicated cysts are hypointense (see Fig. 69A.2). After gadolinium injection, an enhancement of the periphery of the cyst is frequently seen when hemorrhage is recent, which corresponds to compressed liver parenchyma (Fig. 69A.4). Contrast US may also prove useful in the future by showing that neither the cyst wall nor the intracystic material is enhanced, unlike cystadenoma (see Fig. 69A.4; Chapter 79B), but larger studies are required (Akiyama et al, 2008). Communication with the bile duct lumen may develop, presumably also by an erosive mechanism; however, bacterial infection in contrast is exceptional.

Spontaneous rupture into the peritoneal cavity (Fig. 69A.5; Akriviadis et al, 1989; Salemis et al 2007)—or, more rarely, into the pleural cavity or the duodenum (Williamson et al, 1978)—is exceptional. In contrast to hydatid cysts, peritoneal perforation of simple cysts is self-limited. Severe hemoperitoneum has been described only in patients with PCLD undergoing dialysis.

Because simple cysts are tense, they may compress the bile ducts or the inferior vena cava (Fig. 69A.6), and although anecdotal, there have been reports of pulmonary embolism after clot formation (Buyse et al, 2004). As discussed in Chapter 69B, compression of biliary branches or hepatic veins is a potential source of intraoperative or postoperative complications.

POLYCYSTIC LIVER DISEASE

PCLD—or, more precisely, *diseases*—is a term for genetic disorders responsible for the progressive development of multiple cysts in the liver. PCLD was initially considered to exclusively develop in the context of ADPKD (Moschcowitz, 1906). However, identification of families with PCLD but no ADPKD proved that PCLD may also occur alone (Berrebi et al, 1982; Tahvanainen, et al, 2003). These two forms of PCLD—those with and without ADPKD—are linked to distinct gene mutations. Both, however, have an autosomal dominant transmission and an almost identical clinical course. Of note, one third of patients with isolated PCLD may have a few kidney cysts, usually one or two (van Keimpema et al, 2010), as does the general population of adult patients (Carrim & Murchison, 2003). Distinction between the two forms of PCLD is addressed below.

Genetics

Polycystic Liver Disease and Autosomal Dominant Polycystic Kidney Disease

PCLD associated with ADPKD is linked to mutations in either the *PKD1* or *PKD2* gene. *PKD1* (Ward et al, 1996) is located on the short arm of chromosome 16 and encodes polycystin-1; its mutation accounts for 85% of mutations in ADPKD patients. Most of the rest are related to a mutation in *PKD2* (Mochizuki et al, 1996), which is located on chromosome 4 and encodes polycystin-2. *PKD1* mutation is associated with more renal cysts, larger cysts, more prevalent hypertension, and faster progression to end-stage renal disease than *PKD2* mutation.

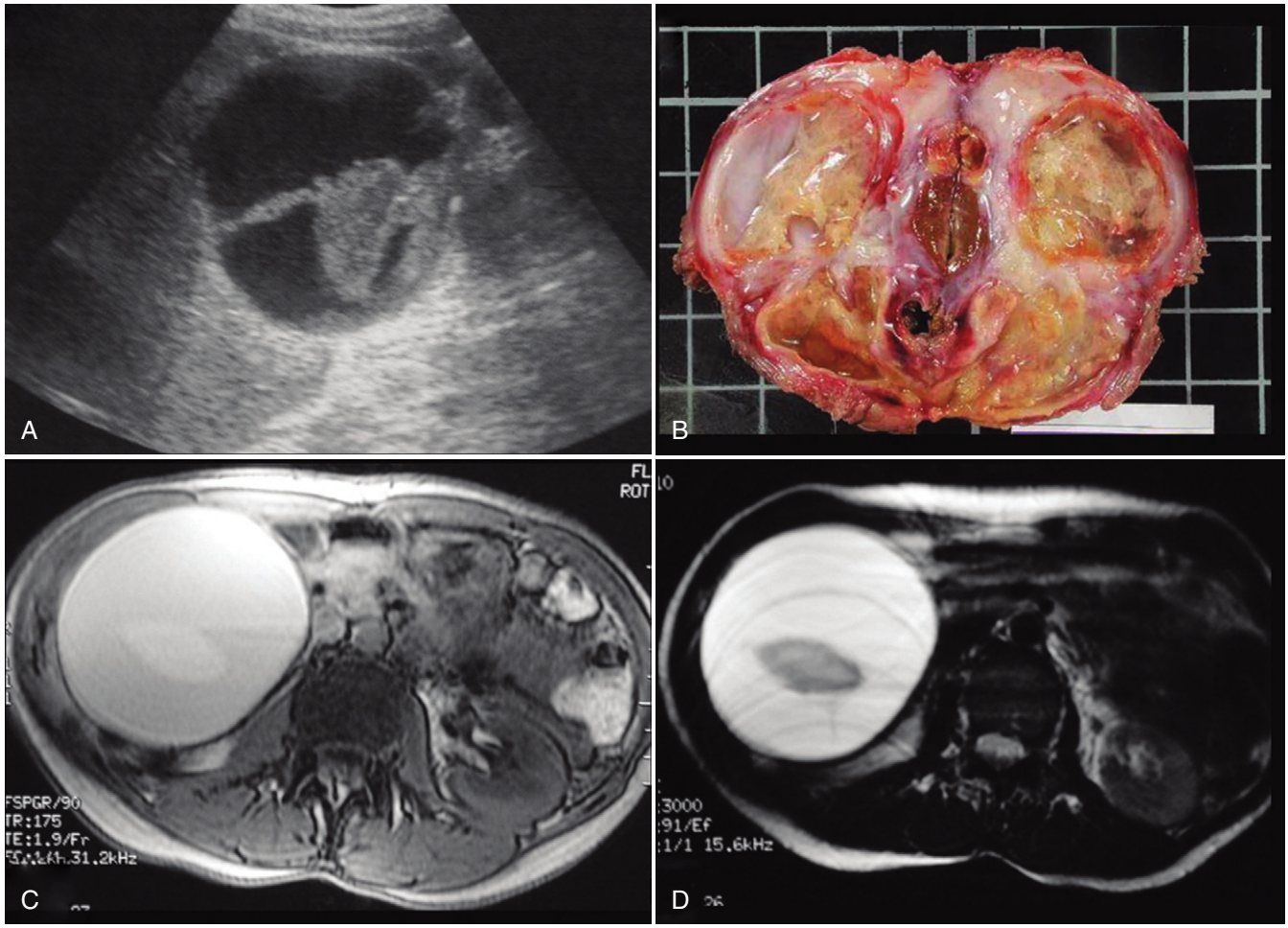


FIGURE 69A.3. Hemorrhagic simple cyst of the liver that has become atypical as a result of intracystic bleeding. **A,** Ultrasound. **B,** Macroscopic view of the resected specimen. **C** and **D,** Magnetic resonance imaging.

Isolated Polycystic Liver Disease

Isolated PCLD—that is, PCLD without ADPKD—is associated with heterozygous mutation in either the *P*rotein *K*inase *C* *S*ubstrate 80K-*H* (*PRKCSH*) or *SEC63* genes. Both genes are located in the endoplasmic reticulum and function in the early secretory route of the cell. *PRKCSH* is located on the short arm of chromosome 19, which encodes the protein hepatocystin (Drenth et al, 2004). Hepatocystin functions as the β-subunit of α-glucosidase II and is involved in the protein-folding processes and quality control of newly synthesized glycoproteins (Trombetta et al, 2001). *SEC63* is located on the long arm of chromosome 6 and encodes the *SEC63* protein involved in protein transport across the endoplasmic reticulum membrane (Brodsky et al, 1995). However, these mutations only explain 25% to 40% of cases (Davila et al, 2004; van Keimpema et al, 2010), which suggests that one or more other genes is involved.

The Two-Hit Theory

PCLDs have an autosomal dominant phenotype but are considered to be a recessive disease at the molecular level because they require a second somatic mutation. According to this theory, a germline mutation is present in either *PKD1* or *PKD2*. However, cell proliferation and cyst formation occurs in individual cells that have in addition received a second loss-of-function somatic mutation in the other gene copy (Everson et al, 2004). This second hit would explain why affected cells are few and why cysts develop from place to place; it may also account for the extreme heterogeneity of the disease. This theory has been designed for PCLD associated with ADPKD but has not been investigated for isolated PCLD. It is unclear as to why these various mutations may affect both the liver and kidney or only the liver.

Pathology and Pathogenesis

Liver cysts in PCLD are macroscopically and microscopically similar to simple cysts of the liver, and their number and distribution are highly variable. They are lined by a single-layered epithelium that has phenotypic and functional characteristics of biliary epithelium (Perrone et al, 1995) and retain in particular a secretory capacity and responsiveness to secretin (Everson et al, 1990). The cysts result from abnormal remodeling of the ductal plate and mainly arise from dilation of biliary microhamartomas, also known as *von Meyenburg complexes,* which have lost their communication with the biliary tree (Melnick, 1975). Some cysts also arise from peribiliary glands surrounding large intrahepatic bile ducts (Fig. 69A.7; Kida et al, 1992).

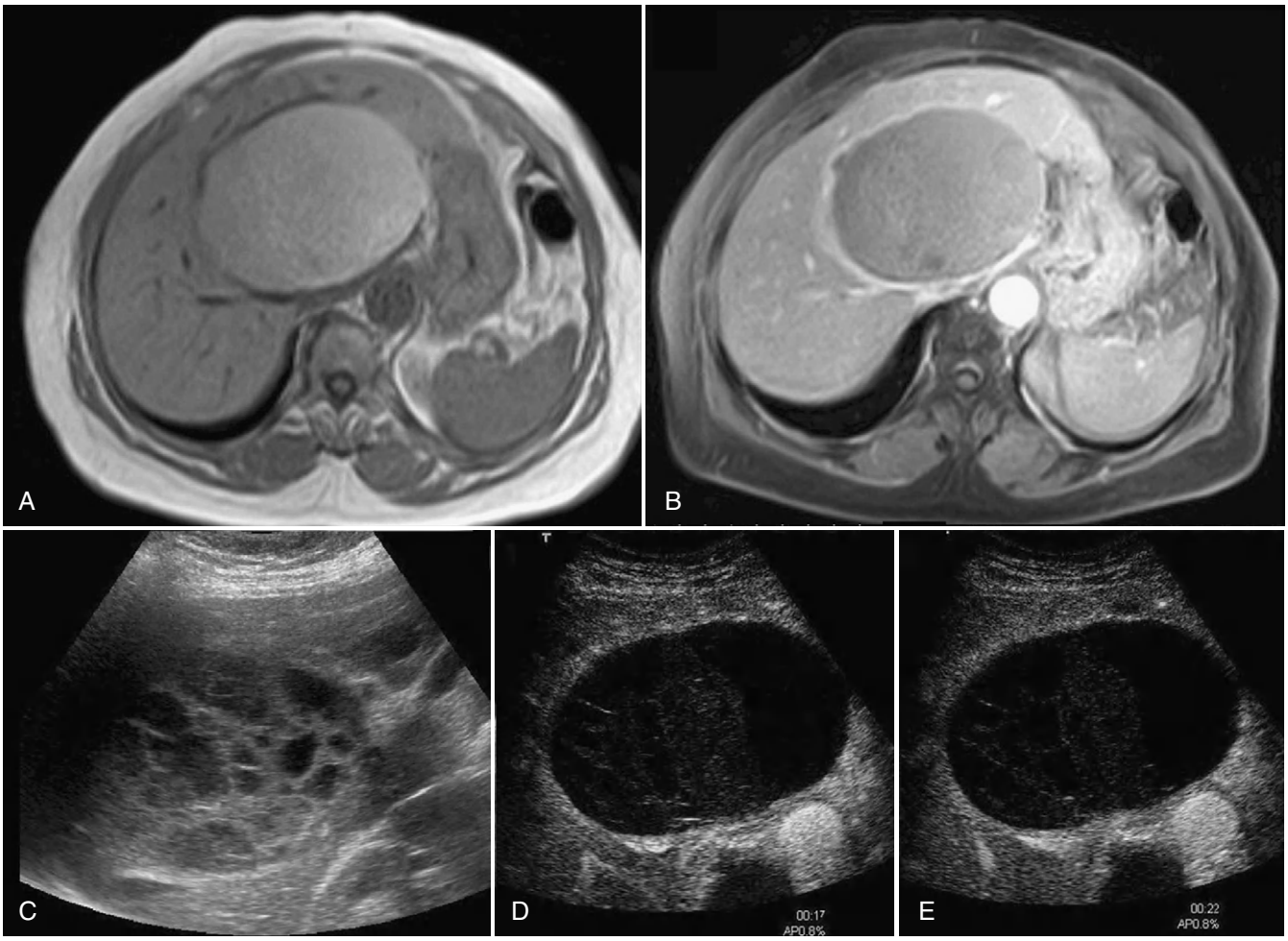


FIGURE 69A.4. Other examples of a hemorrhagic simple cyst. **A,** The cyst is hyperintense on T1-weighted images. **B,** Peripheral enhancement follows injection of gadolinium as a result of compression of the adjacent liver. **C,** On ultrasound, the cystic lesion appears with echogenic and anechogenic portions. **D** and **E,** The echogenic portions do not enhance during contrast ultrasound.

The mechanisms of cyst expansion are still not fully explained but appear similar to those involved in the development of renal cysts. Growth results from a combination of proliferation of epithelial cells, remodeling of the extracellular matrix required for the cyst to invade the surrounding liver parenchyma (Murray et al, 1996), and neovascularization that results in increased density of the vascular bed surrounding the cysts (Bello-Reuss et al, 2001; Nichols et al, 2004).

As in the kidney tubules, the microvilli and long cilia normally on cholangiocytes are believed to play a dominant role. These mechanosensory organelles may be bent by bile flow and can also react to hormonal, morphogen, or growth factor stimuli; they may even function as sensors of cell injury. These cilia and microvilli modulate concentrations of intracellular levels of cyclic adenosine monophosphate (cAMP) and Ca^{2+} that are mediators of proliferation and secretory activity of cholangiocytes. In PCLD, these cilia progressively disappear from the luminal surface of the epithelium as cysts enlarge (Alvaro et al, 2008). Their absence could impair Ca^{2+}-dependent counterregulation of cAMP, which is a key determinant of cholangiocyte proliferation. It is unclear whether the disappearance of these cilia is a primary event or a result of increased pressure. However, polycystin-1 and polycystin-2 are localized to the cilia, and their absence as a result of a *PKD1* or a *PKD2* mutation could result in ciliary dysfunction. In patients with isolated PCLD, it has been postulated that polycystins could be the target of aberrant maturation of newly synthesized glycoprotein caused by *PRKCSH* or *SEC63* mutations.

Two other targets of the cell cycle have been identified. One is the mammalian target of the rapamycin (mTOR)-mediated signaling cascade (Shillingford et al, 2006), which explains growing interest from the industry for mTOR inhibitors (see Chapter 69B). The other is through micro-RNAs, small, noncoding RNAs that inhibit target messenger RNA transcripts via sequence-specific base paring; micro-RNA-15a in particular is downregulated in cyst epithelium, resulting in an overexpression of Cdc25A, which activates cyclin-dependent kinases and progression of the cell cycle (Lee et al, 2008).

Fluid secretion by the epithelium lining the cyst may also contribute to cyst expansion. Ciliary dysfunction could also play a role because it has also been shown to result in maintenance of an immature phenotype by biliary epithelial cells with postnatal expression of developmental proteins. A variety of cytokines and growth factors present in increased

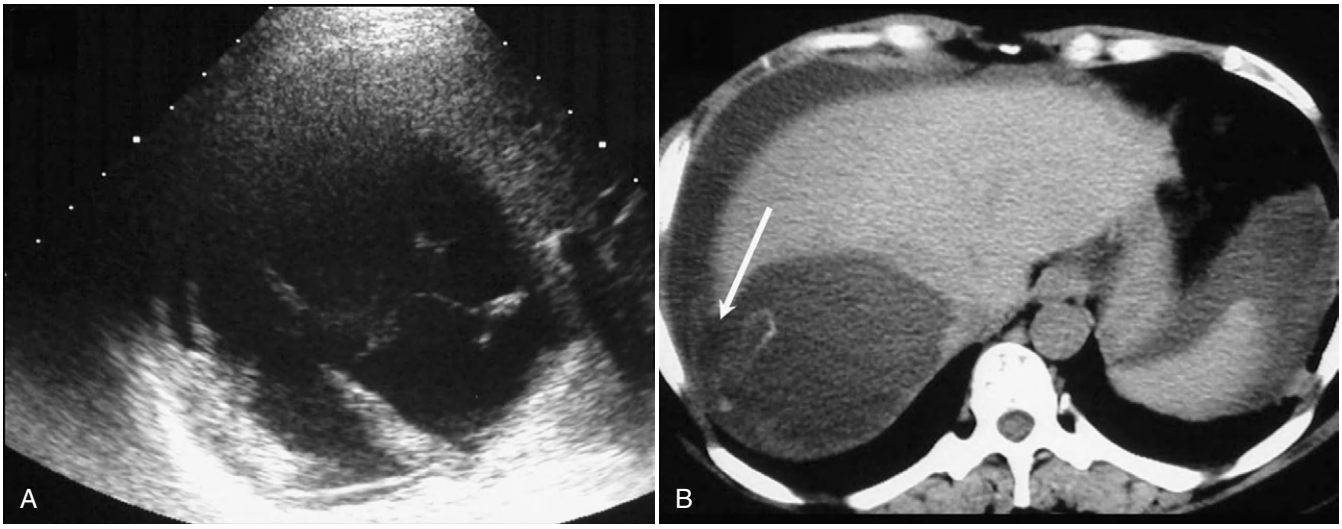


FIGURE 69A.5. Spontaneous rupture of a simple cyst. **A,** Ultrasound. **B,** Computed tomographic scan. The cystic lesion is heterogeneous and poorly limited. A communication is visible with the peritoneal cavity (*arrow*), where ascites is visible.

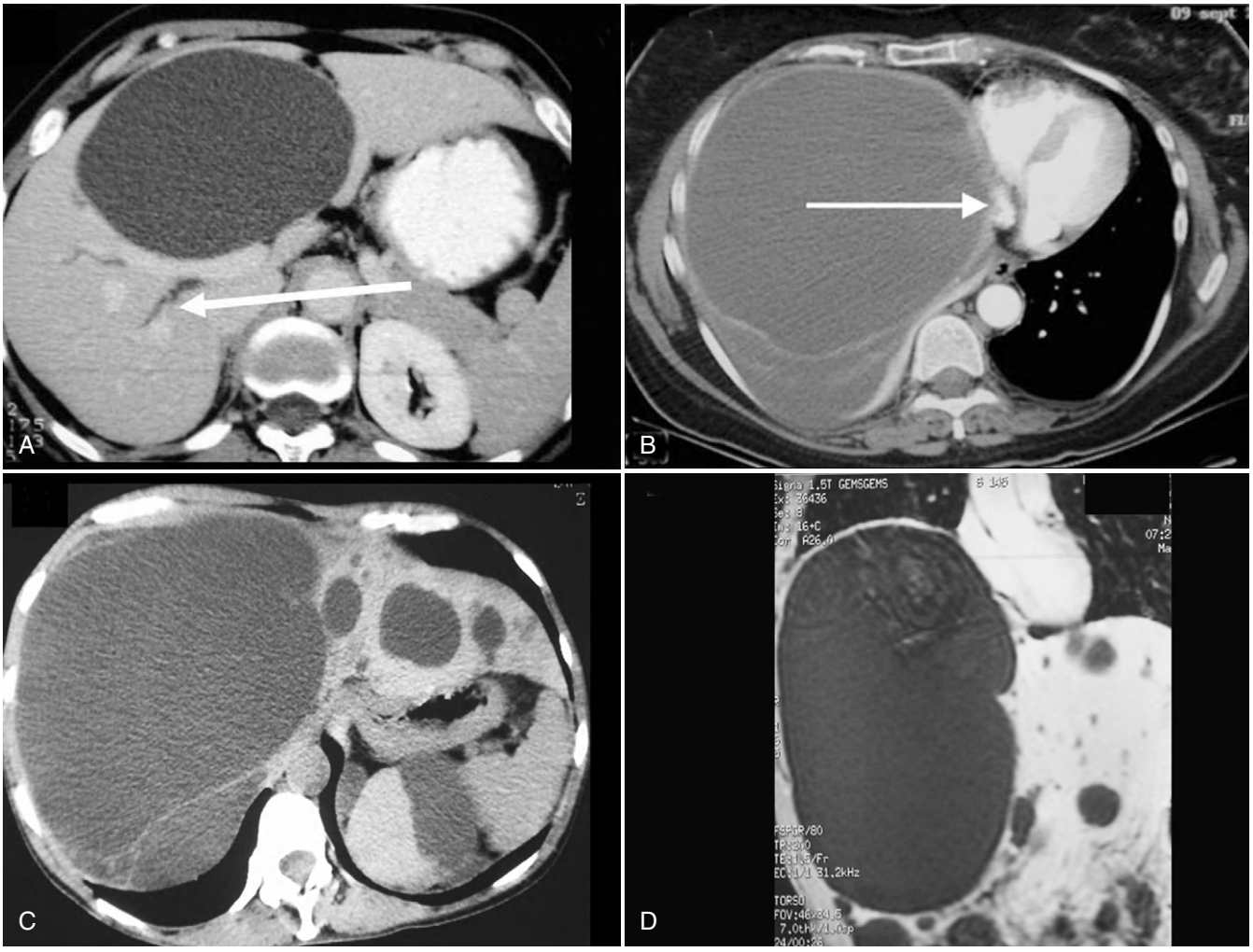


FIGURE 69A.6. Compression by hepatic cysts. **A,** Cyst of the biliary confluence with enlarged bile ducts upstream (*arrow*). **B,** The inferior vena cava with a small clot in the caval lumen (*arrow*). **C,** The stomach is compressed indirectly by a large cyst of the right liver, rotating the left lateral section. **D,** The diaphragm and right atrium are also rotated.

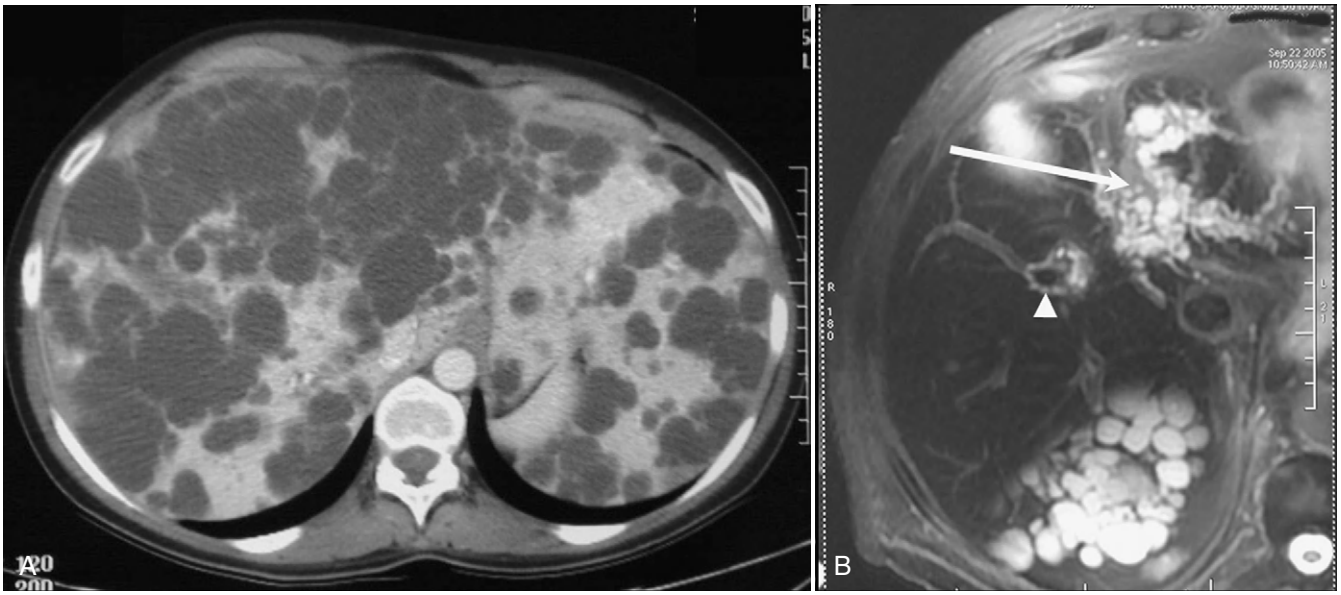


FIGURE 69A.7. Polycystic liver disease. Cysts arise peripherally (**A**) or from peribiliary glands (**B**). Note that they are prominent around the left bile duct (*arrow*) but can also be seen around the right portal pedicle (*arrowhead*).

concentration in the cysts have been implicated in cyst growth by autocrine-paracrine signaling (Alvaro et al, 2008; Fabris et al, 2006; Nichols et al, 2004). Angiogenic factors in particular could play a role by promoting vascularization of the cyst and also by directly stimulating cholangiocytes. Furthermore, the epithelium stains positive for insulin growth factor 1 (IGF-1) and its receptor, as well as for estrogen receptors (Alvaro et al, 2008), and is particularly sensitive to this signaling.

All these observations and hypotheses account for the rationale of using vasopressin antagonists or somatostatin analogues known to inhibit cAMP; sirolimus, an inhibitor of mTOR signaling; or vascular endothelial growth factor inhibitors in the treatment of PCLD (see Chapter 69B). The presence of estrogen receptors also provides a rationale for the influence of the patient's estrogen status on the clinical course of the disease. In particular, women with ADPKD are more likely to develop hepatic cysts than their male counterparts (Chapman, 2003), and nulliparous women are less likely to develop hepatic cysts than their multiparous counterparts (Gabow et al, 1990). Oral contraceptives and postmenopausal hormonal substitutive therapy increases both the number and size of liver cysts (Sherstha et al, 1997).

Epidemiology

PCLD ASSOCIATED WITH ADPKD. ADPKD occurs in approximately 1 in every 800 live births and is characterized by progressive development and enlargement of fluid-filled cysts, ultimately leading to renal failure in 50% of affected individuals. PCLD is the most frequent extrarenal associated condition, but liver cysts develop later than renal cysts. The prevalence of liver cysts also increases with age. This was recently evaluated by MRI in a young adult population with relatively preserved kidney function and was found to be 58% in patients aged 15 to 24 years, 85% in those aged 25 to 34 years, and 94% in those aged 35 to 46 years (Bae et al, 2006). Overall prevalence is the same in men and women, but as for simple cysts, women have more severe liver disease than men; multiparity and use of oral contraceptive drugs or estrogen replacement therapy also tends to worsen the condition (Bae et al, 2006; Sherstha et al, 1997; Torres et al, 2007). Prevalence of liver cysts is also correlated with kidney volume and renal cyst volume (Bae et al, 2006).

ISOLATED POLYCYSTIC LIVER DISEASE. Isolated PCLD is considered rare, with an estimated incidence of less than 0.01%. Compared with PCLD associated with ADPKD, the overall incidence of isolated PCLD is in fact only slightly lower (Karhunen & Tenhu, 1986); however, in clinical series dealing with symptomatic patients, it is two to five times less frequent (Hoevenaren et al, 2008; Schnelldorfer et al, 2009), which may reflect the milder course of isolated PCLD. As for PCLD associated with ADPKD, cysts increase with age, and although the disease is transmitted equally in men and women, 85% of symptomatic patients are women (van Keimpema et al, 2010).

Manifestations and Diagnosis

SYMPTOMS. In most patients, liver cysts are small and sparse and remain clinically silent. Even with massive organ enlargement, significant hepatic complications remain fairly uncommon, although patients or others may have noted a protuberant abdomen. Some patients develop symptoms that may include abdominal pain or discomfort, early satiety, shortness of breath, and leg edema. These result from compression of the stomach, diaphragm, and inferior vena cava by single large cysts (see Fig. 69A.6) or, much more frequently, because of enlargement of the entire liver (Fig. 69A.8C). As symptoms have progressively evolved over a prolonged period, patients have often become used to these discomforts and are either unaware of them or minimize them. At clinical examination, the liver may reach an enormous size, and its inferior border is frequently palpated in the iliac fossa. The cysts may be so tense that they can be confused with solid tumors.

Previous history of self-resolving acute abdominal pain is not unusual and probably witnesses spontaneous bleeding within one or more cysts. However, these episodes may remain

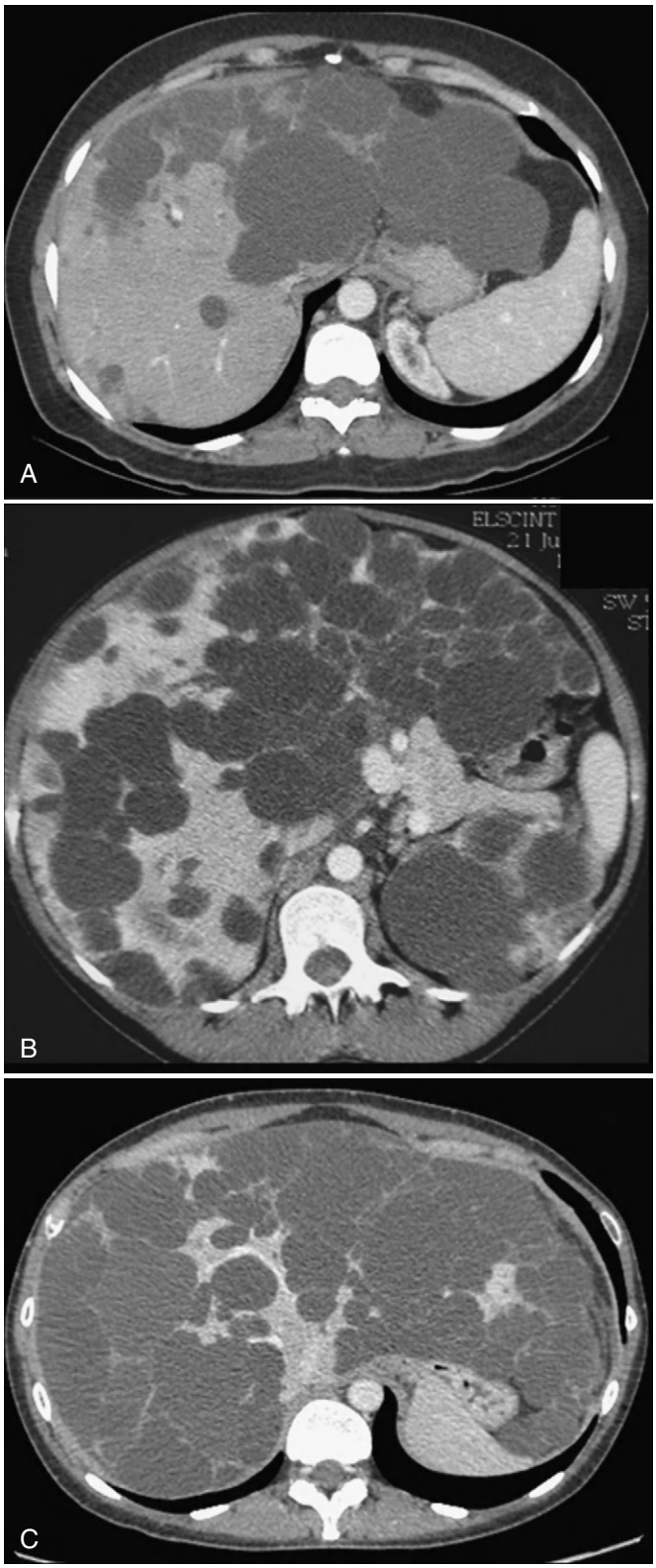


FIGURE 69A.8. Representative examples of the heterogeneity of polycystic liver diease. **A,** *Limited extension:* Several large cysts are evident, but large areas of noncystic liver remain. **B,** *Intermediate form:* Intermediate-sized cysts are scattered throughout the liver, but some areas of noncystic liver remain. **C,** *Severe form:* Almost all the liver is replaced by cysts, and there is likely vascular injury within the few remnant noncystic areas.

clinically silent. As the disease progresses, nutritional deficits may develop and be associated with ascites or pleural effusion (Fig. 69A.9). Body weight is an inaccurate marker because muscular loss correlates with the progressive increase in the weight of the liver, which may reach more than 10 kg. The clinician should instead focus on the thickness of the muscles of the abdominal wall or psoas muscle on imaging studies.

Typically, patients referred to surgeons are women between 35 and 50 years of age with liver cysts diagnosed 10 years previously whose symptoms have become incapacitating for 6 to 18 months. Clinical manifestations, as well as complications and management, are the same whether PCLD is isolated or associated with ADPKD (Hoevenaren et al, 2008; Qian et al, 2003).

BIOLOGY. The only abnormality may be an increase in GGT or alkaline phosphatase, but this is infrequent. Although the liver may be diffusely involved by liver cysts, the hepatic parenchymal volume is preserved (Everson et al, 1988). Therefore no sign of liver failure is evident; when present, a superimposed cause of chronic liver disease is likely. This lack of influence on liver function explains how polycystic livers from brain-dead donors have even been used in the context of emergency liver transplantation (Glanemann et al, 2000).

IMAGING. US shows multiple, fluid-filled, round or oval cysts with sharp margins in the liver and, when associated with ADPKD, in the kidneys. Coalescent cysts may give a false image of septation. On CT scan, the cysts have fluid attenuation values of −5 to +20 Hounsfield units (HU) and have distinct margins with the parenchyma. Calcification of the cysts has been reported but is rare (Coffin et al, 1990; Kutcher et al, 1977). Considering the high prevalence of associated ADPKD, injection of contrast agents should be used with extreme caution. Cysts do not show contrast enhancement, and it may be extremely difficult to identify vascular and biliary structures or even normal landmarks of the liver. Similar to simple cysts, uncomplicated cysts of PCLD are very hyperintense on T2-weighted MRI and very hypointense on T1-weighted images; cysts complicated by hemorrhage become hyperintense on T1-weighted images (see Fig. 69A.2). Identifying peribiliary cysts is difficult but may be suspected when tubular structures run parallel to portal branches, mimicking a biliary dilatation (see Fig. 69A.7; Gupta et al, 1999).

With respect to treatment (see Chapter 69B), attention should be paid to several factors:

1. *The severity of cystic involvement* (see Fig. 69A.8). In a small subset of patients, symptoms are not related to the size of the entire liver but to one or two large cysts. These patients should be identified because even though they may have multiple cysts, management is the same as for those with simple cysts.
2. *The distribution of the cysts.* This is frequently uneven; some areas are relatively spared, in particular segments V or VI, which is the rationale for liver resection.
3. *Peribiliary cysts or cysts located around the biliary confluence and those located in the vicinity of the termination of the hepatic veins.* These may be a common finding. Right hepatic vein compression is frequent and results in an easily identifiable collateral circulation between the right and middle hepatic vein (Fig. 69A.10), which can be a source of intraoperative bleeding.

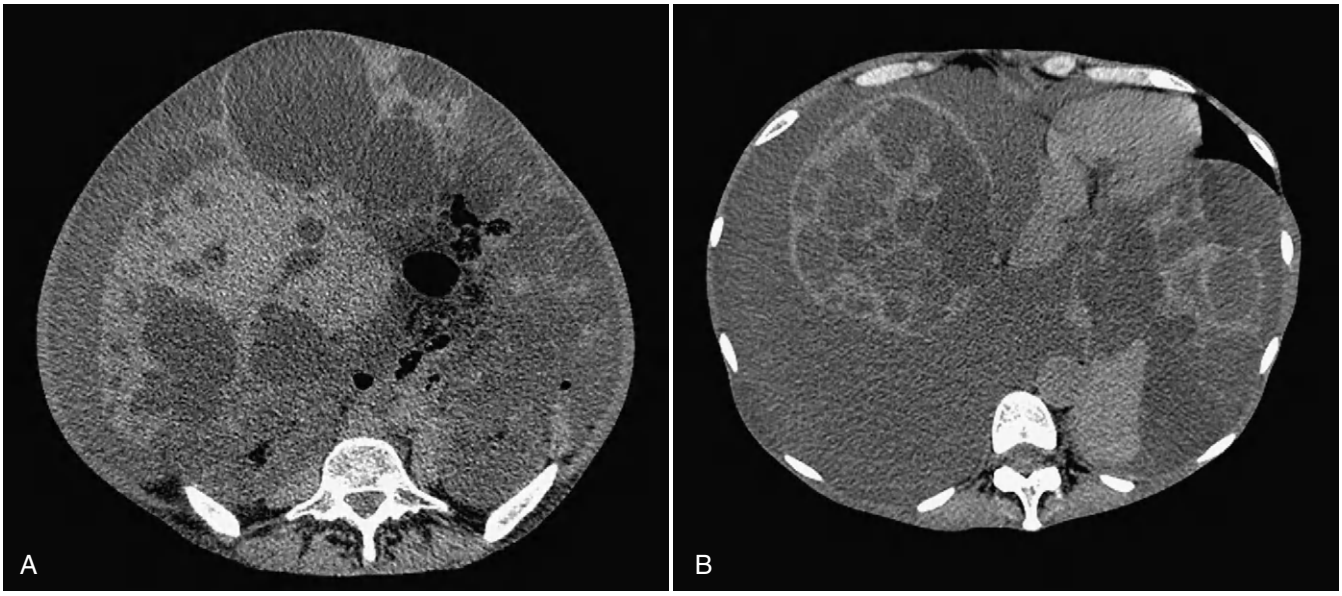


FIGURE 69A.9. Two examples of polycystic liver disease associated with poor nutrition; note that muscles of the abdominal wall are very thin. **A,** Ascites. **B,** Pleural effusion.

Natural History

In patients with ADPKD, the number and size of liver cysts are greater in women than in men, and they increase with patient age and correlate with the size of the kidney (Bae et al, 2006) and the severity of kidney dysfunction. Pregnancy, multiparity, and use of female steroid hormones further increase the risk of severe hepatic cystic disease (Sherstha et al, 1997). The natural course is highly variable from one individual to the other or within members of the same family, but the progression is fairly linear for a given patient. Hence, age at the time of diagnosis, first symptoms, incapacitating symptoms, and kidney involvement are useful markers to predict the future need for transplantation (see Chapter 69B). As the lifespan of patients with ADPKD has lengthened with dialysis and transplantation, liver-related symptoms have become more frequent.

In patients with isolated PCLD, liver involvement also correlates with female gender and number of pregnancies (Qian et al, 2003; Van Keimpema et al, 2010). Apart from kidney

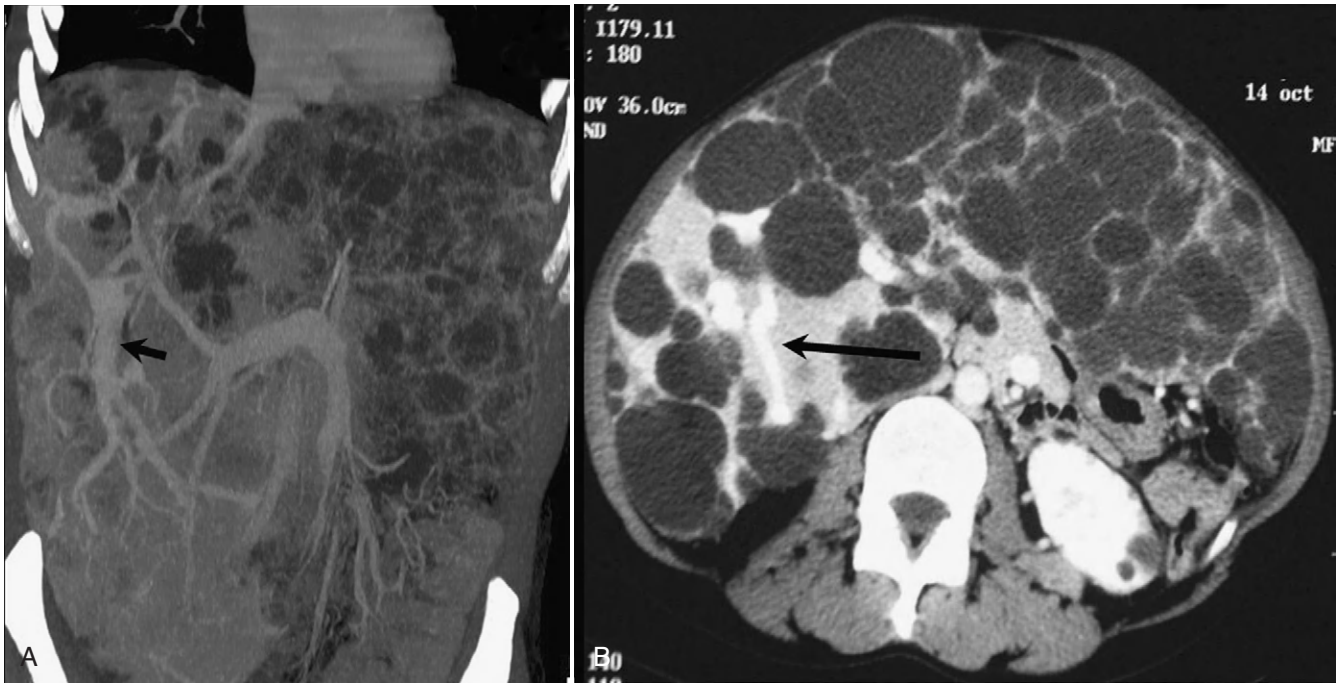


FIGURE 69A.10. A, Polycystic liver disease resulting in compression of hepatic veins (*arrow*). **B,** A collateral circulation between the right and middle hepatic vein is visible (*arrow*).

symptoms, which are absent, the course is the same as that of PCLD associated with ADPKD (Hoevenaren et al, 2008).

Complications

Within Cysts

Bacterial infection is the most severe complication and, although very rare, can be severe enough to be life threatening (Robson & Fenster, 1964; Telenti et al, 1990). Symptoms may include fever, chills, and right upper quadrant pain or less typical symptoms. Cyst infection has mainly been observed in patients with ADPKD under dialysis or in those taking immunosuppressive drugs after renal transplantation (Bourgeois et al, 1983). It is exceptional, if it exists at all, in patients with isolated PCLD (Hoevenaren et al, 2008; Qian et al, 2003; van Keimpema et al, 2010). Differentiating infection within kidney or liver cysts is difficult. The infected cysts can be recognized by US and CT, which show echoic material within the cysts, corresponding to pus (Telenti et al, 1990). Thickened, irregular cyst wall, hyperdense content, and fluid-fluid or air-fluid levels may also be seen. Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose labeled leucocytes or ^{111}In-labeled leukocyte scintigraphy may be used to document and localize infection (Kjaer et al, 2004; Desouza et al, 2009). Treatment of an infected cyst should include aspiration and drainage in addition to antibiotics provided the infection has been documented (Telenti et al, 1990).

Intracystic bleeding is quite common and may occasionally be mistaken for cyst infection. Although it has been claimed that malignant transformation can occur, it is still unclear whether the hepatic cysts predisposes to the development of cholangiocarcinoma; our opinion is that it does not.

Complications from Cyst Compression

Cholestasis secondary to compression of the biliary bifurcation by large cysts (Ergün et al, 1980; Howard et al, 1976) or by peribiliary cysts may occur. In contrast, jaundice is rare and may result from progressive or acute enlargement of cysts, the latter in cases of intracystic bleeding. Mild dilation of the common bile duct is also not unusual (Ishikawa et al, 1996). As a result of portal or hepatic vein compression, portal hypertension with ascites and variceal bleeding have been described (McGarrity et al, 1986; Ratcliffe et al, 1984; Sato et al, 2002). Severe forms may also occur in the few patients with ADPKD who have associated congenital hepatic fibrosis or in patients with autosomal recessive PKD, in which liver cysts are rare.

Compression of adjacent organs by the enlarged liver is responsible for most symptoms, as previously discussed; less common is the compression of the right atrium, which may result in hypotentive episodes (Lasic et al, 2004), or the inferior vena cava. The parenchymal impact of hepatic or portal vein compression is frequent. In our experience with liver resection or transplantation, this is present in more than 75% of the patients and includes centrolobular fibrosis, sinusoidal congestion, peliosis, and nodular regenerative hyperplasia (Fig. 69A.11).

Complications from Associated Conditions

ADPKD is well known for other extrarenal manifestations other than those of the liver. These include, most notably, intracranial aneurysms, but dolichoectasias, thoracic aortic and cervicocephalic artery dissections, and coronary artery aneurysms are also possible. These vascular diseases have directly been linked to *PKD1* or *PKD2* mutations in experimental models (Bichet et al, 2006).

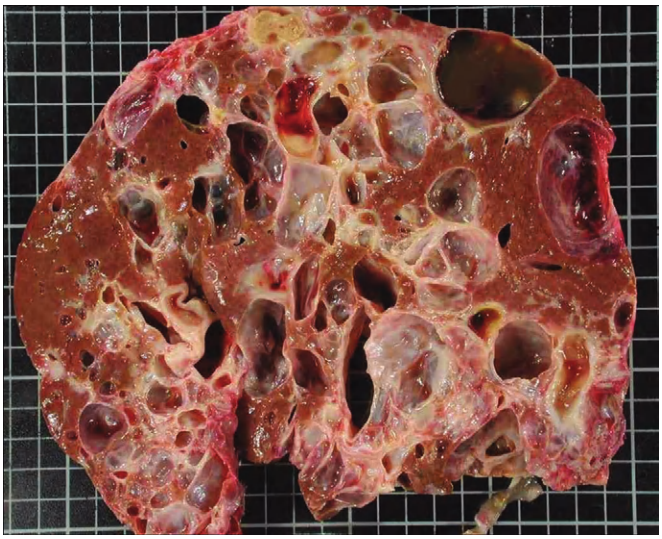


FIGURE 69A.11. Macroscopic view of a resected specimen of polycystic liver disease. Microscopic injuries are frequent because of compression by cysts or inflow/outflow obstructions.

The incidence of cerebral aneurysms is 8%, three to four times higher than in the general population (Pirson et al, 2002). It has been linked to a mutation in the 5′ region of *PKD1*, rather than the 3′ region; therefore the main risk factor is a family history of intracerebral aneurysms or subarachnoid hemorrhage (SAH) (Rossetti et al, 2003). In this context, the incidence is 16%. Most of these aneurysms are small (<6 mm in diameter) and do not seem to be at increased risk of growth or rupture compared with those of the general population (Gibbs et al, 2004). Widespread screening is not indicated and should be restricted to individuals with a family history of aneurysm or SAH, previous aneurysm rupture, preparation for major elective surgery, high-risk occupations (such as airline pilots), and patient anxiety despite adequate information (Pirson et al, 2002). The ideal method of detection is MRI.

Mitral valve prolapse and pericardial effusion are frequently also found in 25% and 35% of patients with ADPKD, respectively. These are generally well tolerated and do not require therapeutic intervention (Lumiaho et al, 2001; Qian et al, 2007). Cerebral aneurysms and mitral valve abnormalities have been reported with the same or a slightly lower incidence in patients with isolated PCLD (Hoevenaren et al, 2008; Qian, et al 2003).

Staging

Several systems have been proposed to grade the severity of PCLD, and the rationale behind their design is different.

Gigot's Classification

Gigot's classification relies on CT imaging and was designed to identify the indications and limits of fenestration in the treatment of PCLD (Gigot et al, 1997): *type I* shows a limited number (<10) of large cysts (>10 cm); *type II* shows diffuse involvement of liver parenchyma by multiple medium-sized cysts with remaining large areas of noncystic liver parenchyma on preoperative CT; *type III* shows massive, diffuse involvement

of liver parenchyma by small and medium-sized liver cysts and only a few areas of normal liver parenchyma between cysts. The drawback of this classification is that some patients may seem to have either one or the other type depending on the CT slice because the distribution of cysts is uneven.

Qian's Classification

Qian's classification has been used in the context of familial screening and relies on cyst number and the presence of symptomatic hepatomegaly (Qian et al, 2003): *grade 0* refers to 0 cysts; *grade 1*, 1 to 10 cysts; *grade 2*, 11 to 20 cysts; *grade 3*, more than 20 cysts; and *grade 4*, more than 20 cysts and symptomatic hepatomegaly.

Schnelldorfer's Classification

Schnelldorfer's classification aims at differentiating patients who could benefit from resection or transplantation. It is more complex but also more reliable (Schnelldorfer et al, 2009). It takes into account the presence of symptoms (absent, mild, or severe), the number and size of the cysts, the presence of relative normal areas of liver parenchyma (≥2 sectors, ≥1 sector, or <1 sector), and whether an isosectoral portal or hepatic vein occlusion of the preserved sector is present.

DIFFERENTIATION BETWEEN SIMPLE CYSTS, ISOLATED PCLD, AND PCLD ASSOCIATED WITH ADPKD

The distinction between isolated PCLD and PCLD associated with ADPKD relies on the number of kidney cysts and familial history. In adults with a positive family history, the diagnosis of ADPKD is established by radiologic evidence of at least two unilateral or bilateral cysts in patients younger than 30 years, at least two cysts in each kidney in those 30 to 59 years, and at least four cysts in each kidney in those 60 years or older (Ravine et al, 1994). Of note, one third of patients with isolated PCLD may have a few kidney cysts, but most usually have one or two (van Keimpema et al, 2010), as does the general population of adult patients (Carrim & Murchinson 2003). In the absence of a family history, the diagnosis of ADPKD is retained if more than five kidney cysts in either one or both kidneys are visible on CT.

Unlike ADPKD, no clinical guidelines have established what distinguishes PCLD from simple cysts that are frequently multiple. Some surgical series have used a threshold of five or six cysts, whereas others have required involvement of more than 50% of the parenchyma. These differences should be taken into account when analyzing the results of these series. More recently, in the case of family screenings, it has been proposed that sporadic cases of PCLD be defined by the presence of more than 15 to 20 cysts, but when there is a positive familial history the presence of four cysts is sufficient (Hoevenaren et al, 2008; Qian et al, 2003). Genetic testing is neither required nor useful in clinical practice for either form of PCLD because not all mutations have been identified.

DIFFERENTIAL DIAGNOSIS

Single Cysts

Hydatid cysts, liver abscesses, cystadenoma, and *cystadenocarcinoma* are the main differential diagnoses, especially when simple cysts have become atypical. These entities are addressed separately in Chapters 68, 66, 67, and 79B, respectively.

Embryonal sarcomas (see Chapter 82) are mostly observed in children between the ages of 2 and 15 years and are exceptional in adults. The tumor is usually large and poorly differentiated with abundant myxoid or necrotic content. Although the tumor may appear as cystic on CT scan and MRI because of the very high water content of the myxoid stroma, US shows that it is, in fact, solid. Late-phase contrast imaging on CT and MRI shows late enhancement, which is incompatible with a cystic tumor.

Other Primary Tumors

Hepatocellular carcinoma and *cholangiocarcinoma* may occasionally be cystic (see Chapters 50 and 80). This cystic appearance corresponds to necrosis that may be either spontaneous, particularly for rapidly growing tumors, or treatment induced. However, with few exceptions, these tumors remain mostly solid. *Giant hemangiomas* may occasionally present as partly cystic; this corresponds to noncirculating areas. Hemangiomas are hypointense on T1-weighted MRI images and hyperintense on T2-weighted images, the same as any cystic lesion, but the kinetics of contrast enhancement is typical (see Chapters 17 and 79A).

In the context of acute pancreatitis or pancreatic duct rupture, *intrahepatic pseudocysts* are exceptional, with fewer than 20 reported cases (Balzan et al, 2005). They may be located in the left liver along the lesser omentum, or in the right liver along the right portal vein. They have a subcapsular location, hemorrhagic or necrotic content, and a fibrous wall that enhances at the late phase of the injection. Pancreatic MRI is occasionally useful to document rupture of the pancreatic duct (see Chapter 54).

Liver hematomas are rarely spontaneous and usually appear in the context of trauma or liver surgery. They have also been described in association with hepatocellular carcinoma, liver adenoma, or, very rarely, metastases. When occurring at the end of a pregnancy, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count) should be suspected. Clinical symptoms are usually obvious, with pain and associated symptoms from intraabdominal hemorrhage if capsular rupture has occurred. When the clots are fresh, these hematomas are spontaneously echogenic on US, hyperdense on CT scan, hyperintense on T1-weighted MRI sequences, and hypointense on T2-weighted MRI sequences. At a later phase, clots liquefy and the content appears cystic (see Chapter 17).

Bilomas are cystic lesions that contain bile as a result of spontaneous, traumatic, or iatrogenic bile duct rupture; such lesions are surrounded by a fibrous capsule. Biliary anomalies—such as dilation, stenosis, or a combination of these—are frequent.

Ciliated Hepatic Foregut Cysts

Ciliated hepatic foregut cysts have been described in all areas where the foregut extends during the embryonic period, including the sublingual area, esophagus, stomach, ileum, pancreas, and gallbladder. They also may be present within the liver.

Although extremely rare, ciliated hepatic cysts warrant special consideration. Such cysts are located within the liver parenchyma and have a characteristic four-layer border that consists of a pseudostratified, ciliated columnar epithelium covering a subepithelial connective tissue, smooth muscle bundles, and an outer fibrous capsule. The lining epithelium may secrete fluids of different composition, from watery to viscous or mucous, which explains why its echogenicity may be variable

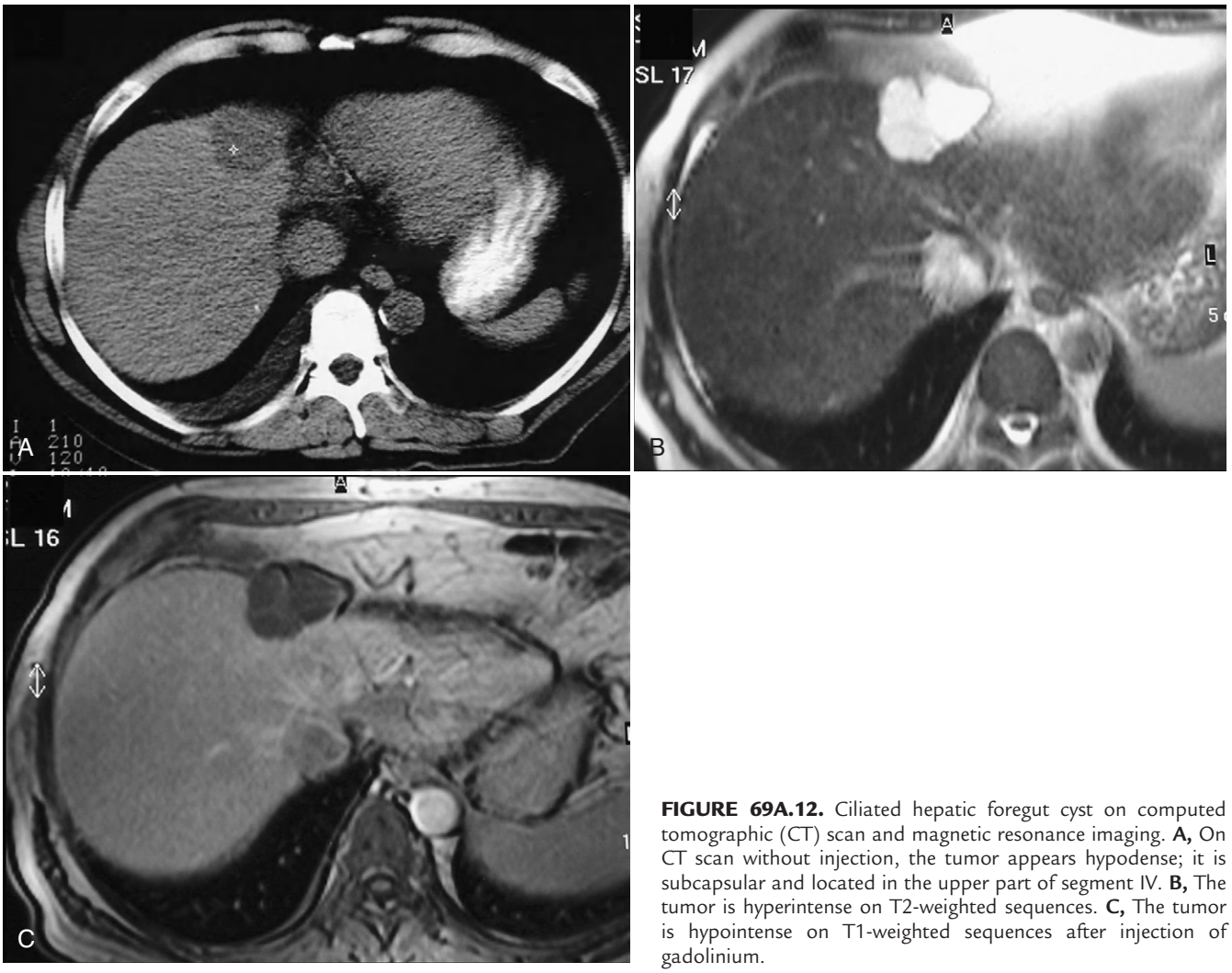


FIGURE 69A.12. Ciliated hepatic foregut cyst on computed tomographic (CT) scan and magnetic resonance imaging. **A,** On CT scan without injection, the tumor appears hypodense; it is subcapsular and located in the upper part of segment IV. **B,** The tumor is hyperintense on T2-weighted sequences. **C,** The tumor is hypointense on T1-weighted sequences after injection of gadolinium.

and why calcifications may be present, although this is exceptional. The second characteristic of these cysts is that they are subcapsular, usually located on the anterior surface of the liver close to the insertion of the falciform ligament. Two thirds are localized in the left lobe of the liver in segment IV, but right lobe cysts also have been described (Takahiro et al, 2003). The final characteristic of these cysts is that they are classically unilocular and usually less than 4 cm in diameter. Typically these cysts do not communicate with the biliary system, although this has been reported, particularly in children.

PREVALENCE AND ETIOLOGY. Although recognized since 1857, ciliated hepatic cysts are exceptional, with approximately 100 cases reported in the literature, most in the past 20 years (Sharma et al, 2008). There is no gender predominance, and patient age ranges from newborn with prenatal diagnosis (Guérin et al, 2010) to 82 years, with a mean age of 48 years.

MANIFESTATION AND DIAGNOSIS. Most ciliated hepatic foregut cysts, two thirds of reported patients, are asymptomatic and discovered incidentally during abdominal imaging studies or surgical explorations. Abdominal symptoms are rare, probably because of the small cyst size. When symptoms are present, the most frequent symptom is epigastric or right upper quadrant pain that can be observed even with small tumors because of their subcapsular location.

Three characteristics that appear on imaging are 1) their predominant location in segment IV, 2) their small size (4 ± 2 cm), and 3) their subcapsular location. Most (>90%) are unilocular. Two thirds of the cysts are hypoechoic on US, hypodense on CT, and do not enhance after injection of contrast material (Fig. 69A.12). They are anechoic as formal biliary cysts in less than 5% (Horii et al, 2003). Some ciliated cysts may also have an atypical, solid tumor appearance on CT and a noncystic appearance on US (hyperechoic), probably as a result of mucinous material, calcium, and cholesterol crystals within the cyst. On MRI the lesion is highly hyperintense on T2-weighted images but highly variable on T1 sequences; they are hyperintense in 52%, isointense in 24%, and hypointense in 14%. When atypical on imaging, the differential diagnosis includes cystadenoma or cystadenocarcinoma and may be difficult, especially because carbohydrate antigen (CA) 19-9 may be expressed by the epithelium of the ciliated cysts, and its serum level may be slightly elevated (Wu et al, 1998). Fine needle aspiration cytology may help by showing ciliated, pseudostratified, tall columnar epithelial cells suspended in a

mucous background. The presence of these cells is virtually diagnostic of this condition, and the positive predictive value of aspiration is 76% (Sharma et al, 2008).

COURSE, COMPLICATIONS, AND TREATMENT. Ciliated hepatic foregut cysts are usually believed to follow a benign course. Compression of adjacent structures is extremely rare, with a single case report of portal compression resulting in portal hypertension (Harty et al, 1998) and another case report of jaundice (Vick et al, 1999). Malignant transformation into squamous cell carcinoma has been reported in four patients in recent years (de Lajarte-Thirouard et al, 2002; Furlanetto & Dei Tos, 2002; Vick et al, 1999; Zhang et al, 2009), and one other patient had extensive squamous metaplasia (Ben Mena et al, 2006), yielding a risk of malignancy of less than 5%. Because this transformation has occurred in patients with cysts larger than 7 cm, most authors agree that excision is indicated when the cyst is larger than 4 to 5 cm, shows abnormalities in its wall, enlarges, or is symptomatic, although other authors recommend broader indications.

Multiple Cysts

Biliary hamartomas, also known as *von Meyenburg complexes*, also correspond to an anomalous arrangement of the ductal plate; long recognized by pathologists and surgeons, they are a frequent finding during liver surgery (see Chapters 47 and 48). Biliary hamartomas may be observed within an otherwise normal liver (6% of the population) but may also be associated with Caroli disease (see Chapter 46) and congenital hepatic fibrosis; in PCLD, they are particularly prevalent—virtually constant. Identification of biliary hamartomas is important because they may be mistaken for liver metastases. These lesions are asymptomatic and are discovered incidentally. They range in size between 2 and 10 mm and may appear on US as hypoechogenic, hyperechogenic, or heterogenous depending on their size, associated biliary dilation, and fibrous stroma (Zheng et al, 2005). They are hypodense on CT and do not enhance; on MRI, they are very hypointense on T1-weighted images, very hyperintense on T2-weighted images, and are best seen on cholangio-MRI sequences (Fig. 69A.13; see Chapters 16 and 17).

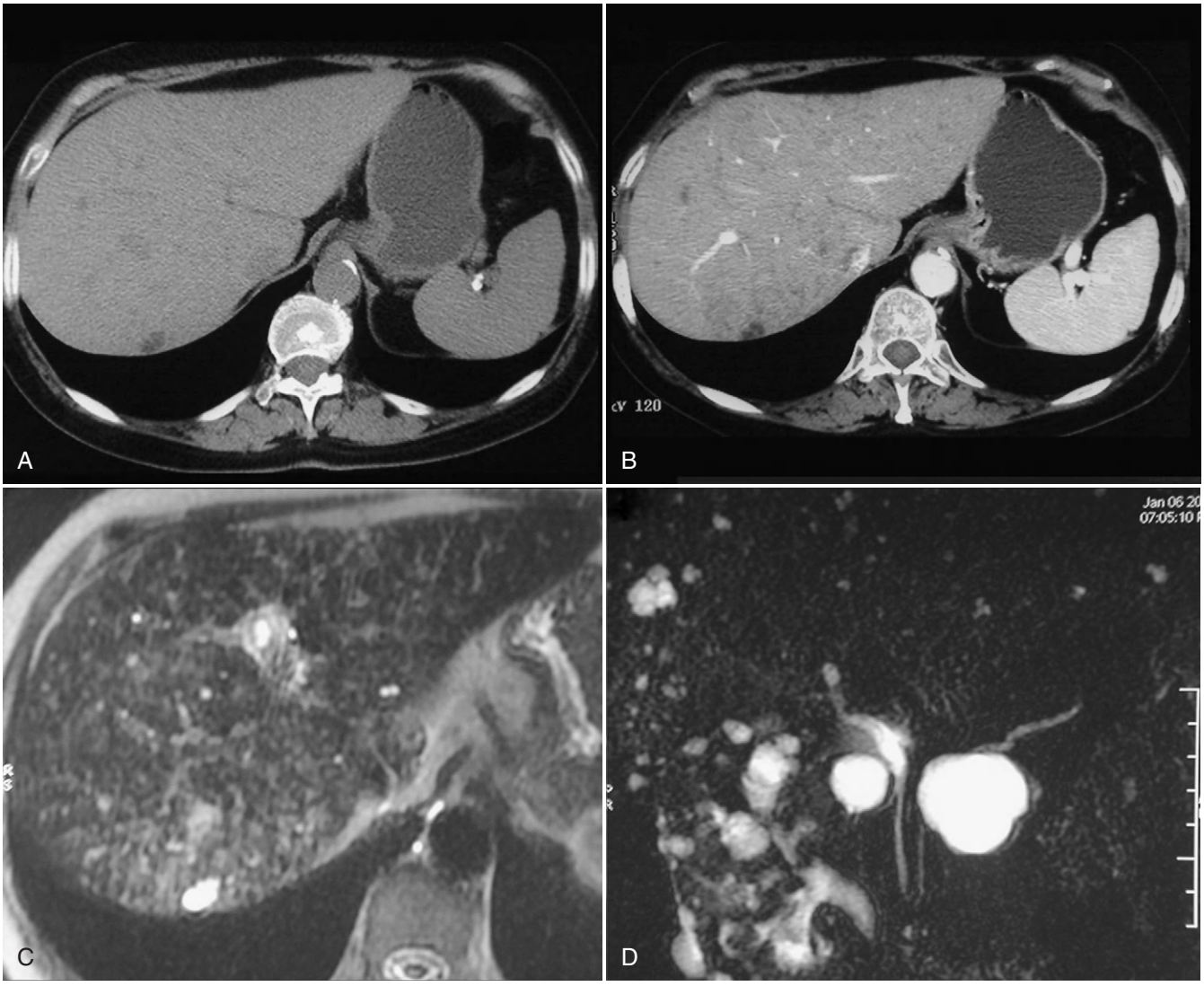


FIGURE 69A.13. Biliary hamartoma. **A,** On computed tomographic scan, hypodense lesions are visible. **B,** They do not enhance after injection but become more visible. They are better seen on T2-weighted images (**C**) and on cholangiographic magnetic resonance imaging sequences (**D**).

Peribiliary cysts arise from cystic enlargement of peribiliary glands located in and around the walls of extrahepatic and large intrahepatic bile ducts. These cysts may have a diameter up to 2 cm and are mainly observed in the context of severe chronic liver disease, including cirrhosis with portal hypertension or PCLD and after liver transplantation. They are usually asymptomatic, but obstructive jaundice has been reported. When known, imaging features are easily recognized. At US, the cysts are located along the main bile ducts or within portal tracts beside portal veins. At cholangio-MRI, they may mimic an enlarged bile duct, but smaller biliary branches upstream are not dilated. Increases in size and diameter are possible but rare (Motoo et al, 2001).

Cystic Metastases

Cystic metastases are solid tumors, and the cystic form is rare. The cystic component may be partial or total, and cystic metastases frequently arise from neuroendocrine, sarcomas or melanomas, or occasionally from bronchial or breast primary tumors. They can also result from ovarian or pancreatic cystadenocarcinomas. Finally, although very rare, metastases from anal carcinoma are frequently cystic. If the primary is unknown, the presence of peripheral hypervascularization and multiplicity of the lesions should raise the suspicion of this diagnosis. MRI diffusion sequences may also be helpful.

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CHAPTER 70A

Cirrhosis and portal hypertension: pathologic aspects

Rish K. Pai and Elizabeth M. Brunt

OVERVIEW

Cirrhosis is the final stage of a variety of chronic diseases involving the liver. Histopathologically, cirrhosis is characterized by remodeling of the vascular architecture with septal formation and nodular groups of regenerating hepatocytes. Biochemically, the cirrhotic liver functions less efficiently than the normal liver. Decompensated cirrhosis manifests as portal hypertension and liver failure, both of which are associated with numerous clinically important complications (see Chapters 70 through 77). In addition, regardless of the underlying etiology, cirrhosis is a major predisposing condition to the development of hepatocellular carcinoma (HCC) (Suriawinata & Xu, 2004). Portal hypertension secondary to cirrhosis develops as a result of the alterations of the hepatic microcirculatory system. Portal hypertension may also occur in the absence of the structural alterations of cirrhosis (noncirrhotic portal hypertension). The conditions associated with this may be idiopathic; all are subdivided into *prehepatic, intrahepatic,* or *posthepatic*. This chapter focuses on the pathology of cirrhosis and noncirrhotic portal hypertension and many of the conditions that result in portal hypertension.

CIRRHOSIS

The true prevalence of cirrhosis in the United States is unknown because many patients with compensated cirrhosis do not exhibit symptoms or signs of liver failure, but cirrhosis is among the top 10 causes of death in the Western world. In autopsy series, cirrhosis is documented in 5% to 10% of cases, but autopsy subjects may not be representative of the general population (Karsan et al, 2004). Currently, the only available and definitive treatment for established cirrhosis is liver transplantation.

Pathogenesis and Reversibility

The transformation from normal hepatic architecture to cirrhosis ultimately results from progressive deposition of fibrous tissue in regions of "extinct" parenchyma and vascular remodeling, regardless of the underlying etiology. Fibrogenesis is dynamic, and it is triggered by liver injury and mediated by a complex interplay of cellular necrosis, inflammation, apoptosis, and various cytokines. The cells that contribute to the development of hepatic fibrosis are the activated hepatic stellate cells and portal myofibroblasts. Once activated, these cell types are primed to respond to a wide variety of chemokines and cytokines (Friedman, 2008). In particular, transforming growth factor (TGF)-α seems to be a major fibrogenic mediator that induces these cells to produce collagens and other types of extracellular matrix and degradatory products (Canbay et al, 2004; Friedman, 2008; Pinzani & Marra, 2001; Ramadori & Saile, 2004). Recent work has shown the fibrogenic nature of leptin, the anorectic hormone produced in adipose tissue (LeClercq et al, 2002). During pathologic fibrogenesis, prevention of matrix degradation by metalloproteinases is orchestrated by the release of potent tissue metalloproteinase inhibitors; apoptosis of fibrogenic hepatic stellate cells also is inhibited. Scar formation ultimately is the consequence of the imbalance of collagen synthesis, deposition, and degradation. Another increasingly recognized pathway of fibrogenesis in the liver is that of epithelial-mesenchymal transformation (EMT), in which "injury" results in a cascade of cytokines that lead to epithelial cells developing and expressing mesenchymal markers (Rygiel et al, 2008); the exact role EMT plays in fibrogenesis is being studied.

Established cirrhosis has traditionally been considered irreversible. Accumulating clinical and experimental evidence

suggests, however, that reversal or regression of liver fibrosis and cirrhosis may be possible (Fallowfield & Iredale, 2004). A study by Poynard and colleagues (2002) analyzed 3010 patients with chronic hepatitis C virus (HCV) included in four major clinical trials to receive randomized treatment regimens with interferon or pegylated interferon, with or without additional ribavirin. Reversal of cirrhosis was reported in 75 (49%) of 153 patients with baseline cirrhosis. Pol and associates (2004) examined 64 immunocompetent patients with HCV-related cirrhosis and found that cirrhosis disappeared in five patients (7.8%) on follow-up biopsies at a mean interval of 4.6 years. In addition, three of four patients undergoing dialysis showed reversal of cirrhosis secondary to HCV infection, and resolution of cirrhosis was shown in two patients upon examination of the whole liver explants at the time of transplantation.

More recently, Falize and colleagues (2006) analyzed 36 patients with hereditary hemochromatosis and demonstrated that regression of fibrosis was seen in 69% of those with bridging fibrosis and in 35% of patients with cirrhosis after institution of venosection therapy. Regression of cirrhosis has also been reported in patients with other diseases, such as hepatitis B virus (HBV), alcoholism, autoimmune hepatitis, and primary biliary cirrhosis (Arthur, 2002; Fallowfield & Iredale, 2004; Serpaggi, et al, 2006; Wanless et al, 2000). Spontaneous resolution of fibrosis also has been described in rats treated with carbon tetrachloride (Iredale et al, 1998; Issa et al, 2004). The proposed mechanisms for breakdown and remodeling of liver fibrosis include loss of activated stellate cells via apoptosis, decreased expression of metalloproteinase inhibitors, and increased production and activity of metalloproteinases or collagenases (Arthur, 2002; Benyon & Arthur, 2001; Fallowfield & Iredale, 2004; Gieling, et al, 2008). It is unclear, however, how these molecular and cellular events are initiated and regulated.

Currently, the extent to which cirrhosis is truly reversible is the subject of debate (Arthur, 2002; Chedid, 2000; Desmet & Roskams, 2003; Geller, 2000; Ray, 2000). Many important questions remain to be answered. Even if scar tissue is resorbed, can normal hepatic architecture be completely restored? Were there sampling differences or interpretation errors on biopsies in the studies showing reversibility? It is possibile that some of the reversed cases might have undergone a conversion of micronodular to macronodular cirrhosis, as shown in animal models (Issa et al, 2004), a condition that made the diagnosis of cirrhosis more difficult on a needle core biopsy sample (Desmet & Roskams, 2003)? Regardless, this discussion may have important clinical implications. Many liver diseases progress insidiously, and patients may seek medical attention only at the advanced stage, when treatment choices are limited. If cirrhosis is truly reversible, many patients with advanced liver disease still may benefit from medical treatment for specific etiologies, particularly with the discovery of new drug therapies.

Role of Liver Biopsy

In modern medicine, investigation of patients with chronic liver disease and cirrhosis involves multiple disciplines that include pathology, radiology, chemistry, biochemistry, virology, serology, and molecular biology. Liver biopsy evaluation remains the primary diagnostic tool, despite the drawback of invasiveness (Rockey et al, 2009). Noninvasive screening methods show promise in excluding patients with advanced fibrosis; however, in a recent study evaluating one of these tests, the positive predictive value for advanced fibrosis was still quite low, and the test fared poorly at distinguishing between intermediate stages of fibrosis (Zaman et al, 2007). For cirrhotic patients, liver biopsy can serve several important purposes, such as establishing or confirming diagnoses; assessing the possible underlying causes of disease; analyzing the grade of ongoing necroinflammatory activity; detecting dysplastic lesions or an occult HCC; and providing tissue for chemical, biochemical, molecular, or ultrastructural studies (Brunt, 2000a).

Two broad types of biopsy are used to sample liver tissue: *needle biopsy* and *wedge biopsy*. Needle biopsy has proved to be the most useful technique to obtain representative liver tissue for analysis. This procedure can be done percutaneously, transjugularly, or during open surgery or laparoscopy; a cutting needle or the Menghini aspiration needle may be used, although the former generates a better biopsy specimen. If cirrhosis is suspected clinically, a cutting needle is the preferred method of biopsy because an aspiration needle often provides a fragmented specimen that makes histologic evaluation difficult. The size of the needle biopsy specimen is important in avoiding sampling error. Traditionally, it has been recommended that an adequate biopsy specimen should be no smaller than 20 gauge and at least 1.5 cm in length, or it should contain at least five portal tracts (Afdhal & Nunes, 2004; Rockey et al, 2009). It has been suggested more recently, however, that for accurate and reliable grading and staging of chronic viral hepatitis, a biopsy specimen of 2 cm in length or longer that contains at least 11 complete portal tracts is needed (Guido & Rugge, 2004).

Usually performed during open surgery or laparoscopy, wedge biopsy is discouraged for evaluation of diffuse parenchymal liver diseases because this technique samples primarily the subcapsular liver parenchyma, which may contain misleading fibrous septa extending from the capsule that could be easily confused with cirrhosis or bridging fibrosis (Fig. 70A.1). The same issue can also occur in a subcapsular needle biopsy. In addition, nonspecific necroinflammatory change can occur quickly in the subcapsular region during surgical procedures, which may further confuse histology. A wedge biopsy is more suitable for focal lesions present on or immediately below the

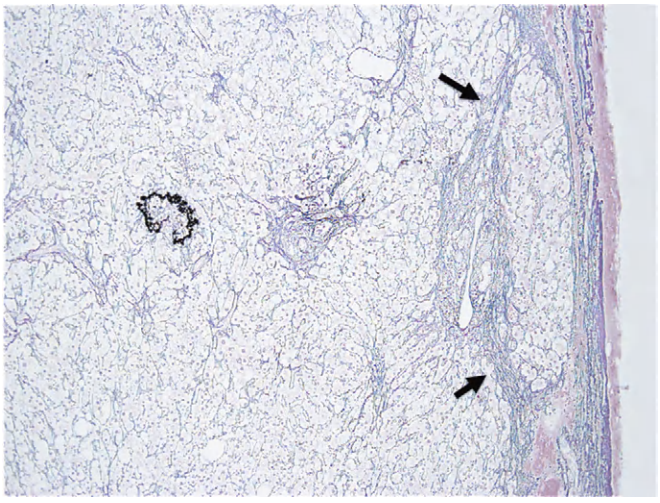


FIGURE 70A.1. Wedge biopsy showing overestimation of fibrosis just beneath the liver capsule (Gomori reticulin stain). *Arrows* indicate fibrous septa extending into the hepatic parenchyma.

capsule. Even during open surgery, a needle biopsy to sample deep liver parenchyma is preferred (Guido & Rugge, 2004).

Prompt fixation of the liver biopsy specimen in buffered formalin is vital to high-quality histology. Many special stains and analyses, such as iron or copper quantitation, can be performed on formalin-fixed, paraffin-embedded (FFPE) tissue. If a metabolic disorder is suspected, and electron microscopic examination is expected, additional tissue should be fixed in glutaraldehyde. If fresh tissue is submitted for molecular analyses, it should never be dry or immersed in saline; the appropriate fixation method is to place the tissue on a piece of saline-moistened gauze in a container. Consultation with a pathologist before the biopsy procedure is encouraged to help avoid inappropriate tissue handling.

Histopathologic interpretation of liver biopsy specimens can be challenging. The importance of communication among surgeons, hepatologists, and pathologists cannot be overemphasized. Clinicians should provide sufficient clinical information when submitting a liver biopsy specimen for pathologists to analyze histologic findings in the appropriate clinical setting.

Morphology

Grossly, the liver with established cirrhosis exhibits a nodular appearance that diffusely involves the entire liver (Fig. 70A.2). Microscopically, the liver parenchyma is divided by variable-sized fibrovascular septa, which contain profiles of ductular structures and diverse inflammatory cell types, into nodules that typically no longer retain a terminal hepatic venule or identifiable portal tracts. The normal portal-central relationship is completely effaced; the exception to this is biliary cirrhosis, in which the terminal hepatic venule may retain its central location. The hepatocytes within the nodules may appear morphologically normal, or they may show evidence of regeneration. The latter may be characterized by thickened cell plates with up to two cells across; anisonucleosis; large cell change with maintenance of nuclear/cytoplasmic (N/C) ratio; or small, crowded cells with markedly increased N/C ratios. The reticulin stain is useful to show cord thickening. The increased ductular profiles (ductular proliferation) are referred to as a *ductular reaction* (Roskams et al, 2004). Some cases may retain lymphoid aggregates in the septa, and some may have interface hepatitis.

According to the size of the nodules, cirrhosis has been classified as *micronodular* if nearly all the nodules are less than 0.3 cm in diameter, or *macronodular* if nodules are greater than 0.3 cm. Mixed micronodular and macronodular cirrhosis is defined by the presence of relatively equal numbers of small and large nodules. Although this morphologic classification may provide clues to the underlying etiology in some cases, it is not recommended for clinical practice because micronodular cirrhosis may progress to a macronodular pattern over time. Mixed micronodular and macronodular cirrhosis is common in end-stage liver disease regardless of the underlying etiology.

Biliary cirrhosis is caused by disorders such as primary biliary cirrhosis, primary or secondary sclerosing cholangitis, and biliary atresia. This type of cirrhosis exhibits unique morphologic features characterized by a highly irregular "jigsaw puzzle" or "geographic" nodular pattern (Fig. 70A.3). As noted, the terminal hepatic venule may be retained, and loss or effacement of native bile ducts by either lymphoid aggregates or scar tissue may be evident. Ductular reaction (proliferation) may be more pronounced than that seen in other types of cirrhosis. A characteristic clue to biliary cirrhosis is the constellation of findings in periseptal hepatocytes referred to as *cholate stasis*. These findings include periseptal hepatocyte ballooning, Mallory-Denk bodies (Mallory's hyaline), and copper deposition. In addition, foamy cell aggregates may be seen in the nodules. Some investigators have attributed large cell change to chronic cholestasis. Another subtle histologic clue to biliary cirrhosis is the presence of nodular regenerative hyperplasia in the regenerative nodules.

Recognition of cirrhosis is usually straightforward when an adequate biopsy specimen is examined, even on hematoxylin and eosin–stained sections. It may be helpful to use Masson trichrome stain to highlight the dense perisinusoidal fibrosis of alcoholic hepatitis and cirrhosis, particularly for fragmented needle biopsy specimens (Fig. 70A.4). Fragmentation of the specimen noted at the time of biopsy should raise the suspicion of cirrhosis. On histologic sections, a thin layer of collagen, better appreciated on trichrome and reticulin stains, tends to adhere to the surface of detached nodules. Cirrhosis also may be difficult to diagnose on needle biopsy specimens, when a

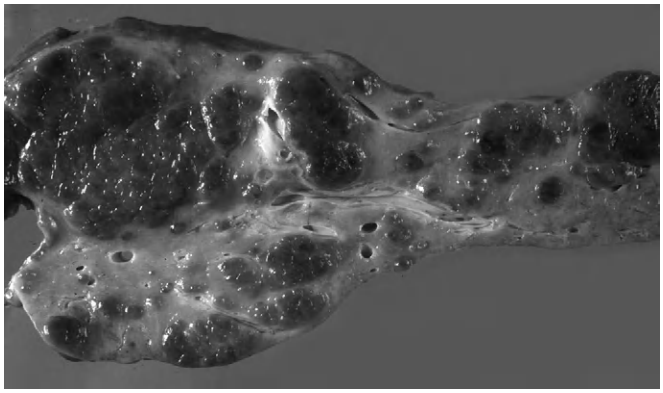


FIGURE 70A.2. Gross appearance of cirrhosis showing diffuse involvement of the entire liver by regenerative nodules and broad fibrous bands.

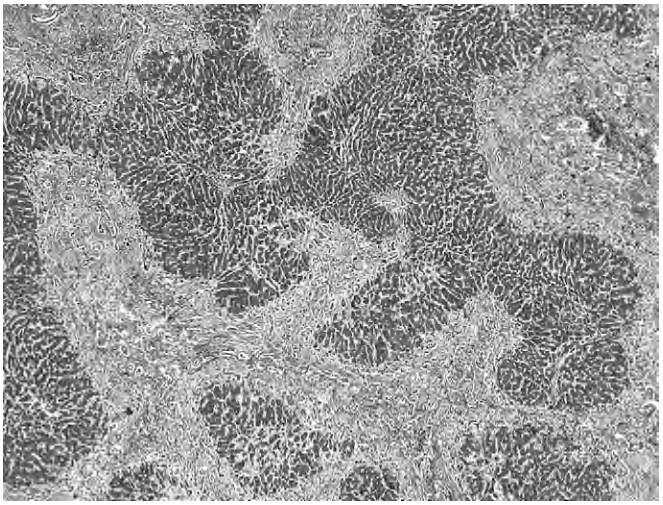


FIGURE 70A.3. Biliary cirrhosis exhibiting a "jigsaw puzzle" pattern (Masson trichrome stain).



FIGURE 70A.4. Cirrhosis visible on a needle biopsy specimen (Masson trichrome stain).

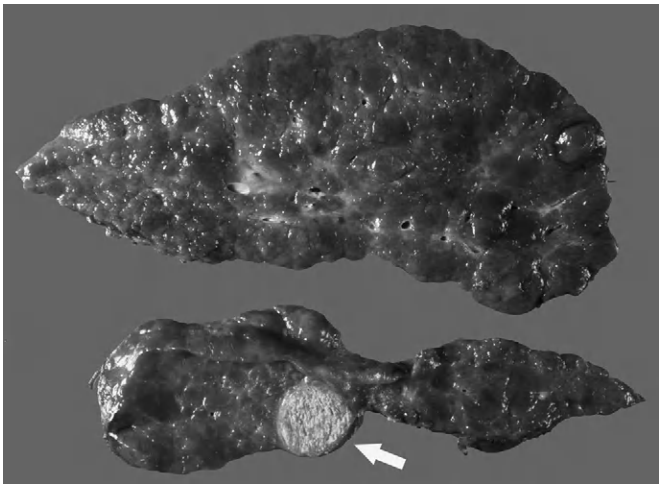


FIGURE 70A.5. Hepatocellular carcinoma (*arrow*) in a cirrhotic liver.

macronodule is sampled, or when cirrhosis is incomplete (incomplete septal cirrhosis). In the last case, the complete spectrum of morphologic features of cirrhosis are not exhibited but vascular relationships are markedly altered, and ectatic, eccentrically located portal veins may be noted. In addition, the septa are thin, and some may be seen to extend into the parenchyma and end blindly. This type of "cirrhosis" is not uncommon in HBV-related liver disease.

Additional stains considered routine by liver pathologists in evaluation of liver biopsies include the iron stain and periodic acid-Schiff stain after diastase digestion (PAS-d). The former is useful in detecting small amounts of hepatocellular or reticuloendothelial iron and highlighting intracanalicular bile plugs, and the latter is useful in detecting PAS-d "globules" characteristic of α_1-antitrypsin deficiency. PAS-d also is quite helpful in noting bile duct basement membranes, perisinusoidal basement membranes, and the PAS-d–laden Kupffer cells and septal macrophages characteristic of recent necroinflammatory activity.

Cancer Risk

The most common cancer that arises in cirrhotic livers is HCC (Fig. 70A.5; see Chapter 80), although cholangiocarcinoma is being increasingly recognized in cirrhosis (see Chapter 50A; Shaib, et al, 2007). Although these cancers may occur in cirrhosis of any etiology, particular risks include HBV and HCV infection, alcoholic liver disease (ALD), and hemochromatosis. Grossly, HCC may be multifocal, or it may grow as a well-circumscribed mass; it may show evidence of necrosis, or it may possess a different color and texture from background cirrhotic nodules. It also may bulge from the cut surface on sectioning. Most cases of HCC arising in cirrhotic livers are found in nodules larger than 1 cm (Bruix et al, 2001). Studies have shown, however, that nodules smaller than 1 cm can be malignant in the setting of cirrhosis (Caturelli et al, 2004). Premalignant lesions, or dysplastic nodules, may be indistinguishable from HCC by gross examination.

Cholangiocarcinoma (CCa) in cirrhosis may or may not be distinguishable grossly from HCC. The diagnosis rests with the microscopic appearance of atypical glandular structures, commonly in desmoplastic stroma. CCa also develops in long-standing primary sclerosing cholangitis and is seen more often than HCC in noncirrhotic livers (see Chapter 50A). The tumor may infiltrate the liver diffusely, or it may occur as a mass lesion that may be intrahepatic or extrahepatic. The cirrhotic liver is considered to be resistant to metastases from extrahepatic tumors.

Not all large nodules detected in cirrhotic livers are HCC. A macroregenerative nodule or large regenerative nodule usually measures 0.5 to 1.5 cm and is rarely 5 cm or more in diameter (International Working Party, 1995). It is seen more commonly in macronodular cirrhosis and may be distinct from surrounding cirrhotic nodules on gross examination. Histologically, a macroregenerative nodule may contain portal structures or short fibrovascular septa. The hepatocytes within the nodule are similar to the hepatocytes in smaller cirrhotic nodules but almost always exhibit hyperplastic change, evidenced by thickened plates. The clonal nature of the macroregenerative nodule has been shown, and its malignant potential is an area of ongoing discussion (Bailey & Brunt, 2002).

A dysplastic nodule is a premalignant lesion that usually measures more than 0.5 cm (International Working Party, 1995). Evolution to HCC within months or a few years has been well documented (Hytiroglou, 2004). A high-grade dysplastic nodule exhibits more clear-cut architectural or cytologic atypia, such as bulging or maplike clonal growth; pseudoglandular formation; unpaired arteries; and small cell change characterized by increased cell density, high nuclear/cytoplasmic cell ratio, and nuclear hyperchromasia. These morphologic changes are insufficient, however, for the diagnosis of HCC because a dysplastic nodule does not invade the surrounding stroma or blood vessels and it maintains cell plates no more than three cells wide (Roncalli, 2004).

Distinguishing a high-grade dysplastic nodule from well-differentiated HCC can be extremely difficult or impossible from a needle biopsy specimen, although it may be less ambiguous when an explant is examined (Kojiro, 2004). Identification of ductular reaction at the periphery aids in positive identification of cirrhosis or dysplastic nodule (Park et al, 2007; Lennerz et al, 2009). Clinical management of patients with cirrhosis and dysplasia in biopsy specimens is challenging.

Box 70A.1

Causes of Cirrhosis

Drugs and Toxins
Alcohol
Methotrexate
Isoniazid
Methyldopa
Amiodarone

Infections
Hepatitis B
Hepatits C
Hepatitis D
Schistosomiasis

Autoimmune Disorders
Autoimmune hepatitis
Primary biliary cirrhosis
Primary sclerosing cholangitis

Inherited Metabolic Defects
Hemochromatosis
Wilson disease
α_1-Antitrypsin deficiency
Galactosemia
Tyrosinemia
Glycogen storage disease
Hereditary fructose intolerance
Urea cycle disorders
Alpha/beta lipoproteinemia
Progressive familial intrahepatic cholestasis
Cystic fibrosis

Acquired Bile Duct Diseases
Biliary atresia
Gallstone obstruction
Common bile duct stricture

Vascular Disorders
Budd–Chiari syndrome
Venoocclusive disease
Congestive heart failure
Hereditary hemorrhagic telangiectasia

Miscellaneous
Nonalcoholic steatohepatitis
Total parenteral nutrition
Indian childhood cirrhosis
Intestinal bypass surgery
Hypervitaminosis A
Sarcoidosis
Cryptogenic

Modified from Maecsween RNM, et al, 2002: Pathology of the Liver, 4th ed. London, Churchill Livingstone.

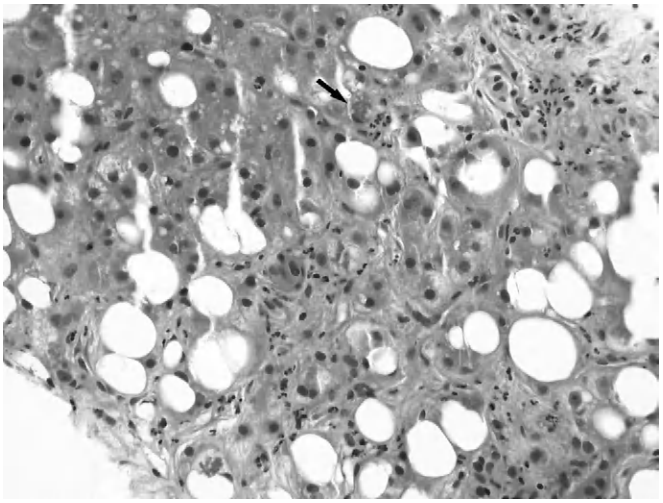


FIGURE 70A.6. Alcoholic hepatitis characterized by macrovesicular steatosis, hepatocyte ballooning, lobular neutrophilic infiltration, and presence of Mallory-Denk bodies. One of the hepatocytes containing a Mallory-Denk body is partially surrounded by neutrophils (*arrow*).

Assessment of Underlying Etiology

Cirrhosis is best classified by its underlying etiology (Box 70A.1), which can be determined by clinical history and laboratory investigation in many but not all cases. Morphologic examination may help establish the diagnosis or guide the clinical investigation. In the following discussion, the morphologic features characteristic of many chronic liver diseases that commonly cause cirrhosis are illustrated. At end-stage liver disease, however, the histopathologic findings may be nonspecific and indiscriminate even to experienced hepatopathologists. Many cases of "cryptogenic" cirrhosis represent burned-out processes, for which no identifying clinical or morphologic features remain. These cases are frequently due to ALD, autoimmune hepatitis, and nonalcoholic fatty liver disease (NAFLD). The contribution of as yet unnamed viral agents is not known but is recognized.

Alcoholic Liver Disease

Excessive alcohol consumption is the leading cause of liver disease in the Western world, which encompasses a clinicopathologic spectrum that includes fatty liver, alcoholic hepatitis, and alcoholic cirrhosis (Haber et al, 2003; Menon et al, 2001; O'Connor & Schottenfeld, 1998; Tome & Lucey, 2004). Alcoholic cirrhosis, or Laënnec cirrhosis, is classically micronodular and may retain some of the features of alcoholic hepatitis at the initial stage. The liver may appear pale or yellow, enlarged, and greasy on gross examination. Histologically, lesions predominate in the perivenular region (zone 3) of the acinus and include various combinations of steatosis (fatty change), ballooning, Mallory-Denk bodies, and satellitosis. Steatosis may be predominantly macrovesicular, defined by the presence of large fat droplets in the cytoplasm of hepatocytes displacing the nuclei. Microvesicular steatosis also can be seen, characterized by fine fat droplets surrounding the central nuclei. Alcoholic hepatitis is characterized by an inflammatory infiltrate rich in neutrophils, most frequently distributed in the lobules adjacent to hepatocytes containing Mallory-Denk bodies, and dense, perisinusoidal fibrosis (Fig. 70A.6). Lymphocytes and histiocytes also may be present, sometimes in the form of lipogranulomas, and megamitochondria also may be evident. In the portal and periportal regions, ductular reaction with numerous neutrophils may occur. Cholangiolitis and canalicular bile plugs are worrisome lesions for concomitant pancreatitis.

The patterns of fibrosis in alcoholic hepatitis are characteristic. Fibrosis usually involves the terminal hepatic venules, leading to the thickening of the wall; luminal occlusion may be seen with necrosis of adjacent hepatocytes and Mallory-Denk bodies within remaining hepatocytes, a lesion referred to as *central hyaline necrosis.* Subendothelial fibrosis is a venoocclusive lesion of alcoholism that may be noted even in end-stage cirrhotic livers. Fibrosis may extend into the lobules in perisinusoidal spaces as delicate or dense strands, giving rise to a distinctive "chicken wire" pericellular (perisinusoidal) distribution (Brunt, 2002). Trichrome stain is particularly useful in detecting this unique form of fibrosis. With time, the liver may be replaced by micronodular cirrhosis; often, the septa of ALD are quite broad as manifestations of the microvascular obliteration.

As alcoholic cirrhosis progresses, the aforementioned morphologic features may become less obvious. The liver may shrink and be nearly replaced by fibrosis, and the cirrhosis may evolve into a macronodular or mixed nodular architecture with characteristic broad septa. Steatosis, ballooning, and Mallory-Denk bodies may not be discernible, especially in patients who have stopped consuming alcohol for several months.

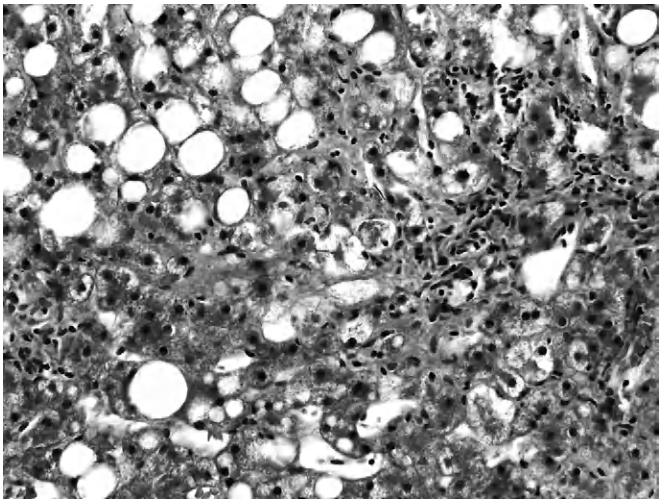


FIGURE 70A.7. Zone 3 "chicken wire" perisinusoidal fibrosis; this feature can be seen in nonalcoholic and alcoholic steatohepatitis (Masson trichrome stain).

Nonalcoholic Fatty Liver Disease

NAFLD is increasingly recognized as a significant form of potentially progressive liver disease. Prevalence studies estimate that approximately 20% to 25% of the U.S. population is affected by fatty liver; of these individuals, 15% to 20% are at risk for progression to cirrhosis (Angulo, 2002). The lesions noted in liver tissue may resemble many of the features of alcohol-induced liver damage in individuals who are not heavy drinkers (Brunt, 2004; Salt, 2004; te Sligte et al, 2004; Zafrani, 2004). The disease is etiologically attributed primarily to insulin resistance and is considered the hepatic manifestation of the metabolic syndrome, a constellation of obesity, hypertension, diabetes, and hyperlipidemia (Marchesini et al, 2001). Studies have also correlated the lesions of nonalcoholic steatohepatitis (NASH) with features of metabolic syndrome.

Most, but not all, of the histopathologic features described for alcoholic hepatitis can be found in NASH. These mainly include steatosis, which is predominantly macrovesicular and commonly of zone 3 (centrilobular) distribution; hepatocyte ballooning; lobular inflammation, which is usually mild and includes neutrophils; small lipogranulomas; and zone 3 perisinusoidal fibrosis (Fig. 70A.7). Hepatocytes also may exhibit prominent glycogenated nuclei in NASH, particularly when associated with diabetes. Portal inflammation may be present in some cases but is usually mild and less intense than lobular inflammation. The presence of heavy portal inflammation, particularly when accompanied by lymphoid aggregates or abundant plasma cells, should raise the suspicion of overlapping disease, such as chronic viral hepatitis or autoimmune hepatitis (Brunt et al, 2003). However, extensive portal chronic inflammation in the absence of an overlapping disease has been shown to correlate with progressive NASH and more severe metabolic features (Brunt et al, 2009). In addition, Mallory-Denk bodies may or may not be seen in NASH; if present, they may be poorly formed. In contrast to ALD, in which Mallory-Denk bodies may be present in apoptotic hepatocytes, in NASH they are restricted to ballooned hepatocytes. Recently, an immunohistochemical stain to detect loss of K8/18 in ballooning, as well as presence of clumped K8/18 in Mallory-Denk bodies, has been introduced (Lackner et al, 2008). If numerous Mallory-Denk bodies are present in the background of steatohepatitis, an alcoholic origin is more likely (Brunt, 2002, 2004). Likewise, marked cholestasis is highly unlikely in NASH but can occur in ALD. The broad septa of ALD are rare in NAFLD as well.

Fibrosis in NASH begins in the pericentral perisinusoidal spaces; with time, portal and periportal fibrosis develop, and eventually bridging fibrosis and cirrhosis may occur. This typically does not obliterate the terminal hepatic venules, a feature dissimilar to alcoholic hepatitis. A grading and staging system has been proposed for NASH primarily based on the extent and severity of the constellation of steatosis, ballooning change, the grade of lobular and portal inflammation, and the stage of fibrosis and remodeling (Brunt, 2004; Brunt et al, 1999). Similar to the widespread use of grading and staging in other forms of chronic liver disease, this proposal was made in recognition of the unique features of steatohepatitis to facilitate further reproducible evaluation for clinical and laboratory investigation. A revision of this system has been introduced as a method of semiquantification for use in clinical trials (Kleiner et al, 2005).

Chronic Hepatitis C

A high proportion of patients infected with HCV develop cirrhosis (Poynard et al, 2003), especially patients with a long duration of infection, concurrent alcohol consumption, coinfection with HBV or human immunodeficiency virus, nonresponse to antiviral therapy, and those of male gender (de Torres & Poynard, 2003; McCaughan & George, 2004). HCV-related cirrhosis is virtually always macronodular or mixed macronodular and micronodular. The fibrovascular septa vary in width and usually are infiltrated by mononuclear cells, predominantly lymphocytes, but also include plasma cells and eosinophils. Lymphoid aggregates, often with well-formed germinal centers, are characteristic although not pathognomonic (Fig. 70A.8). A mild degree of bile duct damage (the Poulsen lesion) also may be seen in some cases, and interface hepatitis may also be present. The lobular inflammation is typically spotty and mild, with or without acidophilic bodies. Subendothelial inflammation in portal veins, identical to endotheliitis, also may occur in

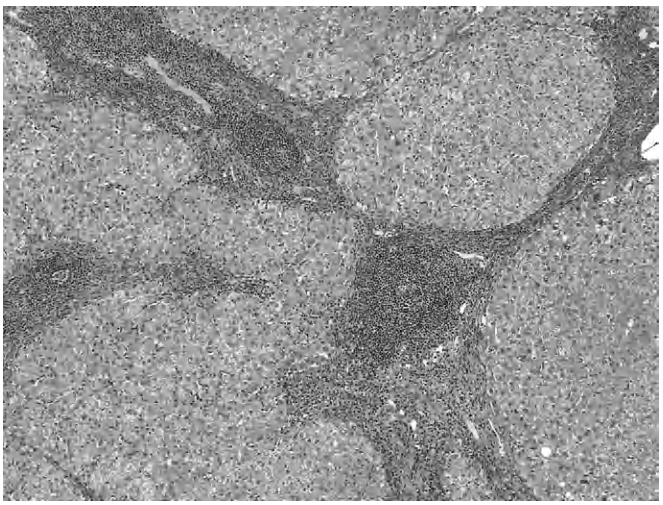


FIGURE 70A.8. Hepatitis C virus cirrhosis with characteristic septal lymphoid aggregates.

HCV infection, but no reliable antibody for immunohistochemical detection of HCV proteins has been found.

Steatosis is a common histologic finding in chronic HCV and may be a manifestation of host phenotype (increased body weight, presence of the metabolic syndrome) or viral cytopathic effect, as in genotypes 3 and 1. Although a small subset of the patients may have concurrent steatohepatitis of either nonalcoholic or alcoholic origin (Brunt et al, 2003; Ramalho, 2003), viral proteins have been shown to promote fat accumulation in hepatocytes directly (Lai, 2002; Lonardo et al, 2004; Ramalho, 2003). Accumulating evidence indicates that steatosis contributes to fibrosis progression, particularly in patients infected with genotype 3 HCV (Brunt & Tiniakos, 2002; Ramalho, 2003; Rubbia-Brandt et al, 2004a).

Liver biopsy plays a central role in assessing the grade of necroinflammation and the portal-based progression of fibrosis and in evaluating the effect of antiviral therapy. Numerous grading and staging systems for chronic hepatitis have been developed; these systems share the assessment of portal and lobular inflammation and necrosis for grade and portal-based fibrosis for stage (Brunt, 2000b).

Chronic Hepatitis B

Chronic hepatitis secondary to HBV infection is another common cause of cirrhosis (Fattovich, 2003; Ganem & Prince, 2004; Lai et al, 2003). Compared with hepatitis caused by HCV, HBV hepatitis may exhibit more severe portal and lobular necroinflammation, particularly when there is an acute exacerbation. Confluent or multiacinar bridging necrosis with collapse of the lobular framework may be seen. A relatively specific finding in chronic HBV hepatitis is the presence of "ground-glass" inclusions within hepatocytes, which are uniform, pale, or eosinophilic cytoplasmic alterations resulting from enriched smooth endoplasmic reticulum filled with hepatitis B surface antigen (Fig. 70A.9). However, changes resembling ground-glass inclusions have been observed in a variety of conditions (Wisell et al, 2006). A definitive diagnosis can be established by histochemical stains (orcein, Victoria blue) or with immunohistochemical detection of hepatitis B surface antigen in the cytoplasm and hepatitis B core antigen in the nucleus.

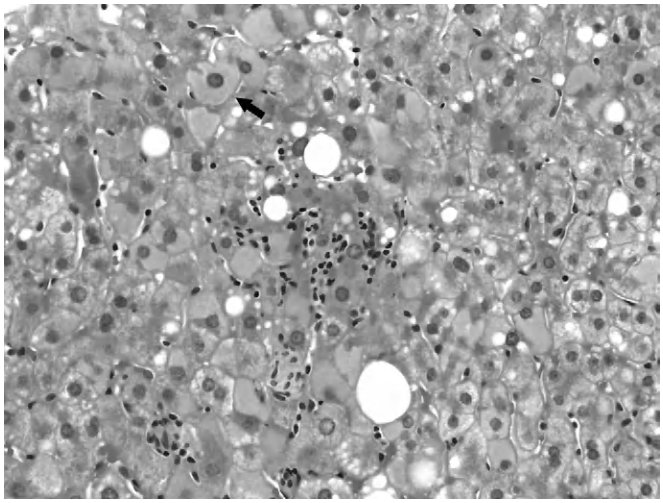


FIGURE 70A.9. Ground-glass hepatocytes (*arrow*) in chronic hepatitis B virus.

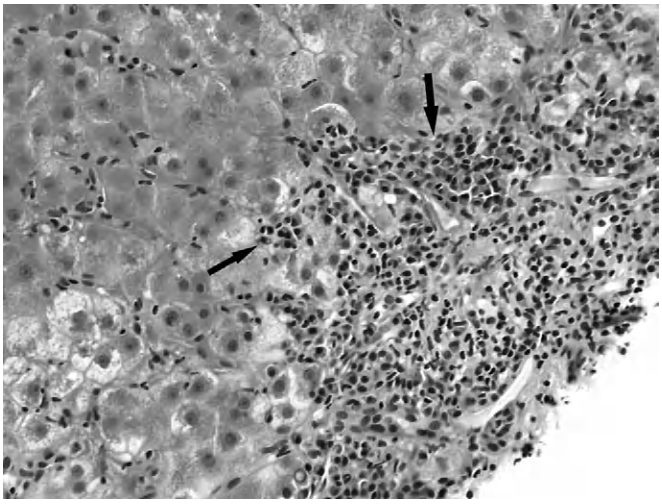


FIGURE 70A.10. Autoimmune hepatitis may be characterized by hepatitic "rosettes" and numerous plasma cells (*arrows*) in the portal tracts and lobules.

Coinfection or superinfection with hepatitis D virus (HDV) in HBV patients usually causes more severe liver damage and accelerates the development of cirrhosis (Farci, 2003). Immunohistochemical detection of HDV intranuclear antigen is helpful in establishing the diagnosis.

Autoimmune Hepatitis

The diagnosis of autoimmune hepatitis relies on a constellation of clinical, laboratory, and histopathologic findings, none of which alone is considered specific (Alvarez et al, 1999; McFarlane, 2002a, 2002b; Vergani & Mieli-Vergani, 2003). Histopathologic examination of liver tissue serves important roles in confirming the clinical concern and excluding diseases secondary to other etiologies (Carpenter & Czaja, 2002). Classic autoimmune hepatitis exhibits a dense portal, septal, and lobular mononuclear cell infiltrate, with marked periportal or periseptal interface hepatitis enriched in plasma cells. The presence of numerous plasma cells in portal inflammation and within lobular foci of necrosis and the formation of hepatitic "rosettes" are characteristic (Fig. 70A.10). In severe cases, confluent or bridging necrosis may be seen, sometimes accompanied by pseudoacinar formation. Predominantly centrilobular necrosis with relatively mild portal inflammation also has been described in autoimmune hepatitis (Misdraji et al, 2004). Fibrosis usually develops rapidly in untreated patients. At the cirrhotic stage, the liver parenchyma is divided by broad, fibrous bands into variable-sized nodules, similar to those caused by alcoholic or chronic viral hepatitis; plasma cells and rosettes may become less prominent. Burned-out autoimmune hepatitis may be a cause of "cryptogenic" cirrhosis, and morphologic features do not separate different types of autoimmune hepatitis, classified by either autoantibody profiles or immunogenetic markers (McFarlane, 2002a).

Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC) is an autoimmune disorder that leads to progressive destruction of intrahepatic bile ducts (Leuschner, 2003; Selmi et al, 2004). In the early stage, the

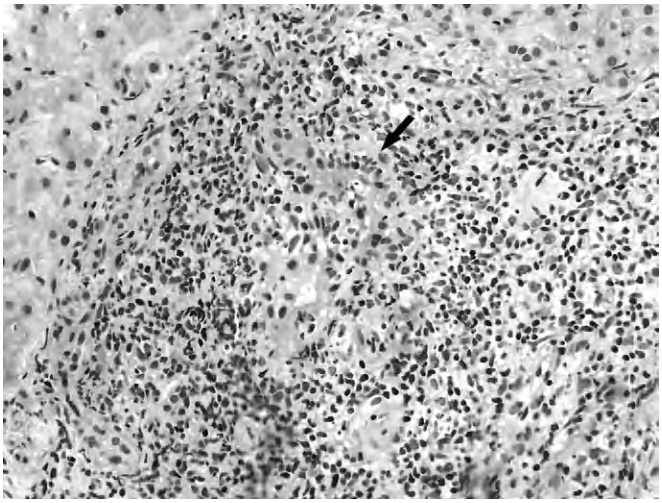


FIGURE 70A.11. Florid duct lesion with granulomatous portal inflammation and damaged bile duct (*arrow*) in early stage primary biliary cirrhosis.

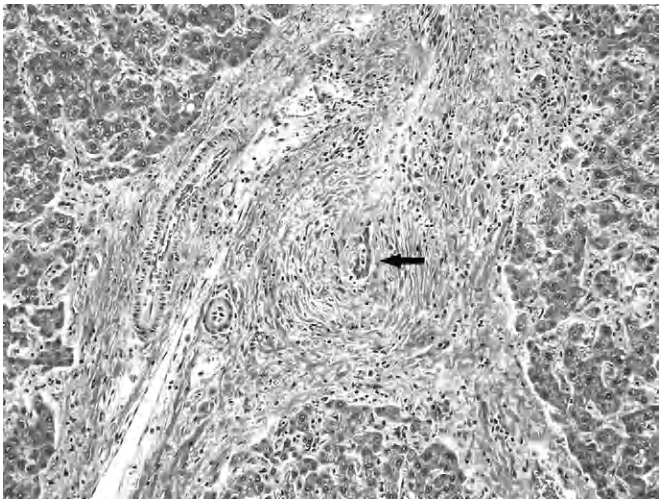


FIGURE 70A.12. Characteristic concentric onionskin periductal fibrosis in primary sclerosing cholangitis. The residual duct epithelial cells show atrophic and degenerative changes (*arrow*) (Masson trichrome stain).

disease is characterized by mixed chronic portal inflammation with lymphocytes, plasma cells, eosinophils, and the pathognomonic florid duct lesion, characterized by lymphocytic or granulomatous bile duct infiltration (Fig. 70A.11). Ductular reaction and interface hepatitis may be seen in more advanced cases. In the setting of positive serum antimitochondrial antibody (AMA), the florid duct lesion is essentially diagnostic. The affected duct may rupture, or the duct epithelium may exhibit degenerative change. With disease progression, ductopenia becomes evident. The native ducts may be absent or obscured by lymphoid aggregates or collections of foamy macrophages. Cholate stasis, as previously described, may be an initial clue to the diagnosis. Features of autoimmune hepatitis also may occur in AMA-positive primary biliary cirrhosis, referred to as *overlap syndrome* (Dienes et al, 2002; Durazzo et al, 2003); however, it must be kept in mind that significant lobular and interface activity can be seen in patients with PBC alone.

Cirrhosis is seen only at the late stage of PBC; it is commonly inhomogeneously distributed and may be micronodular. Florid duct lesions and granulomas may continue to exist where native bile ducts have not been completely destroyed. Canalicular cholestasis with bile plugs may be seen in the late stage and is regarded as a sign of poor prognosis.

The term *autoimmune cholangiopathy*—also known as *antinuclear antibody–positive, AMA-negative PBC*—has been used to describe the disease seen in a small subset of patients who present with typical clinical and histopathologic findings of PBC but are seronegative for AMA. These patients may have other autoantibodies, such as antinuclear antibody and anti–smooth muscle antibody, as seen in autoimmune hepatitis. Accumulating evidence suggests that autoimmune cholangiopathy and PBC are likely to be a single disease with variations in the type and concentration of autoantibodies (Vierling, 2004).

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is another autoimmune inflammatory and fibrosing process that segmentally affects the extrahepatic and intrahepatic biliary tree, leading to biliary stricture and cirrhosis (Cullen & Chapman, 2003; Mendes & Lindor, 2004; Rodriguez & Bass, 2003). It is strongly associated with inflammatory bowel disease, including both Crohn disease and ulcerative colitis (Broomé et al, 2006), and with the development of cholangiocarcinoma.

The definitive diagnosis of PSC rests on characteristic cholangiographic findings. Histopathologic examination of a liver biopsy specimen may or may not reveal diagnostic features because of the patchy nature of the disease. Mild portal lymphocytic infiltration and mild bile ductular reaction may be the only observations. The relatively specific finding of concentric periductal fibrosis with an "onionskin" appearance indicates chronic biliary obstruction of any cause and thus is not pathognomonic of PSC. The duct epithelium usually exhibits atrophic and degenerative changes, and a characteristic fibro-obliterative scar eventually replaces the bile duct (Fig. 70A.12). As in other forms of biliary cirrhosis, inhomogeneity of cirrhosis and histologic evidence of cholate stasis are recognized features in PSC. Careful evaluation of explant livers for occult cholangiocarcinoma with sampling of the entire hilar tissue is recommended.

Hereditary Hemochromatosis

Hereditary hemochromatosis (HH) is an autosomal recessive iron-overload disorder primarily associated with mutation of the *HFE* gene (Limdi & Crampton, 2004; Pietrangelo, 2004). Iron deposition initially occurs in zone 1 (periportal) hepatocytes with a decreasing gradient toward the centrilobular area. The iron granules are concentrated along the border of the canaliculi; this is best shown by Perls' Prussian blue stain (Fig. 70A.13). With progression, untreated HH results in iron deposition throughout the entire lobule, and iron granules are seen not only in hepatocytes but also in Kupffer cells, biliary epithelial cells, and portal macrophages. Kupffer cell clusters, or siderotic nodules, are common, and usually little to no significant portal and/or lobular inflammation is evident. This pattern of iron deposition is not restricted to HH; the diagnosis rests with genetic testing.

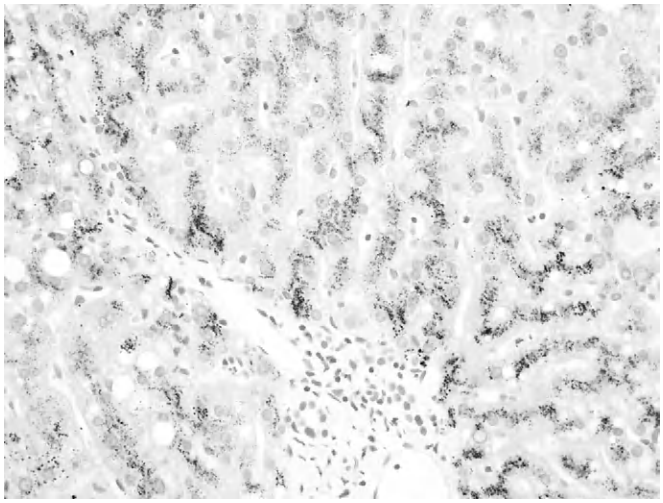


FIGURE 70A.13. Hepatocellular iron deposition in a pericanalicular location in the periportal (zone 1) hepatocytes in hereditary hemochromatosis (Perls' Prussian blue stain).

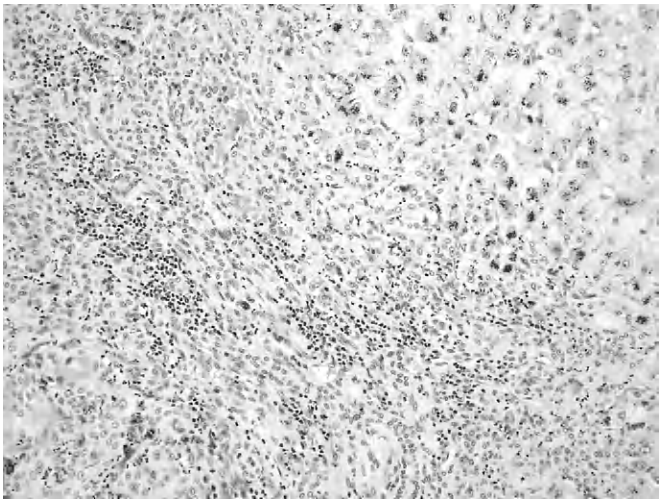


FIGURE 70A.14. Abundant copper deposition in a case of Wilson disease (Rhodanine stain).

Fibrosis in HH is portal based. When cirrhosis develops, it is typically micronodular with exquisite portal to portal bridging and retention of the terminal hepatic venules. Hepatocytes in cirrhotic nodules also are loaded with iron, which may exhibit a periseptal distribution pattern. Occurrence of iron-free nodules or foci is of concern for dysplasia or HCC, which occurs frequently in cirrhotic HH patients.

Secondary iron overload in the liver is a common finding in a variety of conditions, including cirrhosis of nonbiliary origins (Limdi & Crampton, 2004). Iron deposition secondary to transfusion can be heavy, but initially, it principally involves Kupffer cells in the sinusoids. Significant amounts of stainable iron may be detected in chronic HCV and HBV hepatitis, alcoholic steatohepatitis and NASH, and cirrhosis unrelated to HH or the above-mentioned chronic liver diseases. Iron deposition in these conditions is usually mild and rarely exceeds 2+ when a semiquantitative histologic score of 1 to 4 is used. Iron granules may be found in hepatocytes, Kupffer cells, and endothelial cells. If a higher score is appreciated in hepatocytes (e.g., 3+ or 4+, which is more commonly associated with HH), age-adjusted chemical quantitation of iron concentration in dry hepatic tissue, the hepatic iron index, or genetic testing for *HFE* mutations should be performed. An hepatic iron index greater than 2 was developed to distinguish HH from iron overload secondary to alcoholic siderosis, but this is not considered a diagnostic test for HH (Bacon, 2001). Patients with chronic viral hepatitis or steatohepatitis who also have an increased liver iron content have a higher chance of harboring *HFE* mutations. It has been suggested that these patients are less likely to respond to therapy and are more prone to develop fibrosis and cirrhosis (Bonkovsky et al, 2003). Other genetic markers have been developed to correlate with the more unusual cases of non-HFE iron overload (Pietrangelo, 2004).

Wilson Disease

Wilson disease is an autosomal recessive inherited metabolic disorder of copper metabolism. Any young patient with unexplained chronic or fulminant liver disease should be investigated for Wilson disease (Ferenci, 2004; Gitlin, 2003). Morphologic features in the liver vary widely at different stages of the disease and lack specificity. At the precirrhotic stage, lymphocytic portal inflammation with interface hepatitis that mimics chronic viral hepatitis or autoimmune hepatitis may be evident. Hepatocytes may show variable degrees of steatosis, necrosis, anisocytosis, and anisonucleosis. In later stages, atypical lipofuscin, canalicular cholestasis, and Kupffer cell iron accumulation may be noted. Periportal hepatocytes may contain glycogenated nuclei and Mallory-Denk bodies, and cirrhosis is usually micronodular.

Copper and copper binding protein accumulation may be shown on tissue sections by histochemical techniques, such as rhodanine, rubeanic acid, orcein, or Victoria blue stains (Fig. 70A.14) and is most likely present in cirrhosis. Copper deposition also may be seen in other chronic cholestatic liver diseases, such as PBC or PSC, usually in zone 1 or in periseptal hepatocytes. Alternatively, the absence of stainable copper in a noncirrhotic liver does not exclude the diagnosis of Wilson disease. Copper quantitation in hepatic tissue is the diagnostic test, which can be performed reliably on FFPE tissue. A value of greater than 250 μg/g dry hepatic tissue has been used as a cutoff value. Currently, genetic testing has not yet become practical for clinical diagnosis.

α_1-Antitrypsin Deficiency

Liver injury in α_1-antitrypsin deficiency, an autosomal recessive inherited metabolic disorder, results from retention of mutant α_1-antitrypsin molecules in hepatocytes (Carrell & Lomas, 2002; Perlmutter, 2000). The histopathologic hallmark of the disease is the presence of eosinophilic globules of varying sizes in zone 1 hepatocytes in patients older than infants. These globules are best shown by PAS-d stain (Fig. 70A.15), but immunohistochemical stain may confirm the diagnosis. The globules can be seen in homozygous (PiZZ) and heterozygous (PiMZ) phenotypes, which may be determined by serum protein electrophoresis, but homozygous patients seem to be more likely to develop liver disease and cirrhosis. Other morphologic findings in the liver are relatively nonspecific, which may or may not

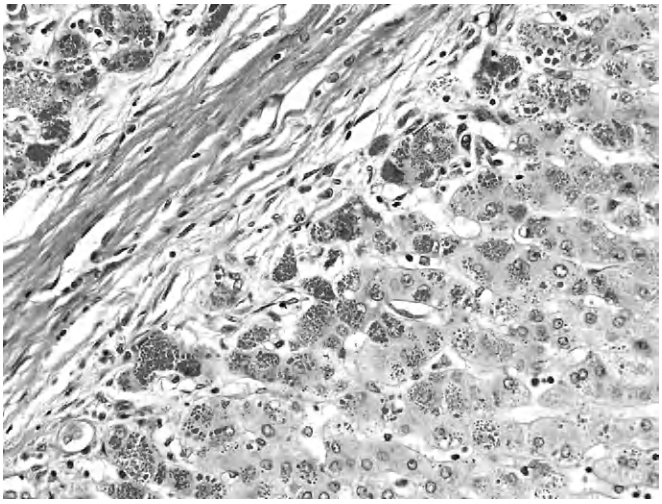


FIGURE 70A.15. Varying sizes and shapes of diastase-resistant hyaline globules in periseptal hepatocytes in α_1-antitrypsin deficiency (PAS-d).

include hepatic inflammatory infiltration. When chronic hepatitis is seen in α_1-antitrypsin deficiency, other causes, such as HCV or alcohol, should be excluded (Ishak, 2002). Cirrhosis developing from α_1-antitrypsin deficiency can be micronodular, macronodular, biliary, or mixed in pattern. Dysplasia and HCC may occur in cirrhotic livers, just as it may in other cases of chronic hepatitis.

Cryptogenic Cirrhosis

In approximately 10% to 15% of patients, no clinically or pathologically identifiable cause of cirrhosis is identified. However, accumulating evidence suggests that a large proportion of cryptogenic cirrhosis may represent burned-out NAFLD. This suggestion is based on reported biopsy series of diagnosed NASH followed by subsequent cryptogenic cirrhosis with complete loss of the features of active steatohepatitis. In addition, several authors have shown that many of these patients have type 2 diabetes, obesity, or both compared with patients with cirrhosis of other etiologies (Ayata et al, 2002; Caldwell et al, 1999; Ong et al, 2001; Poonawala et al, 2000; Sakugawa et al, 2003; Sanjeevi et al, 2003). Development of posttransplant NAFLD also is frequent in this group of patients (Ong et al, 2001; Sanjeevi et al, 2003), but whether this represents actual recurrence of NASH or de novo NASH is an area of discussion (Czaja, 1997).

An autoimmune etiology also has been proposed based on clinical and histopathologic findings (Ayata et al, 2002; Kaymakoglu et al, 1998), but autoantibodies may no longer be detectable in these cases (Carpenter & Czaja, 2002). PSC and alcoholic cirrhosis may present as cryptogenic cirrhosis, and one case report documented prior biopsy-proven Budd-Chiari syndrome presenting as cryptogenic cirrhosis 34 years later (Havlioglu et al, 2003). Finally, the possibility of an as yet unknown viral infection or metabolic condition cannot be excluded in cryptogenic cirrhosis. Evaluation of patients with unexplained cirrhosis should include careful review of all prior liver biopsy specimens, especially those from several years prior.

Box 70A.2

Causes of Noncirrhotic Portal Hypertension

Prehepatic

Portal or splenic vein thrombosis
Arterioportal shunt
Tropical splenomegaly

Posthepatic

Budd–Chiari syndrome
Congestive heart failure

Intrahepatic

Nodular regenerative hyperplasia
Partial nodular transformation
Alcoholic hepatitis
Drugs and toxins
Sarcoidosis
Schistosomiasis
Venoocclusive disease
Hematologic disorders
Congenital hepatic fibrosis
Hereditary hemorrhagic telangiectasia
Idiopathic portal hypertension

Modified from Geller SA, Petrovic LM, 2004: Biopsy Interpretation of the Liver. Philadelphia, Lippincott Williams & Wilkins.

NONCIRRHOTIC PORTAL HYPERTENSION

An increase in the pressure of the portal venous system can be seen in a heterogeneous group of prehepatic, intrahepatic, and posthepatic conditions in the absence of cirrhosis (Box 70A.2). The etiopathogenetic mechanisms leading to portal hypertension in these conditions, the clinical presentation, and the prognoses vary widely (Molina & Reddy, 2001; Okuda, 2002). Portal hypertension in Budd-Chiari syndrome (see Chapter 77) is secondary to posthepatic vein obstruction and may have an acute or subacute clinical course with liver failure. Portal hypertension associated with infiltrative amyloid or hematologic disorders—such as leukemia, mastocytosis, and Gaucher disease—is believed to occur primarily at the intrahepatic sinusoidal level. Precirrhotic alcoholic hepatitis also may cause portal hypertension because of hepatocyte swelling, sinusoidal fibrosis, and central sclerosis, which may be more insidious clinically. Liver biopsy functions to confirm the absence of cirrhosis and helps establish or suggest the diagnosis (Roskams et al, 2003). The histopathologic features of several selected entities associated with noncirrhotic portal hypertension are discussed briefly.

Nodular Regenerative Hyperplasia

Portal hypertension has been reported in about half of patients with nodular regenerative hyperplasia (Al-Mukhaizeem et al, 2004). It is associated with a wide range of conditions, mainly including hematologic disorders, connective tissue diseases, and medications. The pathogenesis is unclear, but it may involve portal venous thrombosis leading to a microcirculatory disturbance in the liver that causes localized, nonlethal ischemia and compensatory hepatocyte hyperplasia. The liver may be normal in size or enlarged when associated with a hematologic disease. On cut surface, the liver is diffusely nodular in appearance, with nodules ranging from 0.1 to 1 cm in diameter. Microscopically, the nodular appearance is best appreciated with reticulin stain (Fig. 70A.16), which highlights regenerative hepatocytes within the nodules and atrophic hepatocytes at the edges of the nodules. Nodular regenerative hyperplasia differs

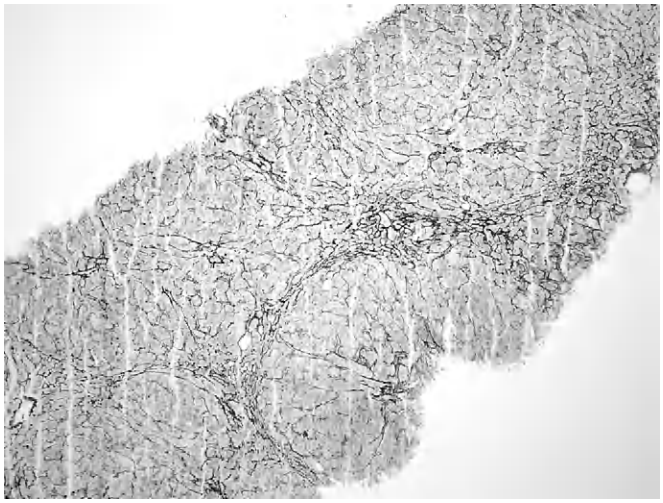


FIGURE 70A.16. Reticulin stain highlights nodularity of the parenchyma in nodular regenerative hyperplasia; no scar tissue (fibrous septum) is present (Sweet's reticulin).

from cirrhosis in that fibrosis, if present, is minimal, and the portal tract architecture is usually unaltered. These characteristic features may be shown more easily on a wedge biopsy specimen but may be difficult to appreciate on a needle biopsy specimen.

Partial nodular transformation is a rare condition with an underlying pathogenesis similar to that proposed for nodular regenerative hyperplasia. Partial nodular transformation is a localized lesion almost always seen in the perihilar region. The hyperplastic hepatocyte nodules are larger than those of nodular regenerative hyperplasia, often well defined, and surrounded by fibrous tissue.

Venous Outflow Obstruction

Obstruction of hepatic venous outflow increases sinusoidal pressure and results in subsequent portal hypertension. Etiologically, it ranges from congestive heart failure, narrowing or occlusion of large hepatic veins (Budd-Chiari syndrome; see Chapter 77), to obliteration of the terminal or sublobular hepatic veins. Liver injury caused by congestive heart failure is characterized by zone 3 sinusoidal dilation and congestion and, when severe or acute, extravasation of red blood cells under the space of Disse into the hepatic cords. Hepatocellular necrosis is usually uncommon but may become evident if accompanied by systemic hypotension and hypoperfusion. The portal tracts are typically unremarkable and devoid of significant inflammatory cell infiltration. In longstanding cases, zone 3 hepatocytes exhibit atrophic change with markedly attenuated cell plates. Lipofuscin pigment and sinusoidal lining cell iron may accrue, and perivenular fibrosis and bridging fibrosis also may develop and rarely may result in septa formation, reverse lobulation, and cardiac cirrhosis.

Budd-Chiari syndrome results from obstruction at any level of the hepatic venous system between the liver and the inferior vena cava or the right atrium. It involves a variety of thrombotic and nonthrombotic causes, among which hypercoagulable states secondary to myeloproliferative disorders are the most common (Menon et al, 2004). The histopathologic features of Budd-Chiari syndrome are similar to those of congestive heart failure, but acute onset also may give rise to a hemorrhagic appearance at zone 3 with extravasation of red blood cells under the space of Disse, to replace hepatocytes within the cords, and more significant hepatocyte necrosis. If unrelieved, Budd-Chiari syndrome results in cord atrophy, replacement by fibrosis, and eventual cirrhosis.

In contrast to Budd-Chiari syndrome, venoocclusive disease rarely results in cirrhosis and has variable clinical manifestations that range from elevation of liver function tests to life-threatening ascites and liver failure. This process affects the distal sinusoids, the intrahepatic portion of the hepatic venous system, and the terminal hepatic and sublobular veins. It has been stressed that the injury in this process is to the sinusoidal lining cells and surrounding hepatocytes. DeLeve and colleagues (2002) recommended a nomenclature change to *sinusoidal obstruction syndrome*. It is common after bone marrow or hematopoietic stem cell transplantation, is more likely to occur in HCV-infected subjects, and is associated with chemotherapeutic agents and hepatic radiation (Coppell et al, 2003; Kumar et al, 2003; Wadleigh et al, 2003).

Oxaliplatin-based chemotherapy is increasingly recognized as a cause of marked damage to the sinusoids, with the subsequent risks of nodular regenerative hyperplasia, perisinusoidal and outflow vein fibrosis, and liver failure (Rubbia-Brandt et al, 2004b). Patients usually present within 30 days after chemotherapy; however, late-onset venoocclusive disease has been reported (Carreras et al, 2007). The lesion is characterized by subendothelial edema, zone 3 sinusoidal dilation, congestion, hemorrhage, and perivenular hepatocyte necrosis, followed by collagen deposition in the subendothelial space and sinusoids. A reticulin stain is useful in highlighting the obstruction of sinusoids and terminal hepatic veins by collagen. As the lesion progresses, the terminal hepatic veins become thickened and narrowed and are eventually obliterated by fibrosis (Fig. 70A.17). Bridging fibrosis, cirrhosis, or nodular regenerative hyperplasia may ensue in more advanced cases.

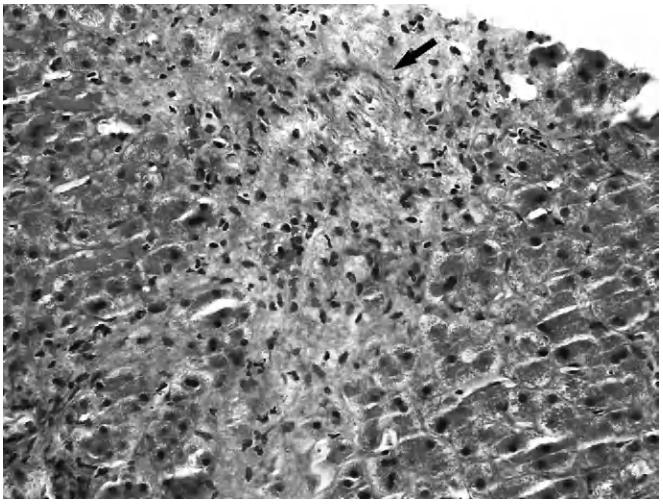


FIGURE 70A.17. This connective tissue stain highlights the lesions of venoocclusive disease (sinusoidal obstruction syndrome). The remnants of the wall of the terminal hepatic venule are seen (*arrow*); necrosis and dropout of the perivenular, zone 3 hepatocytes are demonstrated. (Masson trichrome stain).

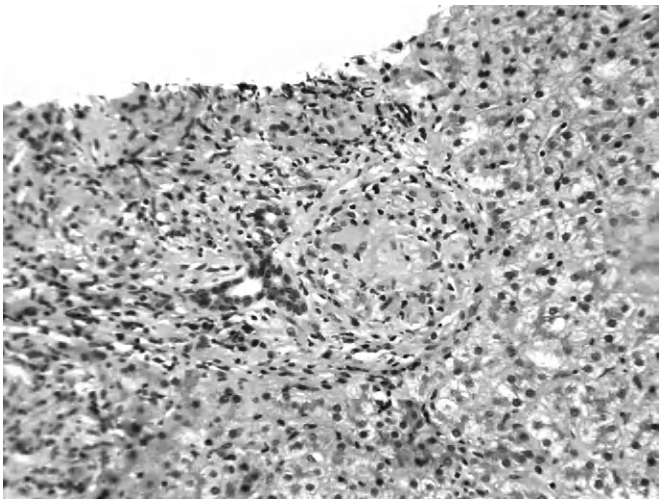


FIGURE 70A.18. Noncaseating, nonnecrotizing epithelioid granulomas in a patient with hepatic sarcoidosis.

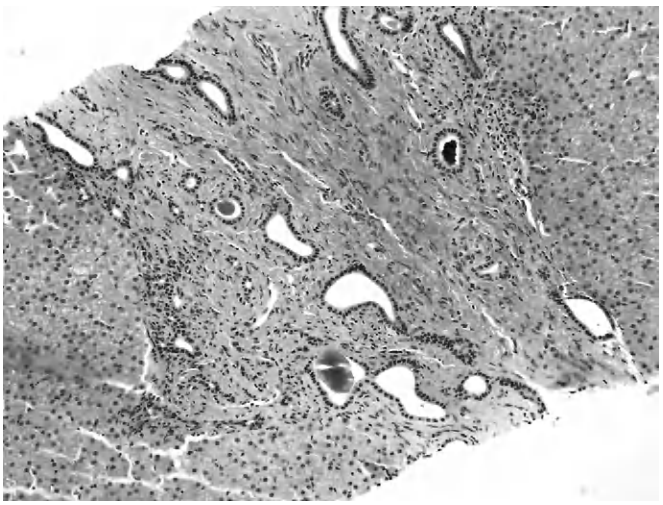


FIGURE 70A.19. Congenital hepatic fibrosis. The duct plate abnormality is manifested by remnant ductal profiles along the limiting plate; some of the duct structures contain inspissated bile.

Sarcoidosis

The histopathologic hallmark of hepatic sarcoidosis is the presence of multiple granulomas composed of well-defined, rounded collections of epithelioid histiocytes rimmed by variable amounts of lymphocytes, multinucleated giant cells, plasma cells, and eosinophils (Ishak, 1998). The giant cells sometimes contain Schaumann and asteroid bodies. Small areas of central fibrinoid necrosis may be noted, but the caseating necrosis seen in tuberculosis is never present. The granulomas typically are traversed by reticulin fibers and surrounded in a concentric fashion by collagen. They are noted scattered throughout the liver but tend to be more frequent in the portal and periportal regions (Fig. 70A.18). They may coalesce to become confluent, masslike lesions. Portal hypertension may develop in some patients as a result of extensive fibrosis or cirrhosis, which may or may not be related directly to fibrous conversion and hyalinization of the granulomas. Portal hypertension also occurs in the absence of marked fibrosis, possibly as a result of compression of portal vein branches and sinusoids by granulomatous inflammation (Blich & Edoute, 2004; Valla & Benhamou, 2000). Nodular regenerative hyperplasia and Budd-Chiari syndrome also have been proposed as potential mechanisms.

Not all granulomas in the liver are due to sarcoid. Noncaseating granulomas can be identified in the liver in a wide variety of disorders, and the pathologist may not always be able to differentiate them (Gaya et al, 2003; Valla & Benhamou, 2000). Common examples include PBC, HCV hepatitis, autoimmune hepatitis, mycobacterial or fungal infections, schistosomiasis, drug reaction, Hodgkin lymphoma, and idiopathic granulomatous hepatitis. A diagnosis of hepatic sarcoidosis requires correlation with clinical, radiologic, and laboratory findings and cannot be rendered solely based on histopathologic examination.

Schistosomiasis

In endemic areas, infestation by *Schistosoma japonicum* or *S. mansoni* is a frequent cause of portal hypertension (Bica et al, 2000; Okuda, 2002). The mechanism involves ova deposition in the portal venules, which incites a granulomatous inflammatory response and extensive, so-called *clay pipe stem fibrosis*, leading to hemodynamic disturbance. Definitive diagnosis can be made by showing the presence of schistosomal ova.

Congenital Hepatic Fibrosis

Congenital hepatic fibrosis is a developmental disorder of the ductal plate predominantly seen in children and only rarely seen in adults. It is inherited in an autosomal recessive or, less commonly, autosomal dominant fashion and may be part of the spectrum of polycystic kidney and liver disease (Kamath & Piccoli, 2003). The affected patient may initially come to medical attention with portal hypertension, and the liver is usually enlarged and of firm consistency. Microscopically, the portal tracts are expanded by fibrous tissue and may show portal-to-portal bridging fibrous bands that do not have the characteristic features of septa described above. An increased number of aberrant duct profiles are distributed at the periphery of the portal tracts, which are believed to represent remnants of incompletely remodeled ductal plates (Fig. 70A.19). Inspissated bile may be noted in the lumina, and the portal vein branches may be hypoplastic or decreased in number, but the branches of hepatic artery may be hypertrophic and abnormally numerous (Desmet, 1992), suggesting arteriovenous anastomosis.

Drugs and Toxins

Chronic liver injury attributable to drugs or toxins may cause extensive fibrosis and cirrhosis, leading to portal hypertension. Examples include methotrexate toxicity, long-term exposure to arsenic or vinyl chloride, and chronic hypervitaminosis A. Drugs and toxins also induce noncirrhotic portal hypertension via different mechanisms, such as venoocclusive disease, Budd-Chiari syndrome, and nodular regenerative hyperplasia. Herbal medicines have been increasingly recognized as hepatotoxic agents in recent years (Stedman, 2002). A classic example found in a variety of herbal medicines is pyrrolizidine

alkaloids, which can cause venoocclusive disease and portal hypertension.

Idiopathic Portal Hypertension

As the name implies, idiopathic portal hypertension is a disorder of unknown etiology, characterized by splenomegaly, anemia, and longstanding portal hypertension in the absence of cirrhosis (Nakanuma et al, 2001; Okudaira et al, 2002). It is primarily a disorder of middle-aged adults and generally has a better prognosis than cirrhotic portal hypertension because liver function is usually preserved. It is also called *hepatoportal sclerosis* and *noncirrhotic portal fibrosis* in the literature (Dhiman et al, 2002). Subtle differences may exist among these terms, however, which may reflect different underlying etiologies (Sarin & Kapoor, 2002).

Although the etiology is obscure, idiopathic portal hypertension is frequently associated with autoimmune disorders; immunologic disturbance is thought to be involved in pathogenesis. Bacterial infection leading to repeated stimulation also has been proposed as a candidate mechanism, but this remains speculative. In addition, some authors (Hillaire et al, 2002; Nakanuma et al, 2001; Sarin & Kapoor, 2002) suggest that prothrombotic disorders and thromboembolism play a role in etiopathogenesis, but this hypothesis has not been accepted by others (Okudaira et al, 2002).

Because idiopathic portal hypertension is essentially a diagnosis of exclusion, morphologic examination of liver tissue is imperative to rule out the presence of cirrhosis or other known etiology. The pathologic changes in idiopathic portal hypertension are believed to represent the effects of longstanding portal venous insufficiency, which may or may not be related to the initiating factors (Nakanuma et al, 2001). They are subtle, heterogenous, and nonpathognomonic and may be missed on a needle biopsy specimen. Macroscopically, the liver may have a reduced weight, and the surface may be irregularly undulant or finely wrinkled, owing to subcapsular parenchymal atrophy (Krasinskas et al, 2005). The cut surface may show portal and perivascular fibrosis, dilation and wall thickening of the veins, and unusual distribution and approximation of the portal and outflow vascular structures. Microscopically, the normal relationship between the portal and central areas is distorted. The portal tracts are either abnormally approximated to each other or widely separated. The terminal hepatic vein may be eccentrically located in the lobule adjacent to a portal tract, and sometimes multiple ectatic tributaries (angiomatous lesions) are seen in a single lobule. Conspicuous fibrosis usually is present in the portal tracts, which may extend into the periportal areas and the lobules in a pericellular fashion. The portal veins may show loss of the normal muscle coat or marked wall thickening, and luminal narrowing or obliteration may also be evident (Fig. 70A.20).

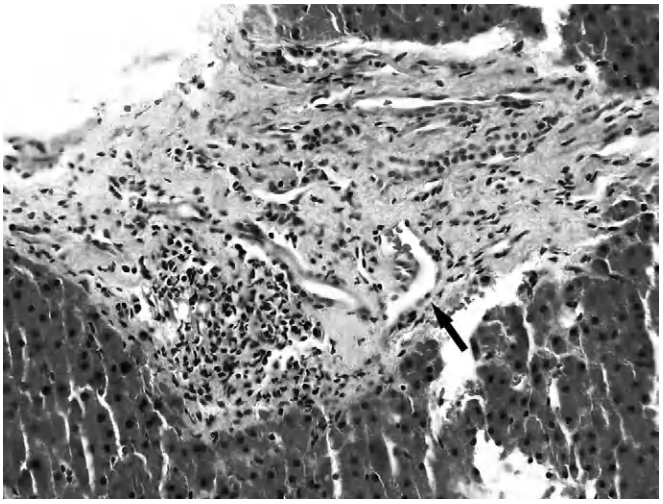


FIGURE 70A.20. Portal fibrosis in hepatoportal sclerosis (idiopathic portal hypertension). The portal vein (*arrow*) is small and has a narrowed lumen (Masson trichrome stain).

CONCLUSION

Longstanding portal hypertension causes serious extrahepatic complications. Common presentations include esophageal varices with variceal bleeding, portal hypertensive gastropathy, congestive splenomegaly with hypersplenism, and ascites with spontaneous bacterial peritonitis. Portal hypertension also contributes to the development of hepatic encephalopathy and hepatorenal syndrome. In general, portal hypertension secondary to a noncirrhotic etiology has a better prognosis than portal hypertension caused by liver cirrhosis because of maintained synthetic function. Pathologic recognition of the characteristic morphologic features of many commonly encountered disorders underlying cirrhosis and noncirrhotic portal hypertension can aid in clinical management of patients with cirrhosis and portal hypertension.

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CHAPTER 71

Portal hypertension in children

Ross W. Shepherd and Yumirle P. Turmelle

SPECIAL FEATURES OF PORTAL HYPERTENSION IN CHILDREN

Portal hypertension secondary to chronic liver disease and prehepatic or posthepatic vascular events is a major cause of morbidity and death in both adults and children (see also Chapter 70A). However, children with these conditions provide a different set of challenges in the understanding and management of portal hypertension because of a predominance of congenital etiologies combined with growth and developmental considerations.

In general, portal hypertension is the result of a combination of increased portal blood flow and increased portal resistance; it occurs when portal blood pressure rises above approximately 10 mm Hg. Signs and symptoms are primarily the result of decompression of this elevated pressure through portosystemic collaterals, but special developmental vascular alterations apply in children (Fig. 71.1). The major problems seen in children are bleeding varices, ascites, and malnutrition. Encephalopathy, portopulmonary hypertension, and hepatorenal syndrome, although important when they do occur, are seen less frequently in children. Splenomegaly and hypersplenism rarely require specific intervention.

CAUSES OF PORTAL HYPERTENSION IN CHILDREN

Portal hypertension may arise as a result of an extrahepatic (portal vein), posthepatic (hepatic vein), or intrahepatic block; the block may be presinusoidal, sinusoidal, or postsinusoidal. Causes in children are shown in Box 71.1.

Extrahepatic Causes

Although possibly declining in frequency, extrahepatic portal venous obstruction, caused by a congenital thrombotic or atretic process, is an important cause of noncirrhotic portal hypertension, especially in developing countries but certainly not confined there (Sarin & Agarwal, 2002). Septic or traumatic umbilical vein injury from omphalitis and/or catherization accounts for some cases, but most cases are idiopathic or represent a congenital malformation of the portal venous system. Portal vein stenosis or thrombosis may also occur in the context of portal vein anastomoses in liver transplantation. In the congenital form, the portal vein is transformed into a cavernoma, resulting in portal hypertension and esophagogastic varices. Importantly, from a treatment standpoint, splenic vein or more extensive portal system involvement results in somewhat different hemodynamics, with an extensive collateral circulation involving a preponderance of gastric varices (Shah et al, 2003) and sometimes ectopic varices involving paracholecystic, paracholedochal, and pancreatoduodenal veins. Esophageal bleeding, or sometimes gastric variceal bleeding, is thus the most important consequence, although the presence of naturally occurring shunts may reduce the risk over time, usually by the second decade of life. Besides variceal bleeding, which is the commonest presentation, hypersplenism is common, and anemia, easy bruising from thrombocytopenia, and abdominal pain may be presenting features. Some patients may develop symptomatic portal biliary obstruction. Growth retardation from malabsorption as a result of failure of the enteropancreatic and enterohepatic circulation is not uncommon. Overt encephalopathy as a result of shunting appears uncommon, but subclinical signs may occur, including disturbed neurocognitive function, particularly attention and short-term memory problems (Mack et al, 2006). Although the liver may appear normal, reversible decompensation may be seen after an acute variceal hemorrhage, and functional compromise may develop over the long term.

Intrahepatic Causes

Portal hypertension may result from a range of presinusoidal, sinusoidal, and postsinusoidal causes of increased portal bed resistance within the liver. Presinusoidal conditions, such as congenital hepatic fibrosis, do not result in impaired liver function. *Congenital hepatic fibrosis* is a developmental disorder that belongs to the family of hepatic ductal plate malformations and is characterized histologically by a variable degree of periportal fibrosis and irregularly shaped proliferating bile ducts (Summerfield et al, 1986). Liver biopsy is highly specific for the diagnosis. In most patients, the first manifestations of the disease are signs or symptoms related to portal hypertension, especially splenomegaly and varices, often with spontaneous gastrointestinal (GI) bleeding that occurs from early childhood and sometimes even into adulthood.

Increased sinusoidal resistance and portal hypertension occur almost invariably in cirrhosis in children. In children, common causes include forms of infant cholestasis, such as biliary atresia, as well as a range of metabolic disorders, infections, toxins, and vascular and nutritional diseases. Cirrhosis is a chronic, diffuse disease characterized by irreversible widespread hepatic fibrosis with regenerative nodule formation (see Chapters 6 and 70). The prominent fibrous tissue contains vascular anastomoses, which cause hemodynamic alterations and portosystemic shunting. This diffuse pathology superimposed on the primary liver disease often obscures the nature of the original insult. The major pathophysiologic consequences are the result of impaired hepatic function and portal hypertension. Progression to cirrhosis and its complications in pediatric liver diseases is highly variable and represents an important consideration in management, particularly when considering surgical options that may compromise later outcomes. In some conditions, such as neonatal extrahepatic biliary atresia, the development of cirrhosis can be extraordinarily rapid, occurring by 12 to 16 weeks of age with liver failure as early as 24 weeks of age.

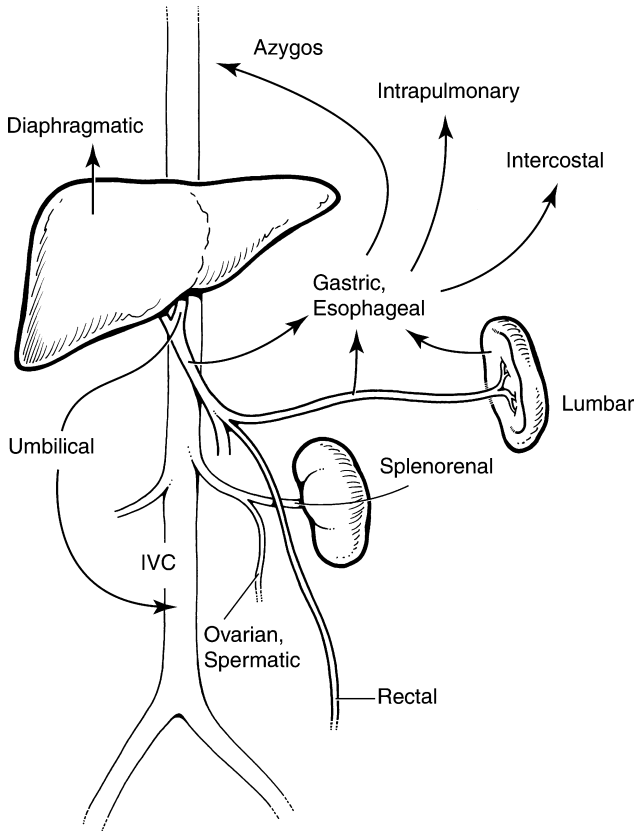


FIGURE 71.1. Sites of portosystemic shunts in children with portal hypertension. IVC, inferior vena cava.

Early diagnosis and surgical treatment by hepatoportoenterostomy improves outcome, but in most cases, liver transplant becomes the only available treatment option. Other disorders, such as cystic fibrosis–associated focal biliary cirrhosis, can be compatible with normal liver function for many years, presenting with signs of portal hypertension in the second decade of life.

Postsinusoidal intrahepatic conditions, such as venoocclusive disease, are rare in children and usually occur only in the context of chemotherapy for childhood cancers (Gharib et al, 2006) or occasionally related to toxin ingestion, such as from eating poisonous mushrooms. However, posthepatic portal hypertension is a significant condition in children (see Box 71.1). Obstruction to hepatic venous outflow, such as from hepatic vein anastomotic stenosis, can occur after liver transplantation, with Budd-Chiari syndrome, or as a result of cardiac lesions that cause an increase in right atrial pressure and/or chronic systemic venous hypertension. Acute Budd-Chiari syndrome is rare in children; although it may occur with some thrombophilic disorders, it is usually idiopathic and is not associated with the causes seen in adults, such as myeloproliferative disorders. A cavopulmonary or atriopulmonary shunt, known as a *Fontan procedure*, allows life-saving systemic-pulmonary blood flow in single-ventricle syndromes in neonates but results in chronic systemic venous hypertension (pressures may be >20 mm Hg) and eventually to portal hypertension (Narkewicz et al, 2003).

Box 71.1

Causes of Portal Hypertension in Children

Extrahepatic

Extrahepatic portal vein obstruction/thrombosis
Congenital malformations and diseases
Acquired conditions (dehydration)
Anastomotic stenosis or thrombus (after liver transplantation)
Portal vein stenosis

Intrahepatic

Presinusoidal: congenital hepatic fibrosis
Sinusoidal: cirrhosis (biliary atresia, metabolic hepatopathies)
Postsinusoidal: venoocclusive diseases

Posthepatic

Budd-Chiari syndrome (webs, thrombophilia, idiopathic)
Anastomotic stenosis or thrombus (after liver transplantation)
Constrictive pericarditis
After a Fontan procedure

EFFECTS OF PORTAL HYPERTENSION IN CHILDREN

An understanding of portal hypertension requires knowledge of the anatomy and physiology of the portal system in infants and children. In fetal life, the ductus venosus connects the umbilical vein and the inferior vena cava (IVC), and the umbilical vein joins the left branch of the portal vein (PV); these may persist, and in some situations they may remain patent postnatally. Portal capillaries originate in the mesentery of the intestine and spleen and in the hepatic sinusoids. Capillaries of the superior mesenteric and splenic veins supply the PV with nutrient-rich and hormone-rich blood. At the hilum of the liver, the PV divides into two major trunks that supply the right and left lobes of the liver, and these trunks undergo a series of divisions to supply various segments of the liver; these terminate in small branches that pierce the limiting plate of the portal tract and enter the sinusoids through short channels. The partly oxygenated portal venous blood supplements the oxygenated hepatic arterial blood flow to give the liver unique protection against hypoxia. Blood flow from both the hepatic artery and the PV is well regulated, allowing the liver to withstand thrombosis of either one of these major vessels.

The major pathologic effect from portal hypertension is the development of collaterals that carry blood from the portal venous system to the systemic circulation in the upper part of the stomach, esophagus, rectum, and falciform ligament. These collaterals may drain into the IVC via the umbilical vein remnant, or they may drain into the left renal vein (see Fig. 71.1). Absence or disconnection of the IVC or interruption to the azygos system, such as occurs in some cases of bilary atresia, may cause special concern. Similarly, in extrahepatic portal venous malformations, the splenic vein can be small and possibly thrombosed.

Only the submucosal collaterals, such as in the esophagus and stomach and rarely in other parts of the intestine, are associated with GI bleeding. Collaterals in other parts of the intestine are more frequent and are more likely to occur at sites of surgery along the GI tract, particularly from stoma and anastomotic sites. Portal hypertensive gastropathy, which is suggested by dilated mucosal veins and capillaries and mucosal congestion in the stomach, may occur after esophageal variceal obliteration.

Although changes in vascular resistance to flow of blood between the splanchnic bed and the right atrium appear to be the initial events in the development of portal hypertension, a number of other hemodynamic changes contribute to and amplify the increased portal blood pressure. There is a

Box 71.2

Clinical Features of Portal Hypertension in Children

- Splenomegaly
- Esophageal varices with bleeding
- Portal gastropathy with bleeding
- Recurrent epistaxis, easy bruising
- Ascites
- Malabsorption
- Protein-losing enteropathy
- Growth failure
- Anemia, thrombocytopenia

hyperdynamic circulatory state with increased cardiac and decreased splanchnic arteriolar tone, both of which increase portal inflow. Changes in intravascular volume also play an important role, as do alterations in adrenergic tone in the splanchnic system. These observations have led to new experimental and clinical studies that suggest possible pharmacologic treatments for portal hypertension (Boyer, 2001). However, because the major clinical effect is that of bleeding from esophageal varices, direct treatment of variceal hemorrhage, or shunt surgery in selected cases, remains the primary approach, except in the presence of liver decompensation, in which case the treatment of choice is liver transplantation (see Chapters 97A and 98A).

CLINICAL FEATURES

The main clinical features are splenomegaly, nutritional growth failure, and ascites, along with esophageal, gastric, and rectal varices (Box 71.2).

In extrahepatic portal hypertension, or in the presence of compensated liver disease, symptoms may be absent. The first indication of portal hypertension may be a GI hemorrhage, an incidental finding of splenomegaly alone, anemia, or thrombocytopenia as a result of hypersplenism. The liver is commonly small and impalpable; with an intrahepatic cause, however, it can be enlarged, hard, or nodular with a small right lobe and/or splenomegaly. Cutaneous features such as spider angiomata, prominent periumbilical veins (*caput medusae*), and palmar erythema may provide a clue to the presence of liver disease. Spider angiomata may also occur in healthy children younger than 5 years and thus are not pathognomonic of liver diseases in children. However, the appearance of new spider angiomata or more than five or six may be indicative. They are frequently observed in the vascular drainage of the superior vena cava and feature a central arteriole from which radiate numerous fine vessels, ranging from 2 to 5 mm in diameter. Other cutaneous features include easy bruising; fine telangiectasia on the face and upper back; white spots, most often on buttocks and arms, which when examined with a lens show the beginnings of spider angiomata; and clubbing of the fingers. On intranasal examination, prominent telangiectasia of the area of Little is common and is associated with recurrent epistaxis.

Although compensated cirrhosis in adults is mostly cryptogenic, metabolic liver diseases, such as Wilson disease, cystic fibrosis, and α_1-antitrypsin deficiency, may present with compensated cirrhosis in children. In Wilson disease, specific features include hemolytic anemia and subtle signs of encephalopathy that include personality changes, loss of memory, or school failure; Kayser-Fleischer rings may also be present, evident to an experienced examiner with a slit lamp. Children with cholestatic liver disease will have predominant signs or symptoms of persisting jaundice or pruritus. The liver is usually enlarged, and xanthelasma, malnutrition, and deficiency of fat-soluble vitamins, particularly vitamins D and K, may be prominent features.

Decompensated liver disease is characterized by clinical and laboratory findings of liver synthetic failure and by the occurrence of complications; in addition to the features mentioned above, the major features include malnutrition, ascites, peripheral edema, coagulopathy, and GI bleeding.

Signs of hepatic encephalopathy are subtle and uncommon in children with portal hypertension. Malnutrition with reduced lean tissue and fat stores as well as poor linear growth is a well-recognized and important feature resulting from malabsorption and impaired protein synthesis (Chin et al, 1992). Spontaneous bruising caused by impaired hepatic production of clotting factors and thrombocytopenia as a result of hypersplenism are signs of advanced disease. Cirrhosis with decompensation may also be associated with changes in the systemic and pulmonary circulations and with arteriolar vasodilation, increased blood volume, a hyperdynamic circulatory state, and cyanosis as a result of intrapulmonary shunting. Renal failure is a late but serious event.

DIAGNOSIS

Confirmation of the diagnosis of portal hypertension is based on the suggestive clinical findings detailed above, with or without signs of chronic liver disease, and on four investigations: ultrasonography, endoscopy, liver biopsy, and angiography.

Ultrasonography allows visualization and measurement of the size, patency, and flow of the portal vein, the occurrence of a cavernoma, and information about liver size and homogeneity. Renal cysts on ultrasound or a suggestive family history may provide a clue to the diagnosis of congenital hepatic fibrosis. Echocardiography is useful to exclude primary cardiac causes of hepatic venous outflow obstruction.

Endoscopy should be performed to evaluate the occurrence of varices, and the presence of cherry-red spots, which correlate with risk of rupture, and to visualize and perhaps treat the source of bleeding varices. Other features can be visualized, such as portal gastropathy and features that help exclude other sources of GI bleeding.

Liver biopsy either aids in the diagnosis of cirrhosis or excludes liver disease, as in the case of extrahepatic obstruction. Differentiation between cirrhosis and presinusoidal and extrahepatic causes of portal hypertension, such as congenital hepatic fibrosis and extrahepatic portal hypertension, can sometimes cause diagnostic difficulties. In both of these latter conditions, no signs of chronic liver disease are apparent, and transaminases and synthetic liver function are normal. In congenital hepatic fibrosis, the liver is enlarged and hard, and hepatocytes are normal histologically, but prominent, abnormal bile ducts appear in wide bands of fibrous tissue, although nodules are absent. In extrahepatic portal hypertension resulting from PV malformation or obstruction, the liver is small but histologically normal, although some steatosis may be evident. Mild derangement of coagulation parameters may be evident secondary to an underlying coagulation disorder, such as a protein C or S deficiency. Obstruction of hepatic venous outflow causes centrilobular hemorrhagic necrosis, with fibrosis that extends from central veins to portal tracts.

A full range of laboratory and imaging investigations should be performed before a liver biopsy. Such investigations may be diagnostic for the underlying cause and may allow appropriate

handling of the liver biopsy specimen in regard to specific histologic and biochemical analysis, particularly for metabolic disorders.

Angiography, either direct venography or computed tomography (CT) angiography, can provide important information about the site of the blockage, the size and patency of major veins in the portal system, and relationship to the coronary esophageal or other varices (see Chapters 16 and 19). Suspected obstruction to hepatic venous outflow requires venography and/or cardiac catheterization, which are the diagnostic procedures of choice in such cases. Pressure gradient measurements may be useful across venous blocks and to determine the magnitude of the portal pressure.

MANAGEMENT (SEE CHAPTERS 74 TO 76E)

Therapy for portal hypertension is primarily directed at the major complication—the prevention and management of variceal hemorrhage—except in cases for which directly treatable causes must be considered, including end-stage liver disease, for which liver transplantation is the primary therapy, hepatic venous outflow obstruction, vena caval webs, and constrictive pericarditis. Encephalopathy rarely requires specific therapy, but ascites can be a major problem and often does require specific treatment. Although common, hypersplenism rarely results in morbidity or death. The management of these and other complications of portal hypertension in children is primarily medical and is beyond the scope of this chapter.

In most cases, direct therapy of varices is indicated before considering surgery because the various options for creation of a surgical shunt are indirect treatments for varices by reduction in portal pressure. The four main factors that influence any decision for the application of shunt surgery in children are the risk of variceal bleeding, the potential evolution of spontaneous shunts over time, the presence or absence of liver disease, and the portal vascular anatomy.

Variceal hemorrhage presents clinically as a need for emergency therapy or as a need for prophylaxis of initial or subsequent rebleeding. Most of the data concerning the management of variceal hemorrhage have come from large controlled trials in adults, and the pediatric literature is generally descriptive or anecdotal, with some exceptions.

Emergency Therapy

Bleeding esophageal varices in children require emergency treatment (Fig. 71.2); no matter how small the hemorrhage, admission to the nearest hospital with blood transfusion facilities is advised. As soon as the blood transfusion available and the patient has a secure intravenous infusion line and is hemodynamically stable, referral to a tertiary center with experience in the management of variceal hemorrhage in children is recommended. Initial melena or other signs of a sentinel hemorrhage may precede sudden hematemesis and shock, which require rapid blood transfusion to prevent death. Significant bleeding with hypotension impairs hepatic perfusion, often causes deterioration of liver function, and precipitates ascites and encephalopathy. Initial fluid management in the form of crystalloids followed by red blood cell transfusion is important, and any coagulopathy should be corrected with vitamin K and fresh frozen plasma. Pharmacologic therapy with a short-acting splanchnic vasoconstrictor may be useful (Boyer, 2001).

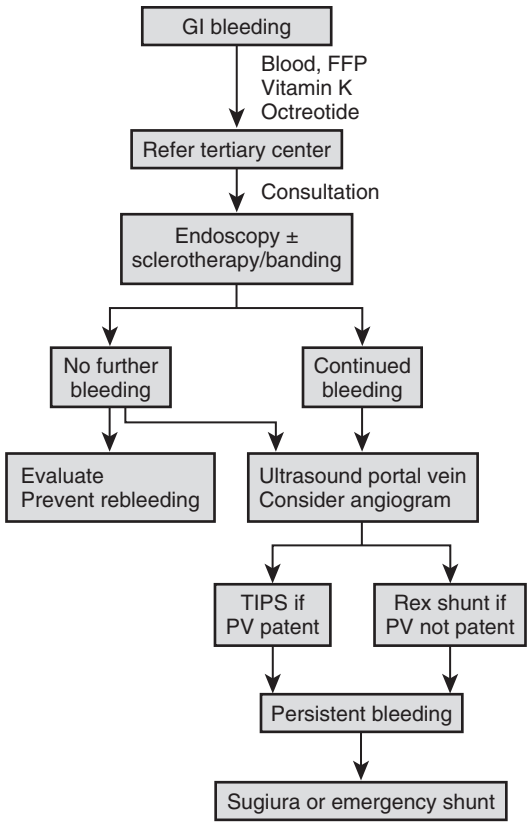


FIGURE 71.2. Management of acute variceal bleeding in children. FFP, fresh frozen plasma; GI, gastrointestinal; PV, portal vein; TIPS, transjugular intrahepatic portosystemic shunting.

Octreotide is the drug of choice in this circumstance (maximum dose 1 μg/kg/h IV or 2 to 4 μg/kg/8 h subcutaneously for 24 h, or until bleeding has ceased) because of fewer side effects (Moitinho, 2001). Alternatives are vasopressin (0.3 U/kg as a bolus over 20 minutes followed by continuous infusion of the same amount on an hourly basis) or its inactive precursor, glypressin (0.01 mg/kg bolus q4-6h or 0.05 mg/kg infusion over 6 h for 24 to 48 h). Common side effects include skin pallor, abdominal colic, and chest pain. Studies in adults have indicated that an adjunctive vasodilator, such as nitroglycerine in the form of a 10-mg patch, may reduce these hemodynamic complications. Nasogastric intubation is an essential part of management, allowing the documentation of ongoing bleeding and the removal of blood that could precipitate encephalopathy.

When the patient is hemodynamically stable, endoscopy is indicated. A significant percentage of patients with known varices have bleeding from sources other than the varices, including duodenal or gastric ulceration. In addition, meta-analysis of multiple controlled adult studies clearly shows that endoscopic treatment plus pharmacologic treatment is currently the best measure to achieve initial control of significant acute variceal bleeding (Banares et al, 2002).

Endoscopic Treatment of Acute Variceal Bleeding

Episodes of minor variceal hemorrhage may spontaneously terminate, but endoscopic treatment by sclerotherapy or band ligation is often necessary (Fig. 71.3). Both techniques are well described in children (Goenka et al, 1993; Goncalves et al,

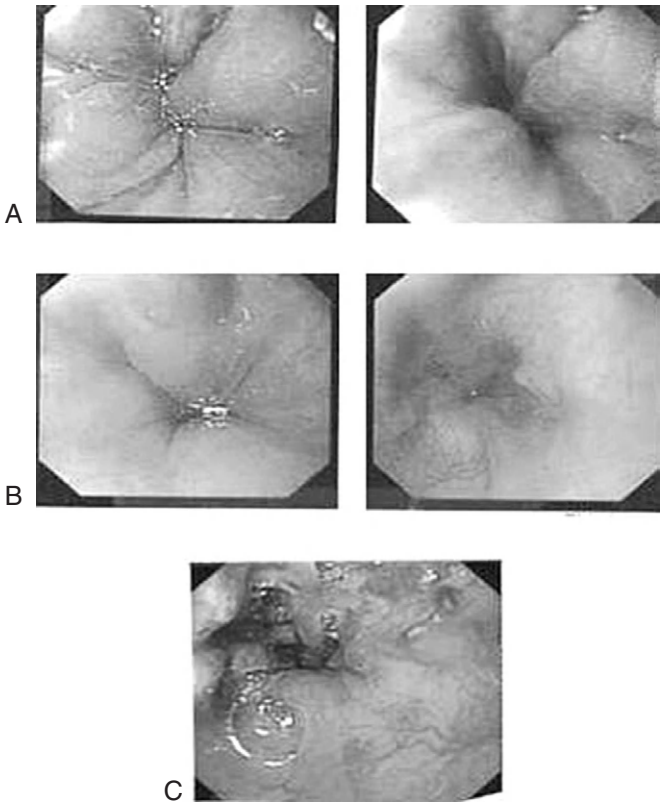


FIGURE 71.3. Ablation of esophageal varices by sclerotherapy in a 6-year-old child with portal hypertension after a Fontan procedure for congenital heart disease.

2000; Zargar et al, 2002). In adults, comparative trials of sclerotherapy and ligation indicate equal efficacy in controlling bleeding, reducing rebleeding, and ablating varices, but fewer adverse effects are reported with banding. The two procedures can be complementary, and access to both procedures may be warranted. Ligation may be technically difficult in an esophagus awash with blood or for small varices, particularly in small infants, where entrapment of part of the esophageal wall with perforation or bleeding can occur. In these circumstances, sclerotherapy is more appropriate.

Sclerotherapy involves injection of sclerosant (ethanolamine or tetradecyl sulfate) either paravariceally or intravariceally in volumes of 0.5 to 1.0 mL just above the gastroesophageal junction. Care should be taken to avoid injecting too high above the cardia, which can increase bleeding from a distal varix. This procedure is associated with bacteremia, and broad-spectrum antibiotics should be prescribed (amoxicillin, cefuroxime, metronidazole). Complications, which should be uncommon in experienced centers, include esophageal ulceration, stricture, and pain.

Sengstaken-Blakemore Tube

Should the measures described above fail to control bleeding, which is rare, temporary cessation of bleeding can be achieved using mechanical compression of esophageal and gastric varices using a pediatric Sengstaken-Blakemore tube or a Linton tube. These devices are best inserted under anesthesia at the time of attempted sclerotherapy but should not be used for longer than 24 or 48 hours because of the risk of ulceration, particularly in the esophagus. A high incidence of rebleeding is reported when the tubes are removed.

Emergency Surgical Approaches and Emergency Portosystemic Shunts (See Chapters 75A to 76E)

Emergency creation of portosystemic shunts or other surgical therapy is usually a last resort for persistent, acute, exsanguinating variceal hemorrhage. Patients with shunts who come to the emergency department often have gastric variceal bleeding. Considerations in these circumstances include potential death, and the range of techniques available include transjugular intrahepatic portosystemic shunting (TIPS), surgical shunting, esophageal transection, and esophagogastric devascularization with splenectomy. TIPS is an attractive approach because it does not require major surgery. It has been used effectively in critically ill adults to control bleeding before liver transplantation, and it has also been used in some children with bleeding stomal varices (Lagier et al, 1994). The procedure appears to decrease portal pressure acutely, although 60% occlude within 3 to 12 months; therefore it is best viewed as a bridging procedure only. Pediatric application is limited by size constraints, but in experienced hands and in selected children older than 2 to 5 years, the procedure has application and is preferable to major shunt surgery for hepatic causes of portal hypertension.

Prophylaxis Against the First Gastrointestinal Bleed

In recognized cases of portal hypertension with varices, controversy exists regarding whether any therapy reduces the risk or prevents the occurrence of GI bleeding. However, in all cases it is reasonable to be prepared for the possibility by ensuring that the child's caregivers understand the importance of seeking early medical advice by attending the nearest hospital for blood crossmatching and appropriate referral to a tertiary unit. β-Blockers, such as propranolol and the more selective atenolol, reduce hepatic arterial and portal vein blood flow and have been studied with respect to reduction in portal pressures to less than 12 mm Hg, thereby reducing the risk of an initial hemorrhage (Shasidhar et al, 1999). Under certain circumstances, prophylactic sclerotherapy may be indicated, but the potential in children for bleeding of known varices that have never bled is conjectural. Goncalves and colleagues (2000) compared sclerotherapy to no treatment in a controlled clinical trial in children and found a reduced risk of bleeding but an increase in portal gastropathy.

Prevention of Recurrent Gastrointestinal Bleeding

Intrahepatic Causes of Portal Hypertension

DIRECT OBLITERATION OF VARICES. Where bleeding has occurred from intrahepatic causes of portal vein obstruction, direct obliteration of the varices is the initial treatment of choice, although consideration of the underlying liver disease is the major determinant of long-term management. Randomized controlled trials in adults have shown a reduction in the frequency of bleeding and improved survival. Although no randomized controlled trials have been performed in children,

several large studies of sclerotherapy or banding in children with portal hypertension indicate that both procedures are safe, and both reduce the chance of rebleeding (Fox et al, 1995; Goenka et al, 1993; McKiernan et al, 2002). Neither technique reduces portal pressure, but both obliterate the dangerous varices. The procedures described above may cause some interference with the vascular hemodynamics; hypersplenism and portal gastropathy temporarily gets worse, but ultimately, with time, spontaneous portosystemic shunts will arise to reduce portal pressures.

In multiple controlled trials in adults, several vasoactive drugs have also now been documented to reduce the risk of rebleeding by reducing portal and systemic pressures (Boyer, 2001). A combination of a nonselective β-blockers and certain nitrates, such as isosorbide 5-mononitrate, are the drugs of choice, aiming at a 25% reduction in resting heart rate. Major adverse effects of β-blockers include reactive airway disease and heart block, in which cases they are contraindicated.

SURGERY. Where there is active liver disease and a significant risk of death from bleeding, surgical management of portal hypertension is a major consideration (Box 71-3). Such patients should ideally be evaluated and treated in a transplant center, where the range of surgical options can be assessed. *Surgical portosystemic shunts* may reduce the risk of GI bleeding, but they cause a decrease in portal blood flow and hepatic perfusion, and they carry the risks of hepatic decompensation and encephalopathy, which either enhances the difficulty of liver transplantation or precludes it entirely. Moreover, randomized controlled trials in adult patients have not shown any significant improvement in survival with portosystemic shunts in patients with intrahepatic causes of portal hypertension. If a shunt operation is contemplated in a critically ill patient, the use of TIPS as a bridging procedure is probably the best choice. Ultimately, the surgical procedure of choice for uncontrolled portal hypertension as a result of intrahepatic disease is liver transplantation. In nonshunt, nontransplant candidates, a Sugiura procedure (esophageal disconnection and devascularization) may be life saving, with the added advantage of a low-risk of encephalopathy.

Special consideration should be given to shunt surgery in some cases of liver disease associated with cystic fibrosis, in which there is a slow evolution of hepatic dysfunction (Debray et al, 1999), and in congenital hepatic fibrosis, a presinusoidal cause of portal hypertension not associated with the occurrence of liver synthetic dysfunction. In these cases, the choice of the type of shunt is determined by the vascular anatomy, the size of the veins, the risk of thrombosis and failure, and the risk of encephalopathy. *Selective shunts* are preferred, such as distal splenorenal or distal splenoadrenal shunts (see Chapter 76; Valayer et al, 1985; Kato et al, 2000); the latter often allows better size matching of the splenic and enlarged adrenal vein and avoids renal vein clamping.

Box 71.3

Surgical Options for Portal Hypertension in Children

- Devascularization
  - Sugiura procedure
- Nonselective shunts
  - Mesocaval (H-graft or direct)
  - Portacaval
  - Central splenorenal
  - TIPS
- Selective shunts
  - Distal splenorenal
  - Splenoadrenal
- Restorative shunt
  - Rex shunt (mesenteric left portal bypass)
- Anatomic repair
  - Hepatic or portal webs, stenosis
- Orthotopic liver transplantation

TIPS, transjugular intrahepatic portosystemic shunting

Extrahepatic Portal Venous Obstruction

Portal hypertension as a result of extrahepatic portal venous obstruction in children is associated with a better long-term prognosis and quality of life than portal hypertension associated with intrahepatic diseases, and management considerations are quite different. Acute variceal bleeding is usually well tolerated because of normal liver function, but recurrent variceal bleeds can be associated with significant morbidity (Zargar et al, 2004). Although long-term outcomes of individual center approaches have been documented (Bambini et al, 2000; Orloff et al, 2002; Zargar et al, 2004), no controlled trials have compared long-term outcomes from the two main approaches to therapy: direct variceal ablation and shunt surgery. This is compounded by the fact that some patients never bleed at all, and anecdotal and published data suggest that some patients develop spontaneous decompression of their varices over time (Goenka et al, 1993; Lykaverios et al, 2000).

DIRECT VARICEAL ABLATION. Endoscopic therapy has gained increasing acceptance in the treatment of bleeding esophageal varices in children with extrahepatic portal hypertension. Zargar and colleagues (2004) reported a 15-year follow-up of 69 children. Almost 90% had no rebleeding after eradication, which was achieved in 90% of patients. Maksoud and colleagues (1991) reported that 7% to 8% of patients did not respond to sclerotherapy and subsequently underwent shunt surgery. Stringer and Howard (1994) reported that only 4 (11%) of 36 patients required shunt surgery after variceal sclerotherapy over an 8-year follow-up. All these studies had little or no morbidity or deaths, but several repeat sessions of sclerotherapy were necessary during follow-up for complete variceal eradication. The main reason for long-term failure was the occurrence of gastric varices, but clearly this does not occur in all cases, and some studies suggest that the occurrence of spontaneous shunts after successful sclerotherapy negates the need for shunt surgery altogether (Goenka et al, 1993).

SURGERY. Surgery may be required for patients with extrahepatic portal hypertension with preserved liver function for recurrent bleeding or, rarely, for massive hypersplenism. Surgical options in the management of extrahepatic portal venous obstruction include portosystemic shunts, Rex shunts (mesenteric left portal bypass), devascularization, and transection (see Box 71.3).

Although earlier outcomes of portosystemic shunts were disappointing, some recent reports of have shown recurrence of bleeding in only 2.5% to 10%, low mortality rates, a continued shunt thrombosis rate of 7% to 13%, and an apparently low risk of encephalopathy (Botha et al, 2004; Kato et al, 2000; Orloff et al, 2002). Nonselective mesocaval shunts and the more selective distal splenorenal shunt have been the procedures of choice in the past, although a central splenorenal shunt with splenectomy is sometimes advocated if massive hypersplenism and pain from splenic infarcts are present. However, these shunts may

not be technically possible because of thrombotic involvement of splenic or mesenteric veins, and in some cases, particularly where varices are derived from the cavernoma, certain shunts may not alter variceal pressures to the coronary esophageal veins.

The *Rex shunt,* usually an internal jugular vein graft and mesenteric to left portal vein bypass, has the major theoretical advantage of restoring portal flow to the liver and reducing risk of encephalopathy, and it obviates the technical problems associated with splenic vein thrombosis (Bambini et al, 2000; de Ville de Goyet, 1999). First introduced for portal vein thrombosis after liver transplantation, this procedure may become the surgical procedure of choice for all causes of extrahepatic portal vein obstruction. Thrombosis and stenosis rates appear to be similar to those of portosystemic shunts. Patency of the intrahepatic portal system can be difficult to prove before the procedure. The use of a preprocedural portal venogram to ensure patency antegrade to the liver is important when performing any type of shunt surgery for extrahepatic venous obstruction, particularly where a cavernoma is present; selective division of the portal system (e.g., coronary branch), where there are residual collaterals, must also be considered.

SUMMARY

Therapeutic options for children with portal hypertension now include a broad range of pharmacologic, endoscopic, radiologic, and surgical procedures, the latter being mainly indicated in those at high risk for recurrent variceal bleeding. Thorough assessment of the causes, effects, venous anatomy, and consequent selective application of some or all of these options can improve quality of life, reduce the complications of portal hypertension, and decrease mortality rate.

Where there is preserved liver function, children with variceal bleeding as a result of extrahepatic portal hypertension can usually be effectively and safely managed with initial direct variceal ablation by sclerotherapy or banding, which in many cases can alter the natural history of the disease and reduce the risk of rebleeding. The development of portal hypertensive gastropathy and/or rebleeding after these palliative procedures can be definitively managed by shunt surgery, preferably with the more physiologic Rex shunt.

Patients with intrahepatic portal hypertension who are transplantation candidates are best palliated with endoscopic treatment but occasionally benefit from TIPS. Those who are not candidates for transplantation and those who have not responded to nonsurgical treatments can have good outcomes with selective portosystemic shunts. Well-planned, definitive surgical treatments will continue to be important components in the treatment of children with portal hypertensive complications or progressive liver disease.

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CHAPTER 72

Management of liver failure

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LIVER FAILURE

Liver failure presents as one of two quite distinct clinical problems: the specific entity of *acute liver failure,* a term used interchangeably with *fulminant hepatic failure,* and the more frequently encountered scenario of an episode of acute decompensation of established chronic liver disease, called *acute-on-chronic liver failure*. Acute liver failure evolves after a catastrophic insult to the liver and results in the development of encephalopathy within a matter of days or weeks of the liver injury. Acute-on-chronic liver failure usually occurs in patients with cirrhosis and is often precipitated by infection or gastrointestinal hemorrhage. The principles of management are similar in some respects, such as the treatment of encephalopathy and coagulopathy, but very different in others; for example, cerebral edema is almost exclusively observed in acute liver failure. The presentation of this chapter is based mainly on acute liver failure unless specified otherwise.

Acute liver failure is a heterogeneous condition that incorporates a range of clinical syndromes. The dominant factors that give rise to this heterogeneity include the underlying etiology, which varies significantly from country to country (Table 72.1); the age of the patient; and the duration of time over which the disease evolves. Natural history studies indicate that survival rates without liver transplantation range from 10% to 90%, with the best outcomes seen in patients with pregnancy-related syndromes, acetaminophen overdose, and hepatitis A. Survival rates are also poor in older patients and possibly in very young children.

The rate of progression of the disease is used to classify patients into groups with differing clinical problems and outcomes. Universal agreement on terminology is lacking, but the main options in use, and the terms used in this chapter, are *hyperacute liver failure,* or encephalopathy within 7 days of the onset of jaundice; *acute liver failure,* encephalopathy within 8 to 28 days of the onset of jaundice; and *subacute liver failure,* encephalopathy that occurs more than 28 days after the onset of jaundice.

ETIOLOGY OF ACUTE LIVER FAILURE

Viruses and drugs account for the majority of cases of acute liver failure, although a significant number of patients have disease for which no definable cause can be found. The latter condition is referred to as *seronegative hepatitis* in this chapter, but it is also known as *non–A-E hepatitis* and *acute liver failure of indeterminate etiology.* In the United States, the overall incidence of acute liver failure as a complication of acute hepatitis is 0.9%, which equates to approximately 2000 deaths annually. Most of the drug-induced cases are rare, idiosyncratic reactions, but some cases, such as those involving acetaminophen, are at least in part dose-related toxic events.

Viral

Acute liver failure is a very uncommon complication of hepatitis A infection, occurring in 0.14% to 0.35% of hospitalized patients and in 0.4% of all cases seen in the United States. The incidence of acute liver failure following hepatitis B infection is 1% to 4% of hospitalized patients. In early studies, hepatitis D coinfection or superinfection was thought to increase the risk, as it was found in 34% to 43% of patients with acute liver failure as a result of hepatitis B infection compared with 4% to 19% of less severe cases. However, the prevalence of hepatitis D appears to have decreased dramatically in recent years. Vaccination and antiviral therapy with drugs that have a rapid onset of action (e.g., lamivudine, tenofovir) should alter the observed pattern of hepatitis B–related acute liver failure (Sjögren, 2003). The risk of developing acute liver failure after exposure to hepatitis C appears to be low, although well-documented cases have been reported. Hepatitis E is common in parts of Asia and Africa but is being increasingly recognized in Western countries. The natural history of hepatitis E in India has recently been revised to show that, although pregnant females are more likely to develop acute liver failure, the outcome is independent of sex, pregnancy status, and trimester of pregnancy (Bhatia et al, 2008).

Seronegative hepatitis accounts for 14% to 32% of acute liver failure in the Western world. In the United States, a proportion of these events are considered to be related to acetaminophen (Davern et al, 2006). There is little evidence to suggest that an unrecognized viral infection is to blame because most cases are sporadic. Unidentified toxins or autoimmune processes may be the underlying mechanisms. Middle-aged females are most frequently affected, and the risk of developing acute liver failure has been calculated at 2.3% to 4.7% of hospitalized cases.

Drugs

Acetaminophen (paracetamol) overdose is the commonest cause of acute liver failure in the United Kingdom and the United States (Bernal, 2003; Lee, 2003). In the United Kingdom, excess amounts are usually taken with suicidal or parasuicidal intent; only 8% of such events were ascribed to inadvertent overdose with therapeutic use. However, in the United States, unintentional overdoses accounted for at least 48% of cases (Larson et al, 2005). Susceptibility to developing acetaminophen hepatotoxicity is increased in people with liver enzyme induction as a consequence of antiepileptic therapy, regular alcohol consumption, or malnutrition.

Table 72.1

Geographic Variation in the Etiology of Acute Liver Failure

Cause	U.K. (%)	U.S. (%)	France (%)	India (%)	Japan (%)	Spain (%)
Acetaminophen	54	46	2	—	—	2
Drug reactions	7	12	15	5	—	17
Seronegative	17	14	18	24	45	32
Hepatitis A or B	14	10	49	33	55	37
Hepatitis E	—	—	—	38	—	—
Other causes	8	18	16	—	—	12

Drug-induced liver injury resulted in liver-related death in 3% to 4% of cases in a prospective study of 300 cases (Chalasani et al, 2008). More than 100 different agents were implicated, with 46% being associated with antimicrobials and 15% with central nervous system agents. Some of the more common offending drugs linked to acute liver failure are listed in Box 72.1. The risk of developing acute liver failure from an idiosyncratic reaction ranges from 0.001% for nonsteroidal antiinflammatory drugs (NSAIDs) to 1% for the isoniazid/rifampicin combination. Nontherapeutic drugs, such as MDMA (3,4-methylenedioxymethamphetamine; "ecstasy") and some herbal remedies, can also cause acute liver failure. The diagnosis is made on the basis of a temporal relationship between exposure to the drug or hepatotoxin and the development of acute liver failure.

Other Etiologies

Acute liver failure associated with pregnancy tends to occur during the third trimester. Three discrete entities have been described, but considerable overlap is frequently observed. *Acute fatty liver of pregnancy* usually occurs in primagravids carrying a male fetus and is characterized by severe microvesicular steatosis. The syndrome is defined as the combination of ***h***emolysis, ***e***levated ***l***iver enzymes and ***l***ow ***p***latelets (HELLP). Acute liver failure complicating preeclampsia or eclampsia typically exhibits very high serum transaminase levels and abnormal tissue perfusion patterns on CT scanning that reflect the microvascular infarction characteristic of this condition.

Wilson disease may present as acute liver failure, usually during the second decade of life. It is characterized clinically by a Coombs test negative for hemolytic anemia and demonstrable Kayser-Fleischer rings in the majority of cases. Poisoning with *Amanita phalloides* mushrooms is most commonly seen in central Europe, South Africa, and the West Coast in the United States. Severe diarrhea, often with vomiting, is a typical feature and commences 5 hours or more after ingestion of the mushrooms; liver failure develops 4 to 5 days later. Autoimmune chronic hepatitis may present as acute liver failure, but by then, it is usually beyond rescue with corticosteroid or other immunosuppressive therapy. Budd-Chiari syndrome (see Chapter 77) may present with acute liver failure, and the diagnosis is suggested by hepatomegaly and confirmed by the demonstration of hepatic vein thrombosis. Malignancy infiltration, especially with lymphoma, is another rare cause of acute liver failure that is typically associated with hepatomegaly. Ischemic hepatitis is being increasingly recognized as a cause of acute liver failure, especially in older patients. Other unusual causes of acute liver failure include heat stroke and sepsis.

Box 72.1

Examples of Drugs Causing Acute Liver Failure

Category 1: Common Causes	Category 2: Rarer Causes
Paracetamol	Benoxyprofen
Halothane	Phenytoin
Isoniazid/rifampicin	Isoflurane
Nonsteroidal antiinflammatory drugs	Enflurane
Sulfonamides	Tetracycline
Flutamide	Allopurinol
Sodium valproate	Ketoconazole
Carbamazepine nimesulide	Monoamine oxidase inhibitors
Lamotrigine	Disulphiram
Rosiglitazone	Methyldopa
Ecstasy	Amiodarone
	Tricyclic antidepressants
	Propylthiouracil
	Clozapine 2,3,-dideoxyinosine

Pediatric Causes

Children are at risk of developing some of the causes of acute liver failure discussed above, but they also are vulnerable to other unique underlying causes, especially in the category of metabolic disease. Neonatal hemochromatosis may occur within the first few weeks of life and has been treated by liver transplantation as early as 5 days of age. Acute liver failure as a result of mitochondrial disorders may be triggered by bacterial infections and are characterized by high lactate levels in blood. Other metabolic causes include tyrosinemia, galactosemia, and fructose intolerance. Young infants can develop acute liver failure with viral infections, such as adenovirus, coxsackie virus, and cytomegalovirus (see Chapter 71).

DIAGNOSIS

The diagnosis of acute liver failure is a clinical one based on the detection of encephalopathy in patients with acute liver disease. The diagnosis of encephalopathy is generally made on overt clinical criteria, but psychometric testing may be useful in patients with subacute liver failure to detect subtle changes in mental state. Commonly, hypoglycemia and, unusually, uremia may mimic hepatic encephalopathy in patients with acute liver failure; these need to be excluded before the diagnosis is confirmed.

The etiology of acute liver failure must be accurately identified; the appropriate investigations are outlined in Tables 72.2 and 72.3 and cover the key essential investigations and those

Table 72.2

Core Investigation of the Etiology of Acute Liver Failure

Etiology	Investigation
Hepatitis A virus (HAV)	IgM anti-HAV
Hepatitis B (HBV) + D (HDV)	IgM anticore, HBV DNA (NB HBsAg may be negative)
Hepatitis E virus (HEV)	Anti-HEV
Paracetamol	Drug levels in blood

IgM, immunoglobulin M; *NB HbsAg,* hepatitis B surface antigen.

that are relevant in certain circumstances, respectively. Imaging assesses the size and shape of the liver and screens for portal hypertension; however, the detection of portal hypertension does not always indicate chronic liver disease because ascites and/or splenomegaly may be seen in subacute liver failure and in the acute presentation of Wilson disease.

Histologic assessment of liver tissue may aid the diagnosis of the cause of acute liver failure (see Chapter 70A). Confluent necrosis is the most common histologic finding; it may be zonal or may involve all of the parenchyma. Necrosis that is zonal within the acinus and coagulative or eosinophilic is more likely to be secondary to a toxic insult or ischemia. The features of necrosis and parenchymal collapse may be interspersed with evidence of regeneration, either occurring in a diffuse pattern of small areas throughout the liver or in randomly occurring larger nodules that give the maplike pattern that has often been described in this condition. The latter pattern is most commonly seen in patients with subacute liver failure.

Histologic features may suggest specific diagnoses, including sodium valproate toxicity, malignant infiltration, Wilson disease, pregnancy-related syndromes, and Budd-Chiari syndrome. Sodium valproate toxicity is characterized by microvesicular steatosis. Screening for malignant infiltration as the cause of acute liver failure is one of the stronger indications for performing a liver biopsy in this condition. Patients with Wilson disease that presents as acute liver failure usually have established cirrhosis, commonly associated with interface hepatitis that resembles autoimmune disease, with hepatocyte ballooning and steatosis. Liver histology may be very useful in making a precise diagnosis within the spectrum of pregnancy-related liver diseases. The histologic features of Budd-Chiari syndrome are extreme sinusoidal dilation, congestion, and coagulative necrosis.

Liver biopsy may also be of assistance in differentiating acute liver failure from established cirrhosis and acute alcoholic hepatitis, whether or not it is associated with cirrhosis. The former scenario can usually be distinguished on clinical grounds, but acute alcoholic hepatitis can present with clinical features very similar to subacute liver failure. A history of high alcohol consumption may not be available, but the diagnosis of acute alcoholic hepatitis is suggested by the investigational findings outlined in Box 72.2.

Box 72.2

Findings Suggestive of Acute Alcoholic Hepatitis

Hepatomegaly
Marked elevation of γ-glutamyl transferase
High white cell count not responding to antibiotics
Elevated immunoglobulin A level
Appearance of fatty infiltration on ultrasound

PROGNOSIS

In acute liver failure, the grade of encephalopathy correlates strongly with outcome; this is true for both the grade of encephalopathy at the time of presentation to a specialist unit and the maximum grade attained. The prognosis deteriorates further when grade 4 encephalopathy is complicated by cerebral edema and is even worse when the latter coexists with renal failure. However, other patients with acute liver failure have a very poor prognosis despite the absence of cerebral edema and renal failure. This is especially true of patients with subacute liver failure who, in addition, often do not manifest severely abnormal coagulation parameters.

The use of transplantation has intensified the need for early indicators of prognosis, so that those in need of this intervention could be identified as quickly as possible (see Chapter 97C). The King's College criteria, with some modifications, are still widely used to identify the patients most in need of liver transplantation (Boxes 72.3 and 72.4). The acetaminophen criteria have been found to be specific but lack adequate sensitivity, and serum lactate levels (>3.5 before resuscitation and 3.0 after) have been suggested as an alternative or supplementary

Table 72.3

Extended Investigation of Etiology of Acute Liver Failure

Etiology	Investigation
Idiosyncratic drug reactions	Eosinophil count, histology
Autoimmune	Autoantibodies, immunoglobulins
Pregnancy-related syndromes	
Fatty liver	Ultrasound, uric acid, histology
HELLP syndrome	Platelet count
Toxemia	Serum transaminases
Wilson disease	Urinary copper, ceruloplasmin, alkaline phosphatase/bilirubin ratio, AST/ALT ratio, slit-lamp examination
Budd-Chiari syndrome	Ultrasound or venography
Malignancy	Imaging, histology
Ischemic hepatitis	Transaminases

HELLP, hemolysis, elevated liver enzymes and low platelets; *AST/ALT,* aspartate aminotransferase/alanine aminotransferase.

Box 72.3

Indicators of a Poor Prognosis in Paracetamol-Induced Acute Liver Failure

Arterial pH <7.25 >24 hours after drug ingestion and after adequate fluid resuscitation
Serum lactate >3.5, or >3.0 after adequate fluid resuscitation
All the following or three of the following concomitantly:
- Prothrombin time >100 sec or international normalized ratio >6.5
- Creatinine >300 μmol/L or anuria
- Grade 3 to 4 encephalopathy

INR, international normalized ratio

Box 72.4

Indicators of a Poor Prognosis in Non-Acetaminophen Acute Liver Failure

Prothrombin time >100 sec or INR >6.7
Acute presentation of Wilson disease
Any three of following:
- Unfavorable etiology (seronegative hepatitis or drug reaction)
- Age <10 years or >40 years
- Acute or subacute categories (e.g., jaundiced >7 days)
- Serum bilirubin >300 µmol/L
- Prothrombin time >50 sec or INR >3.5

INR, international normalized ratio.

assessment of prognosis in these patients (Bernal et al, 2002). Another problem with these criteria is the difficulty applying the coagulation parameters outside the United Kingdom. The scale on which prothrombin times are reported in the United States is dramatically shorter than in the United Kingdom, reflecting differences in technique; in addition, the reagents used and the implementation of the international normalized ratio (INR) have not entirely resolved this problem because of loss of accuracy at higher readings. The Model for End-Stage Liver Disease (MELD) score is being increasingly used to prognosticate in acute liver failure. In France, the factor V levels are used in preference to either the prothrombin time or INR; levels below 20% in patients younger than 30 years and below 30% in older patients are indicative of a poor prognosis once encephalopathy develops. In Germany, the BiLE score—a combination of serum ***bi***lirubin level, ***l***actate, and ***e***tiology—is used (Hadem et al, 2008). A study from India used a combination of six demographic, clinical, and laboratory variables (Dhiman et al, 2007). In reality, these different prognostic tools use a total of 10 variables (Table 72.4), and considerable commonality is found among them (O'Grady, 2007).

Assessment of the volume of viable hepatocytes by histologic examination is considered by some to be of prognostic value, but the potential for sampling error is considerable. The critical mass that suggests a good prognosis has been calculated at between 25% to 40%. A small liver on clinical or radiologic assessment or, more particularly, a liver that is found to be shrinking rapidly is another poor prognostic indicator that is especially useful in subacute liver failure.

Table 72.4

Components of Models to Assess Prognosis in Acute Liver Failure

Factor	King's College	Clichy	MELD	BiLE	India
Age	+	+			+
Etiology	+			+	
Jaundice to encephalopathy	+				+
Coagulation	+	+	+		+
Bilirubin	+		+	+	
Creatinine	+		+		+
pH	+				
Lactate				+	
Encephalopathy grade	+				+
Cerebral edema					+

MELD, Model for End-Stage Liver Disease; *BiLE,* bilirubin level, lactate, and etiology.

MANAGEMENT

Overall Strategy

In acute liver failure, the overall strategy is a combination of intensive medical care (see Chapter 73), liver transplantation in selected patients (see Chapter 97C), and, to some degree, the use of a liver support device (Chapter 73). Management starts with identification of etiology and an initial assessment of prognosis that is then progressively updated as each individual's clinical course evolves. Early referral to specialist centers that offer liver transplantation is recommended; monitoring is instituted, and a decision on the need for immediate liver transplantation is reviewed. Patients are then treated for the complications that may develop to the point of recovery, death, or transplantation. Although considerable variation is found among centers and countries, the outcomes in fully functional programs approximate 40% survival without transplantation, and 40% proceed to liver transplantation; a 20% mortality rate is reported without transplantation.

Patients with acute-on-chronic liver failure often require, and benefit from, intensive monitoring. This is especially appropriate when deterioration has been triggered by a specific, reversible complication, especially variceal bleeding (see Chapter 75). Patients with hepatorenal failure are also frequently admitted to intensive care, which is particularly appropriate in patients who are active candidates for liver transplantation. Liver support systems, particularly the Molecular Adsorbents Recirculation System (MARS; Gambro, Stockholm, Sweden), are being increasingly used in this situation.

General Measures in Liver Failure

A number of drugs have well-defined roles in specific etiologies of acute liver failure. N-acetylcysteine is established as an antedote to paracetamol hepatotoxicity when given within 16 to 24 hours of the overdose, but it has also been shown to be beneficial in reducing mortality rates and cerebral edema when begun as late as 36 hours after the overdose. In the United States, a trial of N-acetylcysteine in nonacetaminophen acute liver failure showed improved transplant-free survival of 52%, compared with 30% in patients receiving placebo, when patients were started on therapy prior to the onset of grade 3 to 4 encephalopathy (Lee et al, 2009). Penicillin, and possibly silymarin, should be added at the earliest opportunity to the standard supportive measures in patients with *Amanita phalloides* toxicity. Patients with Wilson disease complicated by encephalopathy do not respond to chelating therapy, but penicillamine should be considered for acute presentations not yet complicated by encephalopathy. Acute liver failure caused by autoimmune hepatitis rarely responds to immunosuppressive therapy. Patients with severe acute alcoholic hepatitis may benefit from corticosteroid therapy or treatment with pentoxifylline; however, neither of these medications is indicated in acute-on-chronic episodes of alcoholic cirrhosis in the absence of a component of alcoholic hepatitis.

MANAGEMENT OF SPECIFIC COMPLICATIONS

Neurologic Complications

By definition, encephalopathy is present in acute liver failure and is often present in acute-on-chronic liver failure. Encephalopathy in both settings is categorized clinically on a scale from 1 to 4. Patients with grades 1 and 2 encephalopathy exhibit degrees of drowsiness or disorientation, but they can be roused and respond appropriately to verbal stimuli. Patients with chronic liver disease usually have a hepatic flap and *fetor hepaticus*, but these classic features of encephalopathy are absent in most patients with acute liver failure and an equivalent degree of encephalopathy. In acute liver failure, progression to grade 3 encephalopathy may be heralded by a short period of extreme agitation before the patient becomes very confused and, at best, only obeys simple commands. Grade 4 encephalopathy signifies deep coma; at best, patients are responsive to painful stimuli; most patients in this situation require intubation and supported ventilation.

Cerebral edema is common in hyperacute and acute liver failure but unusual in subacute liver failure. Clinically apparent cerebral edema has only been reported on an anecdotal basis in patients with cirrhosis (excluding Wilson disease). Emerging evidence suggests that the incidence of cerebral edema is decreasing with modern management protocols, but the precise reasons for this change have yet to be determined (Stravitz & Kramer, 2009). Nevertheless, in individual patients, cerebral edema remains an important complication that may cause death or may disqualify patients from transplantation; on that basis, treatment of cerebral edema retains its prominent role in management protocols. The clinical features of cerebral edema include systemic hypertension, "decerebrate" posturing, hyperventilation, abnormal pupillary reflexes, and, ultimately, impairment of brain stem reflexes and functions. Papilledema is rarely seen. The risk to life with cerebral edema can be from classic brain stem herniation or hypoxic brain damage.

Encephalopathy with acute-on-chronic liver failure is managed with dietary protein restriction and lactulose and phosphate enemas, usually with good effect. Treatment of triggering events is also fundamental to the management of encephalopathy, and empiric antibiotics and intravenous fluids are standard components of care (Box 72.5). With the possible exception of subacute liver failure, specific management options for encephalopathy have limited impact in acute liver failure. L-ornithine L-asparate given in a dose of 30 g/day for 3 days failed to lower ammonia levels or improve survival in acute liver failure (Acharya et al, 2009). Liver support devices can reduce ammonia and lighten encephalopathy, but no single system has demonstrated improvement in patient survival (McKenzie et al, 2008; Stradlbauer et al, 2009).

Box 72.5

Common Precipitants of Acute-on-Chronic Hepatic Encephalopathy

Infection	Excessive dietary protein intake
Constipation	Narcotic drugs
Gastrointestinal bleeding	Benzodiazepines

Mannitol (0.25 to 0.5 mg/kg) is the first-line treatment for surges in intracranial pressure. This process is repeated as determined by the pattern of clinical relapses, but the serum osmolarity should not be allowed to exceed 320 mOsm. Sodium thiopentone (phenobarbitone) was shown to control cerebral edema that had become unresponsive to mannitol in an uncontrolled study, but it has not been subjected to a controlled trial, nor has it been shown to improve the survival rate. Acute, but not chronic, hyperventilation was reported to be of benefit in reducing critical surges in intracranial hypertension. Nevertheless, hyperventilation to pCO_2 levels below 25 mm Hg is routinely incorporated as a first-line treatment in protocols in the United States. Hypothermia, hypertonic saline infusions, and indomethacin have also been shown in small studies to be useful adjuncts in the management of intracranial hypertension (Auzinger & Wendon, 2008; Stravitz & Kramer, 2009).

In the later stages of the neurologic complications, the emphasis of management changes to the preservation of cerebral perfusion pressure, increased oxygen delivery to the brain, and manipulation of the neuronal microcirculation to promote cerebral oxygen extraction (Auzinger & Wendon, 2008; Stravitz & Kramer, 2009). The patient should be positioned with the trunk at an angle of 20 to 30 degrees to horizontal. The options for increasing the mean arterial pressure, and consequently improving cerebral perfusion pressure, are outlined in the section in this chapter dealing with hemodynamics. These adjustments are made to maintain a cerebral perfusion pressure greater than 50 mm Hg if possible. At this stage of the complication, spontaneous recovery is unlikely without liver transplantation, and hepatectomy is useful to secure transient improvement. Occult seizure activity may contribute to neurologic instability in patients with grade 4 encephalopathy. Phenytoin and diazepam are effective therapies despite the theoretic consideration that the latter may aggravate the underlying encephalopathy.

The use of intracranial pressure monitoring is controversial and has not been subjected to clinical trials (Stravitz & Kramer, 2009). Early detection of cerebral edema and a facility with the appropriate equipment to constantly monitor this complication help to optimize therapeutic interventions. Intracranial pressure monitoring allows earlier and more accurate detection of pressure changes—especially in the ventilated patient, in whom most of the clinical signs are masked—and it facilitates careful monitoring of the intracranial pressure during high-risk therapeutic interventions, such as hemodialysis and tracheal suctioning. It is also considered valuable during orthotopic liver transplantation because increases in intracranial pressure often occur during the dissection and reperfusion phases of the transplant operation. The most commonly used system places transducers on or through a small nick in the dura. The risk of intracranial hemorrhage is a deterrent, although the studies that have systematically addressed safety have favored the use of intracranial pressure monitoring, especially using fiberoptic extradural or subdural devices. Proponents argue that this has been shown to be effective and relatively safe, despite the attendant coagulopathy. Epidural transducers were associated with a low complication rate of 3.8%, but subdural and parenchymal devices had higher complication rates of 20% and 22%, respectively. Noninvasive monitoring using transcranial Doppler ultrasonography may provide an alternative way of assessing intracranial pressure and cerebral perfusion pressure in this setting (Aggarwal et al, 2008).

Infection

Immunoparesis is a feature of acute liver failure (Antonides et al, 2008); it is therefore no surprise that bacterial and fungal infections are prominent complications in all varieties of this condition (see Chapters 9 though 11). Considerable overlap is seen between the clinical features of infection and the systemic immune response syndrome (SIRS), but microbial infection can also be seen in the absence of these typical markers of sepsis. Infection is one of the most common causes of death and plays an integral role in the evolving cycle of hemodynamic instability and multisystem failure (Rolando et al, 2000). It also frequently delays or disqualifies potential candidates from emergency liver transplantation. Bacterial infection occurs in up to 80% of patients, and fungal infection occurs in 30%. Systemic fungal infection is notoriously difficult to diagnose in the setting of acute liver failure, and a high index of suspicion is required, especially in high-risk patients and in those with a very high white cell count or an arrest in the normalization of the parameters of coagulation activity during an apparent recovery phase. Risk factors for both bacterial and fungal sepsis include coexisting renal failure, cholestasis, treatment with thiopentone, and liver transplantation. Surveillance cultures are required on a regular basis (Auzinger & Wendon, 2008; Stravitz & Kramer, 2009).

Clinical trials of prophylactic antibiotics have demonstrated that systemic antibiotics reduced the incidence of culture-positive bacterial infection by half, but this strategy was associated with the emergence of highly resistant organisms in up to 10% of cases. However, this reduction in infection rates was not accompanied by a significant impact on major clinical outcomes (death, progression to transplantation) or economic considerations (length of intensive care unit and hospital stay, overall cost of antimicrobials). Small bowel decontamination was not effective in altering the pattern of infection; however, systemic antibiotics are recommended when infection is suspected, and the precise regimens used are determined by local antibiotic policy.

In chronic liver disease, infection of an apparent trivial nature is common and can be the trigger for an episode of acute-on-chronic liver failure; as a result, antibiotic therapy is a standard component of the management of this condition. Spontaneous bacterial peritonitis is a particularly important infection to consider in this setting, and the diagnosis can only be excluded with confidence if the white cell count in ascites is less than 250/mm^3. Patients with a history of spontaneous bacterial peritonitis should be maintained on low-dose antibiotic prophylaxis, such as with norfloxacin 400 mg daily.

Hemodynamic Instability and Oxygen Debt

The hemodynamic changes in liver failure are very similar to those observed in SIRS. The early hemodynamic profile reflects a hyperdynamic circulation with increased cardiac output and reduced systemic peripheral vascular resistance. Profound vasodilation may cause relative hypovolemia, and invasive monitoring is used to determine appropriate fluid regimens and adequate intravascular volumes. Progressive disease leads to circulatory failure, either as a result of a falling cardiac output or an inability to maintain an adequate mean arterial pressure. Patients with acute liver failure and sepsis exhibit a different hemodynamic profile than patients in septic shock in the absence of liver disease (Tsai et al, 2008). The patients with acute liver failure had higher cardiac indexes and oxygen delivery but lower systemic vascular indexes and oxygen extraction/consumption. Circulatory failure is another important contraindication to liver transplantation and is a common mode of death in liver failure.

Hemodynamic monitoring using volumetric indices of preload is preferred over pressure-derived variables (Auzinger & Wendon, 2008). Circulatory failure is initially managed with appropriate fluid replacement in combinations of colloids, crystalline fluids, and blood products as clinically appropriate. Persistent hypotension after volume repletion indicates vasopressor agents, with a clear preference for norepinephrine as first-line therapy (Auzinger & Wendon, 2008; Stravitz & Kramer, 2009). Dopamine and vasopressin may also be used, although vasopressors may cause or aggravate an oxygen debt, but prostacyclin and N-acetylcysteine have been shown to improve these parameters in patients receiving vasopressors. Some patients with acute liver failure who develop resistance to inotropes may have a hypoadrenal profile that responds to hydrocortisone (Harry et al, 2002).

Renal Failure

Urea synthesis is impaired in acute liver failure. Consequently, serum creatinine levels are preferred for the purposes of monitoring renal function. Renal failure developed in 75% of patients with acetaminophen-related acute liver failure and in 30% of acute liver failure from other causes. Renal failure after an acetaminophen overdose is a consequence of direct renal toxicity and develops early in the course of the illness. Early renal dysfunction is also seen in Wilson disease, *Amanita* poisoning, and pregnancy-related syndromes. In the other etiologies, renal impairment develops relatively late and progresses from a stage of "functional" or prerenal failure (urinary sodium <10 mmol/L; urine/plasma osmolarity ratio >1.1) to acute tubular necrosis. The presence of SIRS correlated with the development of renal dysfunction in nonacetaminophen etiologies of acute liver failure but not in acetaminophen-induced disease (Leithead et al, 2009).

Hepatorenal failure is a serious complication of acute-on-chronic liver failure. Two types are recognized: *type 1* is hepatorenal syndrome with a rapidly progressive decline in renal function, leading to a doubling of the initial serum creatinine to a level greater than 2.5 mg/dL, or a 50% reduction of creatinine clearance to less than 20 mL/min over a period of no longer than 2 weeks. *Type 2* is hepatorenal syndrome with renal failure not fulfilling the parameters outlined above.

Hepatorenal syndrome can improve dramatically after liver transplantation, which reflects the role of vasospasm in the pathogenesis of the condition. However, true hepatorenal syndrome can progress imperceptibly to acute tubular injury that does not recover as quickly.

Optimization of intravascular filling is essential in patients with deteriorating renal function. The prophylactic use of dopamine has been common practice, but its benefits have been challenged, especially in the setting of profound vasodilation that is typical of acute liver failure. The metabolic complexity of combined liver and renal failure suggests that early intervention with hemodialysis, preempting standard indications, is prudent in the setting of acute liver failure. Continuous filtration systems are associated with less hemodynamic instability and run a lower risk of aggravating latent or established cerebral edema than does intermittent hemodialysis. Some evidence suggests

that high-volume, continuous venovenous hemofiltration may reduce vasopressor requirements through modulation of proinflammatory mediators (Auzinger & Wendon, 2008). The role for renal support therapy is less well defined in acute-on-chronic liver failure, but MARS therapy may be especially useful in deeply jaundiced patients with renal dysfunction.

Metabolic Abnormalities

Hypoglycemia is common in acute liver failure and can induce reversible impairment of consciousness prior to the onset of classic encephalopathy. The signs and symptoms of hypoglycemia are often masked, and regular blood glucose monitoring is required. Metabolic acidosis is present in 30% of patients who develop acute liver failure after an acetaminophen overdose, and it is associated with a particularly high mortality rate (>90%) if the pH of arterial blood is lower than 7.30 on the second or subsequent days after the overdose. This acidosis precedes the onset of encephalopathy and is independent of renal function. In contrast, metabolic acidosis is found in 5% of patients with other etiologies of acute liver failure; it occurs later in the disease process and is also associated with a poor outcome. Increased serum lactate levels have been documented in patients with metabolic acidosis, and these correlate inversely with mean arterial pressure, systemic vascular resistance, and oxygen extraction ratios. The hyperlactatemia possibly reflects tissue hypoxia resulting from impaired oxygen extraction as a result of microvascular shunting of blood away from actively respiring tissues. In most etiologies of acute liver failure, alkalosis is the dominant acid-base abnormality and may be associated with hypokalemia. Hyponatremia may reflect sodium depletion in patients with vomiting, or it may be dilutional, resulting from excessive antidiuretic hormone secretion or intracellular sodium shifts. Hypophosphatemia is most frequently encountered in acetaminophen-induced acute liver failure when renal function is preserved.

Hyponatremia is the dominant abnormality seen in acute-on-chronic liver failure. This does not reflect sodium depletion because total body sodium levels are almost always above normal in these patients. Diuretic-induced hyponatremia may be seen in patients with ascites, and withdrawal of diuretic therapy is advised if the serum sodium level falls below 130 mEq/L. Refractory hyponatremia is managed by fluid restrictions of 800 to 1500 mL per day depending on severity. Hemofiltration may be used to correct hyponatremia in severe cases or when the serum sodium is less than 120 mEq/L immediately prior to liver transplantation This is to reduce the risk of central pontine myelinolysis associated with the rapid increase in serum sodium levels that inevitably occur.

Coagulopathy

The liver is responsible for the synthesis of most of the coagulation factors (except Factor VIII, which is produced by endothelial cells) and some of the inhibitors of coagulation and fibrinolysis. In acute liver failure, circulating levels of fibrinogen, prothrombin, and Factors V, VII, IX, and X are reduced, and the prothrombin time is widely used as an indicator of the severity of liver damage. In addition to decreased synthesis of coagulation factors by the liver, increased peripheral consumption is evident. Overt disseminated intravascular coagulation (DIC) is occasionally observed, especially in the pregnancy-related syndromes, but sensitive investigative techniques point to the presence of a low-grade process in most patients. Both quantitative and qualitative defects in platelet function are well described in acute liver failure, and platelet counts of less than 100×10^9/L are seen in up to 70% of patients. Platelet aggregation is impaired, but there is an increase in platelet adhesiveness, a pattern that may be due to increased levels of circulating von Willebrand factor.

Poor correlation is reported between the laboratory and clinical manifestations of the coagulopathy of acute liver failure. This has been attributed to the fact that the decrease in the procoagulant and anticoagulant proteins is proportional (Stravitz & Kramer, 2009). The use of prophylactic repletion of coagulation has never been practiced in the United Kingdom except before significant invasive procedures. Recent data from the United States show that 92% of patients were given fresh frozen plasma at a mean of 14 units during the first week of hospitalization, even though it was acknowledged that only a minority of patients had gastrointestinal bleeding or intracranial pressure monitoring (Munoz et al, 2008). The practice of prophylactic repletion of clotting factors is also controversial because it may interfere with assessment of prognosis, especially in patients being considered for liver transplantation. The highest risk of bleeding is seen in those with an associated thrombocytopenia or a frank DIC syndrome rather than in the patients with isolated severe prolongations of prothrombin time. It has been proposed that the lack of coagulation factors does not result in a bleeding diathesis unless accompanied by an inadequate platelet scaffold on which to propagate a clot (Stravitz & Kramer, 2009). Clinical bleeding is managed by infusions of fresh frozen plasma, cryoprecipitate, and platelets as required. Limited data are available on the utility of recombinant activated Factor VII in this setting (Caldwell et al, 2004).

The severity of the abnormality of coagulation is usually less in acute-on-chronic liver failure, and thrombocytopenia in this setting is usually due to hypersplenism. Patients with protracted cholestasis may have a component to the coagulopathy that responds to parenteral vitamin K. The management of the coagulopathy follows the same principles as in acute liver failure.

Nutrition

Although the standard patient with acute liver failure is well nourished at the onset of the illness, it is important to institute nutrition support as soon as possible (see Chapter 24). The catabolic rate increases in patients with acute liver failure, and this is most apparent in those with complicating sepsis and those undergoing liver transplantation. The theoretical problems that limit nutrition options are legion: gastrointestinal ileus, desire to minimize gastrointestinal protein, difficulty maintaining isoglycemia, fluid restrictions secondary to renal failure, amino acid ratios possibly mediating encephalopathy, difficulty handling lipids, aggravation of sepsis by intravenous feeding, and so on. Despite all these considerations, adequate nutrition support can be obtained in the majority of patients. An element of enteral nutrition is desirable to help maintain the integrity of the small intestinal mucosa, which is titrated against the volume of gastric aspirates and the development of diarrhea.

Nutritional support in acute-on-chronic liver failure is equally important but subject to more constraints. Unlike acute

liver failure, these patients are frequently undernourished prior to the onset of the episode of acute-on-chronic liver failure. Protein intake should not exceed 60 g/day in patients with encephalopathy. There may also be restrictions on fluid volume and the sodium content of feeds. A substantial proportion of patients will have some degree of insulin resistance that may lead to hyperglycemia with high carbohydrate intake. There is little evidence that patients with problematic esophageal varices do not tolerate the presence of nasogastric tubes for feeding purposes.

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CHAPTER 73

Support of the failing liver

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THE FAILING LIVER

A failing liver is a serious condition that warrants a multimodal approach. The best option for a failing liver from either acute liver failure (ALF) or decompensated liver failure, is liver transplantation (Burroughs et al, 2006). However, the rapidity of progression and variable course of ALF, which includes progression to hepatic coma and the possibility of cerebral herniation, limit the effectiveness of transplantation. Furthermore, the downside of orthotopic liver transplantation is lifelong immunosuppression, and the side effects of these drugs include nephrotoxicity, diabetes mellitus, and infections.

The incidence of ALF in the United States is 2000 to 3000 persons per year (Ostapowicz et al, 2002), but the number is much higher for patients with acute decompensation of chronic liver failure (>200,000). The outcome of ALF varies by etiology: those with favorable prognoses are acetaminophen overdose, hepatitis A, and ischemia, with approximately 60% spontaneous survival (Lee et al, 2008). Etiologies with poor prognoses are drug-induced ALF, hepatitis B, and idiopathic cases, with approximately 25% spontaneous survival.

Several promising approaches are being evaluated, including cell transplantation and the application of extracorporeal liver support. These approaches are promising in the setting of ALF because a complete recovery will not impose sequelae such as lifelong immunosuppression with liver transplantation. The aim of extracorporeal support in the setting of decompensated cirrhosis, on the other hand, is to return the patient to the compensated state, but it does not offer the possibility of cure. Extracorporeal liver support serves as a treatment of choice for both ALF and decompensated cirrhosis or as a bridge to transplantation, whereas orthotopic liver transplantation is the definitive treatment. A failing liver may not regenerate or recover completely; buying time to bridge to liver transplantation can be lifesaving. Because of high mortality rates, increasing wait lists, and an expansion of indications for transplantation, interest in liver-assist devices is great.

This chapter emphasizes novel and promising techniques, such as extracorporeal liver support and cell transplantation. A historic summary of the different attempts to support the failing liver is also reviewed. Extracorporeal liver support isdivided into *biologic* and *nonbiologic* systems.

MEDICAL THERAPY

Once a patient is diagnosed with ALF, medical management must be initiated in a coordinated, systematic fashion (see Chapter 72). The goals of medical management are to 1) facilitate recovery, 2) reduce ongoing liver injury with N-acetyl cysteine, 3) prevent systemic manifestations such as cerebral edema, 4) correct hemodynamic instability, and 5) start preparing for liver transplantation if necessary. Treatment measures are initiated according to the severity of hepatic encephalopathy (HE).

For patients in stage I HE, evidenced by behavior changes with no changes in consciousness, baseline laboratory values are obtained for serum electrolytes, Mg^{2+}, Ca^{2+}, lactate, arterial blood gases, liver function tests, lactate dehydrogenase (LDH), ammonia, complete blood count (CBC), albumin, and coagulopathy panel. Twice-daily glucose checks are also recommended. Vitamin K is administered to help prevent or correct coagulopathy (Pereira et al, 2005), and lactulose is given orally for at least two loose stools per day because elevated blood ammonia can be detrimental. Ulcer prophylaxis is also started (Macdougall et al, 1977). Therapeutic measures are initiated when indicated, such as N-acetyl cysteine for acetaminophen overdose (Smilkstein et al, 1988).

If a patient progresses to stage II HE—with disorientation, delayed mentation, and asterixis—the measures for stage I HE are continued, and the patient is transferred to the intensive care unit (ICU) for a multidisciplinary evaluation from a critical care intensivist or hepatologist in consultation with a neurologic intensivist and a liver transplant surgeon. The patient's level of consciousness is scored using both the Glasgow Coma Scale and the Mayo Clinic FOUR (Full Outline of UnResponsiveness) score (Wijdicks et al, 2005). Laboratory work obtained for stage I HE patients is continued on a routine schedule.

A head computed tomographic (CT) scan or a magnetic resonance image (MRI) scan is obtained to evaluate brain edema and rule out other causes for mental status change, such as hematoma. Depending on the clinical picture, either enteral or parenteral nutrition is begun, with a protein load not to exceed 0.5 g/kg/day and with caloric intake based on Harris-Benedict guidelines: ideal body weight plus 20%. Branched-chain amino acids (HepatAmine) are used at the discretion of dietetics, and antifungal and antiviral prophylaxes are considered because of the high incidence of opportunistic infections in the setting of ALF (Rolando et al, 1996). If these patients require sedation, we advocate the use of the short-acting agent propofol (Wijdicks et al, 2002).

As patients progress to stage III HE, endotracheal intubation is performed to protect the airway and initiate mechanical ventilation. Goals of ventilatory support are to maintain a

PaO_2 greater than 70 mm Hg, preferably using an FiO_2 less than 40%. Mannitol is used to control intracranial pressure, with a goal serum osmolality of 310 to 320 mEq/L (Canalese et al, 1982); it is discontinued if oliguria develops. Simple maneuvers are initiated to lower intracranial pressure (ICP), such as keeping the head of the bed elevated between 30 and 45 degrees, limiting endotracheal suctioning, decreasing stimuli from lighting, and controlling agitation with propofol. IV fluids are adjusted to maintain serum Na^+ between 140 and 150 mEq/L. Vasopressors are used to increase the mean arterial pressure (MAP) if the cerebral perfusion pressure (CPP) falls below 60 mm Hg. Vasodilators are used to decrease MAP if the CPP is above 100 mm Hg. More invasive monitoring systems are also instituted, including an arterial line and an ICP monitor (Vaquero et al, 2005). Prior to ICP monitor placement, a coagulation profile is obtained and INR is corrected to 1.5 or less with fresh frozen plasma. If correction requires large volumes of fresh frozen plasma, we consider the addition of recombinant Factor VII (Shami et al, 2003). The cerebral perfusion pressure (CPP = MAP – ICP) is maintained between 60 and 100 mm Hg. If the CPP falls below 60 mm Hg or the ICP rises above 20 mm Hg for more than 5 minutes, the patient is hyperventilated to a $PaCO_2$ of 25 to 30 mm Hg (Strauss et al, 1998). Hyperventilation is only maintained short term.

Intracranial hemorrhage must be excluded if ICP remains high. Ultrasounds to assess hepatic mass and vasculature are obtained every 2 days. Hemodynamic instability often occurs secondary to a systemic inflammatory response (Rolando et al, 2000) or intravascular depletion. Intravascular volume is monitored with a Foley catheter for continuous urine output assessment and either a central venous or pulmonary artery catheter and is maintained for adequate end-organ perfusion. Human 5% albumin is the volume expander. Continuous venovenous hemodialysis is preferred in renal failure and ALF because of the risk of hypothermia and reduced CPP during intermittent hemodialysis (Davenport et al, 1993).

Hypothermia (33° to 35° C) is considered if cerebral edema is refractory to other therapies (Jalan et al, 2004). The duration has not been standardized, although some centers discontinue hypothermia before transplantation because of the risk of bleeding. Other centers continue hypothermia for 24 hours after transplantation because of late risks of cerebral edema.

If patients proceed to stage IV HE (coma, unresponsive to stimuli), the same measures started for the previous three stages are continued. If seizures occur in these patients, metabolic causes, such as hypoglycemia and electrolyte imbalances, must be ruled out. Electroencephalographic monitoring is initiated in the case of status epilepticus, which is treated with benzodiazepines. Stage IV HE patients are also evaluated for evidence of irreversible brain damage or brain death because both are contraindications to liver transplantation.

NONBIOLOGIC LIVER SUPPORT

Plasma Exchange and Hemodiafiltration

Plasma exchange was a natural outgrowth of the less effective blood-exchange transfusion technique. The goals of plasma exchange in ALF are to reduce the level of circulating toxins and to replace deficient essential factors, such as clotting factors produced by the liver. Plasma exchange is achieved by apheresis, with removal of the patient's jaundiced plasma and replacement with normal plasma. The results of early clinical trials were discouraging; encephalopathy often improved temporarily, but patient survival was not affected. Therapeutic gains, such as reduction in serum bilirubin and partial recovery from coma, were short lived and seen predominantly in patients with drug-induced ALF (Freeman et al, 1986; Lepore et al, 1972; Sabin et al, 1968). The overall survival rate of ALF patients treated by plasma exchange remained less than 50% (Takahashi et al, 1991). In addition, a significant complication rate was reported with plasma exchange, including chemical toxicity, viral infections, and death from lung and brain complications (Brunner et al, 1987). However, the effects of repeated, high-volume plasma exchange in patients with ALF have been studied under nonrandomized conditions (Kondrup et al, 1992).

In 1999, Clemmesen and colleagues investigated the effect of repeated, high-volume (15% of body weight) plasma exchange in 23 patients: 14 patients with ALF and 9 with decompensated cirrhosis (Table 73.1). The etiologies of ALF were acetaminophen in 8, hepatitis in 3, and nonhepatitis (A, B, C) in 3. Of the patients with acetaminophen intoxication, 25% died, and 21% were bridged to transplantation.

In Japan, where the option of liver transplantation is limited by the low rate of cadaveric organ donation, a dual approach that combines hemofiltration with plasma exchange has become popularized as a treatment of ALF (Inoue et al, 2009). In this Japanese study, all patients regained consciousness, and no patient developed brain edema or hepatorenal syndrome during plasma exchange and hemodiafiltration treatment. The median number of treatment sessions was 21 (range, 4 to 30), and 4 of 7 patients (57%) with indeterminate etiology and 1 of 5 patients (20%) with acute hepatitis B infection survived.

Despite its limitations and unproven efficacy, plasma exchange continues to be a frequently used method of liver support in patients with ALF. It is used for the correction of coagulopathy and for nonspecific removal of accumulated toxins.

Historic Blood Purification Options

Throughout the 1960s and 1970s, it was believed that small (<5 kD) dialyzable molecules caused coma in ALF (Kiley et al, 1956; Opolon, 1979). As a result, numerous attempts were made to treat ALF patients with hemodialysis (Kiley et al, 1958; Merrill et al, 1950) and charcoal hemofiltration (O'Grady et al, 1988) for removal of these small toxins. Although case reports and controlled studies of both therapies have shown reversal of hepatic encephalopathy and improved survival (Gimson et al, 1982; O'Grady et al, 1988), neither therapy has been proven successful in prospective randomized trials of either ALF or decompensated cirrhosis.

Albumin Dialysis

The MARS and Prometheus (Fresenius Medical Care, Waltham, MA) liver dialysis systems are two extracorporeal therapies that facilitate removal of nonpolar toxins by albumin in patients with ALF and decompensated cirrhosis.

MARS

MARS was developed by Stange and collegues (1993) in the early 1990s. Briefly, MARS is a two-circuit system composed of a blood circuit and a secondary albumin circuit; these are

Table 73-1

Overview of Important Biologic and Nonbiologic Extracorporeal Liver Support Device Trials

Device	Type of Trial	First Author (Year)	No. Patients	Indication	Survival (%)
Biologic					
Latvian trial	CT	Margulis (1989)	126	ALF, DC, sepsis	BAL + SMT: 63 (37/59) SMT: 40 (27/67)
ELAD	CT	Ellis (1996)	24	ALF, PNF	78 (7/9)
TECA	UCT phase I	Xue (2001)	6	ALF, DC, PHF	33 (2/6)
BLSS	UCT phase I	Mazariegos (2001)	4	ALF, DC	25* (1/4)
AMC-BAL	UCT phase I	Van de Kerkhove (2002)	12	ALF	100* (12/12)
RFB	UCT phase I	Morsiani (2002)	7	ALF, PNF	14* (1/7)
MELS	UCT phase I	Sauer (2003)	8	ALF, DC	100* (8/8)
Hybrid-BAL	UCT phase I	Ding (2003)	12	ALF	25 (3/12)
HepatAssist	RCT	Demetriou (2004)	171	ALF, PNF	BAL + SMT: 71* (60/85) SMT: 62* (53/86)
Nonbiologic					
Charcoal hemoperfusion	RCT	O'Grady (1988)	62	ALF	Device + SMT: 35 (10/29) SMT: 39 (13/33)
BioLogic-DT	CT	Ellis (1999)	10	ALF	0 (0/5)
Plasma exchange	UCT	Clemmesen (1999)	23	ALF, DC	53* (8/15)
	UCT	Inoue (2009)	12	ALF	58 (7/12)
MARS	RCT	Heeman (2002)	23	DC	Device + SMT: 92 (11/12) SMT: 55 (6/11)
	RCT	Saliba (2008)	102	ALF	Device + SMT: 85 (45/53) SMT: 76 (37/49)
Prometheus	UCT	Rifai (2003)	11	DC, HRS, PNF	73 (8/11)
	UCT	Grodzicki (2009)	52	ALF, PHF, PNF	54* (28/52)

*Survivors include patients bridged to liver transplantation.

RCT, randomized controlled trial; ALF, acute liver failure; BAL, bioartificial liver; CT, controlled trial; DC, decompensated cirrhosis; HRS, hepatorenal syndrome; phase I, safety assessment trial, PHF, postoperative hepatic failure; PNF, primary nonfunction; SMT, standard medical therapy; UCT, uncontrolled trial

separated by a high-flux dialyzer membrane with a pore size and nominal molecular weight cutoff (MWCO) of approximately 50 to 60 kD. The pore size of this membrane makes it impermeable to albumin but permeable to smaller water and nonpolar waste substances. On the opposing side of this membrane is an albumin circuit that consists of supraphysiologic levels (>10%) of human albumin dialysate. Waste removal occurs by the concentration gradient between the patient's blood and the albumin dialysate in the secondary circuit. The high concentration of albumin is believed to facilitate removal of nonpolar molecules known to bind to albumin. Detoxification of these nonpolar waste molecules occurs when the albumin passes over adsorbent columns, including an anion exchange resin column and an activated charcoal column (Steiner et al, 2004). The secondary circuit also provides conventional low-flux dialysis for detoxification of water-soluble molecules.

One of the earlier MARS trials was an uncontrolled trial of 13 patients who had not responded to standard medical treatment of decompensated liver failure (Stange et al, 1999). The etiologies of liver cirrhosis were hepatitis C in one patient and alcohol abuse in the rest; the precipitating events were unknown in 10 cases. This early uncontrolled study showed an overall survival of 69% (9 of 13). A prospective, controlled trial of the MARS system (n = 12) versus standard medical therapy (n = 11) was performed by Heemann and colleagues (2002) in patients with decompensated cirrhosis. The authors concluded that albumin dialysis was associated with a significant improvement in 30-day survival (11 of 12 survived with MARS, 6 of 11 survived in the control group). An editorial to this study raised concerns regarding stratification, standard medical care before randomization, and the inclusion criteria (Kamath, 2002). A larger randomized controlled trial of the MARS system plus standard medical therapy (n = 39) versus standard medical therapy alone (n = 31) in the treatment of hepatic encephalopathy in advanced cirrhosis was reported by Hassanein and colleagues (2007). In contrast to previous reports on MARS, mostly from European centers, this trial was conducted mostly at centers in the United States. This trial demonstrated that the use of MARS therapy was associated with an earlier and more frequent improvement of grades 3 and 4 hepatic encephalopathy compared with standard medical therapy alone. This 5-day trial did not attempt to assess the role of MARS therapy on survival or cirrhotic patients. A trial that did evaluate survival was reported by Saliba and colleagues (2008). This randomized prospective trial of MARS in the treatment of ALF included 102 patients randomized to MARS therapy (n = 53) or standard medical treatment alone (n = 49). Survival at 6 months was greater after MARS treatment (84.9% vs. 75.5%); however, this difference did not reach a significant level by log rank test.

Along with hepatic encephalopathy, MARS has been shown to improve other secondary end points associated with a failing liver, including renal dysfunction, jaundice, and hemodynamic parameters such as systemic vascular resistance and

mean arterial pressure (Schmidt et al, 2003). One prospective randomized controlled trial showed significant improvement in survival in patients with hepatorenal syndrome (Mitzner et al, 2000). MARS therapy has been associated with prolonged relief of intractable pruritus in patients with cholestatic liver disease (Pares et al, 2004). In addition, in a study by Novelli and colleagues (2007), MARS therapy was associated with an improvement in Model of End-Stage Liver Disease (MELD) scores at 1 and 3 months after treatment.

A meta-analysis of MARS use evaluated patients with ALF or decompensated cirrhosis in four randomized clinical trials involving 67 patients and two nonrandomized trials involving 61 patients. This meta-analysis failed to show a significant survival benefit with MARS treatment (Khuroo et al, 2004). As a result, many clinicians are still hesitant to use MARS therapy on their patients with liver failure because a reproducible survival benefit has not been shown.

Prometheus

Prometheus is another form of albumin dialysis for supporting a failing liver. Prometheus functions by fractionating the plasma component of blood, in which the fractionated plasma is detoxified as it passes through two adsorption columns. Prometheus and MARS differ in the MWCO of their blood-separation membranes. MARS uses a 50- to 60-kD MWCO membrane that does not allow passage of albumin from the blood, whereas Prometheus uses a membrane with a 250-kD MWCO that allows the passage of albumin. Therefore greater potential removal of albumin-bound toxins from the patient's blood is possible with the Prometheus system (Rifai et al, 2003). There have been concerns of dropping the patient's albumin levels using Prometheus (Krisper et al, 2007) and concerns of losing clotting factors, presumably because of reduction in protein C and protein S concentrations after the fractionation and adsorption process (Meijers et al, 2007). As with MARS, a survival advantage of Prometheus over standard medical therapy has not yet been shown in a prospective randomized trial.

BIOLOGIC LIVER SUPPORT

Standard medical care alone has been associated with less than 50% recovery from ALF; therefore an effective liver support device to reduce the need for liver transplantation and increase the possibility of spontaneous recovery is needed. Many investigators believe that liver support at this level of complexity requires the use of a biologic component that comprises a mammalian liver tissue preparation, such as isolated hepatocytes and liver slices, rather than blood detoxification techniques. Accordingly, numerous investigators have used whole livers for cross-perfusion, hepatocyte transplantation, and isolated primary hepatocytes and hepatocyte-based cell lines kept in various configurations to support a failing liver. However, limiting factors that include complexity of the systems, limited availability of high-quality liver tissue, and immunologic barriers have prevented the widespread use of BAL support systems.

Ex Vivo Liver Perfusion

In 1965, Eiseman and colleagues reported the use of xenoliver (porcine) cross-perfusion to treat eight comatose patients. None of these patients survived, but transient clinical improvement, such as awakening from the comatose state, was reported. Later, in 1967, Burnell and colleagues reported the use of human-human cross-circulation in the treatment of three patients with fulminant hepatic failure. Moreover, livers from a variety of species—porcine, dog, and bovine—have been used (Abouna et al, 1970; Chari et al, 1994; Eiseman et al, 1965). Evident after the treatments were symptoms of hyperacute rejection—gastrointestinal bleeding, hemolysis, and thrombocytopenia—and less specific symptoms such as fever and nausea that would subside after each session. Human organs found not to be suitable for transplantation were used in a cross-perfusion setting reported in 1993; in this study, two of three patients were successfully bridged to transplantation, but the last patient did not improve clinically (Fox et al, 1993).

Hepatocyte Transplantation

Transplantation of liver cells, specifically hepatocytes, is promising for patients with inherited liver disorders such as tyrosinemia (Grompe et al, 1994) and hyperbilirubinemia Crigler-Najjar syndrome (Fox et al, 1998), which eventually lead to liver failure.

The possibility of treating liver insufficiencies with hepatocyte transplantation has been investigated over the years. The infusion of purified glucocerebridase in patients with enzyme disorders such as Gaucher disease have been attempted (Brady et al, 1974). Allogeneic hepatocyte transplantation to animals with enzyme deficiencies is a promising option. Studies in 1976 and 1977 showed conjugation of bilirubin in Gunn rats with deficiency in the enzyme uridine diphosphate glucoronyltransferase after alloinfusion of functional hepatocytes in the portal vein (Matas et al, 1976) and both the portal vein and intramuscularly (Groth et al, 1977). Later, a group at University of Minnesota (Sutherland et al, 1977) transplanted hepatocytes both intraportally and intraperitoneally in rats to support the recovery of hepatic necrosis (i.e., acute liver failure induced by dimethylnitrosamine).

Experimental models of liver failure and genetic defects of liver metabolism indicate that transplanted hepatocytes can assume the full range of functions of intact whole livers (Arkadopoulos et al, 1998). Intraportal infusions of hepatocytes in humans succeeded the intraportal infusion of purified enzymes. A limiting factor of enzyme therapy has been only short-term efficacy; the indications for hepatocyte transplantation with functionally intact hepatocytes have been liver failure (Habibullah et al, 1994), as a bridge to liver transplantation because of a failing liver (Strom et al, 1997), treatment of ornithine transcarbamylase deficiency (Horslen et al, 2003), and allogeneic hepatocyte transplantation in humans via the portal vein for Crigler-Najjar syndrome type 1 (Fox et al, 1998). These disorders have been partially corrected by hepatocyte transplantation, and these attempts have shown a proof of principle for cell transplantation therapy despite the effects being only short term (Strom et al, 2006).

Extracorporeal Hepatocyte Systems

Because of the scarcity of donor livers, it is valid to search for artificial means of liver replacement and/or assistance. The aim is to support patients with borderline functional liver cell mass until an appropriate organ becomes available for transplantation, or until their livers recover from injury as a result of a regeneration process. An artificial liver could also support patients during periods of functional recovery after transplantation with marginal livers and after extended liver resections for

trauma or cancer. The development of a bioartificial liver (BAL) is a formidable task that must take into account the vast functions of the liver; this organ is not like the kidneys or lungs, which in a supportive context have one or two functions that need to be supported.

A BAL device can be assessed at different levels, such as relative to short-term and long-term outcomes. Secondary, short-term end points often include improvements in blood levels of bilirubin, ammonia, and alanine aminotransferase (ALT). Other secondary clinical end points often include renal function, pulmonary function, and hepatic encephalopathy. However, the primary and long-term end point is increased survival with or without liver transplantation.

To achieve these effects, an artificial liver should be able to lower blood levels of substances toxic to the brain, liver, and other organs, and it should provide whole liver functions that are impaired or lost. The concept of an artificial liver was developed by Sorrentino (1956), who demonstrated more than 50 years ago that fresh liver tissue homogenate converts urea from ammonium chloride and metabolizes ketone bodies, barbiturates, and salicylic acid. However, it was not until the mid-1970s that Wolf and Munkelt (1975) placed hepatoma cells in the extrafiber space of the hollow-fiber cartridge and showed that an extracorporeal device was capable of performing liver-specific functions, such as conjugating bilirubin.

The first clinically applied BAL support was by Matsumura and colleagues (1987) in California, and the first BAL recipient was a 45-year-old patient in hepatic failure because of an inoperable bile duct carcinoma. The device contained isolated rabbit hepatocytes separated from the patient's blood by a dialysis membrane. Figure 73.1 depicts a schematic overview of a generic BAL.

Clinical Trials of Bioartificial Liver Devices

Nine BAL devices have been evaluated in clinic trials (see Table 73.1). The different systems differ in perfusion rate, cell source, and duration of treatment (continuous vs. intermittent).

Latvian Hybrid Bioreactor Trial

A controlled study with 126 patients from Latvia in the former Soviet Union compared two groups: one group received standard medical treatment (n = 67), and a second group received standard medical treatment and BAL therapy (n = 59) (Margulis et al, 1989). The indications were liver failure caused by viral and toxic etiologies and decompensated alcoholic cirrhosis and sepsis. The device contained pig hepatocytes in liquid suspension along with activated charcoal granules. The 20-mL device was perfused through an external Scribner atrioventricular shunt (i.e., no external pump was applied). The results from this trial are admirable: 63% survival in the BAL-treated group as opposed to 41% in the control group. Of note, there was a selection bias, with 44% comatose patients in the control group as opposed to 33% in the BAL-treated group.

HepatAssist System

The first BAL device to be evaluated in a randomized prospective trial was the HepatAssist System (Circe Biomedical, Lexington, MA) (Demetriou et al, 2004). This was the first biologically based liver-assist device to be tested in an FDA-approved phase II/III trial. This trial enrolled a total of 171 patients, 86 controls and 85 BAL treated. The 30-day survival was 71% for the BAL group and 62% for the control group that received standard medical treatment. A trend was seen toward a better survival in the BAL group, although this difference did not reach statistical significance. Significant improved survival was found in a subgroup of patients with known etiology of ALF treated with BAL. Side effects of ALF included thrombocytopenia, renal failure, and increased intracranial pressure. These were higher in the controls, but the difference did not reach statistical significance. The authors of this proof-of-concept xenogeneic study concluded that the HepatAssist System was safe with regard to zoonosis; all the patients tested negative for porcine endogenous retrovirus after treatment. The HepatAssist System used a hollow-fiber–based configuration with membrane pore size of approximately

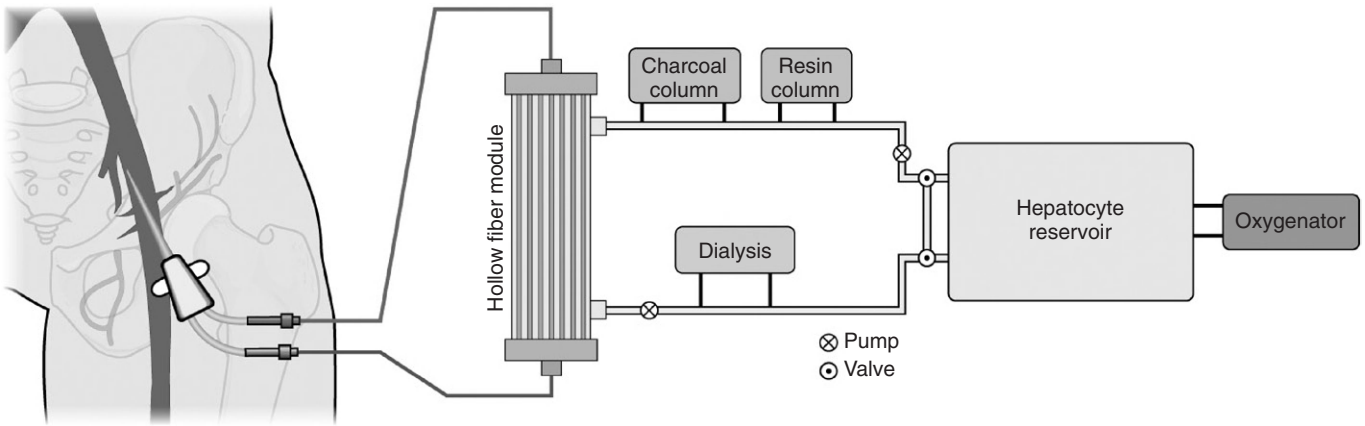


FIGURE 73.1. A schematic overview of a generic bioartificial liver (BAL), which consists of two extracorporeal circuits, a blood circuit, and an albumin circuit in direct contact with the biologic component, liver cells. The two compartments are separated by a semipermeable membrane, consisting of a hollow-fiber module in this example. The molecular weight cutoff of the semipermeable membrane may range from 70 kD to 0.2 μm, and the albumin circuit consists of supraphysiologic levels of albumin (>10%). The patient's blood is detoxified by removal of waste molecules across the membrane into the albumin solution. The waste molecules are eliminated from the albumin solution, when it is perfused through the charcoal and resin columns, or when it is exposed to hepatocytes within the hepatocyte reservoir. Depending on the hydration status and kidney function of the patient, water can be removed from the albumin solution as ultrafiltrate from a high-flux dialysis module. This cycle is repeated continuously during extracorporeal BAL therapy.

0.15 μm to separate the patient's plasma from 7 billion primary porcine hepatocytes in the device. The plasma circuit of the BAL also included a charcoal column and an oxygenator. The future of this system may include a scaled-up version of the device loaded with 14 billion cryopreserved hepatocytes (approximately 140 g) under the new name HepaLife (www.hepalife.com).

Extracorporeal Liver-Assist Device

After several early case reports, the extracorporeal liver-assist device (ELAD) was evaluated by Ellis and colleagues (1996) in a controlled trial of patients with ALF. Two groups of patients were studied: those judged to still have a potentially recoverable lesion (group 1, 17 patients) and patients who already fulfilled criteria for transplantation (group 2, 7 patients). Patients were randomly allocated to BAL treatment or control. The etiologies of ALF were acetaminophen overdose in 17 cases, non-A non-B fulminant viral hepatitis in 5 cases, and hepatotoxicity from antituberculous chemotherapy in 2 cases. Of those who received BAL treatment, 7 (78%) of 9 survived compared with 6 (75%) of 8 in the control group (group 1). Only 1 (33%) of 3 patients from group 2 who received BAL treatment survived compared with one 1 (25%) of 4 in the control group. Biologic activity in the ELAD device was provided by a human hepatoblastoma cell line (C3A) loaded in a hollow-fiber cartridge. Later, Millis and colleagues (2002) reported a study of five ALF patients whose etiologies of liver failure were idiopathic, adverse drug reactions to leukemia treatment, and autoimmune hepatitis. This ELAD device differed from the device used by Ellis and colleagues in 1996 in that four cartridges loaded with hepatoma cells were used by Millis, whereas Ellis only used one cartridge. All patients in the Millis study were successfully bridged to transplantation, and the 30-day mortality rate was 20% (1 patient died). Each ELAD cartridge contained approximately 100 g of C3A cells within the extracapillary space of the hollow-fiber cartridges (a total of 400 g). The membrane used to generate the ultrafiltrate from the patient's blood had a MWCO of 120 kD.

The most recent trial of ELAD (Vital Therapies, San Diego, CA) was reported as an abstract in 2007 (Duan et al, 2007). In that study, 54 patients with decompensated cirrhosis participated in a randomized controlled trial in which ELAD was tested at two different centers in China. The end point was 30-day survival. A significant difference was reached between the control group, with 47% (9 of 19) survival, and the ELAD-treated group, with 86% (30 of 35) survival. A third generation of ELAD will be evaluated in upcoming trials and will include a total of 440 g of C3A cells and increased fiber porosity, from 120 kD to 0.2 μm (www.vitaltherapies.com).

TECA-Hybrid Artificial Liver Support System

The TECA-Hybrid Artificial Liver Support System was tested in a clinical trial (a phase I safety trial) that included six comatose patients with liver failure; isolated primary porcine hepatocytes were used (Xue et al, 2001). The indications were variable and included ALF, decompensated cirrhosis, and postoperative hepatic failure after resection for biliary cancer. The survival rate was at least 33% (2 of 6), and none of the patients was listed for transplantation. The authors applied a hollow-fiber configuration in which plasma circulated inside the hollow fibers with the primary porcine hepatocytes on the outside of the hollow fibers.

Bioartificial Liver Support System

The Excorp Medical (Minneapolis, MN) Bioartificial Liver Support System (BLSS) was evaluated in four patients, two with ALF and two with decompensated cirrhosis (Mazariegos et al, 2001). The etiologies behind ALF were acetaminophen toxicity and adverse effects of chemotherapy, but the etiologies behind the decompensated cirrhosis were Wilson disease and alcoholic hepatitis. One patient was bridged to auxilliary liver transplantation, but the other three did not survive (25% survival). The device contained approximately 120 g primary porcine hepatocytes in a hollow-fiber cartridge perfused with the patient's whole blood.

Radial Flow Bioreactor

A radial flow bioreactor was evaluated in a phase I clinical trial with seven grade III and IV comatose patients (Morsiani et al, 2002). The etiologies included primary biliary cirrhosis, viral hepatitis, primary nonfunction, and liver trauma. Six of seven patients were bridged to transplantation (86% survival rate). Two of seven died, including the patient with liver trauma and subsequent liver transplantation. The trial applied isolated primary porcine hepatocytes (up to 230 g) contained in a radial flow bioreactor.

Modular Extracorporeal Liver Support System

The modular extracorporeal liver support (MELS) system was evaluated in a phase I trial in 2003 that included eight patients with liver failure as a result of etiologies such as hepatitis B (two patients), drug toxicity (two patients), and unknown causes (three patients) (Sauer et al, 2003). The trial demonstrated safety; all 8 patients were successfully bridged to transplantation, and all were alive at the 3-year follow-up. The MELS device is a complex system of four independently functioning hollow-fiber capillary compartments that contain approximately 500 g of primary porcine hepatocytes. The MELS system is the only device clinically tested that has included human hepatocytes (Sauer et al, 2002).

Amsterdam Medical Center Bioartificial Liver

The Amsterdam Medical Center Bioartificial Liver (AMC-BAL) was evaluated in a phase I safety trial conducted in Italy (van de Kerkhove et al, 2002, 2004). The trial enrolled 12 patients; 11 successfully bridged to orthotopic liver transplantation (OLT). One patient survived after BAL treatments without OLT, and four patients died within 1 month after OLT of disease and transplant-related problems. The configuration of AMC-BAL is a three-dimensional, nonwoven, hydrophilic polyester matrix rolled like a mat with oxygen-carrying fibers in between. The patient's plasma is in direct contact with the primary isolated porcine hepatocytes, a configuration that differs from devices that separate the patient's blood and plasma from the cells by a semipermeable hollow-fiber membrane. The AMC-BAL cartridge houses 10 billion hepatocytes.

Hybrid Bioartificial Liver

Ding and colleagues (2003) evaluated their hybrid BAL in a phase I safety trial (Ding et al, 2003). The device was evaluated in 12 patients with ALF. The main etiology was hepatitis B infection after acute decompensation of underlying liver disease. Nine of 12 patients showed clinical and biochemical

improvement. The reported mortality rate was 25%, but the length of the follow-up period was not mentioned. The principle of the BAL was detoxification of plasma with an apheresis unit and a hollow-fiber bioreactor loaded with 10 billion primary porcine hepatocytes.

FUTURE DIRECTIONS

As of today, the BAL devices that have reached clinical testing have been inoculated with hepatocytes from either primary or transformed sources. The trials performed so far have shown safety and proof of concept; however, efficacy data to convincingly demonstrate support of a patient with a failing liver are still missing. Limitations of the first-generation BAL systems have included excess device complexity (Uchino et al, 1988), insufficient hepatocytes to support a failing liver (Margulis et al, 1989), or loss of differentiated function (Matsushita et al, 2003). To address these limitations, a number of research efforts are currently underway. Various novel configurations have been undertaken to improve hepatocyte viability and functional activity in the quest to improve device efficacy. For example, promising reports have shown that combining different cell types of the liver in cocultivation with hepatocytes is a promising option because it more closely mimics the liver environment in vivo (Auth et al, 1998; Bhatia et al, 1999; Nedredal et al, 2007). As another example, Nyberg and colleagues (2005) have developed a novel method of forming hepatic spheroids through gentle oscillation in a rocked bioreactor. Compared with traditional monolayer systems, spheroids show superior function in albumin production, phase I and phase II metabolism, and ureagenesis. In addition, the spheroidal reservoir grown in a bioreactor is capable of supporting 250 to 500 g of primary hepatocytes. This cell mass is increased several times over most first-generation devices. A calculated value of greater than 150 g viable hepatocytes is needed in a BAL to effectively detoxify ammonia, assuming a clinical production rate of 400 μmol/h of ammonia (Nedredal et al, 2009).

Improved detoxification through enhanced mass transfer is another important aspect of future BAL designs. Optimal mass transfer is achieved with the use of semipermeable membranes with an MWCO that provides efficient waste removal and an effective immunologic barrier to protect the nonautologous cells in the BAL. A recent study showed optimal mass transfer with a 400-kD cutoff membrane compared with a 70-kD membrane (Nedredal et al, 2009). Membranes with cutoffs greater than 400 kD, including membranes used for apheresis, may allow immune-mediated damage of xenogeneic hepatocytes in the BAL (Nyberg et al, 2003, 2004).

An abundant source of metabolically active hepatocytes is essential to any successful BAL system. Porcine hepatocytes have been used with limited acceptance because of immunologic concerns and theoretical risks of zoonosis (Cascio et al, 2001; Patience et al, 1997). Meanwhile, immortalized human hepatocytes have yet to be shown to express a full battery of hepatocyte functions that includes ammonia detoxification and normal phase I and phase II activities, along with theoretical risks of malignant spread to an immunocompromised transplant recipient (Mavri-Damelin et al, 2007). These risks of transformed cells have led researchers to explore alternative options for expansion and for hepatocyte-like cells in vitro (Kulig et al, 2004) and hepatocytes in vivo, because efforts to proliferate primary hepatocytes in vitro have been of limited success.

One alternative system for expansion of human hepatocytes in vivo uses u-plasminogen activator–transgenic severe combined immunodeficiency mice (uPA/SCID mice) (Okamura et al, 2006; Sandgren et al, 1991, 1995; Tateno et al, 2004). These transgenic mice express u-plasminogen activator (uPA) under the transcriptional control of a hepatotoxic albumin promoter (Sandgren et al, 1991). Taking advantage of their immunodeficient state, human hepatocytes can be successfully transplanted into these mice without rejection. As the recipient murine hepatocytes die, healthy, unaffected human hepatocytes expand unopposed within the mouse liver, yielding chimeric human/mouse livers (Rhim et al, 1995). This system has led to engraftment levels exceeding 50%. Critics of the SCID-mouse system point to difficulties in animal husbandry, renal disease in the transgenic mice, and difficulties in controlling the mutant phenotype, leading to a narrow window for human hepatocyte transfer (Tateno et al, 2004).

In response to concerns over the SCID-mouse system, an alternative approach has been used to expand human hepatocytes with other transgenic mice. Using immunodeficient $Rag2^{-/-}/Il2rg^{-/-}$ mice, researchers sought to generate an essential hepatocyte deficit and a selective pressure for the stable engraftment of human hepatocytes (Azuma et al, 2007). Fumarylacetoacetate hydrolase (Fah) is an essential enzyme in tyrosine catabolism. Mice deficient for Fah develop tyrosinemia and liver disease in the absence of the protective drug 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione, better known as *NTBC* (Grompe et al, 1995). $Fah^{-1-}/Rag2^{-/-}Il2rg^{-/-}$ triple-knockout mice were shown to be a successful model of stable engraftment and proliferation of human hepatocytes for the treatment of Fah deficiency (Overturf et al, 1998). Animals in this system are easily bred, devoid of renal disease, and are transplantable at a range of ages.

Interesting and promising approaches to hepatocyte production have been made with stem cells (Campard et al, 2008; Basma et al, 2009). Embryonic stem cells are pluripotent, meaning they have the potential to differentiate into most cell types and therefore could be a source of human hepatocytes. This would also increase the possibility of obtaining unlimited numbers of human hepatocytes and thus further the development of cell-based therapies for liver diseases. The potential uses for stem cells are numerous (Fausto, 2004; Karp, 2009). Drawbacks to stem cell–produced hepatocytes are the limited number of approved human cell lines; the lack of recognition of how to control the development of immature stem cells to mature, phenotypic, liver-specific cell types; and the possibility of teratoma formation.

Novel systems for in vivo (Azuma et al, 2007; Sandgren et al, 1991) and in vitro expansion of human hepatocytes are still early in development (Dalgetty et al, 2009; Yu et al, 2007). Critical to any system used to expand human hepatocytes is the ability to produce a large quantity of stable, healthy cells with normal hepatocyte phenotypes. In this regard, in vivo systems appear to be more advanced than in vitro systems; however, in vivo systems are currently limited by the number of hepatocytes that can be expanded from a mouse—approximately 5 g. Therefore cloning studies are underway to extend in vivo systems of human hepatocyte expansion to larger animal models with the prospect of overcoming scale-up limitations. Large animals with humanized livers may someday be a practical source of hepatocytes for cell-based BAL devices.

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CHAPTER 74

Management of ascites in cirrhosis and portal hypertension

Kevin Korenblat

HISTORIC OVERVIEW

One of the most visible manifestations of liver disease is that of *ascites,* broadly defined as the pathologic accumulation of fluid within the peritoneal cavity (Runyon, 2009). The almost reflexive association of ascites with liver disease notwithstanding, ascitic fluid volume and composition demonstrate a variability that reflects the range of disease processes, from benign to sinister, from whence it originates.

Descriptions of ascites exist in both human history and prehistory. Indian medical treatises from 1500 BCE, Mayan figurines with protuberant abdomens and everted umbilici, and the writings of Hippocrates all testify to the experience of varied cultures with this problem. Even the term *ascites*—derived from the Greek *askos*, a bag made of leather or sheepskin used to contain liquids—reflects its ancient origins (Reuben, 2004).

High-volume ascites is readily evident on physical examination; however, smaller volumes may evade detection, particularly in the obese. Ultrasound is the best imaging modality for detection of ascites. It is inexpensive, avoids ionizing radiation, and has the added benefit of providing information on liver architecture and portal vein patency (see Chapter 13).

All clinicians should maintain a low threshold for performing paracentesis. The procedure is necessary in the diagnostic evaluation of newly developed ascites, or when there is a change in the clinical condition in an individual with cirrhosis and ascites. A percutaneous approach that avoids the epigastric vessels offers an avascular plane that is safe even in coagulopathic and thrombocytopenic patients (Wong et al, 2008).

The available fluid can be analyzed for concentrations of proteins (albumin), enzymes (lactate dehydrogenase, amylase), and other molecules (glucose, creatinine, bilirubin, and triglycerides) and for a cell count and differential. Peritoneal fluid can also be cultured and submitted for cytologic evaluation.

PORTAL HYPERTENSION AND MECHANISMS OF ASCITES FORMATION

Ascites is the most common complication of portal hypertension arising from cirrhosis, occurring at an annual incidence of 1% (see Chapter 70; Ginès et al, 1987). Its development heralds a significant change in clinical condition, with a median survival of 50% over 2 years (D'Amico et al, 1986). Portal hypertension can arise from cirrhotic and noncirrhotic causes, although as a manifestation of portal hypertension, ascites is most common in disorders that increase pressures within the hepatic sinusoids, either from sinusoidal processes (cirrhosis) or postsinusoidal processes (heart failure, hepatic venous obstruction). By comparison, ascites is uncommon in presinusoidal portal hypertension.

The normal liver architecture consists of sinusoids that convey blood from the portal vein to the central vein. The sinusoids are separated from cords of hepatocytes by a fenestrated endothelium through which oxygen, cells, and plasma components are permitted to diffuse. The principal collagen-producing cells of the liver, the stellate cells, reside within the space of Disse, and activation of these cells leads to collagen deposition (Friedman et al, 1992). Other cells that contribute to the extracellular matrix within the liver are bone marrow–derived myofibroblasts and fibroblasts derived from epithelial-mesenchymal transition (Forbes et al, 2004; Kalluri & Neilson, 2003).

In cirrhosis, extracellular basement membrane deposition of collagen fibers within the space of Disse results in capillarization of the hepatic sinusoids (Huet et al, 1982). The resulting architectural changes cause a static increase in pressure within the splanchnic circulation (see Chapter 6).

The endothelial cells of the liver also play an important role in controlling dynamic changes to the hepatic microcirculation through the elaboration of nitric oxide (Mittal et al, 1994; Shah et al, 1997) and expression of endothelin-1 receptors (Bauer et al, 2000). Decreased endothelial nitric oxide synthase (eNOS) activity (Gupta et al, 1998; Shah et al, 1999), increased eNOS inactivator activity (Liu et al, 2005), and endothelin-1 overexpression in cirrhosis (Pinzani et al, 1996) have all been proposed as mechanisms that promote endothelial cell dysfunction in cirrhosis (see Chapter 6).

In the splanchnic circulation outside of the hepatic environment, different but equally important changes occur that contribute to portal hypertension. The most prominent of these is splanchnic arterial vasodilation. In experimental models of cirrhosis, vasodilation is mediated by NO-dependent (Sieber & Groszmann, 1992; Sieber et al, 1993) and NO-independent processes. The NO-independent processes include those related to endogenous vasodilatory cannabanoids (Garcia et al, 2001) and overexpression of vascular endothelial growth factor (VEGF) and VEGF receptor-2 to promote splanchnic angiogenesis, thereby augmenting blood flow in the splanchnic circulation (Fernandez et al, 2007). Vasodilation in the splanchnic circulation would decrease the effective arterial circulation if not for compensatory increases in cardiac output (Iwakiri & Groszmann, 2006).

With progression of portal hypertension, other compensatory mechanisms are activated to maintain the arterial circulation in the face of even greater increases in vasodilation and declines in cardiac output. These mechanisms include activation of the renin-angiotensin system and sympathetic nervous

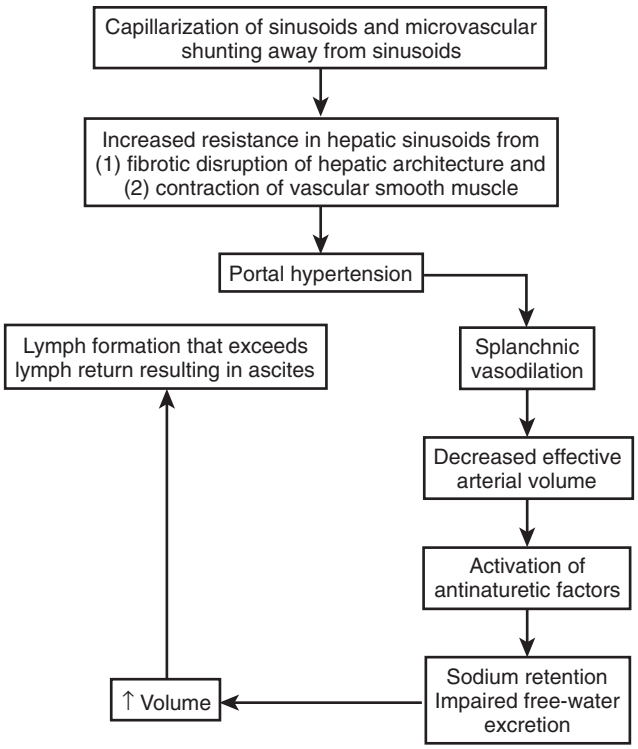


FIGURE 74.1. Mechanisms that lead to the development of portal hypertension and ascites in cirrhosis.

system to stimulate sodium retention by the kidneys (Arroyo et al, 1983). The nonosmotic release of arginine vasopressors is an additional compensatory mechanism to increase the effective arterial volume, even at the expense of tonicity; this is reflected in the development of hyponatremia (Arroyo et al, 1994). The cumulative effect of increased hydrostatic pressure in the hepatic microcirculation in the setting of increased splanchnic volume is that of hepatic lymph formation in excess of its removal; the resulting excess fluid weeps into the peritoneal cavity and is recognized as ascites (Fig. 74.1).

CHARACTERISTICS AND EVALUATION OF ASCITES

Ascitic fluid in cirrhotics is transparent but will generally take on a yellow or amber color. The fluid generally has a low leukocyte (<100 μL/mm) and red blood cell content. The fluid protein is typically less than 2.5 mg/dL, and the protein content varies inversely with the severity of the portal hypertension (Hoefs, 1983). Measurement of the serum albumin ascites gradient (SAAG) is both a highly accurate and clinically facile technique for assessing the origins of ascites. The SAAG is calculated by subtracting the concentration of albumin in the ascites from that in the plasma (Pare et al, 1983). With an approximately 97% accuracy, a gradient greater than 1.1 g/dL indicates the presence of portal or sinusoidal hypertension (Runyon et al, 1992).

Opacification of ascitic fluid can arise from a number of disparate processes. Bloody ascites (hematocrit >0.5) can be seen in traumatic paracentesis or in the spontaneous rupture of hepatocellular cancer. Chylous ascites is milky in appearance from increased concentration of chylomicron-rich triglyceride (Aalami et al, 2000). It arises from processes that disrupt lymphatic flow, most commonly lymphangiectasia and lymphoma, but it can also occur with abdominal trauma and surgical disruption of the cysterna chyli. Cirrhotic ascites can also take on a chylous appearance, owing to rupture of abdominal lymphatics from portal hypertension (Rector, 1984). In these cases, known as *pseudochylous ascites,* the triglyceride concentration is generally less than the threshold value of 110 mg/dL found in pure cases of chylous ascites.

Both malignancy and tuberculosis peritonitis can result in ascites, and in both circumstances the SAAG is less than 1.1 g/dL; however, confusion may arise when liver disease coexists, as in the case of tuberculosis and alcohol-related liver disease (Aguado et al, 1990; Shakil et al, 1996). The diagnosis of malignant ascites is established by the finding of cancer cells within the peritoneal cavity. This can be done by conventional cytology with a diagnostic sensitivity of 40% to 60% (Siddiqui et al, 1992). The accuracy of cytology can be improved when combined with immunohistologic staining (Aslam & Marino, 2001).

The peritoneum is a common site of involvement of tuberculosis (TB), and in the United States, the peritoneum is the sixth most common extrapulmonary site. Peritoneal cell counts typically vary between 500 and 1500 cells/mm^3 with a lymphocyte predominance in 68% (Sanai & Bzeizi, 2005), although the absence of a lymphocyte predominance does not exclude TB, particularly in patients with underlying renal failure, in whom the cells are mostly neutrophils (Lui et al, 2001). Mycobacterial culture of the fluid has a diagnostic sensitivity of 34% and requires several weeks of intubation. Measurement of adenosine deaminase activity in the peritoneal fluid has been proposed as another diagnostic test with high sensitivity and specificity, although the positive predictive value has been reported to be low in the setting of concomitant cirrhosis (Hillebrand et al, 1996). Of all diagnostic strategies, laparoscopy with peritoneal biopsy affords the highest sensitivity and specificity and permits exclusion of other granulomatous and nongranulomatous processes that can produce a low-SAAG ascites. The ascites concentration of lactate dehydrogenase (LDH) tends to be higher than that of serum LDH in malignant ascites and less than half that of serum in tuberculous peritonitis.

MANAGEMENT

Choosing the appropriate treatment for ascites must take into account a number of factors, including the volume of ascites, the severity of liver disease, and the presence of renal dysfunction or electrolyte disorders.

Dietary Sodium Restriction

Avid renal sodium retention is the initial response to splanchnic arterial vasodilation; thus initial treatment strategies involve tipping the balance in favor of a net loss of sodium; this is most simply accomplished with dietary sodium restriction. The estimated mean sodium consumption among nonhypertensive adults in the United States is 3600 mg/day (Ajani et al, 2005). Those with ascites are commonly advised to restrict dietary salt intake to 1.5 to 2 g per day (67 to 87 mmoL/day), the lower value of which is considered adequate for daily needs. In patients with mild degrees of ascites, sodium restriction may be singularly effective. This group usually has baseline rates of sodium excretion of at least 40 mEq/L per day and normal plasma sodium

Table 74.1

Diuretics and Dosages Commonly Used in the Management of Ascites

Medication	Dose	Comments
Aldosterone Antagonists		
Spironolactone	50-400 mg daily	
Amiloride	5-10 mg daily	Suitable substitute when spironolactone use is associated with painful gynecomastia
Loop Diuretics		
Furosemide	20-160 mg daily	Avoid intravenous use

concentrations (Arroyo et al, 1981). Although seemingly a simple intervention, success with dietary salt restriction requires counseling and vigilance. Most of the sodium present is added during food processing, and the patient's actual consumption may not be apparent to them unless food labeling is read and understood (Cook, 2008).

Medical Management

Diuretics

Most patients will at some point require diuretics. Between 500 and 750 mL per day of ascites can be mobilized without intravascular depletion, and greater amounts of ascitic fluid losses may be tolerable in the presence of edema, which tends to act as a buffer (Pockros & Reynolds, 1986). The avoidance of rapid fluid loss is critical because precipitous and excessive volume contraction can give rise to hepatorenal syndrome.

Aldosterone Antagonists

The aldosterone antagonists spironolactone and amiloride (Table 74.1) can be used as either monotherapy or in combination with loop diuretics. These agents prevent sodium reabsorption in the distal tubule and cortical collecting duct. Although aldosterone antagonists are weak natriuretics, they are effective in patients with cirrhosis (Perez-Ayuso et al, 1983).

Urine sodium excretion and plasma aldosterone concentration are hyperbolically and inversely related in patients with cirrhosis, and a greater sensitivity to the dose-response curve is observed in those with ascites (Bernardi et al, 1983). One explanation for the effectiveness of these agents in cirrhotic ascites may be that they target the functional hyperaldosteronism that would otherwise permit sodium reabsorption in the cortical collecting tube of fluid filtered in the loop of Henle. In addition, unlike other diuretics that require access to the tubular lumen, spironolactone enters the principal cell of the collecting duct from the plasma compartment and thereby circumvents decreases in renal blood flow and hypoalbuminemia, commonly encountered in patients with cirrhosis, that might otherwise impair its activity (Horisberger & Giebisch, 1987).

Spironolactone is commonly started at 50 to 100 mg daily. Its dose can be doubled every 3 days to a maximum of 400 mg per day. Its long half-life makes daily dosing permissible even at maximal dosages. Both hyperkalemia and hyponatremia may occur and are best addressed with dose reduction or discontinuation. In men who have tender gynecomastia from spironolactone, amiloride can be substituted at doses of 5 to 10 mg per day.

Loop Diuretics

As monotherapy for ascites, loop diuretics are often unsuccessful. The reasons for this are unclear but may relate to a decreased rate of drug entry into the tubular lumen or to a compensatory increase in distal tubular sodium resorption mediated by aldosterone. By comparison, the combination of loop diuretics and aldosterone antagonists is the most commonly used combination for moderate to severe ascites and can achieve reductions in ascites beyond that of aldosterone antagonists alone. The most commonly used loop diuretic is furosemide (see Table 74.1), beginning at doses of 20 to 40 mg daily. The dose is doubled in a coordinated fashion with increases in spironolactone, until therapeutic effect is achieved. Like spironolactone, a fourfold doubling of the dose (160 mg daily) is considered a maximal dose. An added benefit of loop diuretics is that they counteract the hyperkalemia associated with aldosterone antagonists, and they may also benefit those who develop dependent edema in addition to ascites.

Alhough the parenteral administration of loop diuretics is a common therapy for edema as a result of heart and renal failure, this route should be avoided for the management of ascites because it may precipitate the hepatorenal syndrome. Successful use of diuretics requires diligent monitoring for electrolyte disturbances and azotemia. Advanced cirrhosis is often associated with a catabolic state and lean muscle mass loss; thus even modest increases in serum creatinine may reflect significant impairment in glomerular filtration rate.

The development of azotemia should prompt dose reduction or cessation of diuretics. Renal dysfunction may also be a sign of a complication of liver disease, including spontaneous bacterial peritonitis or portal hypertensive gastrointestinal (GI) bleeding. In these situations, diuretics should be discontinued until the condition resolves.

Albumin

Hypoalbuminemia is a frequent finding in patients with cirrhosis, and it may influence the development of edema and ascites through alterations in plasma oncotic pressure and the activity of loop diuretics in the lumen of the collecting tubule. Limited evidence supports a role for albumin administration as an adjunct to diuretic therapy in ascites that is difficult to control (Gentilini et al, 1999). However, this strategy may not be broadly applicable with the diuretics currently available or when there is recourse to other treatments (Blendis & Wong, 1999). Intravenous albumin administration does have a secure role in the prevention of renal dysfunction, which occurs in the one third of patients who develop spontaneous bacterial peritonitis (Sort et al, 1999). In addition, vasoconstrictor agents used in the treatment of hepatorenal syndrome are more effective when coadministered with albumin than when administered with saline or other crystalloids (Ortega et al, 2002). Thus albumin appears to achieve a successful volume expansion in patients with cirrhosis, greater than that that of crystalloid, which is translatable into improvement in solid clinical end points.

Arginine Vasopression Receptor Antagonists

The nonosmotic release of antidiuretic hormone (ADH) is commonly observed in patients with cirrhosis as a compensatory mechanism for the decrease in effective arterial volume that occurs with splanchnic vasodilation. ADH exerts its effects through arginine vasopressin receptor-2 (AVPR2), which is predominantly expressed in the distal convoluted tubule and

collecting ducts of the kidney (van den Ouweland et al, 1992). Satavaptan is a selective AVPR2 receptor antagonist that has been tested in clinical studies of both the syndrome of inappropriate ADH release (Soupart et al, 2006) and hyponatremia occurring with cirrhosis (Ginès et al, 2008). The study in patients with cirrhosis was a multicenter, double-blind, randomized controlled study of 110 subjects with ascites and hyponatremia. Treatment with satavaptan and spironolactone was associated with improvement in ascites volume concomitant with improvements in hyponatremia more often than the placebo. The use of satavaptan and other aquaretic agents represents a promising area for pharmacologic management of ascites if these early successes are confirmed in other clinical trials.

Refractory Ascites

Ascites that persists despite dietary sodium restriction and high-dose diuretics (spironolactone 400 mg/day and furosemide 160 mg/day) is referred to as *refractory ascites* (Arroyo et al, 1996). *Diuretic-intolerant ascites* describes diuretic failure because of intolerant side effects—such as azotemia, hyponatremia, and encephalopathy—that prevent the attainment of a dose sufficient to effect an adequate ascites loss. The clinical significance of refractory ascites should not be overlooked; the survival curves of individuals with refractory ascites approximate those with type II hepatorenal syndrome (Ginès et al, 2004).

Before labeling a patient as having refractory ascites, it is important to exclude excessive sodium intake and other medications that may influence the diuretic response. In particular, nonsteroidal antiinflammatory agents, including aspirin (Planas et al, 1983), may both decrease the response of diuretics and contribute to azotemia.

Treatment options for refractory ascites includes therapeutic paracentesis, transjugular intrahepatic portosystemic shunting (TIPS) (see Chapter 76E), peritoneal shunting, and liver transplantation (see Chapter 97A).

Paracentesis

High-volume paracentesis, also known as *therapeutic paracentesis,* was a technique known to and practiced by physicians as far back as ancient Greece. It was also the most effective treatment in practice before the development of modern diuretics, after which the practice fell out of favor until it was reintroduced in 1987 as safe and effective (Ginès et al, 1987).

A number of large-bore needles (15 gauge or smaller) of various configurations and features have been manufactured for paracentesis. The procedure can be done with or without ultrasound guidance; commonly chosen sites for needle placement are over the right or left lower quadrant. A variety of techniques have been described for fluid removal, includng drainage by gravity, peristaltic pumps, and vacuum suction, but no single technique is superior to the others (Fig. 74.2).

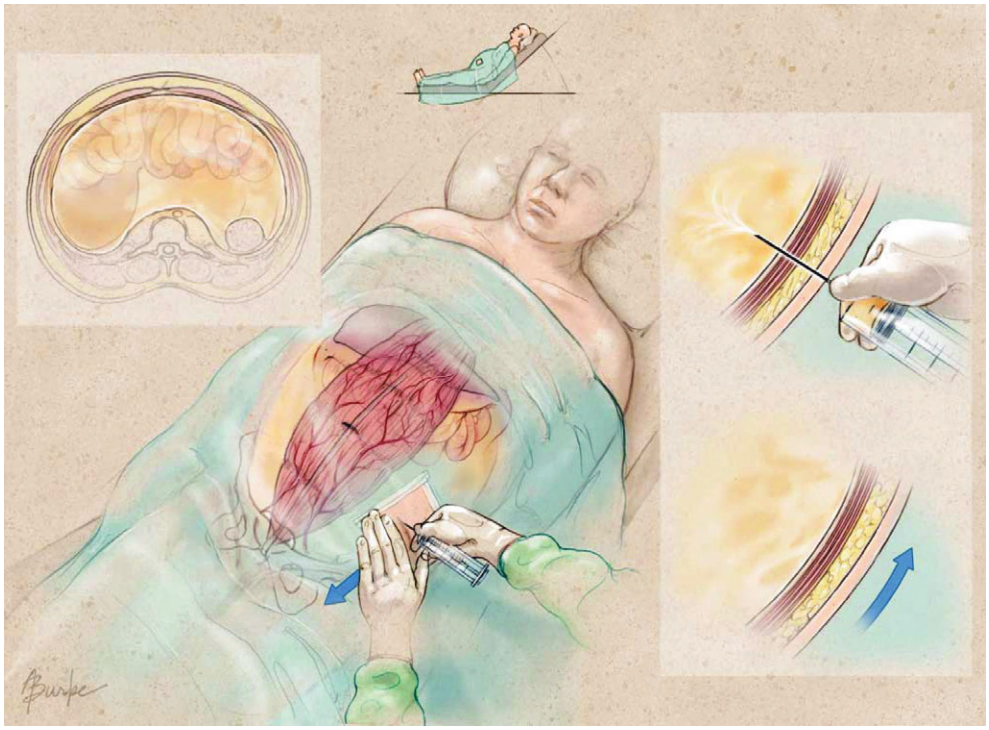


FIGURE 74.2. Patient positioning and performance of diagnostic paracentesis using the Z-tract technique. Diagnostic paracentesis is done with the patient in the supine position with the head of the bed elevated 30 to 45 degrees. Percussion can be used to identify sites of dullness. Commonly chosen sites are the left lower quadrant or 2 cm below the umbilicus, with care taken to avoid the epigastric vessels. The site of needle insertion should be cleaned and draped with sterile technique. With the nondominant hand, stretch the skin 1 to 2 cm caudad to the insertion site. Slowly advance a needle attached to a syringe while gently aspirating. After the ascites is collected, remove the needle, relax tension on the skin, and bandage the insertion site.

There are two central debates in paracentesis. The first centers on the maximal volume of fluid that can be removed at one time, and the second centers on whether circulatory volume expanders are required. Because ascites is extravascular fluid, paracentesis can be safely done until fluid withdrawal is complete. Immediately after paracentesis, cardiac stroke volume and output increase, and the renin-angiotensin-aldosterone (RAA) axis is suppressed. More than 12 hours after paracentesis, a rebound increase in the RAA and increased arterial vasodilation are seen. These changes are reflected in a reduction in systemic vascular resistance and form the basis of *postparacentesis circulatory dysfunction* (Ruiz-del-Arbol et al, 1997), a condition associated with renal dysfunction, a higher incidence of hyponatremia, and decreased survival rate.

The administration of volume expanders at the time of paracentesis is principally done to ameliorate these changes. Studies comparing albumin to other colloidal agents have shown it to be more effective in preventing circulatory dysfunction in paracentesis when the volume removed is greater than 5 L (Ginès et al, 1996). Similar findings have also been described in studies that have compared albumin to saline after total paracentesis (Sola-Vera et al, 2003). In practice, 12.5 g of 25% albumin can be infused for every 2 L of ascites removed. Other groups recommend an infusion of 8 g of 20% albumin for every 1 L of ascites removed (Cardenas et al, 2009). The timing of administration has not been rigorously studied, but because of the long half-life of albumin in the circulation, its administration after completion of paracentesis is likely to be sufficient. The benefits of albumin notwithstanding, no compelling data are available to suggest that albumin administered with paracentesis improves patient survival; however, the sample size of the studies to date may make detecting any survival advantage difficult (Cardenas et al, 2009).

Potential immediate adverse events resulting from paracentesis include hematoma and hemorrhage into the peritoneal cavity. Leakage of ascites can be reduced by using the Z-tract technique (see Fig. 74.2); modest leaks are best controlled by covering the site with an ostomy appliance, but larger volume leaks may require suture closure of the site. No compelling data are available to suggest that repeated high-volume paracentesis predisposes to bacterial peritonitis. There is also no evidence to suggest that the typical patient with high-volume cirrhotic ascites is at risk for abdominal compartment syndrome; thus high-volume paracentesis should not be expected to improve renal function simply by decreased peritoneal ascites volume (Lott, 2010).

Transjugular Intrahepatic Portosystemic Shunts

TIPS (see Chapter 76E) was first introduced experimentally in 1971 (Rosch et al, 1971); its purpose is to create a pathway to bypass sinusoidal hypertension and thereby relieve portal hypertension. To date, four randomized controlled trials have compared TIPS with repeated high-volume paracentesis in the management of ascites. Three of the trials are from sites in Europe (Italy, Salerno et al, 2004; Spain, Ginès et al, 2002; and Germany, Rössle et al, 2000); the fourth is from North America (Sanyal et al, 2003). In all the studies, TIPS was associated with a greater sustained relief of ascites compared with paracentesis; between 49% and 79% of those who received TIPS for refractory ascites were able to achieve sustained relief. The effectiveness of TIPS comes at the cost of an increased risk for episodes of severe encephalopathy. Some studies have shown a survival benefit, but others have not. In one of the multicenter trials, quality of life changes were similar in the two groups (Campbell et al, 2005). A comparison between TIPS and the paracentesis groups for the outcomes of survival, relief of ascites, and incidence of encephalopathy is summarized in Table 74.2.

The magnitude of portal decompression necessary to affect ascites formation is not known. The most common indirect measure of portal hypertension is the hepatic venous pressure gradient (HVPG), which is measured by hepatic vein catheterization with a balloon-tipped, pressure-transducing catheter. However, the HVPG necessary for control of refractory cirrhotic ascites is unknown (Boyer & Haskal, 2009).

A critical ingredient to the success of TIPS is proper patient selection. TIPS is absolutely contraindicated in those with severe pulmonary hypertension and biventricular heart failure. There may also be situations in which TIPS placement would be unfeasible, with extensive portal and mesenteric vein thrombosis, for example, or a large or infiltrative hepatic tumor.

The risk of dying after TIPS is based both on the mortality immediately related to the procedure and mortality after 1 to 3 months, likely reflecting a deterioration of hepatic function from the shunt. The procedure-related risk of death ranges between 1.7% and 3% and may show a dependence on the volume of TIPS done at any particular center (Haskal et al, 2003).

Unlike procedure-related mortality, which cannot be predicted, a number of systems have been offered to predict the

Table 74.2

Comparison of Outcomes for TIPS vs. LVP in Four Randomized Trials

	NO. OF PATIENTS		ESTIMATED 1-YEAR SURVIVAL*		RELIEF OF ASCITES		INCIDENCE OF HEPATIC ENCEPHALOPATHY	
First Author (Year)	TIPS	LVP	TIPS	LVP	TIPS	LVP	TIPS	LVP
Rössle (2000)	29	31	69%	52%	79%‡	24%‡	58%	48%
Salerno (2004)	33	33	77%‡	52%‡	79%‡	43%‡	61%†	39%†
Ginès (2002)	35	35	41%	35%	49%‡	83%‡	77%†	66%†
Sanyal (2003)	52	57	65%	66%	58%‡	16%‡	38%‡	21%‡

TIPS, transjugular portosystemic shunt; *LPV,* large-volume paracentesis

*Survival is defined as 1-year survival without liver transplantation in the studies of Rössle, Salerno, and Ginès. The data for Sanyal are given as overall survival.

†The total number of severe episodes of encephalopathy was greater in the TIPS group compared with the paracentesis group.

‡Identifies comparison with statistically significant *P* values.

short-term mortality. Scoring systems that have been studied include serum bilirubin alone (Rajan et al, 2002), the Acute Physiology and Chronic Health Evaluation II (APACHE II) (Rubin et al, 1995), Child-Turcotte-Pugh (CTP) class, and the Model for End-Stage Liver Disease (MELD) (Malinchoc et al, 2000). The simplest of these is serum bilirubin as a predictor of 30-day mortality, with a 40% increased risk of death for each 1 mg/dL increase greater than 3 mg/dL (Rajan et al, 2002). Although MELD is now most commonly used for organ allocation for transplantation in the United States, it was originally developed to predict the 3-month mortality after TIPS (see Chapter 70B). The MELD score is calculated from the serum bilirubin (Tbil), international normalized ratio (INR), and serum creatinine (Scr) from the equation below, given a maximum value for any variable of 1, a serum creatinine value of 4 or less, and a MELD score no higher than 40.

$$\text{MELD score} = 10\,[0.957\,\text{Ln(Scr)} + 0.378\,\text{Ln(Tbil)} + 1.12\,\text{Ln(INR)} + 0.643]$$

Decreased survival after TIPS has been reported with MELD scores of 15 and greater (Ferral et al, 2004; Pan et al, 2008). In patients with high MELD scores, the risks and benefits of TIPS should be carefully considered, as should the patient's candidacy for liver transplantation as an alternative to TIPS or as a backup if TIPS results in deterioration of liver function.

Peritoneovenous Shunt

Peritoneovenous shunting (PVS) was introduced by Leveen in 1974 for the management of refractory ascites. The shunt is a plastic cannula subcutaneously tunneled with one end in the peritoneal cavity and the other in the central venous circulation. One-way flow is established by a pressure-sensitive valve positioned between the two ends. These surgically placed shunts go by a variety of names—including *Leveen, Minnesota,* and *Denver shunts*—that reflect proprietary differences in their technical details. The placement of shunts results in increases in plasma volume, glomerular filtration rate, and urinary sodium excretion. All these effects reflect favorable physiologic changes to decrease ascites formation; in fact, shunts have been effective in improving ascites.

One of the largest trials to investigate PVS for cirrhotic ascites was the Veterans Administration Cooperative Study on Patients with Alcoholic Cirrhosis with Ascites (Stanley et al, 1989). In this trial, PVS was compared with medical therapy in 299 men with alcoholic cirrhosis. Because the trial predated the discovery of hepatitis C, it is impossible to know how many of the men had cirrhosis from this condition. Regardless, PVS resulted in a slightly faster time to resolution of ascites and a greater time free of ascites. No difference in survival was reported among medically treated subjects and those undergoing PVS. Despite these and other positive clinical trials, PVS is uncommon in current practice. One reason for this is that 40% of shunts stop working within 1 year of placement. This most commonly reflects obstruction, either of the shunt, its valve, or the central vein to which it drains. Adverse events also reported with PVS include pulmonary edema, variceal bleeding, disseminated intravascular coagulation (DIC), and peritonitis (Moskovitz, 1990; Scholz et al, 1989). PVS has also been overshadowed by the widespread availability of both TIPS and liver transplantation; in their own way, each is effective for refractory ascites. Nonetheless, PVS continues to have a role in the management of ascites in children, in the management of chylous ascites, and in patients for whom neither TIPS nor liver transplantation is feasible, such as those with extensive hepatic metastasis.

Liver Transplantation

Liver transplantation is effective in both relieving ascites and improving survival (see Chapter 97A). Although cases of persistent ascites have been reported after liver transplantation (Urbani et al, 2003), these cases are the exception. In all patients with refractory cirrhotic ascites, consideration should be given to liver transplantation as a treatment option.

COMPLICATIONS

Hepatic Hydrothorax. *Hepatic hydrothorax* is defined as a recurrent pleural effusion in patients with end-stage liver disease and portal hypertension in the absence of comorbid cardiac or pulmonary disease (Strauss & Boyer, 1997). Theories proposed to explain the development of hydrothorax include transdiaphragmatic leakage of fluid from lymphatic channels and azygos vein hypertension (Roussos et al, 2007). However, since 1955, it has been known that those who have a hydrothorax develop frequently have defects in the diaphragm that permit egress of ascites into the negative-pressure space of the pleural cavity (Emerson & Davies, 1955). It has been proposed that intrabdominal pressure from ascites leads to herniation of the peritoneum through gaps in the diaphragmatic muscle that eventually rupture into the pleural space. This communication has been further shown by following the passage of various tracers—air, dyes, and radiolabeled substances—from the peritoneal to pleural compartments and by direct thoracoscopic visualization of the defects (Benet et al, 1992; Datta et al, 1984; Huang et al, 2005). Hydrothorax is uncommon; its reported incidence is 5% to 12%, which is remarkably similar to the incidence of hydrothorax with continuous ambulatory peritoneal dialysis (Gur et al, 2004; Lew, 2010). The effusions are mostly right sided, but they can be left sided or bilateral and can be found in patients with minimal or no abdominal ascites (Rubinstein et al, 1985).

Typical respiratory symptoms encountered with a hydrothorax include dyspnea, fatigue, and nonproductive cough. The relationship between hypoxemia and hydrothorax is more complex. Hypoxemia requires ventilation-perfusion mismatching, and the mere presence of a hydrothorax alone, even one large enough to opacify a hemithorax, does not always result in resting hypoxemia. When deoxygenation is documented, the possibility of underlying acute or chronic parenchymal lung disease or the hepatopulmonary syndrome must be considered as a cause of the hypoxemia before attributing it to the hydrothorax.

Hepatic hydrothorax should be suspected in any patient with cirrhosis and portal hypertension with a pleural effusion. Diagnostic thoracentesis should be performed as a starting point in the evaluation. The hepatic hydrothorax is transudative by traditional criteria of Light and colleagues (1972). Tracking the migration of technetium-99m–labeled albumin or sulfur colloid has been proposed and used to establish the diagnosis of hydrothorax (Holt et al, 1999), although in practice, such tests are rarely used. Rather, diagnosis is reasonable in the setting of a rapidly recurring transudative effusion in a patient with cirrhosis in whom other diseases that would predispose to transudative effusion have been excluded. If doubt persists, measurement

of the hepatic venous pressure gradient can help support the diagnosis and exclude right-sided heart failure.

Therapeutic thoracentesis is safe and can provide immediate relief from dyspnea (Castellote et al, 2001; Xiol et al, 2001). By comparison, tube thoracostomy, also known as *chest tube placement,* should be avoided if at all possible. Prominent complications associated with chest tube placement for hydrothorax include infection and acute renal failure, the latter likely reflecting large volume losses. Chest tube placement is also associated with poor outcomes in small, retrospective studies (Orman & Lok, 2009).

The principles of management of a hydrothorax are similar to those of ascites. Dietary salt restriction followed by diuretics is the first line of treatment. Even if these treatments are modestly successful, they may still be inadequate to relieve symptoms given the small capacitance of the pleural space. In these situations, TIPS should be considered early. Although the data supporting a role for TIPS in hepatic hydrothorax are not as certain as those for ascites, in one study of 73 patients undergoing TIPS for hepatic hydrothorax, a favorable clinical response was found in 79% and 75% at 1 and 6 months, respectively (Dhanasekaran et al, 2009). Not surprisingly, liver transplantation is also an effective treatment of hydrothorax.

Surgical repair of the diaphragmatic defects has been described in small series of patients (Mouroux et al, 1996). Obvious limitations to the procedure are the operative morbidity and mortality in patients with end-stage liver disease. Management of hydrothorax is particularly challenging in individuals for whom TIPS is contraindicated and in those whose hydrothorax is refractory to TIPS. One therapy used for refractory hydrothorax is tunneled pleural catheters (Park et al, 1997), which are used for the management of refractory malignant effusions. The risk of infection is theoretically reduced because the catheters are tunneled and it is a closed system. Furthermore, because they are designed for periodic use, the rate of fluid loss can be controlled. Catheters have also been proposed as useful in the palliative care of patients with end-stage liver disease (Sanchez & Talwalkar, 2006), but further studies are needed to determine whether catheters have any role beyond that of palliation.

Spontaneous Bacterial Peritonitis

Spontaneous bacterial infection of cirrhotic ascites in the absence of suppurative infection or bowel perforation was first described by Conn and Fessel in 1971. Since then, this condition, termed *spontaneous bacterial peritonitis* (SBP), has emerged as one of the most common and feared complications of cirrhotic ascites. The prevalence and consequences of SBP are substantial: between 10% and 27% of patients with cirrhosis who have ascites will have SBP at the time of hospitalization (Guevara et al, 1998). It is also both a potentially lethal complication of cirrhosis and a marker of decreased survival. Twenty years ago, studies of patients presenting with their first episode of SBP reported a mortality rate of 47% (Tito et al, 1988). Those who survived the immediate infection still faced a high risk of dying, and in a majority of these late deaths, renal failure was judged to have played a significant role.

The forces that promote infection of ascites remain incompletely understood. The most common organisms to cause SBP are enteric gram-negative aerobic bacteria, and studies of cirrhosis in animal models show increased bacterial translocation (Casafont et al, 1997). The cirrhotic host may also be uniquely susceptible to infection as a combined effect of decreased reticuloendothelial and leukocyte function (Rimola et al, 1984) and diminished opsonic activity of ascites fluid (Runyon, 1988). The opsonic activity correlates with ascites protein levels, and patients with ascites protein less than 10 g/L have a greater probability of developing peritonitis than do those with higher ascites protein levels (Runyon, 1986).

Symptoms of SBP are varied and protean. Obvious symptoms include fever and abdominal pain, but more subtle symptoms are those of decompensation of liver disease, including acute renal dysfunction, encephalopathy, and jaundice. Gastrointestinal (GI) bleeding as a manifestation of SBP illustrates the interrelatedness of these functions in cirrhosis. GI bleeding can both promote bacterial translocation, and therefore increase the risk of SBP, and bacterial infection can result in further mesenteric vasodilation, which increases the risk of portal hypertensive bleeding. Most importantly, patients with bacterial peritonitis can be asymptomatic.

Paracentesis to exclude SBP should be performed in all subjects with new-onset ascites and in those with a change in clinical condition. The diagnosis of SBP rests on the demonstration of an abnormally high neutrophil count in the ascites fluid or culture of an organism from the fluid. The combination of the two is properly termed *spontaneous bacterial peritonitis.* By comparison, *culture-negative neutrascites* (CNNA) is the appropriate term when neutrascites alone is present. These terms notwithstanding, the natural history of SBP and CNNA are indistinguishable and should be treated in a similar fashion (Runyon, 1990). *Bacterascites* is the term applied to a positive ascites culture in the absence of neutrascites. Limited information on this subset of patients suggests that the infection may be transient (Pelletier et al, 1991).

No fewer than 747 citations have been reported to test the diagnostic accuracy of neutrophil counts in the diagnosis of SBP (Wong et al, 2008). The threshold that is commonly accepted is a neutrophil count greater than 250 polymorphonuclear cells (PMNs)/μL. If the ascites is bloody or the paracentesis traumatic, the neutrophil counts in the fluid should be adjusted for the number of red blood cells present. Inoculating ascites directly into blood culture media at the bedside increases the likelihood that organism will be recovered (Runyon et al, 1990). It has been estimated that for every five patients whose ascites is immediately inoculated into culture media rather than delayed by inoculation in the microbiology lab, one additional bacterial infection will be detected (Wong et al, 2008).

Particularly high neutrophil counts or the recovery of multiple microbiologic organisms should raise concern for secondary peritonitis that would reflect either a suppurative abdominal infection or bowel perforation. Measurement of ascites fluid protein, LDH, and glucose can help distinguish between spontaneous and secondary peritonitis. Secondary peritonitis should be strongly suspected when any two of the three following conditions are met: 1) glucose levels are less than 50 mg/dL, 2) ascites protein concentration is greater than 1 g/dL, and 3) LDH is greater than the upper limit of the reference range of serum LDH (Akriviadis & Runyon, 1990).

Antimicrobial therapy should be promptly started after SBP is diagnosed. The initial treatment should be parenteral and cover the typical organisms associated with SBP. In common practice, the antibiotics of choice are third-generation cephalosporins, particularly cefotaxime (2 g/12 h) (Rimola et al, 1995)

and ceftriaxone (1 to 2 g/24 h). Other antibiotic choices may be appropriate when chosen because of local microbial resistance patterns, medication allergies, or the patient's prior pattern of infection. Five days of therapy are as efficacious as 10 days of therapy (Runyon et al, 1991). Antifungal therapy is generally not required as empiric, first-line therapy. This treatment may, however, have a role in surgical patients who develop SBP while receiving antibacterial therapy, patients with peritonitis despite adequate antibacterial therapy, or in patients with secondary peritonitis.

The administration of intravenous albumin has emerged as a critical adjunct to antibiotics for the treatment of SBP. The major benefit of albumin is in the prevention of renal dysfunction, which occurs in as many as 30% of those with SBP despite effective antibiotic therapy. In a trial comparing a control group that received antibiotics alone to a group that received albumin and antibiotics, the rates of renal impairment were reduced from 33% to 10%, and the hospital mortality rate was reduced from 29% to 10%, respectively (Sort et al, 1999). The dose of albumin used was 1.5 g/kg body weight at diagnosis and 1 g/kg body weight on day 3. Subgroup analysis suggests that patients with preexisting renal impairment or serum bilirubin level greater than 4 mg/dL are most likely to benefit from this intervention.

Antibiotic prophylaxis has also been proposed for subjects with prior episodes of SBP or in those with an ascites protein content less than 10 g/L. A Cochrane review of the subject, limited to those without GI bleeding, found that antibiotic prophylaxis was associated with reductions in both episodes of SBP and death, with very few reported adverse events; however, the study also raised concern about the methodology of many of the studies used to reach the conclusion (Cohen et al, 2009).

References are available at expertconsult.com.

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CHAPTER 75A

Medical management of bleeding varices: primary and secondary prophylaxis

Hector E. Nazario and James F. Trotter

OVERVIEW

Variceal bleeding is the most serious complication of cirrhosis, with an up to 50% mortality rate within 30 days of presentation. However, as management has improved, so have patient outcomes (Carbonell et al, 2004; El-Serag & Everhart, 2000; Jamal et al, 2008a; Stokkeland et al, 2006). Specifically, the 30-day mortality rate has decreased from 30% to 43% in earlier eras to only 15% to 21% currently. These lower mortality rates may be attributed to the combined effects of aggressive clinical treatment protocols and the development of more effective therapies such as endoscopic band ligation; intravenous vasoactive medications, such as octreotide and terlipressin; and antibiotic prophylaxis. For example, Carbonell and colleagues (2004) reported that nearly all patients currently admitted for variceal bleeding receive antibiotic prophylaxis (94%) and endoscopic therapy (90%) within 24 hours compared with only 2% and 6%, respectively, 20 years ago. In addition, evidence suggests that prophylactic therapy is reducing the overall rate of bleeding; currently 15% fewer patients are hospitalized than a decade ago (Jamal et al, 2008b). This finding underscores the clinical utility of the early diagnosis of esophageal varices through aggressive screening strategies, careful surveillance for small varices, and prophylatic therapy with either β-blockers or endoscopic band ligation before or after variceal bleeding occurs.

DIAGNOSIS OF ESOPHAGEAL VARICES

Screening for esophageal varices is an important component in the long-term management of patients with portal hypertension because effective therapy may be applied once varices are identified. The gold standard test is upper endoscopy (de Franchis, 2005; Garcia-Tsao, 2007, 2008), during which the variceal size and presence of red wale markings should be noted. Varices are classified in three sizes: *small* varices show minimal elevation of veins above the mucosa; *medium* describes varices with tortuous veins that occupy less than one third of the lumen; and *large* varices occupy more than one third of the lumen. However, as recognized by all experienced endoscopists, the interobserver agreement in size estimation of esophageal varices varies (Bendtsen et al, 1990).

The diagnosis of esophageal varices should be considered in any patient with cirrhosis. (Garcia-Tsao et al, 2007; Garcia-Pagan et al, 2008). Because the risk of variceal progression and bleeding depend on both the severity of the underlying liver disease and appearance of the varices at endoscopy, patients with decompensated liver disease and high-risk endoscopic features (large varices, red wale markings) require more aggressive screening protocols. In addition, screening may also be appropriate in selected patients with bridging fibrosis because 16% may have esophageal varices (Sanyal et al, 2006). The likelihood of finding varices in a particular patient largely depends on the severity of the underlying liver disease, with a prevalence of 60% and 30% in decompensated and compensated patients, respectively (D'Amico et al, 1995; Sanyal et al, 2006). Once endoscopy has been performed, the presence or absence of varices has been established, and the varices have been graded according to severity, the requirement for further screening, surveillance, and therapy may be determined. In general, treatment recommendations for medium varices are the same as for large varices. The general protocol for screening and treatment is outlined in Table 75A.1.

In cirrhotic patients without varices, the risk of varices subsequently developing is approximately 8% per year (Groszmann et al, 2005; Merli et al, 2003). The recommended screening interval to detect varices in such patients is within 3 years. With a yearly risk of new varices of 8%, the cumulative risk of developing new varices over 3 years would only be about 25%, and during this interval the risk of bleeding is quite small (1% per year) (Groszmann et al, 2005; Merli et al, 2003). Because the risk of developing varices is higher in patients with decompensation, the screening interval may be shortened in this instance (North Italian Endoscopic Club, 1988). Prophylactic therapy with β-blockers to prevent the development of varices or bleeding in cirrhotics without varices is not effective, as was determined by two randomized studies, one with propranolol (Cales et al, 1999) and one with timolol (Groszmann et al, 2005). Because both studies failed to show a benefit with nonselective β-blockers in these populations, the pharmacologic prevention of varices, or "preprimary prophylaxis," is not possible at present.

In the patient with small varices identified at initial endoscopy, the yearly risk of developing large varices is 7% to 12% (Cales et al 1999; Merkel et al, 2004) and the risk of hemorrhage is only 5%. Repeat endoscopy should be performed at 2 years or yearly in the case of decompensation. Prophylactic treatment with β-blockers in patients with small varices has led to mixed results. In these studies, one trial reported a higher 2-year rate of developing large varices (31%) with treatment compared with placebo (14%), but the dropout rate in the

Table 75A.1

Screening and Surveillance Recommendation for Esophageal Varices

Patient Characteristics	Screening Interval
Cirrhosis, no prior varices on screening	At diagnosis of cirrhosis
Compensated cirrhosis, no varices on screening	Every 2 to 3 years
Decompensated cirrhosis, no varices on screening	Yearly
Compensated cirrhosis, small varices on screening	Every 1 to 2 years
Decompensated cirrhosis, small varices on screening	Yearly
Medium or large varices on screening	No further endoscopy
Received band ligation	

Table 75A.2

Diagnosis of Esophageal Varices

Technique	Comments
Recommended Diagnostic Strategy	
Upper endoscopy	Gold standard of treatment
Alternative Diagnostic Strategies	
Blood chemistries	Not recommended
Cross-sectional imaging	Not recommended
Transient elastography	Not recommended
Potential for Risk Stratification	
Ultrathin endoscopy	May be useful, rarely applied
Capsule endoscopy	For patients who cannot or will not undergo conventional endoscopy

study was very high. The other trial reported a lower rate of progression to large varices with β-blockers (11%) versus placebo (37%) after 3 years. The risk of bleeding was lower (12%) at 5 years with treatment compared with placebo (22%). However, the benefit of β-blockers was mitigated by the fact that the rate of bleeding in the placebo group, which was started on β-blockers once large varices were discovered, was the same as treatment once β-blocker therapy was initiated. In addition, the rate of withdrawal because of side effects was higher with β-blockers (10%) compared with placebo (1%). Because of these mixed results, patients with small varices should receive prophylactic β-blocker therapy only if they have risk factors for bleeding, such as advanced liver disease or red wale markings. In patients not receiving β-blockers, repeat endoscopy is recommended every other year or annually for decompensation, and repeat endoscopy is not required for patients taking β-blockers.

In patients with medium or large varices identified at screening endoscopy, prophylactic therapy is clearly recommended, as described below. This group of patients clearly derives the greatest benefit from therapy. The primary treatment options are obliteration with esophageal variceal band ligation (EVL) or reduction of portal pressure with oral pharmacologic agents. There is currently no role for decompressive therapy, transjugular intrahepatic portosystemic shunt (TIPS), or surgical shunting for prophylaxis of variceal bleeding. In addition, endoscopic sclerotherapy has no role in prophylaxis (see Chapter 70B).

NONINVASIVE MEANS OF DIAGNOSING ESOPHAGEAL VARICES

Although upper endoscopy is the most effective screening tool for esophageal varices, the invasive nature of this procedure has led investigators to find alternative noninvasive imaging techniques, as well as methodologies for risk stratifying patients for screening, as shown in Table 75A.2. Noninvasive screening techniques have several potential advantages over endoscopy. They are generally better accepted by patients, which could potentially increase adherence to screening protocols. In addition, these methods are typically less expensive than endoscopy. Finally, varices are absent in most patients (60%) with compensensated cirrhosis. Because the diagnostic yield in this cohort of patients is low, alternative noninvasive screening could risk stratify patients eligible for invasive screening. The four general types of alternative screening modalities are 1) blood chemistries, 2) cross-sectional imaging, 3) transient elastography, and 4) alternative endoscopic techniques, such as ultrathin endoscopy and capsule endoscopy.

The least invasive means of screening for varices is through analysis of blood chemistries. Numerous biochemical parameters have been considered to evaluate the presence of esophageal varices, including platelet count, prothrombin time, serum albumin, and Child-Turcotte-Pugh (CTP) class. However, none of these surrogate markers used alone or in combination is sufficiently reliable for use in clinical practice (D'Amico & Morabito, 2004; de Franchis, 2008; Qamar et al, 2008).

In recent years, cross-sectional imaging, including multidetector computer tomography (CT) and gadolinium-enhanced magnetic resonance (MRI), have been evaluated for esophageal variceal screening. However, compared with CT, there is relatively little experience with MRI (Annet et al, 2006; Goshima et al, 2009; Matsuo et al, 2003). Multidetector CT provides better images than conventional CT, thereby increasing the yield in identifying varices (Kim et al, 2009). In a direct comparison of multidetector CT and conventional endoscopy, both modalities identified varices, and radiologists accurately predicted the presence of large varices 93% of the time (Perri et al, 2008). However, the information from CT imaging was much less detailed compared with endoscopy. The absence of varices was accurately predicted by CT in only about 50% of patients; in more than one third of cases, it inaccurately identified small varices when large varices were seen endoscopically. Aside from limited sensitivity and specificity in variceal screening, CT has several other drawbacks . It cannot provide information about the red wale markings or other stigmata associated with increased risk for bleeding. In addition, exposure to ionizing radiation is significant, especially with repeated CT imaging (de Franchis, 2008; Thabut et al, 2008). However, one potential advantage of CT over endoscopy is its ability to identify other relevant abdominal pathology, namely hepatocellular carcinoma. Currently, cross-sectional imaging is not sufficiently reliable for use in routine clinical screening protocols for esophageal varices.

Transient elastography is an ultrasound technique that noninvasively measures tissue elasticity. This technique is studied primarily for measuring liver stiffness as a means to determine the presence and severity of hepatic fibrosis (Abenavoli et al, 2007; Del Poggio & Columbo, 2009). The test can easily be performed by nonphysicians with a dedicated device by generating a low-amplitude shear wave that propagates through the liver parenchyma. The velocity of propagation is directly proportional to liver stiffness and is automatically calculated by the device and expressed in units of pressure (kPa): the higher the value, the stiffer and more fibrotic the tissue and, by correlation, the more pressure required to deform the tissue. Although universally accepted ranges have not been developed, the general ranges for cutoff values for normal are up to 8 kPa and more than 13 to 18 kPa for cirrhosis.

Aside from being noninvasive and easily performed, the advantages of elastography include assessment of a larger hepatic area than liver biopsy and general correlation with the extent of histologic fibrosis. The disadvantages regarding variceal screening are that it is not a direct assessment of varices, and the test may be inaccurate or unreliable in patients with ascites and in obese patients. In fact, up to 10% of cases may not return any reading (Foucher et al, 2006; Sandrin et al, 2003).

Several studies have evaluated transient elastography in the noninvasive diagnosis and staging of esophageal varices. Theoretically, as liver stiffness and hepatic fibrosis progress, the likelihood of developing esophageal varices should increase. However, this methodology is subject to the same problems as other noninvasive techniques. Using a cutoff value of 12.5 kPa, Castera and colleagues (2009) studied 298 patients with hepatitis C virus (HCV) infection and reported only 76% sensitivity and 78% specificity in the diagnosis of esophageal varices. In another study, investigators compared two cutoff values for liver stiffness in predicting the presence of esophageal varices in 61 patients with advanced fibrosis from HCV (Vizzutti et al, 2007). At a lower cutoff of 17.6 kPa, the sensitivity was 90% and specificity was 43%. At the higher cutoff of 27.4 kPa, more patients with varices were missed (sensitivity of 70%), but specificity improved to 78%. Similar results were reported by Kazemi and colleagues (2006), who examined the correlation between liver stiffness and presence of large esophageal varices.

Although more studies are needed, current data suggest that the diagnostic accuracy of transient elastography is sufficiently limited that it cannot supplant upper endoscopy as a recommended screening technique for esophageal varices (de Franchis, 2008; Del Poggio, 2009). In fact, it seems unlikely that it would ever replace endoscopy as the primary screening tool. However, because it is a less invasive technique, elastography could possibly be used as an adjunct screening methodology. Patients could be monitored for changes in their transient elastography profile between recommended endoscopic screening intervals to potentially identify specific patients at higher risk for variceal progression. However, such screening and surveillance recommendations are only speculative at this point.

During the past decade, the utility of alternative video endoscopic devices has been studied in screening for esophageal varices. One of these modalities is the ultrathin endoscope inserted without sedation via a transnasal and transoral approach. The primary advantage of this procedure compared with conventional endoscopy is the avoidance of conscious sedation with its attendant risks, cost, and inconvenience. Unlike cross-sectional imaging or transient elastography, video endoscopy (ultrathin and capsule endoscopy) provides direct visualization of the esophageal mucosa that may improve estimation of variceal size and red wale markings, which is not possible with cross-sectional imaging. The primary disadvantage of alternative endoscopy is that compared with conventional endoscopy, these devices have a limited field of view and cannot perform interventions such as biopsy or banding.

Limited data are available on ultrathin endoscopy in variceal screening, and most studies, but not all, show that this technique is more easily performed, has greater patient acceptance, and provides an acceptable diagnostic yield compared with conventional endoscopy (Catanzaro et al, 2002; Madhotra et al, 2003; Saeian et al, 2002). However, these results are based on a very small number of patients. Despite some initially promising findings, ultrathin endoscopy has largely fallen out of favor; at most centers, ultrathin unsedated endoscopy is not used for screening or surveillance of esophageal varices.

Esophageal capsule endoscopy is perhaps the most promising option for minimally invasive screening of esophageal varices. This technique involves the ingestion of a capsule videoscope that transmits images as it traverses the esophagus. The patient is supine after ingestion of the device and is gradually placed in the upright position, which increases the transit time in the esophagus to provide better imaging. Compared with conventional endoscopy, capsule endoscopy offers the advantages of direct visualization of the esophagus, the absence of sedation, and less procedural discomfort and time.

Several drawbacks are associated with capsule endoscopy. Interventions obviously cannot be performed, the device cannot be manipulated to change its field of view, and it cannot insufflate the esophagus, which most physicians have found to be a critical step in the proper diagnosis and staging of varices. Finally, capsule endoscopy does not properly visualize gastric varices, which could therefore be missed.

Capsule endoscopy has been studied in the detection and grading of esophageal varices, and de Franchis and colleagues (2008) reported a study comparing capsule endoscopy with conventional endoscopy in 288 patients. The capsule and esophageogastroduodenoscopy (EGD) findings were concordant in 86% of cases. However, capsule endoscopy failed to identify varices in 28 cases, of which 24 (13%) were small and 4 (2.2%) were large varices, although the capsule was significantly more preferred by patients over EGD. Lapalus and colleagues (2009) reported similar results in a cohort of 120 cirrhosis patients, with 77% sensitivity and 88% specificity in the detection of grade 2 and higher esophageal varices and/or red signs compared with upper endoscopy. Smaller studies comparing capsule endoscopy and EGD have yielded similar results (Eisen et al, 2006; Frenette et al, 2008; Lu et al, 2009; Pena et al, 2008). Models comparing cost effectiveness of esophageal capsule endoscopy and EGD imply that they are equivalent strategies (White & Kilgore, 2009).

In summary, upper endoscopy remains the gold standard in screening for the presence and staging of esophageal varices. None of the imaging modalities mentioned above has proven sufficiently reliable to supplant the role of endoscopy in evaluation. However, capsule endoscopy may be used as an alternative, albeit a less effective, screening technique in the small number of patients who either cannot or will not undergo conventional endoscopic screening.

Table 75A.3

Primary Prophylactic Therapy for Esophageal Varices: Prevention of Initial Bleeding

Variceal Grade	Recommended Therapy
No varices	No treatment
Small, CTP class A and no red wale markings	No treatment
Small, CTP class B or C or red wale markings	β-Blocker
Medium or large, CTP class A and no red wale markings	β-Blocker preferred, endoscopic variceal ligation for patients who cannot take β-blockers
Medium or large, CTP class B or C or red wale markings	β-Blocker or endoscopic variceal ligation

CTP, Child-Turcotte-Pugh classification

PRIMARY PROPHYLACTIC THERAPY FOR ESOPHAGEAL VARICES: PREVENTION OF INITIAL BLEEDING

Once identified, all medium and large varices should be treated. In addition, small varices associated with high-risk features for bleeding, such as decompensated liver disease and red wale markings, should also be treated (Table 75A.3). The primary treatment options are obliteration with EVL or reduction of portal pressure with oral pharmacologic agents. Portal pressure can be pharmacologically reduced in three ways: 1) diminishing the portal inflow with vasoconstrictors, 2) reducing the intrahepatic vascular resistance, or 3) reducing the resistance in the collateral circulation with vasodilators. The most commonly used pharmacologic agents are nonselective β-adrenergic blockers, namely propranolol or nadolol, which act as antagonists for both the β_1 and β_2 receptors; β_1 blockade reduces portal inflow by decreasing cardiac output, and β_2 blockade reduces portal inflow through vasoconstriction of the sphlanchnic circulation. In addition, venodilators such as isosorbide reduce portal pressure by decreasing intrahepatic and/or portocollateral resistance. Isosorbide also has a systemic hypotensive effect and reduces portal pressure by reducing inflow as much as it does by reducing resistance (Blei et al, 1987).

The goal of pharmacologic therapy is to reduce portal pressure and thereby reduce variceal bleeding. A decrease in hepatic venous pressure gradient (HVPG) to less than 12 mm Hg essentially eliminates the risk of hemorrhage, and reductions less than 20% from baseline significantly reduce the risk of a first variceal bleed (Casado et al, 1998; Groszmann et al, 1990). Some patients are nonresponders to β-blockers, however, in terms of portal pressure reduction. Bendtsen and colleagues (1991) defined *nonresponse* as a less than 10% reduction in portal pressure after an oral dose of 80 mg of propranolol. Because their withdrawal returns the risk for bleeding to that of the untreated population, β-blockers should be continued for life (Abraczinskas et al, 2001).

Numerous published primary prophylaxis trials with nonselective β-blockers have been performed that include hundreds of patients. The pooled odds ratio (OR) of bleeding with β-blockers is almost half that of placebo: 0.54 (95% confidence interval [CI], 0.39 to 0.74; $P < .001$). The number of patients who need to be treated to prevent one adverse bleeding event is 10 (95% CI, 8 to 18). A study of the early trials reported a nonsignificant trend toward a lower mortality rate (OR, 0.75; 95% CI, 0.57 to 1.06) (D'Amico et al, 1999). Another recent meta-analysis similarly found no difference in mortality rate (Tripathi, 2007). Finally, propranolol has been shown to prevent acute and chronic bleeding from portal hypertensive gastropathy in a single-blind, randomized study (Pérez-Ayuso et al, 1991). β-Blockers are typically started at a low dose (propranolol 20 mg bid or nadolol 40 mg qd) and titrated either as maximally tolerated or for a reduction in pulse rate of 25%. However, side effects of β-blockers prevent their use in approximately 15% of patients, and another 15% are intolerant (Garcia-Pagan et al, 2001). In addition, without directly monitoring the effects of β-blockers with HVPG measurements, their clinical effect is difficult to determine because changes in portal pressure correlate poorly with pulse rate (Garcia-Tsao et al, 1986).

In addition to β-blockers, other pharmacologic agents have been evaluated in the prevention of a first variceal bleed, but the results have largely been disappointing. Merkel and colleagues (2000) performed an unblinded study to evaluate the combination of isosorbide mononitrate and nadolol and found the combination to be more effective in reducing bleeding, with only a small increase in side effects. However, a recent larger controlled trial reported no effect with treatment. A double-blind, placebo-controlled trial by Garcia-Pagan and colleagues (2003) composed of 349 patients found no difference in 2-year actuarial probability of variceal bleeding or survival, with adverse effects being more frequent in the combination group. Studies assessing nitrates used alone have failed to demonstrate efficacy (Angelico et al, 1997; Garcia-Pagan et al, 2001). Currently, clinical evidence is insufficient to support the use of nitrates alone or in combination with β-blockers for prophylactic therapy.

Numerous trials have compared endoscopic therapy with β-blockers in primary prophylaxis for variceal hemorrhage (De et al, 1999; Jutabha et al, 2005; Lo et al, 2004; Lui et al, 2002; Psilopoulos et al, 2005; Sarin et al, 1999; Schepke et al, 2004). Meta-analysis showed that variceal ligation significantly reduced the risk of a first bleed compared with propranolol (relative risk [RR], 0.57; 95% CI, 0.38 to 0.85), but there was no difference in terms of mortality rate (RR, 1.03; 95% CI, 0.79 to 1.36) (Khuroo et al, 2005). These data have led to an intense debate as to whether band ligation therapy should replace β-blockers as the first-line therapy for primary prophylaxis.

Proponents of β-blocker therapy point out that band ligation therapy is associated with an inherent risk of bleeding, which can result in death. In addition, there may be a bias toward positive results relative to endoscopic therapy in studies with shorter follow-up and fewer patients. In the analysis of studies that were larger or had longer follow-up—that is, more than 100 patients or follow-up longer than 20 months—no difference in outcomes was reported between the two therapies (Bosch & Garcia-Tsao, 2009). β-Blockers also have a track record of long-term safety, which cannot be said for band ligation therapy. Finally, endoscopic therapy requires ongoing procedures that may be more costly and have lower patient preference compared with pharmacologic therapy (Longacre et al, 2008).

The statements regarding prophylactic therapy from two separate organizations highlight this debate. The recommendations from the 2005 Baveno consensus conference are that β-blockers should be the first-choice treatment to prevent first variceal bleeding in patients with high-risk varices, and EVL

should be offered to patients with contraindications or intolerance to β-blockers (de Franchis, 2005). The American Association for the Study of Liver Diseases (AASLD) practice guidelines indicate that nonselective β-blockers and EVL are safe and effective in patients with medium or large varices that have a high risk of hemorrhage (CTP classes B and C or variceal red wale markings on endoscopy). The choice of therapies may be left to physician preference, although β-blockers are the preferred therapy in patients with medium or large varices that have not bled and that are not at the highest risk of hemorrhage (CTP class A patients, no red signs). EVL should be considered in patients with contraindications, intolerance, or noncompliance to β-blockers. Finally, the addition of β-blockers administered with EVL has been evaluated in one study, which failed to demonstrate a reduction in the risk of first bleed or death (Sarin et al, 2005).

SECONDARY PROPHYLACTIC THERAPY FOR ESOPHAGEAL VARICES (PREVENTION OF REBLEEDING)

Patients who survive a first episode of variceal bleeding are at very high risk of recurrent bleeding (70%) and death (30% to 50%), with the highest risk period occurring within 6 weeks of the index bleed (D'Amico & de Franchis, 2003; Grace et al, 1998). There is consensus that all patients who have previously bled from varices should have secondary therapy to prevent further variceal bleeding (Box 75A.1; Garcia-Tsao et al, 2007). Severity of liver disease (Pagliaro et al, 1994), continued alcohol abuse (Vorobioff et al, 1996), and variceal size have all been associated with variceal rebleeding. In addition, the inability to reduce HVPG to less than 12 mm Hg or achieve a less than 20% reduction from baseline significantly increases the risk of rebleeding. The treatment of acute variceal bleeding is covered in Chapter 75B.

After control of acute bleeding, prevention of recurrent hemorrhage is considered mandatory and should be initiated as soon as the patient is stable. Numerous trials have been performed on β-blockers compared with placebo or no treatment, and nonselective β-blockers have been found to reduce the risk of subsequent bleeding from 63% to 42% and to lower overall mortality rates from 27% to 20% (Bernard et al, 1997; D'Amico et al, 1999; Garcia-Pagan et al, 2008).

The addition of isosorbide to β-blocker therapy has also been evaluated for the prevention of rebleeding. These studies had their impetus from an article that stated approximately one third of hemodynamic nonresponders to β-blockers become responders after the addition of isosorbide (Garcia-Pagan et al, 1991). One of the two trials showed reduced rates of bleeding (Gournay et al, 2000), and one did not show reduced bleeding (Pasta et al, 2001, abstract). Data gathered from other trials compared this regimen with endoscopic therapy and showed that the combination of β-blockers with isosorbide is approximately 33% more effective than β-blockers alone in the prevention of rebleeding (Bosch & Garcia-Pagan, 2003; D'Amico et al, 1999). Therefore the best possible pharmacologic regimen is the combination of β-blockers and nitrates, although in clinical practice this regimen is associated with increased side effects; thus usually only β-blockers are used (Garcia-Tsao et al, 2007). This is especially true for patients with decompensated cirrhosis who are awaiting liver transplantation.

Trials have been conducted comparing pharmacologic therapy with endoscopic treatment in the prevention of rebleeding. The only modern endoscopic therapy for bleeding esophageal varices is band ligation. Sclerotherapy no longer plays a role in treatment because band ligation has clearly been demonstrated as the more efficacious therapy (Laine & Cook, 1995; Garcia-Pagan & Bosch, 2005; Garcia-Pagan et al, 2008) Therefore, although numerous studies have evaluated sclerotherapy in the prevention of rebleeding, these are largely of historic interest only. In general, after an acute variceal bleed, the patient is treated emergently with band ligation therapy and then subsequently receives recurrent EVL until the varices are completely obliterated, which usually requires three to four treatment sessions. Optimal pharmacologic therapy (β-blockers plus nitrates) has been compared with EVL in four published randomized studies with variable results (Lo et al, 2002; Patch et al, 2002; Romero et al, 2006; Villanueva et al, 2001). One study showed a benefit of pharmacologic therapy, another showed a benefit of EVL, and two showed no difference between the two therapies. A meta-analysis (Ding et al, 2009) of these four studies, which included 476 patients, found no significant difference in the rate of rebleeding, overall mortality rate, or complications between β-blocker plus isosorbide and EVL. Therefore both therapies appear to be effective in the prevention of esophageal variceal rebleeding. A more practical approach may be the combination of β-blocker and EVL because endoscopic therapy would obliterate the varices and recurrence would be prevented by β-blockers. Two studies have compared EVL and EVL plus β-blockers, both of which showed that the addition of β-blockers to EVL reduces the risk of rebleeding and variceal recurrence (de la Peña et al, 2005; Lo et al, 2000). Finally, a recent study by Garcia-Pagan and colleagues (2009) compared nadolol plus isosorbide alone or in combination with EVL. These investigators found that both therapies were equally effective in the prevention of rebleeding, but the patients who received EVL and combination drug therapy were more likely to require rehospitalization. They concluded that the addition of EVL to drug therapy was therefore was less efficacious than drug therapy alone.

Four randomized trials have compared TIPS (see Chapter 76E) with EVL, drug therapy, or the combination for the prevention of variceal rebleeding (Escorsell et al, 2002; Gülberg et al, 2002; Pomier-Layrargues & Villenueve, 2001;Sauer et al, 2002). In general, the side-effect profile was worse with TIPS—two studies found significantly more encephalopathy with TIPS, and two found no difference—but generally better control of

Box 75A.1

Secondary Prophylactic Therapy for Esophageal Varices: Prevention of Rebleeding

1. All patients should receive prophylactic therapy to prevent recurrent variceal hemorrhage.
2. The recommended therapy is β-blockers and endoscopic variceal ligation.
3. An alternative strategy is either β-blocker plus nitrates or endoscopic variceal ligation.
4. TIPS is recommended only in patients with recurrent variceal bleeding refractory to pharmacologic and endoscopic therapy.

TIPS, transjugular intrahepatic portosystemic shunt

bleeding was reported with TIPS, with significantly less rebleeding in two studies and no difference in two others. Most importantly, both these studies found no difference in survival rates. Therefore, because TIPS offers no survival advantage and has a worse side-effect profile, it is relegated to salvage therapy for patients with refractory variceal bleeding that is unresponsive to pharmacologic and EVL treatment.

In summary, the current recommendations for the prevention of variceal rebleeding suggest that all patients receive prophylactic therapy to prevent recurrent variceal hemorrhage. The recommended therapy is β-blockers and EVL (Garcia-Tsao et al, 2007; Gonzalez, 2008), although another consensus statement recommends β-blockers plus nitrates or EVL (de Franchis, 2005). TIPS is recommended only in patients with recurrent variceal bleeding refractory to pharmacologic and endoscopic therapy.

Finally, portal hypertensive gastropathy is a recognized cause of upper intestinal bleeding in patients with cirrhosis. The natural history of portal hypertensive gastropathy is that it worsens with increasing severity of liver disease and portal hypertension; acute bleeding is infrequent. Chronic anemia is more common with mild portal hypertensive gastropathy (Merli et al, 2004; Primignani et al, 2000). Propranolol has been shown to prevent acute and chronic bleeding in a single-blind, randomized study (Pérez-Ayuso et al, 1991). The actuarial percentages of patients free of rebleeding from portal hypertensive gastropathy at 12 months were 65% versus 38% ($P < .05$); at 30 months, the figures were 52% versus 7% ($P < .05$). In addition, fewer episodes of acute rebleeding were reported (mean episodes per patient per month were 0.01 vs. 0.12).

HEMODYNAMIC MONITORING WITH HEPATIC VENOUS PRESSURE GRADIENT

HVPG is equal to the wedge hepatic venous pressure minus free hepatic venous pressure. Some centers have advocated monitoring of HVPG to assess target reductions of portal pressure because HVPG measurement is the most reproducible and reliable method of assessing the portal pressure in cirrhosis (Groszmann & Wongcharatrawee, 2004). Wedge hepatic venous pressure is equivalent to portal venous pressure in cirrhosis when the major site of resistance is sinusoidal or presinusoidal (alcoholic and viral hepatitis B and C) or both. A decrease in HVPG of 20% or more from baseline or to 12 mm Hg or less has been shown to correlate with a significant reduction in bleeding. Therefore HVPG measurement offers the opportunity to tailor a patient's reponse to pharmacologic therapy based on changes in portal pressure. Ideally, HVPG could be measured before the initiation of pharmacologic therapy.

After the maximal tolerated dosage is achieved, HVPG could be remeasured. For patients responsive to pharmacologic therapy, no further treatment or adjustment in dosing would be required. However, nonresponders—that is, patients with portal pressure higher than 12 mm Hg or with a less than 20% decrease from baseline—could receive additional pharmacologic therapy. Some data suggest that this approach is efficacious (Bureau et al, 2002; Feu et al, 1995; McCormick et al, 1998; Patch et al, 2002; Villanueva et al, 1996, 2001). However, titration of medication requires multiple invasive procedures to measure HVPG, and some investigators have suggested that patients with early rebleeding are not available for repeated studies; therefore these high-risk patients are excluded from analysis (Thalheimer et al, 2004). Undoubtedly a valuable tool, the applicability of HVPG needs further prospective evaluation in future studies (Bosch et al, 2009; Garcia-Pagan et al, 2008).

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CHAPTER 76A

Location of portosystemic shunting

Stuart J. Knechtle and John R. Galloway

OVERVIEW

Esophageal varices develop in patients with portal hypertension, most commonly secondary to hepatic cirrhosis (see Chapter 70). They occur most frequently in the distal esophagus, although they may be accompanied by gastric varices. Rupture of varices is associated with massive upper gastrointestinal (GI) bleeding with an attendant high mortality rate. Therapy aimed at the prevention and treatment of bleeding varices has included pharmacologic, endoscopic, radiologic, and surgical strategies. All these therapies have evolved technically, and increasing clinical experience has resulted in more accurate definition of the role of each treatment modality. This chapter discusses the appropriate role of surgical shunts for the management of bleeding esophageal varices. An understanding of the role of surgical therapy also requires an understanding of the context in which it is applied, however. The natural history of bleeding esophageal varices is discussed first, followed by a description of the roles of alternative therapies. In current medical practice, it is most appropriate to apply surgical shunts within the context of medical (see Chapter 75A) and endoscopic management (see Chapter 75B), transjugular intrahepatic portosystemic shunts (TIPS; see Chapter 76E), and liver transplantation (see Chapter 97). Many patients are treated sequentially with more than one modality, and algorithms are presented to help establish the appropriate clinical context for surgical shunt therapy.

NATURAL HISTORY OF ESOPHAGEAL VARICES

Esophageal varices may produce massive upper GI bleeding that is difficult to control. Not all varices bleed, and not all patients with cirrhosis or portal hypertension will have esophageal varices develop. Clinical studies have sometimes included control groups without medical intervention, and analysis of these trials has helped define the natural history of esophageal varices. In one series, 46% of 819 patients with biopsy or clinical evidence of cirrhosis and no history of bleeding had esophageal varices by endoscopy (PROVA Study Group, 1991).

Over time, varices may appear, disappear, or change in size depending on alterations in patient physiology. A study of 84 patients with cirrhosis without previous bleeding who were monitored by serial endoscopy over 2 years showed that 31% of patients without varices progressed to large varices over 2 years, whereas in 70% of patients with small varices, the varices enlarged after 2 years (Cales et al, 1990). Dagradi (1972) studied the influence of alcohol on varices in patients with cirrhosis and found that variceal length increased in 65% of patients with cirrhosis who continued to consume alcohol, but it decreased in 80% of patients with cirrhosis who abstained from alcohol. Baker and colleagues (1959) reported that varices regress in 25%, disappear in 32%, and progress in 21% of patients with cirrhosis whose varices are monitored by endoscopy.

Most bleeding episodes in long-term studies occur during the first 1 to 2 years after identification of varices (Baker et al, 1959; Groszmann et al, 1990; Siringo et al, 1994; Triger et al, 1991). Average mortality rates after bleeding from esophageal varices are 23% at 1 year, 34% at 2 years, and 58% at 3 years. Approximately one third of deaths in patients with known esophageal varices are attributable to upper GI bleeding; a larger proportion die as a result of liver failure. The mortality rate directly attributable to variceal hemorrhage is 10% to 17% for cirrhotic patients (Baker et al, 1959; Sauerbruch et al, 1988; Triger et al, 1991). In patients with varices, upper GI bleeding is attributable to variceal hemorrhage in roughly two thirds of patients (Gebhard, 1998). Clinical parameters associated with increased risk of hemorrhage and death from esophageal varices include large varices, those with cherry-red spots (Dagradi, 1972), concurrent gastric varices (Kleber et al, 1991), Child-Turcotte-Pugh (CTP) classification, continued alcohol use (Dagradi, 1972), and infection (Goulis et al, 1999). Death correlates more closely with CTP classification (Merkel et al, 1989) than with any other parameter studied.

Rebleeding and mortality rates markedly increase after varices bleed. Studies have reported rebleeding rates to be 30% within 6 weeks of an initial variceal hemorrhage (Copenhagen Esophageal Varices Sclerotherapy Project [CVESP], 1984; Graham & Smith, 1981) and 60% to 75% within 1 year (Baker et al, 1959; Graham & Smith, 1981). Esophageal varices are the cause of bleeding in approximately 16% of hospital admissions for upper GI bleeding (de Franchis et al, 1991). Mortality rates from all causes within 1 year of initial hemorrhage have been estimated at 40% to 66% (Burroughs et al, 1989; CEVSP, 1984; Graham & Smith, 1981; Le Moine et al, 1992). The risk of dying increases as the interval between initial and second hemorrhage decreases (Gebhard, 1998). If patients survive for more than 12 weeks after a variceal hemorrhage, the risk of rebleeding or dying returns to that of patients who have never bled (Gebhard, 1998).

PHARMACOLOGIC MANAGEMENT OF PORTAL HYPERTENSION (SEE CHAPTER 75)

Prophylaxis

β-Blocker therapy has been studied to test its efficacy in preventing primary variceal hemorrhage in patients with known varices. Nadolol is a *nonselective β-blocker,* meaning it blocks both β_1 and β_2 receptors; patients given nadolol were compared with untreated control subjects. Nadolol reduced the incidence of bleeding from 35% ± 3% to 12% ± 3%, and the incidence of fatal bleeds was reduced from 18% ± 3% to 10% ± 2%. There

was no difference in overall mortality rate (Poynard et al, 1991). This study is used to support the use of prophylactic β-blockade to prevent a first variceal hemorrhage.

Nitrates are vasodilators whose action is mediated by nitric oxide on vascular smooth muscle. Nitroglycerin decreases portal pressure in patients with cirrhosis when high doses are used (Moreau et al, 1989). In animal studies, nitroglycerin lowered portal pressure 13%, and systemic blood pressure decreased 25%. This drug lowers portal pressure less than systemic pressure. Nitrates in combination with β-blockade may offer prophylaxis against an initial variceal bleed.

Randomized, controlled clinical trials comparing nonselective β-blockers (propranolol or nadolol) with no therapy in cirrhotic patients showed that drug treatment effectively reduced the risk of a first variceal hemorrhage (Poynard et al, 1991). The combination of isosorbide mononitrate and β-blockade further reduces portal pressure and has been shown in three studies to effectively reduce the risk of a first variceal bleed compared with β-blockade alone (Garcia-Pagan et al, 1990; Villanueva et al, 1996; Vorobioff et al, 1993). These investigations have noted, however, the difficult problem of compliance, particularly in patients with alcoholism. In addition, fatigue may be a side effect of therapy with β-blockade, and even more seriously, if patients do bleed, their ability to compensate for blood loss by tachycardia is compromised.

Acute Variceal Hemorrhage

The posterior pituitary hormone vasopressin causes splanchnic arteriolar vasoconstriction, reducing portal blood pressure by approximately 15% when given intra-arterially or intravenously (Chojkier et al, 1979; Huet et al, 1987). Intravenous use is preferred for safety and convenience, and the optimal dose of the drug is 0.3 to 0.4 U/min intravenously. As a result of simultaneous vasoconstrictive effects on the cardiac, mesenteric, and cerebral circulations, the complications increase when doses of 0.5 to 0.7 U/min are administered. It is not necessary to taper the dose; the infusion can be stopped when the therapeutic end point is reached. In a controlled study comparing vasopressin with no therapy, approximately half of the patients on vasopressin stopped bleeding, but this result did not differ from control subjects (Chojkier et al, 1979; Fogel et al, 1982).

Nitrogen is often administered concurrently with vasopressin to reduce the systemic vasoconstrictive effects of vasopressin, and it may further reduce portal pressure. Nitroglycerin infusion begins at 40 μg/min and is titrated to a mean arterial blood pressure of 65 to 75 mm Hg (Gimson et al, 1986).

Octreotide reduces bleeding (D'Amico et al, 1995) and enhances the results of sclerotherapy (Besson et al, 1995). Somatostatin and octreotide are endogenous peptides that act by reducing splanchnic, hepatic, and azygos blood flow (Bosch et al, 1981). Their principal advantage over vasopressin is that they do not cause vasoconstriction of the myocardial and cerebral circulations. Somatostatin and octreotide should be administered continuously at 250 μg/h and increased to 500 μg/h if bleeding continues. Preliminary studies showed that octreotide helped arrest acute variceal bleeding in six of six patients (Thulin et al, 1979; Tyden et al, 1978). Randomized, controlled trials comparing somatostatin or octreotide with vasopressin versus no infusion have shown equivocal results, which suggests that vasopressin and somatostatin have similar efficacy (Burroughs, 1996; Burroughs et al, 1990; Imperiale et al, 1995). Neither vasopressin nor somatostatin has been approved by the U.S. Food and Drug Administration (FDA) for treatment of variceal bleeding, although both agents are commonly used for this purpose (Korula, 1998). A prospective, randomized trial showed equivalence of somatostatin and sclerotherapy in the treatment of acute variceal bleeding (Planas et al, 1994).

Prevention of Rebleeding After Initial Control

Propranolol was shown by Lebrec and colleagues (1980, 1981) to reduce rebleeding significantly after acute variceal hemorrhage. This effect may be mediated by a decrease in cardiac output (β_1-blockade), increased splanchnic arteriolar resistance (β_2-blockade), and consequent decrease in portal blood flow (Lebrec et al, 1982) and collateral blood flow via the azygos venous system (Feu et al, 1993). β-Blockade is not widely used in the United States to prevent rebleeding after an episode of variceal hemorrhage because endoscopic sclerotherapy and ligation are preferred, and β-blockade after acute bleeding has not been shown to reduce mortality rate (Pagliaro et al, 1989). Meta-analysis comparing β-blockade with endoscopic sclerotherapy showed a non–statistically significant decrease in pooled relative risk for bleeding in the sclerotherapy group and no difference in mortality rate between the two groups (D'Amico et al, 1995). A randomized, controlled study showed, however, that isosorbide mononitrate (80 mg/day) in combination with nadolol (80 mg/day) was more effective than sclerotherapy in reducing rebleeding (Villanueva et al, 1996), and complications were less frequent in the group treated with drugs (16% vs. 37%). If this study is confirmed by other investigators, pharmacologic therapy may play a larger role than it currently does in the United States in the prevention of rebleeding.

ENDOSCOPIC THERAPY OF VARICEAL HEMORRHAGE

Prophylaxis

The use of prophylactic sclerotherapy to prevent a first hemorrhage was studied in three meta-analyses (see Chapter 75; Fardy & Laupacis, 1994; Pagliaro et al, 1989; Van Ruiswyk & Byrd, 1992). One study concluded that paravariceal injection with polidocanol decreased mortality rates (Fardy & Laupacis, 1994). The other two reports found that prophylactic sclerotherapy did not reduce bleeding or mortality rate and concluded that sclerotherapy was not indicated in this setting (D'Amico et al, 1995; Pagliaro et al, 1989; Van Ruiswyk & Byrd, 1992). The largest trial of prophylactic sclerotherapy was the Veterans Affairs (VA) cooperative trial. This trial included 281 patients but was prematurely closed because of excess mortality rate in the sclerotherapy group (VA Cooperative Variceal Sclerotherapy Group [CVSG], 1991). Sclerotherapy prevented variceal hemorrhage but substituted bleeding from sclerotherapy-induced ulceration. This study effectively ended the use of prophylactic sclerotherapy in the United States.

Acute Variceal Hemorrhage

When it became apparent that the once predominant therapy for variceal hemorrhage, emergency surgical shunts, were not improving survival but rather substituting death from liver

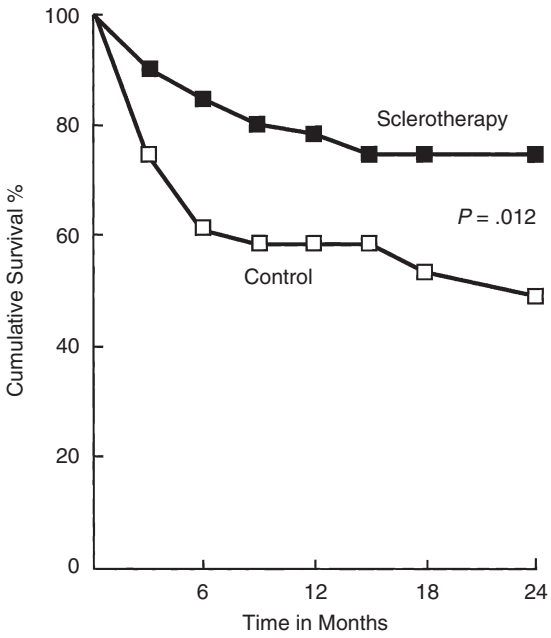


FIGURE 76A.1. Effect of sclerotherapy on survival in patients with cirrhosis: the King's College Hospital and Medical School Trial. Cumulative survivals in sclerotherapy patients (n = 51) and controls (n = 56) are shown. Control group patients received standard medical treatment, including blood transfusions, vasopressin, and Sengstaken-Blakemore tubes when necessary. *(From MacDougall BR, et al, 1982: Increased long-term survival in variceal haemorrhage using injection sclerotherapy: results of a controlled trial. Lancet 1:124-127.)*

failure for death from bleeding, endoscopic variceal injection was evaluated as a less invasive therapy. In 1980, a prospective randomized trial with 107 patients from King's College Hospital showed control of bleeding by sclerotherapy in 57% of 51 treated patients compared with 25% of 56 patients treated medically (MacDougall et al, 1982). Two years later, a follow-up study showed improved patient survival with sclerotherapy compared with controls who received blood transfusions, vasopressin, and a Sengstaken-Blakemore tube when necessary (Fig. 76A.1).

When interpreting this and subsequent trials, it is important to understand that the King's College trial had more nonalcoholic patients than alcoholic patients (60 vs. 47) and had patients with relatively mild liver failure (74 were CTP class A or B, 33 were class C). The more patients in any study of variceal hemorrhage who are alcoholic or who have CTP class C liver disease, the more difficult it is to show a survival advantage of therapy. Death from bleeding in such patients tends to be replaced by death from liver failure (Block & Reichelderfer, 1998). The VA cooperative study showed no reduction of long-term survival when acute hemorrhage was treated with sclerotherapy (CVSG, 1994).

Sclerotherapy has been shown to stop acute variceal hemorrhage effectively (Gregory, 1990; Westaby et al, 1989). Meta-analysis of 20 trials of emergency sclerotherapy versus a variety of alternative therapies supported the superiority of sclerotherapy with its success rate of 71% to 100%; however, the complication rate was high (18%), and 2.7% patients died as a direct result of sclerotherapy (D'Amico et al, 1995).

Endoscopic variceal ligation (EVL) has been developed as an endoscopic alternative to sclerotherapy, potentially lowering the risk of ulceration and perforation of the esophagus. Seven prospective, randomized, controlled trials compared EVL with endoscopic sclerotherapy (Gimson et al, 1993; Hashizume et al, 1993; Hou et al, 1995; Laine et al, 1993; Lo et al, 1995, 1997; Stiegmann et al, 1992). In all studies, EVL and sclerotherapy were equally effective in controlling active bleeding. Complications were significantly lower with EVL in all studies. No esophageal strictures were seen in patients treated with EVL compared with 5% to 33% of patients treated with sclerotherapy. The development of the multiple-band ligating device, which allows banding without repeatedly reinserting the endoscope, has made this modality of endoscopic control of varices much more attractive, such that it has now become the endoscopic therapy of choice (Laine, 1997).

Prevention of Rebleeding

Although sclerotherapy effectively stops acute variceal bleeding, rebleeding remains a problem, and intermediate (2- to 5-year) survival is not improved in many trials. A confounding variable confusing interpretation of the results in many of these trials is continued alcoholism. Alcohol abstinence for 6 months, CTP class, and aspartate aminotransferase level all were independent predictors of survival in the VA trial (CVSG, 1994). Meta-analyses of trials comparing sclerotherapy with pharmacologic management have shown sclerotherapy to prevent rebleeding more effectively and sometimes improve survival (D'Amico et al, 1995; Infante-Rivard et al, 1989). When EVL was compared with sclerotherapy, rebleeding rates were significantly decreased with EVL in three studies (Gimson et al, 1993; Hou et al, 1995; Lo et al, 1995), and mortality rates were significantly lower in three studies (Hou et al, 1995; Lo et al, 1995; Stiegmann et al, 1992). EVL seems to be at least as effective as sclerotherapy in preventing rebleeding.

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT (SEE CHAPTER 76E)

The development and clinical use of TIPS in the treatment of portal hypertension first occurred in the 1990s, and its use for the treatment of variceal hemorrhage has expanded (LaBerge et al, 1992; McCormick et al, 1994). TIPS is used electively far more often than in the emergency setting. Despite the effectiveness of TIPS in abruptly stopping variceal hemorrhage, overall patient mortality rates remain high (Smith & Graham, 1982). Death often is related to multisystem organ failure, progressive liver failure or sepsis, or disseminated intravascular coagulation, reflecting the use of TIPS in patients with end-stage disease. Complications are usually related to the underlying cirrhosis and associated comorbidities. In addition to relieving variceal hemorrhage, TIPS effectively relieves ascites in these patients (Crenshaw et al, 1996; Martin et al, 1993b) because TIPS is functionally a nonselective, side-to-side portacaval shunt. In contrast to all surgical shunts, TIPS creates a shunt to the suprahepatic inferior vena cava (Fig. 76A.2).

TIPS was developed as a minimally invasive procedure performed by radiologists using fluoroscopic imaging to place a noncompressible stent between the portal vein and hepatic vein. Successful TIPS lowers portal pressure, and the procedure is typically well tolerated even in very ill patients. Complications

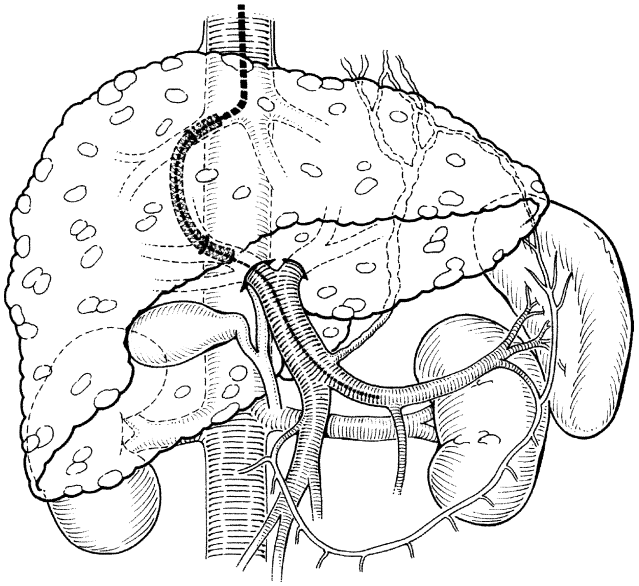


FIGURE 76A.2. Transjugular intrahepatic portosystemic shunting creates an intrahepatic portosystemic shunt from the portal vein to the hepatic vein, held open by a titanium stent.

include encephalopathy secondary to portosystemic shunting, shunt stenosis and occlusion, inability to place a TIPS, and intraperitoneal bleeding if the liver capsule is punctured. Mortality rate at 30 days has been reported at 20%, but half of these deaths were unrelated to the procedure itself (Darcy et al, 1993). In patients with CTP class C cirrhosis, a 30-day mortality rate of 67% has been reported (Martin et al, 1993a, 1993b); in a lower risk population of 100 patients, a 30-day mortality rate of 5.3% was reported (Richter et al, 1994).

Primary patency—that is, patency without radiologic intervention to revise the TIPS—has been reported to be 46% to 85% in the first 3 to 6 months (Richter et al, 1994; Saxon et al, 1993; Sterling & Darcy, 1995) and 27% to 57% at 1 year (Haskal et al, 1994; Malisch et al, 1993; Saxon et al, 1993; Sterling & Darcy, 1995). *Primary assisted patency,* meaning patency after revision, has been reported to be 85% (Haskal et al, 1994). LaBerge and colleagues (1995) reported shunt stenosis or occlusion in 47% of 90 TIPS patients over a 2-year period.

The newer polytetrafluoroethylene (PTFE)-covered stents are associated with less need for intervention, less shunt dysfunction, and better outcomes (Bureau et al, 2007). If post-TIPS ultrasound shows narrowing or thrombosis of the shunt, patency can be restored by repeat balloon dilation and stenting or by thrombectomy. Color Doppler ultrasound of TIPS is routinely performed at 1- and 6-month intervals after the procedure to evaluate luminal narrowing or increased flow velocity, which would suggest impending thrombosis of the TIPS. The rate of TIPS restenosis or occlusion is higher than the rate of recurrent symptoms because in some patients, occlusion does not produce symptoms. Nevertheless, recurrent variceal hemorrhage occurs in approximately 50% of patients with TIPS stenosis or occlusion. A multicenter trial of TIPS involving 100 patients reported that 16% of patients had rebleeding by 6 months, and five of these were from nonvariceal sources (Coldwell et al, 1995). Similarly, LaBerge and colleagues (1995) reported variceal rebleeding in 32% of 90 patients at 2 years.

Prophylaxis of Bleeding with Transjugular Intrahepatic Portosystemic Shunting

The ability of TIPS to prevent an initial variceal hemorrhage has not been studied. Patients awaiting liver transplantation who have intractable ascites are often treated with TIPS as a means of bridging to liver transplantation. Although not a true study of prophylaxis, these patients seem to be at low risk of bleeding.

Acute Variceal Bleeding and Transjugular Intrahepatic Portosystemic Shunting

TIPS may be used effectively in the control of acute variceal hemorrhage when medical management or endoscopic variceal ligation or both are ineffective. Barton and colleagues (1995) found that TIPS controlled acute variceal bleeding in 91% of patients, whereas Helton and associates (1993) reported control in 17 (74%) of 23 patients. A report by Encarnacíon and colleagues (1995) reported on 65 patients with acute variceal bleeding unresponsive to sclerotherapy or not treated with sclerotherapy because of recurrent massive hemorrhage. Acute bleeding stopped before the TIPS procedure in 26 patients, but not in the other 39 patients. Of the 65 patients with acute bleeding, 64 had successful placement of TIPS, and all these patients stopped bleeding within 3 days. The 30-day survival rate of patients who stopped bleeding before TIPS was 96%, but it was only 69% for patients actively bleeding at the time of TIPS. Survival was also linked to CTP class, with a 30-day survival rate of 91% for class A (n = 2) and class B (n = 32) patients, but survival rate was 71% for class C (n = 31) patients.

When used as primary therapy for acute variceal bleeding, TIPS may reduce treatment failure and mortality rate in high-risk patients. Monescillo and colleagues (2004) reported that in patients defined as high risk by a hepatic venous pressure gradient (HVPG) greater than 20 mm Hg randomized to treatment with TIPS (n = 26) versus no TIPS (n = 26), the no-TIPS group required more transfusions ($P = .002$), needed more intensive care unit care, had more treatment failures, and had poorer survival ($P < .05$). The no-TIPS group was treated with β-blockers, variceal banding, or sclerotherapy.

Prevention of Rebleeding by Transjugular Intrahepatic Portosystemic Shunting

TIPS has been used most frequently to prevent recurrent variceal hemorrhage. The results of four large series are shown in Table 76A.1 (Henderson et al, 1998). Rebleeding rates are similar in these series and are approximately 25% at 1 year. Thirty-day mortality rates were 14% to 16% except for the Rössle series (Rössle et al, 1994). Most deaths within 30 days were due to multisystem organ failure, whereas most later deaths were attributable to progressive liver failure. Because TIPS is a nonselective shunt, encephalopathy rates were relatively high at 25%, although in most patients this was not debilitating because it is usually controllable with lactulose, neomycin or rifaximin, and a low-protein, low-ammonia diet.

Most episodes of rebleeding after TIPS were related to stenosis or thrombosis of the shunt. In addition, many asymptomatic patients had shunt stenosis or thrombosis detected by ultrasound. Primary patency was 40% to 67% at 1 year, which improved to 79% to 88% with revision of stenotic stents

Table 76A.1

Patency of Transjugular Intrahepatic Portosystemic Shunt for Prevention of Recurrent Bleeding

Reference	Mean Follow-up	No. Patients (CTP Class C)	Technical Success (%)	Procedure Deaths	Encephalopathy (%)	30-Day Mortality Rate (%)	Survival Rate (%)	Rebleed (%)	Primary Patency (%)	Assisted Primary Patency* (%)	Secondary Patency (%)†
Coldwell et al, 1995	6 mo	96 (34)	100	2	29	14	77‡	16‡	67	88	–‡
LaBerge et al, 1995	1.2 y	94 (42)	95	0	25	16	60§	26§	66	83	96§
							51‖	32‖	42	79	90‖
Rössle et al, 1994	1 y	100 (22)	93	1	25	3	85§	8‡	67	–	100§
								18§			
Fillmore et al, 1996	8 mo	53 (21)	94	0	8	16	72¶	24**	40	–	100‡
									16	–	95§
Bureau et al, 2007	300 days	39 (39)	100	0	22	–	69‖	5%	85.6	–	–

*Includes revised stenotic stents
†Includes revised stenotic and thrombosed stents
‡At 6 months
§At 1 year
‖At 2 years
¶At 3 months
**At 8 months
CTP, Child-Turcotte-Pugh

From Henderson JM, et al, 1998: Portal hypertension. Curr Probl Surg 35:384-452.

(assisted primary patency). *Secondary patency,* which is patency after TIPS thrombectomy or revision, was 95% to 100% at 1 year (Coldwell et al, 1995; Fillmore et al, 1996; LaBerge et al, 1995; Rössle et al, 1994).

In the short time since its introduction, TIPS has had a dramatic impact on the treatment of variceal hemorrhage. In addition to its use in preventing variceal hemorrhage, TIPS has the added benefit of often improving overall liver function, as measured by CTP status, and of effectively bridging patients to liver transplantation (Abouljoud et al, 1995; Menegaux et al, 1994; Millis et al, 1995; Odorico, 1998; Suc et al, 1995). Despite the suggestion that TIPS may reduce operative time and blood loss during liver transplantation, data are not yet available to support this contention. Nevertheless, it has been shown that the TIPS procedure effectively prevents rebleeding (D'Amico et al, 1995; Ring et al, 1992).

TIPS has been compared with endoscopic therapy for the long-term prevention of recurrent bleeding. In a meta-analysis of 11 randomized trials, fewer patients rebled after TIPS (19%) than after endoscopic therapy (47%), encephalopathy was more common after TIPS (34%), and TIPS dysfunction developed in 50% of patients overall (Papatheodoridis et al, 1999).

A major recent change in therapy recommendations is that in creating a TIPS, use of expanded PTFE (ePTFE)-covered stents is now preferred. The basis for this recommendation is the decreased need for shunt intervention and a suggestion of better outcomes with covered stents rather than bare ones (Angermayr, et al, 2003). Although TIPS increases the risk of hepatic encephalopathy, prophylactic use of nonabsorbable disaccharides or antibiotics does not reduce this risk and is not recommended (Riggio et al, 2005).

TIPS also has been compared with shunt surgery. The distal splenorenal shunt showed lower rates of rebleeding, encephalopathy, and shunt thrombosis than TIPS, but ascites was less common after TIPS (Khaitiyar et al, 2000). A multiinstitutional, randomized trial compared TIPS with the distal splenorenal shunt in CTP class A and B cirrhotic patients (Henderson et al, 2004). Initial analysis of the results showed no significant differences between TIPS and the distal splenorenal shunt in variceal rebleeding, shunt occlusion, and survival. However, of the TIPS patients, 80% required reintervention to maintain shunt patency, and close surveillance was required.

TIPS also has been compared with the small-diameter interposition shunt. In a controlled trial, shunt occlusion, death from hepatic failure, and the need for liver transplantation all were significantly more common after TIPS (Rosemurgy et al, 2000). At the 10-year follow-up report, the small-diameter interposition shunts continued to perform better in terms of shunt occlusion, and survival was also superior in CTP class A and B patients and in those with Model for End-Stage Liver Disease (MELD) scores less than 13 (Rosemurgy et al, 2000). Indications for TIPS supported by current data include 1) continued variceal hemorrhage after sclerotherapy or banding, 2) prevention of rebleeding or treatment of ascites in patients awaiting liver transplantation, and 3) prevention of rebleeding in patients who are not candidates for a surgical shunt or liver transplantation because of expected short survival.

Treatment of Budd-Chiari Syndrome with Transjugular Intrahepatic Portosystemic Shunting

Given the advantages of the PTFE-covered stents with regard to patency, this matter was studied in a large series of 221 patients with Budd-Chiari syndrome who were treated with

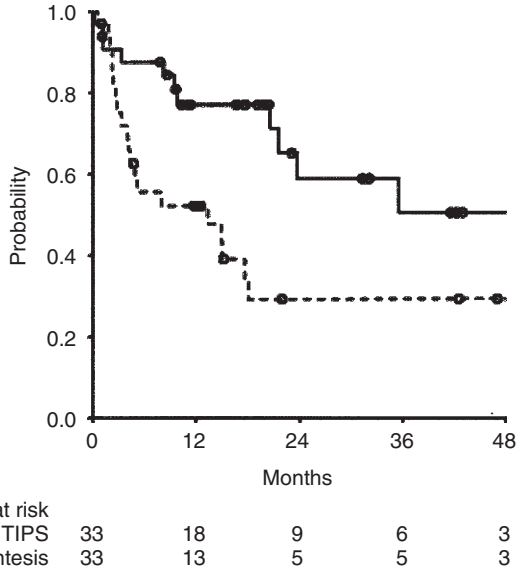


FIGURE 76A.3. Probability of survival without transplantation in patients assigned to transjugular intrahepatic portosystemic shunt (*TIPS*) treatment (*continuous line*) and patients assigned to paracentesis plus albumin (*dotted line*). The probability was superior in patients treated with TIPS (P = .021). *(From Salerno F, et al, 2004: Randomized controlled study of TIPS versus paracentesis plus albumin in cirrhosis with severe ascites. Hepatology 40:629-635.)*

TIPS (133 patients) if they had not responded to anticoagulation treatment (Garcia-Pagan et al, 2008). TIPS is now recommended for patients with Budd-Chiari syndrome who do not improve with anticoagulation therapy.

Treatment of Ascites with Transjugular Intrahepatic Portosystemic Shunting

TIPS has been used effectively to relieve ascites in patients refractory to pharmacologic therapy with diuretics. Salerno and associates (2004) reported a multicenter, randomized, controlled trial comparing TIPS (n = 33) with paracentesis plus albumin (n = 33) in patients with CTP class B and C cirrhosis. Survival without liver transplantation was superior in patients treated with TIPS (P = .021; Fig. 76A.3). By multivariate analysis, a higher MELD score and paracentesis independently predicted death. Treatment failure was more common in patients treated with paracentesis, although encephalopathy occurred more commonly in patients receiving TIPS (Salerno et al, 2004).

SURGICAL SHUNTS FOR BLEEDING ESOPHAGEAL VARICES (SEE CHAPTERS 76C AND 76D)

Prophylactic Surgery

Early trials of prophylaxis for variceal bleeding compared portacaval shunts with medical therapy. Although bleeding was effectively prevented, survival was not significantly enhanced with surgery because of a marked increase in deaths from accelerated hepatic failure (Grace, 1992). Because only one third of patients with varices eventually bleed, surgery cannot be justified as prophylaxis and is not recommended in this setting.

In a prospective, controlled study to evaluate prophylactic surgery in 112 patients with portal hypertension and esophageal varices, Inokuchi (1984) found the bleeding rates were 19.2% in the medical group and 0% in the surgical group. No difference was reported in the survival rate between the two groups at 2-year follow-up, and prophylactic surgery led to a prevention of esophageal bleeding without any increase in the mortality rates. This is the only study to support a role for prophylactic surgery, but it should be noted that the majority of these patients had posthepatic cirrhosis with reasonably well-preserved liver function.

Acute Variceal Hemorrhage

At most American centers, endoscopic therapy is the first option used to treat bleeding esophageal varices. An exception is the series reported by Orloff and coworkers (1994), who used portacaval shunts as a first-line therapy with excellent results. At most other centers, patients who do not respond to endoscopic variceal ligation are referred for consideration for TIPS or a surgical shunt. Emergency surgical shunts prevent bleeding more effectively than sclerotherapy, but overall mortality rate is equivalent (Cello et al, 1987; D'Amico et al, 1995).

Although nonoperative therapies are useful for initial management of bleeding esophageal varices, if these measures fail to control bleeding, emergency surgery should be promptly considered (Rikkers & Jin, 1994). Emergency surgical shunts normalize portal pressure immediately and effectively control variceal hemorrhage, but emergency surgery has been associated with a mortality rate of 20% to 55% (Cello et al, 1987; D'Amico et al, 1995). The high risk of dying after placement of an emergency shunt is presumably related to the frequent decompensation of liver function and associated comorbidity at the time of an acute bleed. Outcomes correlate with CTP classification rather than with the type of shunt performed. Liver failure and encephalopathy often ensue and are the proximate causes of death associated with emergency surgery in most series.

In choosing which surgical shunt to use for emergency control of bleeding, the portacaval shunt (see Chapter 76B) is an acceptable choice because it effectively decompresses the portal venous system and can usually be rapidly constructed. An end-to-side portacaval shunt is adequate, although patients with ascites should have a side-to-side portacaval shunt to relieve their ascites as well. A series by Orloff and colleagues (1994) showed the usefulness of the portacaval shunt in the emergency setting. Other functional side-to-side shunts, such as the mesocaval shunt (see Chapter 76D) and proximal splenorenal shunt (see Chapter 76C), also effectively decompress the portal vein and relieve esophageal variceal bleeding, and they should be effective for relief of ascites. In contrast to portacaval shunts, these shunts do not require dissection in the porta hepatis and do not complicate future liver transplantation. In appropriately selected patients, a distal splenorenal shunt also may be used in the emergency setting to relieve variceal hemorrhage in patients with a large, patent splenic vein and absent or medically controlled ascites (Rikkers & Jin, 1995).

Prevention of Rebleeding After Initial Control

In view of the disadvantages of emergency shunts, the more attractive role of surgical shunts is in the elective setting to prevent recurrent variceal hemorrhage. Because the

natural history of variceal hemorrhage places patients who have bled once at high risk for rebleeding, definitive therapy ought to be considered after control of the acute hemorrhage. In an appropriately selected patient, surgical shunts substantially reduce the risk of recurrent bleeding, maintain stable liver function, and obviate the need for repeated endoscopic procedures.

The role of TIPS versus a surgical shunt for prevention of rebleeding has been recently clarified by a randomized clinical trial comparing the two treatments in patients who did not respond to medical therapy (Henderson et al, 2006). No difference was found in rebleeding rates (5.5% for distal splenorenal shunt [DSRS] vs. 10.5% for TIPS, *P* value not significant), encephalopathy, or survival. TIPS patients required more interventions, although the study used noncovered stents. TIPS was slightly more cost effective than DSRS at 1 year (Boyer et al, 2008), and the study concluded that the two treatments were of equal efficacy in preventing recurrent variceal hemorrhage.

Depending on whether shunts completely divert, partially divert, or compartmentalize the portal venous circulation, they are characterized as *nonselective*, *partial*, or *selective*. Relative to nonselective shunts, the goal of partial and selective shunts is to preserve hepatic portal perfusion and minimize the risk of progressive liver failure and encephalopathy while preventing variceal bleeding.

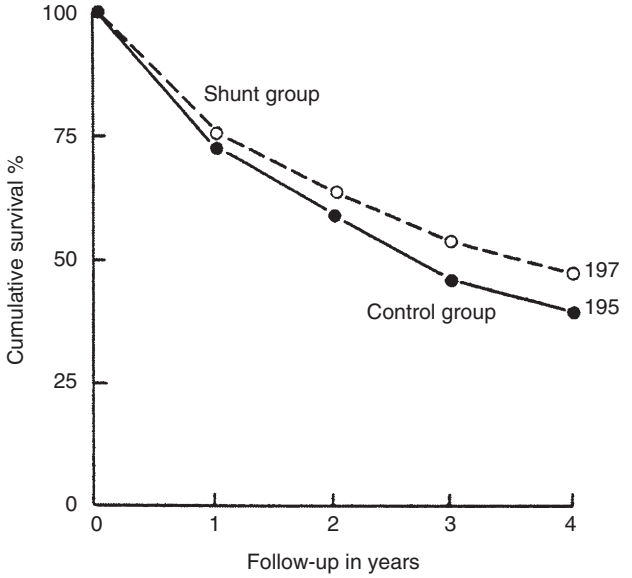


FIGURE 76A.4. Cumulative survival data from four controlled trials of portacaval shunt versus conventional medical management. *(Courtesy HO Conn; from Boyer TD, 1982: Portal hypertension and its complications: bleeding esophageal varices, ascites, and spontaneous bacterial peritonitis. In Zakim D, Boyer TD [eds]: Hepatology: A Textbook of Liver Disease. Philadelphia, Saunders, pp 464-499.)*

General Aspects of Nonselective Shunts

The end-to-side portacaval shunt was the first experimental shunt performed in dogs (Konstantinov, 1997). This shunt is the prototype of the nonselective shunt and has been compared in randomized, controlled trials with conventional medical management for the treatment of portal hypertension and its complications (Rikkers et al, 1992). Figure 76A.4 shows combined data of four controlled studies of the portacaval shunt, comparing shunted patients with medically managed patients according to survival. No survival advantage could be shown for shunt patients, although the four studies were all biased in favor of medical management because failures of medical management were crossed over to surgical therapy. Bleeding was effectively stopped in shunt patients, whereas more than 70% of medically treated patients rebled. Encephalopathy occurred in 20% to 40% of shunted patients.

When the end-to-side portacaval shunt was compared with the side-to-side shunt in a controlled trial, no significant clinical differences were noted between these two shunts (Resnick et al, 1974). The interposition mesocaval shunt (see Chapter 76D), also a nonselective shunt, was studied in a randomized trial comparing it with the direct side-to-side portacaval shunt, and no clinical or hemodynamic differences were evident (Stipa et al, 1981). The same series documented a high graft thrombosis rate after the mesocaval shunt. Nevertheless, the mesocaval shunt avoids dissection in the porta hepatis, which is an advantage for future liver transplant candidates. An additional option is a central or proximal splenorenal shunt with splenectomy. In the current era, indications for a nonselective shunt include an emergency shunt for variceal hemorrhage, an elective shunt in the presence of significant ascites, and treatment of Budd-Chiari syndrome. In some patients not suited for a selective shunt, a nonselective shunt might serve as a long-term bridge to hepatic transplantation, when bleeding is not controlled endoscopically or by TIPS.

Budd-Chiari syndrome (see Chapter 77) with ascites, abdominal pain, and portal hypertension is an indication for a side-to-side portacaval shunt. A side-to-side shunt is necessary because the portal vein (PV) serves as the major efferent conduit in this syndrome. If the disease is fulminant, or if cirrhosis has developed secondary to longstanding hepatic venous occlusion, liver transplantation is a preferable option. If liver transplantation is not anticipated, a side-to-side portacaval shunt may be the ideal procedure. Often the caudate lobe enlarges after occlusion of the major hepatic veins because the caudate lobe communicates directly with the vena cava and may become the major route of venous outflow from the liver. Massive hypertrophy of the caudate lobe may prevent a side-to-side portacaval shunt from being technically possible because of caudal expansion of the caudate lobe, which is interposed between the PV and the inferior vena cava (IVC) and prevents their side-to-side anastomosis. A mesocaval shunt may be technically more feasible in this setting.

When Budd-Chiari syndrome involves occlusion of the hepatic portion of the IVC, the infrahepatic vena cava develops collaterals to the azygos venous system. These collaterals permit the portal circulation to be decompressed into the IVC via a mesocaval shunt, and a mesoatrial shunt is generally not required in such patients. Although a mesoatrial shunt circumvents an occluded IVC, it is a long shunt with a poor patency rate and has been associated with poor outcomes. Successful management of Budd-Chiari syndrome requires accurate diagnosis and treatment of the underlying hypercoagulable state. In experienced centers, TIPS can also sometimes be used in patients with Budd-Chiari syndrome. Anticoagulation is usually necessary to prevent shunt thrombosis in both surgically treated and TIPS-treated patients.

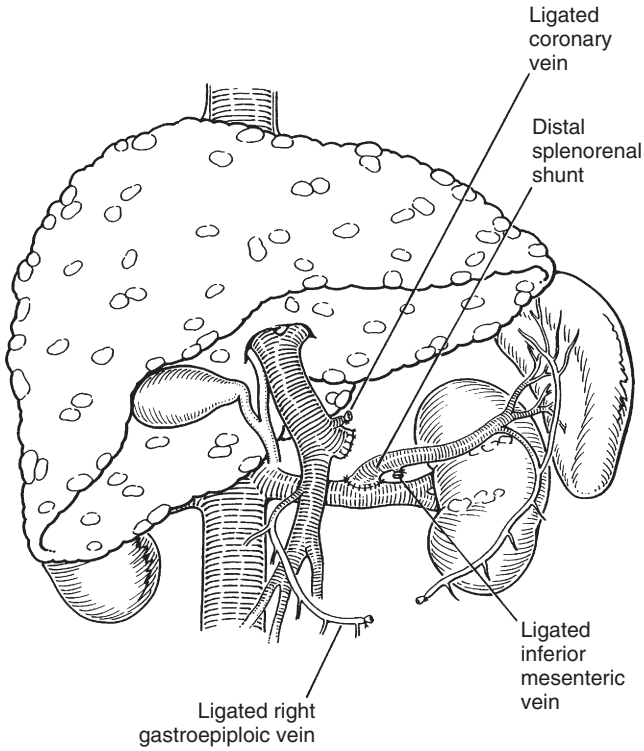


FIGURE 76A.5. Distal splenorenal shunt requires ligation of the coronary vein. Drainage of the splenic vein is into the left renal vein. The right gastroepiploic vein also is ligated and divided. *(From Knechtle SJ, 1998: Surgical shunts for portal hypertension. In Knechtle SJ [ed]: Portal Hypertension: A Multidisciplinary Approach to Current Clinical Management. Armonk, NY, Futura, pp 175-202.)*

General Aspects of Distal Splenorenal Shunt

Warren and colleagues (1967) introduced the distal splenorenal shunt (see Chapter 76C) with the goal of preserving hepatopetal blood flow in the PV while decompressing esophageal varices. The distal splenic vein is anastomosed to the left renal vein, and collateral vessels are ligated, such as the coronary and gastroepiploic veins connecting the superior mesenteric and gastrosplenic components of the splanchnic venous circulation (Fig. 76A.5). This procedure compartmentalizes the portal venous circulation into a high-pressure superior mesenteric venous system to perfuse the liver and a decompressed gastrosplenic venous system to avoid variceal bleeding (Knechtle, 1998).

In patients with advanced ascites, the distal splenorenal shunt is contraindicated because lymphatics are transected during the dissection of the left renal vein and the liver continues to have elevated sinusoidal pressures. In such patients, the distal splenorenal shunt may worsen ascites rather than relieve it. Warren's claim that the operation effectively accomplishes its goal of preserving hepatic function better than nonselective shunts remains controversial. Controlled trials have shown decreased portosystemic encephalopathy after the distal splenorenal shunt. Henderson and colleagues (1983) showed that portal flow is maintained in most patients with nonalcoholic cirrhosis and noncirrhotic portal hypertension, but portal flow rapidly collateralizes to the shunt in patients with alcoholic cirrhosis, particularly if alcohol consumption continues. Failure to ligate the coronary vein (CV) results in early loss of hepatopetal portal flow.

Despite surgical interruption of collaterals that connect the superior mesenteric venous system to the gastrosplenic system, collaterals gradually develop through a pancreatic network termed the *pancreatic siphon.* Surgical splenopancreatic disconnection improves selectivity of the distal splenorenal shunt, especially in alcoholic cirrhotics; however, the complete dissection and ligation of multiple splenopancreatic venous tributaries to disconnect the splenic vein from what is often a very fibrotic pancreas is technically demanding and frequently bloody, and the clinical benefits of this extension of the procedure have not been clearly shown.

Visceral or computed tomography (CT) angiography should be done in any patient considered for a surgical shunt and especially before a distal splenorenal shunt. A distal splenorenal shunt requires a patent splenic vein, preferably at least 7 mm in diameter. Patients who have undergone splenectomy and those who have a thrombosed splenic vein are not candidates for this shunt procedure.

Six of seven controlled trials comparing the distal splenorenal shunt with nonselective shunts have evaluated alcoholic cirrhotic patients and were summarized by Jin and Rikkers (1991). None of these trials showed a survival advantage of either procedure. Four of the seven trials showed less encephalopathy after a selective shunt, whereas the other trials showed no difference in encephalopathy rates. Rebleeding rates did not differ between the two shunt groups, although one trial noted a higher rate of rebleeding after distal splenorenal shunt.

When the distal splenorenal shunt was compared with repeated endoscopic therapy, rebleeding was less frequent with selective shunts, but hepatic portal perfusion was better maintained by sclerotherapy. Encephalopathy rates were similar in both groups (Henderson et al, 1990; Rikkers et al, 1993). These two studies suggest that sclerotherapy effectively controls initial bleeding, but patients who do not respond to sclerotherapy should promptly undergo surgery. Another indication for surgery, rather than sclerotherapy, is poor access to advanced medical care. Such patients benefit from an initial selective shunt, rather than long-term sclerotherapy, because the latter requires multiple visits to a medical center.

Partial Shunt

The partial shunt proposed by Sarfeh and colleagues (1986) is a means of decompressing varices while preserving hepatic portal perfusion. An 8- or 10-mm PTFE graft is interposed between the PV and IVC. A prospective randomized trial of partial (8-mm diameter) and nonselective (16-mm diameter) interposition portacaval shunts showed a lower frequency of encephalopathy after the partial shunt, but similar survival was reported after both types of shunts (Sarfeh & Rypins, 1994). The largest series of partial shunts was reported by Rosemurgy and colleagues (2007) and includes 170 patients older than 18 years. Small-diameter H-graft shunts were performed in patients who did not respond to endoscopic variceal ablative therapy (56% alcoholic, 44% nonalcoholic); 38% were CTP class A or B and 62% were CTP class C. Variceal bleeding after shunt placement was very uncommon (2%). Actual survival was superior to that predicted by MELD scores but did parallel

the degree of hepatic reserve. Small-diameter H-graft shunting was encouraged in those patients who were neither eligible nor suitable for liver transplantation (Rosemurgy et al, 2007).

TYPES OF SHUNTS: TECHNICAL ASPECTS

Portacaval Shunt (See Chapter 76B)

Nonselective portacaval shunts can be performed by using a side-to-side method, an end-to-side method, or with an interposition graft to create a functional side-to-side shunt. Side-to-side shunts have the advantage of relieving ascites by reducing intrahepatic sinusoidal pressure in addition to decreasing the portal venous pressure gradient. They also are effective in decompressing varices and preventing recurrent variceal bleeding. The current recommended indication for a portacaval shunt would be for a patient with significant ascites and bleeding varices unresponsive to nonsurgical treatment who would not be a future candidate for liver transplantation. Patients who may eventually receive a liver transplant ideally should not be treated with such a shunt; rather, they should have a shunt in which the dissection is performed outside the porta hepatis. Portacaval shunts involving dissection in the hilum of the liver inevitably result in postoperative scarring in the hilum and make subsequent liver transplantation more difficult, with the added potential morbidity and mortality. Nevertheless, liver transplantation in patients with previous portacaval shunts can be done safely. If liver transplantation is not anticipated as a future option, a portacaval shunt is technically more straightforward than a distal splenorenal shunt and is a shorter operation in an unstable, actively bleeding patient.

A side-to-side portacaval shunt is performed through a transverse upper abdominal incision. The common bile duct is encircled and retracted to the patient's left. If a replaced right hepatic artery arises from the superior mesenteric artery, this also needs to be encircled and retracted to the left, which makes the exposure of the PV more difficult. The PV is dissected and encircled with a vessel loop, and the IVC is dissected and encircled with a vessel loop between the lower edge of the liver and the right renal vein. Partially occluding vascular clamps are placed on the IVC and PV, and the two are approximated. A venotomy is made longitudinally in each vein approximately 2 cm in length, and stay sutures of 6-0 polypropylene are placed at the corners. These stay sutures are tied down, and the anastomosis is performed with a running technique. Vascular clamps are removed and the wound is checked for hemostasis. The completed anastomosis is shown in Fig. 76A.6.

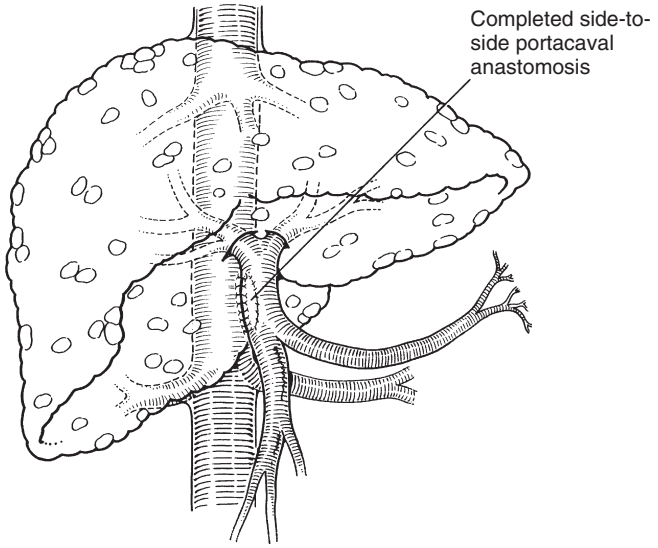


FIGURE 76A.6. The completed anastomosis normalizes portal pressures and results in hepatofugal blood flow through the shunt. *(From Knechtle SJ, 1998: Surgical shunts for portal hypertension. In Knechtle SJ [ed]: Portal Hypertension: A Multidisciplinary Approach to Current Clinical Management. Armonk, NY, Futura, pp 175-202.)*

Mesocaval Shunt (See Chapter 76D)

A mesocaval shunt may be indicated as a long-term bridge to liver transplantation or as definitive therapy in patients whose bleeding is not controlled by endoscopic methods or who have not responded to TIPS placement. Although a PTFE or Dacron graft is commonly used as a conduit between the superior mesenteric vein (SMV) and IVC, we have used an internal jugular vein autograft for this purpose. The better long-term patency rate for a vein graft favors the use of autologous vein over prosthetic material. We have had no complications from removal of one internal jugular vein and have had no shunt thromboses. Such shunts are not difficult technically and have the advantage of keeping the area of dissection away from the porta hepatis, which is an advantage if liver transplantation is a future consideration.

The mesocaval shunt is performed through a transverse upper abdominal incision. By elevating the transverse colon, the middle colic vein can be identified as it courses toward its junction with the SMV. The SMV is anterior and to the right of the superior mesenteric artery. After dividing overlying peritoneum and fat, there is generally a segment about 2 or 3 cm in length that is free of other venous tributaries. This segment of the SMV is dissected free and encircled, and the IVC can be dissected through the right colon mesentery; it is optimal to dissect a segment of IVC that is caudal to the duodenum so that the duodenum does not interfere with shunt placement. Next, the IVC is encircled with a vessel loop. The mesocaval shunt should take a straight path from the SMV to the vena cava rather than coursing around the duodenum.

When using a jugular vein conduit, the left neck is generally preferred because the left jugular vein is often slightly longer than the right jugular vein (Fig. 76A.7). An incision similar to a carotid endarterectomy incision is made along the anterior border of the sternocleidomastoid muscle. The platysma muscle is divided, and the jugular vein is identified. Branches are doubly ligated and divided, and the jugular vein is dissected free from the clavicle to the mastoid. It is ligated with silk ties proximally and distally, and the graft segment is excised and placed in sterile saline until it is used. Next, the neck wound is closed, and the proximal end of the jugular vein graft is anastomosed end-to-side to the SMV with running 6-0 polypropylene (see Fig. 76A.7). The distal end of the graft is anastomosed end-to-side to the IVC also with running 6-0 polypropylene. Partial occlusion clamps are placed on the SMV and IVC during construction of the anastomoses; after completion, the clamps are removed and shunt flow is assessed with an electromagnetic or ultrasonic flowmeter. Flow should be 1 to 2 L/min, and significantly lower flow rates should prompt inspection of the graft for technical problems.

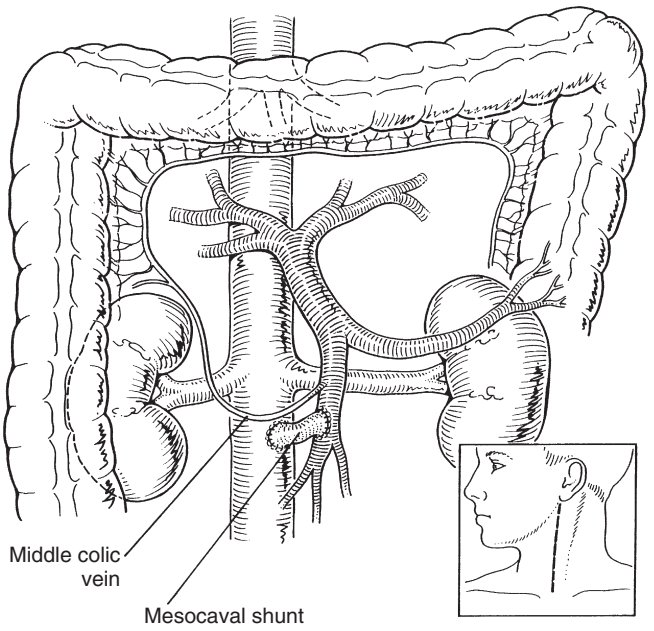


FIGURE 76A.7. The left jugular vein provides an ideal autologous endothelialized vein graft for a mesocaval shunt and is approached through the incision shown (*inset*). The vein can be excised from the clavicle to the angle of the mandible. The proximal end of the vein should be anastomosed to the superior mesenteric vein (SMV). The completed mesocaval shunt uses an 8- to 10-cm graft to decompress the SMV into the vena cava. *(From Knechtle SJ, 1998: Surgical shunts for portal hypertension. In Knechtle SJ [ed]: Portal Hypertension: A Multidisciplinary Approach to Current Clinical Management. Armonk, NY, Futura, pp 175-202.)*

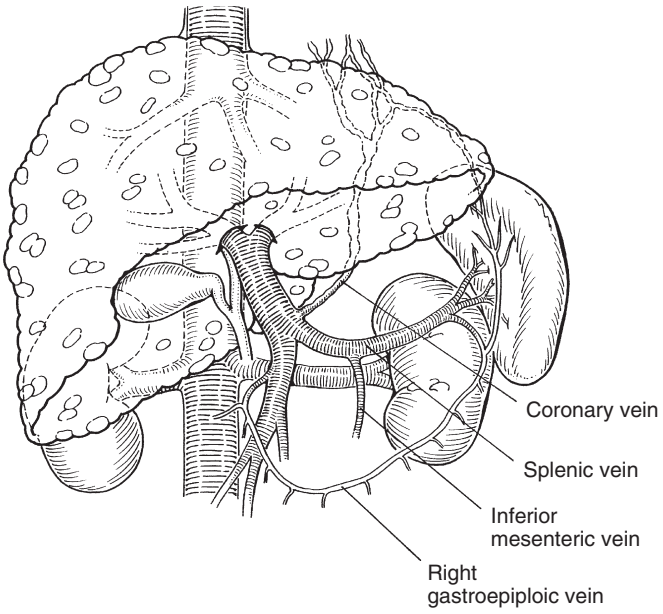


FIGURE 76A.8. The relevant anatomy exposed for a distal splenorenal shunt. The short gastric veins are left intact. The coronary vein and right gastroepiploic veins are ligated. *(From Knechtle SJ, 1998: Surgical shunts for portal hypertension. In Knechtle SJ [ed]: Portal Hypertension: A Multidisciplinary Approach to Current Clinical Management. Armonk, NY, Futura, pp 175-202.)*

Distal Splenorenal Shunt (See Chapter 76C)

A distal splenorenal shunt is performed through a transverse upper abdominal incision. The gastrocolic omentum is taken down such that the right gastroepiploic vein is divided, but the short gastric veins are left intact. The splenic flexure of the colon is mobilized and retracted caudally. The inferior border of the pancreas is retracted anteriorly and cranially to expose the posterior aspect of the pancreas and the splenic vein, which is dissected free from the pancreas, and all tributaries are ligated and divided. The CV may be one of its branches, or it may enter the PV.

The splenic vein dissection is generally the most challenging aspect of the procedure and may be particularly difficult in patients with pancreatic fibrosis from chronic pancreatitis. The splenic vein is dissected medially to its confluence with the SMV and laterally to a point that allows the vein to be brought down to the renal vein without kinking or tension. If splenopancreatic dissection is a goal of the procedure, the dissection continues all the way to the spleen such that all pancreatic tributaries are ligated and divided (Fig. 76A.8).

The left renal vein is dissected next, and adjacent lymphatics are ligated to avoid the complication of chylous ascites. The left adrenal vein is ligated and divided to assist in mobilization of the left renal vein. The gonadal vein and descending lumbrical veins are left intact to give additional venous outflow to the shunt. If a circumaortic left renal vein is present with a small anterior branch, decompression may be compromised. In this case, anastomosis directly to the IVC should be considered (i.e., a distal splenocaval shunt) (Atta, 1992). A vessel loop is placed around the left renal vein, and an adequate length of splenic vein should be dissected such that when it is divided at the PV, it can reach the left renal vein easily without tension.

Identification and ligation of the CV is an essential component of the operation. It is preferable to ligate the CV at its junction with the PV or splenic vein. The CV also can be ligated at the superior border of the pancreas, just before it extends along the lesser curvature of the stomach. The CV is generally large and attenuated and must be ligated if the shunt is to be selective. Blood flow through the completed shunt (see Fig. 76A.5) can be measured with a flowmeter and is generally 300 to 1000 mL/min.

DEVASCULARIZATION PROCEDURES FOR BLEEDING ESOPHAGEAL VARICES

Surgical devascularization procedures were developed with the intent of disconnecting varices from the hypertensive portal venous system, decreasing the risk of variceal hemorrhage (see Chapter 75C). In contrast to most shunts, these procedures avoid encephalopathy by preserving hepatic portal perfusion. The gold standard of devascularization procedures has become the Sugiura procedure, which consists of thoracic esophageal transection and devascularization followed weeks later by laparotomy to control bleeding from esophageal varices (Sugiura & Futagawa, 1973). The Sugiura procedure differs from other devascularization procedures in that extensive esophageal and gastric devascularization is performed in a manner that preserves the venous collaterals connecting the CV to the azygos system, which discourages varices from reforming. The initial report by Sugiura and Futagawa (1973) included 276 patients

and described an operative mortality rate of 4.3% and reoccurrence of varices in 2.3% after follow-up of 1 to 10 years. Actuarial survival was 83%. Survival according to CTP classification was 95% for class A, 87% for class B, and 57% for class C. Survival was better after an elective procedure than after an emergency operation.

The outstanding results achieved in the Japanese series have not been duplicated elsewhere. Many surgeons outside Japan have used modifications of the Sugiura procedure to control bleeding esophageal varices, particularly in patients with extensive mesenteric venous thrombosis or in those with a previous failed surgical shunt. Orozco and colleagues (1992) reported a 10-year experience with the elective Sugiura procedure using a one-stage transabdominal approach. Mortality rate correlated with CTP class. The Toronto experience with the modified Sugiura procedure was reported by Dagenais and colleagues in 1994 and included a 22% operative mortality rate when the procedure was used in the emergency setting; the 5-year survival rates were 100% for CTP class A, 43% for class B, and 25% for class C patients. In a series of 32 patients undergoing transabdominal esophagogastric devascularization for variceal bleeding, 11 of the 12 patients without liver disease survived more than 10 years. The other 20 patients with cirrhosis had a 5-year survival rate of 51% (Jin & Rikkers, 1996). This experience suggests that esophagogastric devascularization is an effective alternative to shunt surgery, particularly in patients whose underlying condition is diffuse splanchnic venous thrombosis in the absence of liver disease. The only prospective, randomized clinical trial comparing the Sugiura procedure with selective or total shunts was performed in patients with bilharzial cirrhosis and bleeding varices (da Silva et al, 1986). This trial concluded that patients treated with devascularization were more likely to survive longer without encephalopathy compared with patients treated with a shunt (da Silva et al, 1986; Raia et al, 1991).

Patients with portal venous anatomy unsuitable for surgical shunts, those who have had shunt failures, and those who do not respond to medical management may be considered for devascularization procedures. Patients who progress to CTP class C liver failure should be considered for liver transplantation. Devascularization procedures should be reserved for those rare patients with bleeding varices refractory to medical management and who also are ineligible for TIPS, a surgical shunt, or liver transplantation.

LIVER TRANSPLANTATION FOR BLEEDING ESOPHAGEAL VARICES

Definitive therapy for patients with advanced liver failure (CTP class B or C) is liver transplantation (see Chapter 97). Variceal hemorrhage is the most common clinical manifestation of portal hypertension to prompt liver transplant evaluation. The acute management of variceal hemorrhage in liver transplant candidates begins with endoscopic diagnosis and endoscopic variceal ligation where feasible, in combination with pharmacologic therapy, TIPS, or both for failures of endoscopic management. In view of the strong correlation between CTP class and long-term outcome, seen with virtually every form of therapy for bleeding varices, compelling evidence suggests that liver transplantation should be the treatment of choice for such patients with advanced liver disease. In the current era, each of the treatments discussed so far, including surgical shunts, should be used in a complementary fashion, and many patients require sequential application of the various modalities. Naturally, liver transplantation is the ultimate solution to cirrhosis and end-stage liver failure, when this is the underlying cause of portal hypertension and variceal hemorrhage.

Because of the disparity between the number of patients awaiting liver transplantation and the supply of donor livers, transplantation is generally accompanied by an unpredictable waiting period that varies depending on the supply of donor livers. Average waiting times for liver transplantation in the United States vary from 6 months to more than 2 years, depending on blood type (U.S. Department of Health and Human Services, 2003). Operative morbidity and mortality associated with liver transplantation correlate with the preoperative condition of the recipient. For this reason, it is advisable to use alternative measures to arrest variceal hemorrhage and to optimize the medical condition of the patient before proceeding to liver transplantation. Liver transplant programs in the United States preclude active alcoholics from liver transplantation and require at least a 6-month period of abstinence. This therapy generally is unavailable to active alcoholics with variceal hemorrhage, and such patients may need to be considered for surgical shunts. Because of immediate normalization of portal pressure, liver transplantation is effective therapy for bleeding esophageal varices resulting from underlying portal hypertension (Ewaga et al, 1994).

A portacaval shunt or surgical shunt involving dissection in the porta hepatis makes subsequent liver transplantation more technically difficult. If liver transplantation is anticipated after a surgical shunt, a shunt should be performed outside the porta hepatis whenever possible. Distal splenorenal and mesocaval shunts are preferred shunts for such patients (Knechtle et al, 1994; Shaked & Busuttil, 1991). A surgical shunt is an attractive means of controlling variceal hemorrhage in a patient who may not need liver transplantation for several years. Most patients eligible for liver transplantation with CTP class C cirrhosis require transplantation in the short term and are managed more appropriately with TIPS as a bridge to liver transplantation. TIPS may significantly improve the CTP class and may reduce morbidity for patients awaiting liver transplantation (Fig. 76A.9; Odorico, 1998).

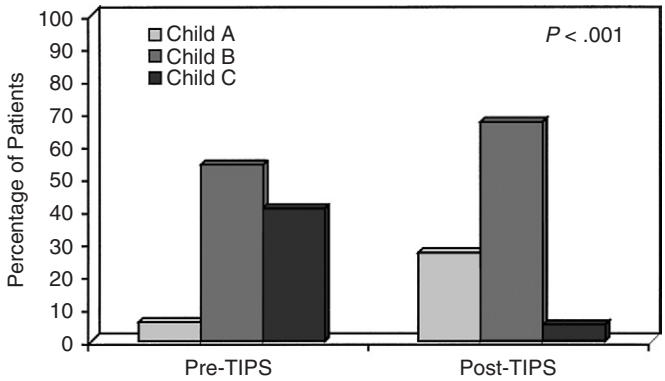


FIGURE 76A.9. Effect of transjugular intrahepatic portosystemic shunting (*TIPS*) on modified Child-Turcotte-Pugh (CTP) score. TIPS resulted in a significant shift toward improved recipient CTP score and pretransplant status ($P = .001$). *(From Odorico JS, 1998: Impact of transjugular intrahepatic portosystemic shunt on liver transplantation. In Knechtle SJ [ed]: Portal Hypertension: A Multidisciplinary Approach to Current Clinical Management. Armonk, NY, Futura, pp 253-263.)*

Meso-Rex Shunt for Portal Vein Stenosis after Liver Transplantation

Especially in children, extrahepatic PV stenosis may occur after liver transplantation, and it is generally seen many months or years after surgery. Often it manifests as portal hypertension, with GI bleeding from the Roux-en-Y, worsening splenomegaly, or even encephalopathy (Chiu & Superina, 2006; Superina et al, 2006). This problem, limiting PV blood flow to the liver and creating portal hypertension, can be addressed with a PV or SMV to left PV shunt graft, termed the *Meso-Rex shunt*. Autologous vein is generally used to create such a shunt, which relieves portal hypertension and restores physiologic blood flow to the liver (Bambini et al, 2000).

Extrahepatic Portal Vein Thrombosis

Extrahepatic PV thrombosis is a relatively uncommon cause of portal hypertension and variceal bleeding. Management of this entity is distinctly different from that of patients with cirrhosis because these patients usually have a normal liver, and survival is not limited by progression of the underlying liver disease. The etiology of PV thrombosis includes direct causes—neonatal peritonitis, trauma, and tumors of the porta hepatis—as well as congenital abnormalities of the PV, and indirect causes such as neonatal systemic sepsis, dehydration, and hypercoagulable states. PV thrombosis results in presinusoidal portal hypertension and the development of hepatopedal collaterals, which often maintain excellent portal perfusion.

Experience in the treatment of variceal bleeding as a result of PV thrombosis indicates three possible treatment options. Expectant medical management of each acute bleeding episode is tempting because the bleeding is generally well tolerated when the liver is normal. This approach may be appropriate in infants because bleeding tends to be self-limited, and half of these patients outgrow their variceal bleeding without therapy. Endoscopic variceal ablation and surgery should certainly be considered in the adult population, in whom the mortality rate for variceal hemorrhage approaches 20% over time with recurrent bleeding. It must be remembered that the same normal liver that allows patients to tolerate conservative management of bleeding also makes them excellent candidates for more aggressive treatment. Typically, the acute episode of variceal bleeding can be managed by resuscitation, vasopressin or octreotide infusion, and then endoscopic variceal ablation (Howard et al, 1988; Warren et al, 1988).

If bleeding becomes recurrent, evaluation of the portal, mesenteric, and splenic veins is performed with visceral angiography to include venous phases and/or magnetic resonance angiography. If the spleen is in situ and the splenic vein is patent, the patient is an excellent candidate for the distal splenorenal shunt, although central splenorenal shunts and mesocaval shunts can also be used if the SMV is also open. If the splenic vein is also occluded or if the spleen is absent, further endoscopic variceal ablation should be attempted. If this fails, exploration is performed. In rare cases, a shuntable vein can be found, such as the CV (a coronary caval shunt). Most often, if the spleen has not already been removed at a previous operation, usually for thrombocytopenia, a gastric devascularization with splenectomy is required. Recurrent variceal hemorrhage after devascularization can occur in 20% to 30% of patients, which requires further endoscopic variceal ablation but rarely esophagogastrectomy (Galloway & Henderson, 1990).

PRESENT ROLE OF SURGICAL SHUNTS

A shunt may often serve as a long-term bridge to liver transplantation in patients who are deemed to be acceptable candidates for liver transplantation. In a report comparing liver transplantation, shunts (82% distal splenorenal) in future candidates for liver transplantation, and shunts in patients without the future prospect of liver transplantation, the operative mortality rate was best in the two shunt groups (5% and 7% vs. 19% in liver transplant recipients). This finding was attributed to more advanced disease in the liver transplant cohort. The patients not considered for liver transplantation were excluded because of active alcoholism or advanced age. Kaplan-Meier survival analysis showed better survival in shunt patients who were transplant candidates—seven of 44 patients had progressed to liver transplantation—than either the liver transplant group or the shunt group without prospective liver transplantation during the first 5 years of follow-up. However, by 10 years no difference was reported between the groups (Fig. 76A.10). These results suggest that patients with CTP class A or early B cirrhosis, who are not actively drinking and are not too elderly or medically unfit, benefit from shunt surgery most. Because it is complicated less frequently by encephalopathy and because it has an excellent long-term patency rate, a distal splenorenal shunt is a good choice for such patients. If they progress to end-stage liver failure, they can be salvaged with transplantation (Rikkers et al, 1997). During the period studied, distal splenorenal shunts and nonselective shunts were more protective against rebleeding than was esophagogastric devascularization (Rikkers et al, 1997).

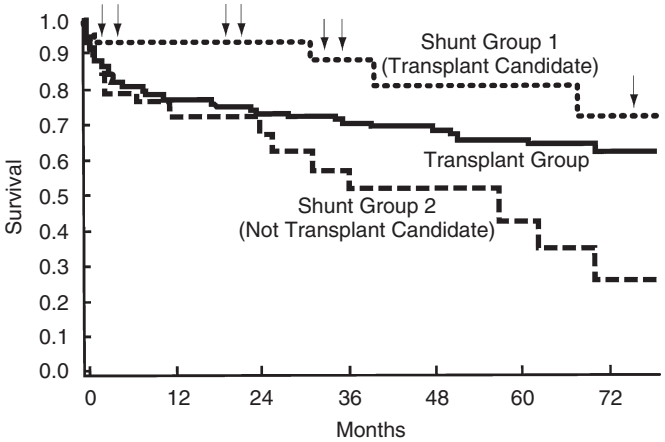


FIGURE 76A.10. Kaplan-Meier survival analysis of shunt group 1 (*dotted line*), transplant group (*solid line*), and shunt group 2 (*dashed line*). The *arrows* on the shunt group 1 curve indicate when patients from that group underwent liver transplantation. Survival of shunt group 1 is significantly different from survival of the transplant group ($P = .003$) and shunt group 2 ($P = .018$) at 1 year (log-rank test). At 5 years, the shunt group 1 and transplant group curves are no longer different, but both are significantly different from the shunt group 2 curve ($P = .006$ and $P = .029$). *(From Rikkers LF, et al, 1997: Shunt surgery during the era of liver transplantation. Ann Surg 226:51-57.)*

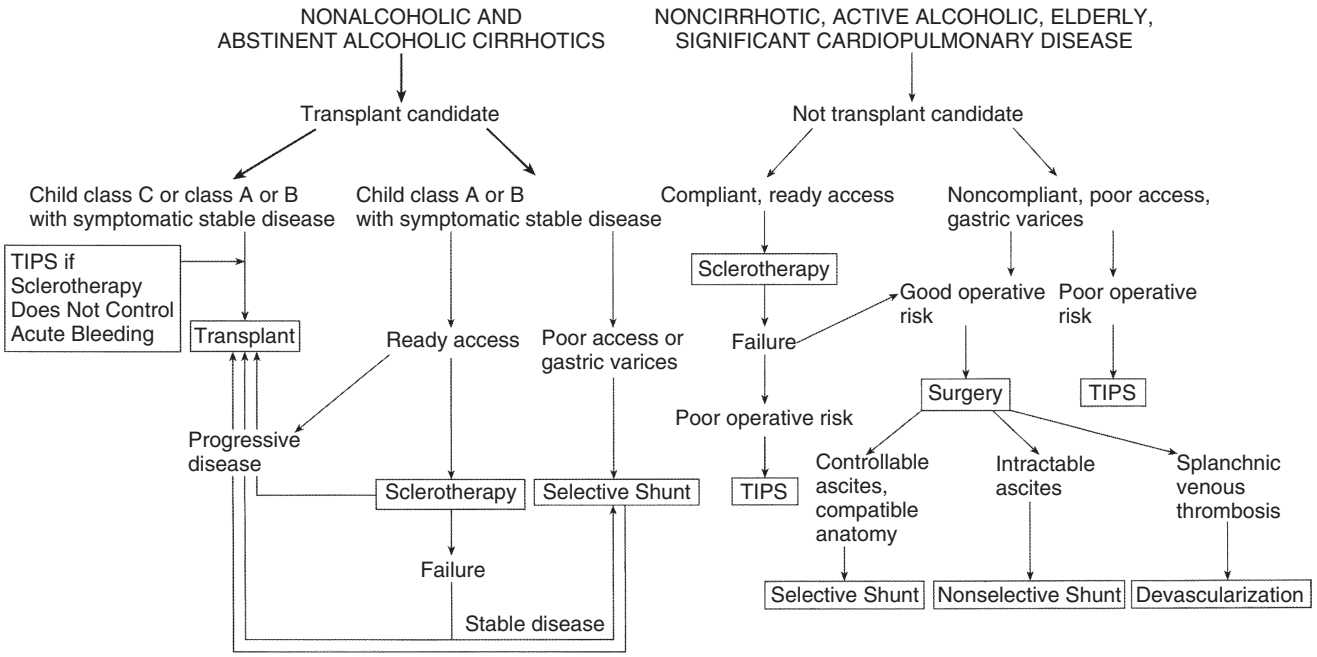


FIGURE 76A.11. Algorithm for definitive therapy of variceal hemorrhage. TIPS, transjugular intrahepatic portosystemic shunt. *(From Rikkers LF, 1995: Portal hypertension. In Levine BA, et al [eds]: Current Practice of Surgery, vol 3. New York, Churchill Livingstone, pp 1-22.)*

Consistent with the aforementioned observations, surgical shunts generally are reserved for patients with good hepatic reserve and variceal bleeding. Excellent results are achieved in this setting (Knechtle et al, 1999).

An algorithm summarizing current decision making in the management of variceal hemorrhage is shown in Figure 76A.11. Patients are divided into those potentially eligible for a liver transplant versus ineligible patients. The sequential use of various modalities is illustrated. The current use of procedures performed for variceal hemorrhage suggests that although banding continues to be used frequently, the use of TIPS has dramatically increased, as has liver transplantation. Nonselective shunts are rarely used today, and selective shunts are performed in a highly select group of patients.

During the past 25 years, liver transplantation and TIPS have evolved into effective therapies and have substantially affected management of this problem and indirectly changed the risk status (CTP class) of patients undergoing shunts. Analysis of this group of patients showed that in recent years the CTP class has progressively improved, and the need for emergency surgery has declined. The use of nonselective shunts declined because of the development of effective alternatives, such as EVL and TIPS, and because advanced liver failure with ascites was managed by liver transplantation, sometimes preceded by TIPS. Consequently, less risky patients were selected to undergo elective shunts for treatment of variceal bleeding. The incidence of postoperative encephalopathy decreased, and long-term (10-year) survival improved, especially because shunt patients could be salvaged if they developed liver failure postoperatively (Rikkers, 1998).

Another role for portosystemic surgical shunts is in children with variceal hemorrhage after endoscopic therapy. Excellent results have been achieved in children with distal splenorenal shunts and mesocaval shunts to prevent bleeding (Botha et al, 2004).

SUMMARY

The clinical management of bleeding esophageal varices has changed radically over the past 25 years. Recent changes include replacement of endoscopic variceal sclerotherapy by endoscopic variceal ligation. The excellent efficacy of EVL and its lower complication rate favor its increased use. Similarly, the minimally invasive nature of the TIPS procedure and its successful implementation by invasive radiologists has reduced further the need for surgical shunts. TIPS is being increasingly used when endoscopic intervention has failed. Another recent change is the use of ePTFE-covered stents, rather than bare stents, which allows better patency rates over time for TIPS. Liver transplantation is routinely recommended for patients with advanced liver failure. Surgical shunts are used more selectively, but with better results than in an earlier era when they were more commonly performed. A multidisciplinary approach to evaluation and treatment of variceal hemorrhage has improved the outcomes of these patients. Selective use of each of the therapies, alone or in combination with other modalities, results in improved outcomes.

We consider the current role of surgical shunts to be 1) less frequent than in the previous era; 2) of benefit in the emergency setting when other modalities—including medical therapy, endoscopic control, or TIPS—have failed; 3) useful in the elective setting as a long-term bridge to liver transplantation; 4) useful in the elective setting as definitive therapy for patients with noncirrhotic portal hypertension or CTP class A cirrhosis; and 5) a beneficial treatment for Budd-Chiari syndrome. We prefer the selective distal splenorenal shunt in patients without ascites because of its lower risk of portosystemic encephalopathy and its potential for preserving portal blood flow.

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CHAPTER 77

Budd-Chiari syndrome and venoocclusive disease

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OVERVIEW

Budd-Chiari syndrome (BCS) is a group of disorders caused by occlusion of the major hepatic veins or the inferior vena cava (IVC) or both at or near the level of the hepatic vein ostia. Although a brief discussion of these disorders first appeared in a book by Budd in 1845, Lambron in 1842 is said to have reported the first case. In 1899, Chiari collected 10 cases and reported three personal cases and presented the first thorough clinical and pathologic description of the syndrome, including the hypothesis that the underlying mechanism is endophlebitis of the hepatic veins. The weight of evidence favors the current opinion, however, that the primary process is usually thrombotic rather than inflammatory. Since publication of the initial description, more than 8000 cases of BCS have been described in the medical literature. In recent years, the incidence has increased substantially, most likely as a result of increased awareness of BCS, improvements in diagnostic methods, and widespread use of thrombogenic agents, such as oral contraceptives (Maddrey, 1987; Valla et al, 1986). Nevertheless, BCS remains a relatively uncommon condition.

Obstruction of hepatic venous outflow produces intense congestion of the liver and the clinical manifestations of ascites, hepatomegaly, and abdominal pain. Depending on the rapidity and extent of obstruction of hepatic venous outflow, the course of BCS may be rapid or chronic, progressing to death in a matter of weeks, or leading to death from liver failure or bleeding esophageal varices after an illness of months or occasionally years. In Western countries, a rapid course is more common, and the outcome has been fatal in many reported cases.

Venoocclusive disease (VOD), more recently called *sinusoidal obstruction syndrome,* is a group of disorders that mimic BCS, but it involves distinctly different populations of patients and is precipitated by distinctly different circumstances. In contrast to BCS, VOD occurs in the sublobular branches of the hepatic veins, the terminal hepatic venules, and the sinusoids within the liver, and the pathologic process involves obliteration of these small vessels by subendothelial sclerosis owing to endothelial injury, with thrombosis occurring secondarily. VOD is caused by a variety of toxic agents, such as pyrrolizidine alkaloids, antineoplastic drugs, and irradiation of the liver. In the Western hemisphere, the most frequent cause of VOD is bone marrow (hematopoietic stem cell) transplantation.

In recent years, effective surgical therapy has been developed that is designed to decompress the obstructed hepatic vascular bed. As a result, the previously dismal outlook for patients with BCS has improved considerably.

PREDISPOSING CONDITIONS FOR BUDD-CHIARI SYNDROME

Box 77.1 lists the specific conditions that are known to predispose to the development of BCS and VOD. Over the past 50 years, a marked change has been observed in the frequency with which a known cause or predisposing condition has been identified in cases of BCS. In the classic collective review of 164 cases of BCS reported by Parker in 1959, a predisposing condition or etiology could not be identified in 70% of the patients. In recent years, the incidence of idiopathic cases of BCS has plummeted to less than 30% (Mahmoud et al, 1996; Menon et al, 2004; Mitchell et al, 1982; Murad et al, 2009; Valla, 2003; Plessier & Valla, 2008), an improvement attributed to two factors: 1) a greater awareness of BCS and 2) improved diagnostic tools for identifying the anatomic lesions and for diagnosing thrombogenic hematologic disorders.

The distinct difference has been recognized for some time between the East and West in the conditions that predispose to the development of BCS and in the anatomic pattern of BCS. Table 77.1 displays these differences. *Membranous obstruction of the vena cava* (MOVC) is rare in the West, but it is a frequent cause of BCS in Eastern countries such as Japan, China, and India and in South Africa. In the West, thrombosis of the major hepatic veins alone is substantially more common than thrombosis or occlusion of the IVC; whereas in India, China, and Japan, IVC occlusion is far more common than hepatic vein occlusion alone. In North America, the acute or subacute forms of BCS predominate, and chronic BCS is observed less frequently, whereas in the East, the reverse is observed. In the West, BCS is seldom found during pregnancy or the postpartum period, whereas in India, pregnancy is a major predisposing condition for BCS. The same difference is seen in the incidence of infections such as hepatic amebiasis (see Chapter 67), which are rare in the West but are reported frequently in series of BCS from India. Finally, oral contraceptives are frequently associated with BCS in the United States, where use of these agents is widespread, whereas use of birth control pills is seldom associated with BCS in Eastern countries, where women use oral contraceptives much less.

Hematologic Disorders

Hematologic diseases that cause vascular thrombosis are the most common conditions that predispose to BCS in North America and Western Europe. Of disorders with thrombotic tendencies, polycythemia rubra vera is the most frequent,

Box 77.1

Conditions Predisposing to Budd-Chiari Syndrome and Venoocclusive Disease

Budd-Chiari Syndrome

- Hematologic disorders
  - Polycythemia rubra vera
  - Paroxysmal nocturnal hemoglobinuria
  - Essential thrombocythemia
  - Primary erythrocytosis
  - Myelofibrosis
  - Acute leukemias and lymphomas
  - Hemolytic anemias
  - Protein-C deficiency
  - Protein-S deficiency
  - Antithrombin-III deficiency
  - Lupus anticoagulant (antiphospholipid syndrome)
  - Factor V Leiden mutation
  - *JAK2* V617F mutation
  - Prothrombin (factor II) mutation
  - Antiphospholipid syndrome
  - Hyperhomocysteinemia
- Oral contraceptives
- Pregnancy and postpartum
- Malignant neoplasms
  - Hepatocellular carcinoma
  - Renal cell carcinoma
  - Adrenal carcinoma
  - Leiomyosarcoma of the inferior vena cava
  - Others (carcinomas of the lung, pancreas, and stomach; melanoma; reticulum cell sarcoma; adrenal sarcoma; tumor of the right atrium)
- Infections
  - Amebic liver abscess
  - Aspergillosis
  - Hydatid disease
  - Schistosomiasis
  - Syphilitic gumma
  - Filariasis
- Trauma
- Connective tissue disorders
  - Behçet syndrome
  - Sjögren syndrome
  - Mixed connective tissue disease
  - Sarcoidosis
  - Rheumatoid arthritis
  - α_1-Antitrypsin deficiency
  - Idiopathic hypereosinophilia syndrome
  - Systemic lupus erythematosus
- Membranous obstruction of the inferior vena cava
- Miscellaneous rare conditions (inflammatory bowel disease, hepatic torsion, lipoid nephrosis, protein-losing enteropathy)

Venoocclusive Disease

- Pyrrolizidine alkaloids
- Antineoplastic chemotherapy
- Irradiation of the liver
- Bone marrow transplantation
- Azathioprine
- Systemic lupus erythematosus
- Familial immunodeficiency
- Oral contraceptives

constituting 8.5% of the cases of BCS in the collected series of Parker (1959) and 10.4% of the cases in the collected series of Mitchell and colleagues (1982). In our series of 77 cases of BCS, 31% had polycythemia rubra vera, which is associated with BCS in some distinctly different ways compared with the classic disease. For one thing, it is found in young adults, rather than in middle-aged and elderly patients, and it is responsive to treatment with hydroxyurea or anagrelide, which should be started as soon as the disease is discovered and should be continued for life. In our experience, the disease runs a benign course if treated. Finally, polycythemia rubra vera associated with BCS is compatible with a long life, if it is treated with hydroxyurea.

Table 77.1

Differences Between West and East in Predisposing Conditions and Anatomic Patterns of Budd-Chiari Syndrome

Feature	West	East
Membranous obstruction of the IVC	Rare	Frequent
Hepatic vein occlusion predominates	+	–
IVC occlusion predominates	–	+
Acute or subacute BCS predominates	+	–
Chronic BCS predominates	–	+
Pregnancy/postpartum	Uncommon	Frequent
Infection	Rare	Common
Oral contraceptives	Frequent	Uncommon

BCS, Budd-Chiari syndrome; IVC, inferior vena cava

Paroxysmal nocturnal hemoglobinuria is another hematologic disorder associated with BCS (Hartmann et al, 1980; Hoekstra et al, 2009; Liebowitz & Hartmann, 1981; Valla et al, 1987). It was responsible for 6.7% of the cases in the collected series of Mitchell and colleagues (1982) and 12% of the cases in the series of Valla and colleagues (1987). In all of the hematologic disorders associated with hepatic vein thrombosis, but particularly in paroxysmal nocturnal hemoglobinuria, thrombosis of other blood vessels outside of the liver has sometimes been observed. These cases of multiple sites of thrombosis have involved the portal, splenic, and superior mesenteric veins; pelvic veins; deep calf veins; splanchnic arteries; pulmonary artery; coronary arteries; and cerebral arteries (Peytremann et al, 1972).

As hematologic diagnosis has become progressively more sophisticated, many other thrombogenic conditions have been identified in BCS, including other myeloproliferative states—such as essential thrombocythemia, primary erythrocytosis, and myelofibrosis—and thrombophilic states, such as protein C deficiency, protein S deficiency, antithrombin III deficiency, and antiphospholipid syndrome with lupus anticoagulant or anticardiolipin antibodies or both (Bertina et al, 1994; Boughton, 1991; Dahlback, 1995; Dahlback et al, 1993; Espinosa et al, 2001; Koster et al, 1993; Mahmoud et al, 1995; Menon et al, 2004; Pelletier et al, 1994; Svensson & Dahlback, 1994; Valla, 2003; Vandenbroucke et al, 1994). Subjects with the factor V Leiden mutation, which leads to activated protein C resistance, have a 5-fold to 10-fold increase in the risk of thrombosis if they are heterozygotic and a 50-fold to 100-fold increase if they are homozygotic (Dahlback, 1995; Deltenre et al, 2001; Janssen et al, 2000). More recent evidence indicates that multiple prothrombotic factors acting concurrently are involved in a substantial percentage of patients with BCS (Denninger et al, 2000; Janssen et al, 2000). Rarely, hematologic malignancies, such as acute leukemia and lymphoma, have been associated with BCS.

In 2005, identification of the underlying cause of BCS was enhanced by the discovery of a very reliable and noninvasive marker for chronic myeloproliferative disorders. The marker is the gain-of-function mutation V617F of the *JAK2* gene (Baxter et al, 2005; James et al, 2005; Jelinek et al, 2005; Jones et al, 2005; Kralovics et al, 2005; Levine et al, 2005; Steensma et al, 2005; Zhao et al, 2005). By combining identification of this marker with results of bone marrow histology and clonality assay, over 50% of the cases of BCS have been found to be due to an underlying chronic myeloproliferative disorder (Primignani et al, 2006).

It cannot be overemphasized that every patient found to have BCS should undergo a thorough hematologic evaluation. The workup that we perform is an expansion of the workup proposed by Mahmoud and Elias (1996) and others (Hirschberg et al, 2000; Valla, 2009) and is shown in Box 77.2. With these studies, it should be possible to diagnose all of the predisposing thrombogenic hematologic disorders known to be associated with BCS. If an evaluation such as this is done uniformly, it is highly likely that the incidence of idiopathic BCS will continue to decline.

Oral Contraceptives

An increased incidence of thromboembolic phenomena involving various blood vessels and organs in women taking oral contraceptives has been well established. The first case of BCS associated with use of oral contraceptives was reported by Ecker and McKittrick (1966), 5 years after these drugs became available commercially. Since then, more than 200 cases of BCS in patients taking oral contraceptive have been described (Janssen et al, 2000; Lewis et al, 1983; Maddrey, 1987; Valla et al, 1986; Zafrani et al, 1983), and the increasing overall incidence of BCS in recent years has been attributed partly to the widespread use of these agents. In the collective review reported by Mitchell and colleagues (1982), use of oral contraceptives was believed to be responsible for 9.4% of the cases of BCS during the period 1960 to 1980. Valla and associates (1986) reported that the relative risk of hepatic vein thrombosis among oral contraceptive users was close to that of stroke, myocardial infarction, and venous thromboembolism. In our series of 77 cases of BCS, 23% of patients gave a history of oral contraceptive use. The incidence is even higher if the denominator consists only of the number of women in each series. In our series, 49% of the 37 women with BCS used oral contraceptives.

Some authors have proposed that oral contraceptives are not a primary cause of BCS but contribute to thrombosis only if there is an underlying hematologic disorder (Valla et al, 1986). In our series, no hematologic disease was identified in users of oral contraceptives, but until relatively recently, our patients did not undergo the extensive hematologic workup shown in Box 77.2. The duration of usage of oral contraceptives before the diagnosis of BCS has ranged from 2 weeks to 10 years. In addition to causing BCS, oral contraceptives have been linked to other liver disorders, including VOD, portal vein thrombosis, cholestasis, hepatocellular adenoma, focal nodular hyperplasia, and possibly hepatocellular carcinoma and angiosarcoma (Zafrani et al, 1983).

Pregnancy and Postpartum

BCS has been observed in women during pregnancy and, more commonly, during the postpartum period. The first case of BCS reported by Chiari (1899) occurred in a woman who developed the disorder after childbirth. In the collective review by Mitchell and colleagues (1982), 9.9% of the cases of BCS occurred during pregnancy or postpartum, and in a series of 105 patients with BCS observed from 1963 through 1978, Khuroo and Datta (1980) reported 16 cases (15.2%) of BCS after pregnancy; 8 of the patients died, and 7 were lost to follow-up after discharge from the hospital. The hypercoagulable state that is known to occur during pregnancy is presumed to be responsible for the association of BCS with this condition, although only 1 of our 77 cases of BCS occurred during pregnancy or postpartum.

Box 77.2

Screening for Hematologic Disorders in Budd-Chiari Syndrome

Complete blood count, prothrombin time, partial thromboplastin time, fibrinogen
Red blood cell mass, plasma volume
Bone marrow biopsy, cell culture, karyotype
JAK2 gene, V617F mutation in peripheral blood granulocytes
Antithrombin-III assay
Protein-C assay
Free protein-S antigen assay
Lupus anticoagulant
Anticardiolipin antibodies
Ham's acid hemolysis test
Activated protein C resistance or Factor V Leiden mutation or both
Endogenous erythroid colony assay
Flow cytometry for blood cells deficient in CD55 and CD59 (PNH)
Molecular test for G20210A prothrombin gene mutation
Anti-β_2 glycoprotein-1 antibodies
Plasma homocysteine level

PNH, paroxysmal nocturnal hemoglobinurea.

Malignant Neoplasms

Malignant neoplasms were responsible for 13.4% of the collected cases of BCS reported by Parker (1959), 8.8% of the collected cases reported by Mitchell and colleagues (1982), and 12% of the cases reported by Powell-Jackson and colleagues (1982). Because we do not operate on patients with BCS caused by cancer, none of our 77 patients had malignant neoplasms. Occlusion of the suprahepatic IVC by invasive tumors has been the cause of BCS in many cases. The most common cancers associated with BCS are hepatocellular carcinoma, renal cell carcinoma, adrenal carcinoma, and leiomyosarcoma of the IVC. Other malignancies that rarely have caused BCS include carcinomas of the lung, pancreas, and stomach; melanoma; reticulum cell sarcoma; adrenal sarcoma; and sarcoma of the right atrium.

Infections

Infections involving the liver were believed responsible for 3% of the collected cases of BCS reviewed by Parker (1959), 9.9% of the collected cases reported by Mitchell and colleagues (1982), and none of the cases in sizable series reported in more recent years, including our own series. The most common infections associated with BCS are those caused by parasites, particularly amebic liver abscess, hydatid disease, and schistosomiasis (see Chapters 67 and 68). Syphilitic gumma of the liver accounted for 1.8% of the cases in Parker's review but has not been reported as a cause of BCS in recent years. Aspergillosis involving the hepatic veins and IVC has been a rare cause of BCS. In India, Victor and colleagues (1994) provided evidence that filariasis can cause BCS.

Trauma

Abdominal trauma has uncommonly predisposed to the development of BCS. Trauma was responsible for 1.2% of the collected cases of BCS reported by Parker (1959) and 2.4% of the collected cases reviewed by Mitchell and colleagues (1982). Blunt and penetrating trauma have been implicated in occasional cases of BCS.

Connective Tissue Disorders

Occasional cases of BCS have been reported in association with various connective tissue and autoimmune diseases, most of which are known to have thrombotic tendencies. Included among these are Behçet disease, Sjögren syndrome, mixed connective tissue disease, sarcoidosis, and rheumatoid arthritis. Numerous cases of BCS in patients with Behçet disease,

including five of our own, have been described (Bazraktar et al, 1997; Orloff & Orloff, 1999).

Membranous Obstruction of the Vena Cava

More than 600 cases of BCS resulting from MOVC have been reported from Japan (Hirooka & Kimura, 1970; Kimura et al, 1972; Okuda, 2002; Ono et al, 1983; Taneja et al, 1979; Yamamoto et al, 1968), China (Wang, 1989; Wang et al, 1989; Wu et al, 1990) and other parts of Asia, India (Khuroo & Datta, 1980), and South Africa (Semson, 1982). In the United States and Europe, MOVC is rare. A congenital cause of this condition has been proposed, but evidence strongly suggests it represents the end result of acquired thrombosis (Kage et al, 1992; Okuda 2002; Okuda et al, 1995).

MOVC usually runs a chronic course over many years, and most patients will have developed extensive hepatic fibrosis and cirrhosis and portal hypertension by the time they come to medical attention. An increased incidence of hepatocellular carcinoma has been observed in association with MOVC (Okuda, 2002; Semson, 1982). The therapeutic implications of this condition and other forms of IVC occlusion are distinctly different from those of occlusion confined to the major hepatic veins.

Miscellaneous Rare Conditions

Other conditions that have been rarely associated with BCS include inflammatory bowel disease, hepatic torsion after partial resection of the liver, lipoid nephrosis, and protein-losing enteropathy.

CAUSES OF VENOOCCLUSIVE DISEASE

In 1954, Bras and colleagues proposed the term *venoocclusive disease* to describe a serious and common liver disease in Jamaican children in which there was occlusion of the central and sublobular hepatic veins and surrounding centrilobular necrosis of the liver parenchyma. More recently, the condition has been called the *sinusoidal obstruction syndrome*. Shortly after his initial description, Bras and others (Bras & McLean, 1963; Brooks et al, 1970; Gore et al, 1961; Stuart & Bras, 1957) showed that VOD was due to ingestion of "bush teas" made from plants of the *Crotolaria* and *Senecio* genera, which contain well-known hepatotoxic pyrrolizidine alkaloids. It has long been known that these plants and plants of the *Heliotropium* genus produce liver failure in herbivorous animals and are common causes of poisoning of grazing cows and horses. Since the initial descriptions by Bras and others, VOD caused by ingestion of toxic pyrrolizidines has been observed in Israel (Ghanem & Hershko, 1981), Egypt (Safouh & Shehata, 1965), Iraq (Al-Hasany & Mohamed, 1970), Afghanistan (Mohabbat et al, 1976), India (Aikat et al, 1978; Tandon et al, 1976), Venezuela (Grases & Beker, 1972), Ecuador (Lyford et al, 1976), South Africa (Steenkamp et al, 2000; Zuckerman et al, 2002), and the United States (Abbott, 1988; Bach et al, 1989; Ridker & McDermott, 1989; Ridker et al, 1985; Stillman et al, 1977). In addition to poisoning by drinking bush teas, humans have been poisoned by eating flour milled from grain contaminated by the seeds of these plants and by taking herbal remedies.

Antineoplastic drugs have been identified as another cause of VOD. Included among these are cytosine arabinoside, thioguanine, and gemtuzumab ozogamicin (Mylotarg) used in the treatment of acute myelocytic leukemia (Cruz et al, 1983; Giles et al, 2001; Gill et al, 1982; Griner et al, 1976); carmustine used in the treatment of diffuse histiocytic lymphoma (McIntyre et al, 1981); dacarbazine used in the treatment of melanoma (Asbury et al, 1980); oxaliplatin used in treatment of metastatic colorectal adenocarcinoma to the liver (Cleary et al, 2009; Pawlik et al, 2007; Mehta et al, 2008; Kandutsch et al, 2008; Rubbia-Brandt et al, 2004); and gemtuzumab ozogamicin and mitomycin C combined with bone marrow transplantation (Kumar et al, 2003; Lazarus et al, 1982; McDonald et al, 1993; Wadleigh et al, 2003). Fatal VOD in renal transplant recipients has been attributed to azathioprine (Liano et al, 1989; Marubbio & Danielson, 1975).

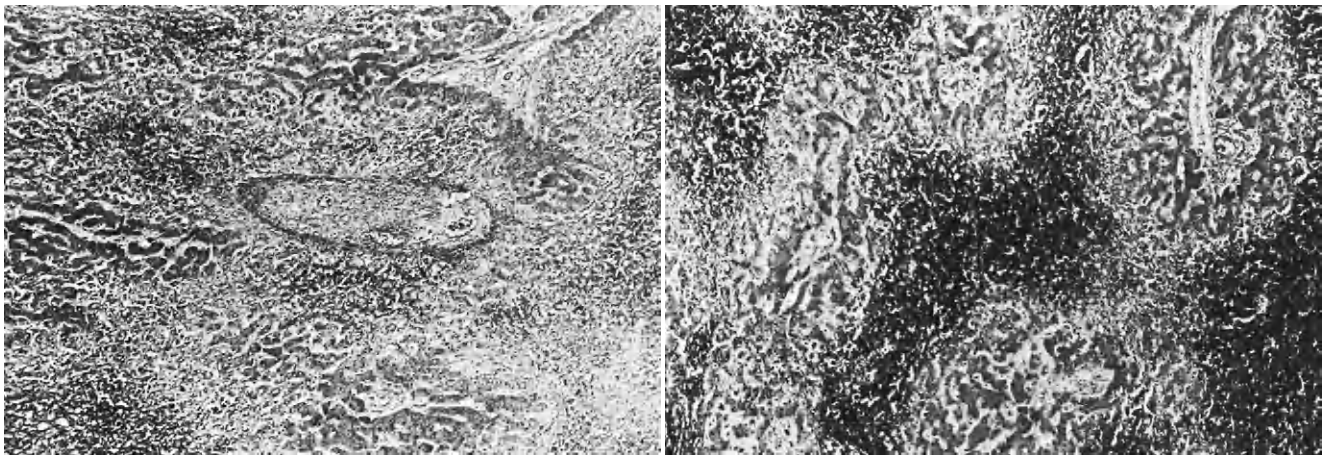
Hepatic injury caused by therapeutic irradiation of malignant neoplasms in and near the liver is an important cause of VOD (Fajardo & Colby, 1980; Reed & Cox, 1966). Although radiation-induced VOD usually does not produce clinical manifestations with doses less than 3000 rad, the condition has been observed after smaller amounts of radiotherapy (Fajardo & Colby, 1980).

Currently, the most common cause of VOD in the Western Hemisphere is bone marrow transplantation (Ayash et al, 1990; Berk et al, 1979; Jones et al, 1987; Kriegshauser et al, 1988; Kumar et al, 2003; McDonald et al, 1984, 1993; Wadleigh et al, 2003; Senzolo et al, 2007; Helmz, 2006; Cacchione et al, 2008). It has been estimated that approximately one fourth of recipients of bone marrow transplants develop the disorder. It is uncertain whether VOD in these patients is caused by the marrow transplant, or if it is a result of the radiation and chemotherapy used in the pretransplant conditioning regimen. Berk and colleagues (1979) proposed that graft-versus-host disease might be responsible for VOD after marrow transplantation, but the studies of McDonald and colleagues (1984) cast doubt on this hypothesis. Finally, there have been rare reports of VOD in association with systemic lupus erythematosus (Pappas et al, 1984), familial immunodeficiency (Mellis & Bale, 1976), and the use of oral contraceptives (Alpert, 1976).

PATHOLOGY

Budd-Chiari Syndrome

The liver receives about one fourth of the cardiac output via its dual afferent blood supply, the portal vein and hepatic artery. After perfusing the sinusoids, the blood is returned to the heart through the hepatic veins and IVC. Obstruction to the egress of blood from the liver at any point along the outflow route results in numerous serious hemodynamic and morphologic alterations. There is a marked increase in intrahepatic pressure, which is reflected by a similar increase in portal pressure. The increased intrahepatic pressure causes extravasation of plasma from the liver sinusoids and lymphatics with formation of ascites. Obstruction to the egress of blood from the liver also results in dilation of the sinusoids and intense centrilobular congestion of the hepatic parenchyma, which is greatest around the terminal hepatic venules (central veins; Fig. 77.1). Ischemia, pressure necrosis, and atrophy of the parenchymal cells in the center of the liver lobule are apparent. With persistence of the obstruction, the necrotic parenchyma is replaced by fibrous tissue and regenerating nodules of liver tissue. The end result is cirrhosis of the type associated with chronic congestive heart failure. The rapidity with which cirrhosis develops is related to



A B

FIGURE 77.1. Photomicrographs of preoperative liver biopsy specimens obtained from Budd-Chiari syndrome (BCS) patients 4 **(A)** and 5 **(B)** in our series, showing a typical picture of BCS consisting of intense centrilobular congestion and necrosis with widespread loss of hepatocytes. A thrombosed hepatic vein is seen in the center in **A** (×50). *(From Orloff MJ, Johansen KH, 1978: Treatment of Budd-Chiari syndrome by side-to-side portacaval shunt: experimental and clinical results. Ann Surg 188:494-512.)*

the severity of outflow obstruction, but it is not unusual for cirrhosis to occur within a matter of months (Parker, 1959).

The reversibility of liver damage in BCS is a direct function of the extent and duration of hepatic venous outflow obstruction. Early in the course of the disease, relief of the obstruction can be expected to result in reversal of the parenchymal and hemodynamic abnormalities. Late in the course, the damage to the hepatic parenchyma becomes irreversible; hence the timing of therapy has profound implications with regard to prognosis.

Three major hepatic veins—the right, left, and middle—conduct blood into the IVC from the bulk of the hepatic parenchyma. The left and middle hepatic veins usually form a common trunk just before joining the IVC, and several small hepatic veins enter directly into the retrohepatic IVC and drain the caudate lobe and small central regions of the right and left lobes of the liver. Our BCS experience indicates that all three major hepatic veins usually are occluded, although occasionally the occlusion is limited to one or two of the major veins. The small hepatic veins that join the retrohepatic IVC, particularly the veins draining the caudate lobe, often are spared.

In most cases of BCS, occlusion of the hepatic veins is caused by thrombosis (Parker, 1959). The thrombus undergoes organization and ultimately is converted to fibrous tissue that permanently occludes the veins. Although recanalization of the occluded veins sometimes occurs, it rarely results in effective new outflow channels. Retrograde propagation of the thrombus into smaller hepatic veins is commonly found. Prograde propagation of the thrombus from the hepatic veins into the IVC, with partial or complete occlusion of the IVC, sometimes occurs and markedly changes the therapeutic approach and prognosis. It is important to determine by imaging studies that include angiography and pressure measurements whether the IVC has become involved in the occlusive process.

MOVC has been reported to be the most common cause of BCS in Japan (Hirooka & Kimura, 1970; Kimura et al, 1972; Okuda et al, 1995; Ono et al, 1983; Taneja et al, 1979; Yamamoto et al, 1968), India (Khuroo & Datta, 1980), China (Wang, 1989; Wang et al, 1989, 2005; Wu et al, 1990), and in the Bantu population of South Africa (Semson, 1982). The "membrane" varies from very thin to several centimeters thick and usually contains fibrous tissue, smooth muscle, and elastic tissue. The location and extent of the membrane vary considerably, and in some cases a long segment of IVC has been replaced by fibrous tissue. Occlusion of one or more of the major hepatic veins often has been associated with membranous obstruction of the IVC. Although some experienced authors have proposed a congenital cause (Hirooka & Kimura, 1970; Kimura et al, 1972; Ono et al, 1983; Semson, 1982; Taneja et al, 1979), a strong argument has been made that suggests MOVC is the end result of thrombosis of the IVC, often occurring early in life (Okuda et al, 2002). Most of the cases have run a chronic course before discovery, and when first seen by a physician, patients have had extensive hepatic fibrosis or cirrhosis with portal hypertension and all of its manifestations. The therapeutic considerations in patients with MOVC differ from those in patients with BCS caused by obstruction of the hepatic veins.

Venoocclusive Disease

VOD of the liver, more recently called *sinusoidal obstruction syndrome*, may mimic BCS clinically, because both conditions involve hepatic venous outflow obstruction. VOD involves the sinusoids and the central and sublobular hepatic veins within the liver, however, rather than the hepatic veins (Kumar et al, 2003; Shulman et al, 1987, 1994). The underlying process in VOD is subendothelial sclerosis of the hepatic veins and sinusoids secondary to endothelial injury caused by a toxic agent, such as a pyrrolizidine alkaloid, antineoplastic drug, radiation, or a stem cell transplant. Thrombosis of the small hepatic veins may occur after damage to the venous intima. Electron microscopic studies of liver biopsy specimens obtained from children with VOD caused by pyrrolizidine poisoning showed marked endothelial damage in the sinusoids and subterminal and terminal hepatic veins in all zones of the liver, with extravasation of erythrocytes into the space of Disse and narrowing of the lumen where the sinusoid entered the central vein (Brooks et al, 1970).

Similar to BCS, hemorrhagic necrosis of the liver parenchyma around the centrilobular veins occurs early in the course of VOD. Extensive occlusion of the small hepatic veins

ultimately leads to diffuse fibrosis and cirrhosis. Patients with VOD caused by chronic pyrrolizidine poisoning often have well-established cirrhosis when first seen by a physician. VOD that develops as a complication of therapy for another condition—such as occurs during cancer chemotherapy, radiation therapy, or bone marrow transplantation—usually is detected early in the course of the disease.

CLINICAL MANIFESTATIONS OF BUDD-CHIARI SYNDROME

The clinical manifestations and course of BCS are determined by the extent of occlusion of the hepatic venous outflow system and the rapidity with which the venous occlusion becomes complete. More often than not, patients in the West have an acute or subacute course, with rapid progression of liver disease and its consequences over periods of a few weeks to a few months. In some patients, however, BCS develops insidiously, with clinical manifestations appearing gradually over months or years. Patients with MOVC observed in Japan, China, India, and South Africa often come to the physician for the first time with manifestations of well-established cirrhosis after tolerating symptoms for many years.

In our series of 77 patients with BCS, 12 were referred with advanced cirrhosis as a result of prolonged hepatic outflow obstruction and were not candidates for portal decompression surgery. The other 65 patients were referred at a mean 14 weeks after onset of BCS (range 4 to 78 weeks). Fifty-nine of the 65 patients (91%) were referred less than 18 weeks after onset of symptoms, relatively early in the course of BCS. The remaining 6 patients were operated on 19, 21, 23, 25, 26, and 78 weeks after onset of symptoms. In the collected series of Mitchell and colleagues (1982), which excluded cases of MOVC, two thirds had had symptoms for less than 3 months, and 83% had had symptoms for 6 months or less at the time of diagnosis. In Parker's (1959) collected series of 133 cases, he observed that 57% had had symptoms for 3 months or less, and 71% had been symptomatic for 6 months or less.

Table 77.2 presents the frequency of symptoms and signs in our series of 77 patients with BCS, 51 of whom had hepatic vein occlusion alone, and 26 of whom had IVC occlusion and hepatic vein occlusion. The only difference between the two groups—and it is an important one—was the absence of lower extremity edema in the group without IVC thrombosis and the high incidence of edema from feet to thighs (81%) that resulted from IVC occlusion.

Symptoms

Abdominal Distension

The initial symptom in all of our patients was abdominal distension secondary to ascites, which increased progressively over a few weeks. Abdominal distension caused by ascites occurs at some time in almost every patient with BCS. In the large collected series (Mitchell et al, 1982; Parker, 1959), abdominal distension was among the first symptoms experienced by most patients.

Abdominal Pain

All of our patients had abdominal pain that was dull, nagging, and chronic. The pain was localized in the right hypochondrium in some patients, diffuse in the upper abdomen in other patients, and diffuse throughout the abdomen in several patients. The pain was probably due to distension of the liver capsule from intense hepatic congestion or to abdominal distension from rapid accumulation of ascites. Abdominal pain has been a prominent symptom in all reported series of BCS.

Weakness

All patients in our series had striking and progressive weakness as a manifestation of their severe acute illness. Weakness has not been as prominent in the chronic forms of BCS.

Anorexia

Anorexia was reported by all patients in our series and has been experienced by many patients in the reports of others (Mitchell et al, 1982).

Jaundice

Clinical jaundice was observed in 52% of the patients in our series but in only 28% of the patients in Parker's collective review (1959) and in only 17% of the patients collected by Mitchell and colleagues (1982). Usually, jaundice has been mild.

Symptoms of Chronic Liver Disease

Patients with the chronic forms of BCS, such as MOVC, often have the usual symptoms of cirrhosis and portal hypertension, including upper gastrointestinal (GI) bleeding secondary to ruptured esophagogastric varices (see Chapter 75), hepatic encephalopathy, hepatorenal syndrome, and edema of the lower

Table 77.2

Symptoms and Signs in 77 Patients with Budd-Chiari Syndrome Treated by the Authors

	% OF GROUP			% OF GROUP	
Symptom	Hepatic Vein Occlusion (n = 51)	IVC Occlusion (n = 26)	Sign	Hepatic Vein Occlusion (n = 51)	IVC Occlusion (n = 26)
Abdominal distension	100	100	Massive ascites	100	100
Abdominal pain	100	100	Hepatomegaly	100	100
Weakness	100	100	Wasting	100	100
Anorexia	100	100	Abdominal venous distension	59	50
Jaundice	53	50	Splenomegaly	100	100
Jaundice	53	50	Edema of thighs, legs, feet	0	81

IVC, inferior vena cava

extremities (see Chapters 72 and 73). Peripheral edema is particularly prominent in patients with MOVC, and some develop varicose veins of the legs (Parker, 1959; Semson, 1982). In our series of patients who underwent surgical portal decompression for acute BCS secondary to occlusion of the hepatic veins, one patient had these symptoms.

Findings on Physical Examination (Signs)

Ascites

All 77 patients in our series had the abdominal signs of massive ascites on physical examination at the time of diagnosis. The incidence of ascites was 93% in the collective review of Parker (1959) and 83% in the series of Mitchell and colleagues (1982).

Hepatomegaly

All patients in our series and in the series of Mitchell and colleagues (1982) had marked hepatomegaly resulting from severe congestion of the liver. In chronic forms of BCS, hepatomegaly may not be as striking, but it is usually present.

Wasting

All patients in our series had substantial wasting as a result of loss of lean body mass over a relatively short time. All of our patients appeared chronically and seriously ill.

Distension of Abdominal Veins

Forty-three of the 77 patients in our series (56%) and 55% of the patients in the collected series of Parker (1959) had distension of the superficial veins of the anterior abdominal wall. Abdominal venous distension is a manifestation of portal hypertension and the formation of portosystemic collaterals early in the course of BCS.

Splenomegaly

Splenomegaly, another manifestation of portal hypertension, was observed in all of the patients in our series, in 50% of those in the collected series of Mitchell and colleagues (1982), and in 30% in the collected series of Parker (1959). Enlargement and congestion of the spleen was sometimes accompanied by the hematologic manifestations of secondary hypersplenism.

Jaundice

Clinical jaundice was observed in 52% of the patients in our series but in only 28% of the patients in the collected series of Parker (1959) and in only 17% of the patients in the collected series of Mitchell and colleagues (1982). The jaundice in our patients who underwent surgical portal decompression was invariably mild; the highest serum bilirubin level was only 6.8 mg/dL.

Edema of the Lower Extremities

Edema of the lower extremities or lower trunk indicates involvement of the IVC in the occlusive process and was observed in 81% of the 26 patients in our series who had IVC occlusion. In our series, none of the 51 patients with thrombosis confined to the hepatic veins had substantial lower extremity edema.

Signs of Chronic Liver Disease

Patients with the chronic forms of BCS, such as patients with MOVC, often have the usual manifestations of chronic liver disease: spider angiomata, palmar erythema, asterixis, breast hypertrophy, testicular atrophy, and fetor hepaticus. In our series, these signs were seen only in patients who were placed in the liver transplantation group because of advanced cirrhosis.

SYMPTOMS AND SIGNS OF VENOOCCLUSIVE DISEASE

VOD has been observed in individuals of all ages, including infants and adults in their sixth decade; however, VOD caused by pyrrolizidine alkaloids has been seen most commonly in infants and children. The clinical manifestations depend on the disease stage at which the patient seeks medical treatment (Brooks et al, 1970; Ghanem & Hershko, 1981; Gore et al, 1961; Safouh & Shehata, 1965; Stuart & Bras, 1957). The acute stage is often preceded for 1 or 2 weeks by a febrile illness with upper respiratory symptoms, vomiting and diarrhea, or both. The patient then experiences abrupt onset of abdominal pain, weakness, anorexia, fever, and abdominal distension secondary to ascites (Kumar et al, 2003; Wadleigh et al, 2003; Senzolo et al, 2007). Jaundice is the rule, and splenomegaly with thrombocytopenia is common. Some patients develop edema of the feet and occasionally of the hands and face, and physical examination in the acute phase invariably shows hepatomegaly and ascites. Many patients have splenomegaly, some have distension of the superficial veins of the abdominal wall, and some have peripheral edema and a pleural effusion. Bone marrow transplant recipients usually develop the clinical features of VOD within 3 weeks after transplantation. Many patients have died during the acute stage from liver failure, bleeding esophageal varices, or intercurrent infection.

Patients other than bone marrow transplant recipients may be initially seen in the chronic stage of VOD with the usual clinical manifestations of cirrhosis of the liver: ascites, hepatomegaly, splenomegaly, wasting, abdominal venous distension, spider angiomata, palmar erythema, asterixis, and peripheral edema. Bleeding from esophageal varices is a major cause of death in the chronic stage, and cirrhosis of the liver has been observed 3 months after acute onset of VOD (Gore et al, 1961).

DIAGNOSTIC STUDIES IN BUDD-CHIARI SYNDROME

Hepatic Angiography and Pressures

The diagnostic study of greatest value in BCS, particularly if surgical therapy is contemplated and venous pressure measurements are required, is angiographic examination of the IVC and hepatic veins with pressure measurements (Clain et al, 1967; Kreel et al, 1967; Redman, 1975; Tavill et al, 1975). This study usually is combined with hepatic and superior mesenteric arteriography and indirect portography. In BCS confined to the hepatic veins, the IVC is patent, and IVC pressure is relatively normal for subjects with ascites (Fig. 77.2). Patency of the IVC is a prerequisite for portacaval shunt (PCS) and is a crucial finding (see Chapter 76). In some patients, the IVC is moderately compressed in its retrohepatic course by the enlarged liver and, in particular, by a hypertrophied caudate lobe (Fig. 77.3). This finding usually is not clinically significant (Clain et al, 1967; Kreel et al, 1967; Redman, 1975; Tavill et al, 1975).

The most important angiographic finding is the demonstration by hepatic venography of occlusion or marked narrowing of the major hepatic veins. Sometimes it is not possible to find



FIGURE 77.2. Inferior venacavogram in Budd-Chiari syndrome patient 3 in our series, showing a widely patent inferior vena cava; pressure was 62 mm saline. *(From Orloff MJ, Johansen KH, 1978: Treatment of Budd-Chiari syndrome by side-to-side portacaval shunt: experimental and clinical results. Ann Surg 188:494-512.)*



FIGURE 77.3. Inferior venacavogram in Budd-Chiari syndrome patient 6 in our series, showing a patent inferior vena cava with side-to-side compression in its retrohepatic course by the enlarged liver. IVC pressure at this time was 102 mm saline. *(From Orloff MJ, Johansen KH, 1978: Treatment of Budd-Chiari syndrome by side-to-side portacaval shunt: experimental and clinical results. Ann Surg 188:494-512.)*

patent orifices of any of the hepatic veins, which is indirect evidence that all of the major hepatic veins are occluded. Usually it is possible, however, to enter at least one major hepatic vein and to show the presence of a thrombus or of narrowing and distortion of the vein (Fig. 77.4A). Injection of dye in the wedged position often shows a characteristic spiderweb pattern of small hepatic venous collaterals connecting to portal or systemic veins (see Fig. 77.4B). Wedged hepatic vein pressure (WHVP) usually is markedly elevated, which reflects the obstruction to hepatic venous outflow. In patients with hepatic vein occlusion alone, IVC pressure is substantially lower than WHVP.

In our series of 77 patients, angiographic studies showed occlusion of the hepatic veins alone in 51 patients and occlusion of both the hepatic veins and IVC in 26 patients. In all of our patients with hepatic vein occlusion alone, all three major hepatic veins were occluded.

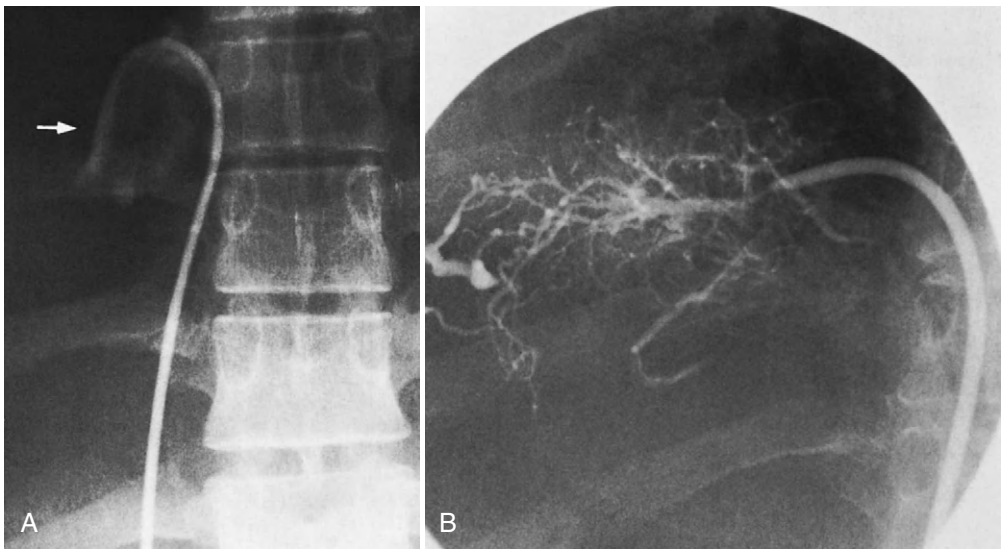


FIGURE 77.4. Hepatic venogram in Budd-Chiari syndrome patient 2 in our series. **A,** Filling defects (thrombi) in the right hepatic vein occupy much of the lumen. **B,** Typical spiderweb pattern of small venous collaterals shown by injection of dye with the catheter in the wedged position. *(From Orloff MJ, Johansen KH, 1978: Treatment of Budd-Chiari syndrome by side-to-side portacaval shunt: experimental and clinical results. Ann Surg 188:494-512.)*

Table 77.3

Results of Diagnostic Studies in 77 Patients with Budd-Chiari Syndrome Treated by the Authors

	% OF GROUP	
	Hepatic Vein Occlusion (n = 51)	**IVC Occlusion (n = 26)**
Angiography and Pressures		
Occluded hepatic veins	100	100
Occluded IVC near hepatic veins	0	100
Spiderweb pattern of hepatic veins	69	50
Patent portal and splenic veins	100	100
Stretched hepatic arteries	100	100
IVC pressure much lower than WHVP	100	0
High WHVP	100	100
Percutaneous Needle Liver Biopsy (73 Patients)		
Centrilobular congestion	100	100
Centrilobular hepatocyte loss and necrosis	100	100
Fibrosis	76	58
Cirrhosis (included also under fibrosis)	34	8
Hepatic Scintiscan		
Decreased hepatic uptake	100	100
Nonhomogeneous hepatic uptake	100	100
Excessive extrahepatic uptake	74	77
Central hot spot in liver	31	12
Computed Tomography (64 Patients)		
Absence of hepatic veins	100	100
Abnormal hepatic uptake of contrast	100	100
Occlusion of IVC	0	100
Ascites	100	100
Real-Time and Doppler Duplex Ultrasound (61/76 Patients)		
Absence of hepatic veins with flat or reversed flow	100	100
Abnormal venous structures in liver	100	100
IVC thrombosis with flat or reversed flow	0	100
Ascites	100	100
Abnormal Liver Function Tests		
Bromosulfophthalein or indocyanine green retention (23% to 90%; 24 patients)	100	100
Serum alkaline phosphatase (138 to 458 IU)	100	100
Prothrombin time (12.4 to 16.5 seconds)	98	92
Partial thromboplastin time (31 to 59 seconds)	98	92
Serum albumin (2.1 to 2.8 g/dL)	96	95
Aspartate aminotransferase (76 to 540 IU)	90	88
Serum bilirubin (3.8 to 6.8 mg/dL)	54	42
Upper Gastrointestinal Radiographs (53 Patients)		
Normal	60	0
Esophageal varices	40	100
Esophagogastroscopy (28 Patients)		
Esophageal varices	44	100

IVC, inferior vena cava; WHVP, wedged hepatic venous pressure

A spiderweb pattern was observed in 48 patients (62%). WHVP was markedly elevated in all patients in whom it was measured. In the 51 patients with thrombosis confined to the hepatic veins, the IVC was patent, with relatively normal pressures for patients with ascites, ranging from 62 to 160 mm saline (Table 77.3). Many patients had moderate compression of the retrohepatic IVC by the enlarged liver, but invariably WHVP was substantially higher than IVC pressure—a crucial finding. In contrast, in the 26 patients with IVC occlusion, IVC pressure and WHVP were similar. All patients had stretched and attenuated hepatic artery branches within the liver and a patent portal vein (PV).

An additional advantage of hepatic venography is that it facilitates performing a transjugular liver biopsy. Some investigators have stated that "at present, there is almost no place for direct or retrograde venography for the sole purpose of making a diagnosis of BCS" (Valla, 2009; Janssen et al, 2003). We hasten to point out that our use of hepatic venography was an essential guide to surgical therapy, not simply a means of making the diagnosis of BCS, as others have agreed (Kamath, 2006; Erdon, 2007).

Liver Biopsy

Percutaneous or transjugular needle liver biopsy yields histologic findings characteristic of BCS early in the course of the disease; along with hepatic angiography, it provides conclusive diagnostic information (Tang et al, 2001). The diagnostic features are quite spectacular and include intense centrilobular congestion combined with centrilobular loss of parenchyma and necrosis (see Fig. 77.1). Mild to moderate fibrosis of the liver parenchyma is found in many patients. As the disease evolves and becomes chronic, cirrhosis of the cardiac type develops. Cirrhosis has been observed within months of the onset of symptoms. Only two other conditions, constrictive pericarditis and congestive heart failure, produce a histologic picture similar to that seen in the acute stage of BCS. Both of these cardiac disorders can be eliminated easily from consideration by appropriate studies.

In our series, percutaneous or transjugular needle liver biopsy was done preoperatively in 73 of 77 patients, and open wedge liver biopsy was done at operation in all 77 patients (see Table 77.3). All patients had intense centrilobular congestion along with centrilobular hepatocellular loss and necrosis. Of the 65 patients in our series who were referred sufficiently early to undergo surgical portal decompression, 39 (60%) had fibrosis of the liver at an early point in the illness. In three patients, the fibrosis had progressed to cirrhosis. All 12 patients who were considered candidates for liver transplantation had advanced cirrhosis (see Chapter 97A).

Hepatic Scintiscanning

Scintiscans of the liver (see Chapter 15) with technetium 99m-sulfur colloid or other colloidal radionuclides show the nonspecific abnormalities of decreased and nonhomogeneous hepatic uptake of radiocolloid, increased uptake of radiocolloid by the spleen and bone marrow, and hepatosplenomegaly. Central localization of radiocolloid in the liver, the so-called central hot spot, has been reported to be of diagnostic importance (Fig. 77.5; Meindok & Langer, 1976; Tavill et al, 1975). It is seen when the thrombotic process spares the small hepatic veins that drain the caudate lobe and central areas of the right and left lobes directly into the IVC, so that these areas of the liver remain healthy and even hypertrophy. The central hot spot was observed in only 19 (25%) of the 77 patients with BCS in our series.

Computed Tomography

Computed tomography (CT; see Chapter 16) of the liver after injection of contrast agents has been shown to be of diagnostic value in BCS (Baert et al, 1983; Mathieu et al, 1987; Lupescu, 2008; Erdon, 2007; Kamath, 2006; Vogelzang et al, 1987). The findings include 1) absence of opacification of the hepatic veins, which in normal subjects usually can be shown clearly; 2) nonhomogeneous and delayed uptake of contrast material in the liver; 3) delayed emptying of contrast material from venous structures at the periphery of the liver; and 4) occlusion of the IVC in patients with IVC thrombosis. CT also shows ascites and hepatomegaly. We performed CT in 64 of our 77 patients and observed these abnormalities in all of them.

Ultrasonography

Real-time and Doppler duplex ultrasonography (US) of the liver have been shown to be of diagnostic value in BCS (Baert et al, 1983; Becker et al, 1986; Bolondi et al, 1991; Chaubal et al, 2006; Grant et al, 1989; Gupta et al, 1987; Hosoki et al, 1989; Powell-Jackson et al, 1986; Rossi et al, 1981; see Chapter 13). Findings include 1) absence of normal hepatic veins draining into the IVC with flat or reversed flow, 2) an abnormal intrahepatic network of comma-shaped venous structures, 3) thrombus in IVC and flat or reversed flow in patients with IVC thrombosis, and 4) enlargement of the caudate lobe. Ascites has been shown regularly. We observed these abnormalities in all 61 patients in whom US was performed in our series. We regularly used Doppler US as an initial screening tool, but we depended on angiography for a definitive diagnosis and guide to treatment.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI; see Chapter 17) is capable of showing patency or obstruction of the hepatic veins and is particularly effective in visualizing the entire length of the IVC. It has been reported to be useful in differentiating the acute form of BCS from the subacute and chronic forms (Noone et al, 2000; Kamath, 2006; Erdon, 2007; Lupescu et al, 2008). Because of the high cost of MRI, it is not a first-line diagnostic procedure in our program; none of our 66 patients underwent MRI.

Abnormal Liver Function Tests

Results of liver function tests are usually abnormal in BCS, although the type of abnormality varies and is nondiagnostic (see Table 77.3). All 24 patients in our series who had studies of injected bromosulfophthalein or indocyanine green dye clearance had marked retention of dye, ranging from 23% to 90% (normal <6%). All 77 patients had elevation of serum alkaline phosphatase, ranging from 138 to 458 IU (normal 25 to 85 IU). Of 77 patients, 74 had prolonged prothrombin time and partial thromboplastin time, and 96% had a marked decrease in serum albumin concentration (range, 2.1 to 2.8 g/dL); 69 patients (90%) had elevations of aspartate aminotransferase (range, 76 to 540 IU), and 39 (51%) had mild to moderate elevations of serum bilirubin (range, 3.8 to 6.8 mg/dL). These biochemical abnormalities are not specific to BCS, but they indicate significant hepatic dysfunction and are an important part of the diagnostic workup.

Ascitic Fluid Analysis

Analysis of ascitic fluid in patients with BCS is of little diagnostic value, because the results vary considerably (Mitchell et al, 1982; Tavill et al, 1975). Protein concentration has been reported to range from 0.5 to 4.9 g/dL.

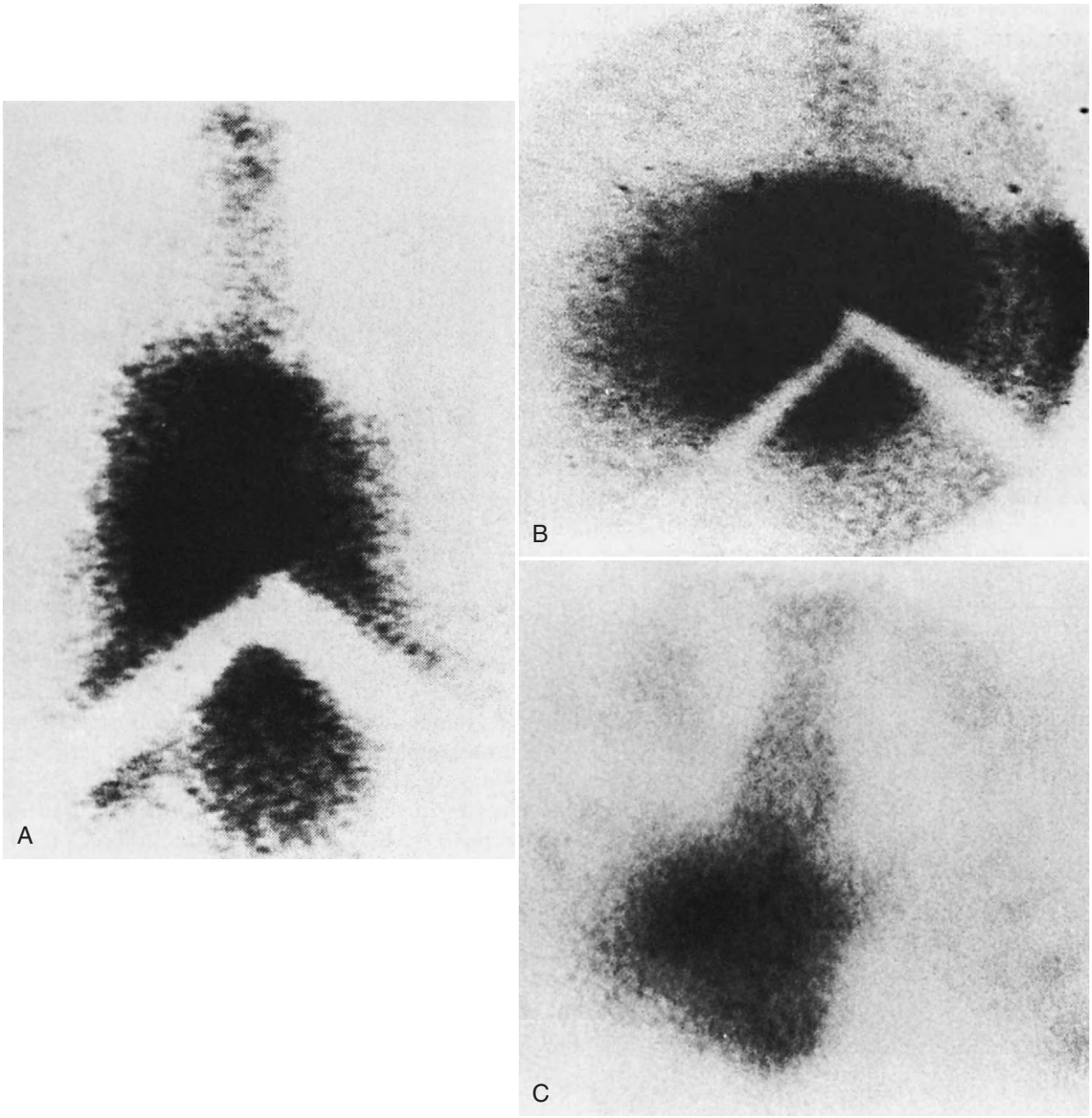


FIGURE 77.5. A-C, Scintiscan of liver in three cases of Budd-Chiari syndrome, showing central accumulation of radionuclide, the so-called central hot spot. *(From Mitchell MC, et al, 1982: Budd-Chiari syndrome: etiology, diagnosis and management. Medicine [Baltimore] 61:199-218.)*

Upper Gastrointestinal Radiographs

Barium contrast upper GI radiographs were obtained in 53 patients with BCS in our series. The results were normal in 31 patients but showed esophageal varices in 22 patients (42%); 13 of the 22 patients with varices had cirrhosis. In the chronic forms of BCS, esophageal varices can be shown regularly by radiography and confirmed by esophagogastroscopy. Currently, we infrequently perform contrast upper GI radiographs.

Esophagogastroscopy

Esophagogastroscopy (EG) was performed in 28 patients, 18 of whom (64%) were found to have esophageal varices (see Chapter 75).

DIAGNOSTIC STUDIES IN VENOOCCLUSIVE DISEASE

The diagnosis of VOD is strongly suspected when, in the proper setting—such as following bone marrow transplantation—patients develop ascites, jaundice, hepatomegaly, and right upper quadrant abdominal pain (Senzolo et al, 2007). The most important diagnostic study in VOD is needle liver biopsy, which shows the specific abnormality of extensive occlusion of the small hepatic veins within the liver (Brooks et al, 1970; Gore et al, 1961; Shulman et al, 1995; Stuart & Bras, 1957). In the acute stage of VOD, an additional biopsy finding is centrilobular hemorrhagic necrosis of the hepatic parenchyma. In the chronic stage of VOD, the biopsy specimen shows diffuse fibrosis or cirrhosis of the liver.

Angiographic studies are not as helpful in VOD as they are in BCS (see Chapter 19). The major hepatic veins and IVC are

normal on venography, but WHVP is invariably elevated, a finding that supports the diagnosis of VOD. Findings on hepatic arteriography and indirect portography are similar to the findings in BCS. Because of the significant risk of bleeding after bone marrow transplantation, it is safest in such patients to perform liver biopsy by the percutaneous transjugular route. WHVP can be measured at the same time.

The abnormalities shown by hepatic scintiscanning in VOD are similar to those in BCS, except that the central hot spot has rarely been reported. Real-time and Doppler duplex US and, to a lesser extent, CT may provide useful diagnostic information in VOD.

Liver function test results are invariably abnormal in VOD and do not differ from the results seen in BCS; in other words, the abnormalities reflect serious hepatic dysfunction but are not specific for VOD. After bone marrow transplantation, elevated plasma levels of plasminogen activator inhibitor (PAI)-1 have been reported to be a useful marker in distinguishing VOD from several other causes of posttransplant hepatic dysfunction, such as graft-versus-host disease, drug-induced hepatotoxicity, sepsis, and viral hepatitis (Salat et al, 1997a). PAI-1 has been implicated in the pathology of VOD.

Because so many patients with VOD caused by pyrrolizidine alkaloids have been seen for the first time when the disease was far advanced, they often have had many or all of the manifestations of cirrhosis and portal hypertension. Esophagogastric varices have been shown in many patients by esophagogastroscopy and barium contrast upper GI radiographs.

FINDINGS AT OPERATION

The findings at operation in the 65 patients who underwent surgical portal decompression in our series are summarized in Tables 77.4 and 77.5, and they typify what can be expected in patients with BCS. All patients had marked ascites ranging in volume from 2.6 to 15.9 L, congestive hepatomegaly, splenomegaly, and extensive portosystemic collateral veins. All of the patients had portal hypertension. In the group of 39 patients with thrombosis confined to the hepatic veins, the mean PV-IVC pressure gradient was 244 mm saline. In all 39 of these patients, portal pressure was substantially higher than IVC pressure so that a direct side-to-side portacaval shunt (SSPCS) was feasible. In contrast, in the group of 26 patients with IVC occlusion and hepatic vein occlusion, the mean PV-IVC pressure gradient was only 11 mm saline, because the high pressure in the obstructed IVC was similar to the high portal pressure. All 26 patients had a large pressure gradient between the PV and right atrium that averaged 202 mm saline. A wedge liver biopsy specimen obtained at operation showed intense centrilobular congestion and marked centrilobular cell loss and necrosis in all but one patient (see Fig. 77.1), and 35 (54%) of the 65 patients had hepatic fibrosis; this was mild or moderate in 30 patients and severe in 5 patients, 4 of whom had cirrhosis. In patients with the chronic forms of BCS, and in most patients with VOD, the operative findings are typical of cirrhosis of the liver by the time the patient receives treatment.

Table 77.4

Findings at Operation in 65 Patients with Budd-Chiari Syndrome Who Underwent Surgical Portal Decompression by the Authors

	HEPATIC VEIN OCCLUSION ALONE	IVC AND HEPATIC VEIN OCCLUSION	
	SSPCS	Mesoatrial Shunt	Combined SSPCS and CAS
No. Patients	39	8	18
Ascites (L)			
Mean	6.7	6.2	6.5
Range	2.6 to 15.9	4.1 to 9.3	4.2 to 9.4
Hepatomegaly (%)	100	100	100
Splenomegaly (%)	100	100	100
Liver Biopsy Results (%)			
Congestion			
Marked	95	100	100
Mild	5	—	—
Necrosis			
Marked	100	100	100
Fibrosis			
Marked	12	0	0
Moderate to mild	64	37	61
None	24	63	39
Cirrhosis	10	0	0

CAS, cavoatrial shunt; IVC, inferior vena cava; SSPCS, side-to-side portacaval shunt

NONOPERATIVE THERAPY

The objectives of nonoperative therapy of BCS are to 1) remove the cause of the venous thrombosis, 2) relieve the high pressure and congestion within the liver, 3) prevent extension of the venous thrombosis, and 4) reverse the massive ascites. It is often impossible to accomplish these objectives.

In many cases of BCS, the cause of the venous thrombosis is unknown or, if known, it cannot be removed. In some cases, however, it is possible to remove or modify the predisposing condition. Examples are cases of BCS caused by oral contraceptive ingestion; hematologic disorders, such as polycythemia rubra vera and paroxysmal nocturnal hemoglobinuria; and pregnancy.

Decompression of the liver by nonoperative measures is often not possible. Thrombolytic therapy with urokinase or streptokinase has been used in many patients in an attempt to dissolve the thrombi and restore hepatic venous outflow (Cassel & Morely, 1974; Gooneratne et al, 1979; Greenwood et al, 1983; Hodkinson et al, 1978; Hoestra et al, 2008; Malt et al, 1978; Mitchell et al, 1982; Powell-Jackson et al, 1982; Thijs et al, 1978; Warren et al, 1972; Plessier & Valla, 2008; DeLeve et al, 2009; Barrault et al, 2004; Sharma et al, 2004; Murad et al, 2009; Zimmerman et al, 2006; Menon et al, 2004). The experience with thrombolytic therapy has been recorded in sketchy anecdotal reports involving short periods of follow-up. Approximately one third of patients were believed to have had a clinical response to treatment for periods of 2 months to 1 year. Half of the patients died as a result of BCS during the brief periods of observation. In the experience of Powell-Jackson and colleagues (1982), all four patients who received thrombolytic treatment in the acute phase of BCS died without evidence of a response.

Table 77.5

Intraoperative Pressure Measurements* in 65 Patients with Budd-Chiari Syndrome Who Underwent Surgical Portal Decompression

	PRESHUNT PRESSURES					POSTSHUNT PRESSURES				
Group	PV	IVC	PV-IVC Gradient	RA	PV-RA Gradient	PV	IVC	PV-IVC Gradient	RA	PV-RA Gradient
Hepatic Vein Occlusion Alone SSPCS (n = 39)										
Mean	376	132	244	—	—	166	161	5	—	—
Range	265 to 438	74 to 250	134 to 338	—	—	116 to 292	118 to 284	–12 to 40	—	—
IVC and Hepatic Vein Occlusion Mesoatrial Shunt (n = 8)										
Mean	320	305	9	101	211	244	—	—	147	78
Range	274 to 368	256 to 348	–8 to 46	90 to 112	162 to 256	196 to 248	—	—	124 to 162	52 to 94
IVC and Hepatic Occlusion Combined PCS and CAS (n = 18)										
Mean	308	296	12	112	196	170	164	6	148	22
Range	266 to 348	264 to 320	–8 to 34	95 to 125	140 to 240	158 to 184	160 to 178	–6 to 10	136 to 162	8 to 42

*In mm saline

CAS, cavoatrial shunt; IVC, inferior vena cava; PCS, portacaval shunt; PV, portal vein; RA, right atrium; SSPCS, side-to-side portacaval shunt

Urokinase and streptokinase have been administered by systemic intravenous (IV) infusion and by infusion directly into the IVC. In the use of thrombolytic drugs to treat deep venous thrombosis (DVT) of the lower extremities, peripheral IV infusion has been as effective as perfusing the agents directly into the clot. The recommended regimen (Greenwood et al, 1983) involves an IV loading dose (urokinase, 4400 IU/kg; streptokinase, 250,000 IU) followed by a constant IV infusion of urokinase at 4400 IU/kg/h or streptokinase at 100,000 IU/h for 2 to 7 days. Pulmonary embolization developed in two patients during thrombolytic therapy and is a potentially serious complication of this type of treatment.

Anticoagulant therapy has been used widely in BCS to prevent propagation of the thrombi (Ecker & McKittrick, 1966; Hartmann et al, 1980; Khuroo & Datta, 1980; Langer et al, 1975; Lewis et al, 1983; Liebowitz & Hartmann, 1981; Mitchell et al, 1982; Peytremann et al, 1972; Powell-Jackson et al, 1982; Thijs et al, 1978; Plessier et al, 2008; DeLeve et al, 2009; Zimmerman et al, 2006; Valla, 2009). Most reports of the effectiveness of this form of treatment have been anecdotal and lack long-term follow-up. There is no evidence that the use of either heparin or warfarin (Coumadin) brings about dissolution of established thrombosis.

In BCS caused by hematologic disorders, such as polycythemia rubra vera and paroxysmal nocturnal hemoglobinuria, some dramatic responses to IV heparin therapy have been reported, although relapses have been common (Hartmann et al, 1980; Liebowitz & Hartmann, 1981; Peytremann et al, 1972). Long-term anticoagulation with oral warfarin has been recommended to follow the initial IV use of heparin during the acute phase of BCS, although initiation or enhancement of bleeding is a potential complication of anticoagulant therapy, particularly in patients who develop cirrhosis and esophageal varices.

Control of ascites is feasible in some patients with BCS by use of the usual diuretic regimens, although ascites is resistant to therapy in many patients (see Chapter 74). Therapeutic measures include stringent sodium restriction, administration of diuretic drugs, and repeated IV infusion of salt-poor albumin or ascitic fluid. Renal function should be monitored closely during diuretic therapy to avoid precipitating the hepatorenal syndrome. There is no evidence that control of ascites influences the long-term outcome.

The prognosis of BCS with nonoperative therapy is poor (Mitchell et al, 1982; Parker, 1959; Powell-Jackson et al, 1982; Tavill et al, 1975). In his large collective review in 1959, Parker wrote, "The majority of cases have proved fatal, and there is little evidence to suggest that recovery from occlusion of the major hepatic veins occurs once symptoms have been produced." Similarly, in 1975, Tavill and associates wrote, "The prognosis of the Budd-Chiari syndrome is almost uniformly bad…." In 1982, Mitchell and colleagues stated in their collective review, "Spontaneous resolution of hepatic vein occlusion rarely, if ever, occurs. Conventional medical therapy does little to reverse the pathophysiology in patients with hepatic vein occlusion." Many patients with BCS that is treated nonoperatively die within a few months of the onset of symptoms. Patients who survive the acute phase usually go on to develop cirrhosis of the liver and die within a few years from hepatic failure, bleeding esophageal varices, or other complications of chronic liver disease. In the 5 years since preparation of the previous edition of this book, despite publication of numerous reviews, expert panels, and case summaries, no data have emerged to indicate that nonoperative therapy of BCS is effective.

TREATMENT OF HEPATIC VEIN OCCLUSION BY SIDE-TO-SIDE PORTACAVAL SHUNT

Experimental Studies

The theoretical basis for the use of SSPCS to relieve BCS resulting from occlusion of the hepatic veins is provided by substantial evidence indicating that the valveless PV can be converted into an outflow tract by an in-continuity anastomosis with the systemic venous system to decompress the obstructed hepatic vascular bed (Britton & Shirey, 1962; Britton et al, 1967; Burchell et al, 1976; Long et al, 1960; Longmire et al,

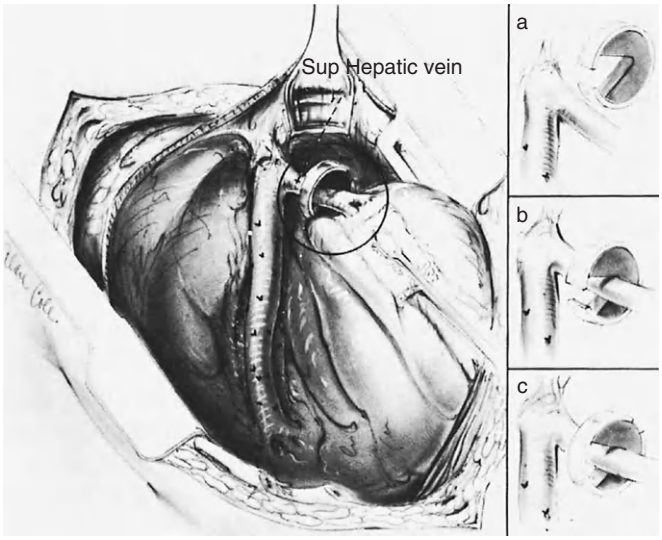


FIGURE 77.6. Our technique of induction of Budd-Chiari syndrome in dogs by ligation and division of all hepatic veins except the large left hepatic vein, which was surrounded by a hygroscopic, casein-plastic ameroid constrictor that gradually swelled centrally and occluded the vein. *(From Orloff MJ, Johansen KH, 1978: Treatment of Budd-Chiari syndrome by side-to-side portacaval shunt: experimental and clinical results. Ann Surg 188:494-512.)*

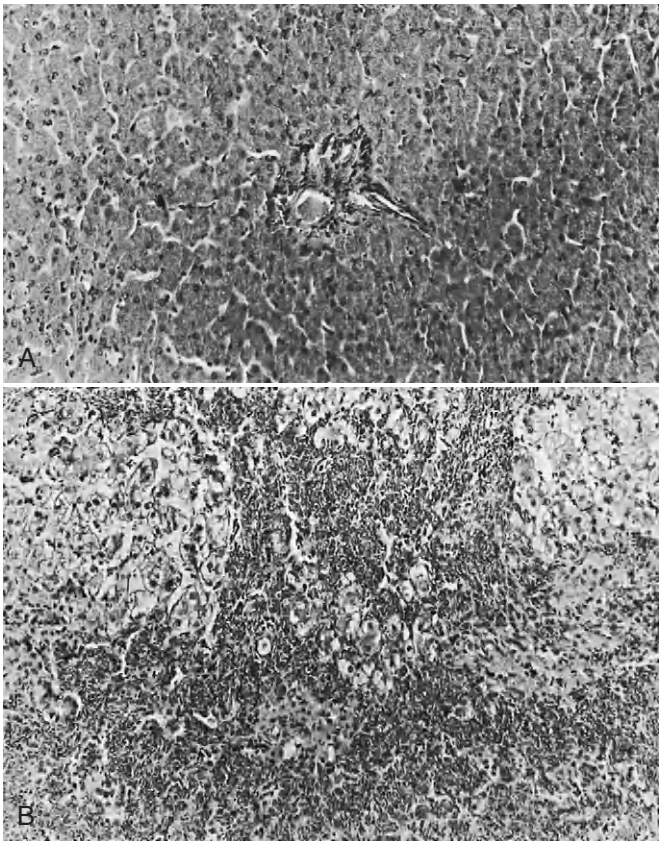


FIGURE 77.7. Photomicrographs of liver biopsy specimens obtained from a dog. **A,** Before hepatic vein ligation, when the liver was normal. **B,** Just before portacaval shunt, when Budd-Chiari syndrome was well established, and ascites was massive. Intense congestion and necrosis of the hepatic parenchyma is evident in the biopsy specimen (×140). *(From Orloff MJ, Johansen KH, 1978: Treatment of Budd-Chiari syndrome by side-to-side portacaval shunt: experimental and clinical results. Ann Surg 188:494-512.)*

1958; Moreno et al, 1967; Mulder & Murray, 1960; Murray & Mulder, 1961; Orloff et al, 1997; Orloff & Snyder, 1961; Tamaki et al, 1968; Warren & Muller, 1959). To test this hypothesis, we conducted an experimental evaluation of SSPCS in dogs with BCS (Orloff & Johansen, 1978). Our method of producing BCS in dogs consisted of ligation and division of all hepatic veins except the large left hepatic vein, which was loosely surrounded by an ameroid constrictor (Fig. 77.6; Orloff et al, 1963, 1965; Sweat et al, 1966). The lumen in the ameroid constrictor gradually narrowed as the hygroscopic casein plastic swelled centrally so that the remaining left hepatic vein was completely occluded within several weeks, and severe hepatic outflow block, portal hypertension, and massive, intractable ascites resulted. BCS was produced in 64 dogs, which were put into three treatment groups when ascites was massive: group I underwent sham laparotomy, group II underwent end-to-side PCS, and group III underwent SSPCS.

Table 77.6 summarizes the results of our experimental study. All dogs rapidly re-formed ascites after either sham laparotomy or end-to-side PCS and died with massive ascites within 6 months. In striking contrast, only 1 of the 24 dogs in group III reaccumulated ascites after SSPCS, and 67% of these dogs survived in good health without ascites until the time of sacrifice 1 year postoperatively. Before hepatic vein ligation, the liver was normal in all dogs on gross and microscopic examinations. At the time of sham laparotomy or shunt, when BCS was well established, all livers were enlarged two to four times normal size and appeared congested and friable. Liver biopsy specimens at this time showed intense centrilobular congestion, necrosis of cells around the central veins, dilated lymphatics, and subcapsular edema (Fig. 77.7). In the dogs in group I, these gross and microscopic abnormalities were unchanged at the

Table 77.6

Reaccumulation of Ascites and Mortality Rates in Dogs with Budd-Chiari Syndrome After Sham Laparotomy, End-to-Side Portacaval Shunt, and Side-to-Side Portacaval Shunt

		ASCITES AT OPERATION			REACCUMULATION OF ASCITES				
		Volume (L)			Volume at Autopsy (L)			Mortality Rate (%)	
Group	N	% of Group	Mean	Range	% of Group	Mean	Range	1 mo	1 yr*
I: Sham laparotomy	20	100	3.2	2.2 to 5.3	100	3.4	1.4 to 7.2	25	100
II: End-to-side shunt	20	100	3	2 to 5.7	100	3.8	1.6 to 6.8	25	100
III: Side-to-side shunt	24	100	3.3	2.5 to 6.2	1.4	1.4	25	33	4

*Excludes 1-month deaths

time of death, and substantial fibrosis was found in many of the liver biopsy specimens. Similarly, all of the dogs in group II had hepatomegaly at the time of death, and severe congestion, necrosis, and fibrosis were found in all liver biopsy specimens; although, in 38% of the animals, the microscopic picture was less severe than at the time of the end-to-side shunt operation. Only one dog with SSPCS in group III, the single animal with ascites, had an enlarged liver and microscopic findings of congestion and necrosis at the time of death. The other 23 dogs in group III had a liver that was normal in size and gross appearance at autopsy; liver biopsy specimens were normal in 35% of these dogs and showed minimal fibrosis in the remaining 65%.

Clinical Results of the Authors

On the basis of the results of our experimental studies, which showed SSPCS was effective in relieving BCS and reversing liver damage, we performed SSPCS in 39 patients with BCS caused by thrombosis of the hepatic veins without involvement of the IVC (Orloff & Girard, 1989; Orloff & Johansen, 1978; Orloff et al, 1992b, 2000); subjects were 21 women and 18 men, and ages ranged from 19 to 45 years. Of the 39 patients, 14 had polycythemia rubra vera, 11 had been taking oral contraceptives, 5 had Behçet disease, and 1 had protein C deficiency. In the remaining 8 patients, no condition predisposing to hepatic vein thrombosis was identified. Patients operated on before 1996 did not undergo the extensive hematologic workup shown in Box 77.2 that is currently performed. The symptoms, signs, results of diagnostic studies, and findings at operation are shown in Tables 77.2 to 77.5.

Tables 77.5 and 77.8 summarize the long-term results of SSPCS in our series. One patient underwent emergency operation, when the thrombosis of his hepatic veins suddenly extended into and occluded his previously patent IVC. An attempt to reverse a rapid downhill course by IVC thrombectomy and PCS was unsuccessful, and the patient died 6 days postoperatively with multiorgan failure and recurrence of IVC thrombosis. The remaining 38 patients (97%) recovered from the shunt operation and were long-term survivors. A striking feature of the early recovery period was a rapid gain in lean body weight that averaged 28 pounds in 3 months.

The 38 survivors of the shunt operation have been followed up for 5 to 37 years (mean follow-up 15 years). All survivors have been followed up for 5 years or more. One long-term death occurred in a patient with Behçet disease, who was relieved of BCS and ascites but died of diffuse vasculitis that caused hemorrhagic infarction of the colon 2 years postoperatively. The other 37 patients are currently alive, for an overall survival rate of 95%. All of the survivors have remained free of ascites without requiring diuretic therapy. Results of periodic liver function tests have been consistently normal except in the three patients who already had cirrhosis when they were referred to us. None of the patients has portosystemic encephalopathy, undoubtedly because they have good hepatic function. Hepatosplenomegaly has disappeared in all patients. Of the 38 survivors of SSPCS, 36 are employed or work full time at home. Of the 37 current survivors, 36 (97%) are leading productive lives of good quality.

One patient had recurrence of ascites 5 years after the shunt operation and was found to have developed marked narrowing of the IVC at the level of the previously occluded hepatic vein orifices. He was treated surgically with a bypass graft extending from below the area of obstruction in the IVC to the right atrium. Twenty-seven years after the bypass operation, the patient is free of ascites, and angiographic studies show a patent bypass graft with normal pressures in the IVC and PV.

Table 77.7

Long-Term Results of Portal Decompression Operations in 65 Patients with Budd-Chiari Syndrome Treated by the Authors

	HEPATIC VEIN OCCLUSION ALONE	IVC AND HEPATIC VEIN OCCLUSION	
	SSPCS	Mesoatrial Shunt	Combined SSPCS and CAS
No. patients	39	8	18
Onset to Operation (Weeks)			
≤17 (%)	92	88	100
Mean	16	12	15
Range	4 to 78	7 to 19	10 to 18
Follow-up (Years)			
Mean	15	17	14
Range	5 to 38	20 to 24	5 to 25
Ascites (%)	0	63	0
Need for diuretics (%)	0	63	0
Abnormal liver function tests (%)	8	63	0
Portosystemic encephalopathy (%)	0	38	0
Employed or housekeeping (%)	95	25	94
Survival (%)			
30-Day	97	100	100
Current	95	38	100

CAS, cavoatrial shunt; IVC, inferior vena cava; SSPCS, side-to-side portacaval shunt

Table 77.8

Results of Follow-up Liver Biopsies Every 1 to 2 Years, Angiography, Ultrasonography, and Pressure Measurements in 64 Surviving Patients with Budd-Chiari Syndrome Who Underwent Surgical Portal Decompression by the Authors

	HEPATIC VEIN OCCLUSION ALONE	IVC AND HEPATIC VEIN OCCLUSION	
	SSPCS	Mesoatrial Shunt	Combined SSPCS and CAS
No. patients	38	8	18
Liver Biopsy Results (%)			
Congestion			
Marked	0	63	0
Mild	3	12	0
None	97	25	100
Necrosis			
Marked	0	63	0
Mild	3	12	0
None	97	25	100
Fibrosis			
Marked	8	75	0
Moderate to mild	42	12	25
None	50	13	75
Cirrhosis	8	63	0
Angiography/Ultrasound Results (%)			
Patent shunt	97	37	100
Patent inferior vena cava	100	0	0
Occluded hepatic veins	100	100	100
Pressures (mm Saline)			
PV			
Mean	94	286	133
Range	54 to 150	174 to 374	114 to 150
IVC			
Mean	90	289	123
Range	41 to 124	240 to 342	106 to 142
PV-IVC gradient			
Mean	4	16	8
Range	0 to 44	−136 to 64	4 to 14
RA			
Mean	—	119	112
Range	—	88 to 118	92 to 130
PV-RA gradient			
Mean	—	186	21
Range	—	88 to 118	14 to 26

CAS, cavoatrial shunt; IVC, inferior vena cava; PV, pulmonary vein; RA, right atrium; SSPCS, side-to-side portacaval shunt

Liver biopsies and angiographic or US studies were performed periodically for 37 years after shunt in the 38 survivors, and the results are summarized in Table 77.8. Cirrhosis persisted in the three patients who already had cirrhosis by the time of the shunt operation, including the patient with Behçet disease. In 97% of the survivors, there was no longer any evidence of hepatic congestion or necrosis in the follow-up biopsy specimens, as shown in Figure 77.8. Mild to moderate fibrosis was found in 42% of the patients, but 50% had normal liver biopsy specimens. Angiography or US showed patency of the PCS and IVC, and pressure measurements showed a wide-open anastomosis with a gradient that ranged from 0 to 44 mm saline and averaged only 4 mm across the shunt. Two patients with polycythemia rubra vera developed thrombosis of the PCS 1 week and 3 months postoperatively. Both patients were operated on immediately, the shunt was taken down, fresh thrombus was removed from the PV, and the portacaval anastomosis was reconstructed with an H-graft of autologous internal jugular vein. Subsequently, both patients were maintained on anticoagulant therapy with warfarin. One patient has remained well for 28 years since revision of the shunt. The other patient developed recurrent shunt thrombosis and required liver transplantation (LT), but he is well 19 years after transplantation. It is now our policy to maintain all patients with a known coagulopathy on permanent anticoagulant therapy.

Our experience with the surgical treatment of BCS differs from almost every other report of surgery for BCS in the following respects: 1) it involved unselected, consecutive patients with BCS who were referred to us and were treated at a single institution; 2) the patients were treated and studied prospectively, and our report is based on prospectively collected data, not on retrospective reviews of medical records with all the known shortcomings; 3) SSPCS was performed by a single senior faculty surgeon, whose experience included performance of more than 2500 SSPCS procedures; 4) follow-up was 100% and was performed regularly for more than 3 decades.

Our series is the single largest clinical experience reported to date involving the use of SSPCS in BCS confined to the hepatic veins. Our clinical experience confirmed our experimental observations regarding the efficacy of SSPCS in relieving hepatic venous outflow obstruction. All 39 of our patients in whom thrombosis remained localized to the hepatic veins survived the operation and remained free of ascites for years without requiring diuretic therapy, and the shunt remained permanently patent in all but one patient. All but three of the survivors were operated on early in the course of the disease, before liver damage was irreversible; in these patients hepatosplenomegaly disappeared, and liver function rapidly returned to normal. The results of serial liver biopsies performed for 5 to 37 years postoperatively are particularly encouraging, because they showed that the shunt had brought about substantial and long-term reversal of the striking pathologic lesions of BCS (see Fig. 77.8). SSPCS seems to be the most effective treatment of BCS confined to the hepatic veins. The long-term survival rate of the patients in our series has not been equaled by any other form of therapy, medical or surgical.

The single postoperative death in our series taught us a valuable lesson. When this 28-year-old man with polycythemia rubra vera was admitted to our hospital, clear clinical and angiographic evidence showed the occlusive process confined to the hepatic veins. During the 8-day course of his diagnostic workup, however, the thrombosis extended into the IVC, and

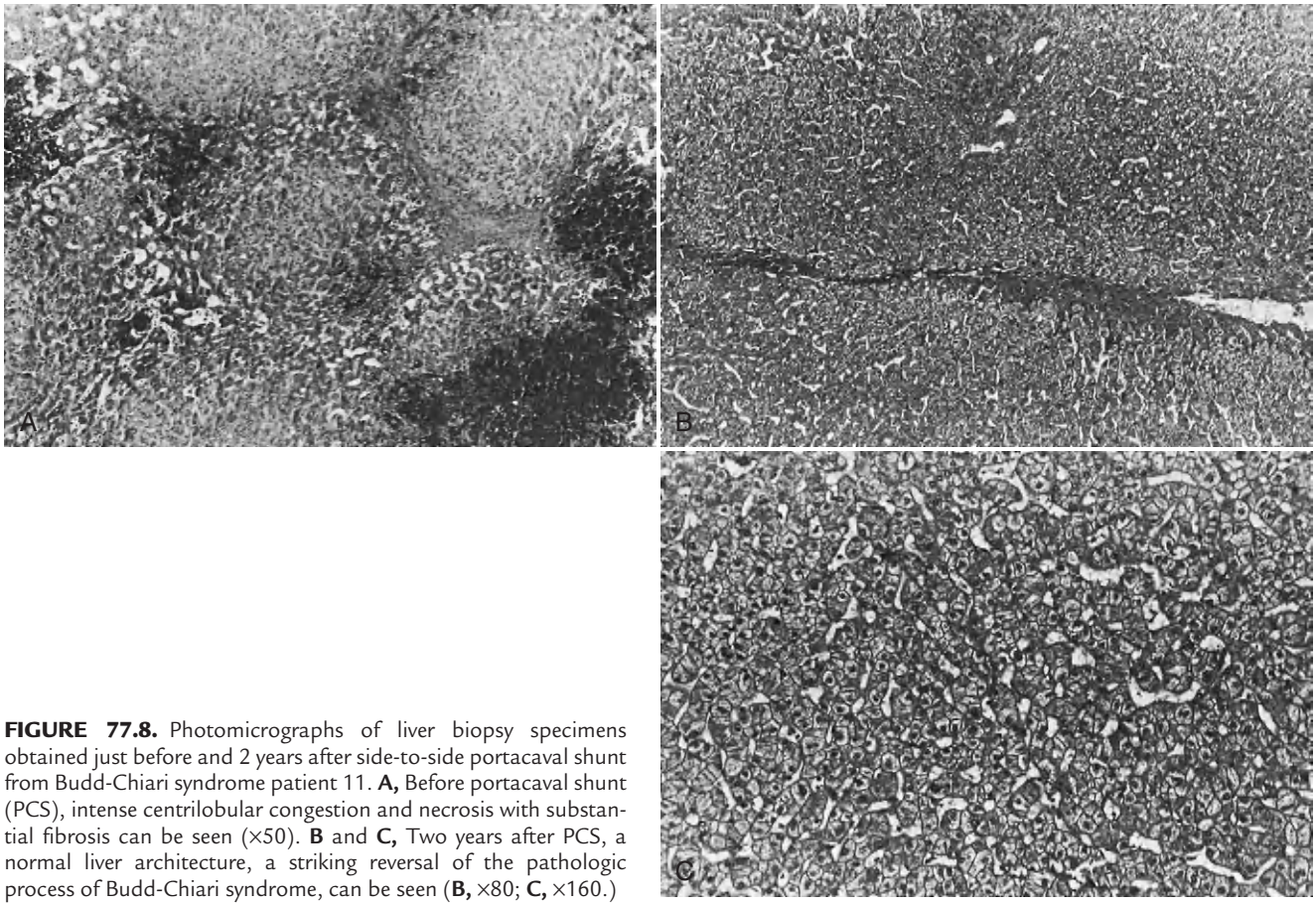


FIGURE 77.8. Photomicrographs of liver biopsy specimens obtained just before and 2 years after side-to-side portacaval shunt from Budd-Chiari syndrome patient 11. **A,** Before portacaval shunt (PCS), intense centrilobular congestion and necrosis with substantial fibrosis can be seen (×50). **B** and **C,** Two years after PCS, a normal liver architecture, a striking reversal of the pathologic process of Budd-Chiari syndrome, can be seen (**B,** ×80; **C,** ×160.)

his condition deteriorated dramatically. An emergency attempt at IVC thrombectomy and PCS failed. Extension of the thrombotic process from the hepatic veins into the IVC is a well-known event in BCS (Parker, 1959), and the potential for this devastating complication exists in every patient; therefore when the diagnosis of hepatic vein occlusion has been made, it seems unwise to delay operation.

SSPCS is indicated only in patients with BCS who have a patent IVC and an IVC pressure that is substantially lower than WHVP or portal pressure. Obstruction or occlusion of the IVC, manifested clinically by edema of the lower extremities and lower trunk and shown by angiography and IVC pressure measurements, is a contraindication to PCS. It is not unusual for patients with BCS caused by hepatic vein occlusion to have an elevated pressure in the IVC as a result of caval compression by an enlarged, congested liver or massive ascites or both. The absolute level of IVC pressure is not crucial to the effectiveness of SSPCS, as long as the portal pressure is substantially higher than caval pressure, and the IVC is shown to be patent. Others have reported relief of BCS by an in-continuity mesocaval shunt in patients with high IVC pressure but substantially higher portal pressure, showing that it is possible to decompress the liver as long as the differential is substantial between pressures in the PV and IVC (Vons et al, 1986). In our long-term follow-up studies after SSPCS, we have observed that compression of the IVC disappears with relief of hepatic congestion, and caval pressure returns to normal.

After SSPCS, the occlusive process in the hepatic veins extended into the adjacent IVC in only one of the 38 long-term survivors in our series. This untoward development occurred 5 years after the shunt operation and was treated successfully by a bypass graft from the IVC to the right atrium. It is possible that the infrequency of this complication is attributable to the PCS, which might inhibit propagation of the thrombus by increasing blood flow in the IVC and relieving stasis of blood in the liver.

The importance of performing SSPCS early in the course of BCS cannot be overemphasized. Hepatic venous outflow obstruction produces widespread destruction of the hepatic parenchyma by pressure necrosis and ischemia, and the liver damage becomes irreversible in a surprisingly short time: some patients have developed cirrhosis within 3 or 4 months of the onset of symptoms. Relieving ascites is far less important than decompressing the liver. Recently, groups of physicians that did not include surgeons have recommended a stepwise approach to treatment of BCS, beginning with a trial of anticoagulants, then angioplasty or thrombolysis and stenting, then transjugular intrahepatic portosystemic shunt (TIPS), and finally liver transplantation (Plessier & Valla, 2009; Janssen et al, 2003; de Franchis, 2005; Hoekstra & Janssen, 2008; DeLeve et al, 2009). The stepwise plan carries with it the danger of permitting liver damage to become advanced and irreversible.

Although a few patients have recovered spontaneously from BCS, most have not. The literature is replete with descriptions of patients who would have been suitable candidates for PCS but were treated nonoperatively and died. Our experience shows that it is imperative to perform SSPCS as soon as possible after the diagnosis of BCS has been made.

Clinical Results of Other Surgeons

Treatment by direct SSPCS or its hemodynamic equivalents—the portacaval interposition graft, mesocaval interposition graft, or splenorenal shunt—of BCS caused by occlusion of the hepatic veins has been reported in more than 300 patients by other surgeons (Ahn et al, 1987; Auvert & Farge, 1963; Bachet et al, 2007; Bismuth & Sherlock, 1991; Cameron et al, 1983; Dong et al, 2005; Eisenmenger & Nickel, 1960; Erlik et al, 1962; Fisher et al, 1999; Gentil-Kocher et al, 1988; Gibson, 1960; Hemming et al, 1996; Henderson et al, 1990; Hoyumpa et al, 1971; Huguet et al, 1979; Klein et al, 1990; Langer et al, 1975; Ludwick et al, 1967; Malt et al, 1978; McCarthy et al, 1985; Millikan et al, 1985; Montano-Loza et al, 2009; Murad et al, 2004; Noble, 1976; Panis et al, 1994; Pezzuoli et al, 1985; Powell-Jackson et al, 1982; Prandi et al, 1975; Schramek et al, 1974; Singhal et al, 2006; Slakey et al, 2001; Vons et al, 1986; Wang, 1989; Wu et al, 1990; Zeitoun et al, 1999). Many of the reports have involved descriptions of single cases. Some more recent retrospective multiinstitutional studies involving reviews of medical records have been based on analyses, as a single entity, of patients with widely different characteristics, such as the stage and type of BCS, time lapsed from diagnosis to treatment, site of hepatic venous outflow occlusion, and type of portosystemic shunt. Portacaval, mesocaval, splenorenal, mesoatrial, mesoinnominate, cavoatrial, portoatrial, and TIPS have been considered as a single entity termed a *portosystemic shunt* (Murad et al, 2004; Zeitoun et al, 1999). It is not possible to compare the results of these studies with our results, which were based on a prospective study of patients with BCS caused by hepatic vein thrombosis alone, all of whom underwent a direct SSPCS early in the course of their disease by a single surgeon at a single institution.

At institutions that have reported series of cases, success rates of portal decompression in BCS have been approximately 85% after direct SSPCS (Ahn et al, 1987; Bismuth & Sherlock, 1991; Hemming et al, 1996; McCarthy et al, 1985; Panis et al, 1994; Pezzuoli et al, 1985) and 67% after splenorenal shunt (Ahn et al, 1987; McCarthy et al, 1985; Millikan et al, 1985; Wang, 1989). Mesocaval or portacaval interposition grafts with autologous internal jugular vein have been reported in about 50 patients with BCS, most of them in France, with a success rate of 89% (Bismuth & Sherlock, 1991; Gentil-Kocher et al, 1988; McCarthy et al, 1985; Panis et al, 1994; Pezzuoli et al, 1985; Vons et al, 1986). Mesocaval or portacaval interposition grafts using synthetic materials, such as Dacron or polytetrafluoroethylene (Gore-Tex), have been successful in approximately 52% of 39 patients with BCS, which is the lowest success rate of the various in-continuity portal decompressive procedures (Ahn et al, 1987; Hemming et al, 1996; Henderson et al, 1990; Klein et al, 1990; McCarthy et al, 1985; Millikan et al, 1985; Pezzuoli et al, 1985; Wang, 1989). In our opinion, use of synthetic interposition portacaval or mesocaval grafts and the splenorenal shunt are inferior to direct SSPCS in the treatment of BCS, although all three shunts are hemodynamically similar. Occlusion of the shunt is a serious complication that may result in death: the splenorenal shunt and the synthetic interposition grafts have a substantial incidence of thrombosis, not only in BCS but also in other diseases that cause portal hypertension (Dowling, 1979; Hemming et al, 1996; Orloff, 1977, 1998; Orloff & Orloff, 1992); in contrast, the incidence of shunt occlusion in our series of more than 2500 direct SSPCS procedures—most of which have been followed up repeatedly by catheterization, angiography, or US—is 0.5%.

Four patients underwent end-to-side PCS for treatment of BCS. One patient had a favorable response during 1 year of follow-up (Marchal et al, 1974), but the other three died (Alpert, 1976; Brink & Botha, 1955; Langer et al, 1975). Because the hepatic side of the transected PV is ligated in an end-to-side PCS, the PV cannot function as an outflow tract to decompress the liver. It has been well established that in the presence of hepatic outflow block, the side-to-side anastomosis is substantially more effective than the end-to-side shunt in overcoming intrahepatic hypertension (Reynolds et al, 1962; Taylor & Myers, 1956; Warren & Muller, 1959).

Since our chapter on BCS was being prepared for the previous edition of this book 6 years ago, a number of reviews by nonsurgeons have been published (Janssen et al, 2003; Bachet et al, 2007; Plessier & Valla, 2008; Hoekstra & Janssen, 2008; Amarapurkar et al, 2008; DeLeve et al, 2009). These reviews, authored by physicians who had no personal experience with surgical treatment of BCS, were based on retrospective data collected from the literature, and they contained negative evaluations of the portosystemic shunt that were contrary to the results of our prospective studies. Examples of these negative evaluations that we believe are erroneous are: 1) "Overall perioperative mortality has been high, averaging 25%" (our perioperative mortality rate is 0%); 2) "The rate of shunt dysfunction due to early or late thrombosis or to late stenosis has reached 30% in series with long-term follow-up" (only 2 [5%] of our 38 patients developed thrombosis of the PCS 1 week and 3 months postoperatively, and this was permanently corrected by reoperation); 3) "Surgical portosystemic shunting … failed to show any impact on survival after adjustment for independent prognostic factors" (the survival rate in our series 5 years to 38 years postoperatively is 95%).

It is noteworthy that recent reviews, authored mainly by surgeons who have had personal experience with portosystemic shunts, have been supportive of the use and effectiveness of this important modality of the treatment in BCS (Menon et al, 2004; Klein, 2006; Zimmerman et al, 2006; Singhal et al, 2006; Montano-Loza et al, 2009).

Authors' Technique of Side-to-Side Portacaval Shunt

We have performed more than 2500 SSPCS operations over 50 years. From this experience, we have concluded that it is possible, with the proper technique, to perform a satisfactory SSPCS in almost every patient who has a patent PV. Contrary to some statements in the literature, we have been able to perform SSPCS without difficulty in every patient with BCS on whom we have operated. We have performed shunt catheterization and angiography or US every 1 to 2 years in almost all of our patients since the 1970s, and we have observed a 99.5% long-term shunt patency rate. Our technique of SSPCS (Orloff, 1983; Orloff & Orloff 1992, 1994; Orloff et al, 2007) is illustrated in Figures 77.9 to 77.18. Important technical features of the operation are as follows:

1. The position of the patient on the operating table is crucial and can make the difference between an easy and a difficult operation.

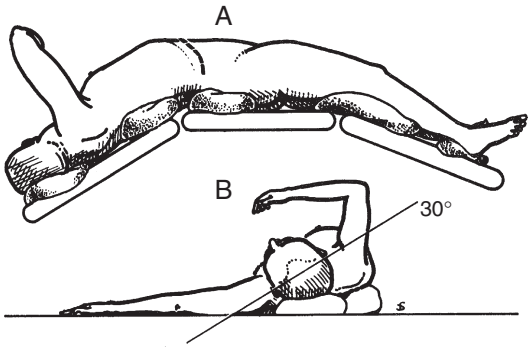


FIGURE 77.9. Position of patient for side-to-side portacaval shunt.

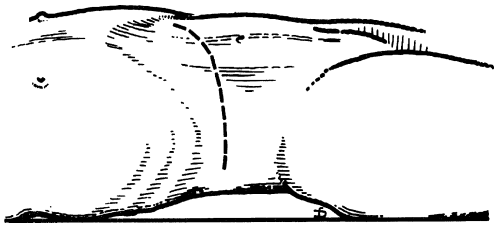


FIGURE 77.10. Long right subcostal incision used for side-to-side portacaval shunt.



FIGURE 77.11. Exposure of the operative field for side-to-side portacaval shunt.

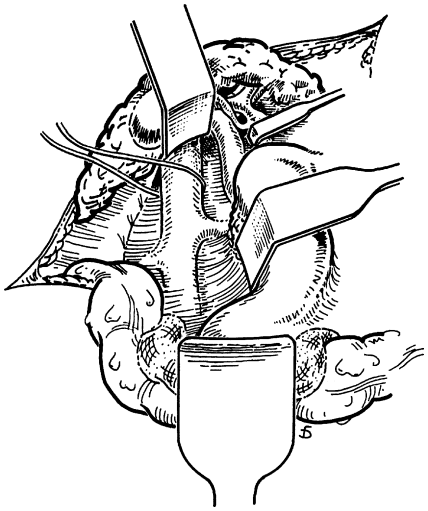


FIGURE 77.12. Circumferential isolation of the inferior vena cava between renal veins and liver in preparation for side-to-side portacaval anastomosis.

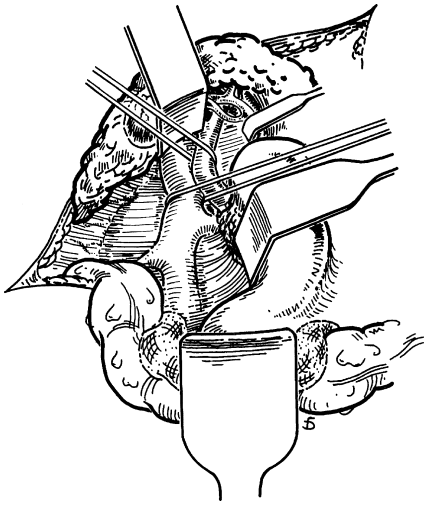


FIGURE 77.13. Exposure of portal vein in preparation for side-to-side portacaval anastomosis.

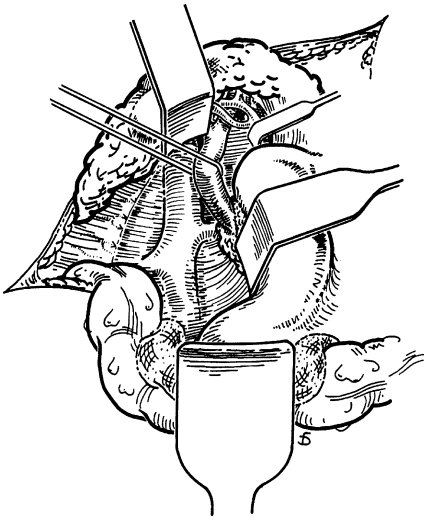


FIGURE 77.14. Mobilization of a long length of portal vein, including the segment behind the pancreas, in preparation for side-to-side portacaval anastomosis.

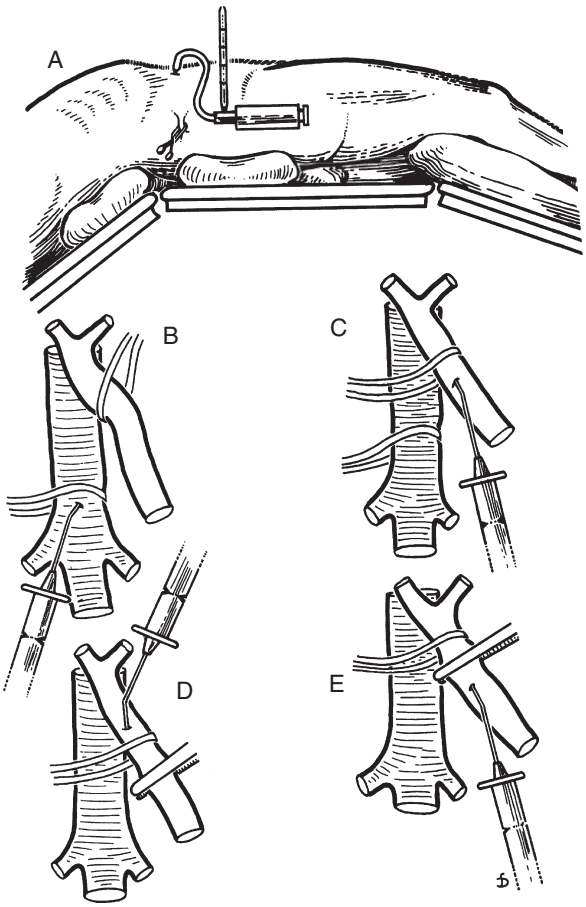


FIGURE 77.15. Measurement of pressures in the inferior vena cava (IVC) and portal vein (PV) with a saline (spinal) manometer by direct needle puncture before performance of portacaval anastomosis. All portal pressures are corrected by subtracting the IVC pressure from the portal pressure. Pressures in the IVC and PV are measured again after completion of the shunt. **A,** For all pressure measurements, the bottom of the manometer is positioned at the level of the IVC, which is marked on the skin surface of the body with a towel clip. **B,** IVC pressure. **C,** Free portal pressure. **D,** Hepatic occluded portal pressure, obtained on the hepatic side of a clamp occluding the portal vein. **E,** Splanchnic occluded portal pressure, obtained on the intestinal side of a clamp occluding the portal vein.

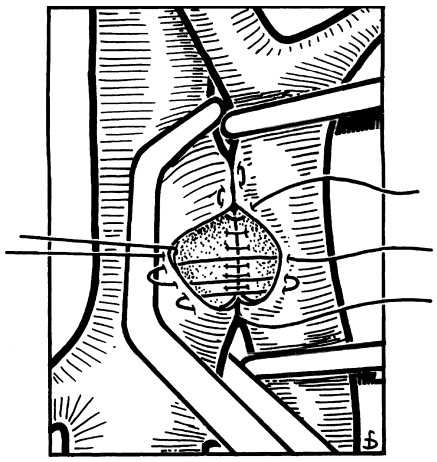


FIGURE 77.17. Side-to-side portacaval anastomosis. Placement of anterior row of two continuous everting sutures of 5-0 vascular material.

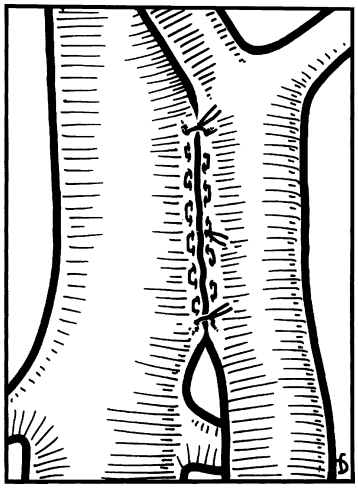


FIGURE 77.18. Completed side-to-side portacaval anastomosis.

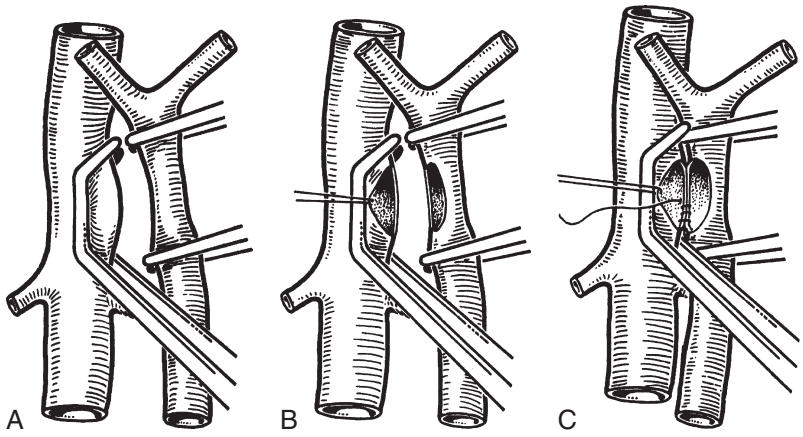


FIGURE 77.16. Side-to-side portacaval anastomosis. **A,** Placement of clamps on the inferior vena cava (IVC) and portal vein (PV). **B,** Strips of IVC and PV 2.5 cm in length have been excised. **C,** Placement of a posterior row of continuous 5-0 vascular suture from inside the lumina of IVC and PV.

2. A long right subcostal incision is associated with fewer postoperative complications than a thoracoabdominal incision and is much preferred.
3. Use of electrocautery throughout the operation substantially reduces both operating time and blood loss.
4. Bleeding from the many portosystemic collateral vessels is best managed by pressure with gauze sponge packs, particularly because most of the bleeding stops as soon as the portacaval anastomosis is completed, and the portal hypertension is relieved. Attempts to control each of the bleeding collaterals with ligatures and sutures prolong the operation and increase blood loss: the objective is to decompress the portal system as rapidly as possible.
5. Circumferential mobilization of the IVC between the entrance of the renal veins and the liver is essential for the side-to-side anastomosis and is neither hazardous nor difficult to perform. Apposition of the two vessels is greatly facilitated by elevation of the IVC toward the PV.
6. Essential for the side-to-side anastomosis is mobilization of a long segment of PV, which includes division of the tough fibrofatty tissue that binds the PV to the pancreas and sometimes includes division of a bit of the head of the pancreas.
7. Beware of the replaced hepatic artery crossing the PV behind the head of the pancreas! Ligation of the hepatic artery may be lethal. Palpate it with the index finger in the tunnel between the head of the pancreas and PV.
8. Resection of an enlarged caudate lobe of the liver to facilitate apposition of the two vessels is hazardous and unnecessary.
9. Pressures in the IVC and PV always should be measured after completion of the PCS. A pressure gradient greater than 50 mm saline is unacceptable and requires revision of the anastomosis.

Figure 77.9 shows the position of the patient on the operating table, viewed from the patient's right side. The patient is positioned with the right side elevated at an angle of 30 degrees to the table, and the table is "broken" at the level of the costal margin and at the knees to widen the space between the right costal margin and right iliac crest.

Figure 77.10 shows the incision. A long right subcostal incision extending from the xiphoid to well into the flank is made two fingerbreadths below the costal margin; we have used this incision in every operation over the course of 50 years. The skin is incised superficially with the scalpel, and the other layers are incised with electrocautery, which greatly reduces blood loss and shortens the operating time. When electrocautery is used, it is usually unnecessary to clamp any blood vessels with hemostats. The right rectus abdominis, external oblique, and transverses abdominis muscles are completely divided, and the medial 3 to 4 cm of the latissimus dorsi muscle is often incised. The peritoneum often contains many collateral blood vessels and is incised with the electrocautery to obtain immediate hemostasis.

Figure 77.11 shows the exposure of the operative field. The viscera are retracted by three Deaver retractors positioned at right angles to each other: the inferior retractor retracts the hepatic flexure of the colon toward the feet, the medial retractor displaces the duodenum medially, and the superior retractor retracts the liver and gallbladder toward the head. The posterior peritoneum overlying the IVC is incised with electrocautery by an extended Kocher maneuver just lateral to the descending duodenum, and the retractors are repositioned to retract the head of the pancreas medially and the right kidney caudally. Alternatively, a self-retaining retractor may be used in place of the three handheld Deaver retractors.

Figure 77.12 shows the isolation of the IVC: the anterior surface is cleared of fibroareolar tissue, and the IVC is isolated around its entire circumference, from the entrance of the right and left renal veins below to the point where it disappears behind the liver above. The IVC is surrounded with an umbilical tape. To accomplish the isolation, several tributaries may have to be ligated in continuity with fine silk ligatures and then divided. These include the right adrenal vein, one or two pairs of lumbar veins that enter on the posterior surface, and the caudal pair of small hepatic veins that enter on the anterior surface of the IVC directly from the liver. When the IVC has been mobilized completely, it can be lifted up toward the PV. Failure to isolate the IVC circumferentially is one major reason for the erroneous claim that SSPCS often cannot be performed, because the PV and IVC are too widely separated.

Figure 77.13 shows the exposure of the PV. The superior retractor is repositioned medially so that it retracts the liver and gallbladder at the point of entrance of the portal triad. The PV is located in the posterolateral aspect of the portal triad and is approached from behind. The fibrofatty tissue on the posterolateral aspect of the portal triad contains nerves, lymphatics, and lymph nodes and is divided by blunt and sharp dissection; this is a safe maneuver, because there are no portal venous tributaries on this aspect of the portal triad.

As soon as the surface of the PV is exposed, a vein retractor is inserted to retract the common bile duct and hepatic artery medially. The PV is mobilized circumferentially at its midportion and is surrounded with an umbilical tape. It is isolated up to its bifurcation in the liver hilum, and several tributaries on the medial aspect are ligated in continuity with fine silk and divided.

Figure 77.14 shows the mobilization of the PV behind the pancreas. Using the umbilical tape to pull the PV out of its bed, it is cleared to the point where it disappears behind the pancreas. The tough fibrofatty tissue that binds the PV to the pancreas must be divided. Several tributaries that enter the medial aspect of the PV and one tributary that enters the posterolateral aspect are divided, but it is usually unnecessary to divide the splenic vein. Wide mobilization of the PV is essential for performance of a side-to-side portacaval anastomosis. Failure to mobilize the PV behind the pancreas is a second major reason for difficulty in accomplishing an SSPCS. In some patients, it is necessary to divide a bit of the head of the pancreas to obtain adequate mobilization of the PV. Bleeding from the edges of the divided pancreas is controlled with suture ligatures. Division of a small amount of the pancreas is a helpful maneuver, and we have never observed postoperative complications, such as pancreatitis, from its performance.

Figure 77.15 shows the measurement of pressures in the IVC and PV before performing the portacaval anastomosis. The performance of an SSPCS is illustrated in Figures 77.16 to 77.18. After it is determined that the IVC and PV can be brought together without excessive tension, a Satinsky clamp is placed obliquely across a 5-cm segment of the anteromedial wall of the IVC in a direction that is parallel to the course of the overlying PV, and the IVC is elevated toward the PV. One 5-cm segment of the PV is isolated between two angled vascular clamps, and the PV is depressed toward the IVC, bringing the two vessels into apposition (see Fig. 77.16). One 2.5-cm long,

thin strip of the IVC and one 2.5-cm strip of the PV are excised with the scissors (see Fig. 77.16B). It is important to excise a thin longitudinal segment of the wall of each vessel rather than simply to make an incision in each vessel. A retraction suture of 5-0 vascular suture material is placed in the lateral wall of the vena caval opening and is weighted by attachment to a hemostat to keep the vena caval orifice open. The clamps on the PV are momentarily released to flush out any clots, then the openings in both vessels are irrigated with heparinized saline.

The anastomosis is started with a posterior, continuous, over-and-over suture of 5-0 vascular suture material (see Fig. 77.16C). The posterior continuous suture is tied at each end of the anastomosis. The anterior row of sutures consists of an everting, continuous, horizontal mattress stitch of 5-0 vascular material started at each end of the anastomosis (see Fig. 77.17). The suture started at the superior end of the anastomosis is discontinued after three or four throws and is deliberately left loose so that the interior surface of the vessels can be visualized as the anastomosis is completed. In this way, inadvertent inclusion of the posterior wall in the anterior row of sutures is avoided. The suture started at the inferior end of the anastomosis is inserted with continuous tension until it meets the superior suture, at which point the superior suture is drawn tight, and the two sutures are tied to each other. Before drawing the superior suture tight, the clamps on the PV are momentarily released to flush out any clots, and the anastomosis is thoroughly irrigated with heparinized saline.

Figure 77.18 shows the finished anastomosis, upon completion of which a single interrupted tension suture is placed just beyond each end of the anastomosis to take tension off the anastomotic suture line. The clamp on the IVC is removed first, the clamp on the hepatic side of the PV is removed next, and finally the clamp on the intestinal side of the PV is removed. Bleeding from the anastomosis occurs infrequently, but it can be controlled by one or two well-placed interrupted sutures of 5-0 vascular suture material.

Pressures in the PV and IVC must be measured after the anastomosis is completed. Usually the pressures in the PV and IVC are similar after the shunt is in place. A pressure gradient of greater than 50 mm saline between the two vessels indicates that there is an obstruction in the anastomosis, even when no obstruction can be palpated. In such circumstances, the anastomosis should be opened to remove any clots, and if necessary, the entire anastomosis should be taken down and done again. It is essential that there be no more than a 50-mm saline gradient between the PV and IVC to achieve permanently adequate portal decompression and to avoid ultimate thrombosis of the shunt.

TREATMENT OF INFERIOR VENA CAVA OCCLUSION BY PORTAL DECOMPRESSION

Mesoatrial Shunt

When BCS is caused by thrombosis of the IVC and of the hepatic veins, SSPCS and equivalent decompressive procedures are ineffective, because the high pressure in the infrahepatic IVC does not permit adequate decompression of the portal system and liver. Under such circumstances, a mesoatrial shunt has been advocated. Synthetic Dacron or Gore-Tex grafts ranging from 14 to 20 mm in diameter have been used in most cases and have been connected end-to-side to the superior mesenteric vein in the abdomen and the right atrium in the thorax.

We performed mesoatrial shunting in eight patients with BCS caused by thrombosis of the IVC and the hepatic veins. A 16-mm ring-reinforced Gore-Tex prosthesis was used. The operation was performed through a midline laparotomy and a median sternotomy. The superior mesenteric vein was isolated circumferentially for a distance of about 3 cm in the root of the small bowel mesentery, and the pericardium was opened to expose the lateral wall of the right atrium. The graft was anastomosed to the side of the superior mesenteric vein with continuous 5-0 vascular suture, tunneled through the root of the transverse mesocolon and greater omentum, then passed anterior to the stomach and left lobe of the liver into the mediastinum through an opening made in the anterior diaphragm. Finally, the prosthesis was anastomosed to the side of the right atrium with a continuous 5-0 vascular suture. To ensure wide-open anastomoses, an ellipse of the wall of the superior mesenteric vein and of the right atrium was excised before connecting the prosthesis.

Our results of mesoatrial shunting are shown in Tables 77.5, 77.7, and 77.8. A mesoatrial shunt reduced the mean gradient between the PV and right atrium from 211 to 78 mm saline. All eight patients survived the operation and left the hospital alive, although five (63%) of the eight patients subsequently developed thrombosis of the graft and died from liver failure. Three of the deaths occurred during the first postoperative year, one occurred in the second year, and one occurred in the fifth year. All five patients developed recurrence of ascites, and three developed portosystemic encephalopathy as their hepatic function deteriorated. The causes of BCS in the five patients whose mesoatrial shunt failed were oral contraceptives in one, polycythemia rubra vera in one, antithrombin III deficiency in one, and a postpartum state in one; the cause of the other one was unknown. These causes were no different from those found in the long-term survivors of portal decompression in our series. The patients whose mesoatrial shunt failed were not a higher risk group; they died because their mesoatrial shunt thrombosed 1 to 5 years after insertion, not because they were poorer risk patients to start with.

The three long-term survivors of the mesoatrial shunt (38%) have been followed up for 23 years, 21 years, and 21 years, respectively. Angiography and US have shown patency of their grafts. They are free of ascites, have normal liver function, and do not require diuretics; two of the three are gainfully employed. Serial liver biopsy specimens show residual congestion in one patient and moderate fibrosis in two. In one patient, the liver appears normal.

Several series of mesoatrial shunting that involve 5 or more patients have been reported in the literature, although the length of follow-up generally has been relatively short. Stringer and colleagues (1989) of London reported excellent results in 5 patients, but the follow-up period of 9 to 16 months was too short to warrant conclusions. Wang and colleagues (1989, 2005) of Beijing reported a survival rate of 61% and 50% at 5 and 10 years, respectively, in 70 patients, but his reports contain insufficient details to determine how many of the patients had patent and functioning grafts, how well the patients were followed, or the exact nature of the BCS that was being treated. Emre and colleagues (2000) of Istanbul reported an 85% survival rate of 13 patients during follow-up of 1 to 76 months, with one known thrombosed shunt. Behera and associates (2002) of Chandigarh, India, described 100% graft patency during 6 to 71 months of follow-up of 10 patients,

with a survival rate of 90%. Khanna and colleagues (1991) of Chandigarh, India, reported a 62% survival rate of 13 patients during follow-up of 2 months to 7.5 years.

The results of Henderson and colleagues' (1990) study of nine patients, of Klein and colleagues (Klein et al, 1990; Slakey et al, 2001) study of 15 patients, and of our own investigations of eight patients are representative of the experience with mesoatrial shunting in the United States. Survival rates ranged from 38% to 67%, and the percentage of patients with grafts that were patent and decompressing was only 33% to 60% during relatively short follow-up periods. Cameron and colleagues (1984; Klein et al, 1990) reported improved results with the use of an 8-cm external silicone rubber sleeve around a 16-mm ring-reinforced Gore-Tex prosthesis to prevent compression of the graft by the sternum. This innovation may reduce the frequency of graft thrombosis, but the results of mesoatrial shunting generally have been disappointing.

The high thrombosis rate of the mesoatrial shunt may be due to the fact that it is a relatively low-flow synthetic graft placed within the venous system. It does not decompress the obstructed IVC. To overcome these shortcomings, we worked in the experimental laboratory to devise a new operation for this form of BCS consisting of a combined SSPCS and cavoatrial shunt (CAS) through a Gore-Tex graft (Orloff et al, 1992a). This combined shunt was aimed at decompressing the hypertensive IVC and shunting the entire systemic venous flow from the lower two thirds of the body and the entire portal venous flow through the graft.

Experimental Studies

BCS was produced in rats by gradual occlusion of the suprahepatic IVC with an ameroid constrictor. As the hygroscopic casein plastic took up fluid and swelled centrally, the lumen in the ameroid gradually narrowed until, after 25 to 30 days, it completely occluded the IVC and produced severe hepatic outflow block, portal hypertension, and massive intractable ascites typical of BCS. One month after insertion of the ameroid constrictor around the IVC, when all rats had massive ascites, hepatomegaly, and portal hypertension, they were randomly divided into three groups (Fig. 77.19). Group I was composed of 16 control rats that underwent a sham thoracolaparotomy when BCS was well established. Group II consisted of 22 rats subjected to a mesoatrial shunt from the superior mesenteric vein to the right atrium with a 3-mm Gore-Tex graft inserted by microsurgical technique. Group III comprised 22 rats that underwent SSPCS combined with CAS from the IVC to the right atrium with a 3-mm Gore-Tex graft. Forty-four rats survived the operations and were studied.

Table 77.9 summarizes the results in the three groups of rats. All control rats that underwent sham thoracolaparotomy in group I rapidly reaccumulated ascites and died within 2 months. Nine of 16 rats with mesoatrial shunts in group II re-formed ascites and died within 2 months. All of these animals were found at autopsy to have thrombosis of the mesoatrial graft. In contrast, only 2 of 16 rats treated by combined SSPCS and CAS in group III developed CAS-graft thrombosis, re-formed ascites, and died. The remaining 14 rats in group III were found to have patent grafts and shunts when they were sacrificed after 3 months. Liver biopsy specimens in all rats were normal before IVC constriction, and after BCS was well established, they showed intense centrilobular congestion and moderate central necrosis. Severe pathologic changes persisted until death or sacrifice in all control rats in group I and in 11 of 16 rats with mesoatrial shunts in group II; however, combined SSPCS and CAS in group III reversed the liver pathology in 14 of 16 rats.

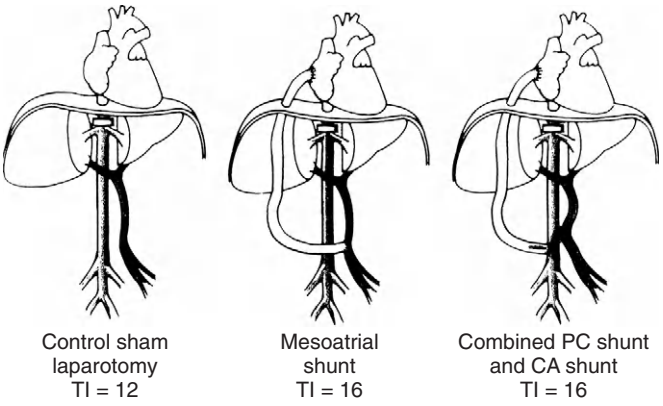


FIGURE 77.19. Experimental groups of rats with Budd-Chiari syndrome produced by constriction of the inferior vena cava by an ameroid constrictor. Control sham laparotomy, mesoatrial shunt, and combined side-to-side portacaval (*PC*) shunt and cavoatrial (*CA*) shunt were compared. *(From Orloff MJ, et al, 1992: Treatment of Budd-Chiari syndrome due to inferior vena cava occlusion by combined portal and vena caval decompression. Am J Surg 163:137-143.)*

Our Clinical Results with Combined Side-to-Side Portacaval Shunt and Cavoatrial Shunt

On the basis of the encouraging results of our experimental studies, we have treated 18 seriously ill patients with BCS caused by IVC thrombosis with combined SSPCS and CAS using a 20-mm ring-reinforced Gore-Tex graft. The characteristics of the patients are summarized in Tables 77.4 and 77.5. The study included 12 men and 6 women, ranging in age from 25 to 37 years. All 18 patients were in good health before the onset of symptoms and signs, which consisted of marked ascites, edema of the lower extremities, hepatosplenomegaly, abdominal pain,

Table 77.9

Results of Treatment in Rats with Experimental Budd-Chiari Syndrome Produced by Inferior Vena Cava Occlusion

Group	N	Graft or Shunt Thrombosis	Re-formed Ascites	Survived 3 Months	Reversal of Liver Pathology
I: Sham thoracolaparotomy	12	—	12	0	0
II: Mesoatrial shunt	16	9	9	7	5
III: Combined portacaval shunt and cavoatrial shunt	16	2	2	14	14

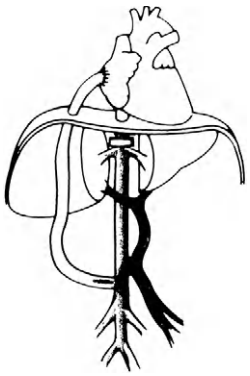


FIGURE 77.20. Combined side-to-side portacaval (*PC*) shunt and cavoatrial (*CA*) shunt using a 20-mm ring-reinforced Gore-Tex graft. The operation was done in 18 patients with Budd-Chiari syndrome secondary to inferior vena cava occlusion. *(From Orloff MJ, et al, 1992: Treatment of Budd-Chiari syndrome due to inferior vena cava occlusion by combined portal and vena caval decompression. Am J Surg 163:137-143.)*

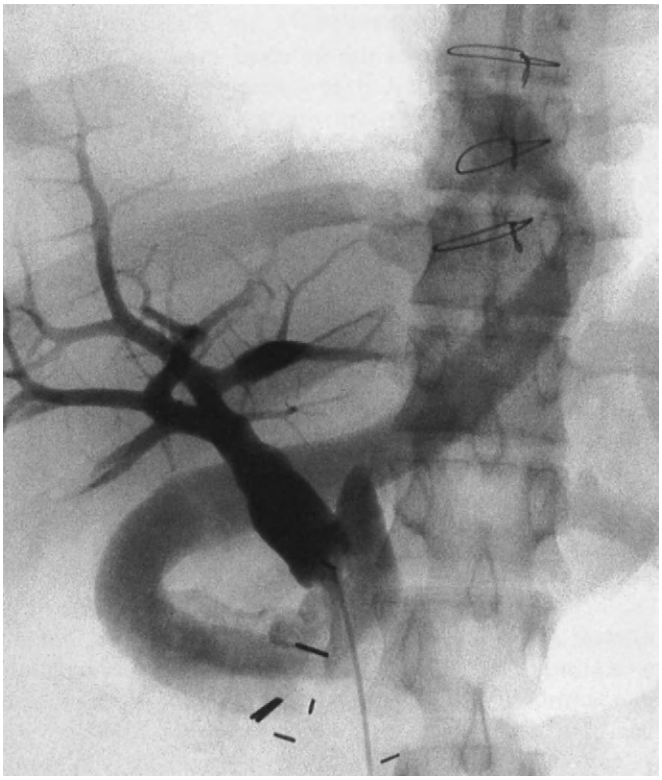


FIGURE 77.21. Shunt catheterization and venogram showing patency of the portacaval shunt (PCS) and cavoatrial shunt (CAS) 1 year after performance of combined PCS and CAS in a patient with Budd-Chiari syndrome secondary to inferior vena cava occlusion. Serial angiographic studies showed patency and excellent function of the PCS and CAS in all patients. *(From Orloff MJ, et al, 1992: Treatment of Budd-Chiari syndrome due to inferior vena cava occlusion by combined portal and vena caval decompression. Am J Surg 163:137-143)*

weakness, and muscle wasting. The combined operation is depicted in Figure 77.20.

The procedure was performed through a long right subcostal incision for the PCS and then a medium sternotomy for the CAS. After completion of the SSPCS, a 20-mm diameter, ring-reinforced Gore-Tex graft was anastomosed to the side of the IVC at the level of the PCS. The graft was channeled anterior to the liver through an opening made in the right leaf of the diaphragm and was anastomosed to the side of the right atrium. Combined SSPCS and CAS reduced the mean gradient between the PV and right atrium from 196 mm saline to 23 mm saline. All 18 patients survived the combined shunt operation and are alive 5 to 25 years postoperatively (see Tables 77.7 and 77.8). Mean follow-up is 12 years. All patients are free of ascites, and none requires diuretics; hepatomegaly and splenomegaly are gone; and liver function tests results are normal in all survivors, with no instance of portosystemic encephalopathy. All survivors are gainfully employed or keeping house and leading productive lives of good quality.

Serial percutaneous liver biopsy specimens have shown normal architecture in 14 patients and mild fibrosis in four. Serial angiographic studies with pressure measurements and Doppler duplex US have shown patency and good function of SSPCS and CAS in all patients (Fig. 77.21). Recanalization of the IVC or hepatic veins has not occurred. Permanent anticoagulation with warfarin and low-dose acetylsalicylic acid (aspirin) has been maintained in all patients. In our program, combined SSPCS and CAS has replaced mesoatrial shunt as the preferred treatment for BCS caused by IVC obstruction.

OTHER TYPES OF SURGICAL AND RADIOLOGIC THERAPY

Transjugular Intrahepatic Portosystemic Shunt

TIPS (see Chapter 76E) is SSPCS inserted percutaneously under radiographic control. As such, it is based on the same rationale for relieving hepatic venous outflow obstruction and intrahepatic portal hypertension as the surgical SSPCS. The attractiveness of TIPS lies in the fact that it can be done without a major surgical abdominal operation in patients who have liver disease, who are often quite ill. Its major disadvantage is a substantial incidence of occlusion of the TIPS that may require repeated revisions and hospitalizations and often involves recurrence of symptoms. In some patients who have complete occlusion of the hepatic veins or complete occlusion of the IVC, an additional disadvantage is technical inability to insert the TIPS. Insertion of the TIPS by direct puncture of the retrohepatic IVC, which sometimes is the only way that the shunt can be created, may be associated with a substantial incidence of complications (Rössle et al, 2004).

Between 1995 and 2004, there were many reports of TIPS treatment of BCS, each involving a few patients (Blum et al, 1995; Cejna et al, 2002; Ganger et al, 1999; Huber et al, 1997; Mancuso et al, 2003; Michl et al, 1999; Perello et al, 2002; Rogopoulos et al, 1995; Rössle et al, 1998; Uhl et al, 1996). The largest and longest reported experience with TIPS in BCS during that period was that of Rössle and colleagues (2004) at the University Hospital of Freiburg, Germany, who described their experience with 35 patients—11 acute, 13 subacute, and 11 chronic—who were followed up for a mean of 37 (± 29) months. Shunt failure occurred in 7 patients (20%): 2 were

technical failures, 2 required LT (1 died), and 3 died after TIPS. Excluding the 2 patients who required LT but including the 2 who could not have TIPS for technical reasons, the 5-year survival rate was 74%. TIPS occlusion requiring revision occurred in 19 (58%) of 33 patients. One patient required 10 revisions during a follow-up period of 53 months.

Results reported by others were not as good as those of the Freiburg group. Mancuso and associates (2003) described a series of 15 patients, with 5 deaths and 1 technical failure—a 40% negative outcome. Cejna and colleagues (2002) reported a series of 8 patients; 2 (25%) died 2 weeks after TIPS, 1 developed TIPS occlusion requiring LT, and 3 others required two to seven revisions for TIPS stenosis. Only 2 (25%) of 8 of the initial series of patients had revision-free TIPS patency. Perello and colleagues (2002) reported a series of 13 patients in which there were three shunt failures (23%). The failures included 1 death, 1 TIPS thrombosis that necessitated a surgical shunt, and 1 patient that required LT. Of the remaining 10 patients, 7 (70%) developed TIPS occlusion. In 5 of these, TIPS dysfunction had not been corrected.

Since 2004, use of TIPS in BCS has increased substantially, mainly in Europe, in part as a result of the availability of polytetrafluoroethylene (PTFE)-covered stents. Most of the reports have involved retrospective reviews of small numbers of cases followed up for short periods of time. In 2006, Rössle and colleagues reported results of TIPS with PTFE-covered stents in 112 patients, 17 of whom had BCS. Of these, 12 patients were lost to follow-up, and 16 developed TIPS failure. The 1-year TIPS failure rate was 10%, 22 patients died, and 3 underwent LT. The mortality rate without and with the patients lost to follow-up was 20% and 30%, respectively. The authors concluded that the TIPS procedure was improved by the PTFE-covered stent.

Other recent reports of TIPS treatment of BCS include a 124 patients (Murad et al, 2008 [16 patients]; Garcia-Pagan et al, 2008; Eapen et al, 2006 [30 patients]; Plessier et al, 2006 [20 patients]; Gandini et al, 2006 [13 patients]; Hernandez-Guera et al, 2004 [25 patients]; Attwell et al, 2004 [17 patients]). Garcia-Pagan and colleagues (2008) conducted a retrospective review of 124 BCS patients treated with TIPS in six European centers between 1993 and 2006. It is noteworthy that 147 of 221 patients with BCS were eligible for TIPS, but 14 were excluded for technical contraindications, and attempts at TIPS failed in an additional nine patients. Thus, in a population of patients with BCS, only 60% actually underwent TIPS. Twenty-two patients had complications associated with the TIPS procedure, and 2 died as a result. Sixty-one (41%) of the 124 patients had TIPS dysfunction during follow-up that required restenting in 35, angioplasty in 20, and thrombolysis in 6. Portosystemic encephalopathy developed in 21% of patients within 1 year. During follow-up, 16 patients died (13%), and 8 required LT (6.5%). Actuarial LT-free survival rates at 1, 5, and 10 years were 88%, 78%, and 69%, respectively.

Surprisingly, Garcia-Pagan and colleagues drew the following conclusions: 1) "Our results show that overall TIPS is an extremely effective therapy for patients with severe BCS in whom medical treatment has failed." 2) "However, treatment with TIPS resulted in excellent long-term survival." 3) "In conclusion, in experienced hands, TIPS is an extremely useful therapy for most BCS patients in whom medical treatment or recanalization fails. It may improve survival and should therefore be considered the treatment of choice."

The survival rate of surgical portosystemic shunt in our series is shown in Table 77.7. In patients with acute and subacute BCS resulting from occlusion of the hepatic veins, operative mortality after SSPCS has been 3%, and 5-year survival has been 97%. In patients with BCS secondary to IVC occlusion treated by combined SSPCS and CAS, the 5-year survival has been 100%. All of the patients have been relieved of the symptoms of BCS, and readmission to the hospital has been infrequently necessary. These results are superior to the best reported results of TIPS in comparable patients. Without doubt, the long-term health care costs of TIPS are substantially higher than the costs of surgical therapy.

Liver Transplantation

LT (see Chapter 97) is a radical, drastic treatment for BCS, but it is effective when a patient's life is at stake, and no other form of therapy would work. LT is not in competition with SSPCS or any other type of treatment. It is useful in far advanced, decompensated liver disease, when it is too late to accomplish survival with portal decompression procedures.

It is imperative that the indications for the use of LT in BCS be established and clearly understood. The indications that we adhere to are as follows:

1. Cirrhosis with progressive liver failure that has reached the point of permitting a reasonable prediction that the patient will die within 1 year—the most common indication for LT and, incidentally, it is the same one used widely in other liver diseases (Scharschmidt, 1984; Schenker, 1984)
2. Failure of a portosystemic shunt or TIPS, usually because of thrombosis, with persistence or recurrence of symptoms and signs of BCS
3. BCS with unshuntable portal hypertension secondary to thrombosis of the PV, splenic vein, and much of the superior mesenteric vein—a rare indication that applies if patent blood vessels are available to vascularize the liver allograft
4. Acute fulminant hepatic failure—a rare indication and one that we have not encountered

Using these indications, 12 of our patients have been approved and listed for LT. Their characteristics are shown in Table 77.10. In 10 of the 12 patients, an underlying thrombogenic hematologic disorder was identified. The time lapse from clinical onset of BCS to LT was much longer than in our patients who were treated by SSPCS, ranging from 11 to 21 months and averaging 15.9 months. These patients had a chronic form of BCS. The indication for LT was cirrhosis with progressive liver failure in 11 patients whose severe hepatic decompensation precluded consideration of SSPCS, and thrombosis of a PCS with recurrence of clinical manifestations of BCS was the indication in one patient. In 11 of our patients, thrombosis was confined to the hepatic veins, and in one patient, the hepatic veins and suprahepatic IVC were occluded. All but one patient, the one with an occluded PCS, had a patent PV.

Table 77.11 shows the clinical findings in our 12 patients. All patients had massive ascites, jaundice, severe muscle wasting, hepatomegaly, splenomegaly, and dilated collateral veins on the abdominal wall. Encephalopathy had occurred in 50%, and one or more episodes of bleeding varices had occurred in 58%. All patients had cirrhosis on preoperative liver biopsy and in the recipient liver removed at LT. This was a group with advanced,

Table 77.10

Characteristics of 12 Patients Approved and Listed for Liver Transplantation for Budd-Chiari Syndrome

Age (Years)	
Mean	31
Range	25 to 37
Female/male	7/5
Predisposing Condition	
Polycythemia rubra vera	6
Oral contraceptives	2
Protein C deficiency	1
Antithrombin III deficiency	1
Unknown	2
Onset of BCS to Liver Transplant (Months)	
Mean	15.9
Range	11 to 21
Indication for Liver Transplant	
Cirrhosis with liver failure	11
Failed portacaval shunt	1
Thrombosed hepatic veins	12
Patent inferior vena cava	11
Patent portal vein	11

BCS, Budd-Chiari syndrome

decompensated liver disease. All of them were Child-Turcotte-Pugh (CTP) class C (Child & Turcotte, 1964) determined by the quantitative scoring method of Campbell and colleagues (1973).

Table 77.12 shows the results of preoperative liver function tests. Serum bilirubin was substantially elevated, and serum albumin was markedly depressed in every patient. Prothrombin activity was invariably low, resulting in a mean international normalized ratio of 2.0. Aspartate aminotransferase and serum alkaline phosphatase were significantly elevated. Liver function test results were highly abnormal and reflected serious hepatic failure.

Table 77.11

Preoperative Clinical Findings in 12 Patients Approved and Listed for Liver Transplantation for Budd-Chiari Syndrome

Finding	%
Ascites (3.8 to 7.2 L)	100
Jaundice	100
Severe wasting	100
Encephalopathy	50
Bleeding varices	58
Hepatomegaly	100
Splenomegaly	100
Dilated abdominal veins	100
Cirrhosis on biopsy	100
Child-Turcotte-Pugh class C	100

Table 77.12

Preoperative Liver Function Tests in 12 Patients Approved and Listed for Liver Transplantation for Budd-Chiari Syndrome

Liver Function Test	Mean	Range
Serum total bilirubin (mg/dL)	6.0	5.1-6.8
Serum albumin (g/dL)	2.1	1.8-2.8
International normalized ratio	2.0	1.7-2.3
Aspartate aminostransferase (IU)	150	122-185
Serum alkaline phosphatase (IU)	233	198-282

Table 77.13 shows the survival rate of the 12 patients who were approved and listed for LT. Three patients died of liver failure while awaiting LT during periods of 4 to 10 months. Two patients died during the immediate period after LT, one from relentless graft rejection and one from sepsis with multisystem organ failure. A third patient died 9 months postoperatively of liver failure, but no patients were lost after the first year. The 1- and 5-year survival rates were 50%. If the three patients who died before LT could be accomplished are excluded, the actual 1-year and 5-year survival rates of the patients who underwent LT are 67%. The 5-year survival rate is comparable to the reported survival rate of LT in CTP class C patients who do not have BCS.

The six long-term survivors of LT have been followed up for more than 5 years and have had a life of good quality (see Table 77.13). Five are working full time, and BCS has not recurred in any. All survivors were placed on anticoagulant therapy postoperatively and are receiving lifelong maintenance warfarin and aspirin treatment.

Table 77.13

Long-Term Results of Liver Transplantation for Budd-Chiari Syndrome in 12 Patients Approved and Listed for Orthotopic Liver Transplantation

Survival	%
Operative mortality rate (n = 2/9)	22
One-year mortality rate (n = 6/12)	50
Five-year survival (n = 6/12)	50
Five-year survival of patients transplanted (n = 6/9)	67
Causes of Six Deaths	
Rejection (25 days; n = 1)	
Sepsis (30 days; n = 1)	
Liver failure (9 months; n = 1)	
Liver failure awaiting OLT (4 to 10 mo, n = 3)	
Quality of Life in Six Survivors of OLT	
Ascites (n = 2)	33
Need for diuretics (n = 2)	33
Normal liver function tests (n = 5)	83
Encephalopathy (n = 2)	33
Working full time (n = 5)	83
Recurrent BCS	0
Receiving anticoagulants (n = 6)	100

BCS, Budd-Chiari syndrome; OLT, orthotopic liver transplantation

Experience with Liver Transplantation in Budd-Chiari Syndrome Reported in the Literature

To date, the English literature contains reports of more than 1000 patients with BCS who have undergone LT, and Table 77.14 summarizes these reports. The largest number of case reports have come from reviews of 248 patients registered in the European Liver Transplantation Registry and 510 patients registered in the United Network for Organ Sharing (UNOS) Liver Standard Transplant Analysis and Research files. All of the reports were based on retrospective reviews of medical records. No prospective studies of LT in BCS have been done.

As shown in Table 77.14, the indications for LT varied greatly, and it cannot be said that LT was done in patients who had 1 year or less to live because of cirrhosis with progressive liver failure. In several series (Jamieson et al, 1991; Melear et al, 2002; Ringe et al, 1995; Segev et al, 2007), the indications were not clearly stated. Ulrich and colleagues (2008) reported 12% of the 39 patients were CTP class A, and 57% were class B, obviously not in liver failure. The report of Halff and colleagues (1990) stated, "The decrease in synthetic function was not as severe as in many other causes of end-stage liver disease." Every series had some patients who underwent LT because of a failed portosystemic shunt. In the registry review of Mentha and associates (2006), 49 of the 248 patients had failure of a portosystemic shunt (Campbell et al, 1988; Krom et al, 1984).

Table 77.15 shows the survival statistics in the reported series. All of the studies suffer from the fact that follow-up of many of the patients was short, sometimes less than 1 year. A substantial variation in patient selection was apparent from one series to the next, particularly with regard to severity of liver disease, so that they cannot be compared with each other. The early mortality rate in series that had 10 or more patients ranged from 5% to 36% and averaged 15%. The 5-year survival rate, when it was reported, ranged from 45% to 95% and averaged 71%. Segev and colleagues (2007) in their UNOS registry review reported that since introduction in 2002 of the Model for End-Stage Liver Disease (MELD) scoring system for organ allocation by disease severity, 3-year patient survival has increased from 72.6% to 84.9%, and 3-year graft survival has increased from 64.5% to 80.6%.

Most of the series did not report the results of pathologic examination of the liver removed from the patient with BCS. The reports of Ringe and colleagues (1995) on 43 patients, Halff and colleagues (1990) on 32 patients, Sakai and Wall (1991, 1994) on 11 patients, and Srinivasan and associates (2002) on 19 patients described the findings in the host liver, however, and confirmed the clinical impression that many patients underwent LT without having decompensated liver disease. Only 17 of the 43 patients of Ringe and colleagues (1995) had cirrhosis; the others had congestion alone (14 patients) and fibrosis alone, lesions that are found in the early stages of BCS. Similarly, in the report of Halff and colleagues (1990), none of the 32 patients had cirrhosis, and Sakai and Wall (1994) reported that 3 of 11 of their patients had central congestion and necrosis but no fibrosis or cirrhosis.

An important concern about LT in BCS is recurrence of BCS in the transplanted liver (Bahr et al, 2003; Goldstein et al, 1991). Table 77.16 shows the incidence of recurrent BCS in the liver allograft. Some investigators reported no recurrence of BCS, whereas others (Knoop et al, 1994a, 1994b; Halff et al, 1990; Cruz et al, 2005) reported substantial recurrence rates of

Table 77.14

Indications for Liver Transplantation in 15 Retrospective Series of Budd-Chiari Syndrome Reported in the Literature

Reference	N	Indications for OLT
Srinivasan et al, 2002	19	Failed shunt, 5
		Acute liver failure, 6
		Chronic liver failure, 8
Melear et al, 2002	17	Not stated
Hemming et al, 1996	10	Failed shunt, 3
		Advanced cirrhosis, 4
		IVC obstruction, 2
Ringe et al, 1995	43	Unclear, 39
		Failed shunt, 4
Knoop et al, 1994a, 1994b	8	Child class C, 5
		Child class B, 3
Galati et al, 1993	32	Failed shunt, 2
		Cirrhosis–?
		Hepatic necrosis–?
Shaked et al, 1992	14	Failed shunt, 2
		Advanced cirrhosis, 4
		Poor synthetic function, 8
Halff et al, 1990; Iwatsuki et al, 1991	32	Failed shunt, 5
		Intractable ascites, 17
		Recurrent variceal bleeding, 14
		Encephalopathy, 15
Sakai & Wall, 1994	11	Chronic BCS, 5
		Acute fulminant BCS, 3
		Failed shunt, 3
Jamieson et al, 1991	26	Failed shunt, 2
		Unclear, 24
Ulrich et al, 2008	42	Cirrhosis, 11
		Portal vein occlusion, 10
		Hepatic necrosis, 12
		Severe acute liver failure, 8
		Hepatocellular carcinoma, 3
		Hepatic artery occlusion, 2
Cruz et al, 2005	11	Failed TIPS, 5
		Failed PSS, 1
		Intractable ascites, 1
		Portal-systemic encephalopathy, 3
Plessier et al, 2006	11	Failed therapy with anti-coagulation and TIPS, 11
Mehta et al, 2006	248	Fulminant hepatic failure, 47
European Liver Transplantation Registry, 1988-1999		Renal failure, 40 Portal vein thrombosis, 47
		Failed PSS, 49
		Failed TIPS, 11
		Failed percutaneous angioplasty, 18
Segev et al, 2007 (UNOS Registry, 1987-2006)	510	Not reported

BCS, Budd-Chiari syndrome; IVC, inferior vena cava; OLT, orthotopic liver transplantation; PSS, portosystemic shunt; TIPS, transjugular intrahepatic portosystemic shunting; UNOS, United Network for Organ Sharing.

Table 77.15

Survival After Liver Transplantation for Budd-Chiari Syndrome Reported in the Literature

Reference	N	Follow-up (mo)	Early Mortality (%)	Survival ≥1 Year (%)
Srinivasan et al, 2002	19	1 to 119	5	1 to 119 mo (84) 1 y (95) 5 y (95) 10 y (78)
Melear et al, 2002	17	1 to 158	6	1 to 158 mo (88) 1, 5, and 10 y: NR
Hemming et al, 1996	10	?	10	1 y (82) 5 y (67)
Ringe et al, 1995	43	2 to 137	30	1 y (69) 5 y (69)
Knoop et al, 1994a, 1994b	8	4 to 59	13	1 y (88), > 1 y: NR
Galati et al, 1993	9	2 to 60	0	2 to 60 mo (100)
Shaked et al, 1992	14	2 to 60	14	1 y (86) 3 y (76)
Halff et al, 1990 Iwatsuki et al, 1991	32	12 to 132	25	1 y (69) 5 y (45)
Sakai & Wall, 1994	11	12 to 72	36	1 to 6 y (64)
Jamieson et al, 1991	26	12 to 60	31	1 y (69) 5 y (50)
Ulrich et al, 2008	42	1 to 203 (median 96)	7	1 y (92) 5 y (89) 10 y (83.5)
Cruz et al, 2005	11	1 to 132	18	1 y (81) 5 y (65) 10 y (65)
Plessier et al, 2006	11	17 to 56	9	1 y (91) 3 y (91)
Mentha et al, 2006	248	Long-term via registry (mean, 48 months)	13	1 y (76) 5 y (71) 10 y (68)
Segev et al, 2007	510	Long-term via registry	15	1 y (82) 3 y (76)

NR, not reported

Table 77.16

Reported Rates of Recurrence of Budd-Chiari Syndrome and Other Thrombosis After Liver Transplantation for Budd-Chiari Syndrome

		RECURRENCE		OTHER THROMBOSIS	
Reference	N	n	%	n	%
Srinivasan et al, 2002	19	2	11	2	11
Melear et al, 2002	17	0	0	3	18
Ringe et al, 1995	43	0	0	10	23
Hemming et al, 1996	10	0	0	1	14
Knoop et al, 1994a, 1994b	8	1	13	1	13
Shaked et al, 1992	14	0	0	NR	NR
Halff et al, 1990	23	3/18	17	4	22
Sakai & Wall, 1994	11	0	0	1	9
Jamieson et al, 1991	26	2	8	5	19
Ulrich et al, 2008	42	3	7	5	12
Cruz et al, 2005	11	3	27	3	27
Plessier et al, 2006	11	1	9	4	36
Mentha et al, 2006	248	5	2	35	14
Segev et al, 2007	510	7	8	36	40

NR, not reported

13% to 27% despite treatment with anticoagulants. Most series have shown a substantial incidence of posttransplant thrombosis in other splanchnic blood vessels, particularly in the PV (range, 9% to 40%), often with disastrous consequences. The frequent development of thrombosis makes it mandatory that patients receive early and lifelong anticoagulation therapy after LT. At the same time, it should be recognized that anticoagulation sometimes fails to prevent thrombosis.

One of the potential benefits of LT in certain thrombogenic disorders, such as antithrombin III deficiency and protein-C deficiency, is correction of the underlying defect by transplantation of a liver from a normal donor. It has been suggested that LT is preferable to SSPCS in the treatment of BCS, because if SSPCS fails, the risk of performing subsequent LT is increased. It has been proposed that mesocaval shunt is preferable to SSPCS, because it is advantageous to avoid dissection of the hepatic hilum, should subsequent LT be required (McMaster, 1994; Bismuth & Sherlock, 1991; Slakey et al, 2001). In our experience, patients with BCS treated by SSPCS infrequently require LT. Of 57 patients with BCS whom we treated by SSPCS, only 1 (2%) subsequently required LT during long-term follow-up. In our experience with more than 2500 PCS procedures in patients with cirrhosis, the long-term shunt patency rate has been 99.5%.

Additionally, at least 10 more recent studies have shown that previous portosystemic shunt, regardless of type, had no influence on the outcome of LT (Aboujaoude et al, 1991; Bismuth et al, 1990; Boillot et al, 1991; Iwatsuki et al, 1988; Langnas et al, 1992; Mazzaferro et al, 1990; Minegaux et al, 1994; Turrion et al, 1991). Aboujaoude and colleagues (1991) emphasized that thrombosis of a portosystemic shunt may seriously compromise performance of LT; long-term shunt patency should therefore be the main factor that determines the type of shunt selected for the potential LT candidate, a point that is all the more true in patients with BCS. Direct PCS has had a thrombosis rate of 0.5% or less in all of our studies, compared with occlusion rates of 24% to 53% reported in the literature for mesocaval interposition shunts using synthetic grafts (Fletcher et al, 1981; Hemming et al, 1996; Smith et al, 1980; Terpstra et al, 1987). Mesocaval interposition shunts using autologous internal jugular vein grafts, which have been used widely in France, have shown patency rates comparable to direct SSPCS (Bismuth & Sherlock, 1991; Gentil-Kocher et al, 1988; Vons et al, 1986).

A second important indication for LT is failure of a portosystemic shunt, usually because of thrombosis, with persistence or recurrence of clinical manifestations of BCS. In experienced hands, and with the routine, long-term use of anticoagulation therapy after portosystemic shunt, this should be a rare indication—but the literature indicates that such is not the case.

The third and fourth indications for orthotopic liver transplantation (OLT) in BCS are rare, and we have not encountered such cases, although they have been reported without many details in the literature. These are unshuntable patients with portal hypertension resulting from thrombosis of the portal venous system, provided that there are patent blood vessels available to vascularize the liver allograft, and acute fulminant hepatic failure (Sakai & Wall, 1994).

It is important to emphasize that SSPCS and LT are not competing forms of treatment. SSPCS is the appropriate treatment in the early and middle stages of BCS, when portal decompression would sustain life by reversing or stabilizing the liver disease. OLT is the appropriate treatment in the late stages of BCS, when the liver disease is no longer reversible, and when stabilization of progressive hepatic decompensation is impossible. Most patients who are candidates for LT should be in CTP class C.

In considering treatment of BCS by LT, it is important to take into account the downside of such therapy, namely 1) insufficient donor livers to treat the many patients who need LT; 2) long periods on the waiting list during which, as was true in our patients, more than one third of the patients die; 3) the unpredictable availability of donor organs; 4) the need for and consequences of lifelong immunosuppression; and 5) the high cost of LT, which our data show is almost five times the cost of portosystemic shunt.

Surgical Removal of Venous Obstruction

Senning (1981, 1983) reported a direct method of removing obstruction of the IVC and hepatic veins in patients with chronic BCS. The operation is performed with cardiopulmonary bypass and involves opening the suprahepatic IVC and right atrium, removing any vena caval thrombus, resecting the dorsocranial part of the liver containing the confluence of the occluded major hepatic veins, and reconstructing the hepatic outflow tract by suturing the right atrium to the liver capsule. Since his initial description, Senning (1987) and others (Pasic et al, 1993) have reported the results of the operation in 17 patients, 2 of whom (12%) died within 2 weeks of operation and 4 of whom died later. Actuarial 1-year and 3-year survival rates were 76% and 57%, LT was required for 2 patients, and 3 developed recurrent thrombosis. During follow-up of 7 months to 11 years, 10 (67%) of the 15 early survivors had prolonged relief of BCS.

Kawashima and colleagues (1991) reported success of the Senning operation in 5 of 7 patients during follow-up of 2 months to 5 years, and Nakao and colleagues (1988) described success in 2 patients followed up for 1 to 2 months. In a modification of the operation, Koja and associates (Koja et al, 1996; Kuniyoshi et al, 1998) described direct removal of the IVC obstruction under partial cardiopulmonary bypass in 32 patients with chronic BCS resulting from IVC obstruction of 1 to 42 years' duration. Koja and associates (Koja et al, 1996; Kuniyoshi et al, 1998) reopened the IVC and occluded hepatic veins under direct vision without resecting the liver and reconstructed the hepatic outflow tract with a patch graft of autologous pericardium. Many of the patients had cirrhosis or severe fibrosis of the liver, and 29 of the 32 had esophageal varices. No operative deaths were reported. During 1.5 to 17 years of follow-up, there were four late deaths, and seven patients developed hepatocellular carcinoma. Survival rates at 5 and 10 years were 93.6% and 81%. In a follow-up to their earlier report, in 2009 Kuniyoshi and colleagues (Inafuku et al, 2009) reported their results from 1979 to 2008 in 53 patients. Overall mortality rate was 32%, and 14% of survivors developed total obstruction or severe stenosis of the reconstructed IVC, therefore it does not appear that radical open-end venectomy is the first-choice operation for IVC occlusion.

Percutaneous Transluminal Angioplasty

Use of percutaneous transluminal angioplasty has been reported in more than 300 patients with BCS (Anonymous, 1982; Baijal et al, 1996; Furui et al, 1990; Griffith et al, 1996; Jeans et al,

1983; Martin et al, 1990; Sato et al, 1990; Tyagi et al, 1996; Wu et al, 2002; Xu et al, 1996; Yamada et al, 1983, 1991; Yang et al, 1996; Li et al, 2009). Most of the patients had chronic liver disease of long duration, and many of them had obstruction of the IVC of the membranous or segmental types. The obstructed vein was dilated with one or more balloon catheters. In all cases, the pressure gradient that existed before balloon dilation was substantially reduced or eliminated at the time of dilation. Stenosis often recurred, however, and required repeated balloon dilations. Most of the patients have not had long-term follow-up, so it is difficult to evaluate the ultimate effectiveness of percutaneous transluminal angioplasty. Of the few patients who have been observed for several years, the long-term success rate is less than 50% (Griffith et al, 1996; Martin et al, 1990; Sato et al, 1990; Yamada et al, 1991), although Wu and associates (2002) reported restenosis in only one of 41 patients during follow-up of 32 (± 12) months.

The use of expandable metallic stents has been added to balloon angioplasty in an attempt to maintain prolonged patency of the IVC (Baijal et al, 1996; Furui et al, 1990; Sawada et al, 1991; Xu et al, 1996, 1999; Li et al, 2009). The follow-up period of the patients who have IVC stents is too short to evaluate the efficacy of this procedure. In our opinion, based on the available evidence, percutaneous transluminal angioplasty and placement of expandable metallic stents warrant consideration only in patients with chronic BCS resulting from stenosis of the IVC. Patients treated by transluminal angioplasty should have careful follow-up that includes venography and pressure measurements every few months to detect recurrent stenosis of the IVC.

Thoracic Transposition of the Spleen

Transposition of the spleen into the left pleural cavity to create collateral venous connections between portal and pulmonary systems has been used sporadically in the treatment of portal hypertension and, in addition, has been advocated for treatment of BCS secondary to occlusion of the IVC (Akita & Sakoda, 1980; Khuroo & Datta, 1980; Schrieber & Gonzalez, 1967; Strauch, 1970). The procedure involves displacing the spleen into an opening in the left diaphragm and suturing the left lower lobe of the lung to the spleen after removing the splenic capsule and abrading the surface of the lung. It is impossible to evaluate the effectiveness of this procedure because of the paucity of information in the few case reports. Akita and Sakoda (1980) of Japan reported the use of "splenopneumopexy" in 15 patients who had diseases that they called BCS. Although few details were given, it seems that most or all of the Japanese patients had a chronic disorder that consisted of cirrhosis and esophageal varices in addition to IVC obstruction. It is possible that many of the patients had the typical MOVC that accounts for most of the cases of BCS in Japan. Portal hypertension, determined by splenic pulp pressure measurements, persisted after splenopneumopexy in all patients. It is doubtful that thoracic transposition of the spleen can decompress the liver and portal system sufficiently to prevent or reverse liver damage in the crucial early stages of BCS caused by occlusion of the IVC.

Peritoneovenous Shunt

Peritoneovenous shunt is a device that relieves ascites by transferring fluid through a one-way valve from the peritoneal cavity into the superior vena cava. It has been advocated as primary treatment for BCS by LeVeen and colleagues (LeVeen et al, 1976). The peritoneovenous shunt may be useful as a palliative measure in patients in whom portal decompression is not feasible or has been tried and failed. The peritoneovenous shunt is not indicated as the primary treatment of most patients with BCS, however, because it does not decompress the obstructed hepatic vascular bed, and it has no effect on the ongoing liver damage. Use of this device early in the course of BCS may squander the opportunity to reverse the liver damage by therapy that effectively decompresses the liver. Long-term studies of peritoneovenous shunting in patients with BCS have not been reported, probably because most patients in whom this device has been used have died from their underlying disease. There is predictable evidence, however, that the liver disease progresses to cirrhosis in the face of a functioning peritoneovenous shunt (Cameron et al, 1983).

SURGICAL TREATMENT OF MEMBRANOUS OBSTRUCTION OF THE VENA CAVA

Patients with MOVC described in the literature by and large have had a chronic disorder that has progressed to cirrhosis and portal hypertension by the time they came to medical attention. The lesion causing IVC obstruction has varied from a thin membrane located in the suprahepatic IVC to an extensive area of stenosis involving the retrohepatic IVC. Japanese surgeons have reported the largest experience with the treatment of MOVC.

When the area of IVC obstruction is short and is located at or above the level of the hepatic vein orifices, two treatment options are available: *percutaneous transluminal angioplasty* and *transcardiac membranotomy*. Reported experience with percutaneous transluminal angioplasty in MOVC has been small, and the recurrence rate of IVC stenosis or thrombosis has been high (Eguchi, 1974; Griffith et al, 1996; Hirooka & Kimura, 1970; Iwahashi, 1981; Sato et al, 1990; Sharma et al, 1992; Tyagi et al, 1996; Yamada et al, 1991; Yang et al, 1996). Long-term IVC patency has been less than 0%. Transcardiac membranotomy has been the most frequently used treatment of MOVC when the membrane is thin. The technique involves fracture of the membrane by the finger or a dilator inserted through the right atrial appendage (Fig. 77.22). More than 125 cases have been described in the literature, with a successful outcome in 70% to 90% during periods of follow-up that ranged from 2 months to 7 years but generally were brief (Espana et al, 1980; Hirooka & Kimura, 1970; Iwahashi, 1981; Kimura et al, 1972; Okamoto et al, 1983; Semson, 1982; Suchato et al, 1976; Takeuchi et al, 1971; Taneja et al, 1979; Wang, 1989; Wu et al, 1990; Yamamoto et al, 1968).

When more than a thin membrane causes obstruction of the IVC, and particularly when a long area of stenosis involves the retrohepatic IVC, the treatment options are different and consist mainly of direct excision and repair of the involved area of IVC (endovenotomy) or a cavoatrial bypass graft. A direct attack on the lesion generally has involved excising the obstructing tissue in the lumen of the IVC and repairing the vein with a synthetic or pericardial patch graft. Twelve such attempts have been described in the literature, with success in five patients and failure in seven, four of whom died (Hirooka & Kimura, 1970; Iwahashi, 1981; Kimura et al, 1972). Koja and colleagues (Koja et al, 1996; Kuniyoshi et al, 1998) reported

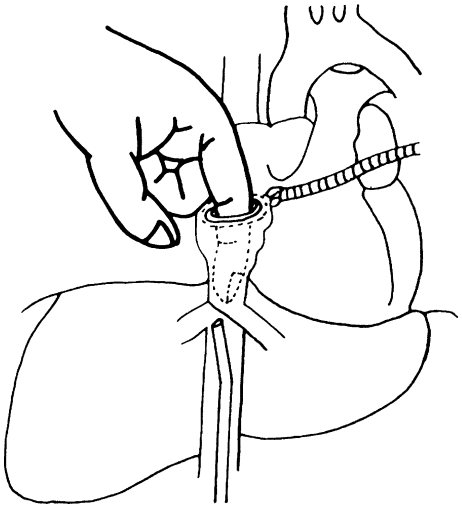


FIGURE 77.22. Technique of transcardiac membranotomy. *(From Iwahashi K, 1981: Surgical correction of the inferior vena cava obstruction with Budd-Chiari syndrome. Arch Jpn Chir 50:559-570.)*

direct removal of the IVC obstruction under partial cardiopulmonary bypass in 32 patients with impressive results, although the reported periods of follow-up were short.

Use of a cavoatrial bypass graft has been reported in 11 patients who had a long segment of IVC stenosis. The procedure succeeded during short periods of follow-up in three patients and failed in eight, four of whom died (Eguchi et al, 1974; Hirooka & Kimura, 1970; Ohara et al, 1963; Reichart et al, 1981; Yamamoto et al, 1968). When the IVC obstruction involves or extends below the orifices of the hepatic veins, cavoatrial bypass does not decompress the liver. Under such circumstances, consideration should be given to adding SSPCS to the cavoatrial bypass. The combined procedure of IVC and portal decompression has not been reported in MOVC.

Finally, patients with MOVC have undergone a variety of operations designed to create portosystemic or portopulmonary collateral venous connections. Included among these are omentosternopexy, hepatopneumopexy, splenopneumopexy, omentonephropexy, ileal stripping, and the Talma operation (Hirooka & Kimura, 1970; Ono et al, 1983; Yamamoto et al, 1968). It is difficult to evaluate the efficacy of these procedures, because insufficient information has been presented in the case reports. We doubt that these procedures are capable of relieving the high pressures in the IVC and portal venous system or of influencing the course of MOVC.

TREATMENT OF VENOOCCLUSIVE DISEASE

Substantial experience has been reported with treatment of patients with VOD caused by pyrrolizidine alkaloids (Bras & McLean, 1963; Ghanem & Hershko, 1981; Gore et al, 1961; Stuart & Bras, 1957). If such patients are seen during the acute stage of VOD, the initial treatment consists of withdrawal of the causative agent and measures to support the damaged liver. About one fourth of patients recover from the acute phase with supportive medical therapy, approximately one fifth die of liver failure or bleeding esophageal varices, and the remainder develop a chronic condition that waxes and wanes as cirrhosis of the liver evolves. SSPCS is indicated during the acute phase in patients who bleed from esophageal varices and in patients who, within 4 to 8 weeks of onset, show no signs of recovery, such as disappearance of ascites, improvement in liver function, and improvement in the lesions seen on percutaneous needle biopsy of the liver. Serial liver biopsy specimens are helpful in assessing the course of the disease.

Patients who are seen during the chronic phase of VOD have the usual manifestations of cirrhosis. The mortality rate of these patients is high, and the major cause of death is bleeding esophageal varices. Gore and colleagues (1961), who accumulated an extensive experience with VOD in Jamaica, recommended PCS when varices develop in the chronic phase, even if no bleeding has occurred. The added advantage of PCS is that it decompresses the obstructed hepatic vascular bed, which might facilitate regeneration of the liver. No sizable series of patients with VOD who were treated by PCS has been reported.

During the past decade there has been a marked increase in the use of bone marrow transplantation and a corresponding increase in the frequency of VOD. This increase has given rise to numerous trials of various interventions aimed at preventing and at treating VOD. In mild forms of VOD, spontaneous recovery is reported in 70% to 85% of patients (Senzolo et al, 2007). However, severe forms do not resolve without treatment (Schlegel et al, 1998).

Agents studied in prophylaxis of VOD include defibrotide, ursodeoxycholic acid (UDCA), tissue plasminogen activator (tPA), antithrombin III (ATIII), prostaglandin E_1 (PGE1), and anticoagulation with low-dose heparin (Senzolo et al, 2007; Ho et al, 2008). Of these, the most promising is defibrotide. In five retrospectively controlled studies of VOD prophylaxis, the incidence and severity of VOD was reduced by defibrotide (Versluys et al, 2004; Chalandon et al, 2004; Dignan et al, 2007; Corbacioglu et al, 2006; Qureshi et al, 2008).

Prophylactic administration of ursodeoxycholic acid (UDCA), an antioxidant and antioptatic agent, has been evaluated in six randomized trials. In five of the trials, UDCA showed a significant benefit, with reductions in both the incidence of VOD and mortality (Tay et al, 2007; Essell et al, 1998; Ohashi et al, 2000; Park et al, 2002; Giles et al, 2002; Ruutu et al, 2002).

Because microthromboses and fibrin deposition in hepatic central veins are hallmark features of VOD, investigational efforts have focused on the use of systemic anticoagulants and potent thrombolytics. Several reports have described series of patients in which tPA was used to prevent VOD (Bearman et al, 1997; Leahey et al, 1996; Hagglund et al, 1995; Yu et al, 1994; Schriber et al, 1999; Kulkarni et al, 1999; Kumar et al, 2003; Wadleigh et al, 2003). In the largest of these studies involving 42 patients treated with tPA and unfractionated heparin (Bearman et al, 1997), 12 (29%) had clinical improvement with at least a 50% reduction in pretreatment bilirubin. However, overall survival was poor, and no patients with multiorgan failure (MOF) responded. Furthermore, 10 patients (24%) developed severe bleeding attributable to tPA, and this proved fatal in a significant number. Based on these results, investigators have concluded that tPA with or without heparin should not be administered in VOD patients.

A number of trials and case studies have evaluated the use of ATIII in prophylaxis of VOD, based on findings that ATIII confers a protective effect on vascular endothelium, and ATIII levels are decreased in patients with VOD (Morris et al, 1997; Mertens et al, 1999; Ibrahim et al, 2004). However, a recent pediatric trial in which 91 children received preemptive ATIII replacement demonstrated that ATIII did not reduce the

incidence of VOD compared with a control group of 71 children (Haussmann et al, 2006).

PGE1 is a vasodilator with a cytoprotective effect on endothelium. It is also an inhibitor of platelet aggregation with prothrombolytic activity. Unfortunately, a large prophylactic trial of PGE1 was complicated by excessive toxicity and no benefit (Bearman et al, 1993).

Anticoagulation with low-dose heparin by continuous infusion, alone or in combination with other agents, has been evaluated as VOD prophylaxis in at least 12 studies. In a review of these studies, Imran and colleagues (2006) found no statistically significant benefit of anticoagulation. Moreover, an increased risk of hemorrhage was reported with low-dose heparin (Attal et al, 1992; Bearman et al, 1990; Marsa-Vila et al, 1991). Low molecular weight heparins seem to be relatively safe and may have some effect in the prevention of VOD, but well-designed, multicenter randomized studies are needed to confirm these preliminary results (Or et al, 1996; Simon et al, 2001; Park et al, 2002; Forrest et al, 2003).

Agents studied in the treatment of established VOD include defibrotide, tPA, ATIII, and methylprednisolone. Of these, defibrotide has been subject to the most extensive investigation. In six studies of defibrotide treatment of patients with established VOD, all or most of them high risk with multiorgan failure, 36% to 76% had complete remission of VOD (Richardson et al, 1998, 2002; Bulley et al, 2007; Chopra et al, 2000; Richardson et al, 2006; Corbacioglu et al, 2004). Encouraging responses to defibrotide have been found in children as well as in adults (Corbacioglu et al, 2004). Additionally, defibrotide was found to be effective in VOD following liver transplantation (Mor et al, 2001), although extensive studies of this serious problem have not been done.

Use of tPA in treatment of VOD has been evaluated in about 130 patients (Senzolo et al, 2007; Vaughan et al, 1989). The response rate has been about 30% in the largest series (Bearman et al, 1997); however, no response was seen in patients with renal, respiratory, or multiorgan failure. Moreover, 24% developed severe bleeding. Thus administration of profibrinolytics and anticoagulants should be avoided in these patients but conversely should be given early in the course of VOD.

Several studies of ATIII in treatment of VOD have been reported. In a retrospective review of the largest series, which involved 48 patients, Peres and colleagues (2008) observed that ATIII failed to reduce the incidence rate of VOD but seemed to be beneficial in mild to moderate VOD and especially in severe VOD. These results were similar to those of Haussman and colleagues (2006) in pediatric patients.

A single study of methylprednisolone treatment of VOD was reported recently (Al Beihany et al, 2008) with results suggesting a therapeutic benefit. However, prospective comparative studies are needed to warrant use of this agent.

Transjugular intrahepatic portosystemic shunting (TIPS) has been used in a small number of patients with VOD. Senzolo and colleagues (2007) summarized the results of TIPS in 27 patients with generally severe VOD, 24 of them following bone marrow transplantation. All but three of the bone marrow transplant patients died. Available data suggest that although portal hypertension and ascites improve after TIPS, long-term efficacy and overall survival remain poor (Senzolo et al, 2005, 2006; Smith et al, 1996; Alvarez et al, 2000; Fried et al, 1996; Azoulay et al, 2000; de la Robia et al, 1996).

Because of the high mortality rate of severe VOD after bone marrow transplantation, LT warrants consideration. Experience with LT in severe VOD is limited, with case reports in the literature on 12 patients (Membreno et al, 2008; Bunin et al, 1996; Hagglund et al, 1996; Nimer et al, 1990; Rapoport et al, 1991; Salat et al, 1997b; Schlitt et al, 1995), and 5 of the 12 were long-term survivors. The problems associated with use of LT, not unique to VOD, include predicting which patients will not survive despite other forms of treatment; the timing of the LT operation, before multiorgan failure is so severe that survival is not possible; and obtaining a suitable liver graft. One fourth of patients with VOD develop the severe form of the disease. The causes of death in severe VOD are hepatic failure, renal failure secondary to hepatorenal syndrome, respiratory failure owing to pulmonary VOD or infection, GI bleeding, sepsis, and congestive heart failure. In the Seattle study of a cohort of 355 patients, the mortality rate of severe VOD was 98% (McDonald et al, 1993).

SSPCS has been used effectively in severe VOD after bone marrow transplantation, but the experience has been limited because of a general reluctance to subject these very ill patients to a major operation despite their almost certain death without effective nonoperative treatment (Murray et al, 1987). Experience is similarly small with the use of TIPS in severe VOD secondary to bone marrow transplantation, and its role remains to be defined. It seems that hematologists have considered TIPS more attractive than a surgical shunt, because it does not involve a major surgical operation.

SUMMARY

More than 8000 cases of BCS caused by occlusion of the major hepatic veins or the IVC or both have been reported, and the condition is being recognized with increasing frequency. Although in many cases of BCS, no etiologic or predisposing condition can be identified, in recent years an underlying disorder has been found in more than 70% of cases. The most common conditions that predispose to BCS are hematologic disorders with thrombotic tendencies, such as polycythemia rubra vera and paroxysmal nocturnal hemoglobinuria (~18% to 30% of cases); use of oral contraceptives (~9% to 28% of cases); pregnancy and the postpartum period (~2% to 10% of cases); malignant neoplasms that invade the IVC and hepatic veins from adjacent organs (~5% to 12% of cases); and infections of the liver, such as amebic abscess, hydatid cyst, and schistosomiasis (~0% to 10% of cases), which are common in the East but rare in the West. Evidence indicates that multiple prothrombotic hematologic factors acting concurrently are involved in many patients with BCS. In Japan, China, India, and South Africa, a common chronic form of BCS is MOVC, an idiopathic condition that probably results from acquired thrombosis and recanalization of the IVC. The membrane has been found to vary from very thin to several centimeters thick and sometimes has occluded a long segment of retrohepatic IVC.

The pathologic lesion of BCS is thrombosis of the major hepatic veins or the IVC or both, which results in hepatic venous outflow obstruction; intrahepatic and portal hypertension; dilation of the liver sinusoids; intense centrilobular congestion of the hepatic parenchyma; and ischemia, pressure necrosis, and atrophy of the parenchymal cells in the center of the liver lobule. Early in the course of BCS, these lesions are reversible, if the obstruction is relieved. Persistence of the high pressure

and congestion within the liver results in irreversible damage, hepatic fibrosis, and progression to cirrhosis, often within a matter of months. The two paramount dangers in BCS are development of irreversible liver damage and extension of thrombosis from the hepatic veins into the IVC. The most striking difference between the East and West in the pathology of BCS is the site of the venous occlusion causing hepatic outflow obstruction: in the East, it is usually in the IVC; in the West, it is most often in the major hepatic veins.

The clinical course of BCS in Western countries is most commonly acute or subacute, with rapid progression of liver disease and its consequences over periods ranging from a few weeks to a few months. In some patients, however, BCS develops insidiously and progresses over months or years. The usual clinical manifestations are abdominal distension secondary to ascites, hepatomegaly, splenomegaly, abdominal pain, weakness, wasting, and anorexia. Some patients additionally have mild jaundice and distension of the superficial veins of the anterior abdominal wall. When the IVC is obstructed, an important additional sign is edema of the lower extremities and lower trunk. In the chronic forms of BCS, all of the manifestations of cirrhosis of the liver are found.

The diagnosis of BCS in the initial weeks and months is based on finding the typical symptoms and signs combined with abnormal results of several diagnostic studies, the most important of which are angiographic examination of the IVC and hepatic veins with pressure measurements and percutaneous transjugular needle liver biopsy. In BCS confined to the hepatic veins, angiographic studies show a patent IVC and relatively normal IVC pressure for patients with ascites, whereas in BCS involving the IVC, cavography shows an area of IVC obstruction, and IVC pressure is markedly elevated. Hepatic venography shows occlusion of the major hepatic veins, and wedge injection shows a distinctive spiderweb pattern of venous collaterals. WHVP is markedly elevated. In BCS confined to the hepatic veins, WHVP is substantially higher than IVC pressure, but in BCS involving IVC obstruction, WHVP is similar to IVC pressure.

Liver biopsy reveals the typical lesions of obstruction to hepatic venous outflow: intense centrilobular congestion and centrilobular loss of parenchyma and necrosis. Other diagnostic studies that may be helpful as screening procedures are 1) CT, which shows absence of opacification of the major hepatic veins; 2) US, which shows absence of normal hepatic veins; and 3) hepatic scintiscanning, which shows decreased and nonhomogeneous hepatic uptake of radiocolloid and sometimes shows central localization of radiocolloid, the so-called central hot spot. Liver function tests invariably show significant hepatic dysfunction. In patients who are operated on for BCS confined to the hepatic veins, the clinical manifestations and results of diagnostic studies are confirmed by the findings of marked ascites; an enlarged, congested liver; splenomegaly; extensive portosystemic collateral veins; IVC pressure that is substantially lower than PV pressure; portal hypertension; and a markedly elevated hepatic occluded portal pressure, which sometimes is higher than the free portal pressure.

Nonsurgical therapy of BCS includes medical treatment with thrombolytic agents, anticoagulants, and diuretics and radiologic therapy consisting of transluminal angioplasty, venous stenting, and TIPS. Infusion of thrombolytic agents, such as streptokinase and urokinase, in hopes of dissolving thrombi in the hepatic veins or IVC or both has had limited short-term success but a high rate of ultimate failure. Anticoagulant therapy to prevent propagation of the thrombi has produced a limited, short-term response when used alone. None of these measures have been effective, and nonoperative medical therapy has been associated with an almost uniformly poor prognosis: most patients in Western countries have died within a few months of onset of symptoms, and the few patients who have survived the acute phase have almost all died from the complications of cirrhosis within a few years. Control of ascites is feasible in some patients with BCS by use of the usual diuretic regimens, although the ascites is resistant to therapy in many patients, and no evidence suggests that control of ascites influences the long-term outcome.

Radiologic therapy consisting of percutaneous transluminal angioplasty with and without the use of metallic stents has had some short-term success in patients with chronic BCS resulting from stenosis of the IVC, but recurrent stenosis has been the rule; the long-term success rate has been less than 50%, although one report from China claimed a high success rate. The TIPS procedure has been used in recent years with increasing frequency for all forms of BCS. The advantage of TIPS is that it does not require a major surgical operation; disadvantages are a high rate of TIPS stenosis and occlusion requiring repeated revisions, frequent recurrence of symptoms, and the need for numerous radiologic procedures and hospitalizations. The incidence of TIPS occlusion has decreased markedly with the introduction of polytetrafluoroethylene-covered stents, but it is still substantial. In the most experienced hands, the 5-year survival rate after TIPS has been well below the 5-year survival rate of surgical shunt therapy in our series (Orloff, 2010).

SSPCS has proved to be the most effective therapy of BCS caused by thrombosis of the hepatic veins. Its use is based on substantial evidence that shows it converts the valveless PV into an outflow tract, decompressing the obstructed hepatic vascular bed. In an experimental evaluation of PCS in dogs with BCS, we found that SSPCS decompressed the liver and cured ascites in 96% of the dogs; reduced the liver to a normal size; reversed the pathologic lesions in the liver, often to normal; and resulted in long-term survival of many of the dogs.

On the basis of these experimental findings, we have performed SSPCS early in the course of disease in 39 unselected patients with acute or subacute BCS confined to the hepatic veins with one operative death and one long-term death. The 37 survivors of operation have lived free of ascites without diuretic therapy for 5 to 38 years (mean follow-up, 15 years). The shunt has remained patent in all but 1 patient. Liver function has returned to normal in the 34 patients who did not already have cirrhosis preoperatively, hepatosplenomegaly has disappeared, and no encephalopathy was reported. Serial liver biopsy specimens obtained for 37 years postoperatively showed substantial reversal of the pathologic lesions of BCS. Our experience shows the importance of performing SSPCS early in the course of BCS to reverse the liver damage and prevent extension of thrombosis from the hepatic veins into the IVC.

Splenorenal shunt, interposition mesocaval shunt, and PCS using synthetic grafts are hemodynamically similar to SSPCS but are inferior operations in BCS because of a high incidence of thrombosis and occlusion. Interposition shunt using an autogenous internal jugular vein H-graft has produced results similar to those of direct SSPCS. Important technical features of SSPCS are proper positioning of the patient, use of a long right subcostal incision, and extensive mobilization of the IVC

and PV so that the two vessels can be brought together. Resection of the caudate lobe of the liver has not been necessary in any of the BCS patients, nor has it been needed in any of the more than 2500 patients in whom we have performed the SSPCS.

SSPCS is contraindicated when BCS is caused by thrombosis or occlusion of the IVC. Under such circumstances, a mesoatrial shunt has been used with some short-term success, although there has been a high incidence of thrombosis of the bypass graft. In our series of eight patients, thrombosis of the mesoatrial shunt developed in five, and the 5-year survival rate was only 38%. Similarly, others have reported thrombosis of the mesoatrial shunt in 40% to 70% of patients, an event that is often followed by death. Because of dissatisfaction with the results of mesoatrial shunt, we worked in the experimental laboratory to devise a shunting procedure aimed at decompressing the hypertensive IVC and shunting the portal venous flow and the entire IVC flow to the right atrium. The new operation, which consists of a combined SSPCS and CAS through a Gore-Tex prosthesis, was found to be effective in relieving BCS in rats and has been successful in each of 18 patients with BCS secondary to IVC occlusion during follow-up of 5 to 25 years. In our program, the combined shunt operation has replaced the mesoatrial shunt as the preferred treatment for BCS caused by IVC occlusion.

LT is indicated in patients with chronic BCS who have cirrhosis with progressive hepatic failure and in patients who have had an unsuccessful portosystemic shunt. In approximately 1043 patients with advanced liver disease secondary to BCS, LT has resulted in a mean actuarial 5-year survival rate of 71%. BCS recurred in 13% to 27% of the liver grafts, and thrombosis of other blood vessels, particularly the PV, occurred in 9% to 40% of patients. In our experience with 12 patients who were approved for LT, 3 died on the waiting list, and the 5-year survival rate of patients who underwent LT was 67%. It is important to note that LT and SSPCS are not competing forms of treatment: LT is appropriate therapy in the late stages of BCS, when the liver disease no longer can be reversed by SSPCS.

Other surgical procedures of uncertain value in BCS are direct surgical removal of the venous obstruction, percutaneous transluminal angioplasty, thoracic transposition of the spleen, and peritoneovenous shunt. The latter two procedures are rarely if ever used today. Direct surgical resection of the occluded hepatic veins and IVC with the aid of cardiopulmonary bypass has produced good short-term results in about 100 patients with chronic BCS involving the IVC, but prolonged and detailed follow-up revealed an overall mortality rate of 32%, obstruction of the IVC in 14%, and development of hepatocellular carcinoma in some patients. The success rate of percutaneous balloon angioplasty has been less than 50%. Peritoneovenous shunt is a palliative procedure that should not be used as primary treatment of BCS, because it does not decompress the liver or influence the ongoing hepatic damage.

Several surgical procedures have been used by Japanese surgeons to treat the chronic form of BCS caused by MOVC. When the area of IVC obstruction has been short, fracture of the membrane by transcardiac membranotomy has been the principal treatment and has had a short-term success rate of 70% to 90% during follow-up periods ranging from 2 months to 7 years. Percutaneous transluminal angioplasty also has had some short-term success, but recurrence of IVC stenosis has been frequent. When the area of IVC obstruction has been long, treatment has consisted of direct excision and repair of the involved area of IVC or cavoatrial bypass graft. Both of these procedures have had some success but have been associated with a substantial incidence of failure and a substantial mortality rate. Finally, patients with MOVC have undergone a variety of operations of uncertain value, all designed to create portosystemic or portopulmonary collateral venous connections.

It is a fact that no treatment has accomplished a survival rate comparable to SSPCS in BCS resulting from thrombosis of the hepatic veins or of combined SSPCS and CAS in BCS resulting from occlusion of the IVC.

VOD, otherwise known as *sinusoidal obstruction syndrome,* is a group of disorders in which hepatic venous outflow obstruction is due to subendothelial sclerosis of the sublobular hepatic veins, terminal hepatic venules, and sinusoids within the liver. VOD is caused by antineoplastic drugs, ingestion of plants containing pyrrolizidine alkaloids, and irradiation of the liver. In the Western Hemisphere, the most frequent cause is bone marrow transplantation. Approximately one fourth of bone marrow transplant recipients develop VOD. Extensive occlusion of the small hepatic veins results in centrilobular hemorrhagic necrosis of the liver parenchyma, which progresses to diffuse fibrosis and cirrhosis. Although it can occur at any age, VOD caused by pyrrolizidine alkaloids has been observed most often in children: after a prodromal febrile illness, acute-onset abdominal distension owing to ascites ensues, along with abdominal pain, hepatosplenomegaly, weakness, and sometimes jaundice and peripheral edema.

The most important symptoms and signs of VOD after bone marrow transplantation are ascites, jaundice, and abdominal pain. Some patients recover from the acute stage of VOD, but approximately one fifth of patients with pyrrolizidine poisoning die; the remainder go on to develop cirrhosis rapidly, with all of its clinical manifestations. The mortality rate of severe VOD after bone marrow transplantation has been reported to be 98%. The most important diagnostic study in VOD is percutaneous needle liver biopsy, which shows the specific abnormality of extensive occlusion of the small hepatic veins within the liver and centrilobular hemorrhagic necrosis. The results of hepatic scintiscanning, liver function tests, and WHVP measurements are similar to results found in BCS, but angiographic studies are not helpful, because the major hepatic veins and IVC are normal in VOD. Elevated WHVP supports the diagnosis of VOD.

Substantial experience with treatment of VOD has been reported in patients who have the disorder as a result of ingestion of pyrrolizidine alkaloids. When such patients are seen in the acute stage, supportive medical therapy is used. SSPCS is indicated during the acute stage if bleeding esophageal varices develop, or if the clinical and liver biopsy signs of hepatic venous outflow obstruction do not subside after 4 to 8 weeks. In the chronic phase of VOD, when the usual manifestations of cirrhosis have developed, SSPCS is recommended even before varix hemorrhage has occurred.

The mortality rate of chronic VOD is high, and the major cause of death is bleeding esophageal varices. Medical therapy of the many patients who have developed VOD after bone marrow transplantation has included defibrotide, tissue plasminogen activator, ursodeoxycholic acid, antithrombin III, prostaglandin E_1, anticoagulation with low-dose heparin, and

high-dose corticosteroids. None of these agents has been uniformly effective, but the most promising agent in prophylaxis and treatment of VOD is defibrotide, which has been reported to produce a complete response rate of 36% and a 100-day survival rate of 35% in severe VOD. In addition, SSPCS, TIPS, and LT have been used in a few patients with severe VOD. These procedures have had some success and deserve further evaluation, particularly because one fourth of patients with VOD develop the severe form of the disease, and the mortality rate of severe VOD has been reported to be 98%.

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SECTION II Neoplastic

A. General

CHAPTER 78

Tumors of the liver: pathologic aspects

Pierre Bedossa and Valérie Paradis

OVERVIEW

Liver tumors encompass a large spectrum of benign and malignant neoplasms, both primary and metastatic. In addition, a variety of nonneoplastic tumor-like masses deserve attention, because they can simulate neoplasms. Despite major advances in imaging procedures, the definitive diagnosis of a liver tumor is based primarily on accurate examination and interpretation of histologic material. The role of the pathologist is to establish the histologic type of the tumor, estimate its potential behavior, and assess any pertinent prognostic indicators.

According to their histogenesis, primary intrahepatic tumors are classified into three main categories—*hepatocellular, biliary,* and *mesenchymal tumors*—although additional rare entities exist. Liver tumor classification has recently been reviewed, and this chapter will present main pathologic aspects of intrahepatic liver tumors according to the 2010 World Health Organization (WHO) classification (Bosman et al, 2010).

HEPATOCELLULAR TUMORS

Hepatocellular Carcinoma

Clinical and Epidemiologic Background (See Chapter 80)

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor in the adult liver. It ranks among the most frequent neoplasms—approximately 6% of all new cancer diagnosed worldwide with an estimated incidence of about 500,000 to a million new cases per year. It is a deadly malignancy and the third most frequent cause of cancer death among men, causing 600,000 deaths worldwide per year (McGlynn & London, 2005; Sherman, 2005; Parkin et al, 2005; Bruix et al, 2004).

One of the striking characteristics of HCC is the marked geographic variation in its frequency, which is mainly related to geographic distribution of chronic liver disease risk factors. East Asia and sub-Saharan Africa have a very high incidence, whereas Italy, Spain, and Latin America are at intermediate risk. A relatively low but increasing incidence is found in Western Europe, the United States, Canada, and Scandinavia. In these countries, the incidence rate is 50 times lower than in Southeast Asia (Bosch et al, 2004; Kahn et al, 2002; Seeff & Hoofnagle, 2006).

The association between cirrhosis and HCC has been well established. Indeed, 60% to 90% of HCC arises in cirrhotic livers. Conversely, approximately 1% to 3% of patients with cirrhosis will develop HCC annually (Colombo et al, 1991; Johnson & Williams, 1987; Zaman et al, 1985). Most of the epidemiologic variation in HCC prevalence is thought to reflect differences in etiologic risk factors for liver cirrhosis that encompasses a large group of environmental factors (El-Serag et al, 2008). The major known risk factors for HCC are hepatitis viruses (chronic hepatitis B and C; see Chapter 64), toxins (alcohol, aflatoxins), metabolic diseases (metabolic syndrome, α_1 antitrypsin deficiency, Wilson disease), hereditary hemochromatosis, and immune-related diseases (primary biliary cirrhosis, autoimmune hepatitis; see Chapter 70A). Given that the burden of chronic liver diseases is expected to rise along with increasing rates of alcoholism, hepatitis B and C infection, and fatty liver disease, it is expected that the incidence of HCC will also increase in the near future (Nordenstedt et al, 2010; El-Serag, 2008).

HCC is primarily a disease of older men, and its incidence generally increases with age. In Western Europe and the United States, most patients with HCC are between 50 and 75 years of age, although there are geographic differences. It occurs more frequently in men than women, with a male/female ratio ranging from 2:1 to 9:1, although the reason for this is not clear (El-Serag et al, 2008). Routine liver function tests are variably abnormal, often reflecting the underlying cirrhosis without a consistent pattern of alterations. Serum α-fetoprotein (AFP) is elevated in most symptomatic tumors, but small cancers are associated with lower or even normal levels. Thus serum AFP is not a reliable diagnostic test for HCC screening in patients with cirrhosis (Bruix & Sherman, 2005).

It is admitted that HCC usually occurs after a mean delay of 10 years following the onset of liver cirrhosis. This observation is highly consistent with the multistep process of liver cirrhosis that implies progressive malignant transformation of preneoplastic lesions, such as macroregenerative and dysplastic cirrhotic nodules. Because of the dismal prognosis of the disease, increasing emphasis has been placed on detecting early, asymptomatic HCC that is potentially curable.

Ultrasound (US) is a sensitive technique for identifying nodules larger than 1.5 cm and is thus often used for detection, whereas magnetic resonance imaging (MRI) is a more accurate procedure for liver mass characterization (Bolondi et al, 2005; see Chapters 13 and 17). Reliable and highly specific imaging criteria now allow confident diagnosis of HCC in cirrhotic patients so that liver biopsy can be avoided when hyperarterialization associated with early washout is present in dynamic imaging (Bruix & Sherman, 2005; Forner et al, 2008). Screening programs have thus been proposed to follow cirrhotic patients by repeat US. These programs have been successful in identifying small and asymptomatic HCCs in high-incidence areas such as Japan, China, and Alaska but have been less effective in regions where the tumor incidence is low (Sangiovanni et al, 2004).

Despite some progress in managing HCC, liver cancer still carries a dismal prognosis, which is partly explained by its late diagnosis and the clinical context of the patient, which may compromise potential therapeutic strategies. Prognosis is also related to the liver tumor itself, which is prone to early angioinvasion.

HCC is a peculiar tumor for several reasons. Indeed, its morphologic patterns are various, beyond the usual classification based on growth pattern and tumor differentiation. Furthermore, molecular pathogenesis of HCC is complex, involving different molecular pathways that may reflect both etiologic factors and underlying liver disease (Thorgeirsson & Grisham, 2002; Villanueva et al, 2007).

Gross Pathology

HCC can adopt a wide range of gross configurations, and several macroscopic classifications of varying complexity have been proposed, but their clinical relevance has not yet been proven. Tumor size ranges from less than 1 cm to more than 30 cm in diameter. At the time of diagnosis, mean size of HCC arising in a cirrhotic liver is usually less than those occurring in nonfibrotic liver. HCC tumors less than 2 cm are recognized as *small* or *early HCC* (International Working Party [IWP], 1995). Recently, small HCC have been subdivided into *vaguely nodular* and *well-circumscribed HCC,* two patterns with differences in prognosis; the vaguely nodular form has a better prognosis (International Consensus Group [ICG], 2009; Hytiroglou et al, 2007). Although the diagnosis of large HCC relies mainly on imaging modalities, biopsy is often requested for the diagnosis of these small nodular lesions. Upon gross examination, HCC may display a nodular, infiltrative, or diffuse macroscopic pattern (Okuda et al, 1984).

NODULAR (EXPANDING) HEPATOCELLULAR CARCINOMA. The nodular (expanding) pattern is the most common type of HCC, and it is typically seen in association with cirrhosis. This group of tumors is characterized by a sharp demarcation between the tumor mass and the compressed and partly atrophic surrounding parenchyma (Fig. 78.1). The presence of distorted hepatic vessels, including arteries, that form curved structures on the surface of the tumor mass or are visible on the cut surface support the concept of an expanding growth pattern. The nodule may be solitary or multiple across the liver, when these develop as a complication of cirrhosis. When nodules are multiple, small (<1 cm in diameter), and adjacent to the main tumor nodule, they are known as *satellite nodules* (Fig. 78.2).

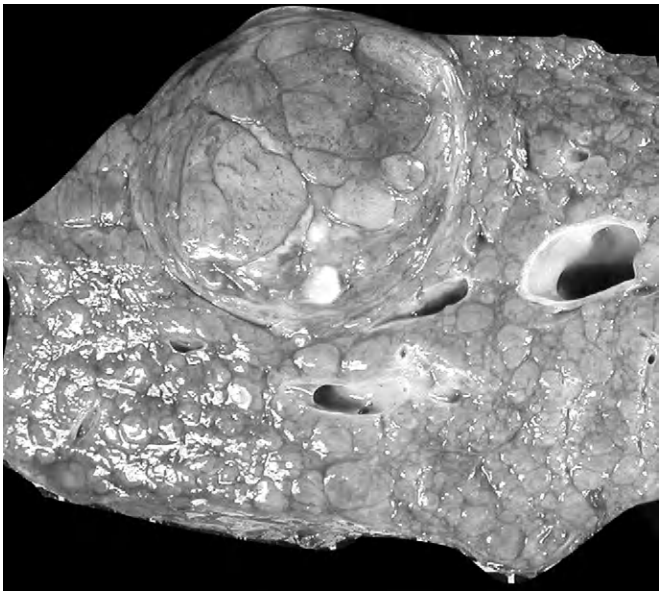


FIGURE 78.1. Hepatocellular carcinoma developed on liver cirrhosis with an expanding growth pattern. The tumor is sharply demarcated from the surrounding parenchyma and limited by a fibrous capsule.

In cases of multiple HCCs, nodules may represent either multifocal independent tumors or intrahepatic metastasis. Such a distinction is quite impossible based on pathologic study alone but could be addressed with surrogate molecular analysis (Paradis et al, 1998; Sakamoto et al, 1989). On cut section, nodular HCC is well delineated from nontumoral liver and circumscribed totally or partially by a fibrous capsule (Okuda et al, 1977). Capsule formation is considered to begin at a tumor diameter of at least 10 mm or greater, because no

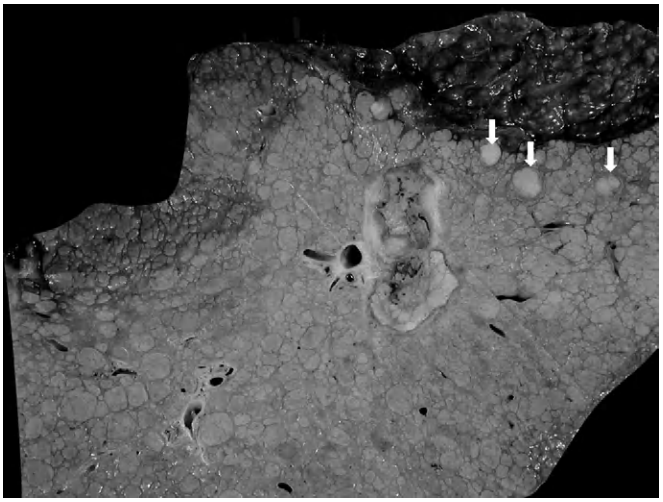


FIGURE 78.2. Hepatocellular carcinoma. The tumor is massively necrotic with minute satellite nodules in the vicinity (*arrows*).

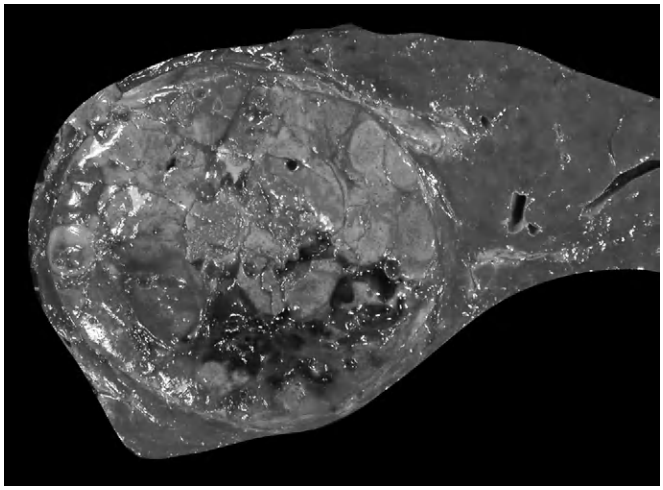


FIGURE 78.3. Hepatocellular carcinoma. The tumor forms soft masses with foci of hemorrhage or necrosis.

distinct capsule has been noted in lesions less than 10 mm (Nakanuma et al, 1986). The prognostic significance of capsule formation has not yet been definitively settled. HCC typically forms soft masses that vary in color from gray, light brown, or yellow-green, often punctuated by foci of hemorrhage or necrosis when the tumor reaches a significant volume (Fig. 78.3).

INFILTRATIVE (MASSIVE) HEPATOCELLULAR CARCINOMA. The infiltrative (massive) pattern is usually characterized by a large, solitary mass that occupies a substantial portion of the liver. The lesion is poorly circumscribed with ill-defined, invasive borders (Fig. 78.4). This pattern has been associated more commonly with noncirrhotic livers (Smalley et al, 1988; Grando-Lemaire et al, 1999). On cut section, the tumor extends into and distorts the adjacent nontumor tissue, interdigitating with surrounding parenchyma. Vessels are incorporated into, not displaced by, the tumor mass so that tortuous vessels around the tumor are not so obvious (Okuda et al, 1982).

DIFFUSE HEPATOCELLULAR CARCINOMA. The diffuse pattern is the least common type of HCC and represents a widespread infiltration by numerous small nodules that virtually replace the entire liver. In this pattern, tumor consists of

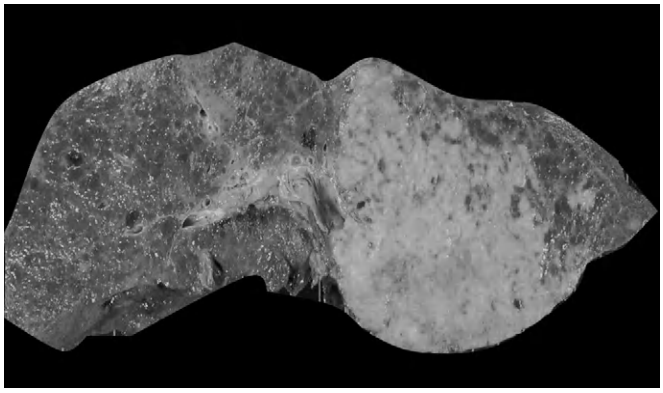


FIGURE 78.4. Hepatocellular carcinoma with an infiltrative growth pattern. The tumor is poorly circumscribed and extends into the surrounding parenchyma. No rim of compressed tissue or capsule is visible.

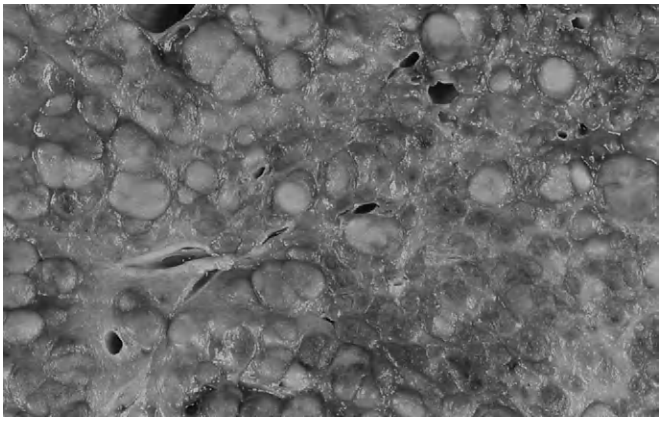


FIGURE 78.5. Hepatocellular carcinoma with a diffuse pattern of growth. The liver is totally replaced by numerous small, round tumor nodules.

several unconnected small tumors of roughly similar size. Multicentric origin or intrahepatic spread after portal vein invasion have been discussed as pathogenic mechanisms (Fig. 78.5; Nakashima & Kojiro, 1986).

PEDUNCULATED HEPATOCELLULAR CARCINOMA. Pedunculation is noted in rare instances, presumably reflecting an origin from an accessory hepatic lobe (Horie et al, 1983). The identification of the pedunculated form of HCC is significant, because even in the case of large tumors, limited resection may give excellent results.

LIMITS OF GROSS CLASSIFICATION. This gross classification has limits, because categorization of a tumor within one single growth pattern may be difficult; for example, expanding HCC may show areas of infiltrative pattern. Furthermore, the reproducibility of this categorization among different pathologists has not been shown. Finally, besides the diffuse pattern, which is associated with a dismal prognosis, the differentiation between expanding and infiltrative patterns does not appear as a prognostic indicator in multivariate analysis.

In nodular, advanced, and infiltrative HCC, invasion of large veins is common even at gross examination. The portal vein is more often involved than hepatic veins, inferior vena cava, or right atrium (Fig. 78.6). Portal vein invasion may be associated with thrombosis, and vascular invasion should be determined with care at the initial gross examination (macrovascular invasion). In some instances, intravascular tumor plugs in the close periphery of a large tumor may be difficult to distinguish from satellite tumor nodules. Invasion of large bile ducts may produce biliary obstruction, and hemobilia might be occasionally found.

Histopathology

Histopathologic evaluation is no more systematic, because dynamic imaging has high diagnostic accuracy for tumors larger than 3 cm. When imaging is not diagnostic, US-guided biopsy must be performed. This is often the case for HCC smaller than 2 cm, when biomarkers have low predictive values, and hyperarterialization may be incomplete or absent. For nodules smaller than 1 cm, biopsy is generally not recommended because of its limited performance. These diagnostic criteria have been endorsed by most international liver disease associations (Bruix & Sherman, 2005; Bruix et al, 2001). Nevertheless,

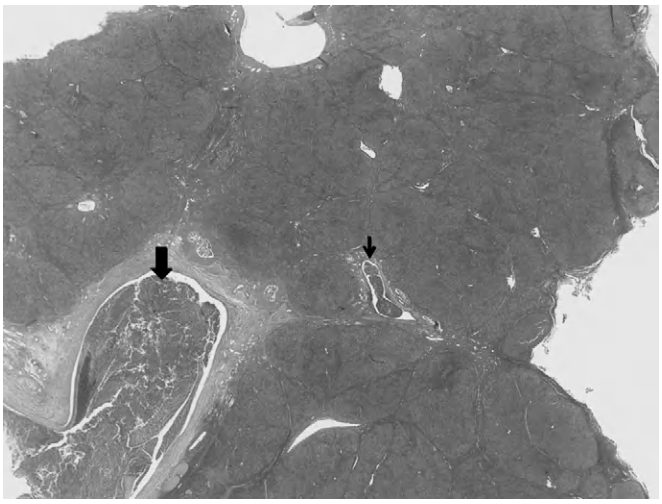


FIGURE 78.6. Invasion of a dilated large portal vein (*large arrow*) and a small vein (*small arrow*) by a tumoral thrombus in a cirrhotic liver close to a hepatocellular carcinoma.

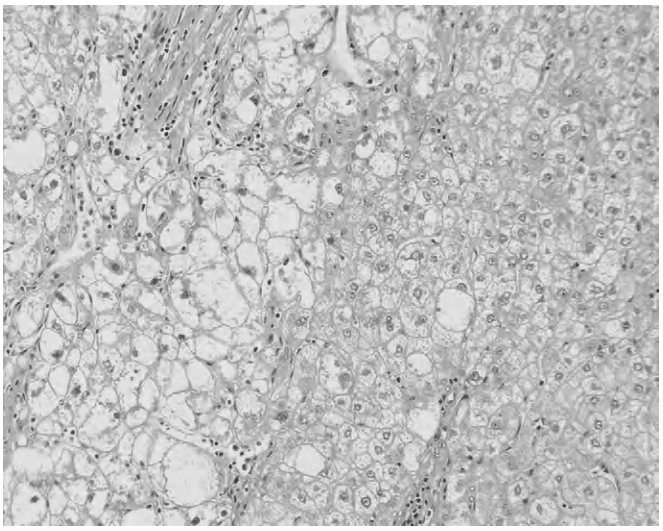


FIGURE 78.8. Hepatocellular carcinoma with a clear-cell pattern. Malignant tumor cells of various sizes are enlarged with a clear cytoplasm.

despite the major advances in radiologic procedures, the definitive diagnosis continues to be based primarily on accurate examination and interpretation of histologic material for any small or atypical nodule.

Histopathologically, the diagnosis of HCC is based on the distinction between tumor cells and normal hepatocytes (Anthony, 1973). Therefore, the microscopic evaluation entails assessment of cytologic characteristics of tumor cells and evaluation of their architectural pattern.

Tumor cells may be seen in varying degrees of hepatocellular differentiation within a single tumor. Nuclei are usually basophilic and often irregular, with prominent nucleoli and a high nuclear/cytoplasmic ratio. In well-differentiated HCC, the tumor cells may closely resemble normal hepatocytes, with a polygonal shape, distinct cell membranes, and eosinophilic granular cytoplasm (Fig. 78.7). Bile canaliculi can often be seen by light microscopy or can be demonstrated by immunostaining. When dilated, they might contain bile pigment, a characteristic feature of hepatocellular differentiation. Accumulation of glycogen or fat in tumor cells may produce a clear-cell appearance (Fig. 78.8). Cytoplasmic fat droplets might be more common in small HCCs. Mallory-Denk bodies, hyaline globules, and eosinophilic or so-called *ground-glass cytoplasmic inclusions* may also be observed.

As the tumor evolves to a poorly differentiated phenotype with cell-to-cell heterogeneity, bizarre nuclei or giant tumoral cells may appear. Mitosis and apoptotic bodies can be observed (Fig. 78.9). Different degrees of cellular differentiation are usually present within a single large tumor, although small HCC tend to be more homogeneous.

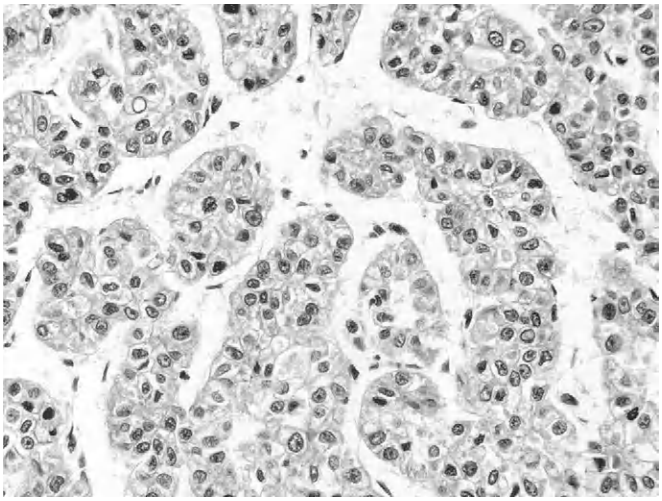


FIGURE 78.7. Well-differentiated hepatocellular carcinoma. Tumor cells are organized in large trabeculae and resemble normal hepatocytes with a polygonal shape, distinct cell membranes, and clear cytoplasm with a high nuclear/cytoplasmic ratio.

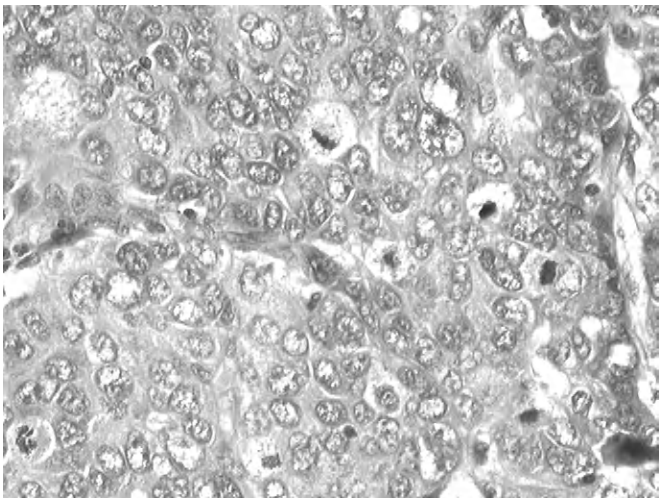


FIGURE 78.9. Poorly differentiated hepatocellular carcinoma. The tumor is highly cellular with tumoral cells organized in large trabeculae with bizarre nuclei, mitosis, and apoptotic bodies.

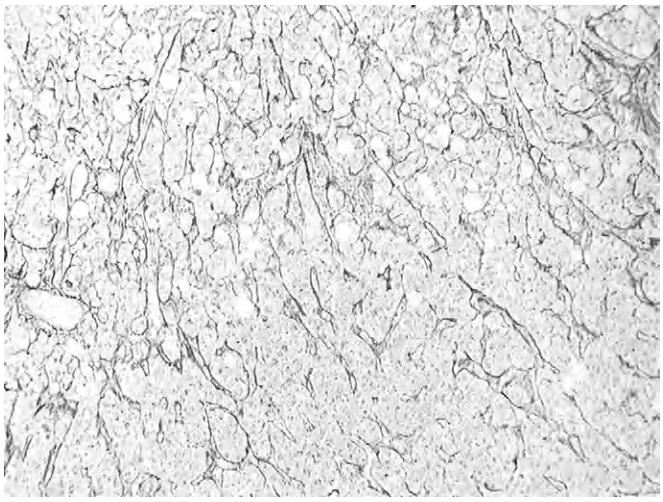


FIGURE 78.10. Reticulin staining in hepatocellular carcinoma. The lower part of the figure displays fragmentation and rarefaction of the reticular framework.

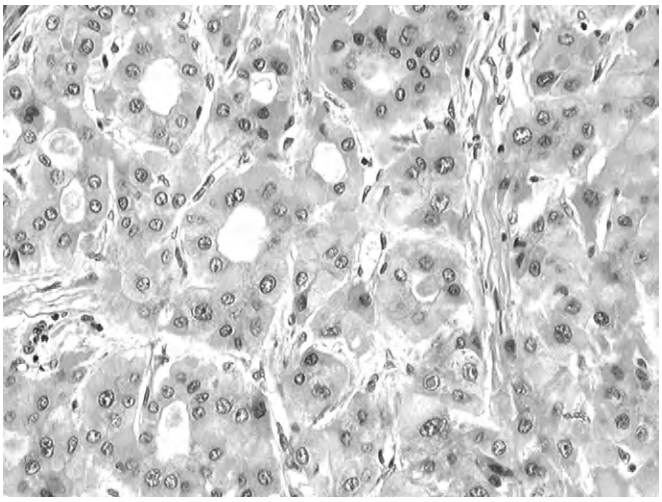


FIGURE 78.11. Hepatocellular carcinoma with a pseudoglandular pattern. Hepatocytes display glandlike organization around dilated canaliculi between tumor cells.

Growth Patterns

The arrangement of the cells contributes to the variability in the microscopic appearance. On this basis, several types of tumor have been categorized, but it has not yet been fully established whether these variations reflect differences in behavior and influence prognosis (Qin & Tang, 2002). The three main architectural patterns of growth of HCC are *trabecular; acinar,* or *pseudoglandular;* and *scirrhous.*

TRABECULAR GROWTH. Trabecular growth occurs when tumoral hepatocytes are arranged in plates in varying thicknesses from 2 to more than 20 cells (see Fig. 78.7). This feature resumes the normal trabecular arrangement of liver plates. Neoplastic cells are organized along simplified sinusoids lined by flat endothelial cells with few or no Kupffer cells. Compared with normal liver plates, the reticulin framework is commonly sparse or absent (Fig. 78.10). A compact or solid pattern occurs when the trabeculae are closely aligned, and the sinusoids become compressed and unapparent.

ACINAR (PSEUDOGLANDULAR) GROWTH. The *acinar*, or *pseudoglandular, pattern* results either from glandlike dilation of the canaliculi between tumor cells, in which the lumens can contain bile, or central degeneration of trabeculae, in which the lumens contain mainly degenerative products with fibrin (Fig. 78.11). As with the trabecular pattern of growth, stroma is typically sparse. The lack of a desmoplastic stroma reaction is a helpful diagnostic clue, when other glandular malignant epithelial neoplasms, especially cholangiocarcinomas, are discussed. On occasion, large vascular lakes resembling peliosis can develop within the pseudoglandular formations.

SCIRRHOUS GROWTH. The scirrhous pattern of HCC is rare, characterized by tumor cells with cytologic and phenotypic features of otherwise typical HCC but within an abundant fibrous stroma. This pattern is different from a subset of so-called fibrolamellar HCC, which will be discussed below.

PUSHING AND MERGING CONFIGURATIONS. At the interface with adjacent nonneoplastic parenchyma, HCCs typically adopt either pushing or merging histologic configurations. With pushing growth, the tumor is completely or partially limited by a fibrous capsule made of dense collagen fibers, often encircling dilated veins. With progressing growth, the tumor steps across the capsule and merges directly into adjoining nonneoplastic cell plates, replacing the normal hepatocytes.

Histologic Variants

FIBROLAMELLAR HEPATOCELLULAR CARCINOMA. This subset, which differs from other types of HCC in clinical features and prognosis, is the only variant with clinical significance. It was first delineated as a distinct entity in 1980 (Craig et al, 1980). In a population-based study, fibrolamellar HCC constituted 0.85% of all cases of primary liver cancer and 13.4% of all cases in patients younger than age 40 (El-Serag & Davila, 2004). The clinical presentation is similar to other HCCs, except that it occurs in young people with equal gender ratio and has no association with chronic liver disease, cirrhosis, or any other known predisposing risk factors.

On gross examination, fibrolamellar HCC is a firm, mostly well-defined but unencapsulated single nodule that can range from 5 cm to more than 20 cm (Saab & Yao, 1996). On cut section, the tumor is gray to brown with scalloped borders and a solid consistency (Fig. 78.12). Prominent fibrous septa subdivide the mass and may connect with a central zone of scarring. Such features may be confused with focal nodular hyperplasia. In addition, several reports in the literature describe fibrolamellar HCC spatially associated with focal nodular hyperplasia, although filiation between these two lesions has never been convincingly demonstrated (Saul et al, 1987). Calcifications may also be observed.

The distinctive histologic features are fibrous stroma and large, eosinophilic tumor cells (Fig. 78.13; Berman & McNeill, 1988). The stroma comprises dense, fibrous bands of varying thickness organized around nests, cords, and sheets of neoplastic cells (Nerlich et al, 1992). The tumor cells are usually larger

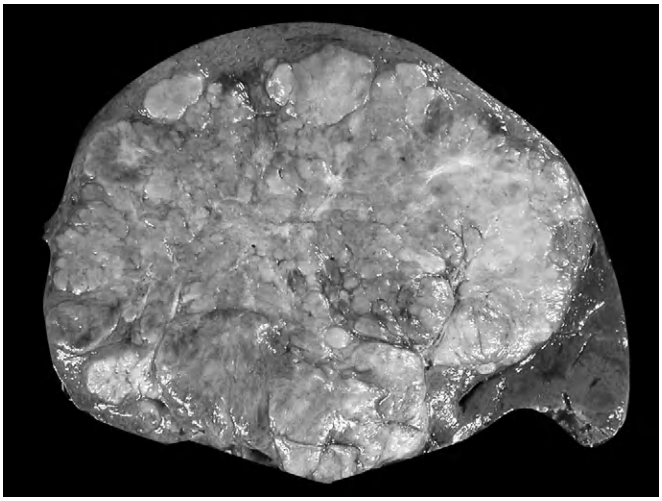


FIGURE 78.12. Fibrolamellar hepatocellular carcinoma. Large lobulated tumor is well delineated from normal surrounding liver.

than normal hepatocytes and display abundant, granular, and deeply eosinophilic cytoplasm with prominent nucleoli. Bile pigment is common, and fat or glycogen accumulation is sometimes seen. Most fibrolamellar carcinomas are histologically low grade, mitoses are usually sparse, and nuclear pleomorphism and multinucleation are infrequent. Cytoplasmic inclusions of various types are common, including ground-glass pale bodies (Fig. 78.14), eosinophilic cytoplasmic globules of variable periodic acid-Schiff positivity, and rarely Mallory-Denk bodies. In contrast to most HCC, fibrolamellar HCC seems to abundantly express type 7 cytokeratin (CK) and, in some cells, biliary-type CK19 (Van Eyken et al, 1990).

Fibrolamellar HCC tends to be slow growing and frequently resectable with a better prognosis than other types of carcinoma. However, when adjustment is made for tumor stage, all series do not demonstrate this better prognosis. Successfully resected patients have good chance of long-term survival despite extrahepatic recurrences.

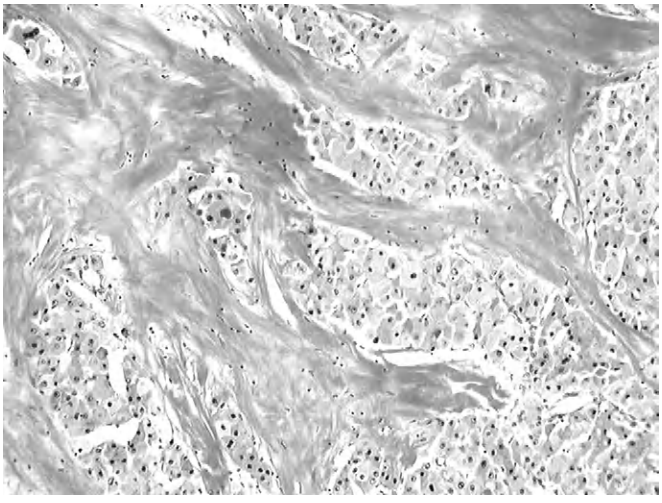


FIGURE 78.13. Fibrolamellar hepatocellular carcinoma. The tumor is composed of large eosinophilic tumor cells organized in cords between dense, acellular fibrous bands.

CLEAR-CELL CARCINOMA. This predominant tumoral cell type is rich in glycogen or lipid and accordingly has a clear cytoplasm (Buchanan & Huvos, 1974). The clear-cell variant has been associated with a better prognosis, but the survival advantage, if present, is minor and has not been confirmed (Kishi et al, 1983). Clear-cell HCC may be associated with hypoglycemia and hypercholesterolemia, and sudden death from severe hypoglycemia has been reported (Sasaki et al, 1981; Ross & Kurian, 1985).

SARCOMATOID HEPATOCELLULAR CARCINOMA. This variant is characterized by a sarcomatous-appearing component of spindle-shaped or giant tumor cells (Kojiro et al, 1989). The elongated spindle cells are arranged in bundles, occasionally with interlacing or storiform patterns. The giant cells are multinucleated, markedly pleomorphic, and cytologically anaplastic, and osteoclast-like giant cells are described in some instances (Kuwano et al, 1984). These tumors have often been referred to as *carcinosarcomas*. The sarcomatoid component varies in its extent, and histologic transitions with the carcinomatous elements are often noted. The spindle-shaped cells are typically immunoreactive for keratin and α-fetoprotein (Kakizoe et al, 1987).

SCLEROSING HEPATOCELLULAR CARCINOMA. Sclerosing HCC is a rare but distinctive variant characterized by abundant, diffusely distributed fibrous stroma and compressed, sometimes elongated malignant hepatocytes. The tumor tends to occur in an older age group, affects men and women equally, and might be associated with hypercalcemia (Omata et al, 1981). A large, firm, gray-white mass is found on gross examination. The hepatocellular nature of the lesion is best appreciated on a cytologic, rather than architectural, basis. Individual tumor cells, especially at the periphery of the mass, correspond to those of the usual HCC. Although generally smaller in size, they exhibit granular eosinophilic cytoplasm, vesicular nuclei, and conspicuous nucleoli. Bile pigment can sometimes be discerned.

Other Morphologic Patterns of Hepatocellular Carcinoma

It is well known that HCCs that arise in hemochromatosis fail to show accumulation of stainable iron, and iron-free foci in siderotic macroregenerative nodules in human cirrhotic livers have been suggested to be a marker for incipient neoplastic lesions (Hirota et al, 1982; Deugnier et al, 1993). Some HCCs accumulate copper, which can be detected using histochemical methods. Accumulation of large amounts of copper and copper-binding protein (orcein-positive) has been found chiefly in the fibrolamellar variant of HCC (Lefkowitch et al, 1983).

There are some unusual instances in which HCC produces substances that occur in some rare metabolic disorders (e.g., black HCC in a patient without Dubin-Johnson syndrome; Roth et al, 1982). A granulomatous sarcoid-like reaction may be encountered within HCC, the granulomas being characterized by epithelioid cells, Langerhans-type giant cells, and varying numbers of lymphocytes (Nakashima & Kojiro, 1986). Massive lymphoid stroma may also circumscribe otherwise typical HCC.

Hepatocellular Carcinoma in Noncirrhotic Liver

HCC in noncirrhotic liver encompasses several entities. It may develop during the evolution of a chronic fibrosing liver disease at the stage of incomplete cirrhosis (septal fibrosis). This is

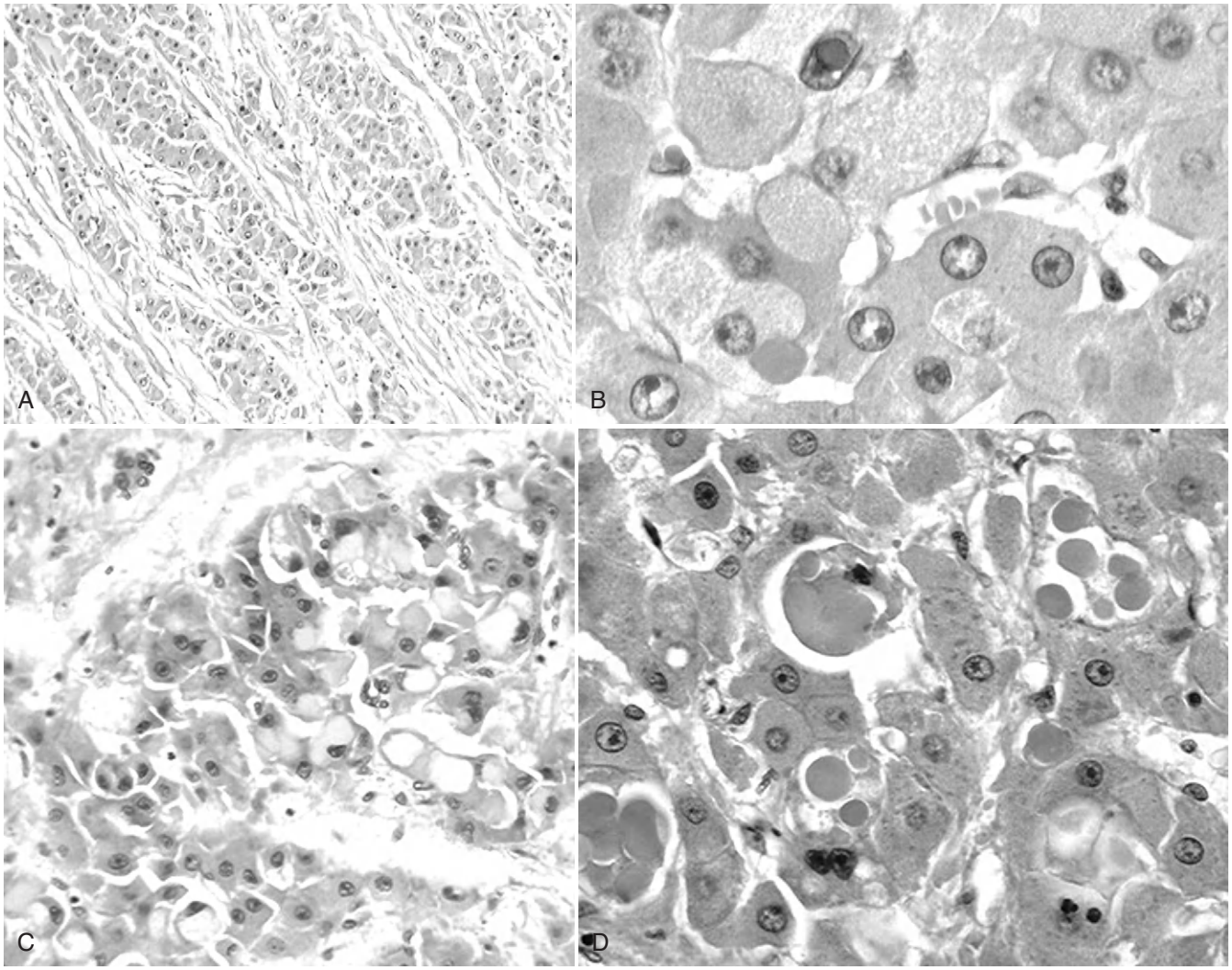


FIGURE 78.14. Fibrolamellar hepatocellular carcinoma. **A,** Tumoral cells organized in trabeculae along fibrous septa. **B,** High magnification showing large eosinophilic tumor cells with intracytoplasmic ground-glass pale bodies. **C,** Intracytoplasmic pale bodies. **D,** Intracytoplasmic eosinophilic globules of various size.

especially common in the context of chronic hepatitis B (Lam et al, 2004). Because of the possible reversibility of cirrhosis, it is not known whether HCC in incomplete cirrhosis develops during an ongoing fibrogenesis or along with the reversion of cirrhosis. In this context, HCC does not show any specific morphologic criteria. HCC may also develop in strictly normal liver or in liver with mild changes, such as steatosis. This group includes the fibrolamellar variant of HCC, that arising from malignant transformation of liver cell adenoma (see below), and a group that develops in the context of other chronic liver disease, including nonalcoholic fatty liver disease (Paradis et al, 2009; Marrero et al, 2002).

Grading and Other Pathologic Prognostic Factors

Grading of HCC relies on the Edmondson and Steiner system, which subdivides HCC into four grades, from I to IV, on the basis of histologic and cytologic resemblance to normal liver (Edmonson & Steiner, 1954). This grading has been shown to correlate with the DNA content and cellular proliferation indices of the tumor (Grigioni et al, 1989). Grade I is the well-differentiated type, in which hepatocyte-like cells are arranged in thin trabeculae. Small HCC tends to be grade I, although these are often not uniform in their differentiation. Grade II HCC is composed of larger tumor cells with abnormal nuclei; glandular structures may also be present. In grade IV, neoplastic cells are much less differentiated, with hyperchromatic nuclei and loss of trabecular pattern. In fact, most HCC seen initially is grade II or III (Kenmochi et al, 1987). Therefore, and as for other carcinomas, the general tendency is to summarize the grading using a three-tiered system comprising well-, moderately, and poorly differentiated HCC.

Nonetheless, tumor grade is a weak independent predictor of the clinical course and conveys little prognostic information (Lai et al, 1979; Chuong et al, 1982). Furthermore, grading of HCC is often heterogeneous alongside the tumor so that liver biopsy might have limited performance for grading HCC. Consequently, the histologic grading of HCC is useful, but rather as a descriptive tool; its practical value is limited (Pawlik et al, 2007).

Besides grading, other histologic features of HCC, such as architectural pattern, have little or no independent prognostic

value. However, several staging systems have been proposed for HCC (Llovet et al, 1999; Marrero et al, 2005). The main prognostic factors are related to general health status; tumor stage, specifically the number and size of nodules, presence of vascular invasion, and extrahepatic spread; liver function, defined by the Child-Turcotte-Pugh classification system and by serum bilirubin and serum albumin levels; and portal hypertension. Etiology has not been identified as an independent prognostic factor.

Size is a major prognostic factor: small or minute carcinomas have a better prognosis, although with larger cancers, the tumor size does not directly correlate with outcome. Presence of satellite nodules around the main tumor has been also recognized as a prognostic factor in several studies. Improved survival has been associated with tumors that are encapsulated or fail to invade surrounding hepatic parenchyma (Ohnishi et al, 1987; Arii et al, 2000; Sutton et al, 1988).

Macroscopic and microscopic vascular invasion are important histoprognostic criteria that deserve special mention. Vascular invasion is a known predictor of recurrence and survival, directly associated with histologic differentiation, degree, and size of the main nodule (Nathan et al, 2009; Pawlik et al, 2005). Characteristically, the prevalence of microscopic vascular invasion increases with tumor size, with up to 60% to 90% in nodules larger than 5 cm. Other histologic findings are not consistently correlated with outcome, although occasional series have reported a better prognosis with clear-cell HCC and tumors of low histologic grade.

Using microarray technology, recent studies have shown that a subset of adult HCC displays phenotypic traits of hepatoblasts. These tumors retent stem cells markers and express CK7 and CK19. Interestingly, worse survival was demonstrated for this subgroup (Lee et al, 2004). Although the significance of CK7 and CK19 expression in HCC is still unclear, it might represent a relevant prognostic factor, although a larger study with multidimensional analysis should be performed.

A major influence on clinical status of the patient is the presence or absence of cirrhosis, which thus becomes a leading indicator for survival. Therefore, simultaneous biopsy of nontumoral liver is of major importance and should be systematically performed for consideration in the therapeutic decision and to help the pathologist in the diagnosis of very well-differentiated HCC.

Molecular Genetics

From experimental hepatic carcinogenesis and epidemiologic studies, it appears that liver carcinogenesis follows a multistep process (see Chapter 8C). Although a few cases of HCC arise in normal liver, the vast majority of them develop from the stepwise pathway: normal liver progresses to fibrosis then to cirrhosis and finally to HCC. Therefore, cirrhosis is recognized as a precancerous lesion (IWP, 1995).

As a result of careful follow-up of cirrhotic patients and detailed pathologic analysis of cirrhotic explanted livers, relevant insights have been gained into the early pathogenesis of HCC. Data are less clear when associated molecular events are concerned; however, a consensus supports the idea that HCC results from cumulative genetic and epigenetic events (Thorgeirsson & Grisham, 2002). Although recurrent gene abnormalities have been reported in fully developed HCC, the early molecular events are far less unknown.

Several studies using different approaches have looked for early molecular abnormalities in regular cirrhosis. Several molecular markers have been evaluated in macronodules, and none of the oncogenes or tumor suppressor genes involved in advanced HCC have been repeatedly found altered in the precancerous lesions. By contrast, proliferation markers, neoangiogenesis, telomerase expression, allelic losses, and clonality have been studied with more consistent results. Interestingly, these studies convincingly demonstrate, using clonal analysis, that among cirrhotic micronodules that looked similar on light microscope, some are already monoclonal (neoplastic), and others are polyclonal (regenerative; Paradis et al, 1998, 2000). Telomerase, an enzyme that allows unrestricted cell proliferation and that is specifically expressed in cancer, can be detected in some but not all of these clonal micronodules without any remarkable histopathologic features (Oh et al, 2003). In the same orientation, and using cell-cycle markers, studies have shown that cirrhosis associated with HCC, or that will give rise to HCC, already expresses increased cell-cycle markers. Therefore even in regular cirrhosis with a bland histopathologic appearance, foci of neoplastic clonal proliferation of liver cells with a limitless capacity of proliferation clearly are already present.

Most genomic studies address advanced HCC, and several efforts have been made to provide molecular classification of HCC based on gene expression (Villanueva et al, 2007; Chuma et al, 2003). Global gene-expression profiling may be the most appropriate technology to unravel the pathogenesis of HCC and explore its heterogeneous origin (Lee et al, 2004; Wurmbach et al, 2007; Llovet et al, 2006; Hoshida et al, 2008). In fact, application of gene-expression profiling of HCC has identified subgroups of patients according to etiologic factors, different stages of the disease, recurrence, and survival (Villanueva et al, 2008; Ladeiro et al, 2008; Boyault et al, 2007). The diversity of these tumors is also found at the molecular level, and a large number of genetic and epigenetic alterations have been described, some of them specific of risk factors. Recently, several comprehensive studies have shown that a molecular classification of HCC can be drawn, linking the transcriptomic pattern of gene expression (Boyault et al, 2007), micro-RNA profiling (Ladeiro et al, 2008), promoter methylations, chromosome gains, and deletions (Xue et al, 2008) to mutation of oncogenes and tumor suppressor genes (de la Coste et al, 1998). Major classes of tumors emerging from these comprehensive analyses are also related to important carcinogenesis pathways, such as activation of ß-catenin (de la Coste et al, 1998), AKT/mTOR (Villanueva et al, 2008), or inactivation of TP53 and RB1. Whether this molecular subclassification may provide a clue to personalized, targeted treatment or to prognosis is under active investigation (Villanueva et al, 2008). Interestingly, using genome-wide expression profiling of formalin-fixed, paraffin-embedded tissues, a recent study demonstrated that a reproducible gene-expression signature correlating with survival was only described in liver tissue adjacent to the tumor in patients with HCC (Hoshida et al, 2008).

Premalignant Hepatocellular Lesions and Small Hepatocellular Carcinomas

It is commonly accepted that in the context of cirrhosis, there is a stepwise progression from cirrhotic nodule to HCC. Several terms have been used in the past to define the intermediate lesions, such as *adenomatous hyperplasia* and *atypical adenomatous hyperplasia*; but in 1995, the IWP proposed a unified nomenclature that has gained wide acceptance and is still

currently used. This classification was recently reviewed and completed by an international group that added definitions of the early and small HCC (ICG, 2009).

Macroregenerative Nodules

A *macroregenerative nodule* (MRN) is a tumor-like hepatocellular mass that can arise in the setting of cirrhosis. These lesions have increasingly been detected, the result of both improved radiographic imaging techniques and more widespread screening of cirrhotic patients. Most MRN are large, discrete nodules that range from 1 to 3 cm in diameter. There is no minimum size threshold for definition; MRNs have to be appreciated according to the size of background cirrhotic nodules, which may be twofold to threefold larger than cirrhotic nodules (Theise et al, 1992; Terada et al, 1993). Macronodules are often well demarcated and surrounded by condensed connective tissue. MRNs are common, and they have been found after careful inspection in about 10% of cirrhotic livers at autopsy or at transplantation (Theise et al, 1992; Furuya et al, 1988; Mion et al, 1996). Histologically, most MRNs are indistinguishable from the usual parenchymal nodules seen in cirrhosis: normal-appearing hepatocytes are arrayed in plates one or two cells thick, limited by a regular sinusoid lining and bounded by typical fibrous septa containing blood vessels, bile ductules, and varying degrees of inflammatory infiltration (Fig. 78.15).

Dysplastic Nodules

Dysplastic nodules (DNs) are sizable lesions arising in cirrhosis, and they differ from the surrounding liver parenchyma with regard to size, color, texture, and degree of bulging of the cut surface. Based on microscopic features, DNs are further subdivided into *low grade* (LGDN) and *high grade* (HGDN), the latter being closer to HCC in the spectrum of hepatocarcinogenesis (IWP, 1995; ICG, 2009). Briefly, LGDNs display features suggestive of a clonal cell population but lack architectural atypia, whereas HGDNs show cytologic and architectural atypia but insufficient for a diagnosis of malignancy.

The premalignant nature of DNs is supported by different clues, including the common association with HCC in resected and explanted end-stage cirrhotic livers (Theise et al, 1992; Furuya et al, 1988; Libbrecht et al, 2005; Sakamoto et al, 1991); the presence of hepatocellular cyto-architectural abnormalities, featuring a lesion on the way to HCC (Ferrell et al, 1992; Ganne-Carrie et al, 1996; Takayama et al, 1990); the morphologic evidence of neoangiogenesis under the form of unpaired arteries supporting the abnormally ongoing vascular supply (Roncalli et al, 1999; Park et al, 2000; El-Assal et al, 1998); the detection of both genetic and epigenetic changes, greater than those in the surroundings but less frequent and consistent than in HCC; and a natural history showing an increased risk for malignant transformation compared with control cirrhotic nodules (Maggioni et al, 2000; Kobayashi et al, 2006; Terasaki et al, 1998; Seki et al, 2000).

Among the various cytologic alterations that characterize DNs are enlarged, crowded, or irregular nuclei with patent nucleoli and an increased nuclear/cytoplasmic ratio. Atypical architectural findings involve expansile proliferative zones, sometimes located within an MRN (nodule-in-nodule formations); focal loss of associated reticulin framework; and foci of abnormal structural patterns that includes irregular thickening of hepatic plates (IWP, 1995; Fig. 78.16). According to Eastern pathologists, *stromal invasion,* defined as the presence of tumor cells invading into the portal tracts or fibrous septa, is the most relevant feature distinguishing HGDN from early HCC (International Consensus Group for Hepatocellular Neoplasia, 2009). The degree and extent of these features vary greatly among patients, thus forming a histologic continuum that stretches between ordinary MRNs and obvious hepatocellular carcinoma.

Dysplastic nodules must be differentiated from *dysplastic foci,* microscopic changes incidentally recognized in cirrhotic tissue. According to histopathologic criteria, dysplastic foci are split into two groups: those with large-cell changes or those with small-cell changes. Although large liver cell change, previously

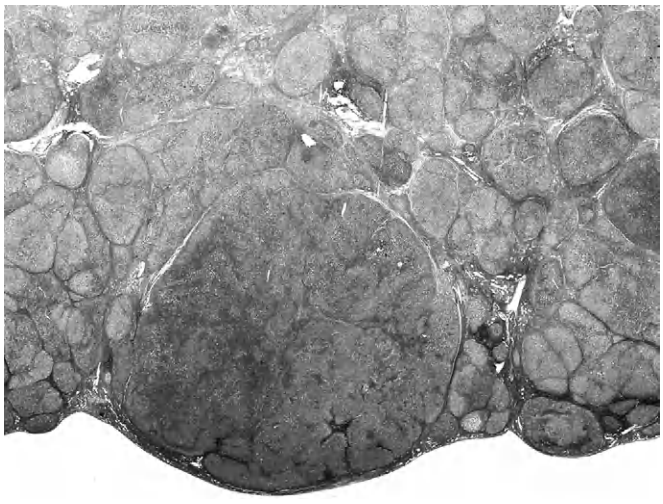


FIGURE 78.15. Low magnification of a benign regenerative macronodule in a cirrhotic liver. The macronodule is well-demarcated from surrounding liver. Fibrous septa and portal tracts are still present within the macronodule.

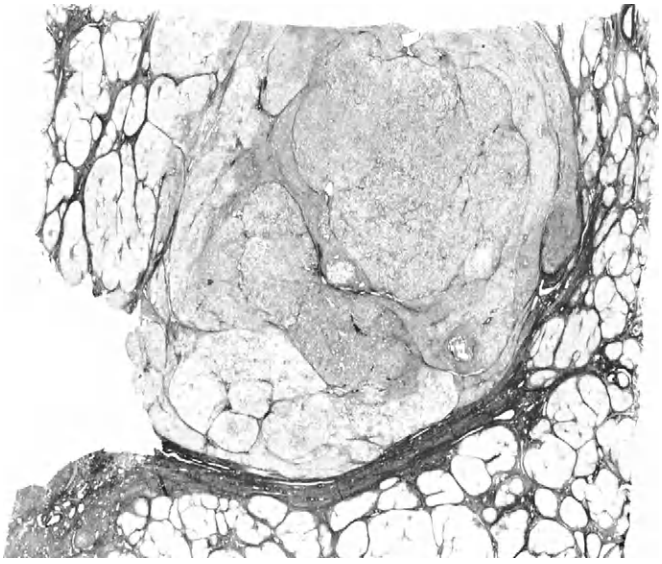


FIGURE 78.16. A macronodule with a nodule-in-nodule pattern of growth. An expansile proliferative basophilic zone is located within a macronodule.

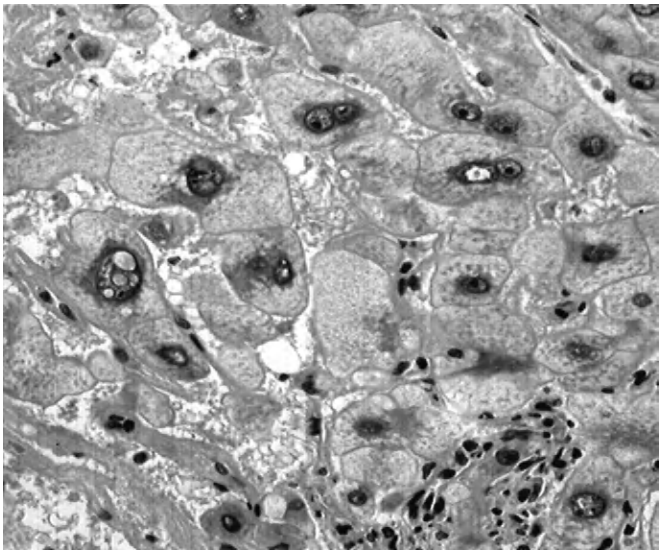


FIGURE 78.17. Large liver cell changes. Cluster of abnormal large liver cells with dystrophic nuclei.

called *large liver cell dysplasia* (Fig. 78.17) consists of abnormal but nonneoplastic hepatocytes that are predictors of HCC development; small liver cell dysplasia is composed of neoplastic cells that are direct precursors of HCC (Lee et al, 1997; Borzio et al, 1995).

Small Hepatocellular Carcinoma

A "small" liver cancer is currently defined as HCC with a maximum diameter of less than 2 cm (Nakashima & Kojiro, 1986). However, the lack of a widely accepted definition has led to confusion, and HCCs smaller than 3 to 5 cm have also been included in this group by others. Small HCCs are usually clinically silent and are often discovered incidentally on explanted liver or at autopsy (Mion et al, 1996). Small HCCs are most often a well-differentiated lesion, sometimes still containing portal triads, growing without substantial destruction of the preexisting hepatic framework and seldom showing angioinvasion (Sakamoto et al, 1991).

Small HCCs have been subdivided into two different entities: those with indistinct margins, called *vaguely nodular HCC,* and those with distinct margins, called *distinctively nodular HCC* (ICG, 2009). Whereas vaguely nodular HCC is the earliest, most indolent, and least angioinvasive type of HCC, distinctively nodular HCC is thought to have already acquired an ability to invade the vessels and to metastasize (Hytiroglou, 2007; Kojiro & Roskams, 2005; Theise et al, 2002). Therefore small HCC with distinct margins seems to be a progressed cancer in spite of its small size. On the liver biopsy, the difference between these two entities cannot be appreciated, because it requires the notion of gross features, which are not recognizable in small fragments. Therefore the term *well-differentiated HCC* may be better used in the biopsy report.

Natural History of Premalignant Lesions and Diagnostic Challenges

Few prospective studies have been conducted in large series of histologically proven nonneoplastic nodules detected by US during surveillance programs in cirrhosis. Taken together, these studies have shown that only a minority of macroregenerative or dysplastic nodules became malignant, those transforming are mostly in the group of HGDN. Furthermore, 40% to 60% stabilized, and a few definitely disappeared during follow-up (Borzio et al, 2003; Kondo et al, 1990). Most of these nodules are 1 to 2 cm, so they seldom display a diagnostic pattern at imaging. Therefore histologic assessment is needed at baseline, and it is worth repeating when sampling is not adequate.

Whether HCC regularly develops from DNs in a low grade–high grade–small and early–small HCC sequence in individual patients is still unclear. This hypothesis is supported by the feature of so-called nodules in nodules, which have been mainly reported in the Eastern literature (Kojiro, 2004; Roncalli et al, 2004, 2007). However, HCC has also been found to originate from outside dysplastic nodules during the surveillance of cirrhotic patients, supporting the notion that HCC can also develop "de novo," by skipping the gradual transition of the sequence (Borzio et al, 2003).

From a clinical point of view, correct classification of hepatocellular nodules, as well as the exact number of truly malignant nodules, is crucial in order to plan the most appropriate therapy. However, the diagnostic approach to these small nodular lesions is a challenge. The prevalence of HCC is closely dependent on the size of the lesion. Indeed, almost half of those lesions smaller than 1 cm are nonmalignant, whereas the large majority of lesions exceeding 2 cm are HCC, so that in the group of lesions greater than 2 cm, a diagnosis of nonmalignancy should suggest the suspicion of a diagnostic error. It has been well established that, in cirrhosis, the progression from nonmalignant nodules to dysplastic to early and advanced HCC is characterized by the progressive loss of the portal blood with a "de novo" arterial vascularization (Hayashi et al, 2002). However, in the group of lesions sized 1 to 2 cm, about 20% of small HCC is hypovascular, so that histology is required in most of these cases, either at baseline or during follow-up, to confirm the nature of the lesions (Forner et al, 2008).

In clinical practice, liver biopsy is today mostly performed to classify small hepatocellular nodules (Bruix & Sherman, 2005). Diagnosis has to be made on tiny and often fragmented material, and clinicians need a conclusive report as to whether lesions are benign or malignant. Nevertheless, the diagnosis is not always straightforward, and other techniques may be required in addition to standard staining. Fortunately, immunocytochemical tools useful to distinguish malignant from nonmalignant nodules within the group of well-differentiated hepatocellular lesions have been developed recently, such as glypican-3 antibody (Di Tommaso et al, 2007).

Hepatoblastoma

Hepatoblastoma is the most common primary liver tumor of childhood, accounting for 45% of the malignant hepatocellular neoplasms of infants and young children (Stocker, 2001; see Chapter 82). Almost all cases of hepatoblastoma occur during the first 3 years of life, although rare cases have been described in older children (Lack et al, 1982). Hepatoblastoma has been associated with congenital or genetic disorders, including Beckwith-Wiedeman syndrome, Wilms tumor, familial adenomatous polyposis, glycogen storage disease, and various congenital anomalies (Ishak & Glunz, 1967).

Hepatoblastomas are typically solitary, well-circumscribed, and occasionally encapsulated masses mostly located in the right lobe; size ranges from 5 to 20 cm in diameter (Stocker,

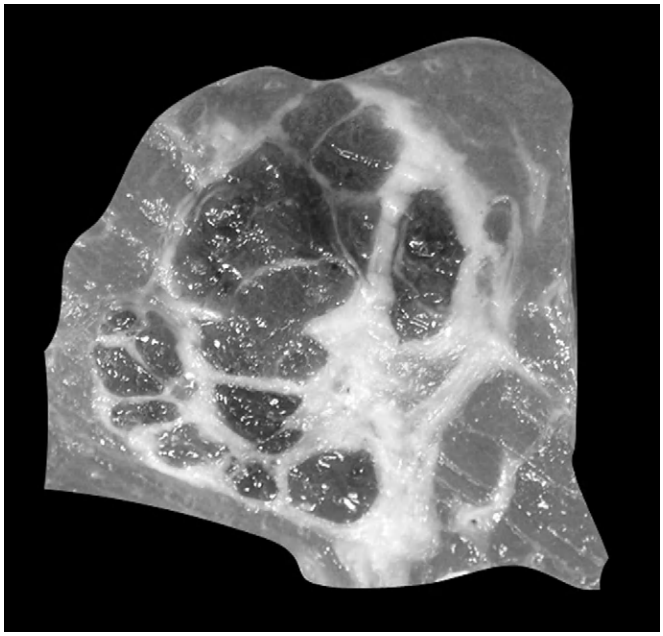


FIGURE 78.18. Hepatoblastoma. Well-delineated tumor with lobulation and hemorraghic foci and areas of cystic degeneration. *(Image courtesy Dr A. Fabre.)*

2001). The cut surface of hepatoblastoma has a bulging, lobulated contour and a variable tan to light brown to gray-white appearance with occasional foci of hemorrhage, cystic degeneration, necrosis, or calcification (Fig. 78.18; Stocker, 2001; Lack et al, 1982).

Histologically, hepatoblastoma is composed predominantly of immature liver cells resembling either fetal or embryonic hepatocytes. In addition, hepatoblastoma may be of either the pure epithelial type or the mixed epithelial and mesenchymal type.

Fetal-type cells are smaller than normal hepatocytes with a uniform monotonous appearance, an abundant polygonal cytoplasm, and round, regular nuclei with inconspicuous nucleoli (Fig. 78.19). The cells are organized in irregular plates; nuclear

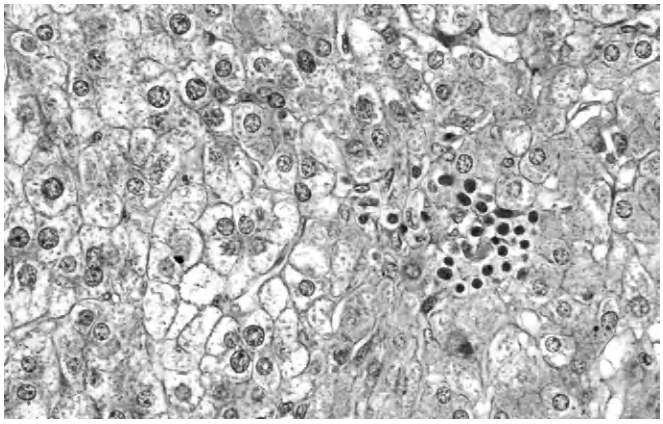


FIGURE 78.19. Hepatoblastoma, fetal type. Tumoral hepatocytes are smaller than normal with an abundant polygonal cytoplasm and round, regular nuclei organized in thin, irregular plates with dark foci of extramedullary hematopoiesis. *(Image courtesy Dr A. Fabre.)*

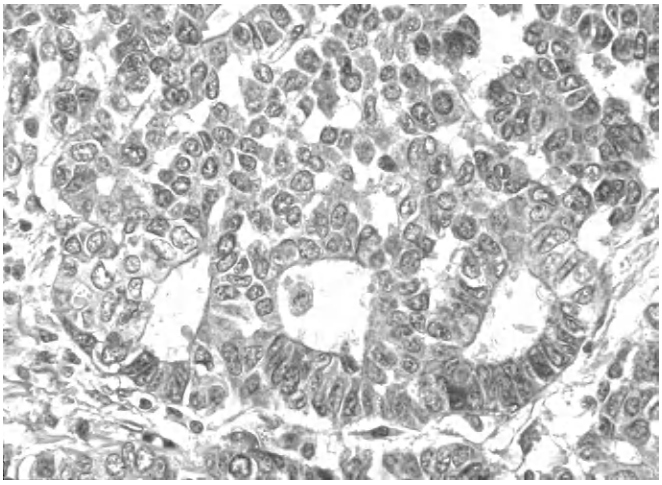


FIGURE 78.20. Hepatoblastoma, embryonal type. Tumoral cells are less mature and made of small, dark, angular cells with compact cytoplasm and poorly defined outlines. *(Image courtesy Dr A. Fabre.)*

pleomorphism is minimal, and mitoses are few, but foci of extramedullary hematopoiesis are a common finding. The embryonal-type cell is composed of less mature tumoral cells—dark, angular cells with compact cytoplasm and poorly defined outlines (Fig. 78.20). Scattered mitoses are regularly noted, and foci of necrosis are occasionally seen.

Fetal-type and embryonal-type cells often coexist, and transitions between the two are frequently present. In addition to the two major patterns, other types are described. The anaplastic type consists of small uniform cells similar to those of neuroblastoma with scanty cytoplasm, hyperchromatic nuclei, and frequent mitoses (Haas et al, 2001).

The mixed hepatoblastomas combine the epithelial component with mesenchymal-derived tissues of various differentiations. Usually this consists of osteoid-like material, sometimes focally calcified, or primitive spindle cells occurring in fasciculated or loose myxoid arrangements. Rarely, trabecular bone formation or cartilaginous or rhabdomyoblastic differentiation is identified.

Hepatoblastoma is an aggressive neoplasm that invades locally and spreads to regional lymph nodes, lungs, adrenal glands, brain, and bone marrow. The most important predictor of outcome is the tumor stage at presentation. Once stage is taken into account, the various histologic subtypes become less important prognostic indicators (Conran et al, 1992). Nonetheless, tumors of pure fetal-type histology tend to have the best prognosis (Haas et al, 1989).

Benign Liver Tumors (See Chapter 79)

Benign hepatocellular lesions encompass two main entities that strongly differ in terms of pathogenesis, clinical presentation, and behavior: *focal nodular hyperplasia* (FNH) and *hepatocellular adenoma* (HCA). Both groups are mainly observed in young women, usually in the context of oral contraception, and lesions develop in an otherwise normal liver. Whereas HCA is a neoplastic, clonal, and proliferative lesion, there is now consensus on the polyclonal, nonneoplastic, and reactive origin of FNH (Paradis et al, 1997; Bioulac-Sage et al, 2007a).

Focal Nodular Hyperplasia

FNH is ten times more common than HCA and is the second most common benign liver process after hemangioma. It is predominantly diagnosed in women 30 to 50 years of age. Most FNH is found incidentally, but some is revealed by clinical symptoms or biologic alterations such as pain, liver mass, or increased γ-glutamyltransferase (GGT) levels. However, complications such as rupture or bleeding are exceptional, and no evidence of malignant transformation has been reported. In contrast to HCA, the diagnosis of FNH is strongly suggested by imaging techniques, so that histopathologic examination is required for diagnosis in a minority of cases. When performed, fine needle biopsy of FNH can be difficult, because fibrous septa and thick abnormal arteries, the hallmarks of FNH, are usually missing (Fabre et al, 2002; Makhlouf et al, 2005).

On gross examination, FNH appears usually as a solitary, discrete, rounded mass, pale to beige, and well-delineated from background normal liver but without a defined fibrous capsule (Fig. 78.21). On cut surface, FNH displays a variegated and partly nodular organization, and frequently, but not always, a central stellate scar with radiating fibrous cords are also visualized at imaging (Wanless et al, 1985; Nguyen et al, 1999).

The typical histopathologic features of classical FNH include fibrous septa, which contain large dystrophic arteries with a peripheral ductular reaction, and an absence of interlobular bile ducts (Fig. 78.22). Hepatocytes are usually unremarkable, arranged in normal or mildly thickened plates without cytologic atypia, lined by a well-preserved sinusoidal framework. Steatosis or cholestatic degeneration with Mallory-Denk bodies may be seen.

FNH has been divided into *classic* and *nonclassic* forms (Nguyen et al, 1999). In forms of FNH other than the classic one, the diagnosis may prove difficult, because some of the distinguishing pathologic features may be unapparent. Such forms consist of FNH without a central scar, a mixed hyperplastic and adenomatous form, FNH with massive steatosis, and a form with atypia of the large-cell type (Nguyen et al, 1999). Strong evidence has been found, based on clonal features and the angiopoietin gene-expression profile, that the previously so-called telangiectatic variant of FNH may, in fact, belong to the HCA group (see below; Paradis et al, 2004).

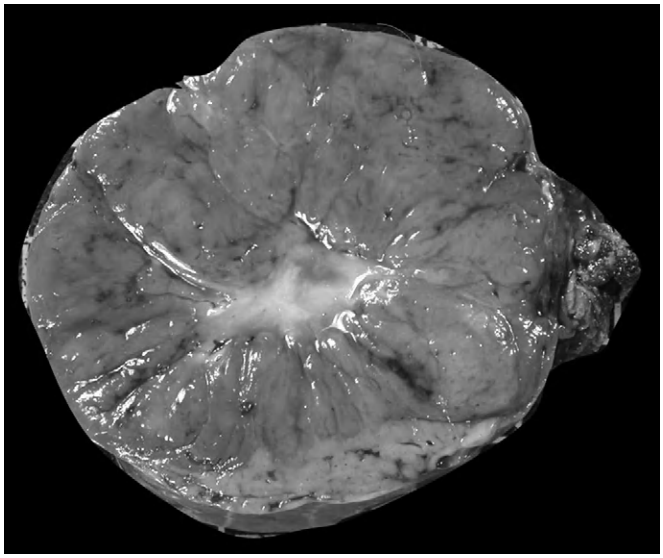


FIGURE 78.21. Focal nodular hyperplasia. A well-circumscribed nodular lesion with a central stellate scar and radiating fibrous cords.

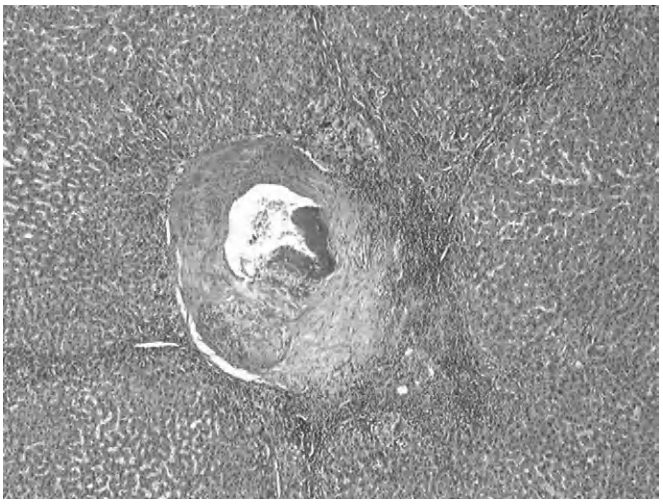


FIGURE 78.22. Focal nodular hyperplasia. Fibrous septa contain often large, dystrophic arteries with thick walls and thin, fibrous septa.

Immunohistochemistry may provide interesting information. Immunostaining with glutamine synthetase that shows focal positive hepatocellular areas, usually centered by hepatic veins and described as a maplike pattern, is highly consistent with the diagnosis of FNH and suggests a focal maintenance of lobular organization (Bioulac-Sage et al, 2009a). In addition, the perisinusoidal spaces in FNH exhibit an aberrant extracellular matrix associated with abnormal fibrillin-1 expression (Lepreux et al, 2004). Further study showed that the phenotype of endothelial cells lining the vascular channels in FNH differs from those in the remaining liver, associated with a downregulation of angiotensin I–converting enzyme/CD143 (Grantzdorffer et al, 2004).

FNH and FNH-like nodules are now well known to develop in the context of hepatic venous outflow obstruction, including Budd-Chiari syndrome (Maetani et al, 2002; Rangheard et al, 2002), and in other circulatory disorders of the liver such as portal vein thrombosis, portal vein agenesis, hereditary telangiectasia, and even in cirrhosis; this supports the concept of a vascular trigger in the pathogenesis of FNH (Kondo, 2001; Kondo et al, 2004; Bureau et al, 2004). Evidence supports that FNH is a hyperplastic reaction resulting from an arterial malformation related to increased arterial blood flow (Wanless et al, 1985).

Similar to HCA, FNH has been observed in association with the use of oral contraceptives, although the relationship remains controversial (Scott et al, 1984). FNH may occur together with HCA (Grange et al, 1987), and it has been found to be associated with a variety of nonhepatic tumors and tumorlike conditions, such as HCA, hemangioma of the liver, and several other tumors (e.g., in siblings with glioblastoma; Handra-Luca et al, 2006). The significance of these associations is unclear, but it suggests that the pathogenesis of FNH is probably heterogeneous.

Hepatocellular Adenomas

HCA is a rare, benign liver cell neoplasm strongly associated with oral contraceptive (OC) use and androgen steroid therapy



FIGURE 78.23. Hepatocellular adenoma. External view of a superficial tumor with large subcapsular and dilated vessels.

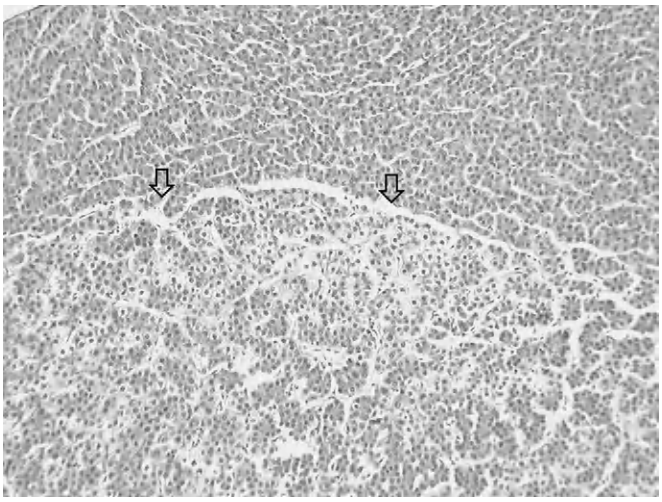


FIGURE 78.25. Hepatocellular adenoma. Proliferation of benign hepatocytes of normal size with a normal nuclear/cytoplasmic ratio pushing the normal liver parenchyma (*arrows*).

(Coombes et al, 1978; Nime et al, 1979). Its estimated incidence is 0.1 per year per 100,000 in non-OC users and reaches 3 to 4 per 100,000 in long-tem OC users. HCA can also occur spontaneously or in association with underlying metabolic diseases, including type 1 glycogen storage disease, iron overload related to β-thalassemia, and diabetes mellitus. Therefore, HCA represents a heterogeneous group of tumors in which histopathologic features may vary according to the etiologic background (Bioulac-Sage et al, 2007b).

HCA is usually solitary, sometimes pedunculated, with size ranging from a few millimeters to 30 cm. Large subcapsular vessels are commonly observed with large superficial tumors (Fig. 78.23). On analysis of cut sections, the tumor is soft, white to brown, and well delineated with little or no fibrous capsule (Fig. 78.24). Heterogeneous areas of necrosis or hemorrhage may be observed, especially in larger tumors. Histologically, HCA consists of a proliferation of benign hepatocytes of normal size or slightly enlarged with a normal nuclear/cytoplasmic ratio. Hepatocytes are arranged in a trabecular pattern without any residual portal tracts; a pseudoglandular growth pattern is possible but rare. Small, thin, and unpaired vessels without other portal tract elements—including connective tissue, bile ducts, or ductular reaction—are usually found throughout the tumor (Fig. 78.25). The cytoplasm of hepatocytes may be normal, glycogen-rich, or fatty, and cellular atypia can be impressive, especially in patients who have taken steroids for many years. In that context, differential diagnosis with HCC may be difficult. Vascular changes are frequent and include sinusoidal dilation, peliosis, infarcts, and hemorrhage. These changes may leave edematous or fibrotic regions, often with hemosiderin-laden macrophages.

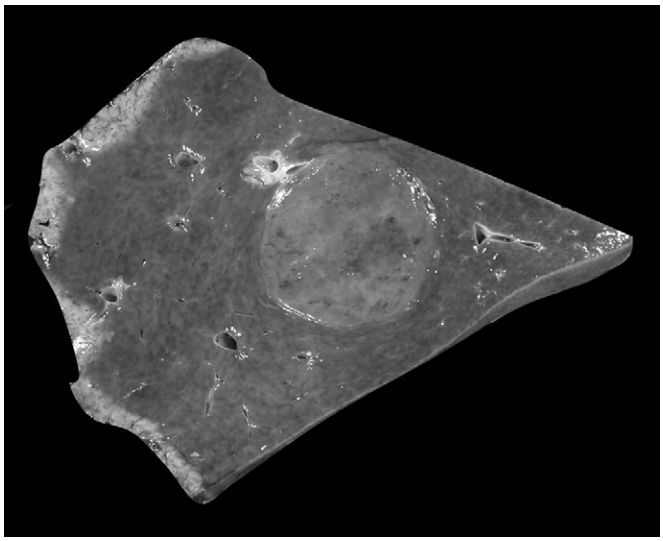


FIGURE 78.24. Hepatocellular adenoma. Soft, well-delineated tumor with little or no fibrous capsule and small, heterogeneous foci of hemorrhage.

Compared with patients with FNH, those with HCA are more likely to come to medical attention with symptoms such as spontaneous bleeding and hemorrhage, with an increased risk according to size for tumors larger than 5 cm in diameter (Dokmak et al, 2009). The risk for malignant transformation of HCA ranges between 4% to 10%, with a higher rate in males and in large HCA (Bioulac-Sage et al, 2007; Dokmak et al, 2009). In addition, recent evidence suggests that metabolic syndrome may favor development of HCC in a preexisting HCA (Paradis et al, 2009). Increased incidence of metabolic syndrome may partly explain the rising incidence of malignant transformation of HCA, especially in the male population (Farges et al, 2011).

Multiple HCA and so-called *adenomatosis* are not so rare (Fig. 78.26). Patients with multiple HCAs are predominantly female, but the use of OC appears to be less prevalent (Fléjou et al, 1985). Patients with glycogen storage disease type I are also at risk of developing multiple HCA (Labrune et al, 1997). Nevertheless, these tumors share the same clinical and imaging characteristics independent of their number (Dokmak et al, 2009; Lewin et al, 2006). In addition, a recent study supports that the risk of complications, including bleeding and malignant transformation, is similar to that in patients with solitary HCA, and it is not influenced by the number of tumors (Dokmak et al,

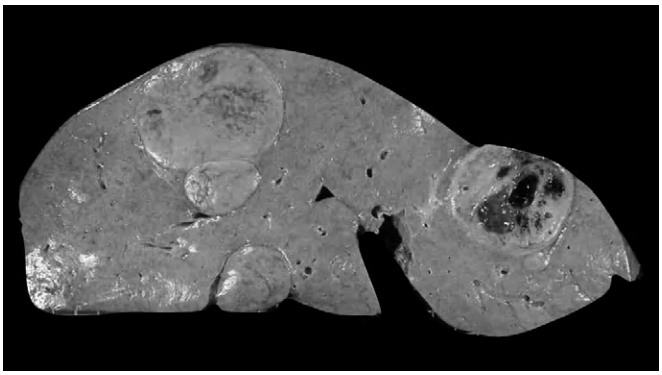


FIGURE 78.26. Adenomatosis. Multiple hepatocellular adenomas of various sizes are dispersed throughout the liver.

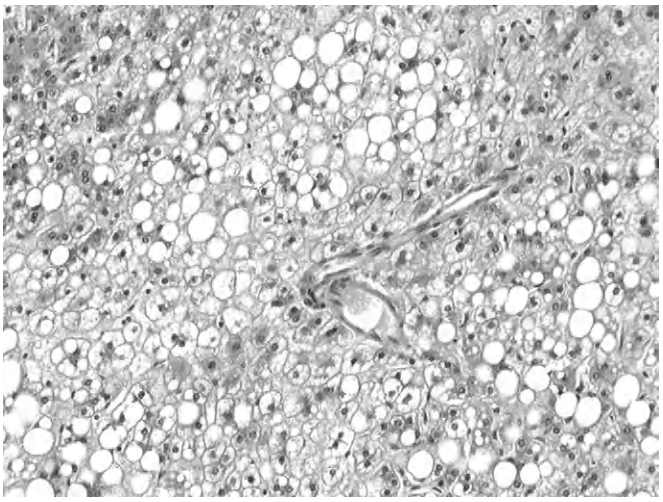


FIGURE 78.27. Steatotic adenoma. Most liver cells display marked steatosis. Unpaired arteries are visible between tumoral cells, but no portal tract.

2009; Bioulac-Sage et al, 2009b). The three main morphologic patterns of liver adenomatosis have been described: 1) *steatotic,* 2) *peliotic/telangiectatic,* and 3) *mixed* (Lewin et al, 2006). To note, the proportion of steatotic HCA is higher, and presence of microadenomatous foci in the "nontumoral liver" is more often observed in patients with liver adenomatosis (Dokmak et al, 2009).

MOLECULAR CLASSIFICATION OF HEPATOCELLULAR ADENOMAS. Molecular comprehensive studies have recently garnered further insights into the structure of HCA, demonstrating some degree of molecular and histologic heterogeneity among the group of HCAs. Today, HCAs are subdivided into three main subtypes according to phenotypic and molecular features: 1) *hepatocyte nuclear factor (HNF) 1α–mutated steatotic,* 2) *telangiectatic/inflammatory,* and 3) *β-catenin–mutated* (Paradis et al, 2004; Rebouissou et al, 2008; Zucman-Rossi et al, 2006). In addition, a small group of HCA that does not display any specific morphologic or genotypic features remains unclassified.

The first group of HCA displays biallelic mutations of the *TCF1* gene, inactivating the HNF-1α transcription factor. This homogeneous group is phenotypically characterized by marked steatosis and absence of cytologic abnormalities or inflammatory infiltrates (Fig. 78.27). Whereas both *HNF-1α* mutations are somatic in most cases, patients with inherited mutation in one allele of *HNF-1α* and an additional somatic mutation may develop HCA in the context of maturity-onset diabetes of the young type 3 (MODY3) and are predisposed to familial liver adenomatosis (Bluteau et al, 2002; Bacq et al, 2003).

The second group of HCA displays β-catenin–activating mutations and is characterized by increased risk for malignant transformation into HCC. These HCAs are mostly encountered in male patients and frequently show significant cell atypias and pseudoglandular formations (Fig. 78.28; Zucman-Rossi et al, 2006).

The third group of HCA is the inflammatory/telangiectatic adenoma group. These tumors, previously called *telangiectatic variant of FNH,* are well-delineated, unencapsulated tumors with areas of vascular changes without any fibrous scar (Fig. 78.29; Paradis et al, 2004; Wanless et al, 1989; Bioulac-Sage et al, 2005). Histologically, the hepatocellular proliferation contains small clusters of arteries embedded in collagen, often associated with an inflammatory infiltrate (lymphocytes and macrophages) and occasionally with ductular proliferation. In addition, foci of sinusoidal dilation and peliotic changes are usually present, and mild or significant steatosis may also be observed within tumoral cells. Although commonly observed in women using OC, telangiectatic/inflammatory HCA is often reported in patients with increased body mass index (BMI) associated with inflammatory syndrome (increased C-reactive protein [CRP] or fibrinogen serum levels; Paradis et al, 2004). Interestingly, in approximately 60% of these lesions, the interleukin (IL)-6 signaling pathway was found to be activated in relation to mutations in the *IL6ST* gene that encodes the signaling coreceptor gp130. As a matter of fact, the gain-of-function somatic mutations in *gp130* may result in the inflammatory phenotype of HCA, which would explain activation of the acute inflammatory phase observed in tumoral hepatocytes (Rebouissou et al, 2009).

The fourth group includes HCAs without any characteristic morphologic features or any of the genetic abnormalities previously described.

Surrogate immunophenotypic markers related to the genetic abnormalities may be used for the classification of the main subtypes of HCA (Bioulac-Sage et al, 2007b). Indeed, expression of liver fatty acid binding protein (LFABP), a protein positively regulated by HNF-1α, is absent in steatotic HNF-1α–mutated HCA, whereas it is expressed in nontumoral liver. Similarly, telangiectatic/inflammatory HCA displays positive immunostaining with acute-phase inflammatory proteins, such as serum amyloid A (SAA) and CRP. Most β-catenin–mutated HCA presents abnormal and cytoplasmic and/or nuclear staining of β-catenin in tumoral hepatocytes, usually with a focal positivity restricted to a few isolated tumoral hepatocytes. Immunostaining with glutamine synthetase, a β-catenin–targeted gene, showing a strong and diffuse cytoplasmic staining increases the sensibility for diagnosis of β-catenin–mutated HCA.

In surgical series of HCA, steatotic and telangiectatic/inflammatory subtypes appear to be equally distributed, accounting for 85% of overall HCA, whereas β-catenin-mutated HCA is reported in 10% to 15%.

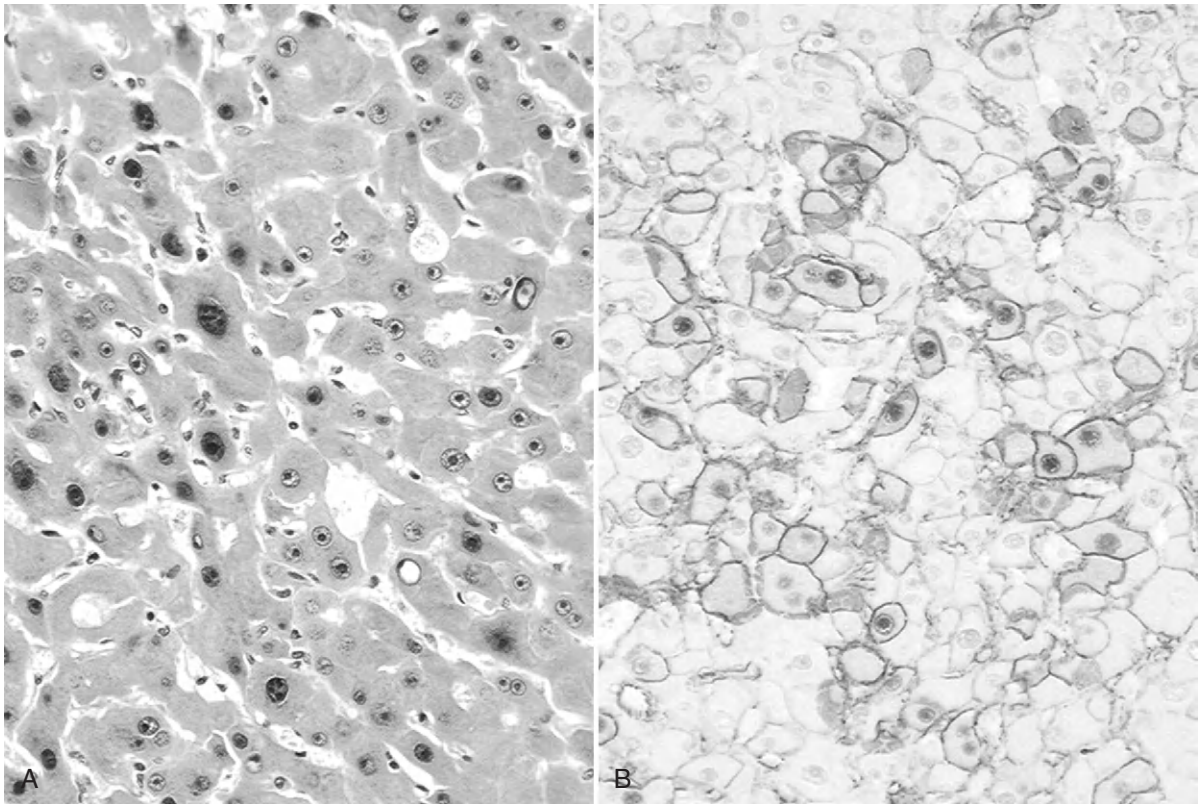


FIGURE 78.28. Hepatocellular adenoma with β-catenin–activating mutations. Liver cells display marked atypia **(A)**; β-catenin immunostaining **(B)** shows that some tumoral cells display abnormal cytoplasmic and nuclear staining.

BILIARY CELL TUMORS

Cholangiocarcinoma

Epidemiology and Clinical Background (See Chapters 50A and 50B)

Cholangiocarcinoma (CC) is a malignancy with biliary differentiation that develops along the biliary tree. It is the second most frequent primary malignant tumor of the liver (5% to 15% of liver primary malignancies; Malhi & Gores, 2006; Welzel et al, 2006). CC is mainly observed in adults with a peak incidence between 60 and 70 years and a male/female ratio of 1.5:1 (Parkin et al, 2005). CC is classified according to the anatomic location, either *intrahepatic* (IH-CC) or *extrahepatic* (EH-CC; Welzel et al, 2006). CC within the intrahepatic bile ducts is referred to as *peripheral cholangiocarcinoma,* arising in the bifurcation of the common bile duct as hilar CC, or Klatskin tumor; those in the extrahepatic bile ducts are extrahepatic CC (Klatskin, 1965). The updated WHO classification divides CC into *IH-CC, hilar CC,* and *EH-CC* (Bosman et al, 2010).

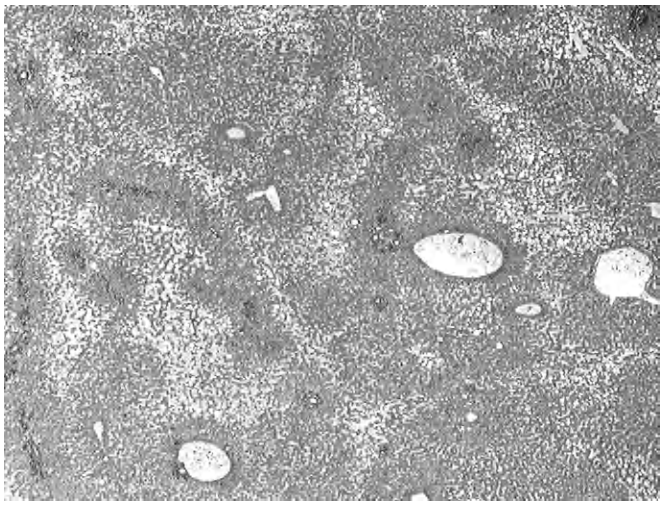


FIGURE 78.29. Telangiectatic/inflammatory adenoma. Extended foci of sinusoidal dilation are visible at low magnification.

Hilar tumors are the most common, accounting for 60% to 70% of CC; peripheral lesions and tumors located in the extrahepatic bile duct represent 5% to 10% and 20% to 30% of CC respectively (Malhi & Gores, 2006; Patel, 2006). Although hilar CCs are usually considered an IH-CC, their characteristics in terms of clinical presentation, morphology, and phenotype are closer to EH-CC.

Prevalence of CC shows a wide geographic distribution largely as a result of variations in regional environmental risk factors, with the highest incidence observed in Asian countries where parasitic infections—namely, *Opisthorchis viverrini* and *Clonorchis sinensis*—are endemic (Kim et al, 1989; Lim et al, 2006; Watanapa & Watanapa, 2002; see Chapter 45). Importantly, incidence of CC is rising in most countries, even in nonendemic areas. Such an increase is specifically observed for IH-CC, including hilar tumors, whereas incidence of EH-CC is stable or even decreased (Khan et al, 2002; Patel, 2001, 2006; Shaib et al, 2004).

Although several risk factors for CC are well established, most occur in patients without evident predisposing factors (Chapman, 1999). Primary sclerosing cholangitis (PSC) associated with ulcerative colitis is one of the most recognized risk factors (see Chapter 41). Indeed, patients with PSC display a 1.5% cumulative annual risk of developing CC, and 10% to 20% will eventually develop CC (Boberg et al, 2002). Fibropolycystic liver diseases that include choledocal cyst, Caroli syndrome, and congenital hepatic fibrosis are also common risk factors (Yamato et al, 1998; see Chapter 46); infections with parasitic liver flukes, such as *Opisthorchis viverrini* and *Clonorchis sinensis,* contribute to the high incidence of CC in Asia (Curado & Shin, 2007; Lim et al, 2006; see Chapter 45). Hepatholithiasis (see Chapters 39 and 44), cholelithiasis, cholangitis, chronic pancreatitis, and Thorotrast exposure are also risk factors (Chapman, 1999; Lipshutz et al, 2002). More recently, associations of CC with obesity, diabetes, human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection, and alcoholic liver disease have been reported in large population databases (Shaib et al, 2005; Welzel et al, 2007).

Clinical symptoms at diagnosis are dependent on the anatomic location, the growth types of the CC, and the tumor-node-metastasis (TNM) stage (Malhi & Gores, 2006). Although IH-CC is usually discovered at a late stage, hilar CC and EH-CC usually are found earlier with cholestasis (Ebata et al, 2009). The prognosis of CC is dismal, partly related to its propensity to invade directly adjacent liver parenchyma and to spread along the portal pedicles. Presence of perineural and vascular invasion is frequent in the hilar tumors. In the intraductal growth type, tumor often spreads intraluminally along the ducts, and intrahepatic metastases develop in nearly all advanced cases. The incidence of metastases to regional lymph nodes is higher than in HCC. Blood-borne spread occurs later, particularly to the lungs (Jiang et al, 2009; Patel, 2001; Suzuki et al, 2002).

Pathology (See Chapter 47)

Most CC develops in noncirrhotic liver. The Liver Cancer Study Group proposed a classification of CC based on growth patterns, and three main types emerged: 1) *mass forming,* 2) *periductal infiltrating,* and 3) *intraductal growing* (Yamasaki et al, 2003). These patterns are associated with different clinical evolution, the intraductal growing and the periductal infiltrating showing the best and worse prognoses, respectively (65% survival at 5 years vs. <5%; Jiang et al, 2009; Suzuki et al, 2002).

The mass-forming variation is the main type of IH-CC, accounting for approximately two thirds of cases. It is a solitary, nodular lesion developed in the liver parenchyma. The tumor is usually well delineated, not encapsulated, and gray to white with a firm and solid consistency (Fig. 78.30). In cases with large tumors, adjacent satellite tumoral nodules are commonly observed. The periductal infiltrating type spreads along the portal tracts with stricture of the involved ducts, potentially leading to obstructive dilation and cholangitis of the peripheral bile ducts (Fig. 78.31). The intraductal growing type is a polypoid or papillary tumor developed within dilatated bile duct lumen (Fig. 78.32). This type represents malignant progression of biliary papillomatosis or intraductal papillary neoplasm (IPN) of the bile duct (see below). These three patterns may overlap in the same tumor. Although most CC occurs in a background normal liver, recent reports suggest that independently to its origin, cirrhosis increases the risk 10-fold for patients

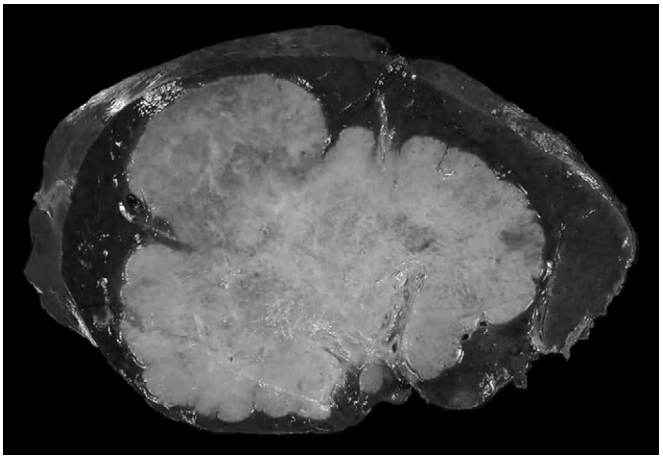


FIGURE 78.30. Cholangiocarcinoma, mass-forming type. Well-circumscribed, unencapsulated tumor is gray to white with a fibrous aspect developed in normal liver.

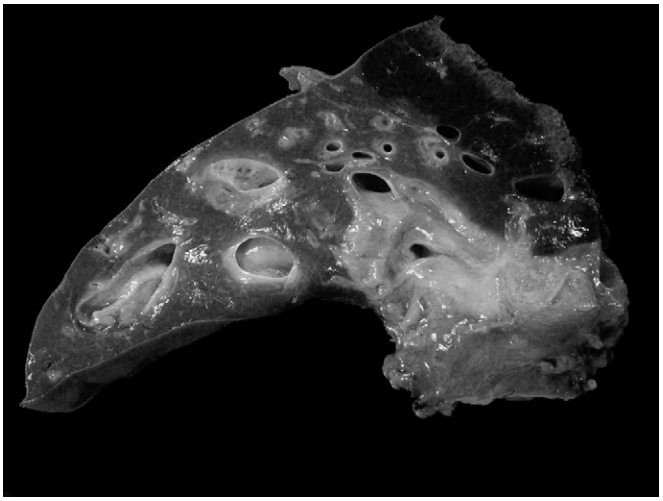


FIGURE 78.31. Cholangiocarcinoma, periductal infiltrating type. On cut section, infiltrating tumor developed along the portal tract and led to narrowing bile duct and obstructive dilation of peripheral intrahepatic bile ducts.

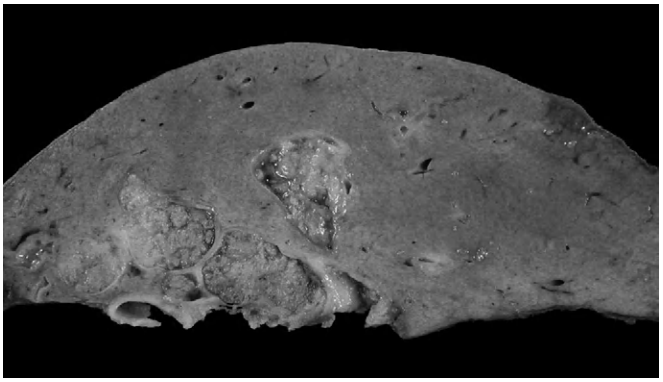


FIGURE 78.32. Cholangiocarcinoma, intraductal growing type. On cut section, endoluminal papillary proliferation growing into the bile ducts in a normal liver.

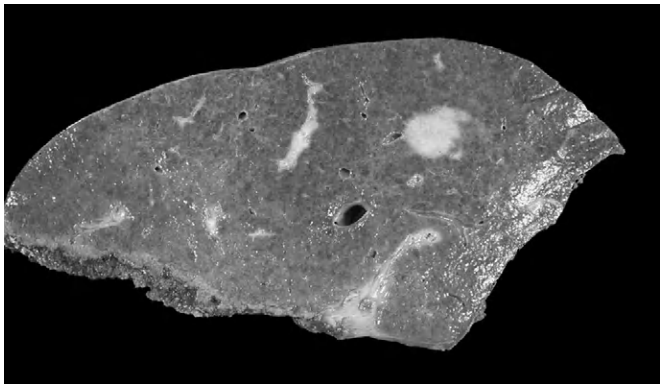


FIGURE 78.33. Cholangiocarcinoma in cirrhotic liver. Gross macroscopy of a small, solitary, well-delineated, unencapsulated white tumor developed on a cirrhotic liver.

to develop CC (Fig. 78.33; Shaib et al, 2005; Kobayashi et al, 2000).

The next most common form is mixed mass forming and periductal infiltrating CC, observed in 25% of cases. The pure peri-infiltrating type and the intraductal growth pattern are seldom observed (Guglielmi et al, 2009). CC arising in the intrahepatic small bile ducts or ductules is usually the mass-forming type, whereas CC arising in the intrahepatic large bile ducts (hilar CC) may be any of the three types (Nakanuma et al, 2008).

Most CCs are adenocarcinomas with a prominent, fibrous stroma. CC can be graded as well-, moderately, or poorly differentiated adenocarcinoma according to morphology. Most CCs are well-differentiated tumors with a glandular or tubular pattern of growth, although micropapillary, acinar, or cordlike patterns also occur. Similar to their normal counterparts, tumor cells are small or medium sized, cuboidal or columnar, with small nuclei and nucleoli (Fig. 78.34). Cytoplasm is usually pale, slightly eosinophilic, and sometimes more abundant and clear. Mucus secretion may be highlighted by Alcian blue staining, though the amount is usually small. Less differentiated tumors may show cribriform formations and/or a cordlike pattern, and poorly differentiated cancers are characterized by marked cellular pleomorphism. Hilar and EH-CC are more often well differentiated compared with peripheral CC (Guedj et al, 2009). Presence of dense, hyaline, fibrous stroma is a key feature of CC. Usually, the center of the tumor is densely sclerotic and hypocellular with focal calcifications, whereas the periphery of the tumors is more cellular. CC frequently infiltrates into portal tracts, invading portal vessels, and perineural invasion is a frequent finding in hilar CC (Fig. 78.35; Guedj et al, 2009).

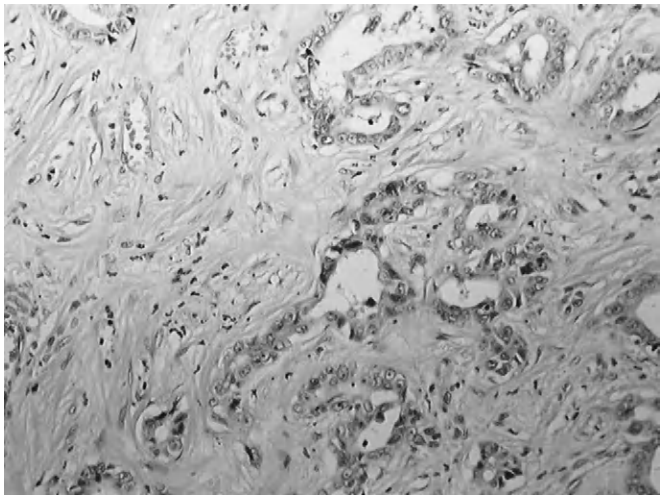


FIGURE 78.34. Cholangiocarcinoma: well-differentiated adenocarcinoma with a glandular pattern composed of small, cuboidal eosinophilic cytoplasm into a prominent fibrous stroma.

Several histologic variants have been reported, including adenosquamous and squamous carcinoma, mucinous carcinoma, signet-ring cell carcinoma, clear-cell carcinoma, mucoepidermoid carcinoma, lymphoepithelioma-like carcinoma, and sarcomatous CC.

Because CC originates from biliary epithelial cells, tumor cells display immunostaining with anti–CK7 and anti–CK19, carcinoembryonic antigen (CEA), and epithelial membrane antigen (EMA). The keratin profile is particularly useful for the differentiation of IH-CC from metastatic carcinoma derived from colorectal origin: CK7 is constantly expressed in CC, and CK20 is constantly expressed in metastatic colon carcinoma (Rullier et al, 2000). The diagnosis of IH-CC may be a challenging main diagnostic issue concerning the differential diagnosis between CC and metastatic carcinoma. In that setting, fine needle aspiration, and especially cytologic smears, have been shown as performant as core biopsy with a specificity of 100%, a sensitivity of 84%, and no false-positive cases of CC (Pupulim et al, 2008). In contrast, performance of biopsy is much more limited in cases of extrahepatic strictures. Additional approaches, including evaluation of ploidy and fluorescence in situ hybridization (FISH), have been shown to increase sensitivity up to 34% and specificity up to 98% (Kipp et al, 2004; Levy et al, 2008).

Biliary Papillomatosis and Biliary Intraepithelial Neoplasia

Biliary papillomatosis is closely associated with the intraductal growing pattern of CC. It is a rare condition characterized by the multicentric proliferation of columnar epithelium within the large bile ducts, although it can diffuse anywhere in the large intrahepatic or extrahepatic bile ducts (Padfield et al, 1988; Mercadier et al, 1984; Gouma et al, 1984). Biliary papillomatosis is a disease of middle-aged or older adults, and men are affected about twice as often as women. Grossly, the neoplasm invades the bile duct lumen, which is filled with soft pink to tan papillary excrescences, although skipped areas may be present (Zen et al, 2006). The surface epithelial cells covering these papillae are pancreatobiliary-, gastric-, or intestinal-type cells (Fig. 78.36). According to the WHO classification, and in similarity with pancreatic lesions, biliary papillomatosis has been renamed *biliary intraepithelial papillary neoplasm* (IPN). Although often cytologically benign, the cells can display greater degrees of nuclear atypia; in situ or invasive carcinoma is occasionally noted (Gouma et al, 1984; Neumann et al, 1976). Specific differentiation of the epithelial lining may be observed, including that of the pancreatobiliary type, intestinal type, oncocytic type, and gastric type. This invasive tumor may be a conventional, tubular-type adenocarcinoma, or in 10% to 15% of cases, it may be a mucinous (colloid) adenocarcinoma (Zen

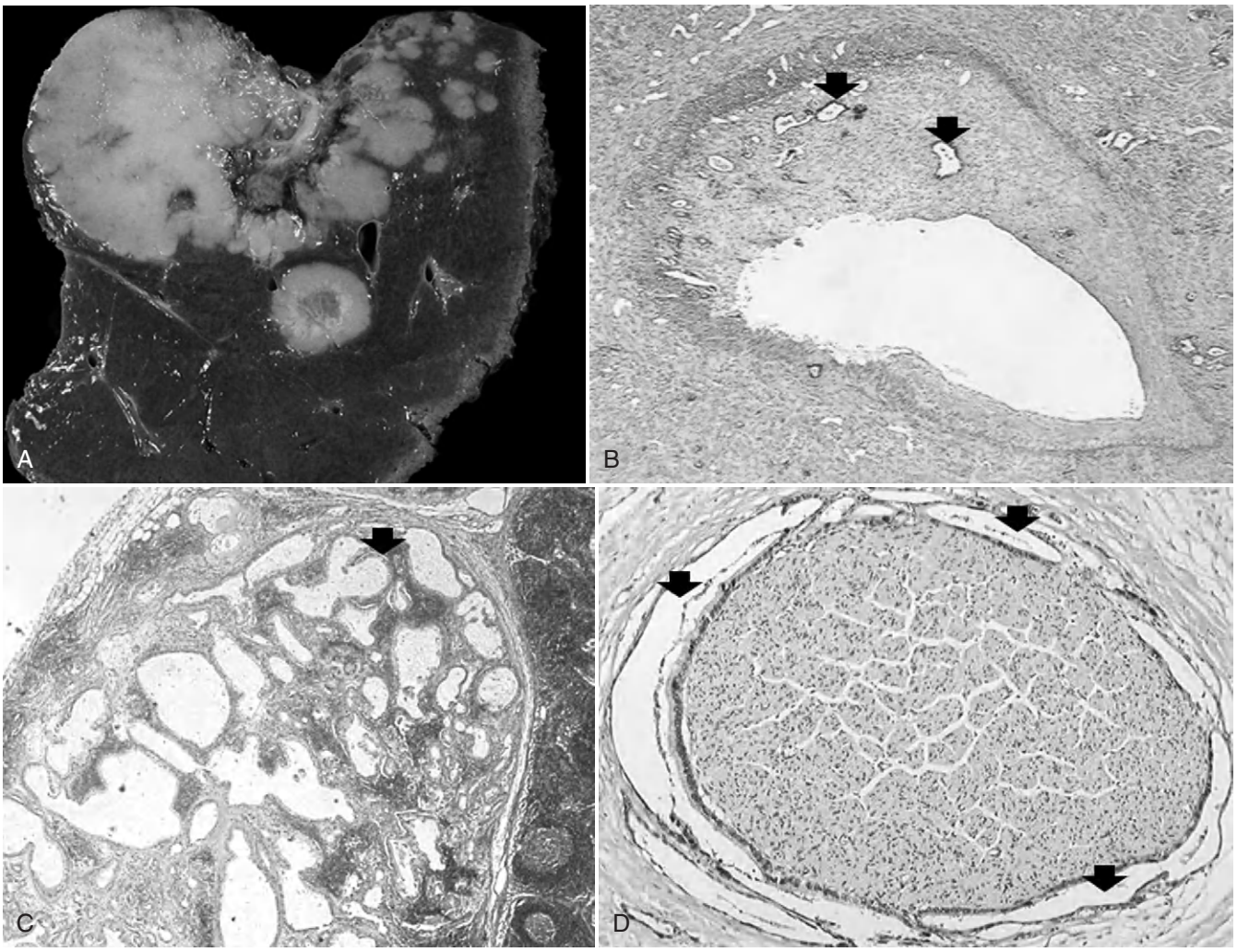


FIGURE 78.35. Histoprognostic factors of cholangiocarcinoma (CC): **A,** Gross macroscopy showing a mass-forming type of CC with satellite nodules. **B,** Lymph node metastasis (*arrows*). **C,** Vascular section invaded by carcinomatous glands (*arrow*). **D,** Perineural invasion with tumoral cells lining the nerve structure (*arrows*).

et al, 2006; Lee et al, 2004). Oncocytic variants of biliary papillomatosis have also been reported that share similar clinical features with their nononcocytic counterparts. The invasive tumors associated with these oncocytic papillary lesions are also oncocytic, as a result of the presence of abundant cytoplasmic mitochondria (Rouzbahman et al, 2007).

A precancerous lesion may also develop on flat bile duct epithelium. This lesion is now termed *biliary intraepithelial neoplasia* (BilIN). BilINs are characterized by abnormal epithelial cells with multilayering of nuclei and micropapillary projections into the duct lumen (Zen et al, 2007). The abnormal cells have an increased nuclear/cytoplasmic ratio, partial loss of nuclear polarity, and nuclear hyperchromasia. They are divided according to degrees of atypia into *low-grade* (BilIN-1), *moderate* (BilIN-2), and *high-grade* dysplastic lesions (BilIN-3) (Fig. 78.37; Zen et al, 2005).

Hepatocholangiocarcinoma

Hepatocholangiocarcinoma—also known as *combined hepatocellular cholangiocarcinoma*, or mixed HCC-CC—is a rare but increasingly recognized neoplasm of the liver, accounting for approximately 5% of primary liver malignancies (Allen & Lisa, 1949; Aoki et al, 1993; Maeda et al, 1995). It shares unequivocal features of both HCC and CC as defined by the WHO classification. Depending on various investigations, patients with combined HCC-CC share similar clinical and pathologic features with patients with HCC (Maeda et al, 1995; Ng et al, 1998) or CC (Tickoo et al, 2002; Jarnagin et al, 2002), or their tumors are clinicopathologically different from those of CC or HCC. Caution must be exercised when interpreting the results of these studies, regarding how combined HCC-CCs were defined in the studies, and there may have been population and etiology differences as well. Taken together, it appears that combined HCC-CCs lack a specific clinical parameter, and this may be explained by various studies across different geographic regions, etiologies, and populations.

Although a unified histopathologic criteria for combined HCC-CC is still not available, it is generally accepted that a firm diagnosis of combined HCC-CC requires evidence of HCC differentiation—a trabecular growth pattern, bile production, or bile canaliculi—and clear evidence of CC, such as true

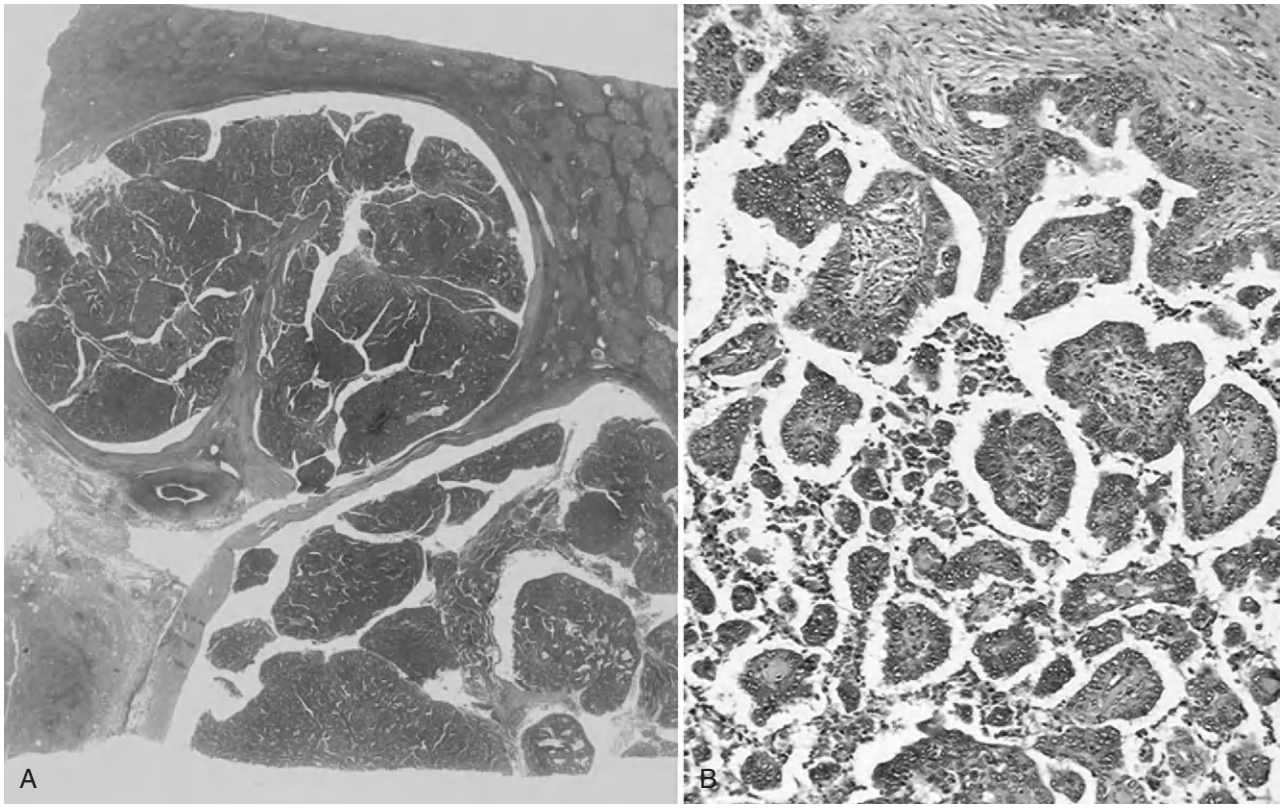


FIGURE 78.36. Biliary papillomatosis. **A,** Low magnification. Bile duct lumen is covered by papillary excrescences. **B,** Tumoral papillae with fibrous stalk covered by proliferation of cuboidal cells.

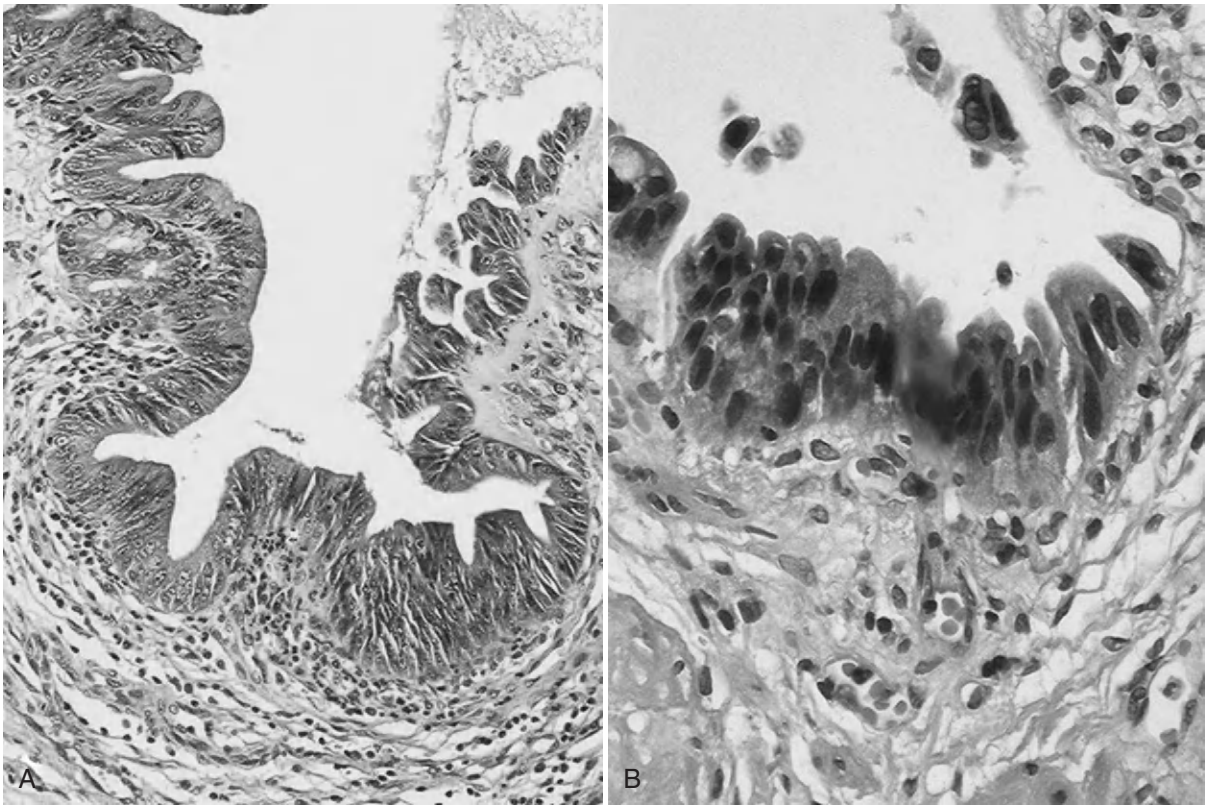


FIGURE 78.37. Biliary intraepithelial neoplasia (BilIN). **A**, BilIN-2 is characterized by micropapillary projections lined by multilayered cells with cell atypias. **B,** BilIN-3 with atypical cells showing increased nuclear/cytoplasmic ratio, loss of nuclear polarity, and nuclear hyperchromasia.

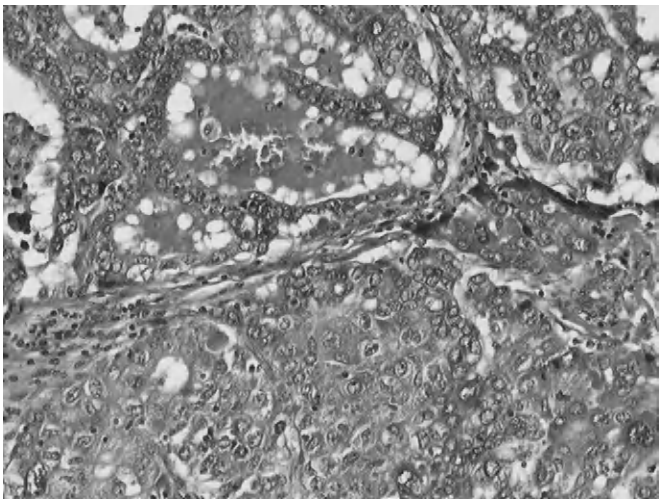


FIGURE 78.38. Hepatocholangiocarcinoma. Association of a hepatocellular differentiation (*top half*) with trabecular and solid growth pattern and cholangiocarcinoma differentiation (*bottom half*) with glandular structures lined by biliary-type epithelium.

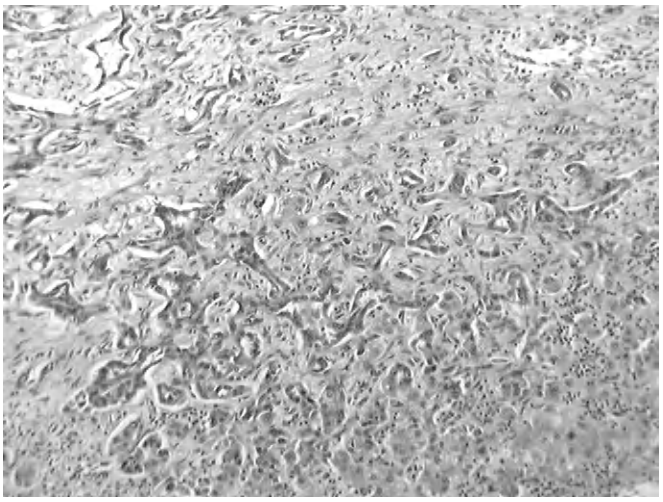


FIGURE 78.39. Cholangiolocarcinoma. Small, monotonous, tubular formation resembles ductular proliferation within dense, fibrous stroma.

glandular structures formed by biliary-type epithelium, mucin production, or prominent desmoplastic stroma (Fig. 78.38; Maeda et al, 1995; Yano et al, 2003; Goodman et al, 1985). Separate HCC and CC coincidentally found in the same liver is generally considered a collision tumor and is excluded by the WHO classification of combined HCC-CC. This has been further supported by the genetic findings that two independent neoplastic clones develop at close proximity, hence no histologic transitions exist (Fujii et al, 2000).

The cell of origin of combined HCC-CC has been a matter of debate. The fact that the HCC and CC elements intermingle with each other in a transitional area strongly supports that both components of the cancer derive from hepatic progenitor cells. Recent molecular investigations support this hypothesis, because single clonal tumors with a homogeneous genetic background in both HCC and CC components of combined HCC-CC have been demonstrated, suggesting that histologic diversity of HCC-CC is a phenotypic expression of the divergent differentiation potential of a single clone (Fujii et al, 2000; Theise, 2002; Cazals-Hatem et al, 2004).

Cholangiolocellular Carcinoma

Cholangiolocellular carcinoma is a very rare neoplasm, accounting for less than 1% of primary liver cancers (Komuta et al, 2008; Steiner & Higginson, 1959). In this tumor, more than 90% of the neoplasm is composed of small, monotonous glands that represent residual ductular proliferation with an antler-like anastomosing pattern (Fig. 78.39). In addition, HCC and CC components may also be present, altogether comprising less than 10% of the neoplasm, although these three histologic components showed transitions among each other (Komuta et al, 2008). The relationship between cholangiocellular carcinoma and combined HCC-CC remains to be clarified, however, they may overlap to some degree and belong to a spectrum of the primary liver neoplasms that arise from the hepatic progenitor cells.

Biliary Cystadenoma and Cystadenocarcinoma (See Chapter 79B)

Biliary Cystadenoma

Biliary cystadenoma is an uncommon cystic neoplasm that accounts for less than 5% of all intrahepatic biliary cysts (Ishak et al, 1977; Van Roekel et al, 1982). The histogenesis of biliary cystadenoma remains uncertain, although an origin from embryonic foregut rests has been advanced (Akwari et al, 1990). Almost all of these tumors occur in middle-aged women, with a peak incidence in the fifth decade (Devaney et al, 1994).

Biliary cystadenomas are characteristically large (2.5 to 28 cm), multiloculated cysts without communication with the intrahepatic biliary system (Fig. 78.40). The tumor is solitary and spherical and contains white to yellow to brown mucinous or gelatinous material. Individual locules vary in size, and the internal surface is typically smooth with occasional

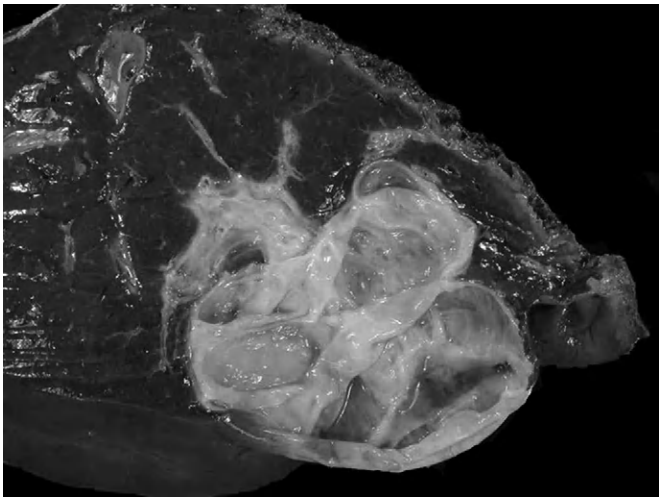


FIGURE 78.40. Cystadenoma. The tumor is cystic, solitary, and spherical with a smooth, white internal surface.

trabeculations or papillations (Ishak et al, 1977). If solid areas are present, concern should be raised for an invasive component (Devaney et al, 1994; Buetow et al, 1995).

Histologically, the cysts are lined by a simple columnar to cuboidal epithelium with mucin-filled cytoplasm. On occasion, the epithelium may be pseudostratified or focally ulcerated, and goblet cells or squamous cells are sometimes seen. Nuclear atypias and mitoses are rare, and their presence should raise the possibility of complicating cystadenocarcinoma. Also recognized is a serous variant of biliary cystadenoma, which is distinguished by a single layer of glycogen-rich cuboidal cells similar to those seen in microcystic adenomas of the pancreas.

Underneath is an ovarian type stroma, which is absent in cases arising in men (Devaney et al, 1994). Typically, this stroma is densely cellular and composed of closely packed spindle cells reminiscent of ovarian stroma. This stroma stains with antibodies to estrogen and progesterone receptor, and growth can occur during hormone replacement therapy and pregnancy (Daniels et al, 2006). As dysplasia may be patchy, and invasive tumors may arise in as many as 25% of cystadenomas (Ishak et al, 1977), the gross specimens of cystic tumors need to be carefully examined for suspicious areas, and extensive sampling of the cyst should be performed.

Biliary Cystadenocarcinoma

This rare malignancy generally develops as a complication of a biliary cystadenoma, which may or may not demonstrate the distinctive mesenchymal stroma (Ishak et al, 1977; Wheeler & Edmondson, 1985b; Woods, 1981). Most patients are between 45 and 70 years of age, and men and women are equally affected. Cysts are generally multilocular and range in size from 5 cm in diameter to more than 20 cm. Although the gross appearance can be difficult to distinguish from a biliary cystadenoma, the suspicion of malignancy should be raised if areas of large, solid, thickening papillary masses are present (Ishak et al, 1977).

Histologically, cystadenocarcinomas are usually well-differentiated adenocarcinomas, often with an intracystic papillary component, and they are composed of malignant epithelial cells with varying degrees of nuclear stratification, pleomorphism, and hyperchromasia; often, the benign epithelium of the preexisting cystadenoma can be identified. Transitions can sometimes be discerned with varying degrees of epithelial dysplasia (Woods, 1981). The tumor infiltrates the underlying cyst wall, and vascular invasion and extension into adjoining hepatic parenchyma or adjacent organs are characteristic of malignancy. These tumors tend to grow slowly, but they eventually invade adjacent structures and metastasize to distant sites. In rare cases the carcinoma demonstrates adenosquamous, oncocytic, or spindle-cell (pseudosarcomatous) differentiation (Moore et al, 1984; Unger et al, 1987; Wolf et al, 1992).

Other Benign Cystic and Bile Duct Lesions: Ciliated Hepatic Foregut Cyst, Biliary Adenoma, and Biliary Hamartoma

Ciliated Hepatic Foregut Cysts

A ciliated hepatic foregut cyst is a rare lesion that is generally solitary and unilocular (Terada et al, 1990). This lesion is smaller than 3 cm and lined by a characteristic ciliated pseudostratified columnar epithelium with mucous cells and an underlying fibrous wall that contains abundant smooth muscle (Fig. 78.41; Vick et al, 1999a). Occasional cases of squamous carcinoma arising in a ciliated hepatic foregut cyst have been reported (Vick et al, 1999b). Because these features are similar to those seen in bronchial and esophageal cysts, an analogous origin from the embryonic foregut is suggested (Wheeler & Edmondson, 1984).

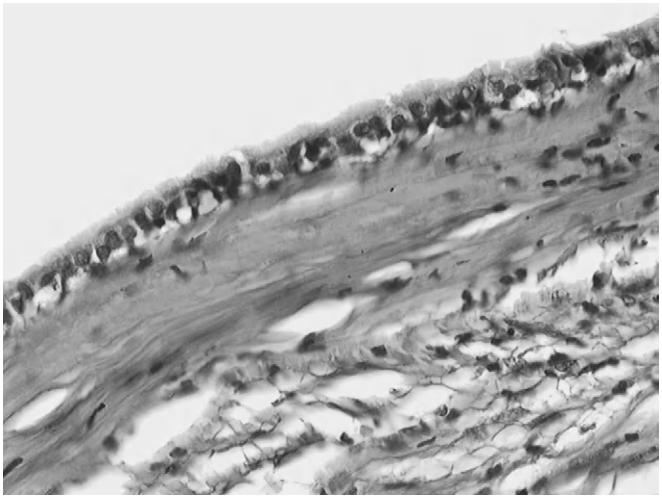


FIGURE 78.41. Ciliated hepatic foregut cyst. The cystic wall is lined by a characteristic ciliated pseudostratified columnar epithelium with an underlying fibrous wall.

Bile Duct Adenoma

Bile duct adenoma is an incidental finding, often discovered at surgery, because most develop superficially under the Glisson capsule (Gold et al, 1978; Allaire et al, 1988). It is an inconsequential lesion that may be mistaken for bile duct hamartoma or metastatic carcinoma (Govindarajan & Peters, 1984). Almost all bile duct adenomas are less than 1 cm in diameter, although cases up to 4 cm have been recorded (Govindarajan & Peters, 1984). The lesion typically appears as a discrete white nodule, usually solitary and subcapsular in location, with a firm consistency and unencapsulated margin. Histologically, bile duct adenoma is made of a compact proliferation of small ductules with small or inapparent lumens lined by cuboidal epithelium with slightly basophilic cytoplasm and bland, regular nuclei (Fig. 78.42). Mitoses, cytologic atypia, and nuclear pleomorphism are absent. Ductular structures are surrounded by a fibrotic, hyalinized stroma that can distort ductal structures, portal tracts are often entrapped within the tumor, and scattered inflammatory cells are sometimes seen. Malignant transformation has not been clearly documented.

Biliary Microhamartoma

Biliary microhamartoma, also known as a *von Meyenburg complex*, is a developmental malformation resulting from the aberrant remodeling of the ductal plate. The lesion is relatively common; it occurs in about 3% of all autopsied patients and is generally found incidentally. Microhamartomas are often multiple, but when numerous, this raises the possibility of early autosomal dominant polycystic disease or congenital hepatic fibrosis (Desmet, 1992). The lesions appear as small, subcapsular white or green nodules that seldom exceed 0.5 cm in diameter, often located within or close to portal tracts. Microscopically, biliary

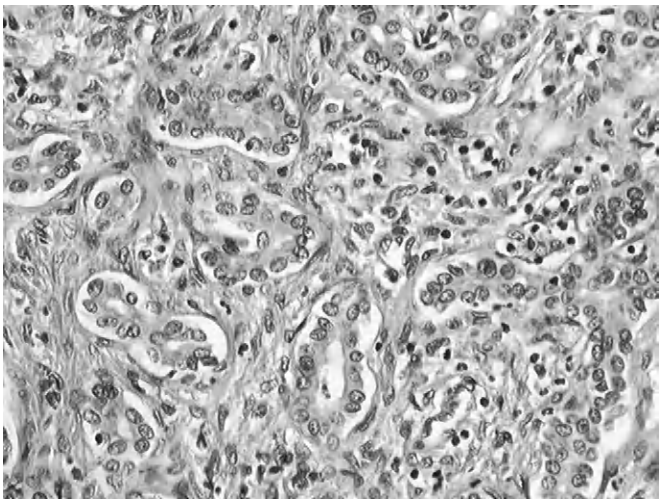


FIGURE 78.42. Bile duct adenoma. Proliferation of small ductules with small or inapparent lumens lined by bland cuboidal epithelium with few inflammatory cells.

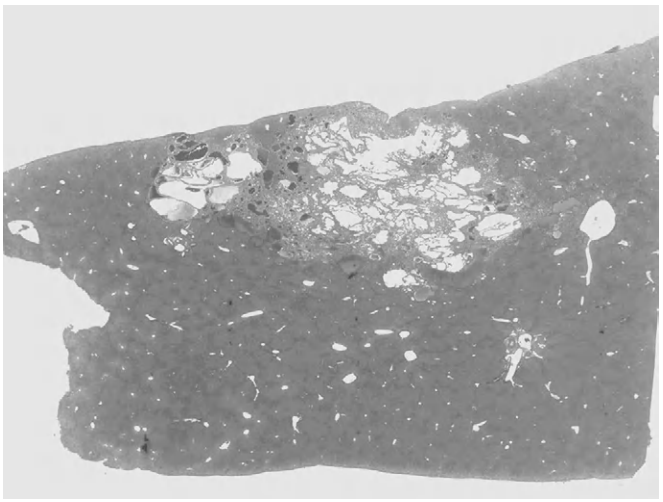


FIGURE 78.44. Hemangioma, low magnification. The lesion is made of vascular cavities, some filled with blood, and is well demarcated from the surrounding liver.

microhamartomas are composed of numerous bile duct–like structures with an angulated or branching configuration with varying degrees of dilation. These structures are lined by a single layer of low columnar or elongated epithelium, and their lumens contain bile plugs or eosinophilic proteinaceous debris; ducts are embedded within a dense, fibrous stroma (Fig. 78.43). In rare cases, microhamartomas have been complicated by the development of cholangiocarcinoma (Burns et al, 1990; Honda et al, 1986).

MESENCHYMAL TUMORS

Benign Mesenchymal Tumors

Hemangioma

Hemangioma is the most common primary tumor of the liver, with a prevalence in autopsy surveys that ranges from 0.4% up to 20% (Karhunen, 1986). This lesion is discovered in all ages and both sexes, although hemangiomas are more frequent in older age groups, and in most series they favor women (Bioulac-Sage et al, 2008).

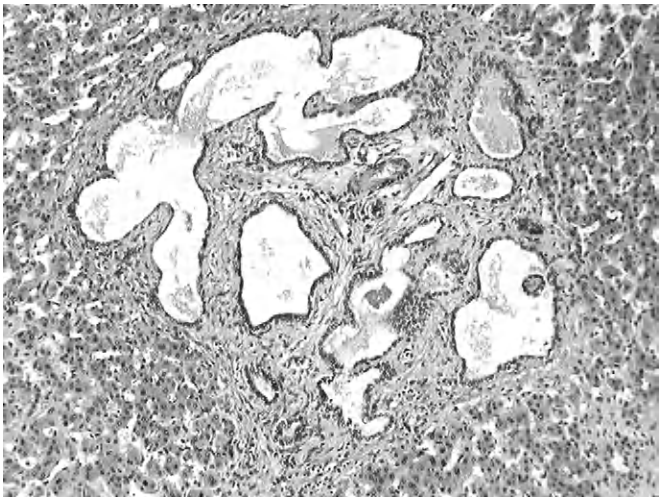


FIGURE 78.43. Biliary microhamartoma. Focal proliferation of bile duct–like structures with an angulated or branching configuration and varying degrees of dilation embedded within a dense, fibrous stroma.

Most hemangiomas are clinically silent and are discovered incidentally during radiologic examination, surgery, or autopsy. However, larger tumors can occasionally become clinically evident with abdominal discomfort, hepatomegaly, or a palpable abdominal mass (Schnelldorfer et al, 2010). Rare reports describe spontaneous rupture with hemoperitoneum or a bleeding diathesis with hypofibrinogenemia or platelet sequestration and consequent thrombocytopenia (Kasabach-Merritt syndrome; Gandolfi et al, 1991). Hemangiomas can be correctly identified in most instances by radiographic imaging (see Chapter 17). Needle biopsy is not necessary and is, in fact, contraindicated because of the risk of severe hemorrhage (Trastek et al, 1983).

Most hemangiomas are solitary lesions less than 4 cm in diameter (Fig. 78.44). Multiple tumors are seen in up to 25% of cases, and hemangiomas up to 30 cm have been recorded. The tumors can occur anywhere in the liver but are frequently located immediately beneath the hepatic capsule. The cut surface demonstrates a soft, dark red, spongy mass with blood-filled cavities and occasional foci of thrombosis, scarring, or calcification. Most are well demarcated from the surrounding liver. Histologically, hemangiomas are composed of dilated vascular spaces lined by flattened endothelial cells and supported by connective tissue septa. The septa consist of poorly cellular fibrous bands with varying degrees of myxoid change and scarring. Thick-walled blood vessels and scattered bile ducts are sometimes found in larger septa, and the vascular spaces are frequently the sites of thrombi in various stages of organization. Hemangiomas may also demonstrate involutional changes with extensive hyalinization, obliteration of the vascular channels, and sometimes calcification.

Infantile Hemangioendothelioma

Infantile hemangioendothelioma is a benign pediatric vascular proliferation of the liver (see Chapter 82). Although uncommon, it is nonetheless the predominant hepatic neoplasm of the first year of life, and only a few cases have been reported in

adults. Most cases manifest clinically with hepatomegaly, diffuse abdominal enlargement, or a palpable abdominal mass. The prognosis is generally good, because the tumors usually undergo spontaneous involution and can completely regress (Dachman et al, 1983); however, a potentially life-threatening feature is not uncommon because of arteriovenous shunting through the tumor that may result in cardiac failure, with a reported mortality rate of about 25% (Vorse et al, 1983).

Infantile hemangioendothelioma typically appears as sharply defined but unencapsulated masses, ranging between 1 and 15 cm in diameter. On cut section, the lesion is well delineated with a gray-tan to pink color and a firm or spongy appearance. Central hemorrhage, necrosis, fibrosis, and calcification may be noted in larger lesions.

Histologically, the tumor is characterized by a proliferation of small, irregular vascular channels lined by a single layer of plump endothelial cells. These channels display small, often compressed lumens and contain varying quantities of red blood cells. The endothelial cells are uniform, with almost no mitoses. The fibrous stroma is composed of scattered fibroblasts and collagen fibers, and small bile ducts are scattered through the mass. The tumor generally grows by expanding into adjacent liver, although hepatic plates can sometimes be entrapped along its advancing edge.

Some hemangioendotheliomas may demonstrate atypical histologic features with atypical crowded and multilayered endothelial cells that show hyperchromatic nuclei and occasional mitoses. This atypical pattern has been referred to as *type 2,* in contrast with the more common *type 1* pattern (Dehner, 1978). Most of the type 2 tumors pursue a benign course, but some exhibit more aggressive behavior with extensive local growth and, in some instances, metastases. Consequently such tumors have been considered by some investigators as a low-grade childhood form of angiosarcoma (Dehner & Ishak, 1971).

Mesenchymal Hamartoma

Mesenchymal hamartoma is a tumor-like lesion arising in young children, usually those younger than 2 years, although sporadic examples are described in adolescents and adults (see Chapter 82; Dehner, 1978; Gramlich et al, 1988). It is thought to represent a developmental anomaly, probably arising from the aberrant formation of primitive portal mesenchyme together with secondary degenerative changes (Siddiqui & McKenna, 2006). Although some cases are discovered incidentally, most are clinically evident because of their large size, causing progressive abdominal distension or a palpable abdominal mass (Srouji et al, 1978).

Mesenchymal hamartoma appears grossly as a solitary mass that ranges from 3 to 30 cm in diameter. Typically, the tumor is well demarcated from the adjacent liver, although an infiltrative border and satellite lesions are not so rare (Stocker & Ishak, 1983). On cut surface, the lesion is composed of multiple small cysts filled with clear or mucoid fluid, lined by a smooth surface, and surrounded by a myxoid tissue with fibrous bands (Dehner et al, 1975).

Histologically, mesenchymal hamartoma is characterized by the association of immature myxoid mesenchymal tissue, bile ducts, blood vessels, and mature hepatocytes. The mesenchymal component consists of elongated bland cells within an edematous myxoid stroma that contains varying amounts of collagen. Focally, this stroma undergoes cystic degeneration, yielding a lymphangiomatous appearance and giving rise to the grossly visible cysts. In addition, numerous thick-walled veins, foci of extramedullary hematopoiesis, and scattered bile ducts can be observed. The ducts often exhibit branching or cystically dilated lumina. Bile duct cells can be atrophic or hyperplastic, and small clusters of unremarkable hepatocytes that lack a lobular arrangement are interspersed within the tumor (Stocker & Ishak, 1983).

Angiomyolipoma

Angiomyolipoma (AML) is a rare tumor that occurs at a median age of about 45 years; it is predominant in women by a ratio of 5:1 (Goodman & Ishak, 1984; see Chapter 79A), and 10% of cases occur in the setting of tuberous sclerosis, usually associated with coexisting renal AML (Petrolla & Xin, 2008). Size ranges widely, from 1 cm in diameter to more than 20 cm. Tumors are usually single, but multiple tumors in the liver and multiorgan involvement have been described (Nonomura et al 1994, 1995). Only one malignant degeneration in a liver AML has been reported in the literature (Dalle et al, 2000).

Most AMLs are well circumscribed but not encapsulated (Fig. 78.45). AMLs have three key components: 1) *tortuous vessels*, 2) *fat*, and 3) *myoid cells.* Liver AMLs demonstrate solid growth with a variable amount of fat and myoid elements. Hematopoietic cells may also be seen in some cases. Myoid cells may be epithelioid or spindled. The fat component is typically mature, but lipoblast-like cells may be found. A hallmark of this lesion is the existence of tortuous, thick-walled vessels that are usually lacking in elastic lamina and are often rimmed by epithelioid myoid cells (Fig. 78.46; Tsui et al, 1999). The diagnosis of AML may be confirmed by immunohistochemistry, because myoid cells are reactive to HMB-45 (Sturtz & Dabbs, 1994).

The histogenesis of AML is unclear, but recent studies suggest AML is a clonal proliferation that favors a neoplastic process (Flemming et al, 2000). Strong arguments suggest that the three cell types are derived from a single precursor cell in the perivascular space, the *perivascular epithelioid cell* (PEC; Tsui et al, 1999; Hornick & Fletcher, 2006). AMLs composed of a large number of epithelioid cells have been termed *PEComas* (perivascular epithelioid cell tumors; Bonetti et al, 1997).

Lipoma

Lipomatous tumors are rarely found in the liver. Most occur in adults as asymptomatic lesions, incidentally detected by

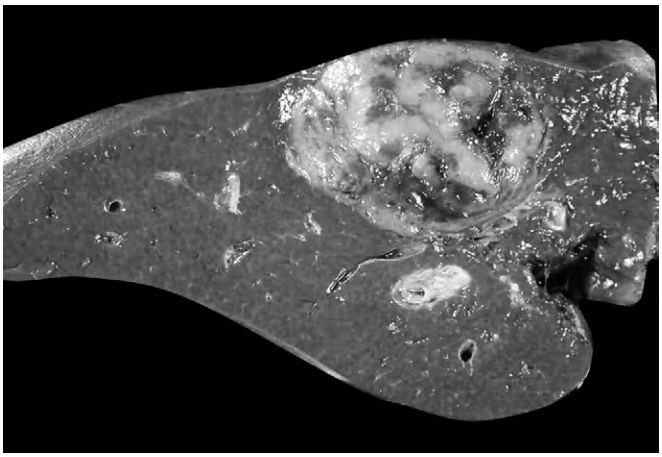


FIGURE 78.45. Angiomyolipoma. A well-circumscribed, soft, white nodular lesion with foci of hemorrhage.

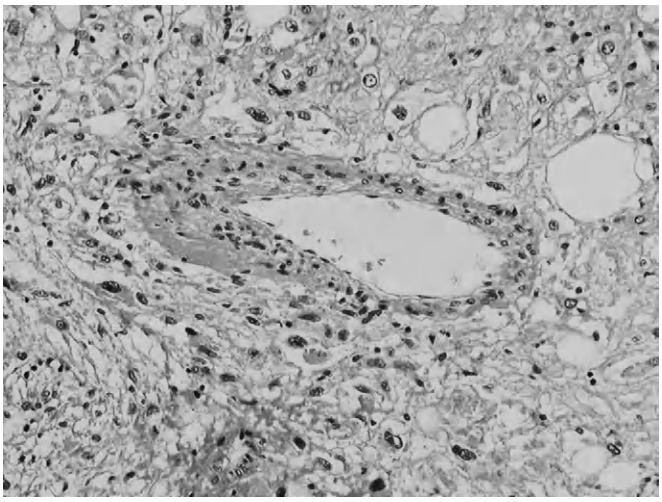


FIGURE 78.46. Angiomyolipoma, light microscopy. The lesion is composed of myoid cells with fat droplets and thick-walled vessels.

radiographic imaging (Roberts et al, 1986). Typically, the tumors are solitary masses ranging from 1 to 20 cm. Microscopically, they are composed of mature adipose tissue, either pure or accompanied by a vascular, hematopoietic, or myeloid component. Depending on the constituents, the tumor is designated a *pure lipoma, angiolipoma,* or *myelolipoma* (Nishizaki et al, 1989; Peters et al 1983).

Coelomic fat ectopia consists of a rounded nodule of fat attached to the hepatic capsule, usually on the anterior diaphragmatic aspect of the right lobe (Komori et al, 2008). The histologic features accordingly entail mature adipose tissue with various degenerative changes, including calcification (Wheeler & Edmonson, 1985b).

Fibrous Tumors

Localized fibrous tumors of the liver have been reported under a variety of names, including *fibroma, solitary fibrous mesothelioma,* and *benign mesothelioma.* Similar to their pleural counterparts, these tumors arise from submesothelial connective tissue and form large masses, from 5 cm in diameter to more than 25 cm, that protrude from the hepatic surface (Komori et al, 2008). The histologic features entail interlacing bundles of bland spindle cells with variable cellularity and intermixed collagen fibers (Kim & Damjanov, 1983; Kottke-Marchant et al, 1989).

Other Benign Mesenchymal Tumors

Sporadic cases of hepatic leiomyoma, lymphangiomatosis, chondroma, hemangioblastoma, and myxoma have been recorded (Rojiani et al, 1991; Van Steenbergen et al, 1985; Fried et al, 1992; Santos et al, 2010).

Malignant Mesenchymal Tumors

Epithelioid Hemangioendothelioma

Epithelioid hemangioendothelioma is a low-grade malignant tumor of endothelial origin that can occur in several sites, including the liver. At diagnosis, most patients are in their fourth or fifth decade of life, and about 60% are women (Ishak et al, 1984). Unlike hepatic angiosarcoma, no strong etiologic associations or predisposing factors have been identified, although a relationship with long-term OC use has been suggested (Dean et al, 1985).

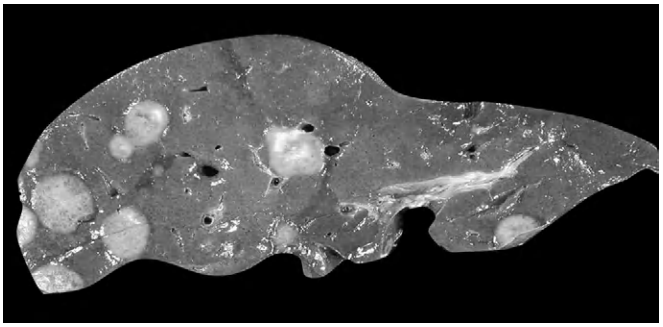


FIGURE 78.47. Epithelioid hemangioendothelioma, characterized by diffuse involvement of both lobes by white to tan tumor nodules of various sizes with a firm consistency.

Epithelioid hemangioendothelioma tends to be an indolent and slowly growing tumor, but the natural history can vary considerably (Woodal et al, 2008). Most patients have a prolonged survival, whereas others suffer rapid deterioration with early death from hepatic failure or extensive tumor spread (Dean et al, 1985; Dietze et al, 1989). Metastases commonly involve the lung, spleen, abdominal lymph nodes, omentum, and peritoneum. Even with metastatic disease, some patients can survive for many years, although the distinction between metastatic spread and multicentric disease is sometimes difficult to make (Mehrabi et al, 2006).

In about 80% of cases, the tumor is multifocal with involvement of both lobes by tumor nodules of various sizes. Nodules are white to tan and have a firm consistency (Fig. 78.47), and the background liver is generally normal (Ishak et al, 1984).

Histologically the tumor comprises small groups of tumor cells surrounded by a distinctive and often abundant stroma of varying myxoid or sclerotic character. The neoplastic cells display abundant eosinophilic cytoplasm and large vesicular and hyperchromatic nuclei with variable nucleoli. These cells reveal their endothelial origin by displaying one or more intracytoplasmic vacuoles that represent intracellular vascular lumina. In addition, they can form small capillary-like lumina, which sometimes contain red blood cells (Makhlouf et al, 1999).

At the actively proliferating margin of the tumor, the neoplastic cells infiltrate the sinusoids, resulting in ductular transformation, atrophy, and eventual obliteration of the adjacent hepatic plates. The underlying lobular architecture is frequently preserved, and remnants of portal tracts can be identified. The tumor also invades the central veins, portal vein branches, and larger blood vessels. This intravascular growth appears as intraluminal papillary clusters or tuftlike projections (Bioulac-Sage et al, 2008). Infiltrating tumor cells are accompanied by a prominent stromal matrix that is initially fibrillar or hyaline, and an attendant mixed inflammatory infiltrate is often also present. Toward its center, the tumor ultimately becomes densely sclerotic, often with focal calcification, and the tumor cells can be difficult to discern (Weiss et al, 1986).

Angiosarcoma

Hepatic angiosarcoma is the most common primary sarcoma of the liver (Brady et al, 1977). Association with exposure to Thorotrast, vinyl chloride monomer, or inorganic arsenic

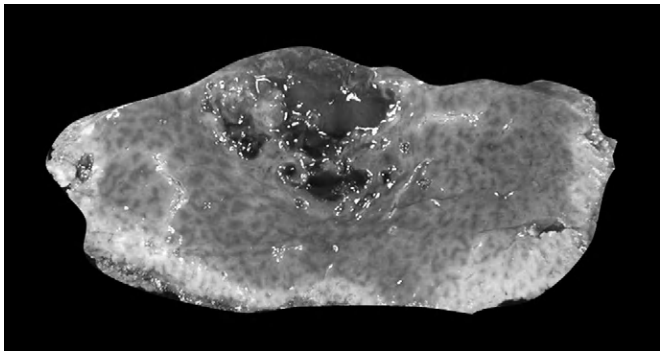


FIGURE 78.48. Angiosarcoma is a hemhorragic mass, ill limited from surrounding liver.

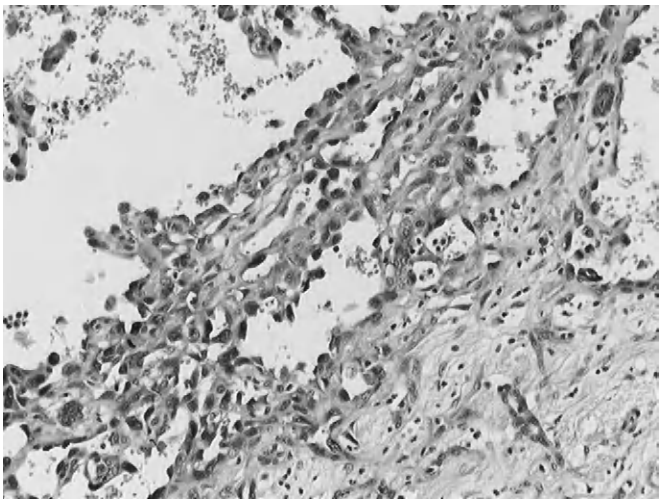


FIGURE 78.49. Angiosarcoma, light microscope. Proliferation of malignant endothelial cells with pale, ill-defined cytoplasm and enlarged, pleomorphic, and hyperchromatic nuclei.

compounds have been identified in 25% to 40% of angiosarcomas (Brady et al, 1977; Falk et al, 1981a; Kojiro et al, 1985; Sherman, 2009). Although these agents either have been discontinued or are under stricter controls, the prolonged latency period suggests that associated angiosarcomas will continue to be encountered for many years (Falk et al, 1981a). The peak incidence is in the sixth and seventh decades of life, and approximately 75% of the patients are men. Rare cases have been reported in children, most in association with infantile hemangioendothelioma (Strate et al, 1984).

The prognosis of patients with hepatic angiosarcoma is very poor. Most patients deteriorate rapidly and die within 6 months of diagnosis, usually from hepatic failure, extensive tumor burden, or tumor rupture. Distant metastases are noted in more than half the patients, most commonly to the lungs, regional lymph nodes, spleen, or bone marrow (Locker et al, 1979).

On gross examination, angiosarcomas typically appear as multiple gray or hemorrhagic masses scattered throughout both liver lobes (Fig. 78.48). The size varies greatly, between 0.1 and 5 cm, and tumors have a spongy consistency with irregular, ill-defined borders. Less often, the tumor is represented by a large solitary mass, typically more than 15 cm in diameter.

The histologic appearance is characterized by a proliferation of malignant endothelial cells with pale, ill-defined cytoplasm and enlarged pleomorphic and hyperchromatic nuclei (Fig. 78.49). The cells usually assume an elongated orientation, but they can also appear rounded or polygonal with conspicuous cytoplasm and prominent nucleoli. Mitoses, although in variable number, are often numerous and bizarre: in some cases the cells show evidence of phagocytic behavior (Bioulac-Sage et al, 2008; Ludwig & Hoffman, 1975).

The tumor infiltrates preexisting vascular structures and eventually destroys the hepatic parenchyma. With early involvement, the malignant cells line the sinusoids and separate the hepatic plates. With progression, the hepatocytes atrophy and are ultimately replaced by fibrosis, and the sinusoids dilate, producing irregular pelioid-like vascular spaces of varying size. These spaces are lined by multilayered tumor cells, sometimes in a papillary arrangement, and contain blood and necrotic debris. Extramedullary hematopoiesis is often present (Kojiro et al, 1985). The tumor also invades central veins or portal vein branches, which can lead to luminal occlusion with subsequent hemorrhage, necrosis, and infarction.

In angiosarcomas associated with Thorotrast, vinyl chloride, and arsenic exposure, an initial precursor stage that precedes the development of overt tumor has been recognized, with hypertrophy and hyperplasia of endothelial cells together with reactive hepatocyte alterations (Tamburro et al 1984).

Undifferentiated (Embryonal) Sarcoma

Embryonal sarcoma of the liver is a highly malignant childhood neoplasm (Stocker & Ishak, 1978; see Chapter 82). It is the third most common hepatic malignancy in the pediatric population after hepatoblastoma and hepatocellular carcinoma. The peak incidence is between 6 and 10 years with an age range that extends from newborn infants to almost 30 years of age (Stocker & Ishak, 1983, 1978; Pachera et al, 2008). The prognosis of undifferentiated sarcoma is very poor. Death often occurs because of massive local tumor growth with direct extension into contiguous structures and even through the diaphragm.

On gross examination, the tumors are large, well-demarcated masses, usually 10 to 30 cm in diameter with a soft gelatinous consistency. Most of the tumors occupy the right lobe of the liver. The cut surface is variegated with areas of solid gray-white tumor interrupted by foci of cystic degeneration, hemorrhage, and necrosis (Stocker & Ishak, 1978).

Histologically, the tumors are composed of malignant spindle-shaped cells separated by myxoid stroma. The neoplastic cells are grouped into closely packed sheets or fascicles or scattered loosely in the stroma. They vary greatly in size and have pleomorphic, hyperchromatic nuclei; inconspicuous nucleoli; and poorly defined borders. Mitoses are often numerous and bizarre, and multinucleated tumor giant cells can be seen. A characteristic finding is the presence of periodic acid-Schiff–positive, diastase-resistant eosinophilic globules within tumor cells and in the extracellular stroma (Ma et al, 2008). The myxoid stroma dominates the less cellular portions of the tumor and harbors numerous thin-walled veins and often contains foci of extramedullary hematopoiesis. Areas of hemorrhage and necrosis are abundant, and bands of dense, hyalinized collagen are occasionally noted. The periphery of the tumor typically entraps bile ducts that are cystically dilated and lined by a cuboidal epithelium that often displays hyperplastic or atypical features. The tumor lacks histologic evidence of cellular differentiation, and its histogenesis remains uncertain

(Lack et al, 1991). Embryonal sarcoma represents a primitive mesenchymal neoplasm capable of divergent differentiation (Choi et al, 2010).

Other Sarcomas

Most primary hepatic sarcomas occur in adults between 40 and 60 years of age who are seen with signs and symptoms indicative of a hepatic mass. These primary hepatic sarcomas should be distinguished from metastatic involvement by sarcomas of other organs and from sarcomatoid hepatocellular carcinoma (Kakizoe et al, 1987). The overall prognosis is poor, and most patients die within a year of diagnosis.

Hepatic sarcomas histologically resemble their soft-tissue counterparts. Among the types reported are fibrosarcoma, follicular dendritic cell sarcoma, desmoplastic nested single-cell tumor, malignant fibrous histiocytoma, hemangiopericytoma, osteosarcoma, malignant schwannoma, and dedifferentiated liposarcoma (Choi et al, 2010; Hill et al, 2005; Li et al, 2008; Kim et al, 1987; Lederman et al, 1987). Leiomyosarcomas are described arising within the hepatic parenchyma, from the ligamentum teres, and from the hepatic vein, where they have been associated with Budd-Chiari syndrome (Shamseddine et al, 2010; Kuma et al, 2008; Fong & Ruebner, 1974; Hilliard et al, 2005).

Kaposi sarcoma is seen primarily in the setting of the acquired immunodeficiency syndrome (AIDS). Histologically, the tumor is characterized by multifocal nodules composed of proliferated spindle cells with slit-like spaces that contain extravasated erythrocytes. These lesions are predominantly centered on portal tracts, but they also spread into and destroy the parenchyma (Bioulac-Sage et al, 2008; Friedman, 1988).

Hepatobiliary rhabdomyosarcoma is a rare neoplasm that usually arises from the common bile duct (Ali et al, 2009). Most patients are young children, with exceptional cases reported in adults (Stocker, 2001; Lack et al, 1981). Histologically the tumor resembles botryoid-type embryonal rhabdomyosarcomas that occur elsewhere in the body. Soft polypoid masses protrude into the ductal lumen and are covered by intact, ulcerated, or inflamed biliary epithelium. The tumor is composed of small hyperchromatic cells with variable eosinophilic cytoplasm and rare cross-striations. Beneath the biliary epithelium, the cells are densely packed and form a so-called cambium layer, whereas deeper in the tumor, they are separated by a loose myxoid stroma. The diagnosis is secured by immunohistochemical demonstration of desmin, muscle-specific actin, or myoglobin expression or with the ultrastructural finding of the characteristic myofilaments.

MISCELLANEOUS TUMORS

Inflammatory pseudotumors of the liver are nonneoplastic masses of unknown etiology (see Chapter 48). They occur at any age and clinically manifest with abdominal pain together with various systemic manifestations that include low-grade fever, weight loss, leukocytosis, anemia, and inflammatory syndrome (Tang et al, 2010). Although the cause is unknown, an as yet unidentified infectious or immunoglobulin G4 autoimmune-related process have been suggested (Horiuchi et al, 1990; Yamamoto et al, 2009).

The masses are often solitary and range between 2 and 25 cm in diameter. They have a variable histologic appearance and consist of proliferated fibroblasts and myofibroblasts, lymphocytes (sometimes with lymphoid follicles), plasma cells, eosinophils, and neutrophils. Fibrosis or granulation tissuelike zones can be conspicuous, particularly in the central portions of the mass. Multinucleated or foamy macrophages, phlebitis, and granulomas are sometimes noted. Inflammatory pseudotumors may regress spontaneously.

Neuroendocrine Tumor

Neuroendocrine tumors in the liver are almost always metastatic, and a primary lesion in the gastrointestinal tract or pancreas is usually identified (see Chapter 81B). In rare cases, however, primary hepatic endocrine tumors have been described in which no extrahepatic site of involvement can be identified (Sioutos et al, 1991; Miura & Shirasawa, 1988). Because of the normal presence of endocrine cells in biliary epithelium, an origin from intrahepatic bile ducts has often been suggested. Histologically, the tumor is composed of small, uniform tumor cells with regular round nuclei and moderate granular cytoplasm arranged in nests, cords, and pseudoglandular patterns. Dense core neurosecretory granules are found on immunostaining.

Other Tumors

Several examples of malignant rhabdoid tumors of the liver have been recognized. These tumors are highly aggressive neoplasms with a distinctive histologic appearance (Hunt & Anderson, 1990). Rare cases of primary hepatic germ-cell tumors of several types—including teratomas, yolk sac tumors, and choriocarcinoma—have been described. The combination of yolk sac tumor and hepatoblastoma has also been described (Cross & Variend, 1992); these tumors exhibit malignant behavior, although occasional long-term survival has been obtained with cancer chemotherapy.

Squamous carcinoma of the liver is uncommon, with most cases developing within simple hepatic cysts, in various forms of fibropolycystic liver disease, or in teratomas (Gresham & Rue, 1985). Adrenal rest tumor and pancreatic heterotopia have also been described and might be misleading (Wolf et al, 1990; Contreras et al, 1985).

HEMATOPOIETIC NEOPLASMS

Primary Hepatic Lymphoma

The liver may represent the sole site of involvement by malignant lymphoma, but these primary hepatic lymphomas are uncommon, although hepatitis C infection may be a risk factor (Santos et al, 2003).

On gross examination, most cases are characterized by a single large mass or, less often, by multiple discrete nodules (Anthony et al, 1990). Rarely, the liver is diffusely infiltrated without a well-defined mass lesion. The tumors are predominantly classified as non-Hodgkin lymphomas of diffuse large cell type, with occasional examples of small cleaved or uncleaved varieties such as mucosa-associated lymphoid tissue (MALT) tumors (Deshald et al, 2010; Doi et al, 2008). Most of the tumors are phenotypically of B-cell lineage, although occasional T-cell lymphomas have also been described (Noronha et al, 2005; Andreola et al, 1988). The neoplastic lymphocytes expand the portal tracts and invade into adjacent parenchyma from large infiltrative nodules. The lobules are otherwise little affected, although occasional cases, particularly with T-cell

lymphomas, demonstrate sinusoidal infiltration (Farcet et al, 1990).

Secondary Involvement

All varieties of lymphomas, leukemias, and hematopoietic proliferations can secondarily affect the liver, usually as a manifestation of disseminated disease and often in conjunction with splenic involvement. As a general rule, the low-grade non-Hodgkin lymphomas tend to produce multiple portal-based infiltrates, whereas the intermediate- and high-grade types give rise to large, irregular tumor masses. Sinusoidal involvement is uncommon except with peripheral T-cell lymphomas (Farcet et al, 1990; Gaulard et al, 1986).

Hepatic involvement in Hodgkin disease can manifest as large, irregular masses or as small, diffusely distributed nodules. The characteristic infiltrate, which predominantly affects portal tracts, consists of a polymorphous collection of Reed-Sternberg cells or variants together with small lymphocytes, large mononuclear cells, plasma cells, eosinophils, and neutrophils in varying numbers (Dich et al, 1989).

Leukemias of both acute and chronic types tend to permeate the sinusoids with malignant cells, with involvement of the portal tracts additionally noted with the lymphoid varieties. Hepatic involvement is especially common and conspicuous in hairy cell leukemia (Zafrani et al, 1987).

Langerhans cell histiocytosis involves the liver in about 40% of cases (Iwai et al, 1988). The most important clinical manifestations include jaundice and portal hypertension, resulting in part from infiltration of large bile ducts to produce a sclerosing cholangitis-like picture.

The liver is commonly involved in generalized mastocytosis. Mast cells accumulate principally in the portal tracts and are accompanied by varying degrees of periportal fibrosis and, on occasion, cirrhosis.

METASTASIS

Metastatic cancers are by far the most common form of hepatic malignancy, accounting for more than 95% of the total (see Chapter 81). In autopsy series, liver metastases are noted in about 40% of patients with malignant tumors, and the sites of origin include virtually every organ in the body (Schulz & Hort, 1981). The more frequent primary sites include carcinomas of the colon, pancreas, lung, and breast in adults and neuroblastoma, Wilms tumor, and rhabdomyosarcoma in pediatric patients (Strohmeyer & Schultz, 1986). Although the origin of the tumor is often known when metastases are biopsied, carcinomas of the pancreas, stomach, and lung are particularly notorious for being occult primary neoplasms.



FIGURE 78.50. Liver metastasis. Confluent and infiltrative masses of varying size made of pale nodules with central necrosis.

Grossly, metastatic tumors in the liver are almost always multiple, but they may appear as solitary nodules, confluent masses, or as small, diffusely infiltrative lesions that can mimic cirrhosis (Fig. 78.50; Borja et al, 1975). The size range varies considerably. Typically these tumors are gray to yellow nodules, sometimes complicated by central necrosis, umbilication, or cystic change, and they can occur anywhere within the parenchymal mass (Strohmeyer & Schultz, 1986). Some metastases may display prominent fibrous changes.

In general, metastatic tumors maintain the histologic features seen in their primary location. A desmoplastic stroma is common with metastatic adenocarcinomas, especially those from the pancreas or breast, and the overall picture cannot be distinguished from cholangiocarcinoma. Some metastatic tumors tend to infiltrate the sinusoids, and tumors such as small-cell carcinoma and melanoma can grow within the hepatic plates and replace the liver cells.

References are available at expertconsult.com.

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CHAPTER 79A

Benign liver lesions

Jacques Belghiti, Safi Dokmak, Valerie Vilgrain, and Valérie Paradis

OVERVIEW

One of the consequences of extensive use of imaging for an ever-increasing number of indications is the detection of asymptomatic tumors. In the absence of underlying chronic liver disease or a history of cancer, the vast majority of these lesions correspond to benign liver tumors, including cystic and solid lesions. Cystic tumors will be covered in Chapter 69A and 69B. Solid benign lesions include a broad spectrum of regenerative and true neoplastic processes (Table 79A.1). Based on the cell of origin, most solid, benign tumors can be classified into two groups: *epithelial lesions* include hepatocellular (focal nodular hyperplasia [FNH] and adenoma) and cholangiocellular tumors (bile duct adenoma); *mesenchymal tumors* include those lesions that originate from blood vessels (hemangioma), adipose tissue (angiolipoma), and muscle (leiomyoma). Except hepatocellular adenoma (HA), which may be associated with serious complications that may require surgery, the vast majority of solid, benign liver lesions remain asymptomatic and do not increase in volume; therefore they do not require any treatment or follow-up.

The understanding of clinical, biologic, radiologic, and pathologic characteristics of each tumor is important for accurate diagnosis and appropriate management. Advances in imaging studies allow an accurate diagnosis in the majority of cases, reducing the use of percutaneous biopsy to only a few patients and limiting the number of resections for final diagnosis to exceptional cases. The most frequent benign liver cell lesions include hemangioma, FNH, and HA. Because radiologic imaging is of critical importance in diagnosis and management, there is considerable emphasis on the role of radiologic study, and this section should be read in conjunction with Chapters 13, 16, and 17.

CAVERNOUS HEMANGIOMA

Hepatic hemangiomas are probably the most common of all liver tumors. These tumors occur at all ages, however, because of the difference of histologic structure between the adult and the infantile forms (see Chapter 82) and the different clinical presentation, they must be regarded as separate entities (Hobbs, 1990). Only hemangioma of the liver in adults will be considered in this chapter.

Pathogenesis and Pathology

The prevalence of hemangioma in the general population ranges from 1% to 20% (Semelka & Sofka, 1997), but it is predominant in women by a 5:1 ratio (Mergo & Ros, 1998; Trotter & Everson 2001; Biecker et al, 2003). In adults, hemangiomas are usually found in patients at a mean age of 50 years and equally in the left and right lobes of the liver; the majority are less than 5 cm in diameter and are rarely pediculated, but hemangiomas measuring 10 cm or more are referred to as *giant hemangiomas* and can present with fibrosis, thrombosis, and calcifications (Fig. 79A.1).

The pathogenesis of hemangioma is not well understood. Some of these tumors have estrogen receptors, and accelerated growth has been observed with high-estrogen states, such as those associated with puberty, pregnancy, oral contraceptive use, and with androgen treatment. These findings suggest that hormonal effect may be one of the pathogenic mechanisms (Trotter & Everson, 2001; Cobey & Salem, 2004). Macroscopic examination demonstrates well-delineated, flat lesions of red-blue color that may partially collapse on sectioning. Some degree of fibrosis, calcification, and thrombosis may be observed, most commonly in the largest lesions (Fig. 79A.2). Microscopically, hemangiomas are made of cavernous vascular spaces lined by flattened endothelium underlying fibrous septa of various widths (Fig. 79A.3). Small hemangiomas may become entirely fibrous, appearing as a solitary fibrous nodule.

Clinical and Biologic Data

The vast majority of hemangiomas are less than 5 cm and are found incidentally during ultrasound (US) or computed tomography (CT) examination of the abdomen for unrelated reasons (Trotter & Everson, 2001). Hemangiomas remain stable in size

Table 79A.1

Histologic Classification of Benign Liver Lesions and Main Clinical Data

Lesion	Type	Comments
Epithelial Lesions		
Hepatocytes	Hepatocellular adenoma	Very rare Associated with oral contraceptives High rate of complications (bleeding, malignant transformation)
	Focal nodular hyperplasia	Rare Female predominance No risk of complication
	Nodular regenerative hyperplasia	Very rare Associated with systemic diseases and drugs Portal hypertension
	Focal fatty change	Common Associated with diabetes, obesity, hepatitis C virus, and malnutrition No risk of complication
Biliary cells	Bile duct adenoma	Rare No risk of complication
	Biliary hamartoma (Von Meyenburg complex)	Very rare Development anomaly No risk of complication
Nonepithelial Lesions		
Mesenchymal	Hemangioma	Common Female predominance Very low risk of complication
	Angiomyolipoma	Rare Associated with tuberous sclerosis No risk of complication
	Lipoma, myelolipoma	Exceptional No risk of complication
Heterotopia	Adrenal, pancreatic, or spleen tissues	Exceptional Very low risk of complication
Others	Peliosis hepatis	Exceptional Associated with androgens, oral contraceptives, drugs, malignancies, and tuberculosis No risk of complication
	Inflammatory pseudotumor	Very rare Associated with general syndromes No risk of complication

(Takayasu et al, 1990) or demonstrate minimal increase in diameter over time (Nghiem et al, 1997). Pain related to an uncomplicated hemangioma is most probably due to associated disorders, such as gallbladder disease, liver cysts, gastroduodenal ulcers, or a hiatal hernia (Farges et al, 1995). Large hemangiomas may be asymptomatic or may manifest with an abdominal mass or pain (Erdogan et al, 2007). Large lesions located in the left lobe of the liver may cause pressure effects on adjacent structures with resulting symptoms. Jaundice as a



FIGURE 79A.1. Giant hemangioma. Portal-venous phase helical computed tomographic and centripetal contrast enhancement.

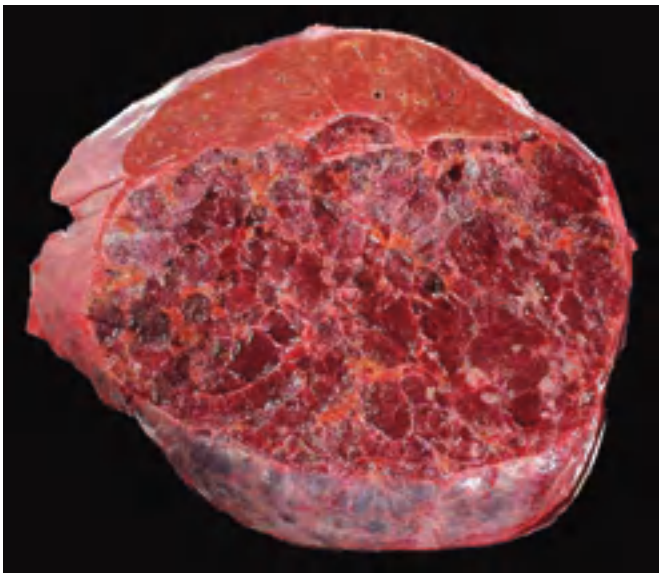


FIGURE 79A.2. Macroscopic view of hemangioma.

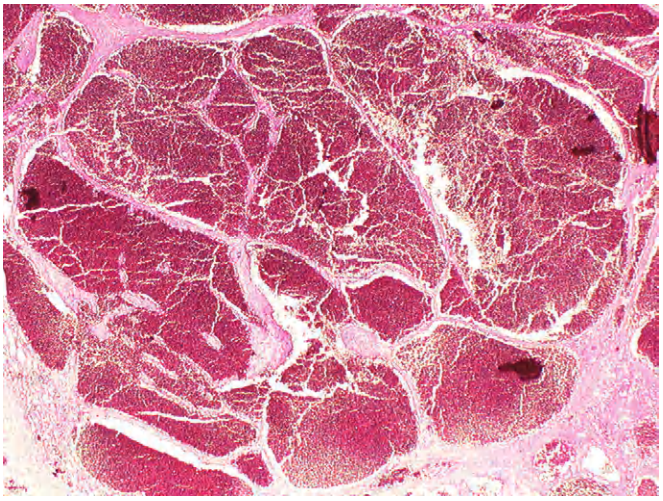


FIGURE 79A.3. Microscopic view of hemangioma showing cavernous vascular spaces lined by flattened endothelium underlying fibrous septa of various widths. The vascular spaces are filled with red blood cells.

result of compression of bile ducts by hemangioma has also been observed, but this is rare (Losanoff & Millis, 2008).

Liver biologic tests, including alkaline phosphatase and γ-glutamyltransferase (GGT), are normal. Normal laboratory tests associated with a large hepatic tumor with mild symptoms could be of help in the diagnosis of hemangioma.

Complications are mostly observed in large hemangiomas and can be divided into 1) alterations of internal architecture, such as with inflammation; 2) coagulation abnormalities, which could lead to systemic disorders such as hemorrhage and subsequent hemoperitoneum; and 3) compression of adjacent structures.

Some cases of inflammatory processes complicating giant hemangioma have been reported (Bornman et al, 1987; Takayasu et al, 1990), and the prevalence is probably underestimated. Signs and symptoms of an inflammatory process include low-grade fever, weight loss, abdominal pain, accelerated erythrocyte sedimentation rate, normal white blood cell count, anemia, thrombocytosis, and increased fibrinogen level. The imaging features are those of giant hemangioma. Clinical and laboratory abnormalities disappear after surgical excision of the mass (Bornman et al, 1987; Pateron et al, 1991; Pol et al, 1998).

Kasabach-Merritt syndrome is an exceptional complication of hepatic hemangioma in adults (Hall, 2001; see Chapter 82). This coagulopathy consists of intravascular coagulation, clotting, and fibrinolysis within the hemangioma, and it may progress to secondary increased systemic fibrinolysis and thrombocytopenia (Concejero et al, 2009); the syndrome is reversible after removal of the hemangioma. Although rarely encountered in hepatic hemangioma, intratumoral hemorrhage can occur spontaneously or after anticoagulation therapy. Spontaneous rupture of a hemangioma is exceptional, and very few indisputable cases have been reported (Corigliano et al, 2003); taking into account the high prevalence of these tumors, the extremely low incidence of this complication should not interfere with the therapeutic management, nor should it influence the specific advice to patients, who are often worried by the presence of a vascular liver tumor (Plackett & Lin-Hurtubise, 2008).

Imaging

The vast majority of hemangiomas are diagnosed accurately by imaging studies alone because of characteristic imaging features. On US the classic appearance of hemangioma is that of a homogeneous hyperechoic mass less than 3 cm in diameter with acoustic enhancement and sharp margins (Fig. 79A.4; see Chapter 13). No vascular pattern is usually identified on color Doppler. Other investigations are required when US does not show typical patterns. Contrast-enhanced US reveals peripheral



FIGURE 79A.4. Hemangioma. **A,** Ultrasound shows a hypoechoic liver lesion with posterior acoustic enhancement. **B** and **C,** Contrast-enhanced ultrasound demonstrates peripheral puddling followed by complete and delayed enhancement.

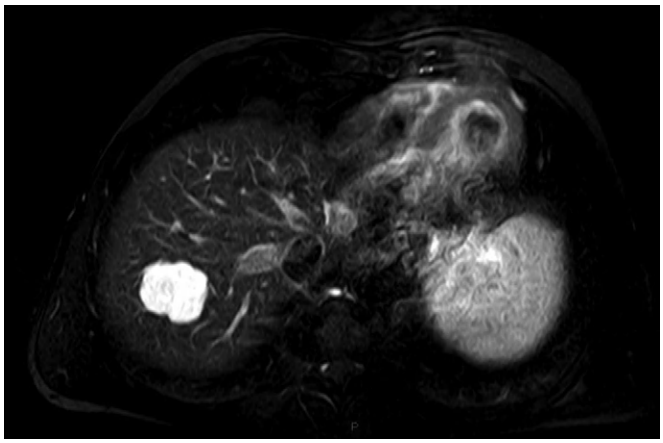


FIGURE 79A.5. Hemangioma. T2-weighted magnetic resonance imaging shows typical bright signal.

globular enhancement in the portal phase and isoechoic pattern on the late phase in most atypical hemangiomas (Quaia et al, 2002).

On CT, the criteria for the diagnosis of hemangioma are the following: 1) low attenuation on noncontrast CT, 2) peripheral and globular enhancement of the lesion followed by a central enhancement on contrast CT, and 3) contrast enhancement of the lesion on delayed scans (Freeny & Marks, 1986; see Chapter 16). Among these criteria, the presence of peripheral puddles on the arterial phase has a sensitivity of 67%, a specificity of 99%, and a positive predictive value of 86% for hemangioma (Nino-Murcia et al, 2000). Magnetic resonance (MR) imaging is the key imaging modality in the characterization of liver hemangiomas (Itai et al, 1985; Starck et al, 1985; see Chapter 17). The classic appearance of a liver hemangioma is that of a hypointense lesion on T1-weighted sequences, a strongly hyperintense lesion on heavily T2-weighted sequences, with a "light-bulb" pattern (Fig. 79A.5). Dynamic multiphasic T1-weighted sequences after gadolinium chelate administration show findings similar to that of contrast-enhanced CT phases (Fig. 79A.6; Semelka et al, 1994). Hemangiomas can be multiple in 10% of cases, and in exceptional cases, the presence of innumerable hemangiomas are called *hemangiomatosis* (Ishak & Rabin, 1975; Keegan et al, 2001).

The two most common imaging atypias are found in giant hemangiomas and in rapidly filling hemangiomas. Giant hemangiomas, which are defined when they exceed 6 or 12 cm in diameter, are often heterogeneous with marked central areas that correspond to thrombosis, extensive hyalinization, and fibrosis (Danet et al 2003; Coumbaras et al, 2002). However, usually the typical early, peripheral, nodular enhancement is observed along with strong hyperintensity on T2-weighted MR images at the periphery. Although present, the progressive centripetal enhancement of the lesion does not lead to complete filling. Rapidly filling hemangiomas are not uncommon and occur significantly more often in small lesions (42% of hemangiomas are <2 cm in diameter) (Hanafusa et al, 1995). CT and MR imaging show an immediate homogeneous enhancement in the arterial phase, which makes differentiation from other hypervascular tumors difficult. Their diagnosis is based on strong hyperintensity on T2-weighted images, the parallel enhancement with arterial structures, and the persistent enhancement on delayed-phase imaging; it is important to note that these rapidly filling hemangiomas may induce arterial–portal venous shunts (Kim et al, 2001). The other atypical hemangiomas are very uncommon and include very slow filling, calcified, hyalinized cystic and pedunculated hemangiomas, those with fluid-fluid levels, and hemangiomas with capsular retraction.

Hemangiomas associated with inflammatory response syndrome are usually due to acute thrombosis of a part or all the hemangioma. These can be diagnosed by showing spontaneous hyperattenuation on unenhanced CT scans. Hemangiomas developing in abnormal liver are difficult to diagnose, and those in fatty liver usually appear isoechoic or hypoechoic at US and hyperattenuating at unenhanced CT (Marsh et al, 1989). MR imaging with fat-suppressed, in-phase and opposed-phase T1-weighted sequences is the key to the diagnosis and is more helpful than CT; strong hyperintensity on T2-weighted images is also a reliable finding.

With progressive cirrhosis, hemangiomas are likely to decrease in size and become more fibrotic and difficult to diagnose radiologically (Brancatelli et al, 2001). In this clinical setting, US cannot be used to confidently make the diagnosis of hemangioma, as half of the hyperechoic lesions are hepatocellular carcinomas (HCCs) (Caturelli et al, 2001). The association of hepatic hemangioma and FNH can be observed in about 25% of cases and is not fortuitous (Mathieu et al, 1989; Vilgrain et al, 2003). FNH is considered to be a hyperplastic response as a result of focal increased arterial flow in the hepatic parenchyma and, like hemangioma, it is thought to have a vascular origin.

Imaging, and especially MR imaging, is therefore able to diagnose liver hemangiomas in nearly all cases, and liver biopsy should be restricted to exceptional cases. Liver hemangioma, which has been considered a contraindication to needle biopsy for many years, is possible without significant risk of hemorrhage (Heilo & Stenwig, 1997; Caldironi et al, 1998). However, as in other tumors, a cuff of normal hepatic parenchyma should be interposed between the capsule and the margin of the hemangioma.

Management

Whatever the size, there is no treatment for *asymptomatic hemangioma*. When the diagnosis is established, it is not necessary to adopt therapeutic or specific measures. The patient should be reassured about the rare occurrence of growth and the extremely low risk of complication; therefore oral contraceptives need not be interrupted, nor should the patient be counseled to avoid pregnancy or discontinue any sporting activity, and follow-up is not justified. Although in specialized centers, liver resection mortality for benign lesions is essentially nil, there is a risk of intraoperative bleeding and postoperative biliary fistula, which should be considered unacceptable given the benign nature of these lesions; indeed, it could be stated that the main complication of hemangioma is surgical operation.

Indications for treatment include severe symptoms, complications, and inability to exclude malignancy (Yoon et al, 2003; Duxbury & Garden, 2010). Symptoms are more frequently encountered with huge hemangioma (Erdogan et al, 2007). Surgical resection remains the definitive treatment, but other less effective options include hepatic artery ligation and radiation therapy; radiation therapy can reduce the size of the lesion (Gaspar et al, 1993), but long-term effects of radiation therapy

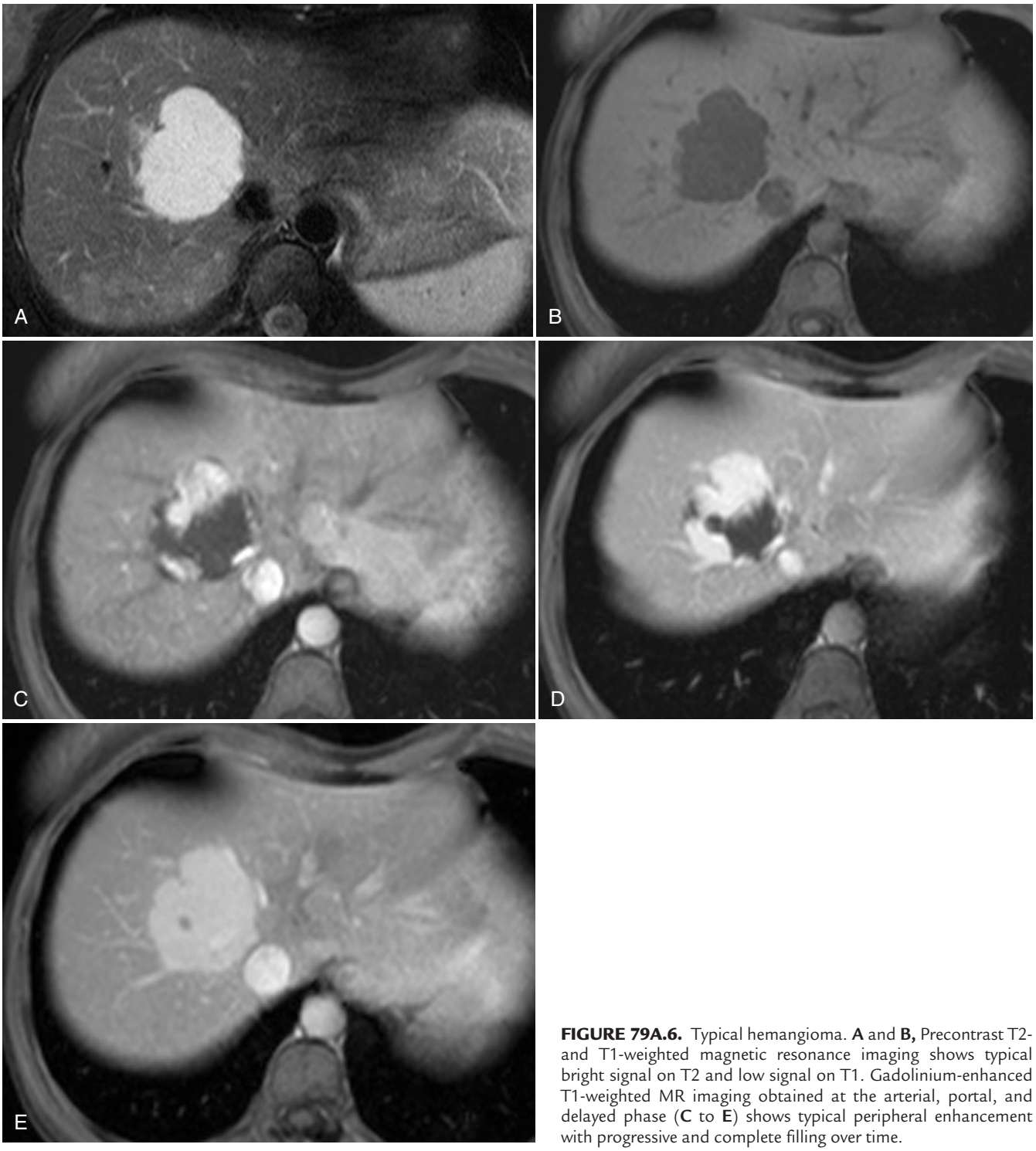


FIGURE 79A.6. Typical hemangioma. **A** and **B,** Precontrast T2- and T1-weighted magnetic resonance imaging shows typical bright signal on T2 and low signal on T1. Gadolinium-enhanced T1-weighted MR imaging obtained at the arterial, portal, and delayed phase (**C** to **E**) shows typical peripheral enhancement with progressive and complete filling over time.

on the liver and adjacent structures can be deleterious. In addition, relief of symptoms is not well documented. Arterial embolization, which may be considered for the temporary control of hemorrhage, has limited success and is occasionally associated with morbidity (Reading et al, 1988). Arterial ligation may be considered during surgical procedures to allow manual decompression of large hemangiomas and facilitate their manipulation and enucleation (Yoon et al, 2003).

When indicated, the only treatment to be considered is resection (Herman et al, 2005; Erdogan et al, 2007), and it should be performed in specialized units, where a variety of techniques and approaches can be used. The choice between enucleation and resection requires consideration of the size and anatomic location of the lesion. Hemangioma located in the peripheral liver area is preferably treated by enucleation, whereas tumors deeply located are more safely resected with a

formal anatomic liver resection (Kuo et al, 1994; Gedaly et al, 1999; Fu et al, 2009). In the majority of cases, patients showed symptoms relief after resection of a symptomatic hemangioma (Erdogan et al, 2007). Although laparoscopic resection is safe for peripheral hemangioma (Karahasanoglu et al, 2001; Jiang et al, 2007), this approach should not extend the rare indication for surgery. Liver transplantation has also been used successfully to treat symptomatic patients with a technically unresectable, complicated giant hemangioma or hemangiomatosis with cardiopulmonary complications (Browers et al, 1997; Tapetes et al, 1995; Ferraz et al, 2004; Keegan et al, 2001; Ercolani et al, 2010).

FOCAL NODULAR HYPERPLASIA

Pathogenesis and Pathology

FNH accounts for the second most common benign liver process, after hemangioma. It is a benign, tumor-like condition predominantly diagnosed in women 30 to 50 years of age, and it is not influenced by oral contraceptives (International Working Party, 1995; Ishak, 1979). FNH is considered a hyperplastic reaction resulting from arterial malformation (Wanless et al, 1985). This hypothesis, suggesting that increased arterial flow hyperperfuses the local liver parenchyma and leads to secondary hepatocellular hyperplasia, has been reinforced by molecular data showing that FNH is a polyclonal regenerative process (Gaffey et al, 1996; Paradis et al, 1997; Rebouissou et al, 2008). This regenerative process induced in a specific vascular territory could explain the absence of size changes in the vast majority of cases. However, an involution of this lesion is possible after menopause (Kuo et al, 2009), which explains the occurrence of this lesion in patients with vascular disorders of the liver, including Budd-Chiari syndrome (Cazals-Hatem et al, 2003), hereditary hemorrhagic telangiectasia (Gincul et al, 2008), congenital absence of portal flow (Kim T, et al, 2004), or portal thrombosis with subsequent hepatic arterialization (Bureau et al, 2004).

Such focal regenerative processes are also described in cirrhotic tissue with the so-called FNH-like macronodules. FNH displays a typical pathologic pattern for both radiologists and pathologists. Grossly, it is a well-circumscribed, unencapsulated, usually solitary mass characterized by a central fibrous scar that radiates into the liver parenchyma (Fig. 79A.7). Histologically, FNH is composed of benign-appearing hepatocytes arranged in nodules, usually partially delineated by fibrous septa that originate from the central scar. The main diagnostic feature is the presence of large and dystrophic vessels in the fibrous septa, which can be accompanied by several degrees of ductular proliferation and inflammatory cells. The hepatocytes

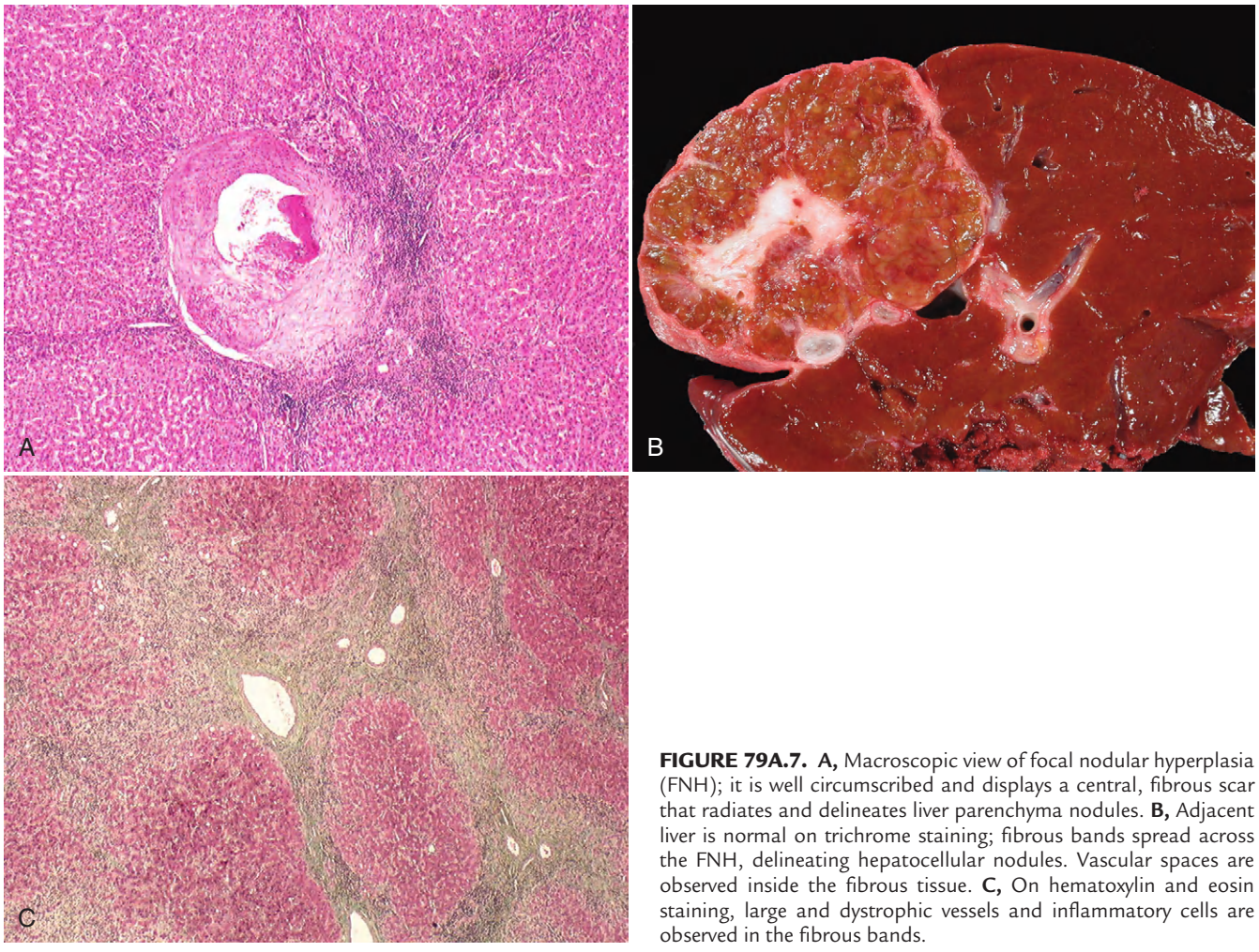


FIGURE 79A.7. A, Macroscopic view of focal nodular hyperplasia (FNH); it is well circumscribed and displays a central, fibrous scar that radiates and delineates liver parenchyma nodules. **B,** Adjacent liver is normal on trichrome staining; fibrous bands spread across the FNH, delineating hepatocellular nodules. Vascular spaces are observed inside the fibrous tissue. **C,** On hematoxylin and eosin staining, large and dystrophic vessels and inflammatory cells are observed in the fibrous bands.

are hyperplastic, arranged in liver plates of normal or slightly increased thickness (see Chapter 78). Hepatocytes may be hydropic, related to cholestatic changes, or they may display some degree of steatosis.

Performance of biopsy in the diagnosis of FNH is often a challenge, because fibrous septa and thick abnormal arteries are usually missing on biopsy specimen (Makhlouf et al, 2005). In that context, glutamine synthetase showing focal positive hepatocellular areas, usually centered by hepatic veins and described as a maplike pattern, is a helpful surrogate marker (Bioulac-Sage et al, 2009a).

Besides this classic form of FNH, several variant lesions are described with increased frequency and commonly classified as *nontypical FNH* by radiologists. This group of lesions is somewhat heterogeneous, including FNH without a central fibrous scar and FNH containing fat (Nguyen et al, 1999). However, molecular studies have demonstrated that in this group of atypical FNH, lesions that display telangiectatic changes, the so-called *telangiectatic* form of FNH, are clonal processes that should be rather regarded as a variant form of liver cell adenoma; it is classified as a specific subgroup of adenoma other than FNH (Paradis et al, 2004; Bioulac-Sage et al, 2005).

Clinical and Biologic Data

FNH represents the second most frequent benign lesion, with an estimated prevalence around 1% (Vilgrain, 2006); it is seen predominantly in women (9:1) and often is discovered in patients aged 30 to 40 years, although men with FNH are usually older than 40 years (Nguyen et al, 1999). The vast majority of FNH is asymptomatic, usually discovered incidentally during liver US examination. In a few patients with large tumors, FNH can be discovered by abdominal pain or discomfort. Large lesions located in the left lobe of the liver may cause pressure effects on adjacent structures with resulting symptoms. The lesion may be felt when it is pedunculated, and it can be responsible for acute episodes of pain because of torsion on the pedicle. Large FNH below the Glisson capsule could also be responsible for pain (Buetow et al, 1996), but in most cases pain related to FNH is probably due to associated disorders.

Complications of FNH, such as rupture or bleeding, are exceptional and are usually related to atypical forms of FNH with specific imaging and biologic features, the so-called telangiectatic FNH, which should be classified as an adenoma. No malignant transformation of FNH has been demonstrated. A reduction in size after menopause may be observed, but in the vast majority of cases, FNH remains stable in size, even after interruption of oral contraception or after pregnancy (Mathieu et al, 2000).

Liver biologic test results are normal in nearly 80% of cases (Belghiti et al, 1993). Abnormalities include mild elevation of GGT and alkaline phosphatase in patients with a large FNH that caused extrinsic compression of intrahepatic biliary ducts. The presence of a slight elevation of serum transaminase levels could be due to the presence of associated steatosis in the underlying liver parenchyma.

Imaging

FNH is usually slightly hypoechoic or isoechoic at US (see Chapter 13). Some lesions are only detected because they displace the surrounding vessels. Lobulated contours and a hypoechoic halo are often observed; the central scar is slightly hyperechoic but is often difficult to visualize at US (20% of cases; Shamsi et al, 1993). Typical findings at color Doppler include the presence of a central feeding artery with a stellate or spoke-wheel pattern that corresponds to the artery running from the central scar to fibrous septa (Fig. 79A.8). Doppler spectral analysis shows, in most cases, an intralesional pulsatile waveform with high diastolic flow and low resistive index (Uggowitzer et al, 1997). Large draining vessels may be identified in the periphery at the tumor margins. US contrast agents and nonlinear continuous imaging modes at a low mechanical index are very interesting tools to better characterize FNH. Most lesions enhance at the arterial phase (Kim MJ, et al, 2004; Dietrich et al, 2005) with a central vascular supply and a centrifugal filling to the periphery. The lesion becomes homogeneously isoechoic in the late portal and delayed phases in the vast majority of the cases (Kim MJ, et al, 2004), and very little FNH is evident with washout; when the central scar is detected, it appears hypoechoic on both arterial and portal phases. By showing centrifugal enhancement with radiated vascularization, differentiation from hepatocellular adenoma is possible in most cases (Kim T, et al, 2008).

On precontrast CT scans, FNH is demonstrated as a focal hypodense or isodense mass. A central hypodense scar is depicted in only one third of the patients (Shamsi et al, 1993). Calcifications within the central scar are very rare and are observed in only about 1% (Caseiro-Alves et al, 1996). Because of the prominent arterial supply to the FNH, the lesion enhances rapidly at the arterial phase of contrast-enhanced CT in most cases (Brancatelli, et al 2001). Lesion enhancement decreases at the portal venous phase, and the lesion may be either isodense or slightly hyperdense relative to normal liver. Additional findings are lesion homogeneity, a lobulated contour, and the absence of a capsule. A central scar is observed more often in large lesions than in small ones, and it enhances over time (Carlson et al, 2000). It has been shown that the enhancement of FNH in the arterial phase is significantly higher than in HA (Ruppert-Kohlmayr et al, 2001).

On MRI, typical FNH is isointense or hypointense on T1-weighted images and isointense or slightly hyperintense on T2-weighted images (Vilgrain et al, 1992; Buetow et al, 1996; see Chapter 17). The central scar is hypointense on T1-weighted images and strongly hyperintense on T2-weighted images (Mortelé et al, 2000; Kehagias et al, 2001). Another key finding is the lesion homogeneity apart from the central scar. After administration of gadolinium chelates, the enhancement is similar to that observed on contrast-enhanced CT. On delayed-phase imaging, 5 to 10 minutes after injection, the central scar shows high signal intensity because of the accumulation of contrast material in the fibrous tissue. Hepatobiliary contrast agents can be used to highlight the hepatocellular origin of the lesions and to differentiate FNH from hepatocellular adenomas; however, the biokinetics are different among those specific contrast agents (Ba-Ssalamah et al, 2002; Grazioli et al, 2005). On diffusion-weighted MR sequences, FNH is often hyperintense on high b values, but their apparent diffusion coefficient (ADC) values are close to that of the liver.

Atypical forms of FNH that are difficult to diagnose include FNH without a scar, especially in lesions measuring less than 3 cm in diameter. In some cases, scars do not enhance on delayed imaging, or they are hypointense on T2-weighted images; this leads the clinician to suspect the diagnosis of

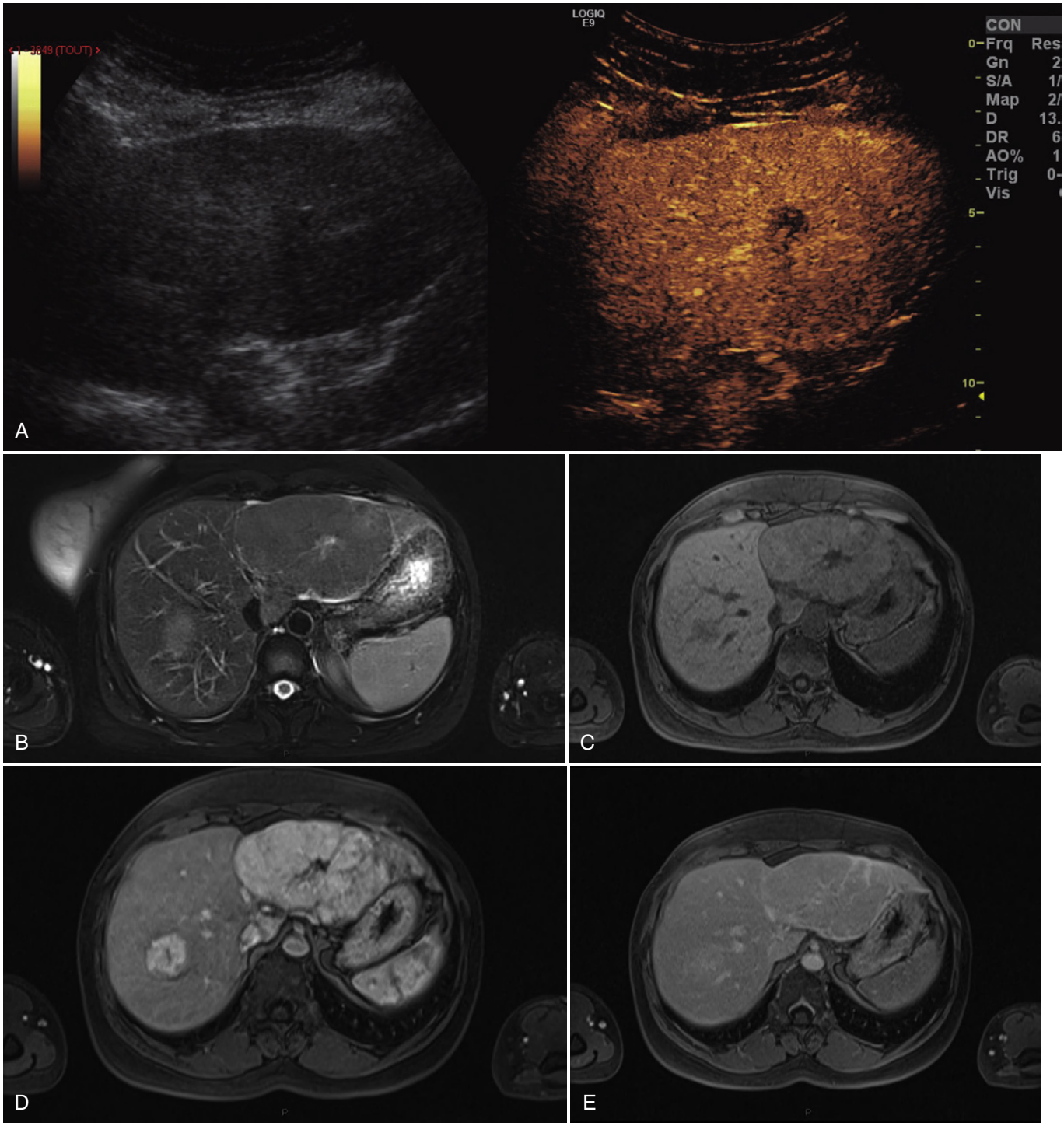


FIGURE 79A.8. Typical focal nodular hyperplasia (FNH). **A,** Contrast-enhanced ultrasound demonstrates strong and homogeneous enhancement apart from the central scar, which remains hypoechoic. Precontrast T2- and T1-weighted magnetic resonance (MR) imaging shows two hyperplastic focal nodules, which are isointense on T2 (**B**) and hypointense on T1 (**C**). Gadolinium-enhanced T1-weighted MR imaging obtained at the arterial and delayed phase (**D** and **E**) shows strong and homogeneous enhancement of the lesion with progressive fading. The central scar is hyperintense on T2 and enhances on delayed imaging. Note that the central scar is more evident in the large FNH.

fibrolamellar carcinoma. Other atypical findings include hyperintensity on T1-weighted imaging, which may be caused by various pathologic changes that include fat deposition (mostly in patients with steatosis; Stanley et al, 2002). FNH heterogeneity is exceptional and should make the diagnosis doubtful.

Although FNH is mainly a solitary lesion, multiple FNH lesions may be observed in 20% of cases and may be associated with hemangiomas or more seldom with HA (Mathieu et al, 1989; Vilgrain et al, 2003; Laurent et al, 2003). Accuracy of contrast-enhanced US has been established, and MR imaging

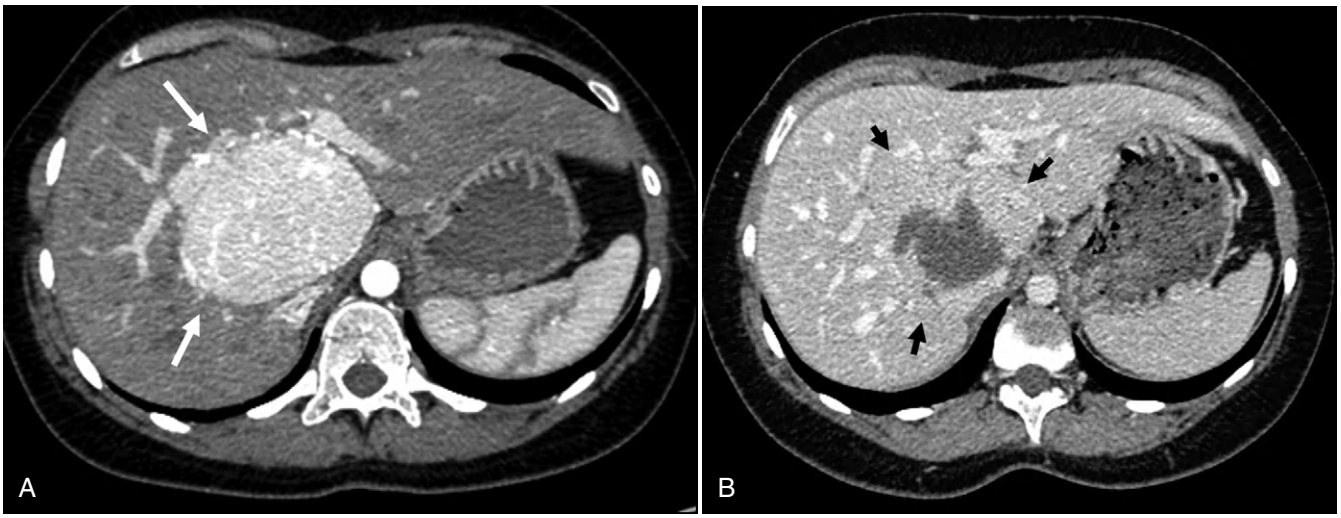


FIGURE 79A.9. Focal nodular hyperplasia (FNH) before and after arterial embolization. **A,** Abdominal computed tomographic scan with contrast injection on arterial and portal phases. Homogeneous centrohepatic FNH shows an immediate and intense enhancement during the arterial phase (*white arrows*). **B,** Postembolization aspect of the lesion. Note the size decrease and complete devascularization of the center of the lesion, appearing as a homogeneous unenhanced central area (*black arrows*).

has the higher sensitivity (70%) and specificity (98%) (Soussan et al, 2010). However, the diagnosis of FNH is based on a combination of features, and none of them are specific for FNH. When imaging cannot establish a firm diagnosis, liver biopsy plays a role in diagnosing FNH (Fabre et al, 2002; Makhlouf et al, 2005).

Management

Whatever the size and number of lesions, no treatment is necessary for asymptomatic FNH, when the diagnosis has been firmly established. This lesion should be considered a regenerative procedure rather than a tumor. In addition, the occurrence of this lesion in men should not modify the indication of conservative treatment; FNH has no risk of malignant potential and no risk of complications. The patient should be reassured about the absence of potential complications and the natural history of this lesion, which remains stable; advise that it could decrease and even disappear after the fifth decade; therefore no argument can even be made for interrupting oral contraceptives or avoiding pregnancy, and a follow-up is not justified.

Surgical resection is restricted to symptomatic patients. Symptomatic patients with confirmed FNH should be thoroughly investigated to exclude other pathology before attributing symptoms to the liver lesion. The development of a liver laparoscopic approach should not extend the indication for resection, which should be performed in specialist hepatobiliary units, as it is clearly indicated in patients with large, symptomatic FNH located in the left liver and in those with a pedunculated lesion. The safer resection procedure is liver resection with a surgical margin, rather than enucleation, because large veins often surround FNH, which renders enucleation difficult. In some symptomatic patients with large FNH located in the right liver or in segment I and necessitating difficult or risky resection, transarterial embolization has been advocated to determine the relationship between the lesion and symptoms (De Rave & Hussain, 2002; Kehagias et al, 2001). Data in the literature (Amesur et al, 2009) and our experience have shown that this is an attractive treatment with reduction of size in conjunction with relief of symptoms (Fig. 79A.9). Percutaneous radiofrequency ablation (RFA) has also been described as an effective treatment modality for symptomatic FNH (Hedayati et al, 2010).

HEPATOCELLULAR ADENOMA

Pathogenesis and Pathology

Hepatocellular adenoma (HA) is a rare, benign liver neoplasm strongly associated with oral contraceptive (OC) use (Rosenberg, 1991). The most important complications of HA are hemorrhage and malignant transformation into HCC. HA is mainly observed in women of childbearing age, and it is rare in men (sex ratio 9:1). Its incidence is estimated to be 0.1 per year per 100,000 in non-OC users, and it reaches 3 to 4 per 100,000 in long-term OC users (Wittekind, 1995). HA is directly related to OC use, and the risk for developing adenoma increases with the duration and estrogen content of the medication (Rosenberg, 1991; Dokmak et al, 2009). This tumor can also occur in men receiving anabolic steroids (Socas, et al 2005), or it may be associated with underlying metabolic disease, including type 1 glycogen storage disease, and iron overload related to β-thalassemia and hemochromatosis (Barthelemes & Tait, 2005; Bioulac-Sage et al, 2008). The prevalence of obesity was high in patients with HA (Dokmak et al, 2009), and it was recently described in patients with nonalcoholic fatty liver disease (Watkins et al, 2009). HA can also occur in patients with portacaval shunt or portal deprivation, and familial cases have been reported in patients with mellitus onset diabetes type 3 (Chiche et al, 2000; Bioulac-Sage et al, 2008).

HA is usually solitary, sometimes pedunculated, with a diameter that can vary from a few millimeters up to 30 cm. The widespread use and technical progress in imaging techniques has revealed that one third of patients have multiple HAs (Dokmak et al, 2009; Deneve et al, 2009; Bioulac-Sage et al, 2009b). Patients with more than 10 HAs are subclassified as having *liver adenomatosis*, considered to be more common in

men and to have an increased risk of complications (Fléjou et al, 1985). However, review of the literature and our experience do not support this arbitrary classification based on clinical and imaging characteristics (Ribeiro et al, 1998; Jovine et al, 2004; Barthelemes & Tait, 2005; Dokmak et al, 2009; Bioulac-Sage et al, 2008). The risk of bleeding and of malignant transformation is similar to that in patients with solitary adenoma and is mainly related to the size and subtype of tumors (Dokmak et al, 2009; Bioulac-Sage et al, 2008; Deneve et al, 2009; Stoot et al, 2010). It also appears that the prevalence of HA is rising in men, mainly as a result of the rising incidence of metabolic syndrome (Farges et al, 2011). Such HA displays a significantly higher risk of malignant transformation to HCC, reaching 47% in the last few years in our experience (Farges et al, 2011); therefore patients should not be managed according to the number of HAs, but rather according to the risk of complications, which is related to sex, the histologic subtype, and mainly to the size of the HA.

Large subcapsular vessels are commonly found on macroscopic examination. On cut sections, the tumor is well delineated, sometimes encapsulated, and has a fleshy appearance; it ranges in color from white to brown (Fig. 79A.10). HA frequently displays heterogeneous areas of necrosis and hemorrhage. Histologically HA consists of a proliferation of benign hepatocytes arranged in a trabecular pattern; however, the normal liver architecture organization is absent (Chapter 78). Hepatocytes may have intracellular fat or increased glycogen. Malignant transformation to HCC may be difficult to assess, especially on biopsy specimen (Deneve et al, 2009; Stoot et al, 2010), but it is observed in 4% to 10% of cases in published series (Barthelemes & Tait, 2005; Bioulac-Sage, 2008; Deneve et al, 2009; Zucman-Rossi et al, 2006).

Four subtypes of HA could be named according to genotype/phenotype classification (Bioulac-Sage et al, 2009). Group 1 includes HA with mutation in the hepatocyte nuclear factor (HNF)-1α gene (*H-HA*). Observed in approximately 35% to 40% of patients, almost exclusively in women and often with multiple HAs, this group corresponds to a histologically homogeneous group of tumors characterized by marked steatosis, no cytologic abnormalities, no inflammatory infiltrates, and a very low risk of complications. Group 2 includes HA with mutation of the β-catenin gene. Observed in approximately 10% of cases, mostly in men, this group is characterized by the presence of cytologic abnormalities with the greater risk of malignant transformation. Group 3 corresponds to telangiectatic/inflammatory HA. Observed in more than 50% of cases, these lesions usually occur in overweight women patients with inflammatory syndrome; tumors are characterized morphologically by the presence of inflammatory infiltrates, marked sinusoidal dilation or congestion, and numerous isolated or clustered arteries. The risk of complication in this group is high. The last group corresponds to HA that does not express any of the above-mentioned phenotypic or morphologic features. Besides the morphologic features associated with the different subtypes of HA, additional immunohistochemical markers have been described that provide significant assistance in the classification of HA, especially in biopsy specimens (Bioulac-Sage et al, 2009).

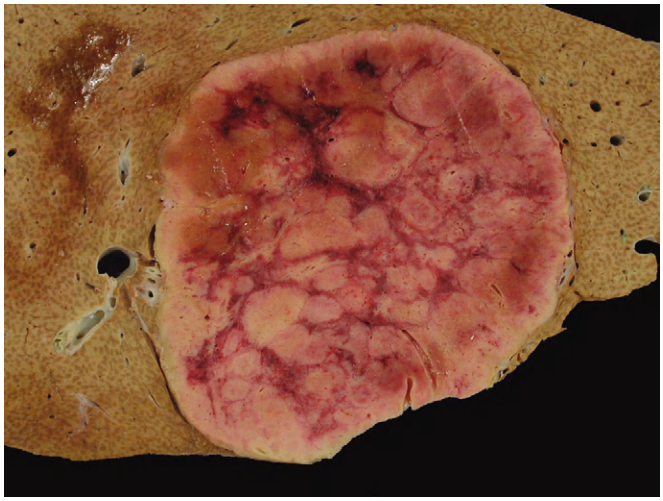


FIGURE 79A.10. Macroscopic aspect of hepatocellular adenoma. The lesion is well delineated, unencapsulated, and tan to yellow with some vascular changes.

Clinical and Biological Data

Although patients with HA can come to medical attention with symptoms, the majority are asymptomatic, especially if they have small tumors (Trotter & Everson, 2001; Weimann et al, 2000; Bioulac-Sage et al, 2009; Dokmak et al, 2009). Tumors are discovered during diagnostic workup of elevated liver enzymes or during liver imaging monitoring in pregnancy or for other reasons. A large adenoma may cause a sensation of right upper quadrant fullness or discomfort.

Adenoma is of clinical importance because of its tendency to bleed spontaneously and result in hemorrhage and infarction in the tumor. The risk of spontaneous bleeding is likely to be between 20% and 40% (Barthelemes & Tait, 2005; Dokmak et al, 2009; Bioulac-Sage et al, 2009; Deneve et al, 2009). Although the risk of bleeding is increased in pregnant women and in those taking OC, this risk is quite exclusively observed in patients with lesions larger than 5 cm (Dokmak et al, 2009; Deneve et al, 2009). About 10% of patients are seen with acute, severe abdominal pain from intraperitoneal rupture and hemoperitoneum, which may be associated with hypovolemic shock. Hemorrhage results in acute pain and discomfort accompanied by anorexia, nausea, vomiting, and fever. Although tumor rupture with hemoperitoneum represents an alarming manifestation, hemodynamic instability is rare, except in patients treated with anticoagulation (Marini et al, 2002). The presence of sudden right upper quadrant pain with some respiratory manifestation leads some clinicians to erroneously suspect the diagnosis of pulmonary embolism; they then treat the patient with anticoagulant therapy, which can exacerbate the bleeding.

The risk of malignant transformation of HA in women is on the order of 5% (Barthelemes & Tait, 2005; Bioulac-Sage et al, 2009; Deneve et al, 2009; Dokmak et al, 2009; Stoot et al, 2010). No clinical or radiologic signs can predict preoperatively the diagnosis of degenerated HA; it is almost exclusively made on the pathologic specimen of resected HA. Malignancy displays well-differentiated HCC, and vascular extension or satellite nodules are exceptional. α-Fetoprotein (AFP) level is usually normal. Most cases of HCC develop at the site of the liver cell adenoma. The risk of malignancy is very high in men (50%), whatever the size of the tumor, and in women with a large HA (>8 cm) (Dokmak et al, 2009; Stoot et al, 2010; Farges et al, 2011). Moreover, HA with β-catenin activation carries a higher risk of malignant transformation (Bioulac-Sage

et al, 2009; Farges et al, 2011). These cases of malignancy developed in HA should be differentiated from exceptional cases of multiple degenerated HA occurring in young women with symptomatic hepatomegaly associated with severe asthenia and high AFP level. The prognosis is poor, because surgical resection is not feasible, and liver transplantation is inevitably followed by rapid and fatal relapse of the disease.

In two thirds of cases, liver function tests are abnormal, including elevated cholestatic enzymes and mild elevation of transaminases (Dokmak et al, 2009). In case of malignancy, serum AFP is generally normal.

Imaging

For years, imaging features of HA were nonspecific and unlikely for FNH. Now, it is well established that the different molecular features correspond to distinct phenotypic features.

The key imaging feature of HNF-1α–inactivated HA is the presence of marked and diffuse fat within the lesion. Fat is responsible for lesion hyperechogenicity on US and strong hypoattenuation on unenhanced CT scan (see Chapter 16). Because of the fat content, the lesion does not enhance markedly and shows rapid washout on multiphasic examination. MR plays a crucial role in demonstrating the presence of diffuse fat (see Chapter 17). The striking finding is a diffuse and homogeneous signal dropout on chemical-shift T1-weighted sequences with a high specificity (Laumonier et al, 2008; Fig. 79A.11).

The key imaging feature of telangiectatic/inflammatory HA is the presence of telangiectatic components (Fig. 79A.12). The lesion is often hyperechoic at US but is also heterogeneous, and Doppler signals are commonly seen. Unlike other HAs, central arteries that could mimic FNH may be seen on contrast-enhanced US (Soussan et al, 2010). On unenhanced CT, telangiectatic/inflammatory HAs are hypoattenuating but often heterogeneous. The characteristic lesion behavior on multiphasic examination is a strong arterial enhancement and a persistent enhancement in the delayed phase (Laumonier et al, 2008). MR imaging is also very important because it shows a strong hyperintense signal on T2-weighted images. On T1-weighted sequences, lesion signal intensity is variable and is often hyperintense. This hyperintensity is not related to fat and persists on fat-suppressed and opposed-phase sequences (Attal et al, 2003; Lewin et al, 2006). Considering two imaging findings—a markedly hyperintense signal on T2-weighted images and persistent enhancement on the delayed phase—Laumonier and colleagues (2008) observed a positive predictive value for the diagnosis of telangiectatic/inflammatory hepatocellular adenoma of 88.5%, a negative predictive value of 84%, a sensitivity of 85.2%, and a specificity of 87.5%. Some of telangiectatic/inflammatory HAs may contain some fat deposition. The two other subtypes, β-catenin–activated and unclassified HA, are less characteristic on imaging. To note, some telangiectatic/inflammatory HA may display β-catenin activation and may therefore have imaging findings similar to classic telangiectatic/inflammatory HA. The others share findings of hepatocellular tumors, strong arterial enhancement with no delayed enhancement after gadolinium injection, and may have heterogeneous content.

Treatment

The management of patients with HA should be mainly tailored according to the patient's gender and the size of the tumor. The follow-up and treatment in some patients can also be influenced by the histologic classification of their HA.

Whatever the size, HA in men represents an indication for resection because of the high risk of malignancy. Whatever the number of HAs, women with small lesions less than 5 cm in diameter have a low risk of complication and could be safely observed after cessation of OC; however, the influence of the discontinuation of OC on the regression of HA is a subject of debate (Gordon et al, 1986), justifying serial imaging examinations in patients with HA managed conservatively. Indeed, long-term follow-up evaluation for nearly 20 years of patients with small residual HAs after surgery showed that HA remains stable or involved in more than 90% of cases (Dokmak et al, 2009). Regression and even disappearance of HAs seem to occur more frequently in older patients. Reappearance or increase in size occurs in 15% of patients, but serious complications are rarely described in this subgroup (Dokmak et al, 2009). It was usually recommended that pregnancy be avoided in patients with a history of HA (Deneve et al, 2009); however, in our experience, pregnancies in several women treated for HA were not associated with reappearance or enlargement of residual HA; this led us to not contraindicate pregnancy in patients with HA (Dokmak et al, 2009).

Resection of HA greater than 5 cm is indicated. The operative approach should be tailored to the location and the size of the tumor. A large resection margin is not needed, allowing complete resection through a laparoscopic approach when feasible (Descottes et al, 2003). In some patients with large bilobar tumors, resection could be performed in two steps. Tumors located in one lobe are resected during a first procedure, followed some weeks later by a second procedure to resect tumors located in the remnant liver. Small tumors need not be resected, and liver transplantation is no longer indicated in patients with multiple HAs (Dokmak et al, 2009). Malignant transformation is often discovered on the pathologic analysis of the resected specimen, because no radiologic features are specific, and AFP level is almost always normal. Vascular invasion is absent, and lymph nodes are not involved. Complete resection of malignant HA is a safe and efficient therapeutic option.

Although surgical resection remains the standard of care of HA, other treatment modalities such as arterial embolization (Kobayashi et al, 2009; Stoot et al, 2007), percutaneous RFA (Atwell et al, 2005), or combinations of both are performed more and more with encouraging results in recent publications. Such modes of treatment are now proposed for tumors around 5 cm in diameter, in case of recurrence after surgical resection, and if the estimated risk of malignancy is very low (see Chapters 83 and 85).

Patients with ruptured HA should be treated electively. After stabilization of the patient and selective hepatic artery embolization, the patient can be observed for several months, until resorption of the hematoma surrounding the tumor (Terkivatan et al, 2001; Marini et al, 2002). The absorption of the hematoma surrounding the tumor allows an easier and parenchyma-sparing elective liver resection with a low risk of transfusion (Marini et al, 2002; Deneve et al, 2009). The involvement of these hemorrhagic HAs, which decrease dramatically in size and even disappear after embolization, may even bring into question the need for subsequent resection, because exceptional cases of hemorrhagic HA had a malignant component.

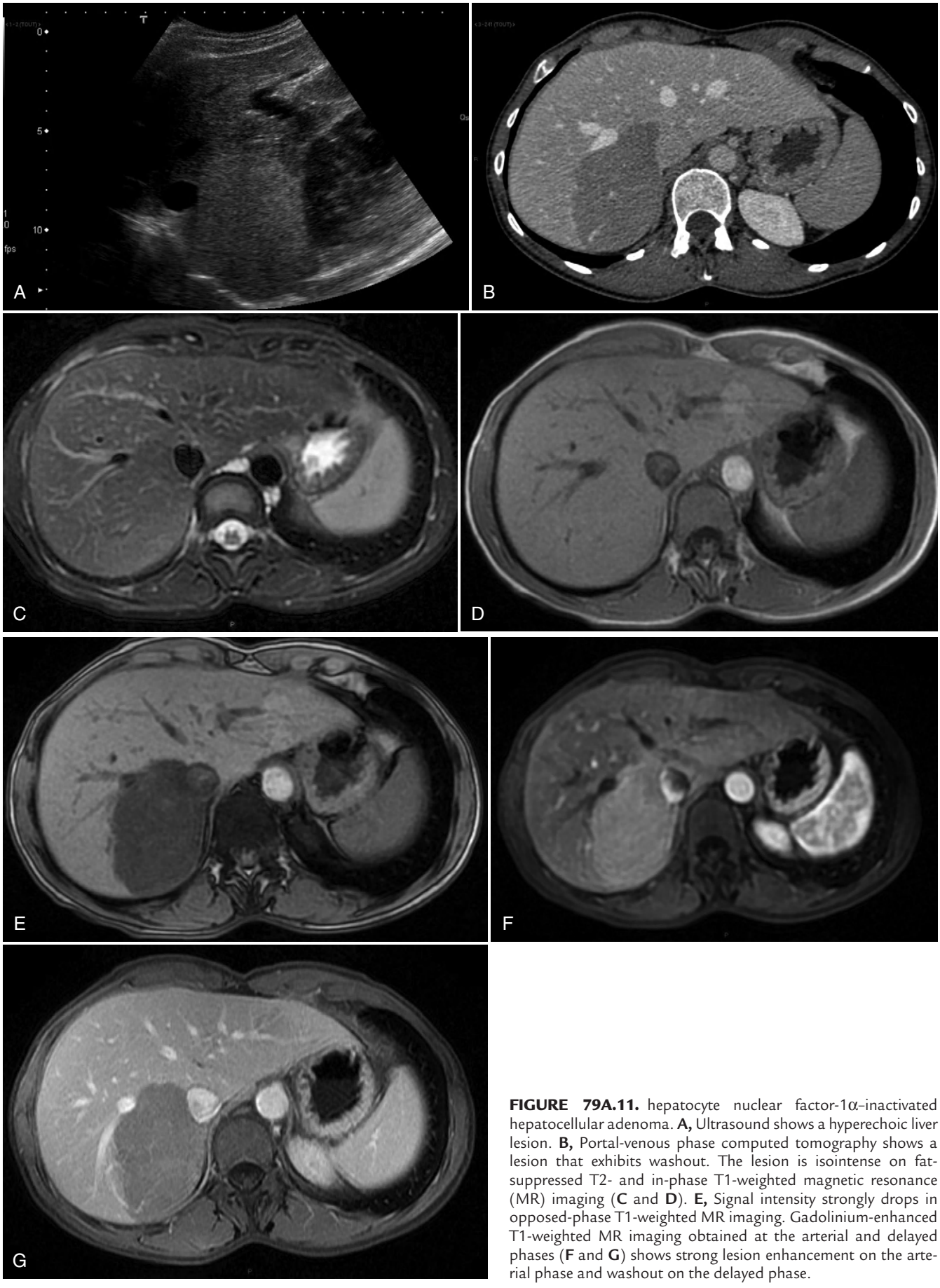


FIGURE 79A.11. hepatocyte nuclear factor-1α–inactivated hepatocellular adenoma. **A,** Ultrasound shows a hyperechoic liver lesion. **B,** Portal-venous phase computed tomography shows a lesion that exhibits washout. The lesion is isointense on fat-suppressed T2- and in-phase T1-weighted magnetic resonance (MR) imaging (**C** and **D**). **E,** Signal intensity strongly drops in opposed-phase T1-weighted MR imaging. Gadolinium-enhanced T1-weighted MR imaging obtained at the arterial and delayed phases (**F** and **G**) shows strong lesion enhancement on the arterial phase and washout on the delayed phase.

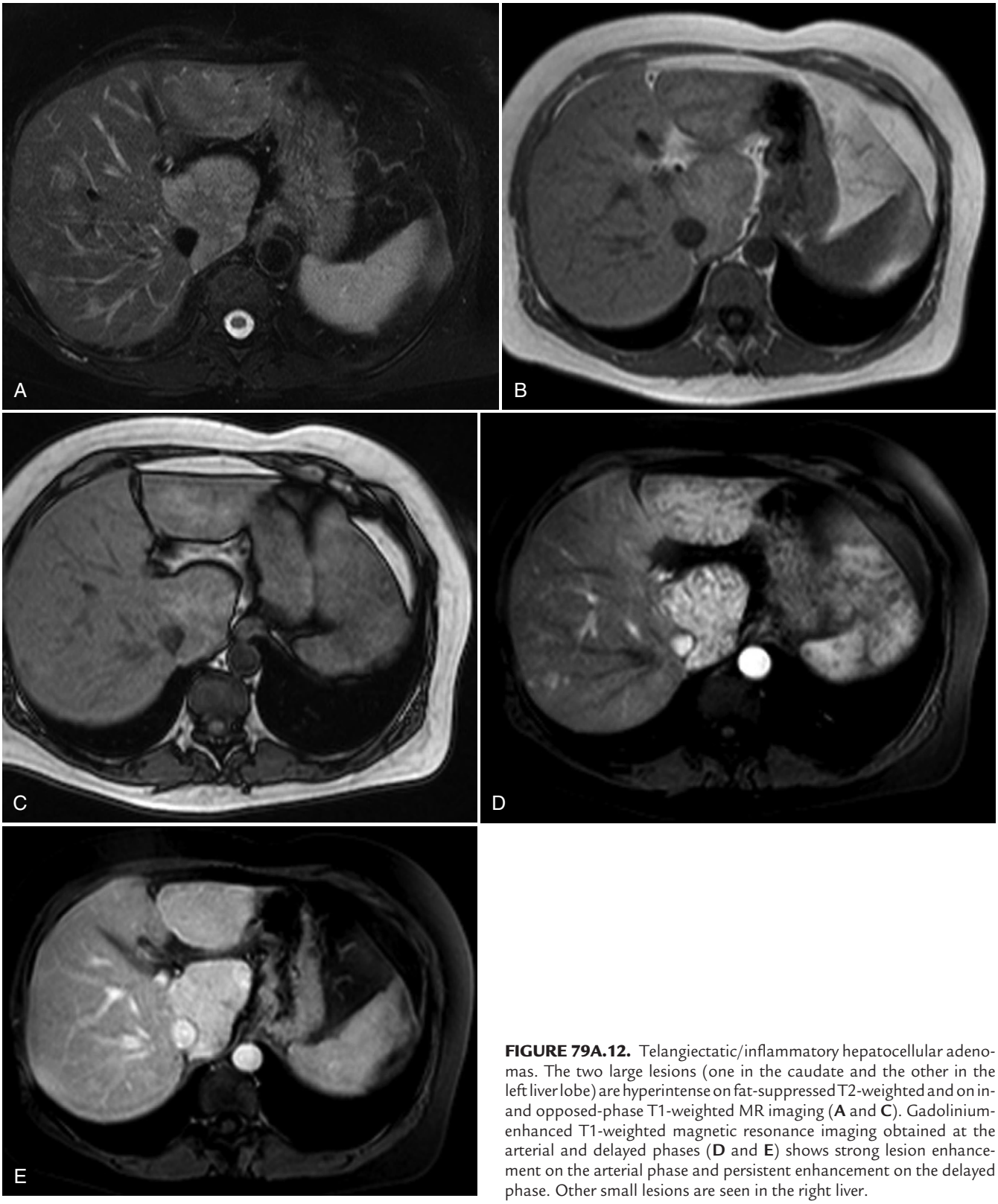


FIGURE 79A.12. Telangiectatic/inflammatory hepatocellular adenomas. The two large lesions (one in the caudate and the other in the left liver lobe) are hyperintense on fat-suppressed T2-weighted and on in- and opposed-phase T1-weighted MR imaging (**A** and **C**). Gadolinium-enhanced T1-weighted magnetic resonance imaging obtained at the arterial and delayed phases (**D** and **E**) shows strong lesion enhancement on the arterial phase and persistent enhancement on the delayed phase. Other small lesions are seen in the right liver.

The impact of the genotype/phenotype classification on the management of HA remains unclear (Terkivatan & Ijzermans, 2009). We are in favor of preoperative biopsy in patients with large (>5 cm) steatotic HA, considering a conservative approach with observation if the HA belongs to group 1, with H-HA mutation. Patients with HA approximately 5 cm, which could be treated by transarterial embolization or RFA, should undergo a biopsy before employing a conservative approach, so that close follow-up or even systematic resection can be considered if the HA belongs to group 2 with β-catenin mutation.

OTHER LESIONS

Fatty Lesions of the Liver

Angiomyolipoma

Hepatic angiomyolipoma is a rare, benign mesenchymal tumor composed of smooth muscle cells, adipose tissue, and proliferating blood vessels in various combinations. It belongs to the group of tumors derived from the *perivascular epithelioid cell,* referred to as *perivascular epithelial cell tumors* or *PEComas* (Tsui et al, 1999). Hepatic angiomyolipoma occurs frequently in the kidney but rarely in liver. This rare tumor may occur as a solitary mass (Zhou et al, 2008; Zeng et al, 2010) or as an associated finding with tuberous sclerosis (Hooper et al, 1994), which is present in about 15% of cases. In this situation, angiomyolipomas are usually multiple.

Hepatic angiomyolipoma predominantly affects women between 30 and 50 years of age, and lesions are often larger than 5 cm in diameter (Yang et al, 2007), and it can increase in size (Zeng et al, 2010). This tumor was once considered benign, but malignant transformation has been reported (Zhou et al, 2008; Rouquie et al, 2006; Dalle et al, 2000). Patients usually have no symptoms, and liver tests are normal; most of these tumors are found incidentally on routine imaging studies. The accuracy of preoperative diagnosis is low as a result of variable imaging appearance because of the varying content of the three components and the rarity of the lesion. The fat component of angiomyolipoma varies between 10% and 90% (Hooper et al, 1994).

Typically, angiomyolipoma appears hyperechoic and hypoattenuated on unenhanced CT scans and markedly enhanced on the arterial phase with central vascular opacification (Fig. 79A.13). The presence of large central vessels, the so-called macroaneurisms, within the lesion is characteristic of angiomyolipoma. On contrast-enhanced US, the vast majority of angiomyolipomas enhance on the arterial phase without washout on the portal or delayed phase (Wang et al, 2010). MRI is also an important diagnostic technique that allows fat suppression and multiphase dynamic contrast-enhanced scanning. In general, MR shows a marked hypersignal in T1-weighted images, which drops on fat-suppressed sequences. However, the lesions have various imaging characteristics because of the different proportions of smooth muscle, fat, and vessels (Yan et al, 2002). The amount of fat may be too small to be detected (<5%), and some angiomyolipomas, especially those with a prominent epithelioid myoid component, may mimic hepatocellular lesions, mostly HA and HCC (Arblade et al, 1996). The accuracy of needle biopsy is reinforced by using the antibody anti–HMB-45, which stains the myoid component (Arblade et al, 1996); the positivity of this antibody in the cytoplasm of smooth cells is characteristic of angiomyolipoma (Arblade et al, 1996). When the diagnosis is established, careful observation with serial follow-up is recommended in asymptomatic patients with lesions less than 5 cm (Hoffman et al, 1997; Sawai et al, 1998). Because some degenerated cases have been reported in patients with large tumors, especially when major epithelioid content was present, liver resection is indicated in large (>5 cm) hepatic angiomyolipoma (Zeng et al, 2010; Fig. 79A.14).

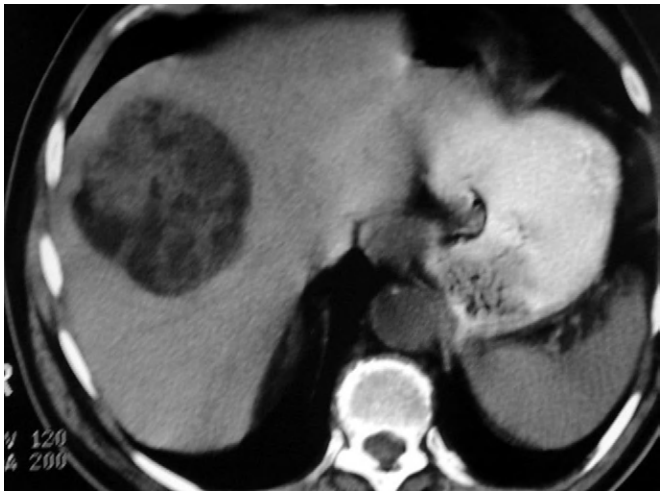


FIGURE 79A.13. Typical angiomyolipoma. Precontrast computed tomography shows a heterogeneous lesion that contains fat.

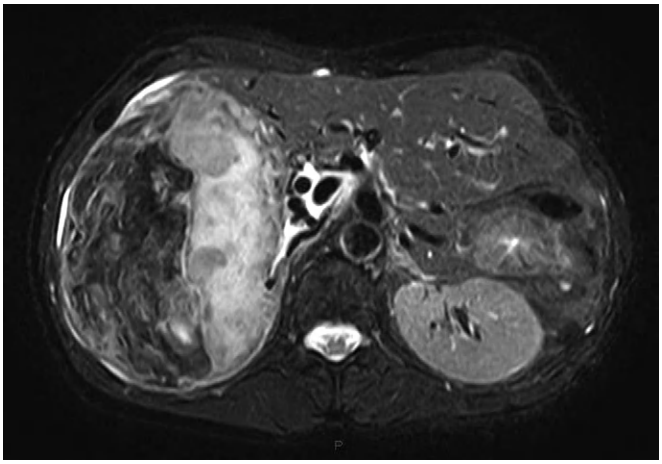


FIGURE 79A.14. Large hepatic angiomyolipoma requiring resection for the risk of malignant components. Lesion heterogeneity is well demonstrated on magnetic resonance imaging.

Lipoma

Hepatic lipoma is a very rare liver tumor that can mimic angiomyolipoma. Lesions of hepatic lipoma are homogeneous and circumscribed, show fat attenuation on CT, and do not enhance after intravenous (IV) administration of contrast material. On MRI imaging, lipomas are hyperintense on T1-weighted images and moderately hyperintense on T2-weighted images. The key finding is the drop in signal intensity on fat-suppressed MR sequences (Horton et al, 1999). Unlike hepatocellular tumors that contain fat, lipomas do not drop in signal intensity on opposed-phase T1-weighted MR images. Microscopic analysis shows well-differentiated adipose tissue without any significant changes. There is no need to resect lipomas (Nakamura et al, 2009).

Bile Duct Adenoma

Bile duct adenoma, also called *benign cholangioma,* is a benign and asymptomatic mass that is typically discovered incidentally at imaging studies, surgery, or at autopsy (Kim et al, 2010). This rare benign lesion of the liver is usually a well-circumscribed,

subcapsular nodule with a diameter of less than 1 cm consisting of a proliferation of noncystic biliary structures within a dense, fibrous stroma (Allaire et al, 1988). No relationship between this tumor and cholangiocarcinoma has been shown, and resection is unnecessary; its only clinical significance lies in the possible confusion with metastatic carcinoma during surgery (Hornick et al, 2005).

Biliary Hamartoma

This lesion, also known as a *Von Meyenburg complex,* is a development anomaly of small intrahepatic bile ducts composed of bile ductules, inflammatory cells, and fibrosis (Table 79A.1; Neri et al, 2004). The main practical problem raised by this tumor is for the pathologist, because its possible discovery during surgery for carcinoma of another abdominal organ leads the surgeon to perform a biopsy for frozen-section diagnosis (Guiu et al, 2009). The pathologist who is unaware of this rare entity may be puzzled and may be tempted to call the lesion metastatic carcinoma. Otherwise, hamartomas are easily recognized on heavily T2-weighted MR images and appear as multiple small lesions that are strongly hyperintense. The presentation is often mistaken for Caroli disease, but the lesions in biliary hamartoma do not communicate with bile ducts (Thomé-Noun et al, 2008). Treatment is not required.

Inflammatory Pseudotumors

Inflammatory pseudotumor of the liver (IPL) is a rare benign tumor that can mimic cholangiocarcinoma (Deng et al, 2010; see Chapter 48). Commonly found in the lung, IPL is a reactive fibroblastic proliferation infiltrated by polymorph inflammatory cells: plasmocytes, lymphocytes, and histiocytes. IPLs are also referred to as *inflammatory myofibroblastic tumors, plasmocytic granuloma, histiocytoma, fibroxanthoma, pseudolymphoma,* and *necrotic tumor of the liver* (Milias et al, 2009). They are more common in men than in women, are more frequently seen in the non-European population, and have an average age at presentation of 50 years (Goldsmith et al, 2009). The majority of patients with IPL typically experience vague constitutional symptoms such as fever (50%), abdominal pain (48%), weight loss (37%), and jaundice (Zamir et al, 1998; Goldsmith et al, 2009). Hematologic tests are generally normal, but one third of patients are seen with inflammatory syndrome. Liver function tests are abnormal in 15% of cases with mild elevations in cholestatic tests (alkaline phosphatase and GGT). The etiology of this pathology is not well known, but the predominantly inflammatory pattern and the associated systemic reaction suggest an underlying infectious agent (Koea et al, 2003) with microorganisms coming from the gut to the liver via the portal vein (Jover Díaz et al, 2009). This etiology can explain the response to antibiotics in some cases. Some authors have suggested an autoimmune etiology such as immunoglobulin G (IgG)-4 sclerosing cholangitis with histologic findings similar to autoimmune pancreatitis (Uchida et al, 2007), and in this case, treatment with steroids can be effective (Anthony, 1993; Kamisawa & Okamoto, 2008). In the tumoral hypothesis, authors suggest that some IPL may be of follicular dendritic cell origin (Shek et al, 1998).

Imaging studies often show diffuse and infiltrative large tumors, although multiple forms can be found (Jover Díaz et al, 2009). The majority of these lesions are located near the gallbladder or are related to the biliary tree, sometimes mimicking a malignant biliary stricture (Koea et al, 2003; Locke et al, 2005; Terada, 2010).

According to clinical and morphologic presentations, three different forms can be distinguished:

1) *Inflammatory form:* Revealed by abdominal pain and fever, inflammatory syndrome can be found in half of patients; weight loss, nausea, and vomiting may also occur but are rare. At imaging, the lesion is generally solitary, ill-defined, large, heterogeneous, and hypervascular. On MRI, the lesion is hypointense on T1-weighted sequences and isointense or hyperintense on T2-weighted sequences. At histology, spindle cells with a dense inflammatory and polymorphic population are seen, associated with anomalies of the portal branches in contact with the lesion (fibrotic portal endophlebitis).

2) *Encapsulated form:* Clinically, this lesion is small and is usually discovered fortuitously. Inflammatory syndrome is absent. At CT, the lesion is hypoattenuating and presents with a peripheral capsule, and no enhancement is depicted within the lesion. On MRI, the lesion is well limited, hypointense on T1 imaging, isointense on T2 imaging, and surrounded by a capsule that enhances on delayed phase. This encapsulated form resembles a lesion called a *solitary necrotic nodule of the liver* (Abbey-Toby et al, 2003), and it can be a chronic sequela of an inflammatory process that has partially healed, circumscribed by a fibrotic capsule.

3) *Infiltrating periportal form:* Frequently revealed by jaundice (Venkataraman et al, 2003), this is a poorly demarcated lesion with periportal infiltration on imaging. The lesion is hypointense on T1-weighted sequences and moderately hyperintense on T2-weighted sequences with dilated bile ducts (Venkataraman et al, 2003). A progressive enhancement is seen after injection of gadolinium chelates. Lymphadenopathy can be observed along the hepatoduodenal ligament and in the retroperitoneum, mimicking cholangiocarcinoma (Fig. 79A.15; Chirica et al, 2005). On histology, periportal inflammation is associated with destruction of bile ducts and intrahepatic extension of inflammatory processes.

On gross sections, IPL is tan, usually unencapsulated, and may show indistinct borders with the surrounding parenchyma. When the diagnosis is suspected, a liver biopsy is often necessary to differentiate IPL from other tumors.

The optimal management has not been well established, with many types of treatment described, from simple observation to surgical resection and even liver transplantation (Milias et al, 2009). In the literature, most patients have been surgically treated, because the diagnosis was not made preoperatively because of the possible destructive nature of IPL, or because its malignant potential leads some authors to propose liver resection (Li et al, 1989). The outcome of patients treated surgically is very good (Goldsmith et al, 2009), but IPL can be associated with some risk, especially IPL that occurs as hilar lesions, necessitating major liver resection. Recurrence can be observed after resection (Lopez-Tomassetti Fernandez et al, 2006). However, IPLs are benign lesions with no malignant potential; once the diagnosis has been made, medical treatment by antibiotics, steroids (Maze et al, 1999), or observation can be undertaken with very good results. A number of reports exist that suggest the natural history of these lesions is of spontaneous complete resolution or regression (Levy et al, 2001; Koea et al, 2003; Goldsmith et al, 2009); therefore IPL can be safely managed nonoperatively.

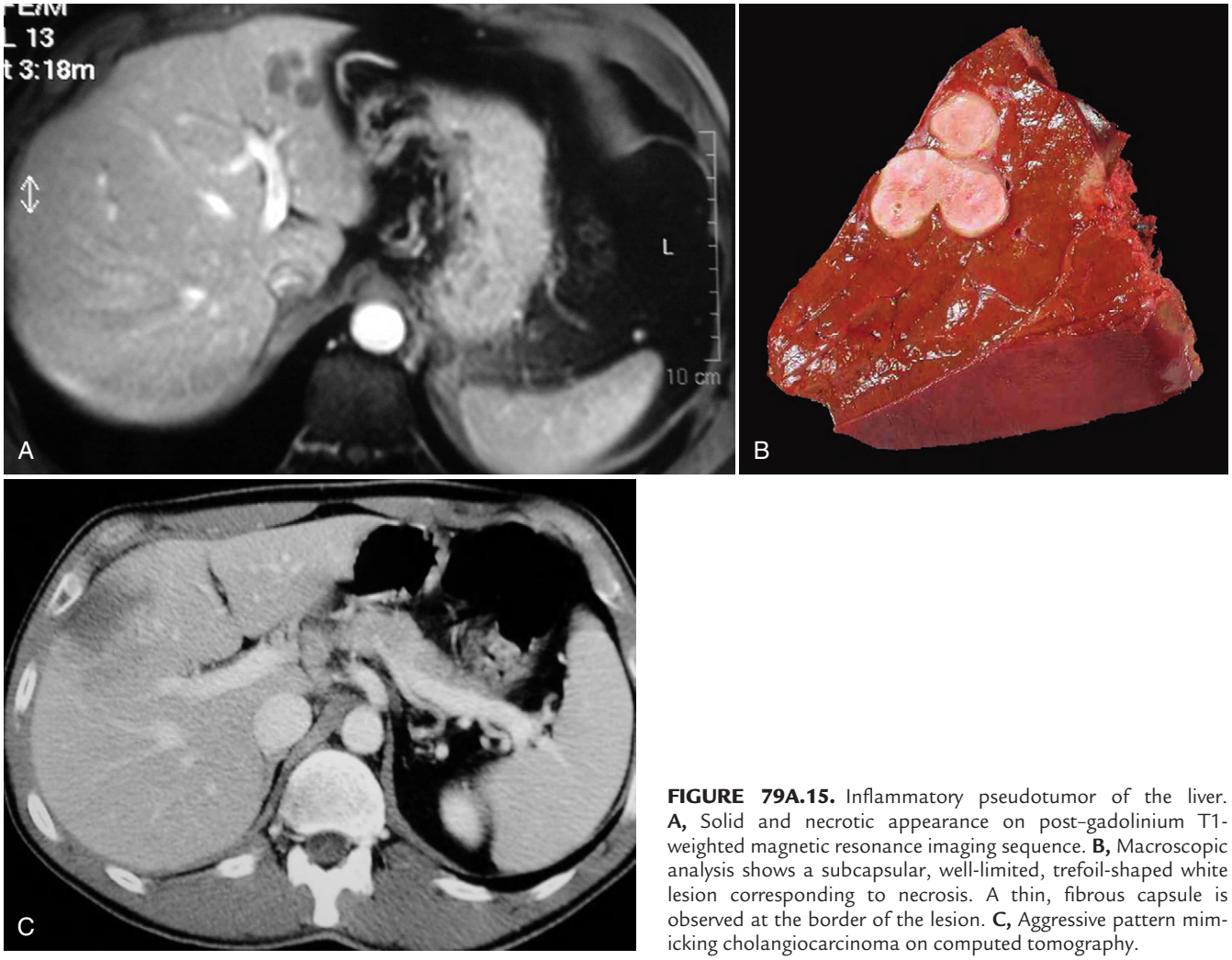


FIGURE 79A.15. Inflammatory pseudotumor of the liver. **A,** Solid and necrotic appearance on post–gadolinium T1-weighted magnetic resonance imaging sequence. **B,** Macroscopic analysis shows a subcapsular, well-limited, trefoil-shaped white lesion corresponding to necrosis. A thin, fibrous capsule is observed at the border of the lesion. **C,** Aggressive pattern mimicking cholangiocarcinoma on computed tomography.

Rare Tumors and Pseudotumors

Solitary Fibrotic Tumor

Also known as a *solitary necrotic tumor,* a *solitary fibrotic tumor* of the liver is rare with only about 100 cases reported in the literature. Slightly more frequent in men, these tumors are found at a mean age of 60 years, and the majority of patients are asymptomatic (Deniz & Coban, 2010). The solitary fibrotic tumor is usually a unique, well-circumscribed, small (<2 cm) lesion (Zhou et al, 2008). Histologically, it is composed in varying degrees of necrosis and fibrosis comprising abundant collagen fibers, and it can contain calcifications. This lesion can mimic liver malignancy, especially metastases (Delis et al, 2009; De Luca et al, 2000).

The etiology of this lesion is still uncertain, but possible causes included thrombi, hemangioma, trauma, and infection, especially parasitic infection such as with a hydatid cyst (Clouston et al, 1993; Deniz & Coban, 2010). On imaging, no findings are characteristic except a progressive enhancement that is related to abundant collagen (Moser et al, 2005), which can be very intense on delayed phase. It is assumed to be benign, but more than half the time, this lesion is associated with extrahepatic malignancy, especially colonic cancer and small metastatic adenocarcinoma; this justifies resection (Deniz & Coban, 2010).

Lymphangioma

Lymphangiomas are benign neoplasms located within the liver parenchyma, regarded as malformations that arise from sequestrations of lymphatic tissue that fail to communicate with the normal lymphatic system during embryogenesis (Weiss et al, 2008). Lymphangiomas are frequently found in the neonatal period and childhood but rarely in adulthood. The occurrence of a solitary lymphangioma in the liver is extremely rare, and very few reported cases—fewer than 10—have been described in the literature (Matsumoto et al, 2010). Contrary to neonatal (Shahi et al, 2009) or childhood cases with symptomatic, large tumors, lymphangiomas are generally small (<4 cm) and asymptomatic in adults. On imaging, this lesion has a solid and cystic component and can contain small peripheral calcifications; histologically, it is composed of vascular lymphatic spaces lined by regular cells. Immunohistochemistry using D2-40, LYVE-1, and Prox-1 are helpful to establish the diagnosis of lymphangioma, as they are able to discriminate between lymphatic and vascular endothelium (Matsumoto et al, 2010).

Leiomyoma

Leiomyomas are very rare, benign liver tumors developed from the smooth muscles of the vessels or bile ducts (Belli et al, 2001;

Urizono et al, 2006) with lesions of variable size. It can be observed in patients with immunosuppression or AIDS (Prévot et al, 1994; Sclabas et al, 2002). On imaging, lesions appear hypoechoic on US and hypoattenuating on CT scan with variable enhancement after injection of contrast material. On MR imaging, leiomyoma is hypointense on T1-weighted sequences and strongly hyperintense on T2-weighted sequences (Santos et al, 2010). Histologic features include spindle-cell proliferation without nuclear atypia, hemorrhage, and necrosis. Immunoreactivity with mesenchymal markers shows positivity of the cell proliferation with vimentin and smooth muscular actin. Because radiologic findings are nonspecific, liver resection is usually recommended.

Heterotopic Tissue

The presence of heterotopic tissue within the liver has been described, and diagnosis is usually established after surgical excision (see Chapter 48). The most frequent is liver splenosis, which corresponds to autotransplantation of splenic tissue; it occurs after traumatic splenic rupture or, less frequently, after surgical rupture during splenectomy (Davidson & Reid, 1997; Labat-Debelleix et al, 2008). Splenosis is asymptomatic, most often localized in the left liver, with a mean size of approximately 4 cm. On imaging, the lesion shows features of a hypervascular tumor but with less enhancement on the delayed phase. These radiologic features make the differential diagnosis with another hypervascular liver tumor very difficult, and this can be misinterpreted in a standard preoperative evaluation as HCC or breast metastatic disease (d'Angelica et al, 1998; Foroudi et al, 1999; Labat-Debelleix et al, 2008; Abu Hilal et al, 2009). Diagnosis can be suspected with scintigraphy using technetium (Tc) 99m–labeled heat-denatured red blood, and it can be established with liver biopsy (Lu et al, 2008; Labat-Debelleix et al, 2008). Other heterotopic tissues include adrenal and pancreatic tissues located around the bile ducts (Suzuki et al, 1999; Heer et al, 2010).

Hepatic Pseudolesions

The development of imaging techniques using thin slices and multiphasic study permits the discovery of many intrahepatic anomalies, especially after injection of contrast material on CT scan and MRI; some anomalies are not really liver lesions but can mimic liver tumors.

1) *Perfusion disorders:* These anomalies are the result of hyperarterialization of a liver segment as a result of decreased or absent portal vein flow. These anomalies are seen on CT after injection of contrast; they predominate on arterial or portal phase images and disappear or attenuate on the delayed phase. These perfusion disorders result from portal obstruction, compression, or arterioportal shunt (Tamura et al, 1997). In general, they have typical straight borders that correspond to segmental or subsegmental locations. The diagnosis can be more difficult in patients with small peripheral or central "pseudonodular" lesions, such as in cirrhotic patients as a result of arterioportal shunts. In patients with hepatic vein obstruction, these abnormalities are not systematized (mosaic form) because of the rapid development of interhepatic venous shunts (Vilgrain et al, 2007).

2) *Localized parenchymal compression:* This can display aspects of pseudolesion because of impaired enhancement in the compressed territory in the portal phase but without hyperarterialization on the arterial phase. In this case, the pseudolesion has no vascular topography and can be exacerbated by deep inspiration with compression by the ribs and diaphragm (Vilgrain et al, 2007).

3) *Confluent fibrosis:* This lesion can also mimic a tumor, and it is mainly observed in chronic liver disease; it corresponds to parenchymal extinction and is located in segments IV and VIII with capsular retraction (Vilgrain et al, 2007).

4) *Radiation:* Pseudolesion of liver parenchyma can be observed after radiation exposure. Previous history of radiation therapy and the appearance of straight borders without anatomic distribution are highly suggestive of this etiology. As a result of associated fibrosis, atrophy of the involved segment can be observed with compensatory hypertrophy (Vilgrain et al, 2007).

Peliosis

Peliosis is a rare condition characterized by multiple, small, blood-filled pools in liver parenchyma that vary from 1 mm to several centimeters without lobular systematization. This lesion results from focal rupture of sinusoidal walls and is mostly observed in adult patients after systemic chemotherapy for colorectal liver metastases using oxaliplatin (Rubbia-Brandt et al, 2010). It can also be associated with androgenic anabolic steroids (Tsirigotis et al, 2007), OC use (Gutiérrez Santiago et al, 2007), HIV infection (Radin & Kanel, 1991), or severe tuberculosis and malignancies such as Hodgkin's lymphoma (Kleger et al, 2009).

Imaging findings often mimic those of true tumors, because lesions are well limited and strongly hyperintense on T2-weighted MR images, and they enhance with arterial phase CT or MR. The persistent contrast uptake within the lesion is due to the blood-pooled condition (Verswijvel et al, 2003). This lesion can lead to extensive fibrosis resulting from parenchymal destruction and collapse (Cavalcanti et al, 1994), which is revealed on histology.

In general, this lesion is asymptomatic, but severe complications such as liver rupture, subsequent bleeding (Choi et al, 2009; Wang et al, 2001; Fidelman et al, 2002), and hepatopulmonary syndrome have been reported (Kallel et al, 2008). Treatment includes withdrawal of the possible causative agents, which can lead to regression of the disease.

Focal Fatty Changes

Hepatic steatosis is generally a diffuse process; however, heterogeneous focal fat distribution seen as spared liver areas, without steatosis, or areas that are fattier than the rest of liver parenchyma may also be present (Wanless, 2002). Although the pathogenesis is not well understood, regional hypoxia of hepatic tissue is thought to play a role (Zeppa et al, 2002). The majority of patients have underlying disease such as diabetes, obesity, hepatitis C, nonalcoholic steatohepatitis, and malnutrition; lesions are often discovered incidentally on imaging studies. Focal steatosis is mainly localized in segment IV, around the gallbladder and the round ligament (Vilgrain et al, 2007). A nodular aspect can mimic liver metastasis (Tom, et al 2004; Rubaltelli et al, 2002).

REGENERATIVE PROCESSES

Nodular Regenerative Hyperplasia

Nodular regenerative hyperplasia (NRH) is a relatively rare, benign, diffuse micronodular transformation of the liver that

has been referred to by many names in the literature, including *nodular transformation*, *noncirrhotic nodulation*, and *partial nodular transformation*. It is a distinct disease entity characterized by diffuse involvement of the liver with nodules composed of hyperplastic hepatocytes, and it should not be confused with the regenerative nodules of cirrhosis or FNH (Federle & Brancatelli, 2001).

The pathogenesis of NRH is not well known, but one of the proposed theories hypothesizes that a primary vascular process leads to obliteration of portal vein, which in turn induces ischemia, atrophy of hepatocytes in the central zone, and the proliferation of hepatocytes (Al-Mukhaizeem et al, 2004). The other theory proposes that a preneoplastic process leads to NRH in association with the reported high prevalence of hepatocyte dysplasia (20% to 42%) and HCC formed in livers of patients with NRH (Nzeako et al, 1996; Dogan et al, 2003). The prevalence of NRH was reported to be around 2% (Biecker et al, 2003).

NRH was classically associated with a wide spectrum of systemic diseases, processes, and drugs; these include myeloproliferative and lymphoproliferative disorders, chronic vascular disorders, rheumatologic and collagen vascular diseases (rheumatoid arthritis, Felty syndrome, polyarteritis nodosa, amyloidosis, and primary biliary cirrhosis) (Morris et al, 2010), primary hypogammaglobulinemia (Malamut et al, 2008), HIV infection (Tateo et al, 2008; Bihl et al 2010), hereditary hemorrhagic telangiectasia (Brenard et al, 2010), hepatoportal sclerosis, congenital absence of the portal vein (Peker et al, 2009), portal veinopathy (Hillaire et al, 2002), malignant disease (Al-Hamoudi et al, 2009), and after solid organ transplantation (Devarbhavi et al, 2007). NRH is also associated with the use of drugs such as steroids (Mortelé & Ros, 2002), azathioprine for inflammatory bowel disease (Vernier-Massouille et al, 2007; Seksik et al, 2010), and chemotherapeutic agents. This lesion is considered the most severe induced histologic liver lesion in patients treated with oxaliplatin-based chemotherapy for colorectal liver metastases, with an incidence up to 24% (Hubert et al, 2007; Wicherts et al, 2010; Rubbia-Brandt et al, 2010); it can be associated with high postoperative morbidity in cases of major liver resection (see Chapter 65).

Clinically, NRH usually causes no symptoms, and lesions are discovered incidentally, mainly on liver biopsy. More than two thirds of reported patients had abnormal liver test results, but liver function was preserved (Arvanitaki & Adler, 2001; Morris et al, 2010); the risk of liver insufficiency leading to liver transplantation is rare (Tateo et al, 2008). The main clinical presentation is portal hypertension, observed in 30% of patients, with subsequent esophageal varices, splenomegaly, and ascites (Arvanitaki & Adler, 2001; Dogan et al, 2003; Morris et al, 2010). Fatal bleeding from varices has been observed (Morris et al, 2010), but the risk of transformation to HCC is rare (Nzeako et al, 1996; Kataoka et al, 2006). Because of these clinical features, the diagnosis of NRH should be considered in patients with clinical signs of portal hypertension and normal or mildly abnormal liver function test results, in whom other causes of portal hypertension have been excluded.

Imaging findings are not specific for NRH. On imaging, three presentations are possible: first, liver imaging is unremarkable; second, imaging shows signs of noncirrhotic portal hypertension without any liver nodules, because the nodules are typically very small; third, NRH appears as multiple liver nodules with or without portal hypertension. In most cases, imaging shows normal hepatic parenchyma. When nodules are seen, they have a variable enhancement, and they are hyperintense on T1-weighted images and isointense or hypointense to normal liver on T2-weighted images (Clouet et al, 1999; Mortelé & Ros, 2002; Casillas et al, 1997; Horita et al, 2002). Contrary to FNH, the central scar is lacking. Differences between these two lesions are mainly based on the presence of multiple small nodules, signs of portal hypertension, and clinical context. Accurate diagnosis should be confirmed with histologic examination prior to treatment. In highly suspicious cases, percutaneous needle biopsy can establish the diagnosis (Hubert et al, 2007). In doubtful cases with negative percutaneous biopsy, open biopsy is indicated to obtain an adequate sample of hepatic tissue, because percutaneous needle biopsies may give falsely normal results (Biecker et al, 2003).

Management depends on the clinical symptoms. In asymptomatic patients, no treatment is recommended. The effect of the withdrawal or specific treatment of the possible causative disease or agents on the course of this entity is not well known. In patients with complications of portal hypertension, appropriate management includes drug therapy, endoscopic therapy, transjugular intrahepatic shunt, or portacaval shunt if necessary (Biecker et al, 2003). Rarely, patients may progress to liver failure and may ultimately require liver transplantation (Trotter & Everson, 2001; Tateo, 2008). Because of the high postoperative morbidity with major liver resection in cases of NRH associated with oxaliplatin-based chemotherapy (Wicherts et al, 2010), it is recommended in this group of patients, who underwent many cycles of preoperative chemotherapy, to perform a liver biopsy—either systematically or in case of portal hypertension—to search for NRH. If NRH is diagnosed, major liver resection should be avoided or prepared for by portal vein embolization.

FNH-like Lesions

FNH-like lesions histopathologically resemble FNH but are seen in patients with liver disease or liver vessel abnormalities. The most common causes of liver diseases responsible for the development of FNH-like lesions are Budd-Chiari syndrome (Cazals-Hatem et al, 2003), hereditary hemorrhagic telangiectasia (Gincul et al, 2008), and congenital hepatic fibrosis (Vilgrain et al, 1999; Zeitoun et al, 2004; Buscarini et al, 2004). All these diseases induce severe liver flow alterations with decreased portal vein blood flow and marked increased hepatic artery blood flow (Kim et al, 2004; Bureau et al, 2004). FNH-like lesions may be a hepatic response to increased arterial inflow. Similarly, FNH-like lesions have been reported in patients with cavernous transformation of the portal vein (Bureau et al, 2004); imaging findings of FNH-like lesions are similar to the FNH that arises on normal liver, and they may contain a central scar. Because the liver signal is abnormal in Budd-Chiari syndrome, the FNH-like lesions are mostly hyperintense on T1- and hypointense on T2-weighted images; however, they still enhance strongly at the arterial phase. Unlike most FNH, they may become more numerous and grow over time.

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CHAPTER 80

Hepatocellular carcinoma

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OVERVIEW

Hepatocellular carcinoma (HCC) is the most common primary liver tumor. It currently represents the sixth most common cancer worldwide and is the third major case of cancer death. Its incidence presents marked geographic differences (Table 80.1; Ferlay et al, 2010). Asia and sub-Saharan Africa constitute high-risk areas with yearly rates exceeding 20 per 100,000 population. Southern Europe and Japan have intermediate rates, and rates are low in Northern Europe and North America (Bosch et al, 2004; El-Serag, 2004; Ferlay et al, 2010). Several registries have shown that the incidence figures have changed slightly during the past several years. Vaccination plans against hepatitis B virus (HBV) and improvement in health standards have decreased the incidence in some high-risk areas, such as Taiwan (Chang et al, 1997; see Chapter 64). The incidence is decreasing in Japan, where the risk of HCC is linked significantly to chronic infection with hepatitis C virus (HCV) that was acquired decades ago, when health care was less concerned by blood-borne viral disease. By contrast, HCC incidence is increasing in the United States (El-Serag & Mason, 1999) and in Northern Europe (Bosch et al, 2004), probably reflecting the different timing in the appearance of risk factors, mostly HCV infection (Tanaka et al, 2002; see Chapter 64). Another major risk factor for HCC is alcohol intake, and this also varies widely in different countries (Morgan et al, 2004). Aflatoxin B1 uptake (Colombo & Donato, 2005), cigarette smoking, and heavy alcohol consumption are independent risk factors and may have synergistic effects (Kuper et al, 2000; see Chapter 64). Finally, recent studies have suggested that coffee intake reduces the risk (Bravi et al, 2007).

In all areas of the world, cirrhosis underlies HCC in almost 90% of the cases (Bruix et al, 2004; Fattovich et al, 2004). Cirrhosis is related to chronic HBV and HCV, which contribute to HCC development in 80% of cases. Alcohol consumption is a frequent cofactor, and surveys indicate that a significant proportion of HCC in cryptogenic cirrhosis is due to nonalcoholic fatty liver disease (Calle et al, 2003; Clark, 2006; El-Serag et al, 2001; Marrero et al, 2005; Regimbeau et al, 2004), a condition associated with diabetes or obesity (Day, 2002; Marchesini et al, 2003; see Chapter 65). Because of the obesity epidemic, this factor may gain greater relevance in the near future. Follow-up studies have disclosed that HCC development is now the most frequent cause of death in patients with cirrhosis (Benvegnu et al, 2004; Degos et al, 2000; Forner et al, 2009; Sangiovanni et al, 2006). Prevention, diagnosis, and treatment of this neoplasm are major areas of clinical and research activity.

The mean annual incidence of HCC in cirrhotic patients in the West is 3% to 4%, and this figure increases in parallel to liver function impairment (Benvegnu et al, 2004; Bolondi et al, 2001; Bruix & Sherman, 2011; Degos et al, 2000; Forner et al, 2009; Sangiovanni et al, 2006). Some specific characteristics have been associated with a higher risk. The most consistent are male sex; advanced age, this being a surrogate for the duration of the underlying liver disease; and increased α-fetoprotein (AFP) concentration (Bruix & Sherman, 2011). HBV and HCV coinfection imply a higher risk (Fattovich et al, 2004).

Data of patients coinfected with the human immunodeficiency virus (HIV) suggest that the incidence of HCC has increased in this population, liver function deteriorates more rapidly, and the HCC appears in younger ages and frequently in symptomatic, advanced stages (Brau et al, 2007) associated with poorer outcome (Puoti et al, 2004). In addition, several authors have reported higher potential of tumoral progression before and after liver transplantation in HIV/HCV-coinfected patients despite similar pathologic findings (Vibert et al, 2011). Further studies are needed to confirm whether HIV coinfection increases the HCC incidence, and if it is an independent prognostic factor. Irregular regeneration, high proliferative stage, and presence of dysplastic foci in biopsy samples also have been correlated with higher HCC incidence during follow-up, but the need for tissue sampling has prevented their robust validation and wide clinical acceptance (Bruix et al, 2004).

Table 80.1

Incidence of Hepatocellular Carcinoma According to Geographic Area and Distribution of Risk Factors

GEOGRAPHIC RISK FACTORS		AGE-ADJUSTED INCIDENCE RATE (%)			
Area	**Male/Female**	**Hepatitis C Virus**	**Hepatitis B Virus**	**Alcohol**	**Other**
Europe		60-70	10-15	20	10
Western Europe	5.8/1.6				
Southern	9.8/3.4				
Northern	2.6/1.3				
North America		50-60	20	20	—
Northern	4.1/1.6				
Southern	4.8/3.6				
Asia and Africa		20	70	10	Aflatoxin
Japan		70	10-20	10	10
Eastern Asia	35.4/12.6				
Southeast Asia	18.3/5.7				
Middle Africa	24.2/12.9				
World	14.9/5.5				

Modified from Llovet JM, et al, 2003: Hepatocellular carcinoma. Lancet 362:1907-1917.

RISK FACTORS AND PREVENTION

All types of cancer are the consequence of genetic changes that accumulate through time, ultimately conferring a survival advantage to cells with an abnormal phenotype. The relationship between chronic hepatitis and long-lasting liver damage with HCC development suggests that persistent inflammation is a key factor leading to cancer. Maintained injury and repair with high proliferation rate increase the risk for DNA mutation (Arbuthnot & Kew, 2001). In addition to genetic damage secondary to inflammation, HBV itself may have direct genetic or epigenetic effects, being able to integrate into the host genome (Brechot, 2004; Farazi & DePinho, 2006). This integration into the host genome is accompanied by rearrangement and increased mutagenesis that may affect crucial target genes (Farazi & DePinho, 2006; Ferber et al, 2003; Ryu, 2003; Villanueva et al, 2007). HCV is an RNA virus and does not integrate into host DNA (see Chapter 8C).

The most effective prevention of HCC is avoidance of viral infection or of toxin intake. Effective vaccination for HBV exists, and the vaccination plans in Taiwan have shown the efficacy of this action in diminishing cancer rates in children and adults (Chang et al, 1997). Proper controls in health care settings prevent HCV dissemination through blood transmission. Alcohol intake should be the target of health campaigns in the community; in addition, aflatoxin contamination of food can be prevented by avoiding grain storage in humid conditions. The epidemic of obesity with associated nonalcoholic steatohepatitis leading to HCC must be controlled by health education.

If viral infection is already present, it has been shown that a decrease in viral replication and subsequently of chronic hepatic damage could result in a reduced incidence of HCC in the long term (Liaw et al, 2004). Effective therapy is available for HBV and HCV, and prevention may be feasible for both agents; however, if chronic liver disease already has caused cirrhosis, it is unclear whether antiviral therapy has any preventive capacity, because cell damage and transformation may already be present (Bruno et al, 2007). Recent studies have shown that long-term interferon administration in does not reduce the risk of HCC in patients with cirrhosis (Bruix et al, 2011; Di Bisceglie et al, 2008). In patients with HBV infection, the genetic damage may occur in the absence of major liver insult, and this would explain the appearance of HCC in an otherwise healthy liver (Pollicino et al, 2004). This circumstance is more frequent in areas where viral transmission occurs early after birth or in childhood, stressing the benefits of HBV vaccination. Secondary prevention in patients with chronic liver disease requires the prior recognition of affected individuals, but currently no proof of the cost-effectiveness of population screening for viral liver disease has been offered, and this is not recommended (Bruix & Sherman, 2005; see Chapter 64).

SCREENING AND RECALL OF HIGH-RISK INDIVIDUALS

A single randomized controlled trial performed in China recruited HBV patients to compare screening versus no screening; it showed the positive impact of screening on survival (Zhang & Yang, 1999). Unfortunately, such proof of efficacy is lacking in the West, and the establishment of surveillance for HCC in patients with cirrhosis is based on expert opinion (Bruix & Sherman, 2011; Bruix et al, 2001). The aim of screening is to detect HCC at an early stage, when the tumor is potentially curable (Bruix & Sherman, 2011; Forner et al, 2010).

Success of screening depends on several factors that include adequate ultrasound (US) performance, accurate diagnostic and staging criteria, and timely availability of curative treatments. If these requirements are not met, screening will never result in an increase of life expectancy. Even when accounting for the potential lead-time bias (i.e., patients apparently survive longer simply because their tumors were diagnosed earlier) and length-time bias (i.e., the interval between screenings misses the more aggressive tumors that will be detected when symptoms appear), it is assumed that screening results in more frequent detection of early stage HCC with more common application of effective treatment and improved outcome (Sangiovanni et al, 2004).

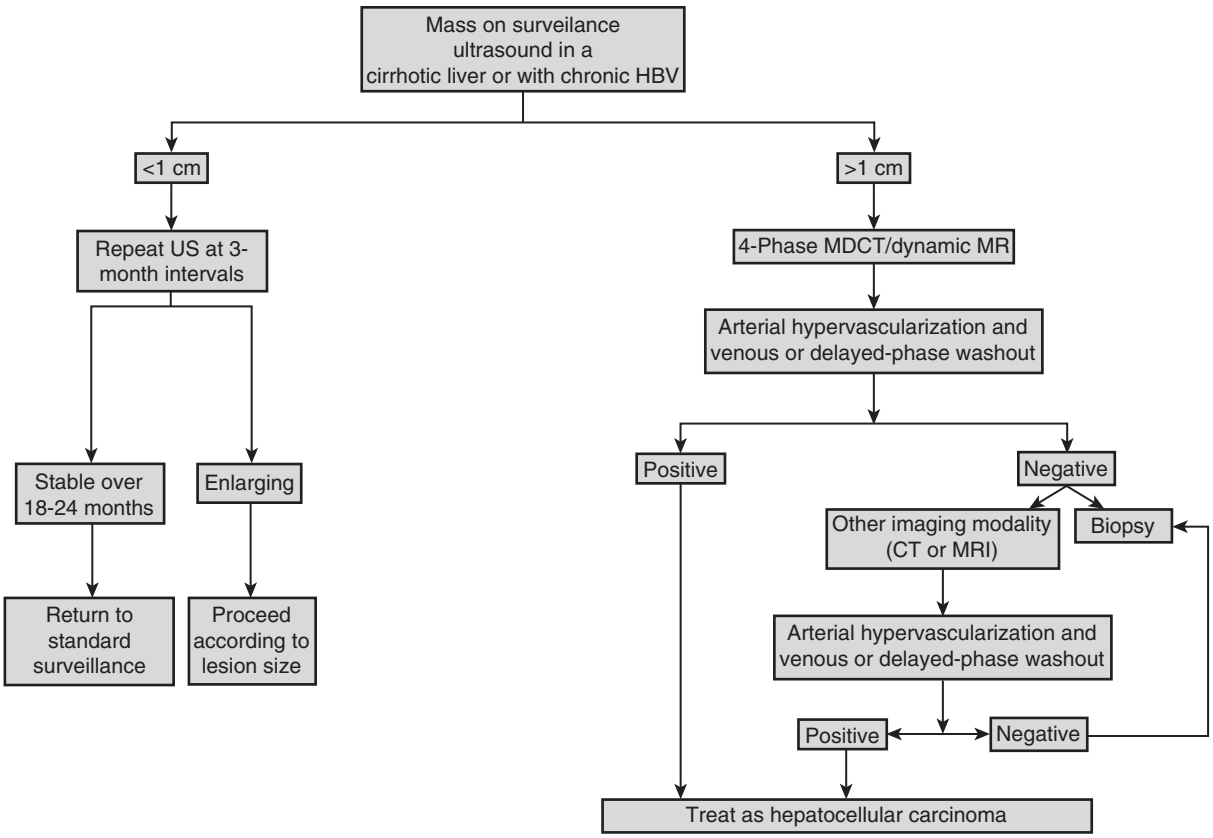


FIGURE 80.1. Screening strategy as proposed in the American Association for the Study of Liver Diseases Practice Guidelines. CT, computed tomography; HBV, hepatitis B virus; MDCT, multidetector computed tomography; MR, magnetic resonance; MRI, MR imaging; US, ultrasound. *(From Bruix J, Sherman M, 2011: Management of hepatocellular carcinoma: an update. Hepatology 53:1020-1022.)*

Effective treatment of HCC and long-term cure are feasible only with early detection; diagnosis at the symptomatic stage reflects an advanced stage and lack of effective treatment. Based on these arguments, the European Association for the Study of the Liver (EASL) panel of experts suggested abdominal US scanning and AFP measurements every 6 months for patients with liver cirrhosis who would be treated if diagnosed with HCC (Bruix et al, 2001). Because of the suboptimal accuracy of AFP (Marrero et al, 2009; Trevisani et al, 2001), the determination of this marker is no longer recommended, and screening is currently based on regular US (Bruix & Sherman, 2011). The screening recommendation excludes patients with severe associated conditions and those with advanced liver disease who are already candidates for transplantation. If this is not an option, screening for HCC aiming to detect early tumor will never be followed by treatment, and it makes no clinical sense.

On detection of an abnormal finding, patients must be evaluated. Figure 80.1 depicts the recall strategy proposed by the American Association for the Study of Liver Diseases (AASLD) panel, and Box 80.1 summarizes proposed diagnostic criteria (Bruix & Sherman, 2011). Nodules measuring less than 1 cm in a cirrhotic liver may not correspond to a malignant focus in more than 60% of cases (Forner et al, 2008); even so, confident diagnosis is difficult with current diagnostic tools. Close follow-up to detect any increase in size is therefore recommended (Bruix & Sherman, 2005). Nodules in a cirrhotic liver that are larger than 1 cm can be diagnosed as HCC if the vascular profile on imaging techniques is characteristic of this neoplasm—that is, intense contrast uptake is seen in the arterial phase followed by contrast washout in the delayed venous phase (Bruix & Sherman, 2005; see Chapters 16 and 17). In a tumor larger than 1 cm in diameter, a single dynamic imaging technique can establish the diagnosis (e.g., computed tomography [CT] or magnetic resonance imaging [MRI]; Fig. 80.2). Contrast ultrasound is no longer recommended because it is not able to differentiate cholangiocarcinoma from HCC (Chen 2010; Vilana 2010). If the characteristic dynamic profile is not recognized by imaging techniques, it is recommended that the

Box 80.1

Diagnostic Criteria for Hepatocellular Carcinoma

Cytohistologic criteria
Noninvasive criteria (cirrhotic patients)
Focal lesion >2 cm: one imaging technique (e.g., dynamic computed tomography, magnetic resonance imaging) with arterial hypervascularization and venous washout

From Bruix J, Sherman M, 2011: Management of hepatocellular carcinoma: an update. Hepatology 53:1020-1022.

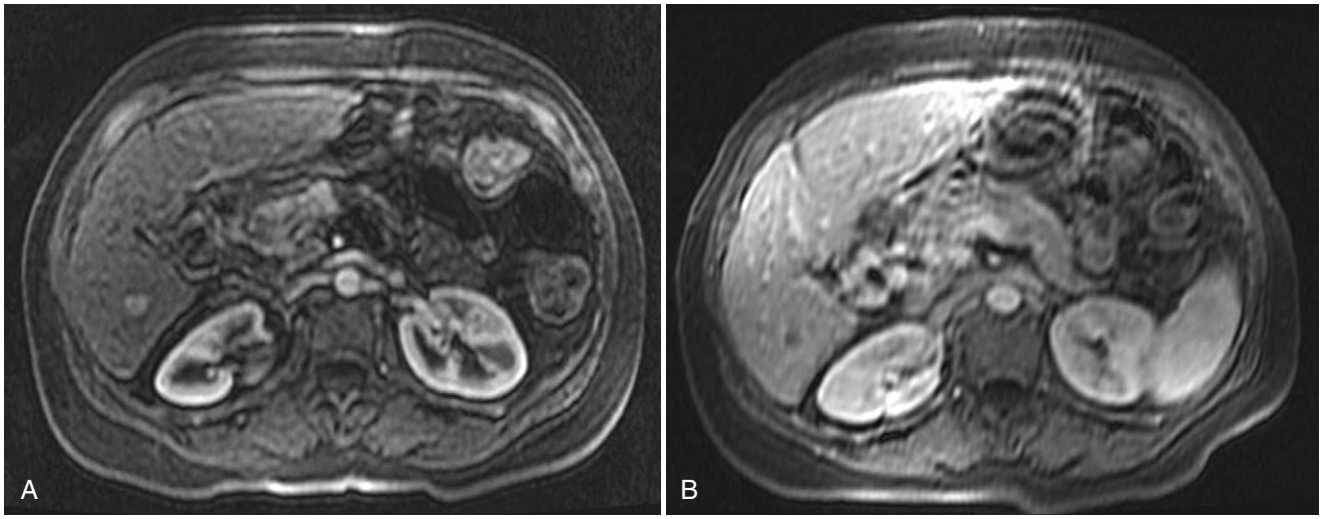


FIGURE 80.2. A, Magnetic resonance imaging depicts a small nodule with arterial enhancement after contrast administration. **B,** The nodule exhibits washout of the contrast material in the venous phase, the characteristic pattern of hepatocellular carcinoma. *(Courtesy Dr. Carmen Ayuso.)*

diagnosis be based on fine needle biopsy (Fig. 80.3; see Chapter 20). This is so even in the presence of increased AFP values, because cholangiocarcinoma and hepatic metastases may produce AFP (Bruix & Sherman, 2011; Rimola et al, 2009). It must be stressed that biopsy is not 100% sensitive, hence a negative result does not exclude HCC (Forner et al, 2008). Tumor staging is done through spiral CT and MRI (see Chapters 13, 16, and 17); MRI is the most sensitive to detect nodules smaller than 2 cm (Burrel et al, 2003). The technical advances in these techniques have made angiography unnecessary for diagnosis and staging (see Chapter 19). Other tumor markers, such as protein induced by vitamin K absence (Marrero et al, 2009), glypican-3 (Capurro et al, 2003), and AFP fractions (Marrero et al, 2009), have been proposed to be used alone or in combination with AFP, but their usefulness in routine clinical practice has not been established (Bruix & Sherman, 2011).



FIGURE 80.3. Small nodule measuring >2 cm located in the right lobe. The nodule is heterogeneous and appears as a thin, hypoechoic capsule. Fine needle aspiration biopsy established the diagnosis of hepatocellular carcinoma. Early detection of this small tumor allows effective therapy to be initiated. *(Courtesy Dr. Luis Bianchi.)*

STAGING AND PROGNOSTIC EVALUATION

Staging systems are crucial tools to stratify patients into different subgroups according to prognosis. Ideally, they should establish a link with treatment and predict outcome after therapy. A well-validated and internationally accepted staging system is lacking for HCC. In most tumors, the prognosis is related mainly to tumor stage at the time of diagnosis. The presence of underlying liver disease makes prognostic evaluation of patients with HCC more complex, because liver disease influences outcome and the possibility of treatment (see Chapters 2 and 70). This must take into account tumor stage and liver function and explains why one-dimensional systems taking into account one of the two aspects have no power to predict outcome or to establish the best treatment (Forner et al, 2010). This is the case for the tumor-node-metastasis (TNM) system used by the American Joint Commission on Cancer (2002) and the Child-Turcotte-Pugh (CTP) classification (Pugh et al, 1973). Despite several modifications over time, the TNM system is still not valid, because it relies predominantly on pathologic findings. Combination with a rough assessment of the underlying liver status (cirrhosis versus no cirrhosis; Vauthey et al, 2002) offers some advantages, but it still lacks accuracy to predict prognosis in nonsurgical cases.

The Okuda classification is based on rough assessment of tumor burden, either on imaging or by surgery, and liver function. It stratifies patients into three groups with different outcomes (Okuda et al, 1985), but its main capacity is to identify end-stage patients. Several additional scoring systems have been proposed in Uganda (Primack et al, 1975), the United States (Stuart et al, 1996), Barcelona (Calvet et al, 1990), France (Bonnetain et al, 2008; Chevret et al, 1999), Italy (1998), Austria (Schoniger-Hekele et al, 2001), Hong Kong (Leung et al, 2002), and Japan (Kudo et al, 2003; Omagari et al, 2004; Tateishi et al, 2005; Table 80.2). The relevant prognostic parameters are not the same in all systems, and despite their capacity to stratify subjects, none of them has shown transportability; that is, strata of patients do not have the same survival in different settings. The major usefulness of

Table 80.2

Prognostic Scores Proposed for Stratification of Hepatocellular Carcinoma Patients According to Expected Outcome

Reference	No. Patients	Treated Patients (%)	Tumor	Liver Function	General Health
Calvet et al, 1990	206	28	Tumor size, metastases	Bilirubin, ascites, GGT, renal function	Age, constitutional syndrome
Stuart et al, 1996	314	None	Portal thrombosis, AFP	Albumin	—
CLIP, 1998	435	42	Portal thrombosis, tumor burden, AFP	CTP score	—
Chevret et al, 1999	761	53	Portal thrombosis, AFP	CTP score, alkaline phosphatase	Karnofsky
Llovet et al, 1999a	102	100	Portal thrombosis, extrahepatic spread	—	PST, constitutional syndrome
Villa, 2000	96	100	Estrogen receptors	Bilirubin	—
CUPI, 2002	926	58	TNM, AFP	Bilirubin, ascites, alkaline phosphatase	Symptoms
Kudo et al, 2003	722	?	TNM Japan	CTP score	—
Omagari et al, 2004	177	8	TNM Japan, PIVKA	CTP score, ICG 15	—
Tateishi et al, 2005	403	100	Size, number	Albumin, bilirubin	—
Bonnetain et al, 2008	489	?	Portal thrombosis, AFP, small HCC	Bilirubin, albumin, Spitzer	Hepatomegaly, ascites, QoL index

AFP, α-fetoprotein; CLIP, Cancer of the Liver Italian Program; CTP, Child-Turcotte-Pugh; GGT, γ-glutamyltransferase; HCC, hepatocellular carcinoma; TNM, tumor–node–metastasis; PST, performance status test; QoL, quality of life; PIVKA, protein induced by vitamin K absence; CUPI, Chinese University Prognostic Index; ICG 15, indocyanine green retention rate at 15 minutes

these systems is the identification of end-stage patients with a poor prognosis, but none of these systems provides any link to treatment indication. This lack of reproducibility indicates major heterogeneity among the different studies, and no widely accepted universal scoring and staging system is currently available.

The Barcelona Clinic Liver Cancer (BCLC) Staging Strategy avoids the use of a single scoring system for all patients. Instead, it divides patients into four major groups: 1) *very early/early,* 2) *intermediate,* 3) *advanced,* and 4) *end stage*. It then develops a prognostic model within each group, taking into account the impact of treatment (Fig. 80.4; Forner et al, 2010, 2012; Llovet et al, 1999a). This model was constructed based on the results obtained in the setting of several cohort studies and randomized controlled trials. The proposal constitutes a regularly updated staging classification derived from the combination of the data of several independent prognostic studies in different disease stages and treatments. Because it links staging with treatment indication, it has become a widely used clinical tool for treatment decision making (Bruix & Sherman, 2011; Llovet et al, 2008b). It considers variables related to tumor stage, liver functional status, physical status, and cancer-related symptoms. Patients at an early stage present with solitary tumors (usually <5 cm) or two or three nodules (none >3 cm). Depending on the degree of liver function impairment, patients may benefit from curative therapies, such as resection, transplantation, or percutaneous ablation (see Chapters 83, 85, 90, and 97D). The 5-year survival ranges from 50% to 70%. The intermediate stage comprises patients with large or multifocal tumors with preserved liver function and no cancer-related symptoms or vascular invasion. The only treatment that has shown survival benefit is transarterial chemoembolization, which achieved a 50% survival at 3 years. Patients at an advanced stage have cancer-related symptoms, vascular invasion, or extrahepatic spread, and their median survival is less than 1 year. They may benefit from sorafenib treatment, the sole agent that has been confirmed to improve the survival of HCC patients (see Chapter 88). Finally, end-stage patients have major impairment of liver function or major cancer-related symptoms with severe deterioration of physical condition as reflected by a performance status (PS) greater than 2. Their short-term prognosis is poor, and they should receive palliative care (Forner et al, 2010).

TREATMENT STRATEGY

The selection of the best treatment in patients with HCC is the result of the evaluation of several factors, the most relevant among which are the status of the underlying liver and the tumor stage. Accurate definition of the status of the nontumor liver is crucial. The few patients in whom HCC appears in a noncirrhotic liver are good candidates for liver resection (see Chapter 90). Major lobectomies are well tolerated, and resection is the first-line option (Llovet et al, 2005). By contrast, in most patients, cirrhosis underlies HCC, and the degree of functional impairment may preclude safe surgery. In these patients, the first-line treatment should be liver transplantation (see Chapter 97D); if this is not feasible, these patients should be considered for percutaneous ablation through any of the available techniques: ethanol injection, radiofrequency, cryotherapy, or microwave (see Chapters 83, 84A, and 85). These options are thought to offer potential long-term cure (Forner et al, 2010). The sole palliative approaches that have been shown to have a positive impact in survival are transarterial chemoembolization (TACE) (Forner 2012; Llovet & Bruix, 2003; see Chapter 83) and sorafenib administration (Cheng et al, 2009; Llovet et al, 2008a; see Chapter 88). Most of these approaches are discussed in other chapters; we briefly discuss the Barcelona strategy to select the best option for each patient (see Fig. 80.4).

Liver function is assessed initially through the CTP classification, and this is combined with a detailed evaluation of tumor extent (Forner et al, 2010; see Chapters 2 and 70). This assessment has to search for the presence of daughter nodules, vascular invasion, extrahepatic disease, and portal vein thrombosis.

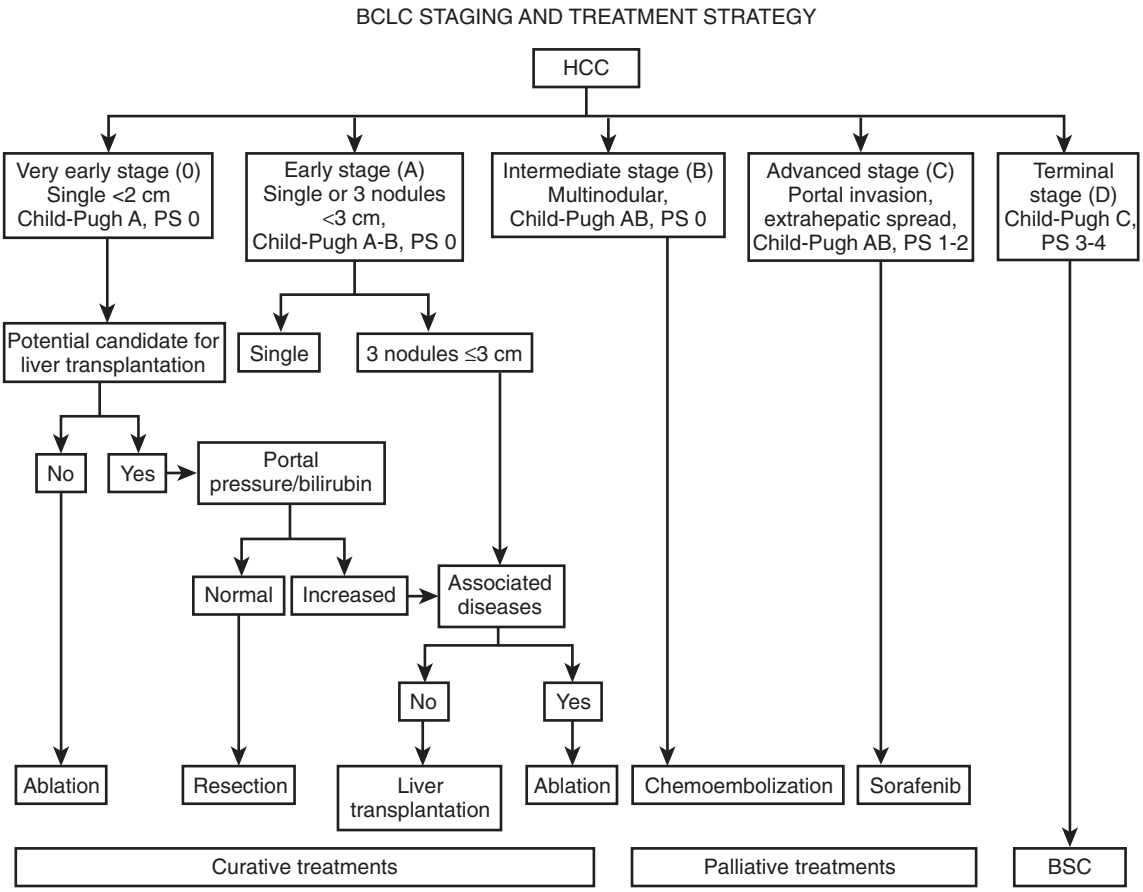


FIGURE 80.4. Staging system and treatment strategy according to the Barcelona Clinic Liver Cancer criteria. Patients are stratified according to clinical, tumor, and biochemical characteristics into four major groups: 1) *early,* 2) *intermediate,* 3) *advanced,* and 4) *terminal.* Treatment selection is decided according to stage allocation. HCC, hepatocellular carcinoma; PEI, percutaneous ethanol injection; PS, performance status; PST, PS test; RF, radiofrequency. *(Modified from Forner A, et al, 2010: Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis 30:61-74.)*

Extrahepatic disease is ruled out by chest CT scan and bone scintigraphy. The general condition of the patient not only includes consideration of comorbid conditions that may increase perioperative or intervention-related morbidity and mortality but also the assessment of cancer-related symptoms as reflected by performance status (Sorensen et al, 1993). This provides an evaluation similar to the Karnofsky index (Schag et al, 1984) but simpler. Heavily affected patients (PS 3 to 4) belong in a terminal disease stage and should receive palliative treatment.

Liver resection (see Chapter 90) is the first-line treatment in patients with solitary tumors who do not present with underlying cirrhosis and in patients with HCC in well-compensated cirrhosis (Belghiti et al, 2002; Forner et al, 2010). This status cannot be assessed through the CTP classification. Only patients with normal bilirubin concentration and an absence of clinically relevant portal hypertension should be considered optimal candidates for resection (Llovet et al, 1999b). These patients tolerate the intervention without risk of hepatic decompensation, and survival at 5 years is approximately 70%. Hepatic vein catheterization is the most accurate tool to measure portal pressure, and a hepatic pressure gradient less than 10 mm Hg is the best cutoff value. Patients with portal hypertension are at high risk of liver decompensation and death after surgery, and their survival at 5 years drops to 50% (Ishizawa et al, 2008; Llovet et al, 1999b).

Liver transplant (see Chapter 97) is offered to patients who do not fit the optimal profile for resection, and the best candidates are those with solitary tumors less than 5 cm, or those with two or three nodules, each less than 3 cm (Mazzaferro et al, 1996). Vascular invasion and extrahepatic dissemination should be ruled out, and patients should not have general contraindications for liver transplantation. Percutaneous treatment is proposed if expected waiting time exceeds 6 months, and all patients also are proposed to enter the live donor program (Sala et al, 2004b; see Chapters 97D and 98B).

If patients are not candidates for surgery, they are offered percutaneous ablation (Forner et al, 2010). Radiofrequency ablation (RFA) is the main technique, but ethanol injection can be used in the presence of contraindications for RFA, such as tumor in a subcapsular location or in the vicinity of the gallbladder or heart. The best results of ablation are achieved in solitary tumors smaller than 2 cm, where these techniques may achieve complete necrosis, and recurrence rates are similar to resection in 90% of the cases (Livraghi et al, 2008; Sala et al, 2004a). Accordingly, ablation may compete with resection in patients with solitary nodules smaller than 2 cm and it has become the preferred treatment option in patients with HCC at a very early stage who are not potential candidates for liver transplantation (Forner et al, 2012).

Patients with more advanced disease (large or multifocal HCC) without portal vein invasion are candidates for TACE

(see Chapter 83), if liver function is preserved, and they are still free of cancer-related symptoms. Response to this locoregional approach is associated with improved survival, and it is the sole locoregional palliative therapy that has a statistically significant impact on outcome at this stage of the disease (Llovet & Bruix, 2003; Llovet et al, 2002; Lo et al, 2002). If chemoembolization is not feasible, but patients still have preserved liver function (CTP class A or B) without major cancer-related symptoms, they should be considered for sorafenib administration (see Chapter 88). Current trials explore the combination of other molecular therapies with sorafenib and the usefulness of second-line alternatives. If patients are diagnosed at a terminal stage, identified by severe liver function deterioration (CTP class C), and the extent of the tumor prevents transplantation and has induced severe cancer-related symptoms (performance status >2), patients are offered palliative care.

FUTURE PROSPECTS

Major research in recent years has been devoted to allowing an earlier diagnosis of HCC and more accurate staging at the time of diagnosis. The improvements in treatment have had a minor impact, because most patients still are diagnosed at an advanced stage, when there is no option for long-term cure. Most of the effective treatments available today should be considered invasive, and it is hoped that active laboratory research translates into new instruments to predict the biology of the tumor and identify new treatment targets. As happened years ago in breast cancer (Perou et al, 2000; Somiari et al, 2003; van de Vijver et al, 2002), prostate cancer (Dhanasekaran et al, 2001; Grubb et al, 2003), lung cancer (Yanagisawa et al, 2003), non-Hodgkin B lymphoma (Alizadeh et al, 2000), and melanoma (Bittner et al, 2000), this is now a reality in HCC; additional molecular profiling is evolving, using gene or protein profiling (Boyault et al, 2007; Chiang et al, 2008; Hoshida et al, 2008) that will further affect how we face diagnosis, evaluation, and treatment of patients with liver cancer (Hoshida et al, 2010; Villanueva et al, 2010).

SUMMARY

The incidence of HCC has a marked geographic heterogeneity. Although years ago HCC was considered an infrequent neoplasm in Europe and North America, more recent epidemiologic surveys have shown that its incidence in these areas has increased significantly. HCC is associated with chronic liver diseases, usually related to viral infection or toxic agents, such as alcohol. Despite major advances in detection, diagnosis, and treatment, only a few patients currently are diagnosed at early stages and become candidates for treatments that offer potential long-term cure: resection, transplantation, and percutaneous ablation. Most patients with this malignancy still are diagnosed at an intermediate or advanced stage, such that the only therapies that have been shown to offer a significant survival benefit are TACE and sorafenib administration, but these can be applied in only a few cases. Better detection and diagnostic strategies are urgently needed, aimed at increasing the proportion of patients diagnosed at an early stage who could receive effective therapy. In addition, active translational research should help to develop new therapeutic tools that could result in a significant improvement of the long-term survival of patients diagnosed at advanced stages.

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CHAPTER 81A

Metastatic malignant liver tumors: colorectal cancer

Jordan Winter and Rebecca Ann C. Auer

OVERVIEW

The liver is the most common site for hematogenous metastasis from colorectal cancers (CRCs). One quarter of patients with primary colorectal carcinoma present with synchronous hepatic metastasis, and nearly half of the patients resected of their colorectal primary will eventually develop metachronous liver metastasis (Bozzetti et al, 1987; Ekberg et al, 1987). In patients with isolated hepatic metastases, the extent of liver disease is the principal determinant of survival, and when left untreated, survival is measured in months (Norstein & Silen, 1997). Despite recent improvements in regional therapies, systemic chemotherapies, and biologic agents, survival is rarely over 3 years in the absence of surgical intervention (Table 81A.1).

Over the past 3 decades, surgery has been clearly demonstrated to be a safe and potentially curative modality in the treatment of colorectal metastases to the liver. The current 5-year survival following a margin-negative hepatic resection is 40%, with a 10-year survival approaching 20%. Although no prospective randomized trials comparing liver resection to systemic, regional, or other local therapies have been performed, the outcome for patients after liver resection for metastatic CRC is sufficiently favorable that surgery is now considered the primary therapy in selected patients (Pawlik & Choti, 2007; Ito et al, 2010).

This chapter will review the data supporting the use of liver resection in the treatment for metastatic colorectal carcinoma. It will review the most 1recent studies describing patient outcomes after hepatic resection. Specifically, current results with operative morbidity, operative mortality, and long-term survival after liver resection are presented. We review current staging systems and discuss the role of various imaging modalities in the preoperative patient; controversies are discussed, such as resection of extrahepatic metastases; and we review a number of systemic medical and biologic therapies that have been approved in the past 2 decades for use in CRC and address their effectiveness in the adjuvant setting.

NATURAL HISTORY OF METASTASES FROM COLORECTAL CANCER

Invasive CRC principally spreads through two mechanisms: cancer cells can metastasize to regional lymph nodes and then through central lymphatics into the systemic circulation, or they can spread directly to the liver via portal venous drainage (Knosel et al, 2004). This has been tested experimentally for CRC. In one study, investigators measured circulating transcripts of guanylyl cyclase C as a surrogate marker for circulating tumor cells and detected these two mechanisms at work in patients. During surgery for stage I or stage II primary CRC, circulating cancer cells were more frequently detectable in the portal blood as opposed to in the periphery, suggesting that the portal route may be more important in early stage patients; however, in some patients with documented lymph node spread, circulating cells were evident in peripheral blood samples but not in the portal blood (Tien et al, 2002).

When cancer spreads through the portal system, the liver acts effectively as a filter and minimizes or even prevents spread to distant sites (Picardo et al, 1998; Wang et al, 2004). At a cellular level, this process has been imaged through the labeling of cancer cells with green fluorescent protein, transplanting them into the ascending colon in mice. In this model, metastatic foci in the liver emerge within days after transplantation (Wang et al, 2004). The importance of portal spread is further validated by clinical data. Liver metastases were not observed in patients with cirrhosis (0 of 40 patients) but were observed in patients without cirrhosis (46 of 210, $P < .001$) in a Japanese study. The authors speculated that decreased portal flow to liver parenchyma in cirrhotic patients accounted for this phenomenon (Uetsuji et al, 1992).

It is unclear why some cancers spread via lymphatics and others spread via the portal circulation, although some theories based on experimental data have been suggested. One study found that in colon primaries, tumors located on the mesenteric side of the colon had a higher rate of lymph node spread than those on the antimesenteric side (207 cases, 51% vs. 30%; $P = .004$), probably related to the distribution and density of lymphatic vessels in the mesocolon (Boni et al, 2007). A separate group analyzed chromosomal copy number in primary and metastatic cancer foci using comparative genomic hybridization and found that certain reproducible allelic losses or gains were observed in hematogenous deposits, as compared with lymph node metastases.

The outcome of untreated metastatic CRC to the liver has been well documented in the older metastatic CRC literature and has been summarized in detail elsewhere (Norstein & Silen, 1997). The median survival of untreated CRC with synchronous liver metastases is just 5 to 10 months, and 3-year survival is very unusual. Survival at 5 years is essentially limited to patients who are seen initially with solitary liver metastases.

The extent of liver disease is an important determinant of prognosis. In a highly cited retrospective study by Wood and colleagues, 113 patients from the Glasgow Royal Infirmary with stage IV CRC were followed. The 1-year survival rate was 5.7% in the setting of widespread liver disease, 27% for those with metastases localized to a single segment or lobe of the liver, and 60% for patients with a solitary metastasis (Norstein & Silen, 1997). The patients with solitary metastases had a 3-year

Table 81A.1

Natural History of Liver Metastasis from Colorectal Cancer

Study	No. Patients	MEDIAN SURVIVAL			
		Mean (mo)	1 Year (%)	3 Years (%)	5 Years (%)
Bengmark & Hafstrom, 1969	40	–	5.7	0	0
Cady et al, 1970	269	13	–	–	–
Oxley & Ellis, 1969	112	–	27	4	1
Wood et al, 1976	113	6.6	15	3	1
Bengtsson et al, 1981	25	–	–	–	–
Wagner et al, 1984	252	–	49	7	2
Scheele et al, 1990	921	–	–	9	0
Stangl et al, 1994	484	7.5	–	–	1
Rougier et al, 1995	318	5.7	–	–	–

survival of 13% and a median survival of 17 months. A similar study by Wagner and colleagues (1984) found that 20% of patients who had an unresected solitary liver lesion lived 3 years.

The authors of these two retrospective natural history studies attempted to distinguish potentially resectable disease from unresectable disease and determined that the survival was substantially better in the former. In the study by Wood and colleagues (1976), 13 patients were believed to have had resectable disease; the 1-, 3-, and 5-year survival of these untreated patients were 77%, 23%, and 8%, respectively, compared with 15%, 0%, and 0% for the unresectable group. Similarly, Wagner and colleagues (1984) reported 3- and 5-year survivals for untreated resectable disease of 14% and 2%, respectively, compared with 4% and 0% for patients with unresectable disease. Notably, even patients with resectable, solitary liver metastases consistently have very poor long-term survival (<10%).

RESULTS OF RESECTION FOR COLORECTAL LIVER METASTASES

The stepwise spread of cancer from primary site to liver through the portal circulation, and from the liver to other organs, provides an opportunity to prevent dissemination of tumor to other sites by direct treatment of hepatic metastases. In addition, the remarkable ability of the liver to regenerate after hepatic resection has enabled aggressive surgical options for hepatic metastases. In patients with normal hepatic reserve, removal of up to 80% of the liver is possible, and regeneration largely occurs in the first few weeks.

Long-Term Results

Since the studies of Wood and Wagner and colleagues, numerous large, single institutional and multicenter reports from around the world have demonstrated that liver resection is safe and results in long-term survival (Table 81A.2). In recent series, 5-year survival rates approach 40%, and median survival exceeds 40 months (Fong et al, 1999; Choti et al, 2002); this represents a dramatic improvement from the seminal study by Foster (1978) on liver resection, when the reported 5-year survival was 20%.

Based on the favorable data reported by these studies, liver resection has now become the standard treatment for metastatic lesions from colorectal primaries. Even in the premodern

Table 81A.2

Results of Hepatic Resection for Metastatic Colorectal Cancer

Study	No. Patients	Operative Mortality (%)	SURVIVAL (%)				
			1-Year	3-Year	5-Year	10-Year	Median (mo)
Schlag, 1992	122	4	85	40	30	–	32
Doci et al, 1991	100	5	–	28	–	28	–
Younes et al, 1991	133	–	91	–	–	–	–
Rosen et al, 1992	280	4	84	47	25	–	–
Scheele et al, 1995	434	4	85	45	33	20	40
Nordlinger et al, 1996	1568	2.3	88	64	28		27
Jamison et al, 1997	280	4	84	–	27	20	33
Fong et al, 1999	1001	2.8	89	57	36	22	42
Minagawa et al, 2000	235	0.85	–	51	38	26	
Choti et al, 2002	226	1	93	57	40	26	46
Belli et al, 2002	181	–	91.2	55.3	39.8	–	–
Kato et al, 2003	585	0	–	–	33	–	–
Mutsaerts et al, 2005	102	3	–	–	29	–	–

chemotherapy era—in studies from the 1990s, before FOLFOX and FOLFIRI were given routinely—long-term survival in patients undergoing resection for metastatic disease far exceeded the survival of unresected patients. This improvement in survival was striking, even in patients with unresectable, low-volume metastatic disease: 20% to 40% 5-year survival with metastasectomy versus less than 10% for patients with unresected solitary metastases.

With newer multimodal treatments and careful patient selection, it is anticipated that 5-year survival approaching 70% can be achieved after resection (Nikfarjam et al, 2009), and comparable outcomes are likely to be reported in larger studies in the near future. Many patients with CRC at stage IV are cured by surgery. A recent review of actual 10-year survivors indicated that one third of actual 5-year survivors will eventually succumb to a cancer-related death; however, 10-year survival is tantamount to a cure in all but the rarest cases (<1%) (Tomlinson et al, 2007).

No prospective, randomized trials have been done that directly compare surgery with nonoperative therapy for metastatic CRC, and such a trial is unlikely to ever occur. The strikingly favorable outcome for surgical patients in retrospective studies compared with patients managed nonoperatively renders such a trial unethical.

Outcome and Surgical Volume

A number of studies have correlated perioperative outcome to hospital volume for hepatectomy. Choti and colleagues (1998) and Glasgow and colleagues (1999) used the state registries in Maryland and California, respectively, and found that hepatectomy performed at a high-volume center resulted in improved outcomes. Surgery at high-volume centers was also associated with reductions in perioperative mortality, length of hospital stay, and cost. A recent study by Fong and colleagues (2005) based on a national Medicare database provides further support for superior outcomes at high-volume centers. The authors demonstrated that perioperative outcome correlated with the expertise of the institution, and the survival advantage persisted after the perioperative period. These data lend support to the concept of regionalization of hepatectomy to high-volume centers.

MEDICAL TREATMENT OF METASTATIC COLORECTAL DISEASE TO THE LIVER

Over the past 3 decades, the most widely used chemotherapeutic agent in the treatment of metastatic CRC has been 5-fluorouracil (5-FU), used either alone or in combination with other chemotherapies. Randomized clinical trials and meta-analyses in advanced CRC during the 1980s and 1990s established that 5-FU was best administered in combination with leucovorin (LV) and that 5-FU should be given as a continuous infusion over several days, as opposed to a series of daily bolus injections (ACCMAP, 1992; D'Angelica et al, 2002; de Gramont et al, 1997; MAGIC, 1998). Tumor response rates with the optimized 5-FU/LV dosing regimen reached 30%, with a median survival around 12 months. This response rate was a substantial improvement over what had been previously reported for 5-FU alone (10% to 15%), although the overall survival rates were similar (ACCMAP, 1992; MAGIC, 1998).

In 2000, two studies compared systemic therapy using irinotecan (CPT-11) in combination with 5-FU/LV with 5-FU/LV alone. Patients had stage IV CRC and had not received treatment for their metastatic disease (Douillard et al, 2000; Saltz et al, 2000). In the study by Saltz and colleagues, patients who recived the irinotecan-containing regimen—referred to as the *IFL regimen,* because it used bolus 5-FU—had a longer progression-free survival (PFS; 7.0 vs. 4.3 months), a higher response rate (39% vs. 21%), and a longer overall survival (median, 14.8 months vs. 12.6). Similar results were observed by Douillard and colleagues; in their study, irinotecan was combined with infusional 5-FU/LV (FOLFIRI). Based on these studies, combination therapy using irinotecan, 5-FU, and LV became the standard treatment for unresectable stage IV CRC. Subsequently oxaliplatin plus 5-FU/LV (FOLFOX) was accepted as second effective first-line combination regimen (de Gramont et al, 2000; Goldberg et al, 2004). In the study by de Gramont and colleagues (2000), PFS was 9.0 months versus 6.2 months with 5-FU/LV alone; the response rate was 50.7%, versus 22.3%; overall survival was 16.2 months versus 14.7 months (P = .1). In the study by Goldberg and colleagues (2004), outcomes were consistently superior with FOLFOX, including an overall survival of 19.5 months versus 15.0 months (P = .0001). This latter trial further demonstrated that FOLFOX was superior to a combination regimen consisting of irinotecan and oxaliplatin.

Two randomized controlled trials have compared FOLFOX and FOLFIRI against each other. Both trials concluded that the regimens had similar efficacy for metastatic CRC as a first-line treatment (Tournigand et al, 2004; Colucci et al, 2005). In the study by Tournigand and colleagues, patients were randomized to one of the two regimens and were crossed over to the opposite treatment arm upon progression. Overall survival was 21.5 months and 20.6 months in the FOLFIRI-first and FOLFOX-first treatment arms, respectively (P = .99). Roughly 15% of the patients in the trial became resectable during treatment and underwent metastasectomy. This was a more frequent occurrence in the FOLFIRI-first arm. In the second trial, no crossover was built into the study design, although a high proportion of patients received second-line treatment. The overall survival in the FOLFIRI and FOLFOX arms were 14 and 15 months, respectively (P = .28; Colucci et al, 2005). Secondary surgery was performed in about 5% in each group. Based on these studies, FOLFOX and FOLFIRI are widely considered to be equivelent in the metastatic setting and are generally selected according to the toxicity profile. The FOLFOX regimen is characterized by a higher rate of grade 3 and 4 neurotoxicity (30% vs. 5%) and neutropenia (44% vs. 24%). The FOLFIRI is associated with more nasuea and vomiting (20% vs. 5%), mucositis (10% vs. 0%), and alopecia (50% vs. 20%).

Falcone and colleagues (2007) explored an aggressive regimen with all three chemotherapeutic agents (FOLFOXIRI) and compared this treatment with FOLFIRI, and an increased rate of neutropenia and neurotoxicity was observed with FOLFOXIRI treatment; however, the more aggressive regimen was associated with better PFS (9.8 vs. 6.9 months), response rate (66% vs. 41%), and overall survival (22.6 vs. 16.7 months). In the FOLFOXIRI group, 15% of patients had secondary metastasectomy compared with 6% in the FOLFIRI group (P = .03). The difference was even greater when patients with liver-only disease were considered (36% vs. 12%, P = .02) (Falcone et al, 2007). In the above trials that evaluated the standard first-line combination regimens, the complete response rate was consistently around 5%.

Several small-molecule and antibody therapies have been developed that target growth factors or cell surface receptors important to CRC biology. Bevacizumab (Avastin), for instance, is a monoclonal antibody against vascular endothelial growth factor (VEGF) and has been approved in the first-line treatment of metastatic CRC in combination with 5-FU–based chemotherapy. FDA approval was a response to a study that compared bevacizumab and FOLFIRI to FOLFIRI alone (Hurwitz et al, 2004). The bevacizumab-containing regimen was associated with longer overall survival (median 20.3 vs. 15.6 months, $P < .001$) and a higher response rate (44.8 vs. 34.8%; $P = .004$). Bevacizumab was also evaluated in the context of oxaliplatin-based chemotherapy using either FOLFOX or XELOX (capecitabine and oxaliplatin; Saltz et al, 2008). Although the PFS was superior in the bevacizumab group (9.4 vs. 8.0 months; $P = .0023$), no improvement in overall survival was found (21.3 vs. 19.9 months; P .077). The response rates were the same in both arms (47% vs. 49%; $P = .3$). The pattern of increased PFS with novel biologic agents despite equivalent response rates is a common finding in trials with targeted agents. This phenomenon suggests that targeted therapies may improve PFS through stabilization of disease or perhaps by causing tumor necrosis, which is a confounding factor with conventional Response Evaluation Criteria in Solid Tumors (RECIST) (Tuma, 2006).

Cetuximab (Erbitux) and panitumumab (Vectibix) are both monoclonal antibodies against the epidermal growth factor receptor (EGFR) and are now an important part of the treatment algorithm for unresectable colorectal metastases (Cunningham et al, 2004; Jonker et al, 2007; Van Cutsem et al, 2007). Cetuximab is a chimeric monoclonal antibody approved for treatment of metastatic CRC in combination with irinotecan in patients with disease refractory to irinotecan (Cunningham et al, 2004) or as a single agent in patients who cannot tolerate irinotecan or oxaliplatin (Jonker et al, 2007).

Cunningham and colleagues (2004) established the first indication in their study, which tested the addition of cetuximab to irinotecan-based treatment in patients who were progressing and compared this strategy with cetuximab therapy alone. The response rates in the two groups were 22.9% and 10.8% ($P = .007$), and the times to progression were 4.1 and 1.5 months ($P < .001$), respectively. Overall survival was not significantly different between the two groups (8.6 vs. 6.9 months; $P = .5$; Cunningham et al, 2004). Jonker and colleagues demonstrated that cetuximab montherapy was superior to best supportive care in patients who were unable to take irinotecan or oxaliplatin-based therapy (Jonker et al, 2007). Overall survival was 6.1 months in the cetuximab group compared with 4.6 months in the control group ($P < .001$). The response rate was 8% with cetuximab, and disease stabilization occurred in 31.4% versus 10.9% in the control group ($P < .05$).

Panitumumab is a fully humanized monoclonal antibody and therefore appears to have a lower rate of serious infusion reactions compared with cetuximab (Van Cutsem et al, 2007). Like cetuximab, panitumumab is approved for single-agent therapy in patients who have progressed on standard chemotherapy (Van Cutsem et al, 2007). Patients on panitumumab had an 8-week PFS compared with 7.3 weeks with best supportive care ($P < .0001$), and it was associated with a 10% response rate; however, the overall survival was 7 months in both groups ($P = .99$). Panitumumab was also evaluated as part of a first-line regimen for metastatic CRC, but a benefit was not apparent in the absence of *KRAS* mutation profiling (Hecht et al, 2009). Hecht and colleagues (2009) compared standard FOLFOX or FOLFIRI plus bevacizumab with or without panitumumab. Interestingly, patients receiving panitumumab had significantly inferior progression-free and overall survival compared with the control arms.

Although both cetuximab and panitumumab are antibodies directed against EGFR, there is no evidence that EGFR expression influences response rate; however, there appears to be a strong treatment interaction with both medications, and *KRAS* is mutated in 40% of CRCs (Bos et al, 1987). A prospective trial of first-line treatment comparing FOLFIRI with and without cetuximab demonstrated prolonged PFS in patients with a wild-type *KRAS* in their tumors (Van Cutsem et al, 2009). Similarly, a recent trial evaluating first-line treatment using FOLFOX with and without panitumumab showed prolonged PFS in the setting of wild-type *KRAS*. Those patients with a *KRAS* mutation actually had significantly worse PFS (Douillard et al, 2010). Peeters and colleagues (2010) evaluated FOLFIRI plus panitumumab versus FOLFIRI alone in chemorefractory patients, demonstrating improved PFS with second-line chemotherapy in patients having wild-type *KRAS* tumors. Additionally, when administered as monotherapy as salvage treatment for metastatic CRC, EGFR inhibitors again were only found to be effective in patients with tumors with wild-type *KRAS*. In the two trials described earlier that compared EGFR inhibitor monotherapy with best supportive care (Jonker et al, 2007; Van Cutsem et al, 2007), cetuximab and panitumumab were associated with improvements in tumor response, PFS, and overall survival (Amado et al, 2008; Karapetis et al, 2008). Based on these studies, EGFR inhibitors are now used just in those patients with tumors that do not have a mutated *KRAS* gene. This paradigm, in which the genotype of a tumor dictates therapy, is likely to become even more prevalent in the future.

In summary, patients who have yet to receive treatment for metastatic CRC, even if adjuvant treatment was previously administered for the colorectal primary, have a 50% or greater chance at responding to modern systemic chemotherapy and can expect a median survival around 18 to 20 months in the absence of resection. Unresected patients, however, still seldom live more than 3 years after the diagnosis of metastatic disease. After a patient fails first-line therapy, the results are discouraging. Response rates of 20% or less are typically seen, regardless of the second-line treatment selected (Bensmaine et al, 2001; Comella et al, 2002; Cunningham et al, 1998, 2004; Falcone et al, 2007).

PROGNOSTIC VARIABLES AND STAGING SYSTEMS

Although all patients with colorectal metastases are grouped as stage IV in the tumor-node-metastasis (TNM) staging system, considerable heterogeneity is observed within this group. For instance, the prognosis for a patient who comes to medical attention with a solitary liver metastasis, found several years after resection of a lymph node–negative right colon cancer, is different than that of a patient with synchronous and bilateral liver-metastatic disease noted during exploration of a perforated lymph node–positive colon cancer. Therefore, a classification system that can discriminate between these patients and provide additional prognostic information is paramount. Such a classification system should also be capable of facilitating

comparisons across studies, and it should guide patient selection for adjuvant therapy or clinical trials.

The development of a sophisticated staging and prognostic classification scheme is dependent on a thorough understanding of the clinical and pathologic variables associated with long-term survival in patients with stage IV CRC. Prognostic variables in the population of patients who develop hepatic metastases from CRC can be classified into three categories: 1) clinical and pathologic variables associated with the primary tumor; 2) clinical variables associated with the liver metastases, such as response to neoadjuvant chemotherapy; and 3) pathologic characteristics of the liver metastases.

Characteristics of the Patient and Primary Tumor

Age has not been found to be a significant prognostic variable for long-term survival, although analyses examining the role of age are confounded by the fact that older patients are carefully selected for surgery (Cady et al, 1992; Ballantyne & Quin, 1993). The location of primary cancer has not been shown to affect outcome, as metastatic rectal and colon cancer have similar prognoses (Doci et al, 1991). On the other hand, the stage of the primary tumor is quite useful in staging metastatic disease. Patients who had positive lymph nodes associated with their primary CRC do worse, as do patients who present with synchronous liver disease. Histologic grade of the primary cancer is not a significant predictor of long-term survival in patients with metastatic disease (Doci et al, 1991; Ballantyne & Quin, 1993).

Clinical Characteristics of Liver Metastases

The most important clinical predictor of outcome related to the liver metastases themselves is the disease-free interval: the shorter the interval, the worse the prognosis (Rosen et al, 1992; Scheele et al, 1995). Other negative factors include multiple liver metastases—four lesions is a commonly used cutoff—bilateral disease, tumor size greater than 5 cm, and a markedly elevated preoperative carcinoembryonic antigen (CEA >200 ng/mL; Nordlinger et al, 1996).

The prognostic value of response to neoadjuvant chemotherapy is controversial, and opinions vary in the literature. In a study by Adam and colleagues (2004), the 5-year disease-free survival was so poor following progression during neoadjuvant chemotherapy—3% versus 20% in patients who had a response or stable disease—the authors proposed that such a finding should preclude liver resection. This phenomenon was confirmed in our own experience (Allen et al, 2003). Although other groups have not found this to be true, such studies were based on patients who received older chemotherapy regimens. Roughly half of the patients only received 5-FU, which might account for the high rate of progression (Gallagher et al, 2009; Neumann et al, 2009). With modern chemotherapy, the expected rates of progression would be less than 20% compared with 60% in the studies mentioned above that used 5-FU (Nordlinger et al, 2008).

Operative and Pathologic Characteristics of Liver Metastases

Higher operative blood loss and transfusion requirements have been found to be associated with an increased number of perioperative complications and mortality but not with a worse long-term survival (Table 81A.3; Kooby et al, 2003). Anatomic resections are believed to indirectly improve long-term outcomes, because this approach is associated with a significantly lower rate of positive margins. In a retrospective analysis from our institution, patients who had an anatomic segmental resection had a better outcome than patients subjected to wedge resections (DeMatteo et al, 2000). In an anatomic resection, planes are developed along major hepatic veins, and inadvertent disruption of the tumor is avoided. Wedge resections are usually guided by palpation and can be complicated by inadequate exposure or retraction. The attendant problems of poor visibility and impaired tactile sense at the depth of the resection will often lead to tearing of the specimen along the hard tumor–soft liver interface, thus resulting in a positive margin.

Perhaps the most informative surgical prognostic factor is the finding of extrahepatic disease (Rosen et al, 1992; Fong et al, 1999; Abdalla et al, 2006). The existence of nonpulmonary extrahepatic disease has long been considered by many surgeons to be a contraindication to hepatectomy (Fong et al, 1999; Abdalla et al, 2006); however, the approach to extrahepatic disease has been reevaluated in recent years, as some studies have demonstrated acceptable survival in selected patients with limited extrahepatic disease managed with resection, particularly in the setting of low-volume pulmonary metastases. The two largest studies on this question evaluated combination resection of liver and lung metastases and noted 5-year survival rates of 30% (Headrick et al, 2001; Miller et al, 2007).

The presence of metastatic disease to the portal lymph nodes remains a particularly poor prognostic factor. Portal metastases are found in 3% to 30% of patients with metastatic CRC to the liver (Abdalla et al, 2006), and disease recurs in virtually all patients with resected portal lymph nodes (Carpizo et al, 2009). A consensus paper on the management of extrahepatic disease concluded that no convincing data suggest that therapeutic portal lymphadenectomy for metastatic CRC improves survival (Abdalla et al, 2006). In contrast to portal lymph node metastases, there appears to be a role for hepatic resection in conjunction with metastases to other sites. The question has been examined in the form of large retrospective studies that included resections of the peritoneum or mesentery, retroperitoneal lymph nodes, and a variety of solid organs (Minagawa et al, 2000; Elias et al, 2003; Carpizo et al, 2009). The 5-year survival rates reported in these series range from 20% to 28%. Based on these studies, hepatectomy combined with surgical resection of extrahepatic disease is believed to be appropriate in selected patients.

A macroscopic positive margin, or R2 resection, is widely accepted as a poor prognostic factor. The presence of microscopic disease at the resection margin (R1 resection) or the precise thickness of the negative margin (R0 resection) is perhaps more controversial. For instance, the preponderance of data on the impact of an R1 resection suggests that a microscopically positive margin is associated with worse survival. The 5-year survivals are consistently above 30% for negative margins but are 20% or less with microscopic disease at the margin (Fong et al, 1999; Pawlik et al, 2005; Nuzzo et al, 2008); however, multivariate analyses that include R1 resection status often do not find it to be a significant predictor of outcome after adjusting for other competing risk factors, which suggests that a positive microscopic margin is merely a marker of poor biology

Table 81A.3

Complications of Liver Resection

	Scheele et al, 1990 (%)	Schlag et al, 1990 (%)	Doci et al, 1991	Fortner et al, 1984 (%)	Nordlinger et al, 1987 (%)	Coelho et al, 2004	Mala et al, 2002 (%)	Jarnagin et al, 2002	Cady et al, 1998
Total resections	219	122	100	75	80	83	146	1803	244
Liver-Related Complications									
Hemorrhage	7 (3)		3	1 (1)	1 (1)		4 (3)	18	1
Bile fistula	8 (4)	5 (4)	4			11	2 (1)		2
Perihepatic abscess	4 (2)	11 (9)	5	5 (7)	2 (3)			110	1
Liver failure	17 (8)		3	3 (4)	1 (1)	6		99	1
Renal failure	3 (1)		1						
Portal vein thrombosis				1 (1)		1	1 (<1)	9	
Infections									
Wound		7 (6)		1 (1)		2		94	2
Sepsis		3 (2)	2		4 (5)		3 (2)	39	2
General Complications									
GI bleed						5		21	0
DVT	2 (1)			1 (1)				24	<1
Pulmonary embolism	4 (2)			1 (1)	1 (1)				<1
Cardiac/MI	2 (1)	6 (5)	1	1 (1)	1 (1)	1	1 (<1)	21	3
Pneumonia		10 (8)	22	3 (4)		7	13 (9)	54	1
Pleural effusion				6 (8)	3 (4)	11		154	2

One patient was reoperated twice for hemorrhage.
GI, gastrointestinal; DVT, deep vein thrombosis; MI, myocardial infarction

(Pawlik et al, 2005; Nuzzo et al, 2008). As adjuvant therapy improves, patients with R1 resections will likely have outcomes that more closely approach patients with negative resection margins. Indeed, a recent report suggests that a microscopic positive resection margin obtained out of necessity does not negatively impact the 5-year survival, although the recurrence rate is increased (de Haas et al, 2008).

With regard to the extent of negative margin, a 1-cm rim of normal liver parenchyma surrounding a resected tumor was traditionally espoused in the older literature (Shirabe et al, 1997); however, recent studies suggest that subcentimeter margins are acceptable (Are et al, 2007) and are perhaps even associated with equivalent outcomes to R0 resections (Scheele et al, 1995; Pawlik et al, 2005; Hamady et al, 2006; Figueras et al, 2007). Low rates of micrometastastic disease, or satellitosis, were found in resection specimens in two Japanese studies, further supporting this idea (Yamamoto et al, 1995; Kokudo et al, 2002). Anatomic segmental resection, as opposed to wedge resections (DeMatteo et al, 2000), and neoadjuvant chemotherapy are two proposed strategies to improve R0 resection rates in patients with colorectal liver metastases (Parikh et al, 2003).

In summary, the prospect of a positive microscopic or close microscopic margin is not a contraindication to liver metastasectomy in appropriately selected patients with modern chemotherapy. In addition to a macroscopically positive resection margin, the findings of hepatic satellite lesions and intrabiliary invasion have also been shown to predict tumor recurrence (Gayowski et al, 1994; Scheele et al, 1995; Okano et al, 1999; Povoski et al, 2000; Kubo et al, 2002).

Predictive Models and Clinical Risk Scores

Four large studies have enabled robust multivariate analyses of prognostic factors with metastatic CRC and design of useful predictive models for favorable survival after metastasectomy (Nordlinger et al, 1996; Fong et al, 1999; Kattan et al, 2008; Rees et al, 2008). Nordlinger and colleagues (1996) reported on a multicenter series of more than 1500 patients. Fong and colleagues (1999) reported on a single institutional series of 1001 patients and later on a cohort of 1477 patients (Kattan et al, 2008), and Rees and colleagues (2008) evaluated long-term survival in 929 patients from a tertiary referral center in the United Kingdom.

In the series by Fong and colleagues (1999), seven parameters were found to be independent predictors of an unfavorable prognosis: 1) the presence of extrahepatic disease, 2) a positive resection margin, 3) nodal metastases associated with the primary CRC, 4) a short disease-free interval, 5) largest liver metastasis greater than 5 cm, 6) more than one liver metastasis, and 7) a serum CEA greater than 200 ng/mL. The presence of extrahepatic disease and a postive resection margin are generally determined intraoperatively. When presumed preoperatively, these two variables are often considered relative contraindications to metastasectomy. A preoperative clinical risk score (CRS) system was therefore created using the last five factors (Box 81A.1), with each positive criterion counting as one point. This CRS is a simple and facile staging system used to classify patients with liver-exclusive metastatic CRC (Fig. 81A.1).

The presence of any one of these characteristics was still associated with a 5-year survival of 24% to 41%; therefore no single criteria can be considered a contraindication to

Box 81A.1

Prognostic Scoring System for Hepatic Colorectal Metastases

Node-Positive Primary Tumor

Disease free interval <12 months between colon resection and appearance of metastases
Size of largest lesion >5 cm

>1 Tumor

Carcinoembryonic antigen >200 ng/dL
Sum of points, with a point assigned for each positive criterion

resection; rather, the total score out of 5 is highly predictive of outcome, with a score of 2 or less suggestive of a particularly favorable prognosis—the optimal candidate for liver metastasectomy. Patients with a CRS of 3 or 4 have less favorable outcomes and may be appropriate for clinical trials involving adjuvant chemotherapy. Long-term disease-free survival is rare in patients with a CRS of 5, and these patients are also typically best served in clinical adjuvant chemotherapy trials. Importantly, actual 10-year survival has been observed in patients with even the highest CRS, as patients with a CRS of 3 to 5 have a 10% disease-specific survival (DSS). This is roughly equal to the cure rate of treatment in these patients; therefore a high CRS should not be considered a contraindication to hepatic resection (Tomlinson et al, 2007).

Current Use of Clinical Risk Score

The above prognostic scoring system has been validated by an independent group from Norway (Mala et al, 2002), which demonstrated that the CRS is generalizable to populations outside of the index cohort from a single, large, tertiary American center. In addition to appropriate patient selection for surgery, the CRS has proven useful in selecting patients for neoadjuvant treatment, ablation, and stratification in clinical trials (Table 81A.4).

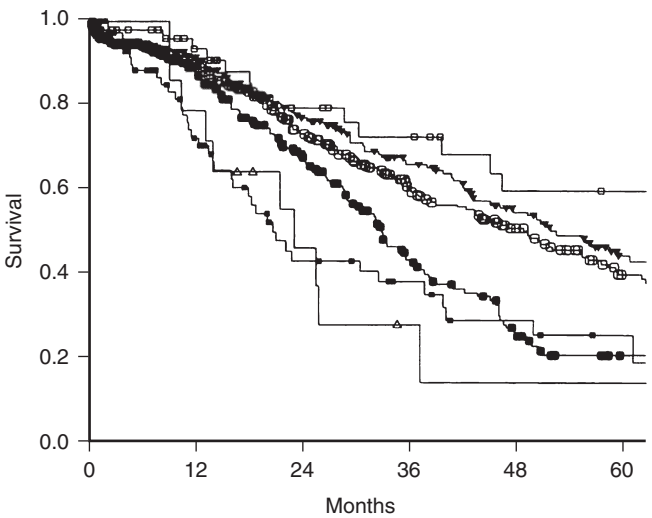


FIGURE 81A.1. Survival as related to clinical risk score after hepatic resection ($P < .00001$). *Open box:* score = 0 (n = 52); *solid triangle:* score = 1 (n = 262); *open circle:* score = 2 (n = 350); *solid circle:* score = 3 (n = 243); *solid box:* score = 4 (n = 80); *open triangle:* score = 5 (n = 14). *Copyright 1999 Lippincott Williams & Wilkins. All rights reserved. Reprinted with permission. (Fong Y, et al, 1999: Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 230[3]:314.)*

Table 81A.4

Clinical Risk Score and Survival in Two Series on Liver Resection for Metastatic Colorectal Cancer

	FONG ET AL, 1999		MALA ET AL, 2002	
Score	5-Year Survival (%)	Median Survival (mo)	5-Year Survival (%)	Median Survival (mo)
0	60	74	42	40
1	44	51		39
2	40	47		30
3	20	33	12	20
4	25	20		37
5	14	22	—	—*

*In Mala et al, no patients were classified with a clinical risk score of 5.

Additionally, the CRS has been shown to be useful in guiding the preoperative evaluation of a patient with metastatic CRC. As the number and cost of available tests increases, there is a growing need to develop effective ways to stratify patients so as to determine which tests are necessary for a given individual. For instance, a CRS of 1 or more was associated with a 14% rate of occult metastatic disease detectable by fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging but not by conventional imaging (Schussler-Fiorenza et al, 2004). PET scanning did not have any utility in patients with a CRS of 0. Similarly, laparoscopy can be helpful for staging patients with a high CRS (>2). The finding of extrahepatic disease at laparoscopy in more than 40% of patients with elevated risk scores can prevent the added morbidity associated with an unnecessary laparotomy; however, the yield of laparoscopy is sufficiently low in the setting of a low CRS (~10% incidence of occult unresectable disease) that the added procedure is unnecessary (Jarnagin et al, 2001).

Predictive models with added sophistication have been developed recently, such as a nomogram (Kattan et al, 2008) and a multifactorial predictive index (Rees et al, 2008). Although these models are based on the same basic prognostic factors as the earlier models described above, they are more complex and difficult to use; however, as computer software and accessible handheld technology progresses, improved and more accurate predictive models will likely achieve clinical relevance in the near future.

MOLECULAR DETERMINANTS OF OUTCOME

Molecular profiling of CRC is an evolving area and will likely become an essential component of prediction models for cancer recurrence in the future. As stated earlier, variable response to EGFR inhibitors based on tumor *KRAS* status is well documented (Bos et al, 1987; Amado et al, 2008; Karapetis et al, 2008; Van Cutsem et al, 2009; Peeters et al, 2010). Similarly, response rate and the presence of microsatellite instability in the tumor are associated (Ribic et al, 2003; Nash et al, 2010). In a manner akin to the *HER2* amplification and breast cancer, it is

easy to imagine that these and other molecular factors will be incorporated into postoperative prognostic scales in the future.

Preoperative Investigations

The selection of patients for hepatic metastasectomy depends upon patient operability and tumor resectability. The criteria for patient operability are similar to those considered for any major laparotomy. A significant history of cardiac and pulmonary disease must be investigated, as these patients are at significant risk for perioperative complications. Pulmonary compromise as a result of a long upper abdominal incision and the development of a right sympathetic pleural effusion may predispose to pneumonia. In addition, dramatic intravascular fluid shifts and electrolyte imbalances may occur perioperatively that can precipitate cardiac ischemia and arrhythmia. Finally, any previous liver disease that might have impaired hepatic function should be evaluated, as this will determine the volume of liver than can be safely resected.

Preoperative investigations prior to resection of metastatic colon cancer are directed at 1) establishing the diagnosis, 2) anatomic definition of the liver lesion for surgical planning, and 3) staging to rule out extrahepatic disease. A confirmatory biopsy of hepatic lesions is only indicated to confirm the diagnosis when the clinical picture is unclear. The differentiation between metastatic tumors and benign hepatic lesions can usually be done with imaging modalities, including ultrasound (US), magnetic resonance imaging (MRI), and PET scan as discussed below (see Chapters 13, 15, and 17). The risk of tract seeding from percutaneous fine needle aspiration appears to be quite small, with only a few case reports in the literature. The workup to determine the extent of disease includes imaging, as outlined below, and recent colonoscopy (within 6 months). Although a detailed discussion of each imaging modality is beyond the scope of this chapter, the following sections will focus on the practical aspects of imaging for preoperative workup of patients with hepatic colorectal metastases.

THE ROLE OF PREOPERATIVE IMAGING

Computed Tomographic Scans

Computed tomographic (CT) scans have become indispensable in the staging of patients with metastatic CRC (see Chapter 16). A contrast-enhanced CT scan of the chest, abdomen, and pelvis are routinely obtained, although the yield from scanning the chest with regard to detecting metastatic disease is limited to just a few percent (Kronawitter et al, 1999). The most important images in the evaluation of the liver in the setting of metastatic CRC are obtained in the portal venous phase, because the lesions are not typically well vascularized. Arterial phase images are principally used to distinguish metastatic disease from benign vascular lesions, such as hemangiomas, or to better define the arterial anatomy of the liver. Such a step is necessary when planning for the placement of hepatic arterial infusion pumps. Standard CT scanning involves a triple-phase protocol through the liver that includes arterial, portal venous, and delayed phases. Slices are usually 5 to 7 mm thick through the liver, but these are reduced to 1.5-mm thick overlapping slices when high-resolution hepatic angiography is desired. Coronal and sagittal reconstructions are performed to further delineate the anatomy.

Metastatic lesions from colorectal primaries tend to push structures away, rather than invade directly, respecting the liver capsule and intersegmental planes (Baer et al, 1989; Scheele, 1989). Even when large lesions appear to involve the inferior vena cava on preoperative imaging, they often do not on surgical exploration; therefore such a finding on CT should not preclude an operation. Diaphragmatic invasion is a rare event as well (Weinbren & Blumgart, 1986).

Magnetic Resonance Imaging

MRI is most useful to evaluate indeterminate hepatic lesions and to better define the relationship of tumors to the hepatic vasculature and biliary tree using magnetic resonance cholangiopancreatography (MRCP; see Chapter 17). In particular, MRI is excellent at distinguishing between benign lesions such as hemangiomas, adenomas, and fibronodular hyperplasia. Moreover, MRI is better than CT for investigating pathology in the background of a fatty liver, such as in patients who have a history of obesity, diabetes, alcoholism, or previous chemotherapy treatment (Bipat et al, 2005; Fernandez et al, 2005). Because MRI is much more expensive than CT, this modality is not used routinely; however, it is warranted to better characterize indeterminate lesions or for the patient with an elevated CEA and a fatty liver with no evidence of disease on CT.

Ultrasonography

Ultrasonography is a relatively inexpensive test that can provide detailed information about the number, extent, and anatomic relationships of liver metastases (see Chapter 13). Duplex US can define the proximity of the tumor to the portal vessels, hepatic veins, and inferior vena cava, and US is particularly useful for characterizing cystic lesions within the liver. In expert hands, it can be very sensitive at detecting small metastatic lesions, although the test is highly operator dependent.

Hepatic Angiography and Computed Tomographic Portography

Direct hepatic angiography has largely been replaced by CT and MR angiography, which are less invasive alternatives (see Chapter 19). The main role for direct angiography in the modern era of high-resolution cross-sectional imaging is CT portography. In this technique, contrast is administered directly into the splanchnic bed by injection into the superior mesenteric artery, and a CT portal venogram of the liver is acquired after a suitable delay. This technique is highly sensitive at detecting small metastatic tumors (Sica et al, 2000); however, because the test requires arterial catheterization and is associated with a relatively high false-positive rate because of perfusion abnormalities, its primary role is in the setting of a planned portal vein embolization (PVE; see Chapter 93).

Positron Emission Tomography

The role of whole-body positron emission tomography as an adjunct to CT in the evaluation of metastatic CRC has been growing in recent years (see Chapter 15). In the United States, the use of FDG PET for staging and diagnosis of CRC was approved by Medicare in 2001 (Kelloff et al, 2005). The imaging test utilizes an intravenously administered radioactive tracer,

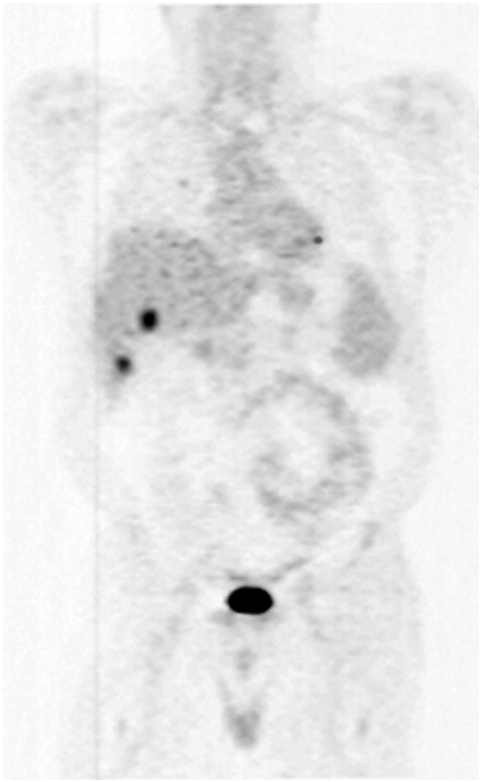


FIGURE 81A.2. A patient with two potentially resectable hepatic metastases in the right lobe of the liver. An FDG PET scan identified abnormal uptake in the left ligula of the lung, which was biopsied and found to represent an extrahepatic colorectal cancer metastasis.

which in most cases is ^{18}F-FDG. The radioactive glucose analogue cannot proceed down the glycolytic pathway and therefore accumulates within glucose-avid cancer cells. PET capitalizes on this phenomenon, as ^{18}F-FDG reveals the distribution of metabolically active metastases overexpressing cell surface GLUT1 transporters (Fig. 81A.2). The limitations of PET include poor sensitivity for lesions less than 1 cm, that some larger lesions are not FDG avid, and that the test lacks a high degree of anatomic detail. Moreover, false positives occur in the setting of inflammation, which may exist early after surgery and radiotherapy, or in the context of an infectious process. Integration of FDG PET imaging and CT addresses some of these limitations, particularly with regard to anatomic details.

PET has emerged as a relevant test in several areas of metastatic CRC management. Reported applications include patient selection for metastasectomy, evaluation of a patient with a suspected recurrence, radiotherapy planning, response assessment, and the discovery of incidental colorectal lesions (Herbertson et al, 2007). With regard to the initial staging of patients with metastatic CRC, FDG PET imaging leads to a change in management in 2% to 36% of patients. For instance, Strasberg and colleagues (2001) examined the utility of PET in evaluating patients with hepatic colorectal metastases for possible hepatic resection. Out of 43 patients, the authors identified 6 with unresectable disease detected by PET imaging, which amounted to a 14% rate of occult disease detection by PET. Futile surgery was avoided in these patients. This improved detection rate is comparable to the experience described above by Schussler-Fiorenza and colleagues (2004) in the section on uses of the CRS. Interestingly, Strasberg and colleagues (2001) report quite favorable outcomes after metastasectomy, which they attribute to improved patient selection from the use of preoperative PET imaging: the resectability rate, 3-year disease-free survival, and 3-year overall survival were 95%, 40%, and 77% respectively. A meta-analysis on the subject found that the sensitivity and specificity of FDG PET were 91.5% and 95.4% for extrahepatic disease compared with 60.9% and 91.1% for CT (Wiering et al, 2005). The advantage of FDG PET over CT alone in the evaluation of a patient with a suspected recurrence, in the setting of a rising serum CEA, is similar to the experience described above for the patient undergoing a complete staging workup for stage IV disease (Huebner et al, 2000). FDG PET may also be particularly useful at identifying omental or peritoneal disease. Finally, the prospect of using functional imaging to assess treatment response is a promising application of PET technology. For instance, multiple studies have demonstrated that early metabolic response to chemotherapy correlates with eventual RECIST response, based on CT imaging, for both CRC and other cancer types (Findlay et al, 1996; Weber et al, 2003; Juweid & Cheson, 2006). One can imagine treatment adjustments based on FDG PET scans after just a few cycles of chemotherapy.

The National Comprehensive Cancer Network (NCCN) guidelines do recommend that an FDG PET scan be considered in the follow-up of a patient with CRC in the setting of CEA elevation and suspected recurrence and also in the setting of a resectable synchronous or metachronous liver metastasis. The utility of preoperative staging with FDG PET in metastatic CRC is the focus of a currently accruing randomized Phase III trial (PET START). Enrollment for this 400-patient study is nearing completion, with results expected in the near future.

THE ROLE OF LAPAROSCOPIC STAGING (SEE CHAPTER 21)

Laparoscopy has been shown to have a role in staging patients with metastatic CRC, particularly in patients with associated poor prognostic factors or an elevated CRS (Babineau et al, 1994; John et al, 1994; Jarnagin et al, 2000). The principal advantage of laparoscopy is that it allows the detection of occult peritoneal or periportal disease that would preclude resection, but it is not appreciated on preoperative imaging. In a study by Jarnagin and colleagues (2001), laparoscopic evaluation identified the majority of cases of unresectable metastatic disease (14 of 26), sparing a laparotomy in many instances. Moreover, the authors demonstrated that laparoscopic detection of extrahepatic or unresectable disease resulted in decreased surgical morbidity, a shorter hospital stay, decreased hospital costs, and shorter delay to systemic therapy.

Of course, a negative laparoscopy lengthens anesthetic time and increases operating costs; therefore the technique is typically reserved for patients deemed to be at high risk for having unresectable or extrahepatic disease. Such patients include those with findings on imaging that are suspicious, but not diagnostic for, extrahepatic disease and those with a CRS greater than 2 (Jarnagin et al, 2001).

SYNCHRONOUS METASTASES AND TIMING OF RESECTION

The timing of hepatic resection in patients presenting with liver metastases during workup for the primary tumor is

controversial. Certainly, studies have demonstrated that synchronous metastatic disease portends a worse prognosis compared with metachronous metastases (Scheele et al, 1995), which factors into the discussion of whether to resect the primary and metastatic disease in one operation. Several factors related to perioperative and long-term outcome should be considered when deciding between simultaneous and delayed liver resection for metastatic CRC to the liver. With regard to surgical morbidity, de Haas and colleagues (2010) demonstrated that fewer complications were observed in patients who underwent simultaneous colorectal and liver resection (11% vs. 24%), but perioperative mortality was the same. Patients in this study were included if their liver resection involved three segments or less. A similar or decreased complication rate associated with simultaneous resection has also been validated by other groups (Vogt et al, 1991; Martin et al, 2003; Chua et al, 2004; Capussotti et al, 2007).

In the above mentioned study by de Haas and colleagues (2010), the 3-year overall survivals were 74% and 70% in the two groups, respectively; however, the simultaneous resection group experienced more recurrences (85% vs. 63%; $P = .002$), resulting in a decreased 3-year PFS compared with the staged resection patients (8% vs. 26%, respectively). The authors concluded that although simultaneous resection is safe, there is an associated detriment in PFS. When interpreting such a study, it is important to recognize that the group of patients who underwent simultaneous resection may have included some patients who would have progressed to unresectabilty during the interval between removal of the primary and metastasectomy. This would bias the long-term results in favor of the delayed resection group. Indeed, Lambert and colleagues (2000) showed that roughly two thirds of patients can be spared unnecessary hepatic resection by using a delayed-resection approach to liver metastases. Taking the data together, it is reasonable to perform a simultaneous resection in patients with low-volume disease in the liver, when the risk of early and rapid progressive disease is relatively low. Simultaneous resection should be avoided in patients who appear frail and in certain clinical scenarios in which the liver disease is best addressed in a delayed fashion, such as with obstruction or bleeding.

PREOPERATIVE ALGORITHM

The preoperative preparation and planning before hepatic resection of colorectal metastases should be thorough and carried out with the intent to avoid unexpected findings at the time of laparotomy. A systematic approach to the CRC patient who is referred for consideration of hepatic resection both facilitates the preoperative evaluation and minimizes unnecessary investigations.

OPERATIVE MANAGEMENT

The principles of hepatic resection are similar for colorectal metastases as for any other hepatic surgery (see Chapter 90B). The immediate preoperative preparation includes a single dose of prophylactic antibiotics and placement of sequential compression devices to prevent the development of deep vein thromboses. The choice of incision includes a subcostal, long midline, or short midline incision with a rightward extension approximately 3 cm above the umbilicus. The latter is most frequently used at our institution, as it provides excellent exposure while minimizing the length of the midline incision in the upper abdomen, potentially reducing postoperative pulmonary compromise. The maintenance of a low central venous pressure (<5 mm Hg) reduces operative blood loss by decreasing bleeding from the hepatic venous radicles during dissection (Cunningham et al, 1994; see Chapter 22). This is facilitated by performing the dissection with the patient in a 15-degree Trendelenburg position, which increases the venous return to the heart and improves cardiac output.

Intraoperative Staging and the Role of Intraoperative Ultrasound (See Chapters 21 and 95)

As with any laparotomy for cancer, the abdomen should be carefully explored for evidence of extrahepatic metastases. In particular the celiac axis and portocaval and hilar lymph nodes must be palpated, and any suspicious nodes should be removed and examined by frozen section. Most surgeons routinely use intraoperative US after mobilization of the liver. With experience this practice may detect 5% to 10% of lesions missed on noninvasive imaging with CT, MRI, and transabdominal US (Boldrini et al, 1987; Machi et al, 1987, 1991; Olsen, 1990; Stone et al, 1994). In addition, intraoperative US is useful to delineate the interior anatomy of the liver, such as the intrahepatic vessels; therefore hepatic resection can be performed more safely with an anatomic approach. Intraoperative US is also useful throughout parenchymal transection, so that the resection line can be viewed in relation to the lesion and blood vessels. Prior to the development of PET imaging, several reports demonstrated that surgical management of hepatic tumors was influenced by intraoperative US in 30% to 50% of operations (Castaing et al, 1986; Rifkin et al, 1987).

Recently, interest is mounting with regard to contrast-enhanced intraoperative liver US with contrast agents that consist of microbubbles of air or gas that create greater contrast between tumors and normal liver parenchyma. Typically, the contrast is delivered in the form of a 4-mL intravenous bolus of SonoVue, sulfur hexafluoride gas stabilized by a phospholipid shell (Bracco SpA, Milan, Italy), followed by a flush of normal saline. In a series of 60 patients from the United Kingdom with metastatic CRC, the acccuracy of preoperative MRI/CT, standard intraoperative US, and contrast-enhanced US were 74%, 79%, and 96% respectively. The median size of lesions identified on contrast-enhanced US, but not on preoperative imaging, was 0.8 cm. In 17 patients (29%), findings on intraoperative contrast-enhanced US changed the surgical plan (Leen et al, 2006). In a second study from the United Kingdom, contrast-enhanced US altered the management plan in 4 (19%) of 21 patients compared with standard intraoperative US (Shah et al, 2010).

POSTOPERATIVE MANAGEMENT

Immediate Postoperative Care (See Chapter 22)

Metabolic derangements are common in the postoperative period following liver resection and are due to both hepatic insufficiency and hepatic regeneration. Hypoproteinemia and hypoglycemia may indicate early hepatic insufficiency, but they are usually transient. Hypokalemia and hypophosphatemia occur on the second postoperative day, as the liver begins to

consume these electrolytes for regeneration. Such metabolic abnormalities should be treated supportively. We prefer maintenance intravenous fluid with 5% dextrose and half-normal saline with the addition of 15 to 30 mEq/L of potassium phosphate. Alkaline phosphatase and transaminase elevations are common, and hyperbilirubinemia may occur. Abnormalities in coagulation or platelets may also occur and should be treated when the international normalized ration (INR) exceeds 1.5, or the platelets are less than 50,000/μL. Hepatic regeneration occurs rapidly after surgery. DNA synthesis is initiated in hepatocytes within 10 to 12 hours after surgery, and most of the hepatic mass returns within 1 week. Subsequent architectural rearrangements continue over the next few weeks, and in the majority of cases, this process is complete in 6 weeks.

Perioperative Mortality and Morbidity

For a surgical approach to be widely accepted, it must be efficacious, safe, and feasible. Without a doubt, major liver resection can be performed with acceptable mortality and morbidity. Using proper patient selection, preoperative staging, and surgical expertise, metastatic hepatectomies can be performed safely and result in prolonged disease-free survival and cure.

Mortality

The mortality associated with an elective liver resection for colorectal metastases has decreased significantly over the past 3 decades, and in the last 10 years, it has been shown to be less than 10% across major series (Butler et al, 1986; Hughes et al, 1986; Pagana, 1986; Cobourn et al, 1987; Nordlinger et al, 1987; Schlag et al, 1990; Scheele et al, 1991; Younes et al, 1991; Rosen et al, 1992). Advances in the understanding of liver anatomy, resection techniques, and anesthetic care have translated into favorable survival rates even with major resections. At the highest volume centers, operative mortality rates are now 3% to 5% (see Table 81A.2). The majority of deaths occur from perioperative hemorrhage or liver failure. Further improvements in mortality rates will be challenging, despite ongoing advances in surgical technique, as surgeons have taken an increasingly aggressive approach to hepatic resections.

Morbidity

The complication rate associated with hepatectomy is attributable in large part to the metabolic and immunologic derangements associated with liver surgery. The reported complication rate in most series is over 20% (see Table 81A.3), but this is likely an underestimate and reflects the fact that these reports are retrospective. Nonspecific or nonliver morbidities include cardiac, pulmonary, and infectious complications. The incidence of cardiovascular complications is around 9%, but the overwhelming majority of these are arrhythmogenic in nature (Jarnagin et al, 2002). The low rate of severe cardiac complications reflects careful selection of patients for liver resection. Pulmonary complications occur in close to 20% of patients and are related to the large upper abdominal incision and postsurgical sympathetic pleural effusions. Specifically, symptomatic pleural effusions occur in 10% of cases, pneumonia in 3%, and pulmonary embolism in 1% (Jarnagin et al, 2002).

Liver insufficiency and liver failure remain the most dangerous liver-related complications and occur in 3% to 8% of major hepatic resections (Schlag et al, 1990; Doci et al, 1991; Scheele et al, 1991; Cunningham et al, 1994; Jarnagin et al, 2002). Other hepatobiliary complications include bile leak in 4% of patients and perihepatic abscess in 2% to 10% (Schlag et al, 1990; Scheele et al, 1991; Jarnagin et al, 2002). Significant hemorrhage is rare (1% to 3%) but can be an important cause of perioperative mortality.

It is worth emphasizing that a high complication rate does not always translate into a prolonged hospital stay. If recognized and treated promptly, most complications do not result in a poor outcome. For instance, in the experience by Jarnagin and colleagues (2002), with more than 1800 liver resections performed at a single center, the median hospital stay was 8 days, and intensive care unit (ICU) admission was required for only 112 patients (6%). On the other hand, an association between the development of complications and decreased long-term outcome, both disease-free and overall survival, has been observed for liver surgery (Ito et al, 2008; Farid et al, 2010); this is similar to the findings in a large, population-based analysis of patients undergoing surgical procedures (Khuri et al, 2005), a finding that again underscores the importance of safe liver surgery.

Follow-up After Resection

No consensus exists regarding the extent and frequency of follow-up after surgery for primary CRC, as no specific strategy has been shown to conclusively improve survival (Makela et al, 1995; Ohlsson et al, 1995; Kjeldsen et al, 1997; Schoemaker et al, 1998). Similarly, no conclusive data demonstrate improved survival with close follow-up after hepatic resection for CRC metastases (Metcalfe et al, 2004). Nevertheless, patients who have undergone hepatic resection are usually monitored closely with the goal to identify early and potentially curable resectable recurrences. Our paradigm is as follows: physical examination, serum CEA level, and CT of the abdomen and pelvis every 3 to 4 months for the first 2 years and then every 6 months thereafter, and patients undergo chest imaging annually. We continue surveillance for more than 5 years, because roughly a third of 5-year survivors will still recur (Tomlinson et al, 2007).

ROLE OF ADJUVANT THERAPY

Patterns of Recurrence

Although the cure rate for liver metastasectomy is now considered to be roughly 20% (Tomlinson et al, 2007), the majority of patients with metastatic CRC to the liver die from recurrent disease. It stands to reason that these patients harbored occult disease at surgery that ultimately progressed and led to their demise. The most common sites for failure include the liver and lung (Table 81A.5). Indeed, the recurrences occur within the liver in 60% of patients (de Jong et al, 2009) and exclusively in the liver in up to 40% (Nordlinger et al, 1987).

Adjuvant Systemic Chemotherapy

A number of nonrandomized studies have evaluated the utility of perioperative systemic chemotherapy in the setting of hepatic resection for CRC metastases with equivocal results. Most of these studies compared patients receiving 5-FU–based chemotherapy with or without irinotecan or oxaliplatin. A large retrospective cohort study from European and American centers compared 792 patients who underwent hepatic resection alone to hepatic resection with perioperative 5-FU chemotherapy.

Table 81A.5

Sites of Initial Recurrence after Liver Resection for Colorectal Metastasis

Study	No. Patients	Recurrences	Median Follow-up (mo)	Liver (%)	Liver and Other (%)	Lung (%)	Lung and Other (%)	Colon/ Rectum (%)	Other (%)
Hughes et al, 1986	607	424	—	149 (35)	42 (10)	73 (17)	—	33 (8)	61 (14)
Schlag et al, 1990	122	80	—	17 (14)	55 (45)	—	—	—	8 (7)
Butler et al, 1986	62	30	—	10 (33)	10 (33)	—	—	—	10
Ekberg et al, 1987	68	53	20	19 (28)	25 (47)	3 (6)	12 (23)	8 (15)	—
Bozzetti et al, 1987	45	28	18	11 (39)	5 (18)	5 (17)	—	—	—
Nordlinger et al, 1987	80	51	—	21 (42)	13 (26)	11 (22)	—	11 (22)	—
Fortner, 1988	69	45	—	8 (12)	—	16 (23)	—	—	—

The basis for receiving chemotherapy was largely a function of where the patients were treated, thereby removing the bias toward chemotherapy in higher risk patients, which confounds other studies (Hewes et al, 2007). In this study, chemotherapy was associated with an improved 5-year overall survival (37% vs. 31%; Parks et al, 2007). Postoperative systemic 5-FU chemotherapy was evaluated in two prospective, randomized, controlled trials, the Fédération Francophone Cancerologie (FFCD) trial 9002 and the ENG trial, but both studies were closed early as a result of poor accrual. The pooled results included 278 patients randomized to surgery alone or surgery with 6 months of 5-FU. The authors demonstrated a marginal improvement in PFS (18.8 vs. 27.9 months; $P = .058$) without an improvement in overall survival at 3 or 5 years (Mitry et al, 2008).

More recently, Nordlinger and colleagues (2008) reported the results of the European Organization for the Research and Treatment of Cancer (EORTC) intergroup trial 4098. This prospective and randomized trial included 364 patients with resectable hepatic colorectal metastases who were treated by surgery alone or surgery with perioperative FOLFOX chemotherapy, six preoperative cycles and six postoperative cycles (Nordlinger et al, 2008). Based on an intention-to-treat analysis, an insignificant improvement was seen in PFS at 3 years of 7.3% (28.1% vs. 35.4%; $P = .058$); however, when only eligible patients were analyzed, the absolute difference in 3-year PFS was 8.1% and reached statistical significance ($P = .041$). The difference was 9.2% when just patients who underwent surgical resection were included ($P = .025$). This was technically a negative study, because the groups were statistically equivalent in the intent-to-treat analysis, but this is frequently quoted as a study demonstrating that perioperative chemotherapy improves PFS in patients undergoing hepatic resection for CRC metastases. Furthermore, one cannot comment on the role of neoadjuvant therapy from this study, because patients received chemotherapy before and after surgery in the adjuvant arm. No prospective and randomized study to date has examined the role of newer, biologic agents in the adjuvant setting in patients with resectable metastatic CRC.

Adjuvant Hepatic Arterial Infusion Chemotherapy (See Chapter 86)

Although regional liver-directed chemotherapy is not universally used, some liver surgeons and gastrointestinal oncologists support a role for this strategy in the setting of metastatic CRC to the liver. The rationale for this approach is that the liver is the most common site for tumor recurrence after liver resection, and it is often the only site of recurrence. Moreover, most metastatic liver tumors preferentially derive their blood supply from the hepatic artery, as opposed to normal hepatic tissue, which relies on the portal venous blood supply. In addition, the hepatic parenchyma can extract and metabolize chemotherapy drugs to less toxic byproducts, which allows the administration of very high doses to tumor cells with minimal systemic toxicity. For a more detailed discussion of the technical aspects of regional chemotherapy, refer to Chapter 86.

The most extensively studied agent used in hepatic artery infusional therapy is 5-FU-2-deoxyuridine (FUDR). This agent is a 5-FU analogue, which is concentrated 100 to 400 times in the liver as a result of its 95% hepatic extraction ratio (Ensminger et al, 1978). Most of the data on regional hepatic chemotherapy focuses on unresectable metastatic CRC. Randomized trials have clearly demonstrated that the technique is safe and is associated with a higher response rate than systemic chemotherapy alone; responses are 48% to 62% versus 0% to 21%, respectively (Chang et al, 1987; Kemeny et al, 1987; Hohn et al, 1989; Martin et al, 1990; Rougier et al, 1992); however, improved treatment response has translated into an improved survival in just a single study (Chang et al, 1987). Four relatively large randomized trials of adjuvant regional chemotherapy have been completed, and three were positive trials in favor of regional chemotherapy (Kemeny et al, 1999; Lygidakis et al, 2001; Kemeny et al, 2002). The fourth trial by Lorenz and colleagues (1998) found no difference in outcome for patients treated with resection alone versus resection plus regional 5-FU chemotherapy in an intention-to-treat analysis; however, the patients randomized to regional therapy had a very high operative mortality (8%), and 5-FU was used instead of FUDR, which has a much higher hepatic extraction rate and therefore less systemic toxicity. In addition, implanted ports were used as opposed to pump devices. Technical complications prevented chemotherapy administration in many of the patients randomized to regional therapy, so that just 74% and 30% of patients in the experimental arm initiated and completed treatment, respectively. These findings highlight the importance of technical expertise with regional liver chemotherapy (Lorenz et al, 1998).

Two of the positive adjuvant trials were large American studies. The Eastern Oncology Cooperative Group/Southwest Oncology Group (ECOG/SWOG) study consisted of 109

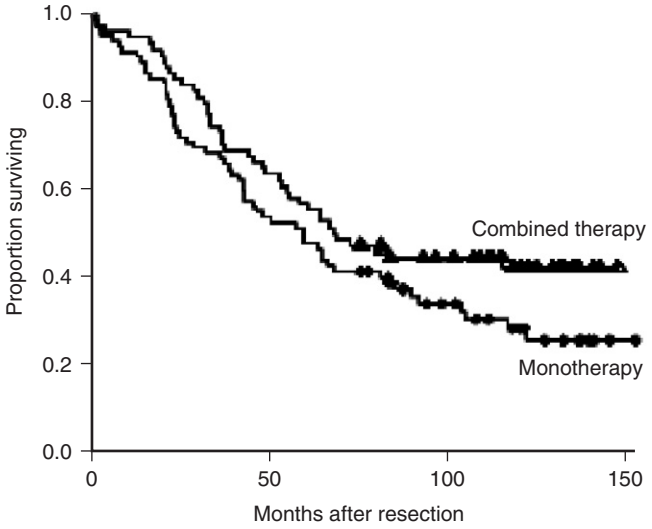


FIGURE 81A.3. Overall survival among patients with metastatic colorectal cancer treated with hepatic arterial infusion plus systemic chemotherapy (combined therapy) or systemic chemotherapy alone (monotherapy). *(From Kemeny N, Gonen M, 2005: Hepatic arterial infusion after liver resection N Engl J Med 352[7]:734. Copyright 2005 Massachusetts Medical Society All rights reserved. Reprinted with permission.)*

patients randomized to surgery alone or surgery plus hepatic arterial infusion (HAI) with FUDR. The 4-year hepatic disease-free survival was significantly better in the HAI group (67% vs. 43%; $P = .03$) (Kemeny et al, 2002). No difference in overall survival was found, although the study was insufficiently powered to test this end point. In a larger single-institution study from Memorial Sloan-Kettering Cancer Center (MSKCC), 156 patients were randomized to resection plus systemic 5-FU or resection plus combined systemic 5-FU and HAI with FUDR. The patients who were treated with regional therapy had a significantly higher 2-year survival (86% vs. 72%; $P = .03$) and markedly improved liver disease control, and 10-year follow-up demonstrated significantly improved PFS associated with regional therapy (31.3 vs. 17.2 months; Fig. 81A.3). Survival rates at 10 years were 41.1% and 27.2% in the two groups, although the difference was not statistically significant ($P = .1$) (Kemeny & Gonen, 2005).

Future prospective trials should explore regimens combining HAI chemotherapy with FUDR and modern systemic chemotherapy with agents such as irinotecan (CPT-11), oxaliplatin, bevacizumab, and cetuximab. Phase I and II studies combining systemic CPT-11 and HAI-FUDR or systemic oxaliplatin with HAI-FUDR are presently ongoing. As second-line therapy in the palliative setting for unresectable hepatic colorectal metastases, systemic CPT-11 and/or oxaliplatin combined with HAI-FUDR was associated with a response rate of over 70% (Kemeny et al, 2001; Kemeny & Gonen, 2005). This compares quite favorably to second-line systemic chemotherapy, which has a response rate of only 20%.

Recent Phase I and II studies of HAI with floxuridine and dexamethasone combined with systemic irinotecan (Kemeny et al, 2003) or oxaliplatin (Kemeny et al, 2009) demonstrated safety and feasibility in the adjuvant setting. Active investigation is now directed at determining the efficacy of this strategy. While awaiting the results of larger scale trials, regional FUDR should be considered an option in the adjuvant setting in patients at high risk for liver recurrence, particularly after failure of first-line systemic therapy.

Neoadjuvant Chemotherapy for Downstaging of Unresectable Disease

Several practical and conceptual advantages attend neoadjuvant chemotherapy for metastatic CRC involving the liver. Improved efficacy of modern chemotherapy has the potential to convert unresectable metastatic CRC into resectable disease, or it may reduce the extent of resection required to remove the hepatic disease (see Chapters 65 and 87). In addition, neoadjuvant chemotherapy can treat micrometastatic disease early as opposed to addressing it in a delayed fashion. Finally, this strategy may function as an in vivo test of chemoresponsiveness to a particular agent. Bismuth and colleagues (1996) were the first to publish this observation in a study of 330 consecutive patients with unresectable disease. They found that a combination of 5-FU/LV and oxaliplatin converted 53 patients to resectability (16%). Furthermore, the long-term outcome of these individuals after resection was similar to patients who were initially resectable. Since then, the potential to downstage unresectable into resectable disease with neoadjuvant chemotherapy has been validated in a number of studies and ranges between 3% and 41% of patients (Giacchetti et al, 1999; Adam et al, 2001; Wein et al, 2001; Clavien et al, 2002; Adam et al, 2004; Pozzo et al, 2004; Vauthey et al, 2006; Adam et al, 2009). Patients who undergo complete resection have a median survival between 30 and 60 months. Of course, patient selection plays a vital role when estimating the potential benefit of neoadjuvant treatment. In the largest prospective study to date, 138 of 1104 unresectable patients (12%) became resectable after a course of neoadjuvant chemotherapy using either FOLFIRI or FOLFOX. Factors associated with a poor long-term outcome in these patients included large tumors, an increased number of tumors (≥3), increased preoperative CEA, and periportal or celiac lymph node metastases (Adam et al, 2004).

Regional chemotherapy alone or in conjunction with systemic chemotherapy may also convert unresectable disease into resectable disease. For example, 6 (26%) of 23 patients became resectable after HAI-FUDR treatment (Clavien et al, 2002). The 3-year actual survival rate was 84% for the patients who responded to HAI treatment compared with 40% for nonresponders. As part of a Phase I trial conducted at MSKCC, 21 patients with unresectable metastastic CRC received systemic oxaliplatin and CPT-11 in conjunction with HAI-FUDR. Seven of these patients (33%) became resectable after treatment (Kemeny et al, 2005).

Chemotherapy-Induced Liver Damage (See Chapters 65 and 87)

Neoadjuvant chemotherapy has been shown to cause liver injury in some patients. Specifically, oxaliplatin is associated with hepatic sinusoidal obstruction (Rubbia-Brandt et al, 2004), and CPT-11 is associated with hepatic steatosis (Kooby et al, 2003; Parikh et al, 2003); these agents can even cause severe steatohepatitis (Fernandez et al, 2005). Obese patients are at increased risk, and a preoperative liver biopsy should be considered to evaluate the liver parenchyma in such patients. When a major hepatic resection is planned in a patient

suspected of having impaired liver function after exposure to systemic chemotherapy, preoperative portal vein embolization may be warranted to induce hypertrophy in the future liver remnant. In some instances, concern about the function of the future liver remnant should push the liver surgeon to proceed straight to surgery, and plan for chemotherapy postoperatively, after the liver has regenerated. In addition to steatohepatitis, the treated liver may become fibrotic and may develop perivascular adhesions, which can complicate a planned resection.

Despite well-documented histologic changes in the liver that can occur with chemotherapy, the actual clinical impact is not entirely clear. Indeed some studies have demonstrated a negative impact of oxaliplatin or irinotecan chemotherapy on postoperative morbidity (Karoui et al, 2006; Vauthey et al, 2006; Nakano et al, 2008) and mortality (Vauthey et al, 2006), whereas other studies have not confirmed these findings (Hewes et al, 2007; Mehta et al, 2008).

Disappearing Hepatic Metastases

A *radiologic complete response*, defined as the disappearance of a lesion on cross-sectional imaging, occurs in approximately 6% to 9% of lesions treated with neoadjuvant chemotherapy (Benoist et al, 2006; Elias et al, 2007; Auer et al, 2010). A lesion that disappears during chemotherapy may represent a pathologic complete response or a reduction in the sensitivity of cross-sectional imaging secondary to chemotherapy-induced steatosis. When a hepatic metastasis is present in a segment of the liver that cannot be removed, disappearance of this lesion during chemotherapy may preclude wedge resection or ablation and thereby jeopardize a complete resection. Moreover, in some patients, resection is only a consideration because previously apparent liver disease had disappeared during chemotherapy. When approaching such a patient, surgeons must understand that removal of visible disease is likely to be ineffective if occult and viable tumor remains in the foci that correspond to the "vanished" lesions.

Three institutions have published retrospective studies on the significance of liver metastases that disappear with chemotherapy (Benoist et al, 2006; Elias et al, 2007; Auer et al, 2010), and although all three studies agree that a complete radiologic response does not often equate to a true clinicopathologic response, the strength of this association varied across the studies. Benoist and colleagues (2006) found the lowest rate of true clinicopathologic response. The authors identified 38 patients with at least one or more disappearing liver metastases, a total of 66 complete radiologic responses, by CT scan (Benoist et al, 2006). All of these patients eventually underwent surgical exploration after a lesion disappeared. In 20 of 66 instances, macroscopic disease was appreciated at the site of disappearance. In 15 cases, the area of disappearance was resected, even though no residual disease was observed at surgery, and viable tumor cells were seen on histologic examination in 12 of these specimens. The remaining 31 sites were left in situ, and 23 recurred within 1 year of surgery. In summary, a true and durable response was only appreciated in 17% of the disappearing lesions.

Elias and colleagues reviewed data from 16 patients who had complete disappearance for at least 3 months during HAI or systemic chemotherapy in at least one liver metastasis in the future liver remnant on cross-sectional imaging. The disappearing lesion reappeared in 6 patients (38%) but represented a complete response in 10 patients (62%) based on a minimum of 2 years of follow-up. Interestingly, none of the lesions that disappeared with HAI therapy reappeared in follow-up. In the most recent study by Auer and colleagues, 38 patients had 118 disappearing liver metastases; a total of 68 disappearing lesions were resected, and 50 were followed clinically (Auer et al, 2010). In the resected liver that harbored the 68 vanished lesions, a complete pathologic response was observed in 44 patients (65%). Similarly, there were 31 recurrences (62%) in the 50 disappearing lesions that were followed clinically for a median of 41 months. Factors associated with a true complete response included HAI chemotherapy, inability to visualize the disappearing lesion on MRI, and normalization of serum CEA with treatment.

RE-RESECTION FOR RECURRENCE AFTER RESECTION

As stated previously, the most common site of recurrence after hepatic resection for colorectal metastases is the liver, and the liver is the sole site of recurrence in 15% to 40% of cases (see Table 81A.5). In the absence of extrahepatic disease, and in the patient with a good performance status and adequate hepatic reserve, a repeat hepatectomy may be considered. In approximately one third of liver recurrences, such an operation is feasible (Table 81A.6). The presence of adhesions and the altered anatomy of the liver, particularly the position of the vasculature and biliary system, make these operations very challenging from a technical standpoint. Series of repeat liver resections report an operative mortality rate less than 3% and a perioperative complication rate that is similar to initial resections (Lange et al, 1989; Bozzetti et al, 1992). The most common complications include biliary fistula, hepatic duct stenosis, hemorrhage, hepatic failure, and subphrenic abscess. Reported 5-year overall survival was 30% to 40%, and the median survivals were often more than 30 months after repeat resection.

The largest published series of repeat liver resection for metastatic CRC is a combined series of 126 patients from MSKCC and the University of Frankfurt Medical Center (Petrowsky et al, 2002). The operative procedures included 90 minor resections and 36 major hepatic resections. The 1-, 3-, and 5-year survivals were 86%, 51%, and 34%, respectively, and there were 19 actual 5-year survivors (15%). On multivariate regression analysis (proportional hazard model), the number of lesions greater than 1 ($P = .01$) and tumor size greater than 5 cm ($P = .04$) were independent prognostic indicators of reduced survival. Contrary to previous smaller studies (Bozzetti et al, 1992; Adam et al, 1997), the interval between the first and second liver resection was not associated with long-term survival.

In summary, for selected patients with a low tumor burden, a repeat liver resection is feasible, and safe and long-term survival is possible. We believe that repeat hepatic resection should be considered the standard of care for resectable metastatic recurrences in the absence of other distant sites of disease or medical contraindications. Notably, the risk of future recurrence remains high; therefore adjuvant therapy is often appropriate when good systemic options remain for the patient.

CONCLUSION

Hepatic resection for metastatic CRC to the liver is the standard of care for patients with resectable hepatic disease in the

Table 81A.6

Results of Past Studies on Repeat Hepatic Resections

Author	All Liver Resections	Liver-Only Recurrence	Repeat Liver Resections	Deaths	Median Survival (%)	Survivors at 5 Years	Survivors NED	Follow-up (Patients, mo)
Butler et al, 1986	62	10	2	0/2	—	0	0	6, 17
Nordlinger et al, 1987	80	21	6	0/6	—	1	0	2, 12
Fortner, 1988	380	8	3	0/3	—	1	0	5
Lange et al, 1989	82		9	0/9	15.0	3	0	1, 3, 23, 35
Griffith et al, 1990	106		9	1/9	23.0	3	1	17, 42, 40, 6, 17
Hohenberger et al, 1990	105	12	6	0/6	23.0	1	0	—
Stone et al, 1990	95	27	10	0/10	25.0	5	0	31, 15, 43
Bozzetti et al, 1992	120	34	10	1/11	23.0	3	0	15, 17, 24, 42
Vaillant et al, 1993	189	60	16	1/16	33.0	9	2	26, 33, 38, 93
Elias et al, 1993	279	—	28	1/28	30.0	—		—
Que & Nagorney, 1994	—	—	21	1/21	40.8	—	1	—
Fong et al, 1994	499	—	25	0/25	30.2	—	0	8, 10, 24, 26, 29, 30, 59
Adam et al, 1997	—	—	—	—	—	—	—	—
Tuttle et al, 1997	—	—	23	0/23	—	7	—	—
Yamamoto et al, 1999	—	—	75	0/75	—	23	—	—
Muratore et al, 2001	—	—	29	1/29	—	—	—	—
Suzuki et al, 2001	—	—	26	0/26	—	8	—	—
Petrowsky et al, 2002	—	—	126	2/126	—	43	—	—

NED, no evidence of disease

absence of extrahepatic disease. Hepatic metastasectomy can be performed with an acceptable morbidity and mortality, and it results in prolonged survival and offers the best possibility for cure. The advent of more effective chemotherapy will continue to extend the therapeutic options and increase the number of patients who might benefit from resection, which is particularly true given the prospect of new and potentially more effective targeted agents. Aggressive surgery combined with improved adjuvant treatments will likely continue to improve the cure rate in a disease that was believed to be terminal just a few decades ago.

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CHAPTER 82

Hepatic tumors in childhood

Barrie S. Rich and Michael P. La Quaglia

OVERVIEW

An appreciation of hepatic segmental anatomy (see Chapter 1) has led to major advances in hepatic surgery, especially for tumors. In addition, the irresistible but still mysterious stimulus to hepatic regeneration has allowed larger and more extensive resections. In small infants, 85% of the liver can be removed safely, greatly increasing the scope for cure. Advances have also been made in understanding tumor biology and clinical behavior. This chapter addresses benign and malignant tumors of the liver and biliary tract encountered in infancy, childhood, and adolescence.

HISTORY

Between 310 and 280 BCE, Herophilus and Erasistratus first presented a description of hepatic anatomy. In the late 1880s, hepatic resection was attempted, but advances in anesthesia and antisepsis would be required before a successful outcome could be realized. Wendel used avascular anatomic planes in the liver to perform a hepatic resection in 1910 (McClusky et al, 1997), and progress in hepatic surgery has been based on an appreciation of hepatic segmental anatomy as described by Couinaud (Bismuth, 1982; Couinaud, 1986, 1992; see also the Introduction to this text). The distribution of the portal and hepatic veins delimits each hepatic segment, which has a unique portal vein and hepatic artery branch and bile duct. Knowledge of this anatomy allows control of the vascular structures before division of the hepatic parenchyma, making major hepatic resections feasible (see Chapter 1).

Bloodless hepatic dissection is crucial in infants and small children, who may have a total blood volume of less than 1 L. In the pediatric literature, Martin and Woodman (1969) reported that hepatoblastomas could be treated by hepatic lobectomy, and modern hepatic resection is soundly based on principles of segmental hepatic anatomy.

A second important historic finding was the sensitivity of some tumors, especially hepatoblastoma, to systemic chemotherapy (Fegiz et al, 1977). Chemotherapy caused significant reductions in tumor volume, and previously unresectable hepatoblastomas became resectable (Filler et al, 1991; Reynolds, 1995). Presently, the standard of practice is to administer neoadjuvant systemic chemotherapy to patients with hepatoblastoma, unless the tumor is clearly resectable at diagnosis.

In addition, appreciation of the biology of hepatic epithelial malignancies has increased, especially the differences between hepatoblastoma and hepatocellular carcinoma (HCC). These differences include the relatively good prognosis of hepatoblastoma compared with HCC in childhood, the importance of complete surgical resection of the primary hepatic tumor, and the association of hepatoblastoma with certain clinical syndromes (Exelby et al, 1975; Koishi et al, 1996; Schneid et al, 1997; Simms et al, 1995; Tsai et al, 1996; Vaughan et al, 1995). Finally, the first application of hepatic transplantation to a childhood liver tumor was reported by Heimann and colleagues in 1987, and a series of pediatric liver tumor patients treated by hepatic transplantation was reported by Tagge and colleagues in 1992. There is continued interest in using this modality for unresectable hepatic malignancies in childhood and adolescence (Pichlmayr et al, 1995; Pinna et al, 1997; Superina & Bilik, 1996).

MALIGNANT TUMORS

Primary malignant liver tumors constitute approximately 1.1% of childhood malignancies in Western nations. The overall incidence of primary liver cancer, as published by the Surveillance Epidemiology and End Results (SEER) program, is 5 cases per 1 million children in the 0 to 4 year age group and 1 case per 1 million in the 5 to 9, 10 to 14, and 14 to 19 year age groups (National Cancer Institute, 1995). Liver cancers constitute 0.5% to 2% of all pediatric solid tumors and about 5% of abdominal tumors in childhood (Weinberg & Finegold, 1983). The distribution of the most common malignant hepatic tumors is depicted in Figure 82.1. Hepatoblastoma is the most common, and its treatment is a success story in pediatric oncology.

Hepatoblastoma

Incidence

Hepatoblastomas are the most common primary hepatic tumors of childhood, constituting 43% to 64% of all hepatic neoplasms in one large series (Mann et al, 1990; Stocker, 1994; Weinberg & Finegold, 1983). Hepatoblastoma accounts for 91% of primary hepatic tumors in children younger than 5 years (Darbari et al, 2003) but comprises less than 1% of hepatic malignancies when adult age groups are included (Kaczynski et al, 1996). The Liver Cancer Study Group (LSCG) of Japan (1987) identified 30 hepatoblastomas (0.6%) in a cohort of 4,658 patients of all ages diagnosed over a 2-year period.

Hepatoblastoma affects 1 child younger than 15 years old in 1 million per year (Finegold, 1994), and approximately 50 to 70 new cases per year are reported in the United States, with a male/female ratio of 1.7:1 (Lampkin et al, 1985). Although hepatoblastoma has been reported sporadically in adults (Bortolasi et al, 1996; Harada et al, 1995; Inoue et al, 1995; Kacker et al, 1995; Parada et al, 1997), the median age at diagnosis is about 18 months, and most cases occur before the age of 3 years (Exelby et al, 1975). Hepatoblastoma is the most prevalent malignant neoplasm of the fetus and neonate and results in death within 2 years if not treated (Dehner, 1978; DeMaioribus 1990; Isaacs, 1985, 2007; Patterson et al, 1985). Finally,

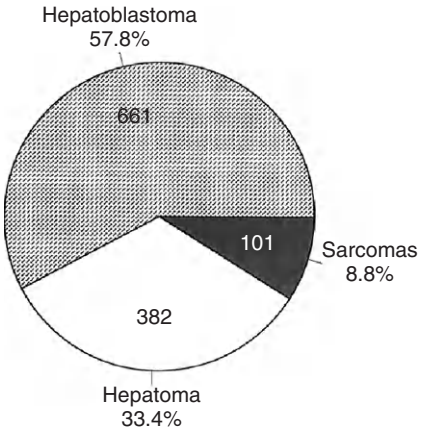


FIGURE 82.1. The frequency distribution of malignant hepatic tumors in childhood as compiled from reported large series. *(From Exelby PR, et al, 1975: Liver tumors in children in the particular reference to hepatoblastoma and hepatocellular carcinoma: American Academy of Pediatrics Surgical Section Survey 1974. J Pediatr Surg 10:329-337; and Weinberg AG, Finegold MJ, 1983: Primary hepatic tumors of childhood. Hum Pathol 14:512-537.)*

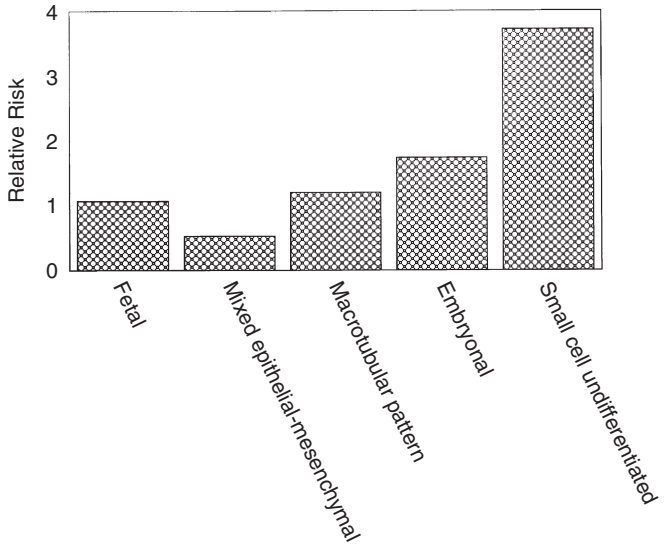


FIGURE 82.2. Graph depicts the risk of death for patients with fetal histology hepatoblastoma adjusted for age, sex, and stage and compared with other histopathologic subtypes.

the incidence of hepatoblastoma may be increasing (Blair & Birch, 1994). The incidence of hepatoblastoma was 0.6 per 1 million in the years 1973 through 1977, and it increased to 1.2 per 1 million from 1993 through 1997 (Darbari et al, 2003).

Hepatoblastoma may occur in siblings (Fraumeni et al, 1969; Ito et al, 1987; Napoli & Campbell, 1977; Surendran et al, 1989). It is most strongly associated with familial polyposis (Giardiello et al, 1996; Iwama & Mishima, 1994), Gardner syndrome (Hartley et al, 1990), and Beckwith-Wiedemann syndrome (Koishi et al, 1996; Tsai et al, 1996). In familial polyposis, incidence of hepatoblastoma seems to be increased in first-degree relatives of the patients with polyposis. Beckwith-Wiedemann syndrome is associated with Wilms tumor, rhabdomyosarcoma, adrenocortical carcinoma, and hepatoblastoma with a possible association between hepatoblastoma and trisomies 2, 8, 18, and 20 (Bove et al, 1996; Tomlinson, 2005).

Hepatoblastoma is also associated with low birth weight (Ikeda et al, 1997; Reynolds et al, 2004). It is unknown whether the causative agent is developmental abnormalities associated with prematurity or interventions, such as early total parenteral nutrition. These tumors also are reported in patients with congenital anomalies, such as cleft palate, and cardiovascular and renal anomalies, including multicystic kidney and absence of the right adrenal gland (Rao et al, 1989). There are also at least two reports of hepatoblastoma occurring in patients with biliary atresia (Taat et al, 2004). No evidence associates hepatoblastoma with hepatitis B or C infection or any other chronic viral hepatitis. These patients usually do not have cirrhosis or inborn errors of metabolism.

Pathology

Hepatoblastomas are large tumors that can contain fibrous bands, producing a spoked-wheel appearance (Jha et al, 2009). The five histologic subtypes observed in hepatoblastoma are 1) fetal, 2) embryonal, 3) mixed epithelial, 4) mesenchymal/macrotubular, and 5) anaplastic or small-cell undifferentiated. These subtypes are differentiated based on the findings with light microscopy, but all tumor cells appear smaller than nonneoplastic hepatocytes. Extramedullary hematopoiesis is notably present and may be related to constitutive cytokine production by the tumor cells (von Schweinitz et al, 1995a). The fetal type grows in trabeculae and resembles fetal hepatic cells, whereas embryonic hepatoblastoma cells grow in incohesive sheets and resemble embryonic cells. Some hepatoblastomas contain mesenchymal tissue along with the epithelial component. Calcification also may appear in these tumors, and one patient was reported with osteosarcomatous elements in the hepatoblastoma and associated pulmonary metastases (Alcantar, 1985). The anaplastic or small-cell type consists of small, round blue cells reminiscent of neuroblastoma. This subtype is rare but particularly virulent, with a strong metastatic potential (Dehner & Manivel, 1988). The importance of subtyping in hepatoblastoma is due to the association between prognostic risk and subtype, illustrated in Figure 82.2 (Gonzalez-Crussi et al, 1982; Lack et al, 1982). Some studies have indicated that the fetal histologic subtype has a better prognosis; in contrast, patients with the rare anaplastic variant usually do poorly (Dehner & Manivel, 1988).

Basic Biology

Few cellular models of hepatoblastoma exist, and immortalized cell lines have been difficult to establish. One cell line, isolated from a human hepatoblastoma, clearly expresses the MYC and Hras1 oncogenes and epidermal growth factor receptor (EGFR) (Manchester et al, 1995). Antibodies that blocked the EGFR inhibited cell growth, but the significance of oncogene expression remains to be determined. A new cell line was established from primary hepatoblastoma tumor tissue and contains an identical genotype to tumor cells, with morphologic, molecular, and immunohistochemical confirmation.

In immunodeficient mice, hepatoblastoma is tumorigenic (Chen, 2009). Elevated hepatocyte growth factor levels have been demonstrated in the serum of 10 (45%) of 22 patients with hepatoblastoma (von Schweinitz et al, 1997a). Addition of hepatocyte growth factor causes proliferation in hepatoblastoma-derived cell lines.

Small epithelial cells, characteristic of hepatic stem cells, have been observed in human hepatoblastomas of various

subtypes (Ruck & Xiao, 2002). Additionally, various genetic abnormalities have been reported in hepatoblastoma. Chromosome 8q amplification is associated with a worsened prognosis and has been correlated with overexpression of the transcription factor pleomorphic adenoma gene 1 (PLAG1) (Zatkova et al, 2004). Telomerase and its regulatory protein expression levels have been correlated with poor outcome in human hepatoblastoma (Hiyama et al, 2004), and tamoxifen may inhibit hepatoblastoma cells by reducing telomerase levels (Brandt et al, 2005).

Loss of heterozygosity on chromosome 11p15.5, the region associated with Beckwith-Wiedemann syndrome, and on chromosome 1p36 has been described in hepatoblastoma (Albrecht et al, 1994; Kraus et al, 1996). Investigations into both of these regions suggest that each may contain a tumor suppressor gene, but this has not been proven. Trisomy 20 and trisomy of all or part of chromosome 2 also have been reported (Swarts et al, 1996). In addition, an abnormality of chromosome 2q may provide a common genetic link between hepatoblastoma and rhabdomyosarcoma (Rodriguez et al, 1991). Finally, frequent genetic losses found using comparative genomic hybridization included regions 13q21-q22 (28%) and 9p22-pter (22%), and the most frequent genetic gains were on chromosomes 2q23-q23 (33%) and 1q24-q25 (28%; Gray et al, 2000). Recently, differentially expressed microRNA has been shown to be deregulated in hepatoblastoma (Magrelli et al, 2009), and mutations of β-catenin have also been recognized (Curia et al, 2008).

Perhaps the most exciting insight is the association between hepatoblastoma and familial adenomatous polyposis syndrome (Bala et al, 1997; Cetta et al, 1997). In one study of 13 hepatoblastomas obtained from nonfamilial adenomatous polyposis patients, 69% had mutations in the adenomatous polyposis coli (*APC*) gene (Oda et al, 1996). In one case of siblings with hepatoblastoma, a shared *APC* gene mutation was identified (Thomas et al, 2003). In addition, the well-known thrombocytosis associated with untreated hepatoblastoma is fascinating, as is the presence of extramedullary hematopoiesis in these tumors. It was shown that hepatoblastoma cells secrete interleukin (IL)-1β, which causes secretion of IL-6 from surrounding fibroblasts and endothelial cells (von Schweinitz et al, 1993). Other factors, such as erythropoietin and stem cell factor, have been localized to the cytoplasm of hepatoblastoma cells. Thrombopoietin has been identified in hepatoblastoma tissue and serum from a patient, but its correlation with the thrombocytosis associated with this neoplasm is unclear (Komura et al, 1998).

Clinical Findings

The most common presenting sign of hepatoblastoma is an asymptomatic abdominal mass. The child is often in good health, and the tumor usually is discovered incidentally, when an attentive parent, grandparent, or clinician discovers the mass on a routine examination or while bathing the child (Fabre et al, 2004). Patients with the anaplastic variant of hepatoblastoma, who often have distant metastases at diagnosis, are more frequently symptomatic. Accompanying symptoms such as pain, irritability, minor gastrointestinal disturbances, fever, and pallor occur in smaller numbers of patients. Significant weight loss is unusual, although patients may fail to thrive. In most series of hepatoblastomas and HCCs, a few patients present acutely with tumor rupture and intraperitoneal hemorrhage (Brown et al, 1993). Rarely, hepatoblastoma manifests with sexual precocity secondary to a β-human chorionic gonadotropin (hCG)-secreting tumor (Muraji et al, 1985), and one patient with a hepatoblastoma was reported presenting with a biliary fistula (Daniel & Kifle, 1989). Finally, hepatoblastoma may present as a cardiac tumor (Wang et al, 2003).

A mild anemia associated with a markedly elevated platelet count is observed in most patients at diagnosis, and the platelet count can range into the millions. As noted previously, the cause is probably secondary to abnormal cytokine release.

Measurement of serum α-fetoprotein (AFP) is well established as an initial tumor marker in the diagnosis of hepatoblastoma and a means of monitoring the therapeutic response (Van Tornout et al, 1993). The normal level in most laboratories is less than 20 ng/mL, whereas the AFP level at diagnosis in hepatoblastoma patients can range from normal to significantly elevated (7.7×10^6 ng/mL); it is estimated that the AFP is elevated in 84% to 91% of patients with hepatoblastoma (Lack et al, 1982). One study reported a mean AFP level in hepatoblastoma of 3 million ng/mL, whereas the mean in pediatric patients with HCC was about 200,000 ng/mL (Ortega et al, 1991). In infants younger than 1 year, the AFP is normally elevated and is highest at birth (Fig. 82.3).

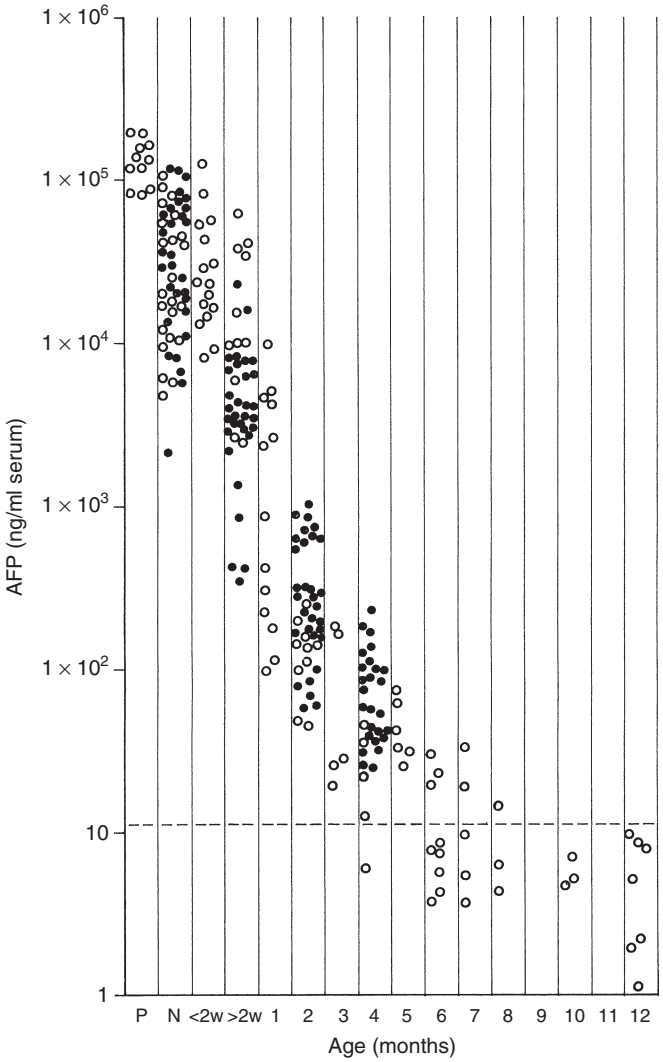


FIGURE 82.3. Graph shows the time decay of α-fetoprotein (*AFP*) levels in normal infants during the first year of life. *(Data from Wu JT, et al, 1981: Serum alpha fetoprotein [AFP] levels in normal infants. Pediatr Res 15:50-52.)*

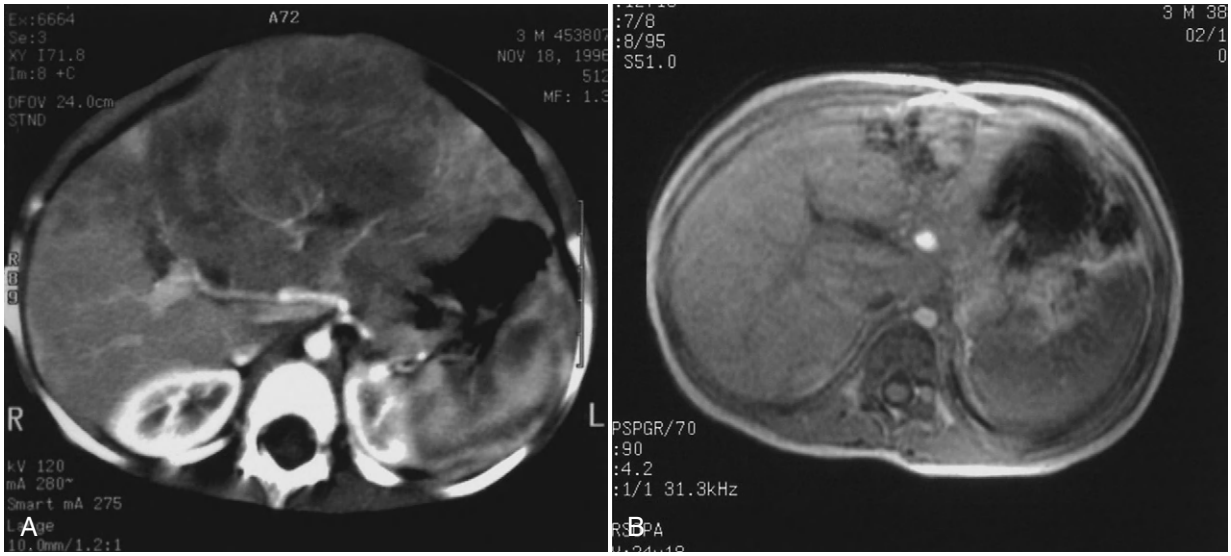


FIGURE 82.4. A, Computed tomographic image of a patient with hepatoblastoma before induction chemotherapy. **B,** Magnetic resonance image of the same patient after four courses of vincristine, cisplatin, and 5-fluorouracil.

Some authors suggest that subfractionation more reliably indicates whether the increased AFP is secondary to a hepatoblastoma or HCC, an endodermal sinus tumor, or benign liver disease (Tsuchida et al, 1997). The half-life of AFP is about 6 days, and in one study, 24 (77%) of 31 patients had levels decline by at least 1 log before second-look surgery (Walhof et al, 1988). Of these patients, 16 (50%) of 32 eventually had AFP levels decline to normal at the end of therapy and had no clinical or radiographic evidence of hepatoblastoma at this point. Finally, 15 (94%) of 16 patients who attained a complete response also showed a decline in AFP levels of 2 logs or more before second-look surgery (Van Tornout et al, 1997). A large, early decline in AFP levels was an independent predictor of survival in multivariate analysis; it has also been stated that a low initial AFP level is associated with worse survival (von Schweinitz et al, 1995b), but this has not been confirmed in multivariate analysis (von Schweinitz et al, 1994a). Anaplastic hepatoblastomas may also be associated with lower AFP levels (Tsunoda et al, 1996).

When interpreting the AFP level, it is important to realize that normal levels are very high at birth and decrease over the first 6 months of life. Premature newborns may have AFP levels in the range of 100,000 ng/mL. Term newborns also can have relatively high levels (10^4 to 10^5 ng/mL). By 2 months of age, most infants have levels ranging from 100 to 1000 ng/mL, and by 6 months, levels should be less than 100 ng/mL. Usually, levels decrease to normal (<20 ng/mL) after 6 to 7 months, but levels may remain elevated for 1 year after birth (Ohama et al, 1997). AFP may also be elevated in the setting of liver damage, liver regeneration, or in the presence of another tumor.

Imaging

The first imaging study is usually an abdominal ultrasound (US) (see Chapter 13). If duplex technique is used, tumor vascularity can be gauged, and the hepatic veins can be assessed (Bates et al, 1990). The ultrasonographer also should search for anomalies of the genitourinary system and rule out tumor thrombus in either the vena cava or the hepatic veins. Computed tomography (CT) (see Chapter 16) is useful to identify pulmonary metastases, identify diffuse hepatic involvement, and determine resectability. Oral and intravenous contrast material is used (Fig. 82.4A). CT scans can be performed quickly and can be completed in less than 2 minutes in helical scanners; this greatly shortens the required period of sedation for infants or small children, and it has the added advantage of being a quick and reliable screening method for pulmonary metastases. Hepatoblastoma will appear as a well-demarcated tumor, without a capsule. CT angiography (CT portography) uses CT with fine cuts and an increased amount of intravenous contrast material to image hepatic tumors and the hepatic venous anatomy. CT portography may provide as much information as magnetic resonance imaging (MRI) (see Chapter 17), which is useful for evaluating hepatic lesions and their relationship to vascular structures. MRI can show the hepatic veins, vena cava, and bile ducts (Ohnuma et al, 1991). MRI of a hepatoblastoma patient after neoadjuvant chemotherapy is shown in Figure 82.4B. Positron emission tomography (PET) has been used to identify hepatoblastoma recurrence and to search for sites of metastatic disease, but it may not be reliable for lesions smaller than 6 to 10 mm (Wong et al, 2004).

Staging

In the United States, the commonly used staging system is that from the Children's Oncology Group (COG), based on operative findings (Table 82.1). A tumor-node-metastasis (TNM) classification has also been used (Table 82.2; Brower et al, 1998). The *PRE-T*reatment *EXT*ent (PRETEXT) system of disease staging has been used extensively by the International Society of Pediatric Oncology liver group (SIOPEL) (Fig. 82.5; Aronson et al, 2005). It relies on radiographic findings prior to any therapy, including surgery, and does not take into account the independent surgeon's judgment at the time of surgery regarding resectability. This staging system is based on Couinaud's system of segmentation of the liver and is thought to predict the degree of tumor infiltration, the extent of surgical resection, and the complexities involved in the resection

Table 82.1

Children's Oncology Group Staging for Hepatoblastoma

Stage I	Complete Resection
Favorable histology	Purely fetal histology with a low mitotic index
Other histology	All other stage I tumors
Stage II	Gross total resection with microscopic residuals or total resection with preoperative or intraoperative rupture
Stage III	Unresectable tumors as determined by the attending surgeon, partially resected tumors with macroscopic residual involvement or any tumor with lymph node involvement
Stage IV	Measurable metastatic disease to lungs or other organs

From Finegold MJ, et al, 2008: Liver tumors: pediatric population. Liver Transpl 14(11):1545-1556.

(Couinaud, 1992; Otte, 2010). This system classifies the tumor into one of four categories, depending on which sections of the liver do not include tumor (Table 82.3; Roebuck et al, 2007). Additional criteria added in 2005 (Table 82.4) further classify these tumors (Otte, 2010; Roebuck, 2007).

PRETEXT was compared with pathologic findings in 110 patients and was correct in 51%, overstaged in 37%, and understaged in 12%. The authors compared this system with the Children's Cancer Group/Pediatric Oncology Group (CCG/POG) and TNM schemes and claimed a better correlation with risk status. This study analyzed data from patients who had

Table 82.2

Tumor-Node-Metastasis Staging for Hepatic Malignancies

Primary Tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Solitary tumor without vascular invasion		
T2	Solitary tumor with vascular invasion or multiple tumors, none >5 cm		
T3a	Multiple tumors >5 cm		
T3b	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein		
T4	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum		
Stage Grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T4	N0	M0
Stage IVA	Any T	N1	M0
Stage IVB	Any T	Any N	M1

From Edge SB, et al (eds) 2009: American Joint Committee Cancer Staging Manual, 7th ed. New York, Springer, p 237.

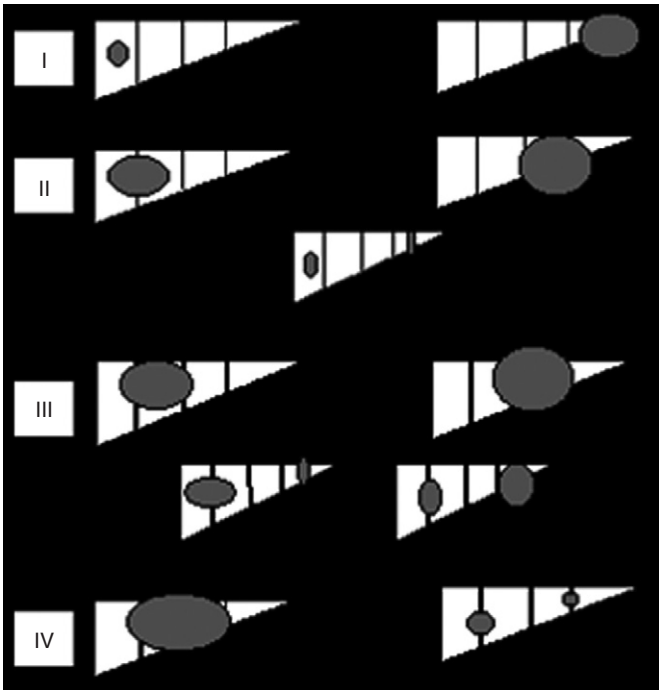


FIGURE 82.5. The PRE-Treatment EXTent (PRETEXT) staging system used by the International Society of Pediatric Oncology.

neoadjuvant chemotherapy, whereas a recent study from the COG analyzed data from patients with a hepatoblastoma at diagnosis and reported that both the COG stage and PRETEXT were useful prognostic indicators. The PRETEXT system has been described as showing improved predictive value for survival compared with other staging classifications (Aronson et al, 2005). Moreover, this system can be valuable for recognizing patients who are surgical candidates (PRETEXT stages I and II) and those who may benefit from lower dose chemotherapy (Meyers et al, 2009). It is recommended that all liver tumor patients in future COG studies undergo PRETEXT staging.

Treatment

Multiple studies support the effectiveness of systemic chemotherapy combined with complete surgical resection of the primary hepatic tumor (Gauthier et al, 1986; von Schweinitz et al, 1994a, 1994b, 1995b). Survival depends on removal of

Table 82.3

PRETEXT Staging System

PRETEXT Number	Definition
I	One section is involved, and three adjoining sections are free
II	One or two sections are involved, but two adjoining sections are free
III	Two or three sections are involved, and no two adjoining sections are free
IV	All four sections are involved

PRETEXT, PRE-Treatment EXTent

From Roebuck DJ, et al, 2005: PRETEXT: a revised staging system for primary malignant liver tumours of childhood developed by the SIOPEL group. Pediatr Radiol 37:123-132. Copyright 2007, Springer Science + Business Media.

Table 82.4

PRETEXT Staging: Additional Criteria

C: Caudate lobe involvement	C1: Tumor involving the caudate lobe C0: All other patients All C1 patients are at least PRETEXT II
E: Extrahepatic abdominal disease	E0: No evidence of tumor spread in the abdomen (except M or N) E1: Direct extension of tumor into adjacent organs or diaphragm E2: Peritoneal nodules Add suffix "a" if ascites is present (e.g., E0a)
F: Tumor focality	F0: Patient with solitary tumor F1: Patient with ≥2 discrete tumors
H: Tumor rupture or intraperitoneal hemorrhage	H1: Imaging and clinical findings of intraperitoneal hemorrhage H0: All other patients
M: Distant metastases	M0: No metastases M1: Any metastasis (except E and N) Add suffix or suffixes to indicate location
N: Lymph node metastases	N0: No nodal metastases N1: Abdominal lymph node metastases only N2: Extraabdominal lymph node metastases ± abdominal lymph node metastases
P: Portal vein involvement	P0: No involvement of the portal vein or its left or right branches P1: Involvement of either the left or the right branch of the portal vein P2: Involvement of the main portal vein Add suffix "a" if intravascular tumor is present (e.g., P1a)
V: Involvement of the IVC and/or HVs	V0: No involvement of the HVs or IVC V1: Involvement of 1 HV but not the IVC V2: Involvement of 2 HVs but not the IVC V3: Involvement of all 3 HVs and/or the IVC Add suffix "a" if intravascular tumor is present (e.g., V3a)

IVC, inferior vena cava; HVs, hepatic veins

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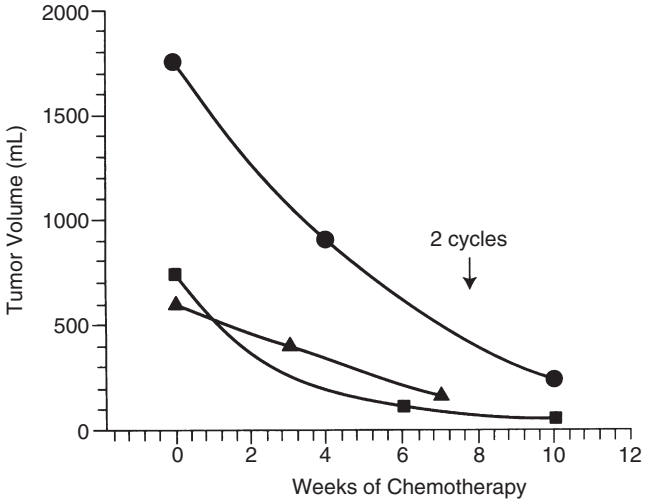


FIGURE 82.6. Tumor volumes of three hepatoblastoma patients are plotted versus time from initiation of chemotherapy. A significant reduction in tumor volume is apparent that is most rapid during the first two cycles of induction chemotherapy. *(Data from Medary I et al, 1996: Kinetics of primary tumor regression with chemotherapy: implications for the timing of surgery. Ann Surg Oncol 3:521-525.)*

the primary liver tumor, when imaging suggests that complete resection is feasible.

The first clinical decision is whether to initiate neoadjuvant chemotherapy or proceed with resection. Often, resection is not feasible if tumors are large and involve both hepatic lobes. Preoperative (neoadjuvant) chemotherapy results in tumor shrinkage and makes subsequent resection easier (Reynolds, 1995). In one study, the rate of shrinkage was high after initiation of chemotherapy, but it declined after two cycles had been administered (Fig. 82.6; Medary et al, 1996). Exquisite clinical judgment and good communication between members of the multidisciplinary team are crucial, because about 60% of hepatoblastomas are resectable at diagnosis.

To confirm the diagnosis, an initial biopsy is required. For unresectable tumors, the initial surgical procedure should include a diagnostic biopsy and placement of a vascular access device for chemotherapy. A second laparotomy is performed after four cycles of chemotherapy, if imaging studies show a good response, and the tumor appears resectable.

Complete resection of the primary tumor is necessary for survival and may require extended hepatic lobectomies or complex biliary reconstructions. For hepatoblastoma, reports have suggested that gross total resection of the primary lesion may be adequate for cure in chemoresponsive tumors (Dicken et al, 2004; Schnater et al, 2002).

For resected tumors (stage I) with fetal histology, further therapy is not recommended. All other stage I tumors without pure fetal histology, in addition to stage II patients, should receive four cycles of cisplatin, 5-fluorouracil (5-FU), and vincristine (C5V). Patients with stage III and IV disease should receive four cycles of chemotherapy, followed by resection or transplantation, followed by two more cycles of chemotherapy. C5V is administered, followed by doxorubicin if there is minimal response to C5V. Recent reports have suggested the use of doxorubicin from the start in this subgroup (Finegold et al, 2008; Malogolowkin et al, 2008). The combination of cisplatin plus doxorubicin was compared with cisplatin plus 5-FU plus C5V in a combined CCG/POG (intergroup) study (Ortega et al, 2000). The efficacy was thought to be similar, but more complications resulted with the regimen containing doxorubicin, accounting for equivalent event-free survivals; however, a more detailed review of the analysis suggested that the doxorubicin-containing arm had an improved disease-specific survival. This finding implied that with better management of toxicity, patient outcome might be better with a doxorubicin-containing regimen. In addition, a clinical trial that used a combination of cisplatin and carboplatin had to be terminated because of poor tumor response, suggesting that platinum-based monotherapy, as proposed by SIOPEL, was not as effective as combination chemotherapy. Clinical trials by the COG and SIOPEL are planned to evaluate the use of doxorubicin, irinotecan, and other agents, especially in high-risk patients.

In patients with unresectable primary tumors, the use of liver transplantation is increasing. A recent analysis stated an approximate 80% long-term disease-free survival in those receiving transplantation in large, solitary, or multifocal tumors invading all four sectors of the liver (Otte et al, 2005). The

United Network for Organ Sharing (UNOS) database consists of over 200 patients, with a median age of 2.9 years, who underwent orthotopic liver transplantation (OLT) for hepatoblastoma between 1987 and 2006. Approximately half of the patients had a recurrence. Overall survival was 80%, 69%, and 66% at 1, 5, and 10 years, respectively (Austin et al, 2006). In a recent multicenter review, 147 patients with hepatoblastoma were analyzed after liver transplantation. In almost three quarters of these patients, the original surgery was OLT; the remaining patients either had residual disease after prior resection or had recurrent tumor. The first group of patients had an improved outcome, with 82% overall disease-free survival, compared with 30% in the second group. Smaller, single-center reports have reinforced findings that liver transplantation for hepatoblastoma has the best outcome when done as the primary procedure rather than as a salvage (D'Alessandro et al, 2007; Otte et al, 2004; Pham et al, 2007; Reyes et al, 2000).

Transplantation, however, does require the use of immunosuppressive treatment, which comes along with its own set of side effects. Moreover, there is in increased chance of thrombosis of the hepatic artery after transplantation in children (Jain et al, 2006). The main causes of mortality after transplantation, accounting for 54% of this population, are metastases and recurrence (Austin et al, 2006). The COG is continuing to investigate the role of liver transplantation in hepatoblastoma. A global database has been instituted to aid in this endeavor.

In one study, the 1-year survival for patients presenting with metastases was no different from that in patients with localized tumors (Van Tornout et al, 1997). In another study by SIOPEL, the 5-year overall and event-free survival for children with hepatoblastoma who presented with pulmonary metastases were 57% and 28%, respectively (Perilongo et al, 2000). This study suggested that 25% to 30% of patients with synchronous pulmonary metastases are curable. It is still necessary to resect the primary liver tumor, and pulmonary metastasectomy should be done only if the primary site is controlled (Schnater et al, 2002). Many pulmonary metastases resolve with chemotherapy, but thoracotomy and resection are sometimes required for larger or persistent metastatic lesions (Passmore et al, 1995).

No current prospective studies are underway for pulmonary metastasectomy, but one recent study describes the advantage of pulmonary metastasectomy for diagnosed lesions that remain after neoadjuvant therapy (Meyers, 2007). Some radiation oncologists have treated pulmonary metastases with external-beam radiotherapy in an approach similar to that used for Wilms tumors, but with 18 to 20 Gy administered (Habrand et al, 1992); however, this may be associated with significant pulmonary toxicity and has not resulted in cure. There is no reported cure in patients with spread to sites outside of the lung or local lymph nodes.

Outcome

Following a gross total resection, the 5-year event-free survival is 83%, but this drops to 41% in patients with tumor remaining after surgery (Ortega et al, 2000). Some patients with microscopic residual tumor are curable with continued chemotherapy and may benefit from external-beam radiotherapy to the primary hepatic site. Resection of many hepatoblastomas may be easier after chemotherapy, and complete resection of the primary hepatic tumor is necessary for survival. In multivariate analysis, factors that have been independent predictors of worse prognosis include a high TNM stage, unresectable tumor, bilobar involvement and multifocality, AFP less than 100 ng/mL or greater than 10^5 ng/mL, distant metastases, embryonal versus fetal histology, and vascular invasion (von Schweinitz et al, 1997b). The COG has reported a 3-year event-free survival of 90%, 50%, and 20% for stage I to II, III, and IV, respectively (Malogolowkin et al, 2008).

Future Directions

Advances in hepatic anatomy have allowed more extensive resections so that even very large and bilobar tumors can be removed successfully. Segmental resection is also feasible and may allow resection of multifocal lesions.

The uses of various novel treatments are currently being investigated. First, transcatheter selective arterial chemoembolization, which involves the direct injection of chemotherapeutic agents to the tumor, hypothetically decreases systemic toxicity. The average decrease in tumor size was 84% in one study (Clouse et al, 1994), and unresectable hepatoblastomas may become resectable with this intervention (Berthold et al, 1986). Doxorubicin, cisplatin, and fluorodeoxyuridine have been promising, as these agents have a high hepatic extraction; case reports exist with striking results. For example, Yokomori and colleagues (1991) describe the total regression of a tumor in a 4-month-old infant with fetal hepatoblastoma treated for 1.5 years with 5-FU, vincristine, doxorubicin, and cisplatin. No recurrence was seen after 6 years of follow-up. Risks involved with this technique include infection, thrombosis, or shifting of the catheter. Furthermore, it is challenging to carry out in children, and prospective studies are needed. Other new approaches include treatment with anti-AFP antibodies, IL-2, and viral transfection vectors to attack malignant hepatic cells (Geiger, 1996; Huber & Richards, 1996; Ji & St, 1997; Ramani et al, 1997).

Hepatocellular Carcinoma (Hepatoma)

Epidemiology

HCC (see Chapter 80) accounts for 23% of pediatric liver tumors but is rare in infancy (Finegold, 1994). Approximately 1.4 cases per 1 million children exist in the United States (Ni et al, 1997). The LCSG (1987) reported no cases in children age 4 years or younger in a series of 2286 patients with histologically reviewed tumors. Historic series without pathologic review may report a higher rate of infantile HCC owing to misdiagnosis of some early hepatoblastomas (Exelby et al, 1975). We have had personal experience of infants with well-documented HCC, and it affects about 0.5 children younger than age 15 years per 1 million annually. SEER data indicate that HCC accounts for 87% of primary hepatic malignancies in the 15- to 19-year age group (Darbari et al, 2003). The incidence is bimodal, with an early peak that is lower than that of hepatoblastoma. Most of these early cases occur before 5 years of age. A second peak occurs between 13 and 15 years of age. The median age at presentation of fibrolamellar carcinoma, a variant of HCC, is 20 years, and it is rarely observed before age 10 years. HCC has a male predominance (1.3 to 3.2:1), and in areas endemic for hepatitis B, the male/female ratio may be reversed, at 0.2:1. Approximately 35 to 40 new HCCs are diagnosed per year in the pediatric age group in the United States. Incidence reported for the years 1973 through 1977 versus 1993 through 1997 showed a decrease from 0.45 to 0.29 cases per 1 million (Darbari et al, 2003).

Hepatitis B and C infection correlates with the incidence of HCC. In Asia, 85% of HCC patients, both adult and pediatric, are hepatitis B surface antigen positive, whereas this is found in only 10% to 25% of patients in the United States. The relative risk for the development of HCC is 250:1 for patients with chronic active hepatitis compared with patients without hepatitis surface antigen positivity (Brower et al, 1998). Hepatitis C antibodies are found in 20% of patients with HCC. In one report, an infant with a history of neonatal hepatitis developed HCC (Moore et al, 1997a). Other conditions associated with the development of HCC include cirrhosis, α_1-antitrypsin deficiency, tyrosinemia, aflatoxin ingestion, hemochromatosis, hepatic venous obstruction, androgen and estrogen exposure, Alagille syndrome (arteriohepatic dysplasia), and Thorotrast administration (Wegmann et al, 1996). One case of childhood HCC developing in a patient with neurofibromatosis has also been reported (Ettinger & Freeman, 1979).

A universal vaccination program against hepatitis B has reduced the incidence of HCC in Taiwan. The average annual incidence of HCC in children 6 to 14 years old declined from 0.70 per 100,000 children in the years 1981 through 1986 to 0.36 in the years 1990 through 1994 ($P < .01$) coincident with widespread administration of the hepatitis B vaccine (Chang et al, 1997). The mortality rate also decreased during this period. Antiviral therapy with lamivudine reduced the risk of development of HCC in patients with chronic hepatitis B infection and cirrhosis or fibrosis (Liaw et al, 2004). In contradistinction to HCC in adults, however, conditions associated with cirrhosis occur in only 30% to 40% of children with HCC; the remaining 60% to 70% of tumors are present without any cirrhosis (De Potter et al, 1987; Fattovich et al, 2004; Ismail et al, 2009; Llovet & Beaugrand, 2003; Marsh et al, 2004; Reynolds, 2001).

In one comparative study of pediatric HCC and hepatoblastoma, numerous discriminating features were reported (Chan et al, 2002). The mean age at presentation was 18 months for hepatoblastoma versus 10 years for HCC. The initial resectability of HCC was 45% and did not improve with chemotherapy, whereas 91% of hepatoblastomas could be completely resected before or after chemotherapy. Tumor rupture occurred in 36% of hepatoblastomas versus 9% of HCCs. Most importantly, the survival of patients with HCC was much worse.

Pathology (See Chapter 78)

HCCs are highly invasive and often multicentric at diagnosis with frequent hemorrhage and necrosis. Nuclear pleomorphism, nucleolar prominence, and the absence of extramedullary hematopoiesis are observed, and the cells are larger than normal hepatocytes. Low-grade HCCs may look similar to normal hepatocytes, especially if a limited amount of tissue is sampled. Invasiveness, and vascular invasion in particular, is a hallmark of these tumors. Extrahepatic dissemination to portal lymph nodes, lungs, and bones is frequent at diagnosis and strongly affects survival. HCCs naturally progress from capsular invasion to extracapsular extension, then vascular invasion, and finally to intrahepatic metastases (Toyosaka et al, 1996). A strong correlation has been found between intrahepatic metastases and portal vein thrombosis; this suggests that efferent tumor vessels anastomose to the portal, rather than the hepatic, veins, allowing intrahepatic spread and explaining the multicentricity that is a hallmark of HCC. Fibrolamellar HCC is a histologic variant seen in older children and young adults. It was once thought that this variant was associated with a better prognosis (Greenberg & Filler, 1989); however, studies indicate that when stage is controlled for, the survival is similar between standard HCC and its fibrolamellar variant.

Biology and Molecular Biology

Most investigations into the basic biology of HCC involve the study of hepatitis B and its relationship to carcinogenesis (Scaglioni et al, 1996). In one in vivo model in which rats developed HCC after prolonged feeding with glyceryl trinitrate, *KRAS* point mutations were identified in 8 of 18 animals that developed tumors (Tamano et al, 1996), and no *TP53* mutations were seen. Cytogenetic data indicate that chromosomal abnormalities are complex, but no consistent patterns have been established (Terris et al, 1997).

Clinical Findings

Children and adolescents with HCC are often seen initially with palpable abdominal masses (40%), but many are symptomatic at diagnosis (Ni et al, 1997). Pain is frequent (38%) and may occur in the absence of an obvious mass. Constitutional disturbances such as anorexia, malaise, nausea and vomiting, and significant weight loss occur with greater frequency. Jaundice is an uncommon feature of either disease, but AFP is elevated in approximately 85% of patients, with most levels greater than 1000 ng/mL (Brower et al, 1998). Although elevated, these levels are usually less than those measured in hepatoblastoma patients; 10% may come to medical attention with tumor rupture and a hemoperitoneum (Brower et al, 1998).

Staging

The staging schemes listed for hepatoblastoma also are used for HCC in childhood.

Treatment

In over a quarter century, no significant progress has been made in treatment of the pediatric population with HCC (Ismail et al, 2009). This tumor remains extremely resistant to current chemotherapy agents, and long-term survival is impossible without complete resection. Because of a high incidence of multifocality within the liver, extrahepatic extension to regional lymph nodes, vascular invasion, and distant metastases, complete resection is often impossible. Infiltration with thrombosis of portal and hepatic venous branches is common, and even the vena cava may be involved. Furthermore, the cirrhosis found in a number of HCC livers may preclude an extensive resection. Most analyses report a 10% to 20% resectability rate among children with HCC. In contrast, patients with a fibrolamellar histologic pattern have a higher resection rate and essentially do not have cirrhotic livers. Even with complete resection, however, the prognosis remains poor secondary to the high rate of recurrence.

Historically, the same chemotherapy protocols used for hepatoblastoma were also applied to HCCs in childhood; however, HCC is rather unresponsive to chemotherapy overall, although cisplatin in particular has shown activity against it (Bower et al, 1996). The utility of external-beam radiation therapy is unclear; it can aid with temporary control of gross disease, but it has not been shown to reduce the risk of relapse in patients with residual disease after resection. Because of the poor survival of patients with HCC, present thinking is to apply new and innovative approaches to these cancers.

Unresectable HCCs can be palliated with embolization with or without added chemotherapeutic agents or radioisotopes (Maini et al, 1996; see Chapter 83). Percutaneous intralesional injection of ethanol also has been of palliative benefit when lesions are small (Ryu et al, 1997; see Chapter 85A). Radiofrequency ablation (RFA) of these tumors, percutaneously or at laparoscopy/laparotomy, has been associated with tumor resolution and prolonged survival (Inamori et al, 2004; Koda et al, 2004; Raut et al, 2005; Santambrogio et al, 2003; see Chapter 85C). Lin and colleagues (2004) reported that radiofrequency ablation was superior to ethanol injection in HCCs 4 cm or less in diameter. Moreover, preliminary research using metronomic chemotherapy and adjuvant antiangiogenic treatments is currently underway (Gille et al, 2005; Meng et al, 2007; Meyers, 2007; Pang & Poon, 2006).

As standard therapies have proven unsuccessful, liver transplantation has been used more widely. The Milan criteria used for adults have been extrapolated to children. They stipulate a single tumor no larger than 5 cm in diameter, or up to three tumors each 3 cm or less in diameter, an absence of macroscopic portal vein invasions, and absence of extrahepatic disease; however, no current data support the efficacy of using the Milan criteria in this population. The UNOS database analyzed 41 patients with HCC who received OLT from 1987 through 2006. The overall survival was 86%, 63%, and 58% for 1, 5, and 10 years, respectively. Analogous to hepatoblastoma, mortality was mainly secondary to recurrence, which occurred even more often than it did in hepatoblastoma (86% vs. 54%) (Austin et al, 2006).

Outcome

The overall survival from HCC in childhood approaches zero, and it remains a therapeutic problem (Table 82.5). Occasionally, resection of localized lesions results in long-term survival. Results from the LCSG (1987) are consistent with these findings, showing a 1-year survival rate of 40% for resectable disease and 10% for unresectable lesions. The trend is to separate HCC from hepatoblastoma in clinical studies because of its greatly differing biologic behavior.

Future Directions

Gene therapy with viral vectors that attack dividing cells is being investigated. Hepatocytes rarely divide unless stimulated by liver resection. Viruses such as herpes attack dividing cells and can be molecularly manipulated to contain cytotoxic genes, and modified herpesvirus can be transfected efficiently into hepatoma cells (Carew et al, 1998; Tung et al, 1996). One group has used an adenovirus vector to deliver murine endostatin to tumors in nude mice injected with HCC cells with a resultant reduction in tumor growth (Li et al, 2004).

Rhabdomyosarcoma of the Extrahepatic Bile Ducts

Incidence

Although embryonal rhabdomyosarcoma of the extrahepatic bile ducts is extremely rare, it is the most frequently seen malignancy in the biliary tree of children (Martinez et al, 1982). Ten cases were reported in intergroup rhabdomyosarcoma studies I and II, constituting 0.8% of confirmed tumors in those studies (Ruymann et al, 1985). Fewer than 50 cases have been reported since 1975 (Zampieri et al, 2006).

Pathology

Most tumors are of the embryonal histopathologic subtype. They often show botryoid characteristics similar to other rhabdomyosarcomas that arise in a hollow viscus. Immunohistochemistry and nuclear staining are informative for diagnosis of embryonal rhabdomyosarcoma (Ali et al, 2009; Morotti et al, 2006). About 40% of patients develop distant metastases, but mortality is most often due to the effects of local invasion (Lack et al, 1981). Rhabdomyosarcoma of the liver and the ampulla of Vater, but not involving the bile ducts, also has been reported but is very rare (Horowitz et al, 1987; Perera et al, 2009).

Presentation

Patients range in age from 1 to 9 years at diagnosis, and this tumor is seen more frequently in males. The typical presentation includes intermittent jaundice and may include loss of

Table 82.5

Comparison of Resectability and Survival for Hepatoblastoma and Hepatocellular Carcinoma in Childhood

	HEPATOBLASTOMA		HEPATOCELLULAR CARCINOMA	
Reference	**Resectability (%)**	**Survival (%)**	**Resectability (%)**	**Survival (%)**
Exelby et al, 1975	60	35 overall; 60 in complete resection	34	13 overall; 35 in complete resection
Ehrlich et al, 1997	77	87	—	—
Stringer et al, 1995	90	67	—	—
Ni et al, 1997	—	—	9.8	10 at 1 years
Hata, 1990	—	42	—	—
Ortega et al, 1991	48	67	13	21
Douglass et al, 1993	77 (group III)	90% groups I and II; 67% group III	—	—
von Schweinitz et al, 1995b	89	73	—	—
Moore SW, et al, 1997	—	—	33	16.6 at 5 years
Weitman et al, 1997	—	0 progression-free survival at 2 years	—	—
Lee & Ko, 1998	—	47% at 5 years	—	17 at 5 years
Chan et al, 2002	91	—	45	—
Ho et al, 2004	—	55% at 3 years	—	0 at 3 years

appetite and episodes of cholangitis (Charcot's triad) (Perisic et al, 1991). Hepatomegaly and a palpable abdominal mass are usual (Lack et al, 1981; Nagaraj et al, 1977). The diagnosis may be confused with hepatitis with resultant delay in specific therapy, but rhabodmyosarcoma of the bile ducts can also be mistaken for a choledochal cyst (Sanz et al, 1997).

Imaging

Ultrasonography (US) shows a hilar or intrahepatic mass that may be confused with a choledochal cyst (Friedburg et al, 1984; Geoffray et al, 1987). Although CT or MRI may provide information about extension and metastases (Ng et al, 1997), they do not establish the diagnosis. Imaging may be more accurate for extrahepatic ductal involvement (Roebuck et al, 1998).

Treatment

Surgical exploration and biopsy are necessary to establish the diagnosis in most cases. Often a hilar lymph node provides diagnostic material, but carefully sampling the primary tumor may be necessary. A core needle biopsy or aspiration cytology may be adequate for diagnosis, and entry into the bile ducts should be avoided if possible. Intraoperative US (see Chapter 21) is helpful in identifying the course of biliary structures. Initial complete resection before chemotherapy may be difficult or impossible because of the extensive nature of these tumors. Also, microscopic submucosal extension is common, and resection margins are often microscopically positive despite the normal appearance of the intrahepatic bile ducts.

It is probably better to first establish the diagnosis with a biopsy and then begin systemic chemotherapy, which reduces the tumor size and allows a cleaner resection at second-look surgery. During the initial biopsy, hilar and left gastric lymph node sampling is performed to determine whether these nodal echelons require added radiotherapy. In the series reported from the intergroup rhabdomyosarcoma study, six of the 10 patients underwent initial resection, but all had microscopic or minimal gross disease left behind (Ruymann et al, 1985). The only four survivors were in this group; however, none of the four patients survived in whom resection was not attempted. In another report of three consecutive cases from a single institution, all patients presented with jaundice, cachexia, and abdominal mass (Martinez et al, 1982). The tumor arose in the common hepatic duct in two children and in the left hepatic duct in the third. The technical difficulty of prechemotherapy resection is illustrated by the fact that intrahepatic extension was noted in all, making complete resection impossible. Two of these patients are alive and disease-free at 9 months and 14 years, whereas the third died as a result of progressive disease at 33 months. All received radiotherapy in addition to multiagent chemotherapy. Jaundice was not a late problem.

The need for aggressive surgical resection of biliary rhabdomyosarcomas was challenged in a report by Spunt and colleagues (2000). They reported 25 patients with this diagnosis from intergroup rhabdomyosarcoma studies I through IV and noted that although only 29% of these patients underwent a gross total resection before or after multiagent chemotherapy, the overall 5-year survival rate was 78%. They concluded that surgery was important for diagnosis and staging but that it was not necessary for long-term survival with present chemotherapeutic agents. They also noted that the use of biliary drains in patients undergoing aggressive surgery was associated with a high rate of serious infections.

The surgical approach is a bile duct resection, and a Roux-en-Y jejunostomy is the favored reconstruction. Intraoperative cholangiography is recommended to ensure adequate bile drainage. The four of these 10 patients who survived were alive and free of disease free from 6 months to over 6 years from diagnosis.

Future Directions

Presently, the need for radiation, or even surgical resection, has been questioned. In the future, some of these patients may be treated by chemotherapy alone after establishment of the diagnosis. If a complete radiologic response is documented after neoadjuvant chemotherapy, no further intervention except observation may be needed, although this requires further study. Embryonal rhabdomyosarcoma of the extrahepatic bile ducts is rare, locally invasive, and requires multidisciplinary treatment. Initial biopsy followed by chemotherapy and resection at a second-look procedure is the standard course.

Embryonal Sarcoma

Incidence

Embryonal sarcoma, also known as *malignant mesenchymoma* or *undifferentiated sarcoma* in the older literature, is a rare primary hepatic neoplasm that occurs in older children. In one study, two cases were reported out of 1102 (0.2%) primary liver tumors analyzed (Flemming et al, 1995). The age at diagnosis ranges from 5 to 16 years (Newman et al, 1989; Vetter et al, 1989). Embryonal sarcoma constitutes 14% of malignant liver tumors occurring in children 6 to 10 years of age (Yedibela et al, 2000).

Pathology

Microscopically these tumors appear as a pleomorphic or undifferentiated sarcoma, and areas of the liver may be entrapped. Primitive mesenchymal cells with occasional small cysts and ducts lined with benign-appearing epithelium are sometimes present at the periphery (Gallivan et al, 1983). Some reports have suggested that embryonal sarcoma of the liver may represent malignant degeneration of a mesenchymal hamartoma (Begueret et al, 2001; O'Sullivan et al, 2001).

Clinical Presentation

A right upper quadrant abdominal mass and pain are significant presenting symptoms, and fever also may be prominent. Spontaneous rupture has been reported (Yedibela et al, 2000).

Imaging

Embryonal sarcoma often appears hypodense (dark) on CT and has a bright peripheral fibrous pseudocapsule, as shown in Figure 82.7. They can be very bulky tumors and sometimes are confused with cystic liver disease (Orozco et al, 1991; Tozzi et al, 1992). These tumors may have the appearance of a solitary liver cyst in childhood (Chowdhary et al, 2004) or may mimic a hydatid cyst (Aggarwal et al, 2001).

Treatment and Outcome

Embryonal sarcomas of the liver are treated with resection and adjuvant chemotherapy (Kadomatsu et al, 1992). Cisplatin, doxorubicin, cyclophosphamide, dacarbazine, actinomycin, and other agents have been used in combination with radiotherapy (Newman et al, 1989; Vetter et al, 1989). Complete



FIGURE 82.7. Computed tomographic image showing the radiologic characteristics of embryonal sarcoma (malignant mesenchymoma).

surgical resection should be attempted and usually requires a major hepatectomy for tumor clearance. Although past reports have cited a poor prognosis, we have seen long-term survival with a combination of modern multiagent chemotherapy and complete resection.

Leiomyosarcoma

Patients with human immunodeficiency virus (HIV) infection experience an increasing incidence of smooth muscle tumors (Norton et al, 1997; Ross et al, 1992). Leiomyosarcoma of the liver has been reported in more than 20 patients; the youngest was 9 years old. Adjuvant therapy is ineffective; these tumors must be resected for control. They tend to be low grade or have an indeterminate malignant potential. Supportive and antiretroviral therapy is given through the perioperative period. A case of HIV-associated leiomyosarcoma is shown in Figure 82.8.

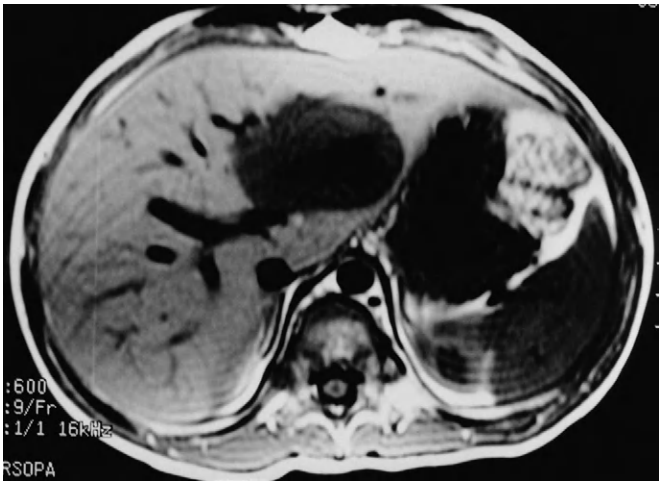


FIGURE 82.8. Leiomyosarcoma of the liver in a patient with acquired immunodeficiency syndrome (computed tomographic scan).

Primary Hepatic Rhabdoid Tumor

Incidence

Rhabdoid tumors are very rare, highly malignant, sarcoma-like neoplasms that usually involve the kidney or central nervous system (Vujanic et al, 1996). They can be primary in extrarenal sites, including extremity, paraspinal, and cervical soft tissues and the liver (Honda et al, 1996; Jimenez-Heffernan et al, 1998; Kelly et al, 1998). In a recent literature review of 19 cases of primary hepatic rhabdoid tumor, the median patient age was 16.7 months, and 89% of patients were younger than 2 years. The overall mortality rate was 89%, and the median time to death was 15.3 weeks (Yuri et al, 2004).

Pathology

Histopathologic examination shows a high-grade round-cell neoplasm with abundant cytoplasm and containing cells with cytoplasmic filamentous inclusions (White et al, 1999). The cells are frequently positive for vimentin and cytokeratins, and deletions at chromosome 22q11 are often seen (White et al, 1999).

Imaging

Rhabdoid tumors have no distinct radiologic features.

Clinical Presentation

The diagnosis may be suspected if widespread metastases, including central nervous system dissemination, are found with a hepatic mass. Cases with spontaneous rupture have been reported (Clairotte et al, 2006; Kelly et al, 1998; Ravindra, 2002; Yuri et al, 2004).

Treatment

These tumors are highly resistant to treatment. Disease confined to the liver should be resected if possible. Treatment with dose-intense, antisarcoma-type chemotherapy is also warranted.

Outcome

Although an initial period of control is feasible, these tumors are likely to recur and metastasize.

Angiosarcoma

Some authors describe angiosarcoma as the malignant form of hemangioendothelioma in children (Falk et al, 1981; Noronha & Gonzalez-Crussi, 1984). Arsenic exposure has been associated with malignant progression from hemangioendothelioma to hemangiosarcoma (Falk et al, 1981); however, no clear association has been reported between angiosarcoma and arsenic, Thorotrast, or vinyl chloride (Dimashkieh et al, 2004). Angiosarcoma is typically evidenced by a swiftly growing liver. Histologically, hypercellular whorls of spindled sarcoma cells are observed interspersed with bile ducts, blood vessels, and collagen. Intracellular periodic acid-Schiff–positive globules are present in most cases, and focal factor VIII staining may be seen.

Complete resection is required for cure of angiosarcoma, but recurrence rates are high, and the tumor is often not resectable; it is typically present in both lobes of the liver, and consideration should be given to adjuvant chemotherapy. Early metastasis, most commonly to the lung, is seen frequently (Awan et al, 1996; Falk et al, 1981; Kaufmann & Stout, 1961; Selby et al,

1992; Weinberg & Finegold, 1983). A recent review stated an average survival of 16 months (Dimashkieh et al, 2004). In one report of 10 cases of hepatic angiosarcoma in childhood, six patients were female, and four were male (Selby et al, 1992). The median age at diagnosis was 3.7 years (range, 1.5 to 7 years), with a mean follow-up of 10 months, and six of seven patients with follow-up died from disease.

Malignant Germ Cell Tumors

Primary malignant germ cell tumors of the liver are very rare and may present as teratomas, choriocarcinomas, or yolk sac tumors (Theegarten et al, 1998). In childhood, these may respond well to neoadjuvant chemotherapy followed by resection. Usually, a regimen containing cisplatin, ifosfamide, and bleomycin is employed.

Primary Hepatic Non-Hodgkin Lymphoma

Primary non-Hodgkin lymphoma of the liver occurs in childhood and may comprise 5% of primary hepatic malignancies in this age group (Gururangan et al, 1992). Burkitt lymphoma and other types of small-cell, noncleaved lymphoma have been reported (Huang et al, 1997; Mills, 1988). One or many lesions may be involved (Mantadakis et al, 2008). The primary treatment of lymphoma in childhood is chemotherapy, which usually results in complete resolution of the hepatic mass. Resection is rarely, if ever, indicated.

Hepatic Metastases

The liver is a relatively frequent site of metastatic disease in childhood. Non-Hodgkin lymphoma, neuroblastoma, rhabdomyosarcoma, rhabdoid tumors, Wilms tumor, desmoplastic small round-cell tumor, adrenal cortical carcinoma, osteogenic sarcomas, and a host of other malignancies may metastasize to the liver. Few data are available to determine the correct surgical approach to these lesions. Criteria for surgical removal of hepatic metastases include control of the primary site, a solitary or limited number of metastases, adequate hepatic reserve, good performance status, and a reasonable expectation of prolonged survival or cure. A helpful finding is some response of the metastatic lesions to adjuvant chemotherapy, and MRI is helpful in the diagnosis and evaluation of hepatic metastases.

We have had experience with 11 patients (age range, 4.3 to 21 years) who underwent hepatic metastasectomy. The overall survival in this group was 20%, but local hepatic control was greater than 85%. Advantages of hepatic metastasectomy include amelioration of liver function abnormalities, improvement of biliary obstruction, and possibly prolonged survival (Su et al, 2007).

Neuroblastoma

Hepatic metastases from neuroblastoma may be encountered in stage IV neuroblastoma and in newborns and infants with stage IV-S disease. In the latter situation, the liver involvement is a hallmark of the disease (Komuro et al, 1998). In stage IV-S, hepatic tumors generally resolve, although they may increase alarmingly in size before this happens. The increase in size usually causes pulmonary and vena caval impairment and may require relief by placement of an abdominal silo similar to that used for congenital abdominal wall defects. For stage IV disease, it may be advantageous for patients to undergo hepatic metastasectomy, which may aid in diminution of treatment or prolonged survival (Su et al, 2007). One patient with neuroblastoma and hepatic metastasectomy had disease-free survival with a follow-up time of 59 months (Su et al, 2007).

Wilms Tumor

Wilms tumor metastasizes to the liver in about 12% of patients (Cohen & Siddiqui, 1982), and this usually is associated with unfavorable histology (Breslow et al, 1986; Thomas et al, 1991). Resection of localized residual disease may be beneficial in well-selected cases. In one report, 15 cases of metastatic Wilms tumor with hepatic metastasectomy were analyzed and showed a 2-year survival of 62% and a 5-year survival of 44% (Foster, 1978). In one report, four patients with Wilms tumors metastatic to the liver underwent hepatic resection with a 2-year survival of 80%, and two patients survived 14 and 17 years, respectively (Morrow et al, 1982). This experience is also noted in other reports of Wilms tumor (Hagiwara et al, 1982). Experience with three patients, however, did not show survival greater than 9 months (Su et al, 2007).

Osteogenic Sarcoma

Calcified hepatic metastases sometimes may be observed in patients with osteogenic sarcoma (Shapiro et al, 1988). Although pulmonary metastasectomy for this disease is well described (La Quaglia, 1993; Saltzman et al, 1993; Torre et al, 2004), the role for hepatic metastasectomy has not been clarified. We reported a case of a child with osteogenic sarcoma with isolated liver metastases resected by a formal right lobectomy. This patient remained without disease for 2 years afterward and then developed recurrence in a limb, which required amputation. Hepatic metastases returned 46 months after this, and the patient died thereafter (Su et al, 2007).

Desmoplastic Small Round-Cell Tumor

Hepatic involvement with desmoplastic small round-cell tumor is frequent and is usually associated with a fatal outcome (Kushner et al, 1996; Mazuryk et al, 1998; Ordonez, 1998). The pattern of metastases is diffuse, leaving no spared segments that would allow resection, and complete resection is associated with a significant survival advantage in this disease (Schwarz et al, 1998). Future strategies include chemoembolization and arterial infusion therapy. Hepatic radiation to a level of 3000 cGy is ineffective.

Rhabdomyosarcoma

The liver follows regional lung, lymph nodes, and bone as a site of rhabdomyosarcoma metastases (Shimada et al, 1987). Resection of liver metastases is usually not feasible because of diffuse hepatic involvement and the presence of metastases in other sites.

Colon Cancer

Colon cancer can occur in childhood (La Quaglia et al, 1992). About 50% of these patients have signet ring tumors. The pattern of spread is over peritoneal surfaces, rather than through

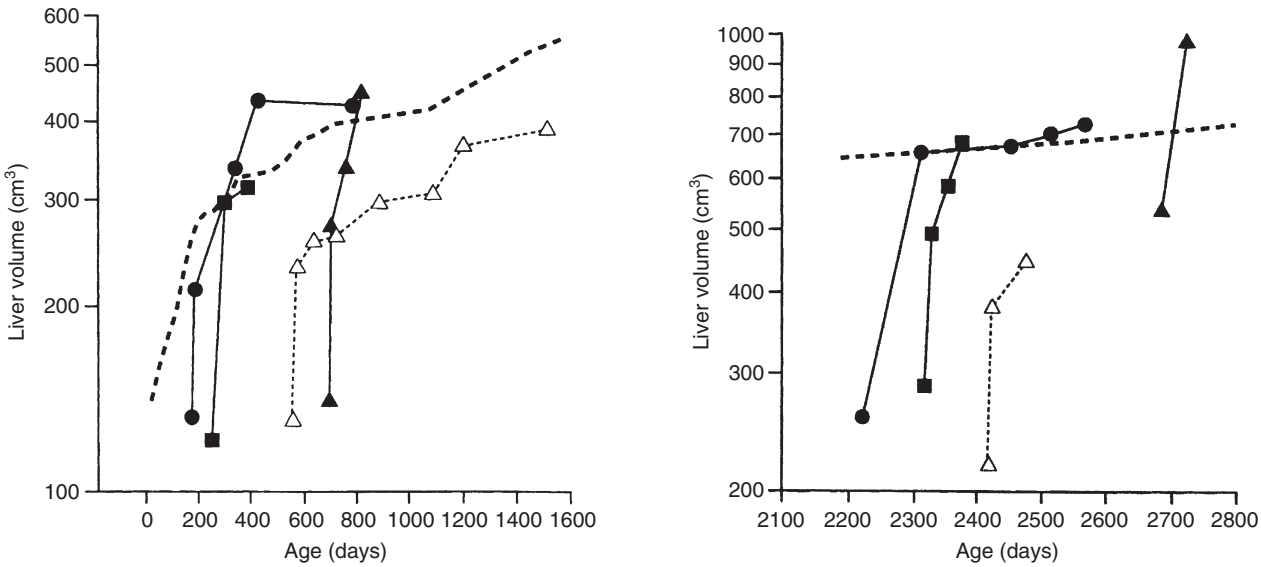


FIGURE 82.9. Graphs show the rapid recovery of hepatic volume to normal levels for age after major resections in childhood. The graphs show regeneration in two different age groups. *(Data from Wheatley JM, et al, 1996: Liver regeneration in children after major hepatectomy for malignancy: evaluation using a computer-aided technique of volume measurement. J Surg Res 61:183-189.)*

the portal system, and hepatic metastases usually occur late despite massive peritoneal disease.

Malignant Peripheral Nerve Cell Tumor

Malignant peripheral nerve cell tumors are likely to metastasize to the liver in childhood and adolescence. The pattern of metastases is usually miliary, and the tumors do not respond well to chemotherapy (Probst-Cousin et al, 1997).

Adrenocortical Carcinoma

Adrenocortical carcinoma also may metastasize to the liver, although concomitant pulmonary and retroperitoneal metastases are usually also present (Arico et al, 1992). Treatment is usually with platinum-based chemotherapy, and surgery is rarely done.

Rhabdoid Tumor

Rhabdoid tumor most commonly originates from the kidney and can metastasize to liver (White et al, 1999). It also may be primary to the liver, but this is rare. The pattern for hepatic metastases is usually diffuse and is not amenable to surgical resection. Chemotherapy protocols suitable for sarcoma are usually used (Vujanic et al, 1996).

Hepatic Evaluation and Resection

Surgical Anatomy

The schema of hepatic anatomy most useful for the surgeon is based on the work of Couinaud; this is described in other chapters (see Chapter 1). The principles of hepatic resection in small children and infants are the same as those for adults (see Chapters 90A through 90F).

Hepatic Regeneration

The liver in a child is able to regenerate quickly, even after massive resection (see Chapter 5) and administration of systemic chemotherapy (Shamberger et al, 1996; Wheatley et al, 1996). In most patients, recovery to the normal volume for age is rapid (Fig. 82.9).

EVALUATION OF A CHILD WITH A HEPATIC MASS

Patients presenting with a suspected hepatic mass first undergo a thorough history and physical examination. Blood work should include a complete blood count, liver function tests, coagulation studies, and tumor markers that should include serum AFP and β-hCG. Doppler US is done to determine whether a mass is cystic or solid, determine the patency of the portal and hepatic veins and vena cava, and identify satellite lesions. At present, MRI provides the greatest amount of information concerning the lesion and surrounding veins and bile ducts, and CT portography has been shown to give anatomic information equal to MRI. If a malignant tumor is suspected, thoracic CT is done to identify metastases. A tissue diagnosis is mandatory if malignancy is suspected after the workup. Percutaneous needle core or aspiration biopsy is useful for hepatoblastomas but may not be definitive in the case of HCC; open or laparoscopic biopsy is acceptable if necessary. Before exploration, the surgeon must do a thorough diagnostic workup to determine resectability. Often a team approach with a pediatric surgeon and an experienced hepatobiliary surgeon is helpful.

BENIGN HEPATIC TUMORS

Benign hepatic tumors (see Chapter 79A) accounted for less than 35% of 1250 pediatric liver tumors in one study (Finegold, 1994). Benign tumors of the liver that occur in childhood

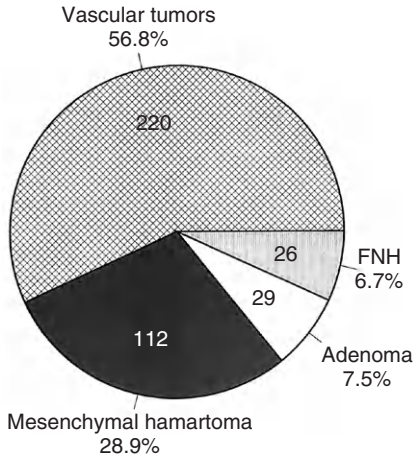


FIGURE 82.10. The frequency distribution of benign hepatic tumors in childhood (Exelby et al, 1975; Weinberg & Finegold, 1983). This graph is based on surgical or pathologic series of patients. With modern imaging techniques, the frequency of asymptomatic vascular tumors discovered incidentally is undoubtedly much higher (Flemming et al, 1995). FNH, focal nodular hyperplasia.

include hemangiomata or vascular malformations, hepatocytic adenomas, focal nodular hyperplasia, mesenchymal hamartomas, and various types of cysts and cystic disease. The distribution of common benign hepatic tumors of childhood is illustrated in Figure 82.10.

Hemangiomata and Vascular Malformations

Hemangiomata are lesions characterized by endothelial-lined vascular spaces that vary in size and extent (Ehren et al, 1983; Ishak, 1976). They are sometimes classified as hamartomas and are the most common skin lesions observed in childhood. Hemangioendotheliomas are highly proliferative cellular lesions of variable malignant potential. In contrast, venous malformations and cavernous hemangiomata are distinguished by a lack of cellularity and large vascular spaces. Arteriovenous malformations are the rarest pathologic subtype and are distinguished by abnormal anastomoses between arteries and veins. Venous malformations, cavernous hemangiomata, and arteriovenous malformations may be associated with significant shunting that results in congestive heart failure.

Incidence

The overall incidence of endothelial-lined vascular tumors of the liver in childhood is probably unknown, because many are asymptomatic. Vascular lesions taken together represent 13% to 18% of symptomatic hepatic tumors in childhood (Exelby et al, 1975; Finegold, 1994). Hepatic hemangiomata are more common in girls by 2:1 (Mulliken, 1988).

Presentation and Diagnosis

An abdominal mass is probably the most frequent sign of a vascular tumor of the liver. Multiple hemispheric, cutaneous hemangiomata may be present and warn the physician of possible visceral lesions. A systolic bruit sometimes can be heard over the enlarged liver. Infants with large, actively perfused vascular lesions may come to medical attention with congestive heart failure. Rarely, jaundice, disseminated intravascular coagulation (DIC), or hemorrhagic shock from intraperitoneal rupture may be present, and rupture can be precipitated by percutaneous needle biopsy (Hobbs, 1990).

Imaging studies are usually all that is required to confirm the diagnosis. Tumor extent and tissue characterization are assessed using MRI with standard spin echo T1-weighted and T2-weighted imaging (Powers et al, 1994). Intravenous administration of gadopentetate dimeglumine (gadolinium) can produce greater resolution. Vascular lesions can be seen as intensely white on T2-weighted images, and this study is often accurate enough to be definitive. Contrast-enhanced CT scan will demonstrate a focus with decreased density, with contrast enhancement from the edges toward the middle of the tumor, which will then be homogeneously enhanced (Meyers et al, 2007). Arteriography is rarely indicated given the detail and accuracy of modern imaging techniques, and open biopsy can result in massive hemorrhage.

Treatment

Asymptomatic lesions do not require treatment, and many hepatic hemangiomata regress after the first year of life. Patients with congestive heart failure are admitted to the intensive care unit and treated with digitalis and furosemide. If the heart failure remains refractory to these maneuvers, hepatic artery embolization or direct surgical ligation may be necessary (de Lorimier et al, 1967; Herlin et al, 1988). Hepatic arterial embolization may be successful in controlling symptoms, but rapid development of collateral vessels can make subsequent resection or embolization difficult. Transfusion of blood and platelets may be required for DIC. Interferon-alfa therapy for symptomatic angiomatosis and hemangioendothelioma is being used with success in individual patients (Le Luyer et al, 2000).

Patients who are seen in hemorrhagic shock with rupture of a vascular tumor usually require hepatic resection; however, initial hepatic arterial embolization may control bleeding temporarily and may allow stabilization and safer surgery (Takvorian et al, 1988). Hepatic resection may also be required in some patients in association with congestive heart failure. Blood loss in these complicated procedures may be reduced using hemodilution techniques (Kitahara et al, 1995; Schaller et al, 1984).

Outcome

The overall prognosis for benign hepatic vascular lesions is good. Most patients do not require operative intervention, and most cellular lesions start to regress after the first year of life. Angiosarcomatous degeneration of benign hemangioendotheliomas has been reported in five patients from one institution (Weinberg & Finegold, 1983). Three of the five were treated with radiotherapy to the benign hemangioendotheliomas before the development of angiosarcoma. This and other reports from the literature have correlated radiotherapy of benign vascular tumors with subsequent malignant degeneration, usually to angiosarcoma (Costello & Seywright, 1990).

Hemangioendothelioma

The incidence of hemangioendothelioma is 1%, and it is the most prevalent hepatic vascular tumor in pediatric patients younger than 6 months (Sari et al, 2006). In one report of 16 infants and children with hemangioendothelioma, 15 were seen

initially with hepatomegaly, 7 with congestive heart failure, and 4 with associated cutaneous lesions (Holcomb et al, 1988). Kasabach-Merrit syndrome, a platelet-trapping coagulopathy, also has been observed (von Schweinitz et al, 1995c). These lesions may appear very cellular, but they do not metastasize. If a primary lesion produces symptoms, resection is indicated for relief.

Hemangioblastoma

Hemangioblastoma of the liver usually is associated with von Hippel-Lindau disease (Rojiani et al, 1991). In infancy and childhood, these lesions appear very cellular, but distant metastases are uncommon. Complete resection should be performed and is usually curative. Hemangioblastomas of the central nervous system and retina have been treated with interferon alfa-2a, but without striking resolution, although two retinal lesions showed shrinkage (Niemela et al, 2001).

Mesenchymal Hamartoma

Mesenchymal hamartomas are usually solitary hepatic masses occurring in infants. They are usually multicystic, and the cysts are lined with flattened biliary epithelium or endothelium. Actively growing mesenchyme is abundant, associated with distended lymphatics. It is postulated that mesenchymal hamartomas arise in areas of focal intrahepatic biliary atresia; this results in distal bile duct obstruction and hepatocellular necrosis (Cooper et al, 1989). Others have hypothesized that these lesions arise in conjunction with anomalies of vascular development. This explains the occurrence of small hemangiomata observed in close proximity to mesenchymal hamartomas (Srouji et al, 1978). Cytogenetic analysis has only rarely been performed on these tumors, but a consistent 19q13.4 breakpoint has been identified (Mascarello & Krous, 1992).

Epidemiology

Mesenchymal hamartomas account for 6% of primary liver tumors in childhood, and a male predominance is reported. In one study, four of 134 patients with space-occupying liver lesions had mesenchymal hamartomas (Yen et al, 2003). Two thirds of these tumors are diagnosed in infants younger than 1 year, although presentation in the teenage years has been described. In one study of 18 such tumors, the mean age at diagnosis was 16 months (DeMaioribus et al, 1990).

Presentation and Diagnosis

Most mesenchymal hamartomas are seen as an enlarging abdominal mass or hepatomegaly and are usually not otherwise symptomatic (Srouji et al, 1978), but they can grow to great size and may cause respiratory distress or evidence of caval obstruction. Mesenchymal hamartomas are typically found within the right lobe of the liver, and US, CT, and MRI are the most useful diagnostic studies, although an open biopsy is often necessary to make the diagnosis. Figure 82.11 shows an MRI of a huge mesenchymal hamartoma. Giant hepatic cysts in fetuses also have been diagnosed on ultrasound (Tsao et al, 2002).

Treatment

Anatomic resection (hepatic lobectomy) is effective treatment, especially for large lesions. Because of the mesenchymal component, these lesions have a definite capsule that facilitates enucleation of large, central mesenchymal hamartomas not amenable to lobectomy. Enucleation was done in the case illustrated in Figure 82.11. Occasionally, it is necessary to marsupialize a large cystic lesion, but only if it is not feasible to remove this lesion completely. This approach may not be successful (Meinders et al, 1998). One report using sequential CT scans documented initial expansion followed by involution of a mesenchymal hamartoma (Barnhart et al, 1997). Because many reports exist describing spontaneous regression, the role of surgery is being contested in the asymptomatic patient (Meyers, 2007; Leary et al, 1989). It has been postulated that in utero decompression of giant hepatic cysts would improve the outcome in these patients (Tsao et al, 2002).

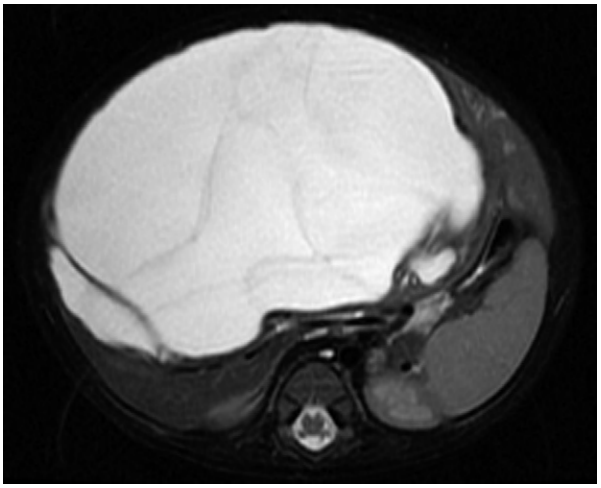


FIGURE 82.11. T2-weighted magnetic resonance image of a massive mesenchymal hamartoma.

Outcome

Patients with mesenchymal hamartomas do well with all forms of therapy. In one study of 18 patients, 13 who were available for follow-up were alive and well 1 month to 24 years after treatment (mean, 5 years; DeMaioribus et al, 1990).

Focal Nodular Hyperplasia and Hepatocellular Adenoma

Focal nodular hyperplasia (FNH) and hepatocytic adenomas are benign hepatocellular proliferations that are more common in adults than in children (see Chapter 79A). Hepatic adenomas are expected with type I glycogen storage disease after the first decade of life and may be multiple (Saito et al, 1984). FNH has also been described in a patient with type I glycogen storage disease (Sakatoku et al, 1996). Hepatic adenomas also have grown in patients undergoing androgen therapy for hematologic disorders, after danazol use, and in woman on oral contraceptives (Fermand et al, 1990). Both tumors have been correlated with a high-estrogen environment (Sakatoku et al, 1996). One report in the literature is of FNH developing in children treated for other solid malignancies (Bouyn et al, 2003). These authors postulated that a vascular injury secondary to chemotherapy or radiation was the causal factor.

FNH is distinguished from adenoma by the presence of fibrous septa that contain bile ducts and an inflammatory

infiltrate. In one report, five of 39 unresected hepatic adenomas developed HCC (Foster & Berman, 1994).

Epidemiology

Less than 2% of hepatic tumors in childhood are FNH or hepatocellular adenomas (Weinberg & Finegold, 1983). Both lesions have been described in infants and teenagers. Most patients are younger than 5 years at presentation and predominantly female (Nagorney, 1995). An association with contraceptive use has been found in adults, but no defined association between exogenous hormone administration in childhood and adolescence has been reported, although FNH has been reported in an infant antenatally exposed to corticosteroids (Prasad et al, 1995). In one report of 48 benign liver tumors in childhood, there were three cases (6%) of FNH and two cases of hepatocellular adenoma (4%) (Ehren et al, 1983).

Presentation and Diagnosis

Patients with hepatocellular adenomas usually come to medical attention with an asymptomatic abdominal mass; they are more likely to be symptomatic and may present with rupture and resultant hemorrhage, causing an acute abdomen. Both FNH and adenoma are well encapsulated on imaging studies. Because FNH is associated with fibrous septa, abdominal US and CT may show a distinctive central "scar." Hepatic adenomas may show encapsulation on imaging studies, but histologic sections may be difficult to distinguish from HCC. In childhood, these tumors may attain great size, contributing to symptoms. In one report of six cases in childhood, the average tumor size was 7.5 cm (range, 2.5 to 10 cm) (Lack & Ornvold, 1986). The tumor was localized to the right lobe in four of the six and was bilobar in the remaining two. Superparamagnetic oxide-enhanced MRI may discriminate between hepatic adenoma and FNH (Beets-Tan et al, 1998).

Treatment

It is best to remove adenomas because of the difficulty of differentiating them from low-grade HCCs, uncertainty about future malignant degeneration, and the possibility of rupture and hemorrhage (Westaby et al, 1983). Resection also results in relief of preoperative symptoms (Hutton et al, 1993). An anatomic liver resection usually is required, and we have employed extended left hepatectomy successfully in children to treat this lesion (Glick et al, 2000). Laparoscopic resection of these lesions has also has been done (Marks et al, 1998; Samama et al, 1998), and percutaneous RFA has recently become an option for treatment (Rocourt et al, 2006). Embolization of unresectable lesions is another alternative, if the masses are large or symptomatic. Unresectable and asymptomatic cases of FNH are observed using serial abdominal US, MRI, and clinical examination. Spontaneous regression has been documented, and patients with symptoms are typically treated with either surgical resection or ablation (Meyers, 2007).

Outcome

Most patients do well after hepatic resection, and in general, anatomic resection provides the best result. In one study of six patients with FNH and two with an adenoma, six were long-term survivors (Lack & Ornvold, 1986). Three patients with FNH were alive 4 to 17 years after hepatic lobectomy, and two other patients were followed with observation alone and were alive and well 13 and 15 years later. The one death in this group was from leukemia with an incidental finding of FNH. One of the two patients with an adenoma survived for 10.5 years after lobectomy, whereas the second died as a result of postoperative hemorrhage.

Cysts and Cystic Disease (See Chapter 69)

Multiple cases of solitary, congenital, nonparasitic liver cysts in childhood have been reported (Hernandez-Siverio et al, 1988; Pul & Pul, 1995). They are extremely rare but have been increasingly noted as incidental findings on US and CT performed for other reasons. Cysts are simple and not multilocular, they often have a bluish appearance at laparotomy, and the wall usually has three layers. The lining is generally cuboidal or columnar, although mucinous or squamous epithelium is reported. The middle layer comprises vascular elements, and the outer layer comprises compressed hepatocytes, collagen, muscle fibers, and bile ducts (Jones, 1994). The central contents are straw-colored and clear and are not under high pressure, as is the case with parasitic cysts. Most of these cysts are located in the right, anteroinferior hepatic lobe (segment V), and occasionally they are pedunculated.

Most solitary cysts are asymptomatic and do not require therapy. Older patients sometimes complain of abdominal pain or sensations of fullness. Rarely, a large cyst ruptures; torsion of a pedunculated cyst has been reported, and 9% of solitary cysts may be associated with extrahepatic biliary obstruction and jaundice secondary to external bile duct compression by the cyst. These cysts do not affect longevity, although malignant degeneration has not been reported. This must be considered when planning therapy. Solitary, asymptomatic cysts do not require therapy. If the cyst is symptomatic or doubt persists about the diagnosis, simple percutaneous aspiration usually is followed by recurrence, but aspiration followed by ethanol injection (sclerotherapy) may also be an effective treatment. More commonly, operative intervention is required.

Preoperative MRI or Doppler US is necessary to determine proximity to the portal and hepatic veins. Cysts that are neither adherent nor in proximity to these vascular structures are excised. Hepatic lobectomy may be necessary for symptomatic cysts that adhere to major veins, and marsupialization is sometimes a viable alternative. Injection of contrast media into the cyst can rule out a rare communication with the biliary tract. Cysts discovered incidentally at laparotomy should be left alone when less than 5 cm in diameter, but aspiration of cysts that are between 5 cm and 10 cm in diameter should be performed to confirm the diagnosis. Aspiration is followed by excision of the cyst wall. For large cysts—especially if there has been previous inflammation, or the cyst wall is near major venous or biliary branches—an anatomic liver resection is indicated (Iwatsuki et al, 1990). This resection avoids unnecessary bleeding and risk of postoperative biliary fistula.

Adult-type polycystic disease involving the liver has been reported with right lobar replacement and sparing of the left hepatic lobe (Marcellini et al, 1986); this was effectively treated by right hepatic lobectomy. Embryonal sarcoma of the liver sometimes can be confused with a solitary cyst (Chowdhary et al, 2004), and percutaneous needle aspiration and biopsy may be required to establish the diagnosis.

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CHAPTER 83

Hepatic artery embolization and chemoembolization of liver tumors

Chang Jin Yoon and Jin Wook Chung

OVERVIEW

Primary and secondary liver tumors cause tremendous neoplastic morbidity and mortality. Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third most common cause of cancer-related death in the world (Bosch et al, 2005). The highest incidences of HCC are found in Eastern Asia and sub-Saharan Africa, where hepatitis B is endemic; however, the incidence of HCC has been increasing steadily in the United States and Western Europe, largely owing to increased prevalence of viral hepatitis C in the past 2 decades (El-Serag et al, 2003). The majority of metastatic cancers involve the liver at some point as disease progresses. Despite the presence of extrahepatic spread, many patients with liver involvement die as a consequence of local tumor growth and hepatic parenchymal destruction.

Although surgery remains the best treatment in patients with most primary and secondary liver tumors, less than one third of patients are candidates for surgery when the diseases are initially found. This may be due to the extent or distribution of disease, underlying liver function, or general condition of the patient. Therefore, in the absence of effective systemic therapy, much effort has been put into developing and testing liver-directed therapies for local tumor control. Hepatic artery embolotherapy (HAE) has been outstanding among these methods as the most commonly used procedure to palliate symptoms and prolong survival.

BASIC PRINCIPLES OF HEPATIC ARTERIAL EMBOLOTHERAPY

Blood Supply of Liver Tumors

The basic physiologic principle that makes HAE feasible in patients with liver tumors is the dual blood supply to the liver (see Chapter 1B). The portal vein provides more than 75% of the blood flow to the normal hepatic parenchyma and is the primary trophic blood supply. Conversely, most of the blood supply (90% to 100%) to liver tumors comes from the hepatic artery (Breedis & Young, 1954), thus embolization of tumor-feeding arteries leads to selective ischemic damage of the tumor, while sparing the normal liver parenchyma, mainly supplied by the portal vein. Moreover, the pharmacokinetic advantage of locoregional drug administration enhances the theoretic benefit. For example, hepatic drug exposure has been estimated to be double for doxorubicin, 7 times greater for cisplatin, 8 times greater for mitomycin, 10 times greater for 5-fluorouracil, and up to 400 times higher for 5-fluorodeoxyuridine, when these were given through the hepatic artery rather than through the systemic veins (Ensminger & Gyves, 1983; see Chapter 86).

Hepatocarcinogenesis is a multistep process that causes gradual arterialization in blood supply to tumors (Pang & Poon, 2006), therefore the blood supply of liver tumors can be variable, according to the carcinogenetic stage of the tumors. For example, encapsulated nodular HCC is almost exclusively supplied by the hepatic artery, and well-differentiated HCC and the extracapsular infiltrating edge of advanced HCC can be supplied by the portal vein or both the portal vein and the hepatic artery (Goseki et al, 1995). Similar observations have been made in metastatic liver tumors; in its early stage, less than 200 μm is supplied almost exclusively by sinusoidal blood. As the tumor grows, its blood supply becomes progressively arterialized, but even in the advanced stage, most liver metastases still have a distinct portal blood supply (Strohmeyer et al, 1987); therefore early stage tumors and some fraction of advanced tumors may be resistant to hepatic arterial embolotherapy.

Chemoembolization

In the past 3 decades, many papers have been published describing a myriad different techniques for performing HAE; combined with intraarterial chemotherapy (chemoembolization), HAE has been paramount among them as the most

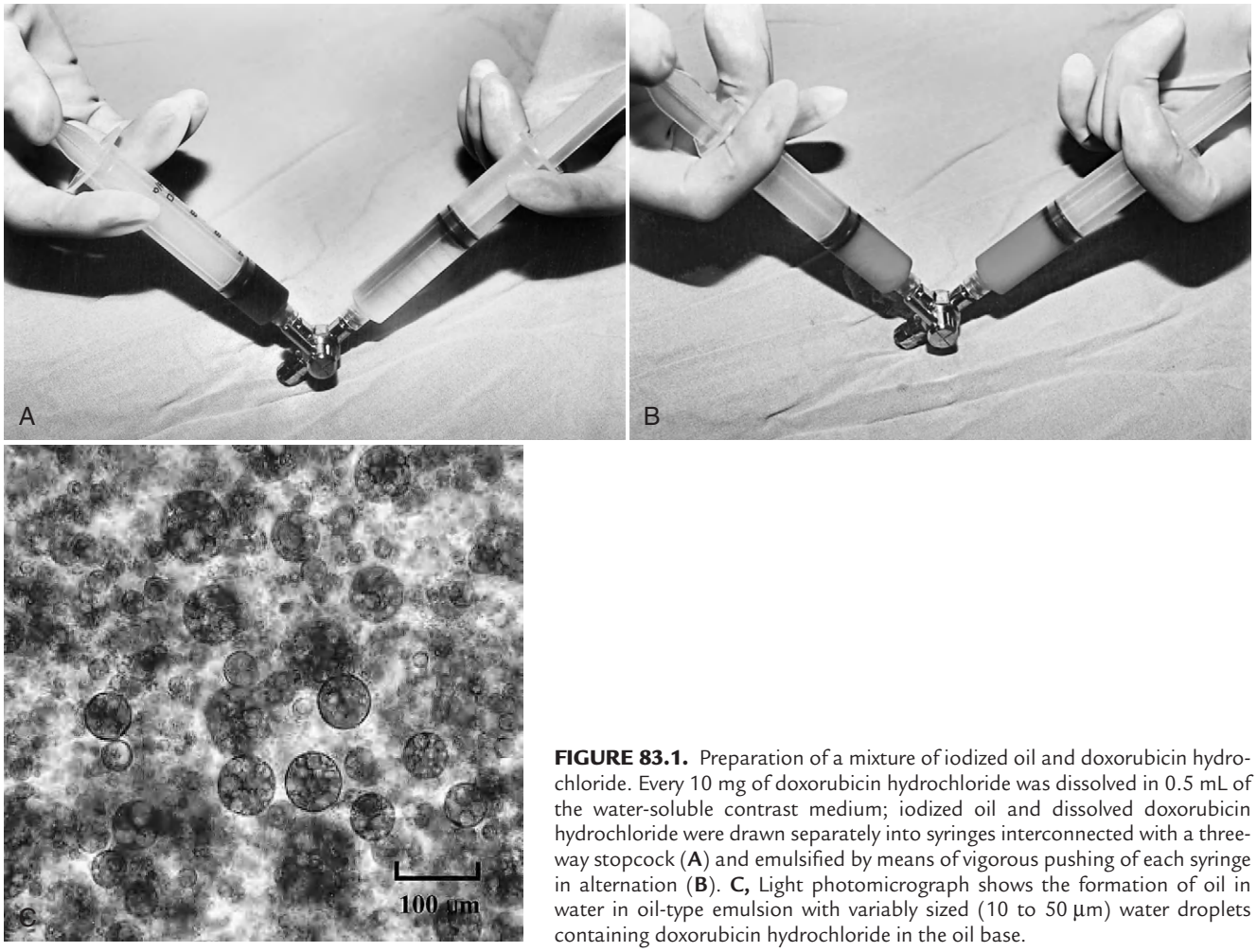


FIGURE 83.1. Preparation of a mixture of iodized oil and doxorubicin hydrochloride. Every 10 mg of doxorubicin hydrochloride was dissolved in 0.5 mL of the water-soluble contrast medium; iodized oil and dissolved doxorubicin hydrochloride were drawn separately into syringes interconnected with a three-way stopcock (**A**) and emulsified by means of vigorous pushing of each syringe in alternation (**B**). **C,** Light photomicrograph shows the formation of oil in water in oil-type emulsion with variably sized (10 to 50 μm) water droplets containing doxorubicin hydrochloride in the oil base.

widely used procedure. The goal of chemoembolization is to combine the effects of targeted tumor ischemia by embolization with intraarterial chemotherapy. To date, the most common sole-agent chemotherapeutic drug has been doxorubicin, followed by cisplatin, epirubicin, mitoxantrone, mitomycin C, and a chemical conjugate of a synthetic copolymer of styrene maleic acid and neocarcinostatin (SMANCS) (Marelli et al, 2007). The chemotherapeutic drug is dissolved in water or water-soluble contrast agent and is then mixed with iodized oil (Lipiodol; Laboratoire Guerbet, France) and administered as an emulsion (Fig. 83.1). When injected into the hepatic artery, iodized oil is trapped selectively in the tumor because of the hemodynamic difference between the tumor and normal liver parenchyma and presumably the absence of Kupffer cells in the tumor (Kan et al, 1993; Nakajo et al, 1988). Thus mixing iodized oil with a chemotherapeutic drug allows slow release of the chemotherapeutic drug over a period of 6 to 12 weeks (Raoul et al, 1992). In contrast, in the normal liver parenchyma, the iodized oil does not occlude the hepatic artery; rather it accumulates in the peripheral portal vein through arterioportal communications and subsequently passes through sinusoids into the systemic circulation (Chung et al, 1993). HAE after infusion of chemotherapeutic drugs increases drug dwelling time in the tumor by slowing the rate of efflux from the hepatic circulation. Furthermore, ischemic damage by embolization potentiates absorption of chemotherapeutic drugs by impeding the function of transmembrane pumps in tumor cells (Yu & Keeffe, 2003).

After infusion of the chemotherapeutic drug and iodized oil mixture, tumor-feeding peripheral hepatic arteries are embolized. Proximal arterial occlusion is not desirable, because it will not only induce development of intrahepatic and extrahepatic collateral vessels, it will also preclude repeat procedure. Thus it is important to select embolic materials of the proper size. The optimal size should be small enough to reach and occlude the capillaries to the tumor but bigger than the arteriovenous shunt and peribiliary plexus, to avoid the risk of pulmonary embolization and bile duct necrosis. To date, gelatin sponge particles have been the most frequently used agent, but polyvinyl alcohol (PVA) particle (Ramsey et al, 2002), absolute ethanol (Matsui et al, 1993), starch microspheres (Maluccio et al, 2008), cyanoacrylate (Berghammer et al, 1998), and even autologous blood clot (Gunji et al, 2002) have also been used.

Gelfoam is used as 500- to 1000-μm cubes, which only occludes the artery temporarily, with recanalization taking place within 2 weeks (Coldwell et al, 1994). It was proved not to cause serious hepatic damage in patients with good hepatic functional reserve (Kan et al, 1993; Sonomura et al, 1997);

however, gelfoam powder should not be used, as it may cause biliary stenosis and biloma resulting from embolization and necrosis of small arteriolar branches, which may cause biliary damage (Makuuchi et al, 1985). PVA particles cause a permanent or semipermanent arterial occlusion and can achieve more distal obstruction because of their smaller size (50 to 250 μm in diameter; Coldwell et al, 1994). Autologous blood clot achieves the same temporary artery occlusion as a gelatin sponge. Because the clot is lysed faster after embolization, there might be less chance of arterial thrombosis after several sessions of chemoembolization (Gunji et al, 2002). In a recent comparative nonrandomized study, no difference in patient survival was found between chemoembolization using gelatin sponge particles and that using PVA particles (Brown et al, 2005).

It is important to evaluate tumor-related arteriovenous shunt for safe procedures. In patients with HCC, angiographic incidence of shunting has been reported in 31.2%, shunting into the portal vein has been reported in 28.8%, and hepatic vein shunting has been reported in 2.4% (Ngan & Peh, 1997). The more liver parenchyma is occupied by the tumor, the more arteriovenous shunts exist; these are associated with poor prognosis (Granov et al, 1992) and are frequently problematic in chemoembolization of liver tumors (Izaki et al, 2004). Severe arterioportal shunt can cause hepatofugal portal flow, ascites, and variceal bleeding. In patients with a prominent arteriovenous shunt, embolization of the shunt is recommended prior to HAE (Huang et al, 2004). After embolization for massive arterioportal shunt, hepatofugal portal flow may convert to hepatopetal flow, and performance status and ascites may be improved (Izaki et al, 2004).

PATIENT SELECTION

Chemoembolization is indicated for the treatment of unresectable hypervascular liver tumors, which receive more blood supply from the hepatic artery than normal liver parenchyma, which makes the tumor suitable to HAE. The hemodynamic characteristics of a tumor may be documented on contrast-enhanced ultrasonography (Suzuki et al, 2003), computed tomography (CT) (Tajima et al, 2002b), and magnetic resonance imaging (MRI) (Levy, 2002).

The most common indication of chemoembolization is unresectable HCC. The determination of resectability of HCC should be based on either the extent of tumor involvement, underlying liver function, or a combination of these (see Chapters 2 and 90A). The majority of patients with HCC have underlying liver cirrhosis, which often requires a larger remnant liver after surgery to maintain hepatic function than in patients without underlying liver disease; therefore tumors that might be resectable in patients with normal liver parenchyma may not be resectable in patients with cirrhosis. Hepatic dysfunction also acts as a limitation in selecting patients for chemoembolization. Patients with poor hepatic function are not likely to tolerate extensive arterial embolization, because their livers are more dependent on arterial blood supply than normal liver, and moreover, patients with severe cirrhosis are more likely to die of their underlying liver disease than of HCC. Thus chemoembolization is typically recommended in patients with reasonably preserved liver function (Child-Turcotte-Pugh [CTP] class of A or B) and performance status (Eastern Cooperative Oncology Group [ECOG] 0 or 1). In general, patients with class C cirrhosis should not undergo chemoembolization as a primary treatment.

The extent of tumor is another important consideration in selecting patients for chemoembolization. Several methods have been proposed to weigh both hepatic function and the extent of tumor. In Okuda staging, patients are given points for presence of ascites, serum bilirubin and albumin levels, and the extent of tumor, and the patient is staged as I, II, or III (Okuda et al, 1985). The Cancer of the Liver Italian Program (CLIP) group proposed a more complex scoring system that includes the CTP score, tumor morphology and extension, presence of portal vein thrombosis, and serum α-fetoprotein (AFP) levels. The CLIP score was validated worldwide in multiple clinical trials and was proven to give more accurate prognostic information and greater survival predictive power than the Okuda staging system (CLIP, 2000; Ueno et al, 2001); however, those staging systems for predicting prognosis of patients with HCC did not indicate which patients would benefit from HAE. Recently, the Barcelona Clinic Liver Cancer (BCLC) staging system was developed to allow for the indication of the best therapy for each stage of HCC (Llovet et al, 1999a). In this staging system, chemoembolization is recommended as first-line therapy for intermediate stage HCC (Okuda staging 1 to 2, performance score 0, and large or multinodular disease) and some advanced-stage HCC (Okuda 1 to 2, performance score 1, no extrahepatic disease).

Spontaneous rupture of HCC is an indication for emergency HAE, regardless of underlying liver function (Kirikoshi et al, 2009). Even in patients with advanced liver cirrhosis, nodular HCC showing exophytic growth can be managed safely by selective embolization to prevent tumor rupture without diminishing liver function. Chemoembolization plays additional neoadjuvant roles as a downstaging therapy before resection or as a bridge therapy for patients awaiting liver transplantation (see Chapter 97D).

In general, the selection criteria for patients with HCC apply to patients with metastatic liver tumors; patients with unresectable hypervascular tumors will benefit from HAE. Typical hypervascular metastatic liver tumors include neuroendocrine tumors (NETs), gastrointestinal stromal tumors (GISTs), ocular melanoma, islet cell tumors, carcinoids, and sarcomas. The goal of HAE is symptomatic relief and improvement of survival. Most common indications are rapid progression of liver tumor with stable or absent extrahepatic disease, symptoms related to tumor bulk, and symptoms related to hormonal excess, especially in metastasis from neuroendocrine tumors.

Although no absolute contraindications to HAE exist, patients with two or three major poor prognostic indicators should not be treated. Generally accepted relative contraindications are extensive tumor involvement of more than 50% to 75% of the liver and class C cirrhosis. Major portal vein invasion by the tumor has been considered another relative contraindication, but this can be safely and effectively managed by an adjustment of the embolization protocol to reduce the amount of chemoembolic agents and the extent of the embolization, especially in patients with a limited parenchymal tumor and adequate liver function (Chung et al, 1995). Recent evidence demonstrates that HAE can be safely performed, even in patients with main portal vein occlusion, if hepatopetal collateral flow is present (Lee et al, 1997; Tazawa et al, 2001; Georgiades et al, 2005). In addition, active gastrointestinal bleeding, refractory ascites, extrahepatic spread, hepatic encephalopathy, and biliary obstruction are also considered relative contraindications. Regardless of the liver tumors, anaphylactoid reaction

to contrast media or renal insufficiency, uncorrectable coagulopathy, and severe peripheral vascular disease can preclude embolotherapy.

PROCEDURE

Before any chemoembolization procedure, laboratory tests should be done that include a complete blood cell count, prothrombin time, creatinine levels, and liver function testing. The baseline serum levels of tumor markers should be measured before treatment to monitor changes after treatment. By means of cross-sectional imaging studies, the size and extent of the tumor, its growth pattern (expansile vs. replacing or infiltrating), and macroscopic angioinvasion into the hepatic or portal veins are evaluated. For successful chemoembolization, accurate segmental localization of the tumor is crucial, and cross-sectional images are useful for that purpose (Yoon et al, 2008). In addition, imaging studies of the chest, abdomen, and pelvis are recommended to assess comorbid disease and ensure the presence or absence of metastatic disease.

Patients are fasted overnight and hydrated with normal saline at a rate of 200 to 300 mL/h. Antiemetics are administered intravenously, and patients with contrast allergies receive oral prednisone 1 hour before the procedure. The use of prophylactic antibiotics is controversial except in patients with a bilioenteric anastomosis or biliary stent (Geschwind et al, 2002; Ong et al, 2004; Tarazov, 1995). After infiltration of local anesthetic, the Seldinger technique is used to gain access to the common femoral artery, and initial diagnostic visceral arteriography is performed to determine arterial anatomy to the liver and patency of the portal vein. For complete angiography, all hepatic arteries should be adequately opacified, and all feeding arteries of the tumor should be identified.

Anatomic variations of celiac trunk and hepatic arteries are commonly encountered. With the introduction of multidetector row CT, these anatomic variations can be predicted before the procedure by careful review of the arterial phase scan (Song et al, 2010). Most common hepatic artery variations are the right hepatic artery arising from the superior mesenteric artery and the left hepatic artery arising from the left gastric artery, thus celiac and superior mesenteric arteriography is mandatory to identify the variations. Frequently, additional views in different angles and magnifications and selective contrast injection with use of a microcatheter are necessary to identify small feeding arteries (Yoon et al, 2008). To avoid nontargeted embolization, it is important to recognize the origin of the cystic artery and the right gastric artery, presence of a large falciform artery, and the accessory left gastric artery originating from the left hepatic artery (Song et al, 2006).

The treatment protocol should be individualized according to the hepatic functional reserve, extent of the tumor, and major portal vein invasion. Every effort should be made to preserve nontumorous liver parenchyma from ischemic damage by embolization. The best way to maximize treatment effect and to minimize procedure-related complications is to perform embolization of all tumor feeding arteries as selectively as possible. Patients with focal lesions should undergo segmental or, ideally, subsegmental embolization, in which a catheter or microcatheter is placed more selectively into the feeding artery in closer proximity to the tumor.

After the catheter is positioned appropriately, the mixture of iodized oil and chemotherapeutic drug is injected (Figs. 83.2 and 83.3). If there is a prominent arteriovenous shunt that precludes chemoembolic agents reaching the tumor vasculature, it is recommended first to embolize the shunt before injection of chemotherapeutic drugs (Fig. 83.4). The dose of iodized oil and chemotherapeutic agent depends on the size and vascularity of the tumor. The generally accepted upper limit of iodized oil is 15 mL. For a small tumor, enough iodized oil to saturate the entire tumor neovasculature could be administered. The end point for the mixture administration is stasis in tumor-feeding arteries or appearance of iodized oil in portal

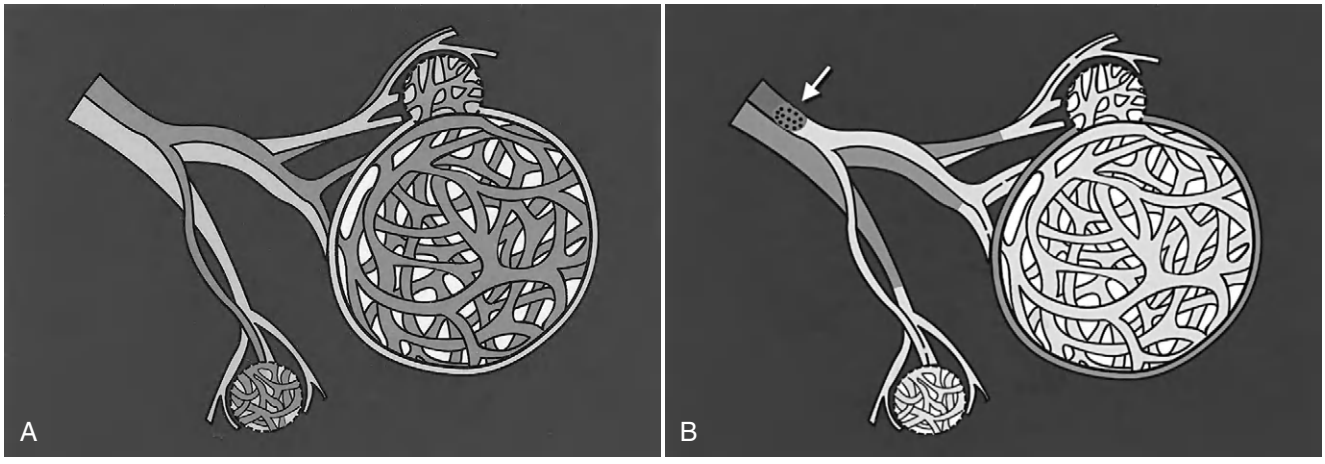


FIGURE 83.2. The concept of subsegmental or segmental chemoembolization using iodized oil. **A,** Exclusive arterial supply for encapsulated nodular hepatocellular carcinoma (HCC) and mixed arterial and portal venous supply for the portion of extracapsular invasion and small HCC without capsule formation. **B,** If a sufficient amount of a mixture of iodized oil and anticancer drug is injected through a tumor-feeding artery, not only the tumor neovasculature but also the peripheral portal veins around the tumor are filled with the emulsion. Subsequent hepatic artery embolization (*arrow*) may result in the effect of combined arterial and portal blockage; tumor fraction with mixed arterial and portal venous supply can be treated effectively by the combined effect of high-dose chemotherapy and ischemia.

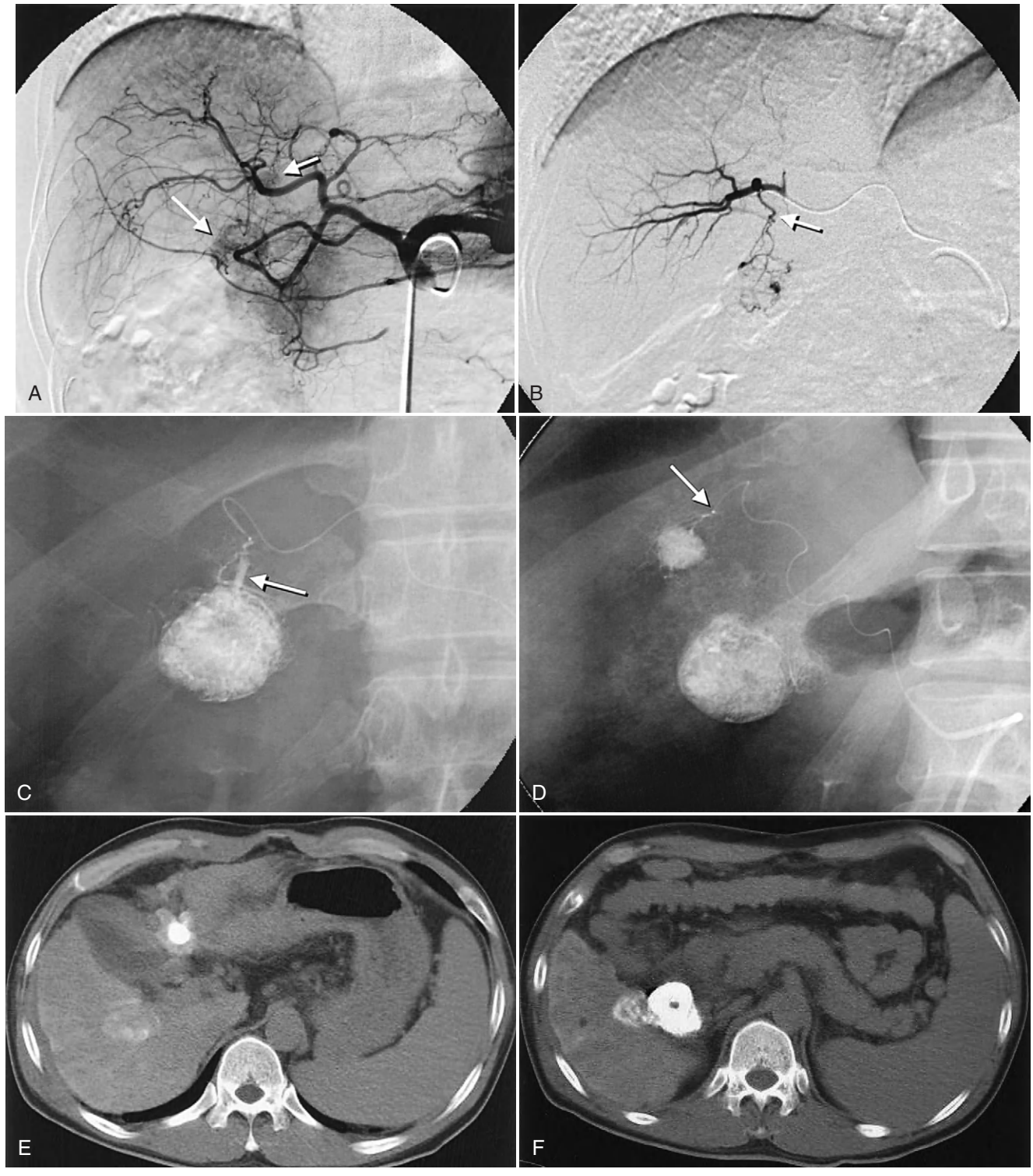


FIGURE 83.3. Subsegmental chemoembolization in a 43-year-old man with multinodular hepatocellular carcinoma. **A,** Celiac arteriogram shows two hypervascular tumor nodules (*arrows*) in the liver. **B,** The larger mass is supplied by a feeding artery (*arrow*) from the right posterior segmental branch. **C,** Subsegmental chemoembolization was performed by selective catheterization of the tumor-feeding artery and injection of an emulsion of 5 mL of iodized oil and 30 mg of doxorubicin hydrochloride. Gelfoam embolization was not performed because sufficient stagnation of blood flow was achieved after injecting the emulsion. Note the filling with iodized oil of the peripheral portal branch (*arrow*) accompanying the tumor-feeding artery. **D,** Subsegmental chemoembolization also was performed for the tumor located in hepatic segment IV by selective catheterization of the tumor-feeding artery (*arrow*). **E** and **F,** Iodized oil computed tomography (CT) reveals compact retention of iodized oil in the nodules.

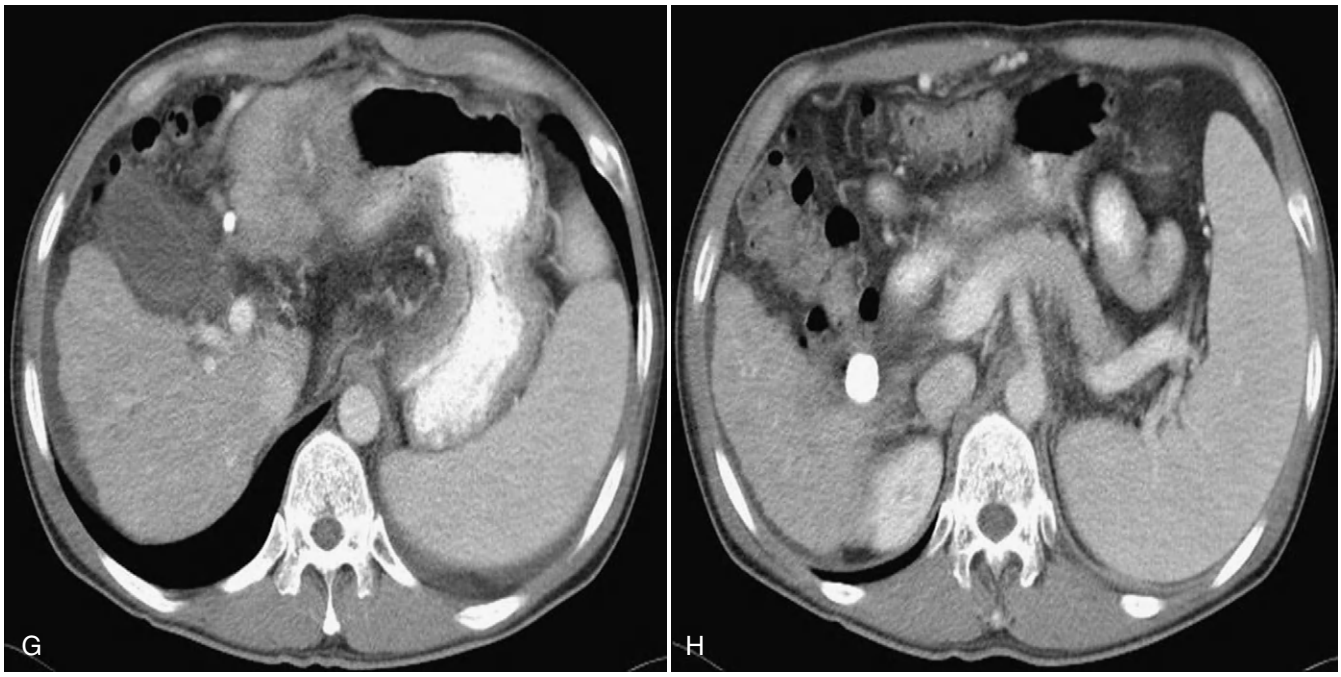


FIGURE 83.3, cont'd G and **H,** Follow-up CT scan 2 years later shows shrunken tumors without evidence of any viable portion.

vein branches (see Fig. 83.3). If flow is a persistent in the tumor-feeding arteries after infusion of chemotherapeutic drug, HAE should be performed. Gelatin sponge particles are the embolic agents most frequently used, because they degrade in a few weeks, allowing repeat treatment. PVA particle is another commonly used embolic agent, which causes a more permanent arterial occlusion (Ramsey et al, 2002).

Embolization of extrahepatic collaterals supplying the tumors is crucial to achieve successful outcomes. When a tumor is adjacent to a hepatic bare area or suspensory ligaments, or it invades into an adjacent organ, selective arteriogram of possible extrahepatic arteries should be obtained. With recent advances in CT imaging, those collateral vessels can be detected in preprocedure imaging studies (Kim et al, 2005). Common extrahepatic collaterals include the inferior phrenic artery, omental artery, internal mammary artery, colic branch of superior mesenteric artery, adrenal artery, intercostal artery, renal capsular artery, and gastric arteries (Chung et al, 2006; Kim et al, 2005, 2007, 2009; Won et al, 2003; Figs. 83.5 and 83.6). When the hepatic artery and extrahepatic collaterals supply the tumor, additional chemoembolization of the extrahepatic collaterals can be tried to increase the therapeutic efficacy of chemoembolization. These extrahepatic collaterals can be used as an access route to the tumors in patients with hepatic artery occlusion.

Recently, the use of C-arm cone-beam CT has been increasing. It can provide information about a patient's vascular anatomy, associated liver parenchyma, and the target lesion that constitutes a substantial improvement over conventional digital-subtraction angiography (DSA) and fluoroscopy (Carlson et al, 2001). C-arm cone-beam CT enables more selective catheterizations, which increases the amount of therapeutic agent delivered to the target area and decreases nontumorous liver parenchymal exposure to the agent (Meyer et al, 2007; Wallace et al, 2008; Fig. 83.7) In addition, confident identification of extrahepatic arteries supplying nontarget organs, such as supraduodenal or retroduodenal arteries, right gastric artery, phrenic artery, and falciform artery, is crucial to avoid nontarget embolization (Kim et al, 2009; Liu et al, 2005). When feeding arteries for a tumor are multiple, the portion of the tumor supplied by a catheterized feeding artery can be estimated, and the chemoembolic regimen can be proportioned accordingly. Iodized oil preferentially accumulated within tumors can be imaged without use of additional contrast media; thus completeness of therapy can be assessed immediately after treatment. If the oil has not accumulated in a portion of the tumor, the operator can search for hepatic or extrahepatic collateral tumor supply (Meyer et al, 2007; Wallace et al, 2007).

Intraarterial lidocaine and intravenous narcotic analgesics are given before the procedure to relieve pain during and after (Lee et al, 2001b). After the procedure, hydration is continued with normal saline. Narcotic analgesics, chlorpromazine, and acetaminophen are additionally supplied for 1 to 3 days as needed. Patients can be discharged once they have resumed adequate oral intake, and intravenous analgesics are no longer required.

Laboratory studies of liver function and serum levels of tumor markers should be repeated 2 to 4 weeks after the procedure. Multiphase contrast-enhanced CT or MRI is recommended 4 to 8 weeks after the procedure to evaluate the efficacy of the treatment and to detect local or remote tumor recurrences. If viable tumor is evident on imaging studies, serum levels of tumor markers are elevated, or both, patients return for another session of embolotherapy according to their hepatic functional recovery. No consensus has been reached on the ideal protocol for repeat procedures, but based on a retrospective comparison, survival rates and patient tolerance seemed to be higher when treatment was repeated, but only when progression of HCC was noted radiographically (Ernst et al, 1999).

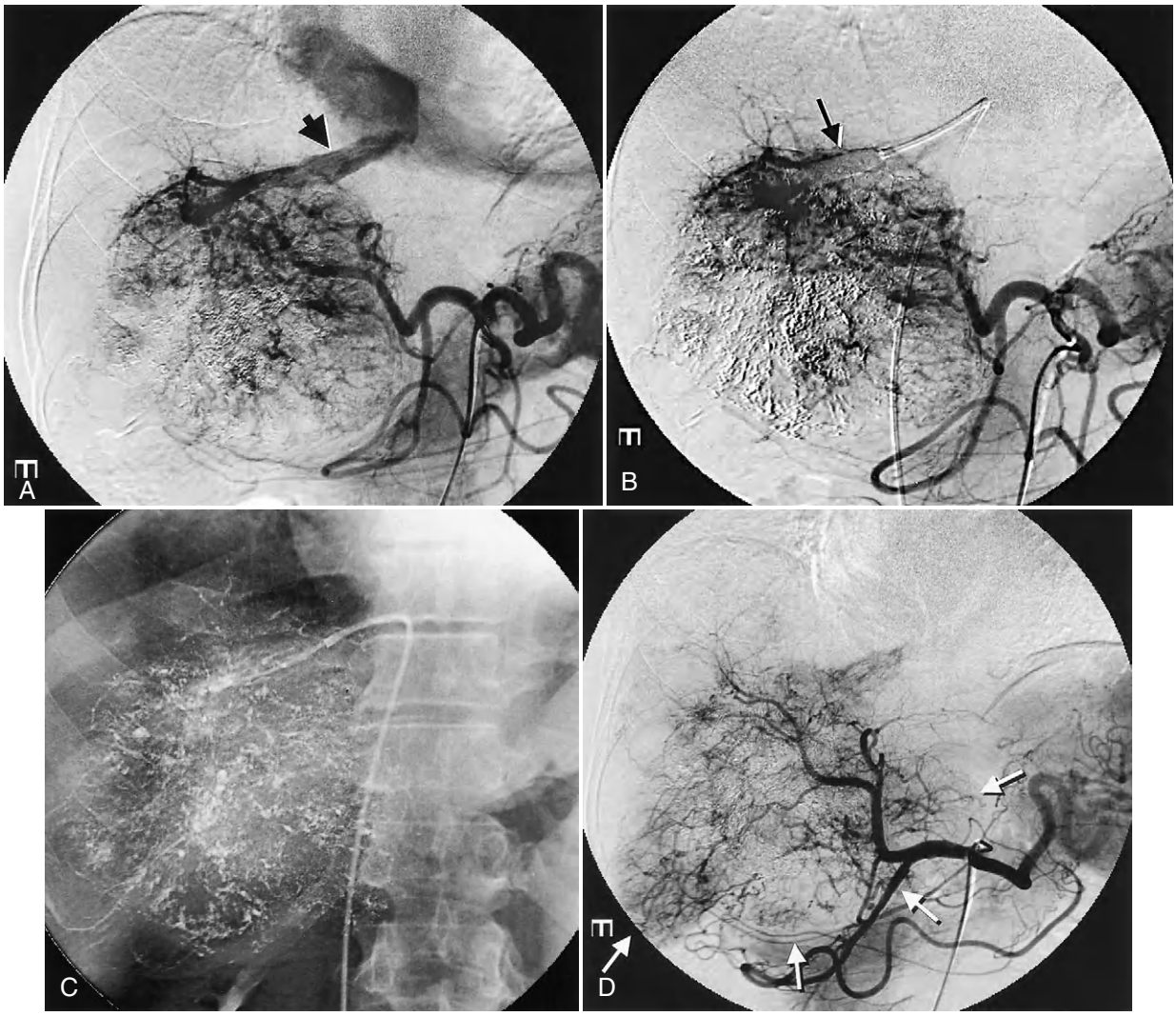


FIGURE 83.4. Severe arteriovenous shunt into the middle hepatic vein managed by chemoembolization after balloon occlusion of the middle hepatic vein in a 66-year-old man with hepatocellular carcinoma. **A,** Celiac arteriogram shows huge hypervascular mass with severe arteriovenous shunt into the middle hepatic vein (*arrow*). **B,** After balloon occlusion of the middle hepatic vein (*arrow*), celiac arteriography was repeated and confirmed the disappearance of the shunt. With the balloon inflated, chemoembolization was performed with a mixture of 10 mL of iodized oil and 50 mg of doxorubicin hydrochloride followed by Gelfoam embolization. **C,** Completion radiograph with the balloon deflated shows successful accumulation of iodized oil in the mass without untoward pulmonary embolization. **D,** Three months later, follow-up angiogram shows remarkably decreased arteriovenous shunt and the tumor fraction supplied by the hepatic arteries. An overgrowth of the tumor fraction is supplied by omental arteries (*arrows*).

THERAPEUTIC EFFICACY OF CHEMOEMBOLIZATION

Hepatocellular Carcinoma

Although the primary outcome after chemoembolization should be increased patient survival time, many other factors have been published in an effort to assess the efficacy of chemoembolization. These factors include objective response determined on imaging studies (reduction of tumor size, fraction of tumor necrosis, Lipiodol retention), biologic response (decrease in serum tumor markers), quality of life, and improvement of symptoms.

Numerous studies have shown that chemoembolization induces a significant tumor necrosis without negative influence on liver function in patients with preserved liver function. The extent of tumor necrosis has been reported to range from 60% to 100%. With introduction of subsegmental chemoembolization using a microcatheter, the tumor necrosis rate was markedly improved. Matsui and colleagues (1993) reported complete necrosis in about 70% of 100 small hypervascular HCCs less than 4 cm in diameter treated by subsegmental chemoembolization; however, especially in large tumors, even though necrosis may appear macroscopically complete, histologic examination reveals viable neoplastic cells responsible for the high rate of recurrence after treatment. During follow-up the



FIGURE 83.5. Massive hepatocellular carcinoma supplied by multiple extrahepatic collaterals in a 43-year-old man. **A,** Arterial phase computed tomographic (CT) scan shows a huge hypervascular mass in the right hepatic lobe (*arrows*). **B,** Celiac arteriogram shows a well-demarcated hypervascular mass with multinodular confluent appearance. **C** and **D,** Selective angiograms of the renal capsular artery (**C**) and the right inferior phrenic artery (**D**) also show multifocal tumor stain. Chemoembolization was performed with a mixture of 20 mL of iodized oil and 100 mg of doxorubicin hydrochloride followed by Gelfoam embolization at the right hepatic artery and extrahepatic collaterals. **E,** Postembolization plain radiograph shows diffuse uptake of iodized oil in the tumor. **F,** Follow-up CT scan shows a markedly shrunken primary tumor with a thick capsule, persistent iodized oil retention, and well-preserved, nontumorous hepatic parenchyma.

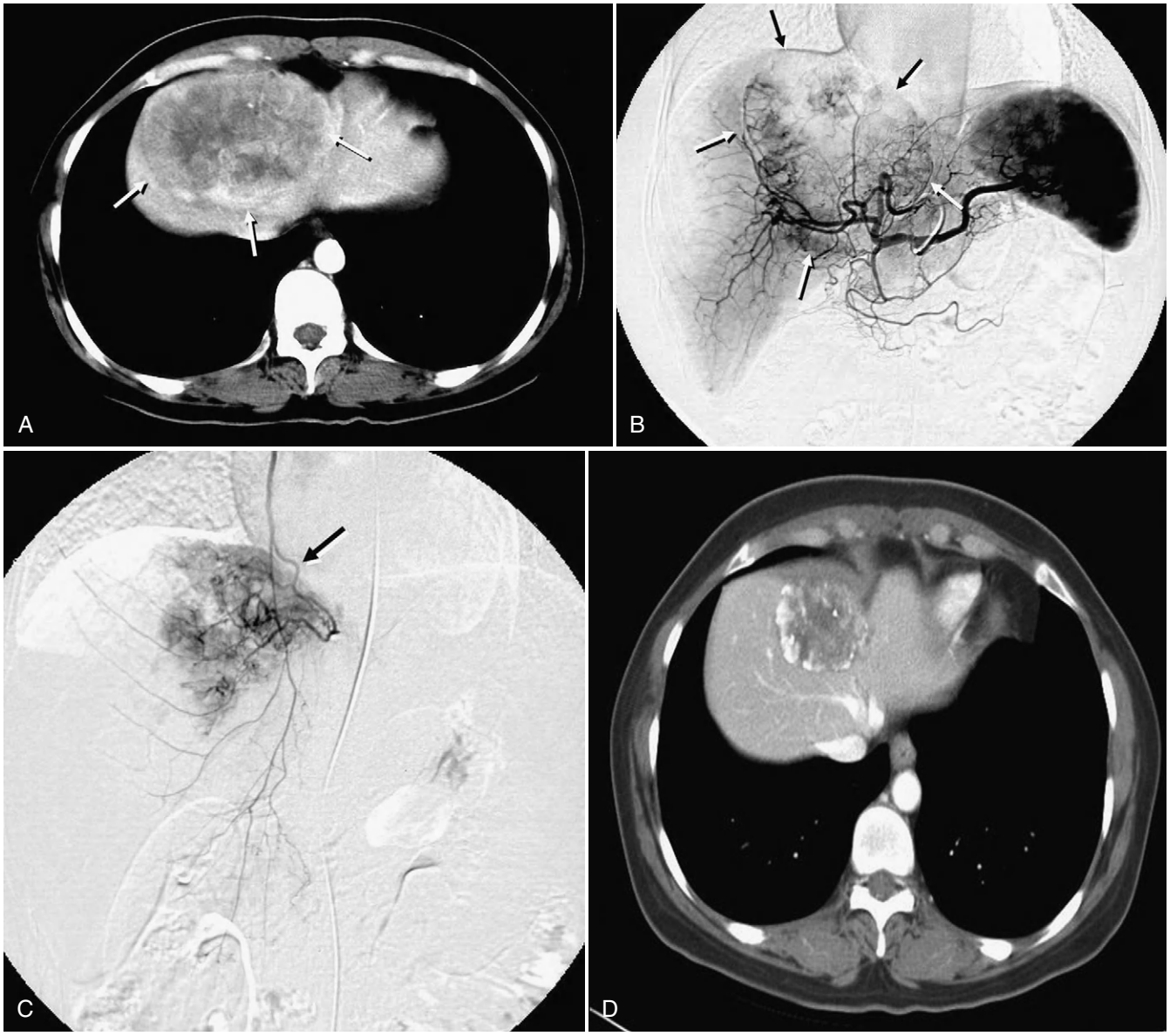


FIGURE 83.6. Hepatocellular carcinoma supplied by the right internal mammary artery as an extrahepatic collateral at its initial presentation in a 34-year-old woman. **A,** Initial computed tomographic (CT) scan shows a large tumor abutting the anterosuperior aspect of the diaphragm (*arrows*). **B,** Celiac arteriogram shows a large hypervascular mass occupying the medial segment of the left hepatic lobe and extending to the adjacent segments (*white arrows*). A defect in tumor stain appears at the superior aspect of the tumor (*black arrows*), suggesting the presence of an extrahepatic collateral supply. **C,** Right internal mammary arteriogram shows tumor stain at the area exactly matched with the defect in tumor stain on the celiac arteriogram. Chemoembolization was performed with a mixture of 15 mL of iodized oil and 50 mg of doxorubicin hydrochloride followed by Gelfoam embolization at the right hepatic artery and the diaphragmatic branch of the right internal mammary artery (*arrow*). **D,** Nine-year follow-up CT scans show a markedly shrunken tumor with no evidence of enhancing viable tumor.

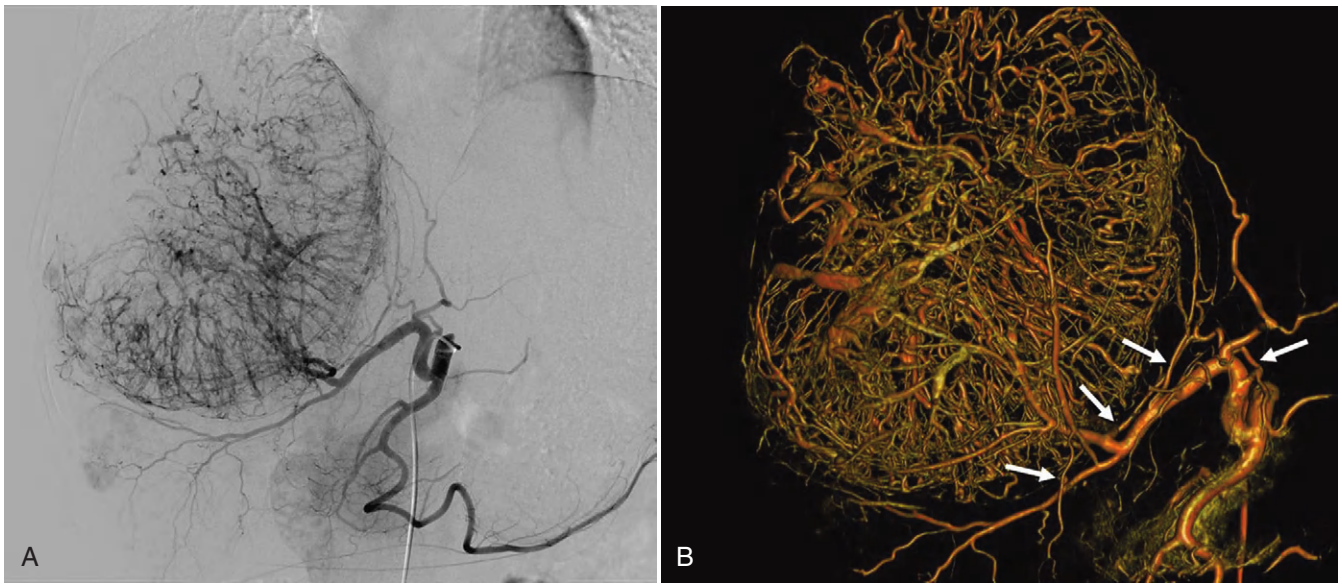


FIGURE 83.7. Application of cone-beam computed tomography (CT) for chemoembolization of hepatocellular carcinoma in a 49-year-old man. **A,** Common hepatic arteriography shows a huge hypervascular mass in the right hepatic lobe supplied by multiple feeding vessels. **B,** Three-dimensional volume-rendered image from cone-beam CT clearly demonstrates tumor feeders, including multiple, small, central feeding vessels (*arrows*). Real-time interactive anatomic information provided by cone-beam CT helps achieve successful superselective catheterization of tumor feeders and complete chemoembolization.

residual tumor nests recover their blood supply, and the tumor continues to grow. Additional treatments may be administered, either at specified intervals or as needed, but no data plainly favors either strategy (Bruix et al, 2004). Several studies have suggested that tumor characteristics lead to favorable response after chemoembolization—including small, encapsulated, expansile, hypervascular tumors—and long-term retention of iodized oil may be seen on CT (Itsubo et al, 2002; Kuroda et al, 1991; Nakamura et al, 1993). Pathologically, trabecular-type HCC showed more prominent necrosis than scirrhous, compact, or well-differentiated HCC (Jinno et al, 1992).

Several case-control and retrospective studies have shown a survival benefit in patients treated with chemoembolization compared with untreated patients or historic control subjects (Aoyama et al, 1992; Bismuth et al, 1992; Bronowicki et al, 1994; Rose et al, 1999). Bronowicki and colleagues (1994) performed a case-control study that stratifed 254 patients according to CTP classification and Okuda staging. The survival rates of the chemoembolization group were significantly higher (64%, 38%, 27%, and 27% at 1, 2, 3, and 4 years, respectively) than those of the conservative management group (18%, 6%, and 5% at 1, 2, and 3 years, respectively). The survival benefit from chemoembolization was not confirmed in early randomized, controlled trials (RCTs) performed in the 1990s (Camma et al, 2002; Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire, 1995; Pelletier et al, 1990). However, two newer RCTs, one from Barcelona (Llovet et al, 2002) and one from Hong Kong (Lo et al, 2002), reported a significant positive impact of chemoembolization on patient survival. This permitted a positive result in a cumulative meta-analysis of all RCTs published from 1978 to 2002; thus, according to the guidelines published by the American Association for Study of Liver Diseases (AASLD) (Bruix & Sherman, 2005) and the European Association for the Study of the Liver (EASL) (Bruix et al, 2001), chemoembolization is recommended as first-line noncurative therapy for nonsurgical patients with large or multifocal HCC who do not have vascular invasion or extrahepatic spread. The improvement in survival in treated patients ranges from 20% to 60% at 2 years (Bruix et al, 2004), but it is clear that the relevance of the improvement, as compared with the outcome if untreated, is largely dependent on the patients' baseline characteristics regarding tumor stage, liver function, and general health status (Llovet et al, 2003). In a recent prospective cohort study that included 8510 patients with unresectable HCC, the median survival rate was 34 months, with an overall survival at 1, 3, 5, and 7 years of 82%, 47%, 26%, and 16%, respectively (Takayasu et al, 2006).

Chemoembolization as a neoadjuvant therapy in candidates for hepatic resection is controversial (see Chapter 90A). Several retrospective studies reported a possible survival benefit in patients treated with chemoembolization before resection of HCC when compared with resection alone (Gerunda et al, 2000; Zhang et al, 2000). Zhang and colleagues (2000) retrospectively analyzed postoperative outcomes of 1457 HCC patients treated with hepatectomy and concluded that effective preoperative chemoembolization can improve disease-free survival after hepatectomy. On the contrary, in a randomized trial by Zhou and colleagues (2009), preoperative chemoembolization did not improve surgical outcomes, and no significant difference was found between the preoperative chemoembolization group and the control group in disease-free survival rates and overall survival rates. Moreover, the preoperative chemoembolization group had a lower resection rate and longer operative time. Choi and colleagues (2007) studied 273 patients who underwent curative resection for HCC; 120 of them underwent preoperative chemoembolization. The 1-, 3-, and 5-year

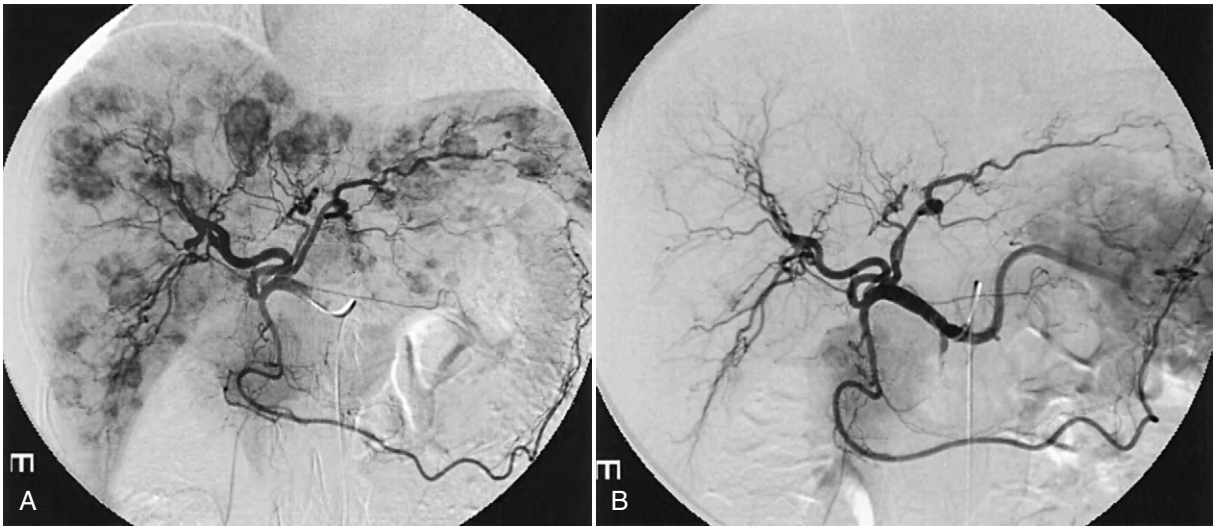


FIGURE 83.8. Liver metastasis of a rectal carcinoid in a 36-year-old woman. **A,** Celiac arteriogram shows numerous metastatic nodules scattered in both hepatic lobes. Initial chemoembolization was performed with a mixture of 7 mL of iodized oil and 40 mg of doxorubicin hydrochloride followed by Gelfoam embolization. **B,** Follow-up celiac arteriogram 2 years later after eight sessions of repeat chemoembolization shows markedly improved metastatic lesions.

disease-free survival rates were 76.0%, 57.7%, and 51.3%, respectively, in the chemoembolization group and 70.9%, 53.8%, and 46.8%, respectively, in the nonchemoembolization group. Although a difference was noted between two groups, it was not significant. Chemoembolization has also been performed to reduce tumor volume (downstaging) before hepatic resection. Majno and colleagues (1997) showed that downstaging (42%) or complete necrosis (50%) was achieved in 49 patients.

Orthotopic liver transplantation (OLT) has been shown to be the best treatment for early-stage HCC (see Chapter 97D); however, because of a steadily increasing waiting time, a noteworthy proportion of patients are excluded from OLT because of tumor progression. Llovet and colleagues (1999b) reported a 23% dropout rate as a result of tumor progression in the first 6 months of waiting for OLT without any neoadjuvant therapy. Chemoembolization has been performed as a bridge therapy prior to liver transplantation, to inhibit tumor growth while a patient awaits an organ, but no controlled study is available for comparing patients who underwent OLT for HCC with and without neoadjuvant chemoembolization. Four noncomparative studies reported dropout rates in patients who underwent chemoembolization that ranged from 0% to 46%. Other trials used chemoembolization prior to transplantation to prevent tumor dissemination during surgery, which may result in better posttransplantation outcomes (Decaens et al, 2005; Stockland et al, 2007), although the role of chemoembolization for this purpose is still being debated. In a case-control study that included 100 patients who received pretransplant chemoembolization and 100 control patients, pretransplant chemoembolization does not influence posttransplantation survival or disease-free survival (Decaens et al, 2005). Another purpose of pretransplantation chemoembolization is to downstage advanced HCC and expand selection criteria for liver transplantation. Chapman and colleagues (2008) performed pretransplantation chemoembolization in 76 patients with advanced HCC (American Liver Tumor Study Group stage III/IV). Of these 76 patients, 17 (22.4%) were successfully downstaged to qualify for OLT under the Milan criteria. Importantly, patients who are successfully downstaged and transplanted have excellent midterm disease-free and overall survival, similar to stage II HCC. Similarly, Yao and colleagues (2008) showed that successful downstaging of HCC can be achieved in the majority of carefully selected patients, and it is associated with excellent posttransplantation outcome.

Neuroendocrine Tumors (See Chapter 81B)

NETs are the most common secondary liver cancer, and they have also been managed with hepatic embolotherapy (Fig. 83.8). They are slow-growing tumors, frequently found when the disease has become metastatic. Curative surgery should always be considered as a first-line treatment, but less than 10% of patients have resectable tumors because of the diffuse nature of the disease. The development of liver metastasis causes synthesis and release of hormonal substances that lead to a constellation of symptoms, including rash, hypertension, diarrhea, and electrolyte disorders; these are collectively known as *carcinoid syndrome*. In the later stages of the disease, significant hepatomegaly by bulky metastatic tumors may cause progressive pain and dyspnea, and the primary goal of hepatic embolotherapy is to reduce liver tumor burden and palliate symptoms.

To date, partial or complete response after embolotherapy has ranged widely in reports, from 6.7% to 100%, and median survival has been reported from 13 to 80 months. Although many studies have reported median survival of more than 3 years, it is unclear whether embolotherapy significantly improves survival because of the indolent nature of the tumor; however, it is clear that outcomes are inversely related to the degree of liver replacement by tumor, and patients with carcinoid tumor have significantly prolonged survival compared with patients with islet cell tumor after embolization. Recently, Gupta and

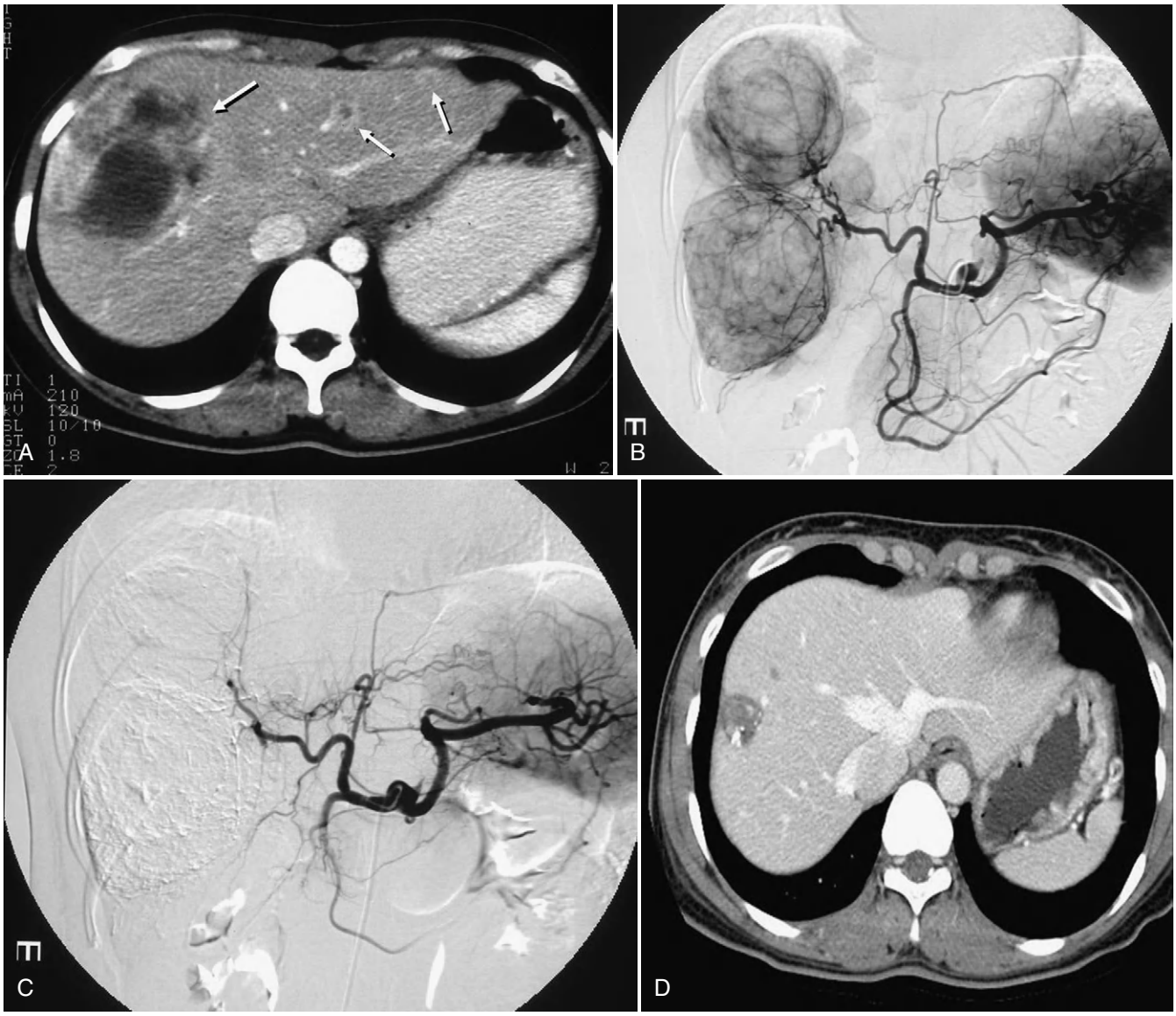


FIGURE 83.9. Liver metastasis of gastrointestinal stromal tumor of the stomach in a 34-year-old woman. **A,** Computed tomographic (CT) scan of the liver shows multiple metastatic tumors in the both hepatic lobes (*arrows*). **B,** Celiac arteriogram shows multiple and variably sized hypervascular tumors in the liver. **C,** Initial chemoembolization was performed with a mixture of 10 mL of iodized oil and 50 mg of doxorubicin hydrochloride followed by Gelfoam embolization. Completion arteriogram shows successful devascularization of the tumor. **D,** After three sessions of repeat chemoembolization, 8-year follow-up CT scan shows no evidence of viable tumor in the liver.

colleagues (2005) performed bland embolization or chemoembolization in 69 patients with carcinoid tumors and in 54 with pancreatic islet cell carcinomas. In patients with carcinoid tumors, bland embolization had a higher response rate than chemoembolization. In contrast, patients with islet cell carcinomas treated with chemoembolization had a prolonged overall survival time and improved response rate compared with those treated with bland embolization; this was not an unexpected result, because carcinoid tumors have a lower response rate to systemic chemotherapy than do islet cell tumors.

Some authors recommend a tumor burden greater than 50%, but others recommend a burden greater than 75% as an exclusion criterion for embolization, because poor outcomes and response rates have been documented. In these high-risk patients, embolotherapy should be performed in stages, with only a part of the vascular tumor embolized at each session. Using this approach, one series treated patients with greater than 75% replacement of the liver by tumor and reported response rates of 43% and 25% and overall survival of 20.1 and 16 months for patients with carcinoid tumor and islet cell carcinoma respectively. For small tumors and for patients with fewer than three tumors, hepatic embolotherapy can be combined with local ablation therapies to maximize tumor necrosis and improve local disease control.

Prior to the introduction of pharmacologic antagonists of tumor metabolites, exacerbation of the symptoms of carcinoid or carcinoid crisis was common after embolotherapy. The increased availability of somatostatin analogues has

allowed remarkable reduction of this complication after embolotherapy.

Sarcoma and Gastrointestinal Tumors (See Chapter 81C)

A small number of investigations have addressed hepatic embolotherapy for the treatment of sarcoma and GISTs. Most gastrointestinal soft-tissue neoplasms previously classified as leiomyomas, schwannomas, leiomyoblastomas, or leiomyosarcomas are today classified as GISTs on the basis of molecular and immunohistologic features. The liver is the most common site of metastasis from malignant GISTs. Surgical resection is the treatment of choice for a single metastasis, but the majority of patients with liver-dominant metastases have unresectable disease. Because this tumor is frequently hypervascular, hepatic embolotherapy has been an effective palliative treatment for unresectable liver metastases (Fig. 83.9). Mavligit and colleagues (1995) treated 15 patients with metastatic leiomyosarcoma with chemoembolization using PVA particle, cisplatin, and vinblastine, which produced a major tumor response—more than 50% regression—that lasted 8 to 31 months in 70% of patients. Similarly, in a small series by Rajan and colleagues (2001), partial response rate was 69% with a median survival of 13 months after chemoembolization. A more recent study that employed bland embolization demonstrated a radiologic response of 60% and a median survival of 24 months (Maluccio et al, 2006). A significant survival benefit was documented in patients with a radiologic response (median, 63 vs. 19 months). Because imatinib mesylate (Gleevec), a tyrosine kinase inhibitor, proved to be highly effective against GISTs (Demetri et al, 2002), hepatic embolotherapy is currently recommended for patients who failed therapy or became resistant to Gleevec.

Colorectal Metastases (See Chapter 81A)

Colon cancer is the second leading cause of cancer-related death in the Western world, and the liver is the commonest site of distant metastasis of colon cancer. Approximately 50% to 60% of patients with colorectal cancers will develop liver metastasis in their lifetime, and over half will die from their metastatic liver diseases. Surgical resection is the only potentially curative treatment for liver metastasis from colon cancer, but less than 30% of patients have resectable disease at initial evaluation (Fusai & Davidson, 2003; Meyers et al, 2003). Systemic chemotherapy remains the standard of care for this population.

Recent advances in chemotherapeutic drugs have resulted in improved survival, but overall median survival is still just more than 20 months. Bland hepatic artery embolization and chemoembolization have been used as a second-line therapy, when a liver tumor progresses during systemic chemotherapy. A limited number of series have documented that survival rates are significantly improved in selected patients with good performance status, no extrahepatic disease, and solitary lesions (Martinelli et al, 1994; Salman et al, 2002; Sanz-Altamira et al, 1997).

Preoperative chemoembolization has been proposed as a possible means of decreasing perioperative tumor dissemination and downstaging of tumor to allow resection, but only in a small number of patients. Vogl and colleagues (2003) suggested chemoembolization combined with ablation therapy as a viable treatment option. They performed sequential chemoembolization to reduce tumor size to 5 cm or less, and then treated tumors with laser-induced thermal ablation. This regimen resulted in a mean survival of more than 26 months, versus 12.8 months for patients treated by chemoembolization only.

Ocular Melanoma (See Chapter 81C)

Ocular melanoma is a rare but highly malignant disease with median survival of 2 to 6 months. Liver metastasis is found up to 40% of patients at initial evaluation, and a sole metastasis is found in more than 80% of patients. A few series used chemoembolization for local control of metastatic uveal melanoma (Feldman et al, 2004; Mavligit et al, 1988), and a retrospective study of 201 patients compared cisplatin-based chemoembolization with systemic chemotherapy and reported that chemoembolization produced a better response rate (36%) (Bedikian et al, 1995). These results were similar to those of a previous study that reported a response rate of 46% and a median survival of 11 months (Mavligit et al, 1988). Because most patients die of systemic disease, chemoembolization is unlikely to improve survival of patients.

COMPLICATIONS

Hepatic embolotherapy is associated with diverse complications. Procedure-related mortality rate is less than 5%, and the incidence of major complications has been reported to be less than 5%, including liver failure or infarction, liver abscess, biliary necrosis, and nontarget embolization (Chan et al, 2002; Ramsey et al, 2002; Song et al, 2001). Important predisposing factors for major complications are major portal vein obstruction, compromised hepatic functional reserve, biliary obstruction, previous biliary surgery, excessive use of iodized oil, and nonselective embolization (Chung et al, 1996). Recognition of predisposing factors before the procedure, selective embolization with an adequate amount of chemoembolic material, and careful postprocedure monitoring of patients is mandatory to prevent these complications.

Postembolization Syndrome

Postembolization syndrome (PES) occurs in approximately 80% of patients and consists of pain, fever, nausea, and vomiting. PES is more of a side effect than a complication of hepatic embolotherapy. The etiology of PES is not fully understood, but it is thought to be a type of tumor lysis syndrome. Abrupt tumor cell death by ischemic damage causes release of intracellular toxins into circulation, which may cause fever, nausea, and vomiting (Patel et al, 2000). Possible causes of pain are acute ischemia of liver parenchyma, distension of the liver capsule, and gallbladder ischemia secondary to inadvertent embolization of the cystic artery. Leung and colleagues (2001) reported that inadvertent gallbladder embolization and the dose of chemotherapeutic drug are associated with this syndrome. PES is treated with supportive management that includes antiemetics, analgesics, and antipyretics; it typically subsides after 1 to 3 days.

Liver Failure

The most serious complication of hepatic embolotherapy is hepatic insufficiency. In a prospective study that included 197 sessions of chemoembolization, acute liver failure developed in

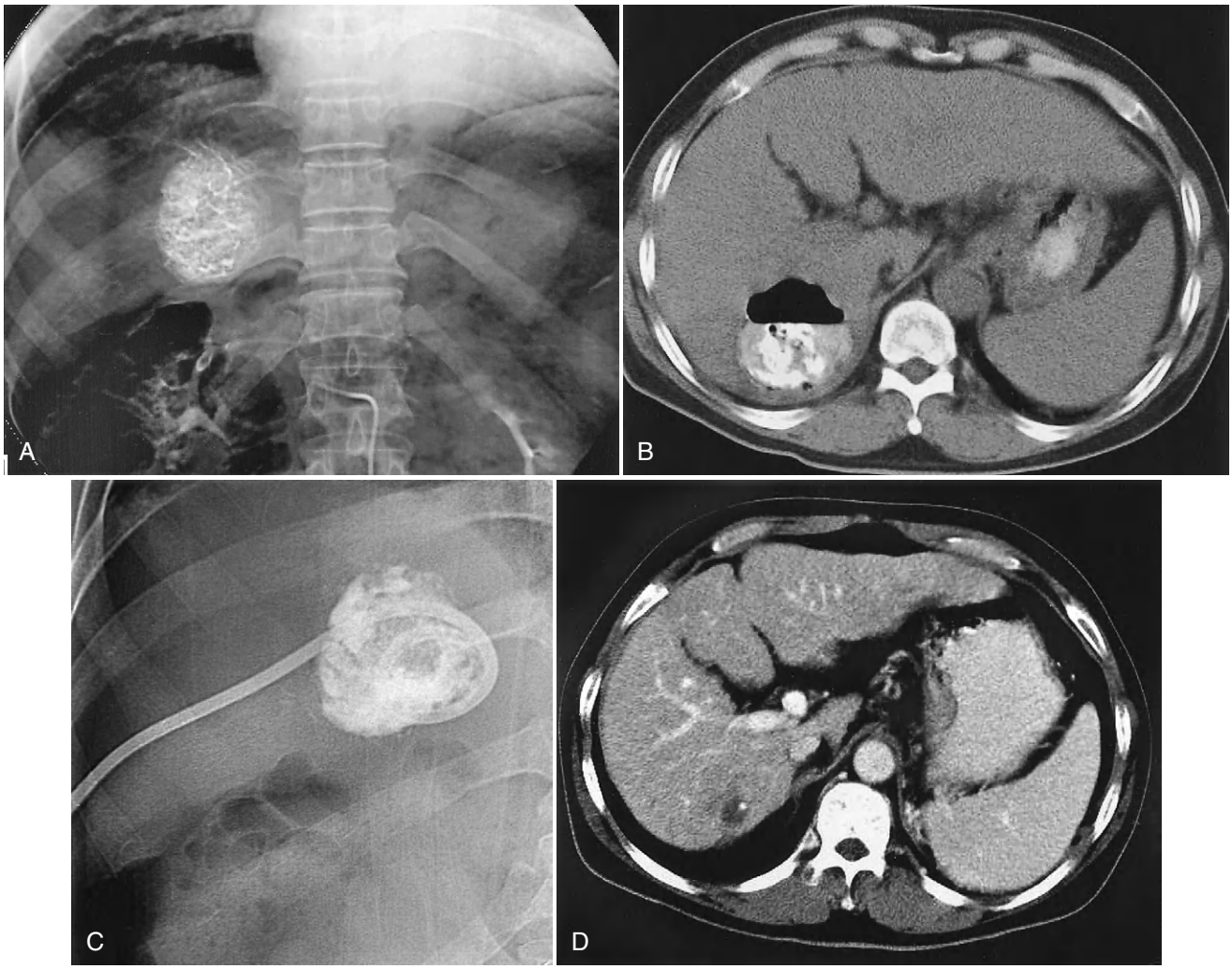


FIGURE 83.10. Liver abscess formation after chemoembolization and treatment with percutaneous drainage in a 55-year-old man. **A,** Plain radiograph obtained after chemoembolization shows selective iodized oil accumulation in the tumor. **B,** Noncontrast computed tomographic (CT) scan 2 weeks later shows air-fluid level in the tumor. **C,** The abscess cavity is drained with a percutaneous drainage catheter. **D,** Follow-up CT scan 1 month later shows remarkable shrinkage without evidence of viable tumor.

20% of patients, and 3% of these cases were irreversible. Hyperbilirubinemia, prolonged prothrombin time, higher dose of chemotherapeutic drug, and advanced cirrhosis were associated with irreversible failure (Chan et al, 2002). In general, chemoembolization does not influence liver function in patients with class A or B cirrhosis, and most liver dysfunction that requires hospitalization develops in patients with class C disease (Shah et al, 1998).

Liver Abscess (See Chapter 66)

Liver abscess is a rare (0.5% to 2%) but serious complication of hepatic embolotherapy (Kim et al, 2001). In a study by Song and colleagues (2001), predisposing factors for liver abscess included portal vein obstruction, metastatic tumors, and biliary abnormalities. Prior bilioenteric bypass surgery or sphincter of Oddi dysfunction for any reason have been reported as the most important predisposing factors for intrahepatic abscess following embolotherapy (Kim et al, 2001; Ong et al, 2004). Biliary concentrated antibiotics, such as piperacillin, with bowel preparation before the procedure is recommended to prevent liver abscess in these patients (Geschwind et al, 2002), who typically have leukocytosis and spiking fever that occur 7 to 10 days after the procedure. Liver abscess can be managed with percutaneous drainage and parenteral antibiotics (Song et al, 2001; Fig. 83.10).

Bile Duct Injury (See Chapter 42)

Intrahepatic and extrahepatic bile ducts may be damaged by hepatic arterial embolotherapy, because they are supplied by the peribiliary capillary plexus from the hepatic artery. This complication is relatively common (2% to 12.5%) and manifests as intrahepatic biloma, focal stricture of the common bile duct, or diffuse dilatation of intrahepatic bile duct (Kim et al, 2001; Kobayashi et al, 1993; Miyayama et al, 2010). The intrahepatic bile duct injury may cause obliteration of adjacent portal vein, liver parenchymal atrophy, and liver abscess (Yu

et al, 2001). Sakamoto and colleagues (2003) reported that bile duct injury is more frequent in patients with metastatic tumor, noncirrhotic liver, and in those who underwent selective embolization of distal hepatic arteries. Most patients are asymptomatic, but when signs of biliary infection are present, parenteral antibiotics and percutaneous drainage are required.

Extrahepatic Nontargeted Embolization

Nontarget embolization is the most dreaded complication of hepatic embolotherapy, but it occurs infrequently if diagnostic angiogram has been carefully performed, and the appropriate technique of embolization has been followed. The gallbladder is the most common nontarget organ, because the cystic artery is often not opacified on arteriogram. Inadvertent embolization of the cystic artery causes prolonged PES with fever, pain, nausea, and vomiting. Most cases follow a self-limited clinical course, but more serious conditions have been reported, such as gallbladder perforation and gangrenous or emphysematous cholecystitis, in which cholecystectomy or percutaneous cholecystostomy is required (Tarazov et al, 2000).

Skin complications can develop after chemoembolization of extrahepatic collateral vessels, such as the internal mammary artery and intercostal artery (Lee et al, 2001a; Hama et al, 2000). Painful induration and discoloration are often observed, but transmural necrosis that requires skin graft is rare. A supraumbilical skin rash can develop, if the emulsion of iodized oil and chemotherapeutic drug flows into the falciform artery. To avoid this complication, when a well-developed falciform artery is identified on hepatic arteriogram, it should be embolized using coils before injection of chemoembolic agent into the left hepatic artery (Ueno et al, 1995).

Gastroduodenal ulcer can occur as a result of inadvertent embolization of the accessory left gastric arteries that arise from the left hepatic artery and the right gastric artery that arises from the proper or left hepatic arteries (Morante et al, 2006). If these gastric branches are not recognized before the procedure, and appropriate protective measures are not taken, gastric complications are unavoidable. Embolization of gastric branches with coil or balloon occlusion of the proper hepatic artery can redirect the blood flow.

Chemoembolization of the inferior phrenic artery frequently results in pulmonary complications, including iodized oil accumulation in the lung field, consolidation, and pleural effusion (Tajima et al, 2002a). Diaphragmatic weakness can also develop in about one third of patients as an ischemic complication (Lee et al, 2009; Shin et al, 2006). In the presence of an arteriovenous shunt, a potential risk of pulmonary embolism or infarction exists, because the iodized oil can pass through the shunt. The incidence of pulmonary oil embolization increases to 43% when a large amount of iodized oil is used for chemoembolization (Chung et al, 1993). Respiratory symptoms of cough, hemoptysis, and dyspnea developed in 2 to 5 days and completely cleared 10 to 28 days after chemoembolization in most cases, but serious complications such as respiratory arrest may occur. To prevent pulmonary oil embolism, it is recommended to use no more than 15 mL of iodized oil, administered superselectively, and to observe arteriovenous hepatic shunts carefully on initial arteriograms and during the procedure. An intracardiac right-to-left shunt via a patent oval foramen or intrapulmonary arteriovenous shunt can lead to cerebral Lipiodol embolism (Matsumoto et al, 2007).

Iatrogenic Vascular Injury

Iatrogenic arterial injury, such as dissection, may occur in the visceral arteries during hepatic embolotherapy. The two most common sites of dissection are the celiac and proper hepatic artery. Although iatrogenic dissection of the arteries heals spontaneously in most patients, it may result in complete obstruction or pseudoaneurysm formation (Jang et al, 2009; So et al, 2003; Yoon et al, 1995).

COMBINED THERAPY WITH OTHER TREATMENT

It has been proposed that chemoembolization might be combined with other local therapeutic options to enhance therapeutic efficacy. In combination treatment, the purpose of chemoembolization is to reduce the size of tumors (downstaging) for percutaneous treatments or to obtain a synergistic effect on tumor necrosis by combining procedures. Combination with percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), laser interstitial thermotherapy (LITT), and radiotherapy has been studied, and better results were reported with the combination treatment than with either of these therapies alone.

Chemoembolization enhances the diffusion of ethanol within tumor tissue, causing more extensive tumor necrosis by PEI. Several trials compared this combination therapy with stand-alone PEI or chemoembolization in small HCC (Kamada et al, 2002; Koda et al, 2001) and large HCC (Allgaier et al, 1998; Bartolozzi et al, 1995; Yamamoto et al, 1997). Koda and colleagues (2001) compared the combined therapy versus PEI alone in 52 patients with HCC 2 cm or smaller. In their study, combined therapy improved local recurrence rates (8.7% and 19.3% at 1 and 3 years, respectively) and survival rates (100%, 80%, and 40% at 1, 3, and 5 years, respectively). Kamada and colleagues (2002) compared combined therapy versus chemoembolization alone in 69 patients with HCC 3 cm smaller. The 5-year survival rates were better in the combined-therapy group than in the group that received chemoembolization alone (50% vs. 22%). In a prospective comparative study of 132 patients with unresectable large HCC, median survival time was better in the chemoembolization-PEI group (25 months) compared with the PEI group (18 months), chemoembolization group (8 months), and conservatively treated group (2 months) (Allgaier et al, 1998).

RFA is designed to destroy tumor by heating tissue to lethal temperatures, exceeding 60° C (see Chapter 85C). It has proved to be an effective treatment of small HCC, but tumor volume that can be effectively ablated is limited. HAE eliminates the heat-sink effect by blood flow, thus it induces a larger ablation area by RFA (Rossi et al, 2000; Fig. 83.11). Many reports have demonstrated this combination to be a useful therapeutic method to control large HCC. Rossi and colleagues (2000) performed RFA after bland embolization in 62 patients with HCC (3.5 to 8.5 cm) and observed a 1-year survival rate of 87% and a recurrence rate of 19%. Takaki and colleagues (2009) treated 20 patients with HCC larger than 5 cm with a chemoembolization-RFA combination and reported an encouraging 5-year survival rate of 41%. A recent retrospective study that included 104 patients with early stage HCC, defined as three or fewer tumors 3 cm or smaller each or a single tumor 5 cm or smaller, demonstrated that a chemoembolization-RFA combination resulted in a disease-free and overall survival

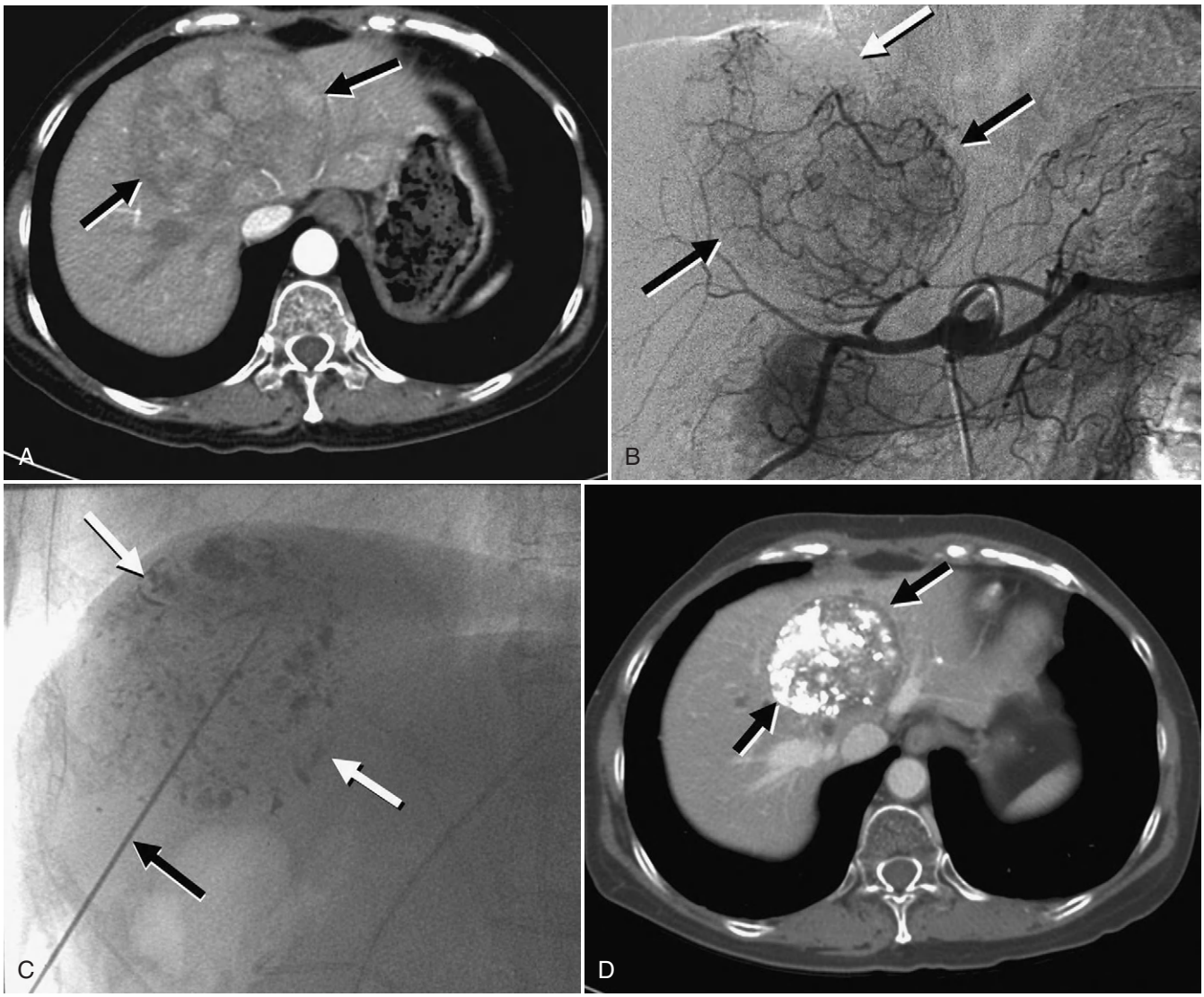


FIGURE 83.11. Combined therapy using chemoembolization and radiofrequency ablation (RFA) in a 48-year-old woman with massive hepatocellular carcinoma (HCC). **A,** Liver computed tomography (CT) arterial phase scan shows a heterogeneously enhanced massive HCC (*arrows*). **B,** Celiac arteriogram shows a hypervascular tumor stain supplied by left hepatic artery (*arrows*). Chemoembolization was performed with a mixture of 7 mL of iodized oil and 40 mg of doxorubicin hydrochloride followed by Gelfoam embolization. **C,** Immediately after chemoembolization, RFA was performed. Under fluoroscopic guidance, an expandable electrode (*black arrow*) was placed, aiming iodized oil accumulated in the tumor (*white arrows*). **D,** Follow-up CT obtained 1 year later shows remarkable shrinkage with no evidence of viable tumor (*arrows*).

similar to those achieved by surgical resection (Yamakado et al, 2008); however, the synergistic efficacy of chemoembolization with RFA has not been proven in RCTs. Recently, a prospective study did not find any survival benefit with the combined treatment compared with stand-alone RFA in HCC 3 cm or smaller (Shibata et al, 2009). Therefore, considering the increased cost and patient discomfort of additional chemoembolization, it may be reasonable to restrict this combination to large HCC or small lesions with infiltrative margins. Regarding the safety of this combination and the ability of patients to tolerate it, recent trials have demonstrated that chemoembolization and RFA can be safely performed, even in a single session (Kang et al, 2009), and it can improve quality of life scores better than chemoembolization alone (Wang et al, 2007).

Some investigators combined chemoembolization with laser thermal ablation and used chemoembolization to downsize a tumor that could be ablated with LITT. Zangos and colleagues (2007) performed repeated chemoembolization (mean, 3.5 sessions/patient) in 48 patients with HCC 50 to 80 mm in diameter to reach a favorable size for LITT, and then the patients were treated with MR-guided LITT. Repeated chemoembolization reduced the tumor size in 32 patients (66.7%), and subsequent LITT resulted in a median survival of 36 months after the first treatment. The same combination was used by Vogl and colleagues (2003), who also showed that chemoembolization can be used as a downsizing tool before LITT in 50.6% of patients with unresectable liver metastasis. Pacella and colleagues (2001) used LITT to reduce tumor volume and then performed chemoembolization in HCCs ranging from 3.5 to 9.6 cm in diameter. After combined treatment, complete response was achieved in 90% of the tumors with a local recurrence rate of 7% at 3 years.

The combination of chemoembolization and three-dimensional conformal radiotherapy (3D CRT) have involved three strategies (Hawkins & Dawson, 2006; see Chapter 84B). The most common approach is chemoembolization followed by radiotherapy (RT), in which RT is used to treat portal vein and inferior vena cava tumor thrombus to enhance the therapeutic effect by chemoembolization. From 40 Gy to 60 Gy over 5 to 6 weeks have been delivered safely to the macrovascular disease (Ishikura et al, 2002; Tazawa et al, 2001; Zeng et al, 2005). In a case-control study, 15 (34.1%) of 44 patients who underwent the combination therapy showed complete disappearance of venous tumor thrombi, and the 1-year survival rate was better in the combination group compared with the group that received chemoembolization alone (34.8% vs. 11.4%). A second approach involves RT sandwiched between chemoembolization, with RT used as a planned "consolidation" procedure to target residual viable tumor after chemoembolization (Hawkins & Dawson, 2006); in addition, the chemotherapeutic drugs retained in the tumor by chemoembolization may have a radiosensitizing effect (Seong et al, 2001). In the third approach, repetitive chemoembolization for large HCC is given until optimal response, followed by RT.

Tumor shrinkage after chemoembolization allows the use of smaller irradiation fields, which permits higher tumor doses and improves the normal liver tolerance (Guo et al, 2003). Despite the heterogeneity of disease, patients, and treatment techniques, the majority of studies have suggested a benefit of the combined therapy compared with stand-alone therapies in treatment of advanced HCC (Zeng, 2005; Guo et al, 2003; Meng et al, 2009). The introduction of molecular targeted therapies that attack pathways critical for cancer survival and progression has created a new hope against advanced HCC. Sorafenib, an oral multitarget tyrosine kinase inhibitor with antiangiogenic and antiproliferative actions, is the first systemic therapy to prolong the survival of patients with advanced HCC (Llovet et al, 2008; see Chapter 88). Currently underway are studies to investigate the effects of sorafenib as an adjuvant therapy after chemoembolization, to prevent microscopic tumor residues from reestablishing their blood supply and thus reduce tumor recurrence.

EMERGING TECHNIQUES OF HEPATIC ARTERIAL EMBOLOTHERAPY

Some controversy remains regarding the use of chemotherapeutic drugs in hepatic arterial embolotherapy. Although the concept of delivering high-dose chemotherapy to the tumor is sound, no evidence-based findings support the routine use of chemoembolization. Bland embolization with small particles has been shown to be as effective as chemoembolization in treatment of hypervascular primary and metastatic liver tumors and can be used instead of chemoembolization, thereby avoiding the added expense and systemic toxicity of chemotherapy.

In bland embolization, because the therapeutic efficacy depends on terminal vessel blockade, the smallest particles commercially available have been used. Until the late 1990s, 50-μm PVA particles were the smallest particles available, when Embospheres (BioSphere Medical, Rockland, MA), a hydrophilic tris-acyl gelatin microsphere, become available in 100- to 700-μm particles. Despite the larger size, Embospheres have several ideal characteristics of an embolic agent: they are spherical and have a hydrophilic surface that prevents aggregation, which results in a lower rate of catheter occlusion and better penetration into the more distal small vessels (Rand et al, 2005). Recently, 40- to 120-μm Embospheres became available. Maluccio and colleagues (2008) performed bland embolization using PVA particle (50 μm) or microspheres (40 to 120 μm) in 322 patients with HCC and reported 1-, 2-, and 3-year overall survival rates of 66%, 46%, and 33%, respectively. In patients without extrahepatic disease or portal vein involvement by tumor, the overall 1-, 2-, and 3-year survival rates increased to 84%, 66%, and 51%, respectively. Subgroups of patients with solitary HCC who also underwent thermal ablation the day after bland embolization had similar survival results after surgical resection (Maluccio et al, 2005). The same authors reported results of bland embolization in metastatic NETs and metastatic sarcomas that parallel those reported by others using chemoembolization (Brown et al, 1999; Maluccio et al, 2006).

Drug-eluting beads (DEBs) are specifically designed PVA beads that release chemotherapeutic drugs over an extended period. DEBs consist of nondegradable hydrogel microspheres based on PVA with a smooth surface and a precisely calibrated size that ranges from 100 to 900 μm. They are characterized by a high content of negatively charged 2-acrylamido-2-methylpropanesulfonate (AMPS). The unsaturated AMPS monomer crosslinks the PVA backbone and allows the load and release of positively charged drugs, such as doxorubicin hydrochloride or irinotecan hydrochloride, by an increased number of negatively charged sulfonate moieties (Hong et al, 2006). DEBs can achieve higher doses of the chemotherapeutic drugs and can prolong contact time with cancer cells and thus enhance therapeutic efficacy and at the same time reduce toxicity because of minimum systemic exposure (Hong et al, 2006).

The DC Bead (Biopcompatibles, Surrey, UK) is a DEB that has proven favorable kinetics and clinical characteristics (Lewis et al 2006a, 2006b; Varela et al, 2007). Malagari and colleagues (2008) treated 62 patients with single, unresectable HCC 3 to 9 cm using DC Beads impregnated with doxorubicin. After three sessions of chemoembolization, a complete response was seen in 12.2%, and an objective response was seen in 80.7%, according to EASL criteria. Lammer and colleagues (2010) conducted a prospective randomized trial to compare conventional chemoembolization with chemoembolization using DC Beads. The DEB group showed higher rates of complete response, objective response, and disease control compared with the conventional chemoembolization group (27% vs. 22%, 52% vs. 44%, and 63% vs. 52%, respectively) determined by EASL criteria at 6 months. A subgroup with more advanced disease (CTP class B, ECOG 1, bilobar disease, and recurrent disease) showed a significant increase in objective response compared with conventional chemoembolization. Moreover, DC Beads were associated with improved tolerability, with a significant reduction in serious liver toxicity and a significantly lower rate of doxorubicin-related side effects. DEBs loaded with irinotecan and oxaliplatin for treatment for metastatic liver tumors are under investigation (Martin et al, 2009; Poggi et al, 2008).

CONCLUSION

Hepatic artery embolotherapy is an effective palliative treatment in primary and secondary liver tumors. It is useful in local tumor control, prevents tumor progression, prolongs patient survival, and controls symptoms. Chemoembolization is the first-line treatment in selected patients with unresectable HCC.

The treatment protocol should be tailored according to each individual patient's condition. Most complications of hepatic embolotherapy are controllable and can be avoided by strict selection of patients and use of proper technique during the procedure. Combination with other liver-directed therapy improves local tumor control, but survival benefit has not been verified. New embolic agents that include microspheres and drug-eluting beads have shown encouraging preliminary results.

References are available at expertconsult.com.

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CHAPTER 84A

Radioembolization for liver tumors

Ahsun Riaz and Riad Salem

OVERVIEW

Interventional oncology is a field that is establishing its role in the management of liver tumors. The techniques used in this field are targeted to the tumors to allow delivery of toxic chemotherapeutic, radiotherapeutic, and thermal doses with minimal toxicity to normal structures; this minimizes the systemic toxicity associated with these therapeutic options and allows delivery of doses to the tumor that would not be possible using systemic delivery methods. In this chapter, the general concepts associated with radioembolization and its specific use in different primary and secondary malignancies of the liver will be discussed (Table 84A.1)

Vascular Anatomy of the Liver and Its Tumors (See Chapter 1B)

Portal Vein

The normal hepatic parenchyma is predominantly supplied by the portal vein. This unique vascularization lets the hepatocytes carry out their metabolic functions on the numerous substances absorbed from the gastrointestinal (GI) tract. It also makes the liver a common site of metastasis for GI cancers.

Hepatic Artery

The proper hepatic artery that supplies the liver is a continuation of the common hepatic artery, a branch of the celiac trunk. The proper hepatic artery branches into the right and left hepatic arteries, which supply the corresponding lobes of the liver. The cystic artery supplying the gallbladder usually arises from the right hepatic artery, and the right and left hepatic arteries give rise to the segmental branches; these eventually branch into the small vessels found in the portal triads.

Unlike the normal hepatic parenchyma, liver tumors are supplied primarily by hepatic arterial blood and are hypervascular structures compared with the surrounding uninvolved parenchyma (see Chapter 86). Hepatic tumors may parasitize arterial blood flow from the arteries that supply segments adjacent to the segment the tumor is in and those of surrounding organs, such as the stomach. This relative arterial hypervascularity of the tumors with respect to the normal parenchyma has been the basic principle behind transarterial therapies for targeting liver tumors.

HISTORY OF RADIOEMBOLIZATION

External Radiation (See Chapter 84B)

The use of external radiation for liver tumors has traditionally held limited value because of the sensitivity of the normal hepatic parenchyma to the radiation dose (Ingold et al, 1965; Geschwind et al, 2004). A dose greater than 35 Gy has led to the development of a radiation-induced liver disease (RILD); a clinical syndrome of ascites, anicteric hepatomegaly, and elevation of liver enzymes. Conformal-beam therapy, which uses a three-dimensional approach rather than broad axial plane techniques, has been shown to minimize the toxicity to normal hepatic parenchyma (Dawson et al, 1999). However, even when using conformal-beam therapy, the radiation delivered to normal hepatic parenchyma limits the maximum dose that can be delivered to the tumor without compromising safety.

External-beam radiation had limitations in treating liver tumors in specific locations; this includes tumors near the dome of the liver, which carry the risk of exposing the lungs to radiation and increasing the risk of radiation pneumonitis, and tumors in the caudate lobe in close proximity to the porta hepatis, where risk of damage to the major biliary and vascular structures is a consideration. *Dose fractionation,* dose delivery to the tumor in fractions, is beneficial in targeting radiosensitive and radioresistant malignant cells at different sessions, but multiple treatments are required. The normal tissue complications probability (NTCP) is an important parameter when calculating radiation dose delivery (Dawson et al, 2002), but its use has been challenged (Langer et al, 1998). Respiratory movement must be considered to minimize the incidence of normal tissue complications, although recent advances in the technology of external-beam radiation have been shown to increase safety and efficacy of this technique, such as stereotactic body radiotherapy, proton radiotherapy, and carbon ion radiotherapy; these are establishing the role of external-beam radiotherapy in the management of liver tumors (Dawson & Guha, 2008; Fukumitsu et al, 2009; Nomiya et al, 2008).

Radioembolization

Given the distinct vasculature of hepatic tumors described above, radioembolization provides a mode of delivering localized radiotherapy to the tumor. A radiation dose of up to 150 Gy can be administered, minimizing the complications of external radiation. Radioembolization has been shown to have promising outcomes in primary and secondary hepatic malignancies by numerous investigators.

Radioembolization was first studied by Nolan and Grady (1969) using yttrium-90 oxide ($^{90}Y_2O_3$) contained in a metal particle 50 to 100 μm in size. Their study consisted of a small number of patients but showed a favorable response, observed by the reduction in size of palpable masses. The next ^{90}Y study was published in 1982 by Mantravadi and colleagues and studied the effect and distribution of ^{90}Y after whole-liver delivery via the hepatic artery; the authors concluded that patients with hypervascular tumors are much more likely to benefit from this treatment. A dose-escalation study on animals

Table 84A.1

Radionuclide Carrier Combinations for Radioembolization

Radionuclide	Device	Carrier	Half-Life (hours)	Maximum β-Emission (MeV)	Maximum γ-Emission (keV)	Size of Particles (μm)
^{90}Y	SIR-Spheres*	Resin microspheres	64.2	2.3	0	20-60
	TheraSphere†	Glass microspheres	64.2	2.3	0	20-30
^{166}Ho	Milican‡	Chitosan	26.8	1.8	80.6	NA
	^{166}HoMS	Poly-L-lactic acid	26.8	1.8	80.6	25-35
^{188}Re	^{188}Re HDD-Lipiodol	Iodized oil	16.9	2.1	155	N/A
^{32}P	^{32}P-GMS	Glass microspheres	342.7	1.7	0	46-76
^{131}I	^{131}I-Lipiodol	Iodized oil	192.5	0.6	364	NA

*SIR-Spheres, Sirtex Medical, Woburn, MA
†TheraSphere, MDS Nordion, Ottawa, ON, Canada
‡Milican, Dong Wha Pharmaceutical, Seoul, Korea
GMS, glass microspheres; HDD, 4-hexadecyl-1,2,9,9-tetramethyl-4, 7-diaza-1, 10-decanethiol; HoMS, holmium microspheres; NA, not available

was performed, which formed the basis of the Phase I dose-escalation evaluations in humans (Wollner et al, 1987). Shepherd and colleagues (1992) conducted a Phase I dose-escalation study using ^{90}Y microspheres in 10 patients. Extrahepatic shunting was assessed using technetium-99m–labeled macroaggregated albumin (^{99m}Tc-MAA). In contrast to earlier studies, none of the patients in this study experienced hematologic toxicity, a fact that emphasizes the value of assessing angiographic findings and extrahepatic shunting before treatment (Shepherd et al, 1992). The technical aspects of dosimetry, radioassays, safety, and efficacy were discussed by many studies that followed (Andrews et al, 1994; Yan et al, 1993). Lau and colleagues (1994) showed that tumor response was proportional to the dose delivered, with improved survival in patients receiving more than 120 Gy. Recent data on the safety and efficacy of this treatment are discussed below.

^{90}YTTRIUM MICROSPHERES

Overview

^{90}Yttrium is the radioactive element most commonly used for radioembolization. It is a pure β-emitter with a half-life of 64.2 hours, and it decays into the stable element zirconium-90. Tissue penetration of the emissions ranges from 2.5 to 11 mm.

Pretreatment Evaluation

Clinical Evaluation

Clinical evaluation is required to stratify patients according to the Eastern Cooperative Oncology Group (ECOG) performance status, and those with a score greater than two are not considered ideal candidates for this treatment.

Laboratory Workup

The laboratory workup is important to assess the pretreatment functional status of the liver. This should include assessment of liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase), bilirubin, albumin, and tumor markers such as α-fetoprotein (AFP).

Pretreatment Angiography and Coil Embolization

Radioembolization requires pretreatment diagnostic mesenteric angiography. The aortogram, superior mesenteric angiogram, and celiac trunk angiogram allow the interventional radiologist an opportunity to study the vascular anatomy of the liver and its surrounding structures in detail. The patency of the portal vein and the presence of arterioportal shunting are assessed. The inadvertent spread of the microspheres is prevented by a meticulous study of the vascular anatomy of the liver and collateral nontarget flow (Covey et al, 2002). Coil embolization of nontarget vessels may be necessary to decrease the unintended deposition of microspheres. Some examples of vessels that may need to be embolized are inferior esophageal, left inferior phrenic, accessory left gastric, supraduodenal, and retroduodenal arteries. The minimal incidence of complications following coil embolization and the grave clinical consequences associated with the inadvertent deposition of microspheres in the stomach, duodenum, or pancreas favor prophylactic coil embolization before radioembolization in select cases.

^{99m}Technetium Macroaggregated Albumin Scan

The ^{99m}Tc-MAA scan is used to assess splanchnic and pulmonary shunting. This pretreatment nuclear scan is important to prevent certain complications associated with the treatment. The proximity of the duodenum and stomach to the liver may make it difficult to assess shunting to these portions of the GI tract by using nuclear medicine scans alone. Thus, it is important to correlate the findings of angiography to the findings of the ^{99m}Tc-MAA scan. The lung shunt fraction (LSF) is used to calculate the dose delivered to the lungs, and adjustment for this parameter minimizes the risk of radiation pneumonitis that may be seen after radioembolization.

All hepatic vessels are assessed during the angiogram, and the arteries feeding the tumor are studied in detail. As the tumor may parasitize blood flow from surrounding vessels, it is necessary to study its vascular supply in detail. Failure to recognize a vessel supplying the tumor may lead to the incomplete targeting of the lesion and treatment failure.

Available Devices

TheraSphere

TheraSphere (MDS Nordion, Ottawa, ON, Canada) consists of nonbiodegradable glass microspheres with diameters ranging from 20 to 30 μm. It was approved by the Food and Drug Administration (FDA) in 1999 and recently has been approved for use in hepatocellular carcinoma (HCC) patients with portal

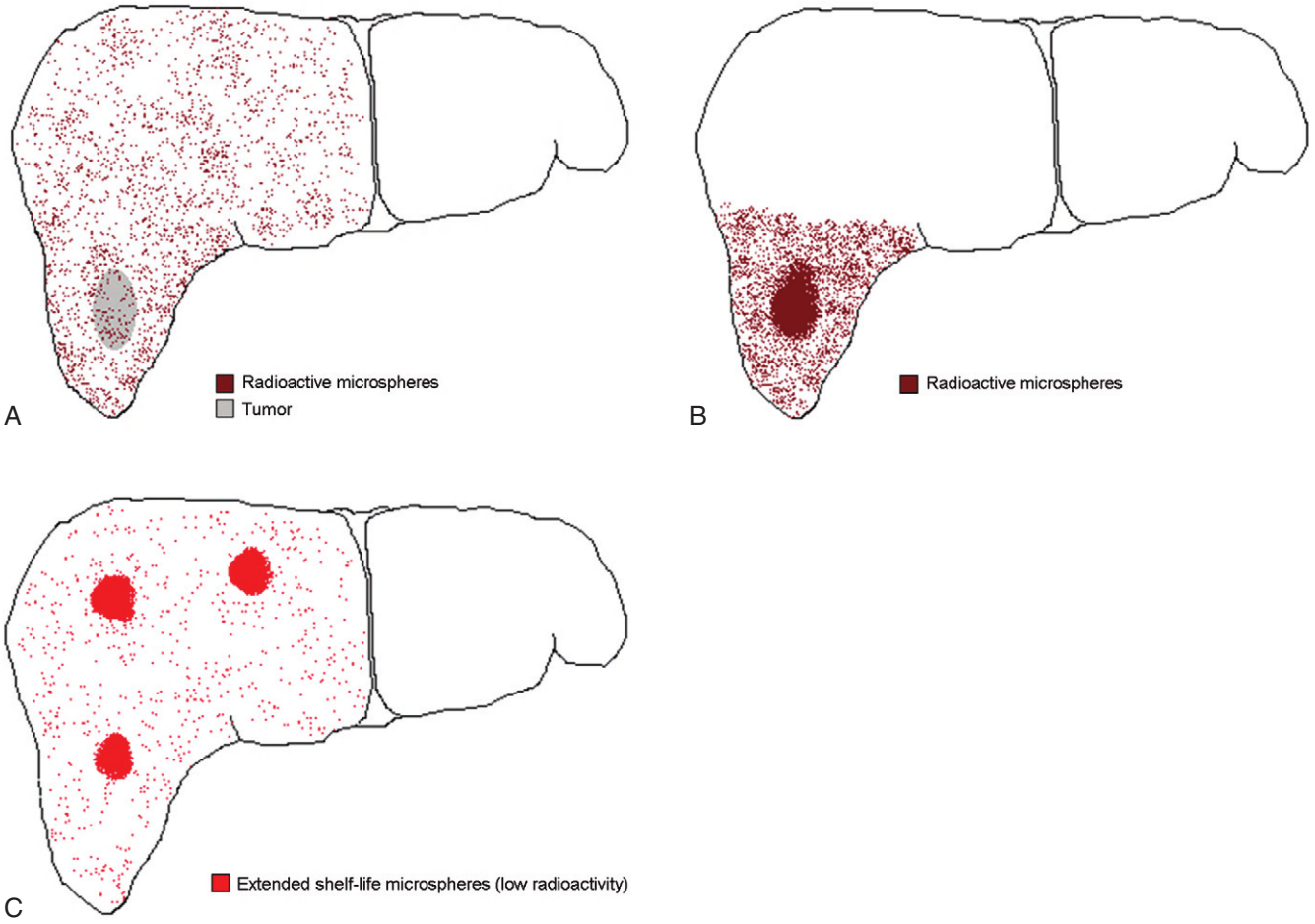


FIGURE 84A.1. A, Schematic representation of the current dosimetric model for TheraSphere (MDS Nordion), which assumes uniform distribution of the microspheres in the normal parenchyma and tumor. **B,** Schematic representation of radiation segmentectomy with highly radioactive particles preferentially accumulating in the tumor because of its arterial hypervascularity and microspheres accumulating in the surrounding parenchyma of the injected segments. **C,** Schematic representation of extended shelf life microspheres with microspheres with lower activity preferentially accumulating in the tumor, because of its arterial hypervascularity, and in the surrounding parenchyma of the injected lobe.

vein thrombosis (PVT). Vials of six different activities are available; the only difference in the vials is the number of spheres; 1.2 million microspheres are present in a vial with an activity of 3 GBq. Each microsphere has an activity of 2500 Bq at the time of calibration. The activity of the vial varies inversely with the time elapsed after calibration.

DOSE CALCULATION FOR THERASPHERE. The calculation of the dose requires the use of three-dimensional reconstruction of the target site to calculate the volume of the liver to be infused. The volume in cubic centimeters is then used to calculate the mass in grams by multiplying it by a factor of 1.03.

The activity (A) in GBq administered to the target area of the liver, assuming uniform distribution of microspheres (Fig. 84A.1A), is calculated using the following formula:

$$A = D \times m/50$$

D is the dose administered in Grays, and m is the mass in kilograms. Using this formula, it can be said that a dose of 50 Gy will be administered to 1 kg of tissue if 1 GBq of ^{90}Y is given.

The dose given to the treated mass also depends on the percent residual activity (R) in the vial after treatment and the LSF, which is calculated beforehand. These factors are accounted for in the following formula:

$$D = A \times 50 \times (1 - LSF) \times (1 - R)/m$$

SIR-Spheres

SIR-Spheres (Sirtex Medical, Woburn, MA) consist of biodegradable resin microspheres that have a slightly increased diameter and lower specific gravity per microsphere than TheraSphere. The use of SIR-Spheres was approved by the FDA for metastatic colorectal cancer to the liver in 2002. One vial of 3 GBq is available with 40 to 80 million microspheres, with each microsphere measuring from 20 to 60 μm.

As suggested by the small particle size, the embolic effect of the available microscopic spheres is minimal. They are known to lodge in the precapillary arterioles, but their small size also allows deep penetration into the tumor with minimal changes in the vascular supply to the tumor. It has been suggested that hypoxia of the tumors induced by embolization, instead of anoxia, may lead to the release of vascular endothelial growth

Table 84A.2

Empiric Method for Dose in SIR-Spheres*

Tumor Involvement of Liver (%)	Dose (Whole Liver)
≤25	2 GBq
25-50	2.5 GBq
>50	3 GBq

*Sirtex Medical, Woburn, MA

factor (VEGF) and hypoxia-inducible factor-1, which may lead to neovascularization of the tumor and subsequent incomplete necrosis and tumor recurrence.

DOSE CALCULATION FOR SIR-SPHERES. Three methods for dosimetry of SIR-Spheres are recommended by the manufacturers. The *partition method* is seldom used, as it is applicable only in special circumstances. The *empiric method* is outlined in Table 84A.2.

The model of dosimetry for SIR-Spheres is based on whole-liver infusion. The calculated gigabecquerels of the whole liver are multiplied by the percentage of the target site as a proportion of the whole liver. The most widely used body surface area (BSA) method is as follows:

$$A = BSA - 0.2 + (\%\ \text{Tumor burden}/100)$$

A is the activity in gigabecquerels, *BSA* is the body surface area in meters squared, and *% tumor burden* is the percentage of the liver involved by tumor.

New Concepts

Radiation Segmentectomy

Recently, the concept of radiation segmentectomy has been discussed. This is schematically shown in Figure 84A.1B. The current dosimetry models assume lobar infusion; however, if the tumor is localized to two or fewer liver segments, the interventional radiologist can infuse the dose at the segmental level. This maximizes the dose delivery to the tumor and minimizes delivery of radioactive microspheres to the normal parenchyma (Riaz et al, 2010), an approach that has proven to be a safe and effective method of treatment delivery.

Extended Shelf Life Microspheres

Lewandowski and colleagues (2009b) recently published a report on the concept of extended shelf life microspheres, which can be used for large or multifocal tumors. As stated above, the difference in vials of different activities is the number of microspheres. If the vials of high activities (more microspheres) are allowed to stay on the shelf longer, the activity per microsphere will decrease. This allows the delivery of a higher number of microspheres to larger volumes of the liver with minimal radiotoxicity to the normal parenchyma (Lewandowski et al, 2009b).

Radiation Lobectomy

An animal study concluded that portal fibrosis was seen after the use of radioactive microspheres (Wollner et al, 1988). Gaba and colleagues (2009) recently published a comprehensive analysis on the concept of radiation lobectomy, whereby infusion at the lobar level was used to treat the tumors. Because of fibrosis of the normal parenchyma, decreases in volumes of the treated lobe were seen. Furthermore, compensatory increases in the volumes of the untreated lobes were also observed.

New Concepts

Blood Flow Patterns for Dose Calculation

Kennedy and colleagues (2010) have recently published their analysis on computer modeling of ^{90}Y resin microsphere transport in the hepatic arterial tree. They conclude that computer simulations of both blood flow patterns and microsphere dynamics have the potential to provide insight on methods to optimize microsphere implantation into hepatic tumors while sparing normal tissue.

Transcatheter ^{90}Y Radioembolization

Radioembolization is a transcatheter therapy performed by interventional radiologists. The tumor is approached using its arterial supply, and the vial is injected into the vessel feeding the tumor. The distribution of the tumor is the factor that allows the treatment to be selective, allowing delivery to one lobe, or superselective, allowing delivery to one segment. The apparatus for the administration of ^{90}Y is designed to minimize the radiation exposure to those involved in the procedure, but a physicist should be present throughout the case to ensure that proper protocols are followed to minimize accidental radiation exposure. The procedure is performed on an outpatient basis, and the patient is discharged on the same day (Salem et al, 2002).

OTHER RADIONUCLIDES

Iodine-131–Labeled Iodized Oil and Iodized Oil (Lipiodol)

Lipiodol is a poppyseed oil that contains 38% iodine by weight. Normal hepatocytes are able to remove Lipiodol in 7 days, whereas HCC retains it for weeks. Stasis is associated with Lipiodol, hence an embolic effect is associated with this conjugate. It is a radiopaque substance and is visualized on posttreatment CT scans in the target lesion.

Overview

The half-life of ^{131}I is 8 days. This radionuclide is a β- and γ-emitter. The use of ^{131}I-Lipiodol has been studied in a prospective trial and compared in efficacy to chemoembolization (Raoul et al, 1997). The iodine moiety of Lipiodol can be substituted for the radionuclide ^{131}I.

Administration

Angiography is performed, and the ^{131}I-Lipiodol is administered only after studying the vascular anatomy of the liver. The dose is usually given via a 3-mL injection in the main hepatic artery, if the vascular anatomy is found to be normal. Extreme caution must be taken during administration, as dissolution of the plastic catheters has been seen. In addition, the thyroid gland is susceptible to the toxicity of ^{131}I; hence the thyroid is medically blocked before and after the treatment to minimize toxicity to the gland. Because the radionuclide is excreted in urine, the patient must be hospitalized for 6 to 7 days after treatment as a radioactivity safety measure. Patients are also

told to refrain from possible conception until 6 months after treatment.

Conclusion

The outcomes associated with ^{131}I-Lipiodol are comparable to those of transarterial chemoembolization (TACE; see Chapter 83), but significantly fewer serious adverse events are reported with the use of this radionuclide as compared with using TACE. ^{131}I is expensive, but the isotope has high γ-energy with a short β-range, which decreases its cytotoxic effect. Furthermore, hospitalization after the procedure decreases the cost-effectiveness of ^{131}I (Raoul et al, 1997).

Rhenium-188 HDD–Labeled Iodized Oil

Overview

Transarterial radionuclide therapy (TART) with rhenium-188 4-hexadecyl-1,2,9,9-tetramethyl-4, 7-diaza-1, 10-decanethiol (HDD)–labeled iodized oil has been recently studied for use in inoperable HCC. ^{188}Re has a shorter half-life (16.9 hours), high β-energy (maximum 2.1 MeV) and low γ-energy (155 keV) emissions, and it is available through a tungsten-188 (^{188}W-^{188}Re) generator.

Administration

The quantity of ^{188}Re-HDD iodized oil (Lipiodol) administered is based on the radiation absorbed dose (RAD) to critical organs, which is calculated after transarterial administration of a test dose of the radioconjugate (Kumar et al, 2007). The critical organs include the bone marrow, lung, and normal liver, and the dose limitations to them are 1.5 Gy, 12 Gy, and 30 Gy, respectively. A scout dose of 185 MBq activity of the radioconjugate is injected, and a whole-body nuclear scan is performed to calculate the RAD to the critical organs. The dose is then calculated and administered on the same day.

Conclusion

The incidence of serious adverse events is low with this treatment, and a survival benefit in HCC patients has been reported in published literature (Kumar et al, 2007); Liepe and colleagues (2007) have also published their experience of 10 patients. Its easy availability and published data make TART seem a promising mode of treatment of HCC; however, as of this writing, data are insufficient to recommend use of this radionuclide in metastatic disease to the liver.

OTHER ^{188}RHENIUM CARRIER COMBINATIONS. There are other ^{188}rhenium carrier combinations under study, such as ^{188}Re-bis-(diethyldithiocarbamato) Lipiodol (^{188}ReN-DEDC Lipiodol), ^{188}Re-(S_2CPh)(S_3CPh)$_2$ Lipiodol (^{188}Re-SSS Lipiodol), and ^{188}Re-labeled human serum albumin (HSA B20) microspheres (Lambert et al, 2009). ^{188}Re–hyaluronic acid combinations are also being studied as a systemically administered agent for HCC in animals, as hyaluronic acid selectively binds to CD44 receptors (Melendez-Alafort et al, 2009).

Phosphorus-32 Glass Microspheres

Overview

^{32}P is a radioisotope that emits high-energy β-particles during decay. It has a half-life of 14.28 days and a maximum tissue penetration of 8 mm, with an average of 3.2 mm (Wong et al, 1999). It is administered as an integral constituent of nonbiodegradable glass microspheres.

Administration

The dose is calculated by the following formula based on the pharmacokinetics and distribution of ^{32}P glass microspheres:

$$D = 20 \times A/m$$

D is the dose in grays, *A* is the activity in gigabecquerels, and *m* is the mass in kilograms. The administration is via a transarterial approach, after angiography has been performed to study the vascular anatomy of the liver.

Conclusion

The half-life of this radionuclide gives it the advantage of a lower required dose and a potential to have a decreased radiation exposure to handlers, compared with the other radionuclides available. It has been tolerated well in animal and human trials, although its role in the management of liver tumors is yet to be established.

Milican/Holmium-166 Microspheres

^{166}Ho is a β- and γ-emitter. This radionuclide is highly paramagnetic; hence it acts as a negative contrast agent, like iron, on magnetic resonance imaging (MRI; Bult et al, 2009). It is also radiopaque and visible on computed tomography (CT) (Bult et al, 2009).

Holmium/chitosan complex (Milican; Dong Wha Pharmaceutical, Seoul, Korea) has been shown to be effective in treating small HCC in a novel study from Korea (Kim et al, 2006). Chitosan is a unique substance derived from chitin. It has the ability to liquefy in an acidic environment and form a gel in basic environments, and the gel has embolic effects.

Microspheres of ^{166}Ho poly-L-lactic acid are being studied in animal models and have been shown to be safe, but they have yet to be studied in humans (Vente et al, 2010). ^{166}Ho has also recently been studied with hydroxyapatite as the carrier in animal models (Das et al, 2009).

PRIMARY LIVER TUMORS

The role of radioembolization has been studied in detail for the treatment of the most common primary malignant tumor, HCC. Its use in the management of cholangiocarcinoma has also been studied.

Role of Radioembolization in Management of Hepatocellular Carcinoma (See Chapter 80)

Patient Selection

The various diagnostic criteria and staging systems for HCC are beyond the scope of this chapter (Bruix et al, 2001). The management of HCC requires a multidisciplinary approach with the involvement of hepatologists, oncologists, transplant surgeons, and interventional radiologists. Patients should be selected for this treatment modality based on a consensus of the team. As discussed below, the role of radioembolization is not limited by the stage of the disease, but no survival benefit has been seen in patients with distant metastases.

Indications and Efficacy

PATIENTS WITHIN TRANSPLANT CRITERIA. The use of surgical options is the gold standard of treatment for these patients. The patients within the Milan criteria, with a single lesion less than 5 cm or three or fewer lesions all less than 3 cm, are eligible for orthotopic liver transplantation (OLT; see Chapter 97D; Mazzaferro et al, 1996). Resection is possible only if liver function is preserved (see Chapter 90F). The limited availability of donor organs for OLT and the dropout of patients as a result of tumor progression limits the number of patients who are able to undergo OLT. Thermal ablation (radiofrequency ablation) has a limited role because of the risk of tract seeding and the size and location of tumor (see Chapter 85). Radioembolization has been shown to limit progression of the disease, which allows the patient more time to wait for donor organs and thus increases their chance of undergoing OLT (Kulik et al, 2006). Thus radioembolization has a role in bridging patients to OLT.

PATIENTS BEYOND TRANSPLANT CRITERIA. Patients outside the transplant criteria as a result of the size or number of tumors but who do not have malignant PVT or metastatic HCC may also be candidates for radioembolization, which has been shown to downstage the disease in these patients to within transplant criteria. This allows patients who were initially outside Milan criteria to become eligible for OLT with an increase in overall survival reported in these patients as well (Kulik et al, 2006). Lewandowski and colleagues (2009a) recently published their experience of downstaging using transarterial therapies for HCC. Their data suggest a superior ability of radioembolization to downstage HCC compared with chemoembolization. The recurrence-free survival and overall survival after OLT in the downstaged patients has yet to be compared with that of the patients who were already within transplant criteria to determine the efficacy of downstaging.

PATIENTS WITH ADVANCED DISEASE. Patients with PVT have been shown to have a favorable response to treatment after radioembolization (Kulik et al, 2007). The presence of malignant PVT excludes these patients from transplantation, whereas its presence is not a contraindication to radioembolization with ^{90}Y. Systemic therapy with sorafenib has been shown to have a statistically significant improvement in survival in patients with advanced disease (Llovet et al, 2008; see Chapter 88). The hepatic artery is the sole vascular supply to the parenchyma in the presence of PVT, hence embolic therapies are relatively contraindicated. However, ^{90}Y may be used in these cases because of its minimal embolic effect (Kulik et al, 2007). A survival benefit (10.1 to 13.4 months from treatment) has been shown with the use of radioembolization in patients with malignant vascular involvement (Kulik et al, 2007). A survival benefit has not been shown in patients with distant metastases (Salem et al, 2010).

Conclusion

Recently, Salem and colleagues (2010) published a comprehensive analysis on the role of radioembolization in 291 patients with HCC. The data presented suggest that radioembolization is a safe and effective treatment modality. The response rate and promising survival associated with this therapy have established its role in the management of HCC in many centers around the world.

Role of Radioembolization in Management of Intrahepatic Cholangiocarcinoma (See Chapter 50A)

Resection is the best treatment option in patients who have limited disease, and it has been shown to improve survival. The role of chemoembolization for intrahepatic cholangiocarcinoma (ICC) has been studied, and an improvement in survival has been shown, but the rate of toxicity remains high. Radioembolization has been shown to be effective in the treatment of HCC, but its role in the management of ICC has not been extensively studied. A study analyzing the use of ^{90}Y in patients with ICC has shown a favorable response to treatment and favorable survival outcomes (Ibrahim et al, 2008). Patients with a better performance status according to the Eastern Cooperation Oncology Group had a significantly better survival in this study. Saxena and colleagues (2010) recently published their analysis of 25 patients with ICC who underwent radioembolization with resin microspheres. They conclude that ^{90}Y radioembolization is safe and effective, and in the absence of other therapeutic options, this treatment warrants further investigation.

SECONDARY LIVER TUMORS

Metastatic disease to the liver is common because of the liver's unique anatomy and dual vascular supply. The presence of multiple metastases and comorbidities limits the role of surgical resection in these patients (Welsh et al, 2006). The role of radioembolization alone and as a conjunct to systemic chemotherapy has been well established.

Role of Radioembolization in the Management of Metastatic Colorectal Carcinoma (See Chapter 81A)

Overview

Resection is the only curative option available for colorectal cancer (CRC) that has metastasized to the liver, although a small fraction of patients have disease that is amenable to resection (Welsh et al, 2006). Systemic chemotherapy for this disease is beyond the scope of this chapter, but some commonly used chemotherapeutic agents are 5-fluorouracil (5-FU), oxaliplatin, irinotecan (CPT-11), bevacizumab, cetuximab, and capecitabine (see Chapter 86). The favorable role of radioembolization in treatment of metastatic CRC to the liver has been published (Mulcahy et al, 2009).

Patient Selection

Patient selection criteria for radioembolization for metastatic CRC to the liver are very similar to those for HCC. Patients who have unresectable disease and are on systemic chemotherapy or those who failed to respond to first- or second-line chemotherapeutic agents are considered as candidates for radioembolization. The carcinoembryonic agent (CEA) is measured, and radiologic studies are performed prior to and following treatment to assess response. Fluorodeoxyglucose positron-emission tomography (FDG PET) has been shown to have better sensitivity in assessing tumor response to internal radiation for treatment of metastatic CRC than CT; however, more data are required before functional imaging can replace the conventional imaging techniques, such as contrast-enhanced CT, for response measurement.

Efficacy of Radioembolization

The effect of systemic chemotherapy alone has been compared to its combined effect with radioembolization in a randomized control trial. The combination has been shown to have a significantly better tumor response, a longer time to progression, survival benefit, and an acceptable safety profile (Gray et al, 2001). The use of internal radiation alone has also been published in many series and has shown promising results (Kennedy et al, 2005; Mulcahy et al, 2009), and dose-escalation studies have shown better response with increasing doses (Goin et al, 2003). A recent study on the concomitant use of irinotecan and radioembolization in fluorouracil-refractory patients with CRC hepatic metastases showed that the maximum-tolerated dose was not reached (Van Hazel et al, 2009).

Role of Radioembolization in the Management of Metastatic Neuroendocrine Tumors (See Chapter 81B)

Overview

Metastatic disease to the liver from a primary neuroendocrine tumor (NET) is common. Although most often nonfunctional, some NETs produce excessive amounts of hormones associated with debilitating clinical syndromes, such as carcinoid syndrome: vasoactive intestinal tumors (VIPomas), gastrinomas, and somatostatinomas are some examples. Systemic chemotherapy and ablative procedures have been shown to have a modest benefit in these patients, and patients with unresectable disease are candidates for radioembolization. Clinical improvement, serum chromogranin A levels, and imaging studies prior to and following treatment are used to assess response to radioembolization.

Evidence

Radioembolization of metastatic disease to the liver from a neuroendocrine neoplasia has been shown to be effective and safe. A prolonged response to treatment, greater than 2 years, has also been seen (Kennedy et al, 2008; Rhee et al, 2008b). King and colleagues (2008) recently published their experience with 34 patients and concluded that radioembolization can achieve relatively long-term responses in patients with nonresectable NET liver metastases.

Role of Radioembolization in the Management of Metastatic Mixed Neoplasia

Overview

The role of radioembolization in hepatic metastases from primary neoplasia other than the ones listed above is discussed under the heading of *metastatic mixed neoplasia*. The following secondary tumors have been treated using radioembolization, but only metastatic breast cancer has been studied in detail (see Chapter 81C).

Internal Radiation to Metastatic Breast Cancer to Liver

Breast cancer is the most common cancer in women and has a tendency to metastasize to the liver. Radioembolization presents an efficacious treatment for unresectable breast cancer metastasis to the liver (Coldwell et al, 2005). Radiologic response has been seen following radioembolization in these patients, but the survival benefit of this treatment in this population has not been established (Jakobs et al, 2008b).

Other

Radioembolization has been used to treat secondary liver tumors from various primary sources. This mode of treatment is an effective alternative to patients who have failed chemotherapy or who have become chemorefractory (Sato et al, 2008). The data suggest a similar benefit in survival and tumor response in metastatic liver tumors from the metastatic mixed neoplasia.

POSTTREATMENT ASSESSMENT

Clinical and Laboratory Parameters

The response to treatment can be monitored clinically and radiologically. The regular follow-up laboratory workup includes the hepatic panel and tumor markers—such as AFP, CEA, and carbohydrate antigen (CA) 19-9—to look for any toxicity as a result of treatment and to assess clinical improvement in the patient. Decrease in AFP in patients with HCC has recently been shown to be an indicator of prognostic benefit following transarterial locoregional therapies (Riaz et al, 2009a).

Radiologic Parameters

The first radiologic study is done 1 month after treatment. Patients are then followed with scans every 3 months to assess response to treatment or progression of disease. The use of the World Health Organization (WHO) and Response Evaluation Criteria In Solid Tumors (RECIST) are based on decreases in the size of the lesion irrespective of the amount of necrosis seen in the tumor. The European Association for the Study of the Liver (EASL) necrosis criteria are also used to assess response in the target lesions (Ibrahim et al, 2009), and the WHO and EASL guidelines have been shown to correlate well with pathologic necrosis (Riaz et al, 2009c). The conventional anatomic imaging studies are not able to assess tumor response until 6 weeks after treatment. Functional MRI may have a role in earlier detection of tumor response (Rhee et al, 2008b); however, more data are required before functional imaging can replace the conventional imaging guidelines for response assessment.

COMPLICATIONS OF RADIOEMBOLIZATION

Postradioembolization Syndrome

Patients may experience a mild postradioembolization syndrome, which comprises signs and symptoms that include fatigue, nausea, vomiting, anorexia, fever, abdominal discomfort, and cachexia. These are usually not severe enough to require hospitalization, although some serious adverse events related to radioembolization are explained below and have been discussed in detail previously (Riaz et al, 2009b).

Hepatobiliary Toxicity

Hepatic Injury

Radiation-induced liver disease (RILD) usually occurs between 4 and 8 weeks after radioembolization. Hepatic toxicity is

measured by a change in the liver enzymes and metabolites, including ALT, AST, alkaline phosphatase, albumin, and bilirubin. Using the Common Terminology Criteria version 3.0 to assess toxicity to the liver following radioembolization, the grade 3 and 4 toxicity rates following radioembolization have been low (Salem et al, 2010; Sangro et al, 2008; Young et al, 2007). The clinical appearance of ascites and jaundice is very rarely seen.

The histologic hallmark of venoocclusive disease (VOD) may be seen in severe cases (see Chapter 77). Hepatic toxicity is rarely so severe as to lead to significant morbidity and mortality (Sangro et al, 2008). The presence of factors such as a deranged hepatic function at baseline, age, and activity delivered may predispose patients to the hepatotoxic effects of radioembolization.

Biliary Injury

The biliary tract is also susceptible to toxicity by radioembolization. According to Rhee and colleagues (2008a), less than 2% of patients required intervention for the biliary toxicity induced by radioembolization. These included two cholecystectomies, drainage of three bilomas, and one abscess. Radiation-induced cholangitis has also been reported following ^{90}Y administration (Rhee et al, 2008a); however, these are not common, and meticulous technique can minimize their incidence.

Portal Hypertension

Radioembolization has been shown to cause fibrosis that may lead to portal hypertension by changing the volume of the treated lobe. The time it takes for development of portal hypertension is variable (Jakobs et al, 2008a), but it is more often associated with bilobar treatment, and its incidence is increased in patients who have chemotherapy-associated steatohepatitis (CASH; see Chapter 65). The presence of preexisting cirrhosis leading to portal hypertension in most HCC patients makes them more susceptible to the aggravation of this complication as well (Riaz et al, 2009b).

Radiation Pneumonitis

Dose adjustment is required, and caution must be exercised, when the LSF is greater than 13% (Leung et al, 1995). A restrictive pulmonary dysfunction is seen after radioembolization in a few cases with a predisposing high LSF. The LSF is used to calculate the dose that would be administered to the lung, and an absolute contraindication to radioembolization is the predicted administration of a dose greater than or equal to 30 Gy to the lungs in a single treatment or greater than 50 Gy as a cumulative dose after multiple treatments (MDS Nordion, 2004). The presence of radiation pneumonitis can be diagnosed clinically and on finding consolidation on CT, evidenced by a bat-wing appearance.

Gastrointestinal Complications

GI complications after radioembolization have been reported and are due to the inadvertent spread of microspheres to the GI tract (Carretero et al, 2007; Murthy et al, 2007a). Ulceration may occur and may require surgery for treatment; however, it can be prevented by meticulous mapping of the blood vessels to look for aberrant vasculature arising from branches of the hepatic artery that supply the GI tract. The prophylactic use of proton pump inhibitors is also recommended (Riaz et al, 2009b).

Vascular Injury

Transcatheter ^{90}Y radioembolization is a minimally invasive procedure with a low incidence of vascular injury, mostly seen in patients who were already on systemic chemotherapy (Murthy et al, 2007b), which may cause weakening of the vessel wall and predispose it to injury.

Conclusion

The adverse events that occur after radioembolization are rare and manageable. Their occurrence can be minimized by careful assessment of angiographic findings before treatment. The precautions that may minimize their incidence have been outlined previously (Riaz et al, 2009b).

SUMMARY

Radioembolization represents a novel treatment approach that has gained increased awareness and clinical use. The minimal toxicity and outpatient nature of the therapy make it an attractive alternative in the management of primary and secondary liver malignancies. Appropriate treatment planning requires certain steps that include but are not limited to 1) calculation of target liver mass to be infused and tumor burden; 2) visceral angiography to map the tumor-perfusing vessels and embolize collaterals that may lead to aberrant microsphere deposition; 3) ^{99m}Tc-MAA scan for assessment of lung shunt fraction; 4) calculation of the optimal therapeutic dose; 5) preparation of the interventional radiology suite; 6) meticulous radiation monitoring and safety procedures; and 7) calculation of residual activity and efficiency of radiation delivery. The safety and efficacy of the treatment is enhanced by following meticulous technique.

Selecting patients with adequate hepatic reserve and good functional status maximizes the beneficial therapeutic effect of this therapy with minimization of the risk of complication. Radioembolization has also been shown to be beneficial for patients with metastatic disease who have intrahepatic progression despite standard-of-care chemotherapy. This treatment modality provides an important tool for all disciplines involved in the management of liver tumors and includes hepatology, medical/radiation oncology, gastroenterology, surgery, and interventional oncology.

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CHAPTER 85A

Percutaneous methods for ablating liver tumors: overview

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OVERVIEW

The term *liver tumor* generally includes a variety of primary and metastatic tumors involving the hepatic parenchyma. More than 90% of the primary tumors are hepatocellular carcinomas (HCCs); the other 10% include cholangiocarcinomas and rare tumors such as hemangioendotheliomas, lymphomas, and sarcomas (McGlynn et al, 2001). Hepatic metastases (METs) can originate from all types of primary tumors, but excluding local and regional lymph nodes, the liver is usually the first organ targeted by tumors of the gastrointestinal tract (Wiess, 1986).

BACKGROUND

Percutaneous Ablation of Hepatocellular Carcinoma

HCC is the fifth most common tumor throughout the world, and its incidence is increasing worldwide because of the spread of infections caused by the hepatitis B and C viruses (see Chapters 64 and 80). Surveillance programs have been developed for patients with cirrhosis, and this approach is associated with annual HCC detection rates ranging from 3% to 8% (Bruix & Llovet, 2002). Unfortunately, although advances in imaging technology have improved the early detection of HCC, these tumors are difficult to treat and are still associated with a poor prognosis.

Conventional approaches, such as systemic chemotherapy and radiation, have proved to be ineffective in HCC, although the results of some recent randomized trials suggest that sorafenib may be associated with slightly improved survival in patients with advanced HCC (Llovet et al, 2008; Peck-Radosavljevic et al, 2010; Vitale et al, 2009; see Chapter 88). Surgical resection can result in tumor eradication and improved survival in patients with small HCCs; however, few patients are candidates for potentially curative resection, which comes with an 80% risk of recurrence (Akriviadis et al, 1998; see Chapter 90B). Liver transplantation is the ideal approach for early HCC, but it is limited by age-related contraindications and a shortage of organs (Llovet et al, 1999; see Chapter 97D). For these reasons, a number of percutaneous methods have been developed for the chemical or thermal ablation of HCC, and all have displayed satisfactory efficacy in terms of local tumor control.

Percutaneous Ablation of Hepatic Metasteses

Percutaneous ablation has been used to treat hepatic METs from primary tumors in various organs, but its systematic use has been limited to those produced by colorectal cancers (CRCs). CRC is the fourth most common tumor worldwide (Greenlee et al, 2000), and the healthy liver is the first site of metastatic involvement in patients with CRC and a source of further spread (Lenhert, 1999). Twenty-five percent of these patients already have liver METs when the primary tumor is diagnosed, and another 50% develop them within 5 years of diagnosis (see Chapter 81A). In more than 30% of the patients with liver METs, the metastatic disease appears to be confined to the liver at the time of detection.

Throughout the world, resection is considered a potentially curative approach for the treatment of CRC liver METs, and it is associated with a 5-year survival rate of 40% (Ballantyne, 1993; Greenway, 1988; Nakamura, 1997). However, more than 70% of patients are ineligible for surgical resection because of the extent of their disease, serious comorbidities, or both. For those who do undergo resection, recurrence is frequent; repeat resections are difficult to propose, and in some cases, they are ineffective. Chemical or thermal ablation methods have been proposed for patients with no surgical prospects, for those with recurrence after resection or tumor progression after systemic or local chemotherapy, and for those who refuse surgery. Chemical ablation has displayed limited efficacy in the local control of liver METs (Livraghi et al, 1991), but thermal ablation has proved to be safe and effective for the treatment of small liver METs from CRC (Lencioni et al, 2004; Livraghi et al, 2003a; Solbiati et al, 1999). It has also produced promising results in the management of lung METs (Rossi et al, 2006). Furthermore, thermal ablation coupled with open surgery seems to increase the overall number of treatable patients (Abdalla et al, 2004).

Pretreatment Studies and Patient Selection

For HCC patients, treatment eligibility screening generally involves routine laboratory tests, abdominal ultrasonography (US), contrast-enhanced US, spiral computed tomography (CT) or magnetic resonance imaging (MRI), esophagogastroduodenoscopy, and other studies as indicated. Diagnosis of cirrhosis is generally based on histology or concordant laboratory and imaging findings. Most investigators believe that HCCs more than 2 cm in diameter can be reliably diagnosed on the basis of characteristic findings documented with at least two imaging modalities. One modality is sufficient if the patient also has an α-fetoprotein (AFP) level greater than 200 ng/mL. For HCC nodules less than 2 cm in diameter, diagnosis requires typical findings of two imaging techniques and AFP levels above 200 ng/mL. Otherwise, biopsy is mandatory (Bruix & Llovet, 2002). We and others believe that diagnosis of the original tumor should be based on histologic examination of US-guided

fine needle biopsy (FNB) or laparoscopic findings (subcapsular tumors), although imaging findings can be useful for recurrences (Rossi et al, 1996, 1998). US-guided biopsy, cutting or aspirative, with an 18- to 21-gauge needle is always indicated when the AFP level is above 200 ng/mL.

Laboratory screening for CRC liver METs is similar to that described above, and diagnosis is generally based on imaging findings. In a patient with a history of CRC, a focal hepatic lesion is generally regarded as metastatic if it displays peripheral contrast enhancement in the arterial phase and complete washout in the portal and late phases on at least two types of imaging studies. US and FNB confirmation should be obtained if the diagnosis is in doubt, and it can also be used to identify the treatment-relevant receptor status of tumor cells (Midorikawa et al, 2009). Patients with CRC liver METs should always undergo colonoscopy before thermal ablation to exclude the possibility of local disease recurrence.

Candidates for percutaneous ablation have tumors with characteristics similar to those of patients who are eligible for surgical resection, but for a variety of reasons, they are not considered suitable for surgery. Thermal/chemical ablation is generally chosen to treat HCC on the basis of findings related to the tumor, residual liver function, and the patient's general health. The criteria most commonly used include documented cirrhosis; no more than three HCC nodules, measuring no more than 3.0 to 3.5 cm each in diameter; no neoplastic thrombosis of the portal or hepatic veins; and no evidence of extrahepatic metastases. Residual liver function is classified according to the Child-Turcotte-Pugh (CTP) system, and patients with scores higher than B7 to B9 are usually considered unsuitable for ablation. Candidates must also have safe coagulation parameters—prothrombin time (PT) ratio of 50% or higher, international normalized ratio (INR) no higher than 1.7, and a platelet count of 50 to 70 x 10^9/L or more—and no esophageal varices at a high risk for bleeding (Ebara et al, 1995; Rossi et al, 1998).

Similar criteria are used to select patients with CRC liver METs for percutaneous thermal ablation (Rossi et al, 1996; Solbiati et al, 1999). The patient's coagulation status still needs to be assessed, because liver disease is not the only cause of clotting defects. Compared with the criteria applied to HCCs, those used for METs are more restrictive, because metastatic tissue is more difficult to ablate than HCC tissue, so METs with diameters exceeding 2.5 to 3 cm are often considered ineligible for curative percutaneous ablation.

In terms of safety, one of the most important factors to consider is the location of the tumor. For nodules located superficially in segments III, IV, or V of the liver; on the subdiaphragmatic surface of the liver; and for exophytic nodules (surrounded by abdominal viscera) or those close to gallbladder, a laparoscopic or surgical approach is preferable, although in experienced hands, percutaneous ablation of these tumors is by no means impossible (Chopra et al, 2003). Caution must be used when the tumor is situated close to a major bile duct, because damage to these structures can lead to biliary stricture or fistula, which often requires additional interventional radiologic procedures or surgical correction (see Chapter 42).

For tumors located near a large hepatic blood vessel, risk of incomplete treatment and treatment failure is increased. Flow through these vessels can increase convectional heat loss near the tumor, thereby reducing the volume of the thermal lesion, and it can also result in more rapid clearance of the chemical ablative substances. It is often useful to devascularize these tumors before chemical or thermal ablation; this can be accomplished with selective transarterial embolization (TAE; see Chapter 83) or balloon-catheter occlusion of the vessels supplying or draining the tumor (Rossi et al, 2000).

Assessment of Local Tumor Control

Evaluation of local efficacy is based largely on evidence of complete tumor ablation that persists during the follow-up (lack of local recurrence). To achieve this, the entire tumor must be included in the volume of tissue that undergoes chemically or thermally induced coagulative necrosis, which renders it completely avascular. Shortly after the procedure, the necrotic area is surrounded by a halo of edematous, intensely hyperemic tissue. A few days later, this halo is replaced by an inflammatory halo, which persists for approximately 1 month. Thereafter, the mass of necrotic tissue shrinks and is replaced by fibrotic tissue (Rossi et al, 1990). The location, size, and evolution of this ablation zone are assessed with radiologic imaging techniques.

Evaluation of Immediate Treatment Response

The immediate response to any type of percutaneous ablation procedure is generally assessed with contrast-enhanced US (CEUS), enhanced spiral CT, or T2-weighted MRI—the gold standards for this purpose (Chen et al, 2007; Cioni et al, 2001). The presence at the ablation site of a well-defined, nonenhancing area as large or larger than the treated tumor itself is regarded as reliable evidence of a complete response, or complete radiologic necrosis. The timing of the imaging study is important. CEUS examinations performed too soon after ablation are characterized by numerous artifacts caused by gases produced during ablation or the diffusion of chemical substances within tissues surrounding tumor. Under these circumstances, it is impossible to distinguish the origin of the hyperechoic signals. If CEUS, CT, and MRI are performed in the days following the ablative procedures, it is impossible to determine whether the peripheral enhancement observed is due to residual tumor tissue or the hyperemic/inflammatory response of the liver parenchyma. This enhancement is a result of inflammatory tissue response, and it resolves within a month of tumor ablation. Therefore the persistence of an enhancing rim after this point must be considered evidence of residual tumor viability. For these reasons, the contrast-enhanced imaging studies should be scheduled at least 4 weeks after the procedure. If the results of this study are ambiguous, US-guided FNB can resolve the problem (Rossi et al, 1998).

Evaluation of Long-Term Results

Abdominal US/CEUS studies and tumor marker assays are performed every 4 to 6 months, or even more frequently if needed. Local recurrence is diagnosed when enhancement reappears within the ablation zone or within 2 cm, 1 cm according to some authors, from its margins, or when there is histologic evidence of tumor viability in this area (Berber et al, 2005). If the ablation zone remains unenhanced but fails to shrink during follow-up, or when levels of tumor markers are elevated in the absence of other intrahepatic or extrahepatic lesions, focused US-guided biopsy of the ablation zone is indicated. Nonlocal recurrence comprises extrahepatic metastases and all new intrahepatic regrowth located more than 2 cm from the ablation zone.

Assessment of Complications

Immediate and late complications have been reported after all types of percutaneous tumor ablation. They should be evaluated according to previously described guidelines (Sacks et al, 2003). Major complications are those that, if left untreated, could threaten the patient's life, produce substantial morbidity, and/or prolong the hospital stay. All other events are considered minor complications. In general, patients treated with percutaneous ethanol injection (PEI)/percutaneous acetic acid injection (PAI) are monitored for 2 to 3 hours in a dedicated recovery room and are then discharged after a postablation abdominal US examination (Ebara et al, 1995; Shiina et al, 1991). Laboratory tests and other studies are indicated only when clinical or US evidence of complications are apparent. The 24-hour study is also accompanied by measurements of hemoglobin, lactic dehydrogenase and aminotransferases levels, and blood studies to assess hepatic function.

CHEMICAL ABLATION

Chemical ablation is based on the cytotoxic properties displayed by certain chemical substances when directly injected into a tissue. The most widely used cytotoxic substance is ethanol, but in some centers, acetic acid has recently been used as an alternative in the treatment of HCCs (Huo et al, 2003), and sodium hydroxide is under evaluation in a tumor model after evaluation in rats (Lin et al, 2001). Chemical ablation has been extensively used to treat HCCs. It has also been evaluated for the treatment of METs, but this experience was abandoned based on unsatisfactory results (Livraghi et al, 1991).

Percutaneous Ethanol Injection

Physical Principles

Direct injection of ethanol into a tumor results in its distribution in the tissue by diffusion and convection. Diffusion is favored by the existence of a concentration gradient between the injection point and the surrounding tissues, by the low molecular weight of the ethanol, by the increase in local pressure determined by the injection, and by the hypervascularity of the tumor (Ho et al, 2007). Ethanol spreads through the tumor tissue, exerting cytotoxic effects that include cytoplasmic dehydration and denaturation of cellular proteins. The endothelial cell necrosis and platelet aggregation it causes occlude tumor vessels and produce ischemic damage in the neoplastic tissue (Shiina et al, 1991; Ebara et al, 1995). The final result is coagulative necrosis within the tissue around the site of injection.

Technique

PEI is usually performed on an outpatient basis. Patients are treated after an overnight fast. Prophylactic antibiotics are not usually administered, and in most cases, general anesthesia is unnecessary, but in some centers, anxious patients are moderately sedated.

The procedure is performed under real-time US monitoring. The ethanol is usually injected with a 20- to 22-gauge endhole needle (Chiba or Chiba-like) or a conical-tip needle with multiple sideholes (Livraghi et al, 1995). The tip is positioned at the desired point in the HCC nodule with the aid of real-time US guidance, and the predetermined amount of ethanol is infused slowly into the tumor. After few seconds, the HCC nodule becomes completely hyperechoic. Light aspiration is applied during withdrawal to prevent excess ethanol from leaking into the peritoneum through the insertion tract. If all goes well, the patient is kept under observation for about 2 hours.

The volume of ethanol required to ablate a tumor nodule depends on the size of the tumor, but the final decision on the total dose is based on the results of imaging studies performed at the end of each session (Livraghi et al, 1995; Shiina et al, 1991).

An alternative to this multiple-session approach is *one-shot PEI*. As the term implies, the total amount of ethanol required for the ablation, based on the calculations reported above, is injected during a single session (Giorgio et al, 1996; Livraghi et al, 1993). This technique has been proposed for HCCs with diameters exceeding 3 cm. It is more painful than conventional PEI and is therefore performed under general anesthesia. In one study, the amounts of ethanol administered with this technique ranged from 20 to 165 mL (mean, 62 mL).

Percutaneous Acetic Acid Injection

Physical Principles and Technique

After ethanol, the most widely used agent for chemical ablation is acetic acid. In vitro studies have shown that it dissolves lipids and extracts collagen from various kinds of tissues (Ho et al, 2007). Compared with ethanol, acetic acid offers certain advantages, including more effective destruction of tumor septa and capsules. In addition, the same degree of cell kill can be obtained with a smaller infusion volume (Ohnishi, 1998).

The technique of PAI is quite similar to that of PEI. The infusion consists of a 50% solution of acetic acid and sterile water injected with the same technique and needles used for ethanol. Observations in animal models and clinical explants indicate that the volume of acetic acid needed to ablate a tumor nodule is roughly one third of the volume calculated with the formula used for ethanol: ablation of a nodule measuring 3 cm in diameter would require 34 mL of ethanol but only 11.3 mL of acetic acid (Giorgio et al, 2000).

Complications of Percutaneous Ethanol/Acetic Acid Injection

Although PEI and PAI are both low-risk procedures, in rare cases they can produce severe complications. Table 85A.1 shows the complication rates reported after these procedures. The mortality rates associated with PEI/PAI are very low, ranging from 0% to 1.4%. Major complications, which ranged from 0% to 4.6%, include hemoperitoneum, hemobilia, subcapsular or intraparenchymal hematoma, hepatic abscess, cholangitis, intestinal perforation, hepatic venous thrombosis, pneumothorax or pleural effusion, hepatic infarction, and tumor seeding along the needle insertion tract.

Local Tumor Control of Chemical Ablation

Several authors have analyzed the risk factors for local recurrence of HCC after PEI, and tumor size seems to be the most accurate predictor of this outcome. The 2-year local HCC recurrence rates reported after PEI are 10% for nodules smaller than 2 cm in diameter, 18% for those between 2.1 and 3 cm, and 30% for those larger than 3 cm (Ishii et al, 1996). In other studies, local recurrence rates ranged from 33% to 38% for

Table 85A.1

Complications Reported after PEI and PAI

First Author, Year	Patients/ Sessions	Mortality Rate, n (%)	COMPLICATIONS, N (%)	
			Major	Minor
Di Stasi, 1997	1066 P	1 (0.09)	15 (0.15)	295 (27.7)
Livraghi, 1998	128 S	1 (0.7)	6 (4.6)	24 (19)
Huo, 2003	62 P	0 (0)	0 (0)	28 (45)
Sung, 2006	248 P	0 (0)	0 (0)	2 (0.8)
Brunello, 2008	69 P	1 (1.4)	1 (1.4)	10 (14.5)
Huo, 2003*	63 P	0 (0)	0 (0)	20 (32)
Fartoux, 2005*	37 P	—	0 (0)	13 (35.1)

*PAI series

PEI, percutaneous ethanol injection; PAI, percutaneous acetic acid injection; P, patients; S, sessions

HCCs smaller than 3 cm and from 43% to 68% for those exceeding 3 cm in diameter (Gaiani et al, 2003; Khan et al, 2000). Thus far, complete response rates observed after PAI seem to be similar to those obtained with PEI, but very few studies are available for comparison.

Long-Term Results

Several investigators have reported 5-year survival rates close to 50% after PEI for HCCs up to 3 cm in diameter in patients with cirrhosis; in other words, results are similar to those achieved with resection (Bruix & Llovet, 2002). In a consecutive series of 685 patients with HCC nodules measuring 3 cm or less, initial treatment with PEI was reportedly associated with a cumulative 5-year survival rate of 49% (Shiina et al, 2009). The Seventeenth Nationwide Follow-up Survey conducted by the Liver Cancer Study Group of Japan revealed survival rates of 91.3%, 77.5%, 63%, 50.2%, and 39.4% at 1, 2, 3, 4, and 5 years, respectively, for 14,726 patients whose HCCs were treated with ethanol injection (Ikai et al, 2007). A randomized trial failed to detect any significant difference in survival between HCC patients treated with PEI or surgical resection (Huang et al, 2005); however, other randomized trials have also shown that radiofrequency ablation (RFA) is superior to all types of chemical ablation for small HCCs, and the difference involved treatment responses, local tumor control, and survival rates (Bouza et al, 2009; Lin et al, 2005; Orlando et al, 2009; Shiina et al, 2005). For this reason, thermal ablation techniques are now preferred over chemical ablation for treatment of HCC. The chemical approach is still the treatment of choice when thermal ablation cannot be performed safely, such as when tumors form adhesions to the gastrointestinal tract, or when tumors are located in difficult sites or close to a bile duct.

THERMAL ABLATION

The goal of thermal ablation methods is to completely destroy a tumor without damaging the surrounding liver tissue. This can be achieved by generating killing temperatures, those exceeding 45° C or less than –40° C, within the mass of tissue that has to be ablated. The temperature reached and the duration of exposure determine how rapidly cell death occurs. Hyperthermia can be produced by delivering electromagnetic (radiofrequency, microwave), light (laser; see Chapters 85C and 85D), or mechanical (high-intensity focused ultrasound) energy into the tissue by means of dedicated probes. Hypothermia is created with cryoprobes (see Chapter 85B), which subtract heat from the tumor tissue by convection. RFA is the thermal technique most widely used for HCCs and liver METs and the one supported by the largest body of published evidence. Microwave ablation (MWA) and laser thermal ablation (LTA) have also been used in these settings, but these experiences are more limited. To date, experiences with high-intensity focused ultrasound (HIFU) have been confined to experimental studies or preliminary clinical investigations.

Radiofrequency Ablation (see Chapter 85C)

Physical Principles

Radiofrequency (RF) energy generates heat in the tissue that is in direct contact with the noninsulated tip of the needle electrode (McGahan et al, 1990; Rossi et al, 1990). The heat is the result of ionic and molecular friction, and it spreads into the surrounding tissues by a process of conduction. The highest temperatures are created in the tissue immediately adjacent to the electrode tip, and the heat rapidly decreases as the distance from the tip increases. Permanent tissue destruction occurs at temperatures of 45° C or higher (Cosman et al, 1983; Organ, 1976). Temperatures ranging from 46° C to 60° C produce irreversible cellular damage only after relatively long periods of exposure. In contrast, temperatures between 60° C and 100° C cause almost instantaneous protein coagulation with irreversible damage to mitochondria and cytosolic cell enzymes. When temperatures exceed 100° C, tissue fluids undergo boiling, vaporization, and ultimately carbonization. The final size of the thermal lesion, an area of coagulative necrosis that is gradually replaced by fibrotic tissue, depends on the total amount of heat deposited in the tissue, the thermal and electrical conductivity of the tissue, and the amount of heat lost through convection; specifically, it depends on heat lost through local blood flow, which acts as a heat sink. Tissue impedance limits the amount of heat that can be introduced into a tissue. It is inversely related to tissue hydration, which in turn reflects the ion content of the tissue (Djavan et al, 1997). During RFA the ions are quickly destroyed, and the tissue undergoes desiccation and charring, and the resultant increases in impedance ultimately prevent further delivery of RF energy.

Conventional RF electrodes used in the monopolar mode produce thermal lesions with a maximum diameter of about 1.8 cm (Rossi et al, 1996). Consequently, the ablation of a relatively small HCC nodule requires the creation of multiple, overlapping lesions. This used to mean multiple needle insertions and multiple treatment sessions; however, second-generation RF electrodes produced thermal lesions with diameters as large as 3 cm, and the volume of tissue that could be ablated with a single pulse of energy increased exponentially. These advances were achieved by increasing the active surface area of the electrode with a set of retractable hooks or prongs (expandable-tip electrodes; Rossi et al, 1998) or by cooling the electrode tip by means of an internal water-circulation system (cooled-tip electrodes) (Goldberg et al, 1998b). The expandable electrodes allow the delivery of larger amounts of RF energy, because rapid charring is less likely when the volume of tissue to be

dehydrated is large. Cooled-tip electrodes achieve the same result by preventing temperatures rising above 100° C in tissues adjacent to the active surface of the electrode. The heat dissipation prevents charring and keeps impedance low, thereby allowing the delivery of larger amounts of RF energy. Larger thermal lesions, those 4 cm or larger, have also been produced with multiple cooled electrodes combined in a cluster (Head & Dodd, 2004), cooled catheter electrodes, and expandable spiral electrodes (Rossi et al, 2006).

Other investigators have attempted to increase thermal lesion volumes by reducing convectional heat loss during the RF procedure (Goldberg, 1998a; Patterson et al, 1998; Rossi, 1999). HCCs are supplied almost exclusively by vessels arising from the hepatic artery (Breedis & Young, 1954); however, when RFA was performed after balloon-catheter occlusion of the hepatic artery, the thermal lesions produced were large as expected on the basis of experimental studies; when RFA was performed after embolization of the feeding arteries with gelatin sponge particles, the thermal lesions produced were larger than expected (Rossi et al, 2000). With this approach, in fact, HCC nodules more than 6 cm in diameter could be treated in a single RF session.

Low impedance during the procedure explains the unexpectedly large thermal lesions. Occlusion of the tumor's arterial supply with gelatin sponge particles reduces impedance in at least two ways: First, it increases the hydrostatic pressure within the HCC (Rossi et al, 2007). As a result, the boiling point of tissue fluid is higher during the thermal ablation procedure, which prolongs the delivery time and allows more energy to be deposited in the tissue, before desiccation and charring occur. Second and more importantly, a gelatin sponge is a hydrogel capable of modifying the electrical and thermal conductivity of the tissue; its presence in the ablation area markedly increases the amount of RF energy that can be delivered.

It is important to recall that liver METs are more difficult to destroy with thermal energy than HCCs. For one thing, the absence of a capsule prevents the buildup of intranodular pressure that occurs in HCCs; therefore less energy can be deposited within a MET, compared with encapsulated HCCs, with a given electrode at a given power setting. More importantly, metastatic lesions are characterized by actively proliferating tissue at the periphery and a devascularized center, and these characteristics create an inhomogeneous field in terms of impedance and conductivity, both thermal and electrical. Further studies are needed to evaluate the behavior of electromagnetic energy in a field of this type.

Technique

Patients undergoing RFA are hospitalized and treated after an overnight fast. In our department, most RFA procedures are performed without general anesthesia or conscious sedation, but some investigators prefer to perform the procedure under general anesthesia or deep sedation. A grounding pad is attached to the patient's back and connected to the RF generator to close the electrical circuit. A local anesthetic (1% lidocaine) is injected along the predefined electrode insertion line, from the skin to the peritoneum. The skin is nicked with a small lancet to facilitate insertion of the electrode, and the tip is then advanced into the HCC nodule under real-time US guidance. The RF generator is activated, and the predefined amount of energy is delivered for 8 to 12 minutes. On US, the nodule becomes hyperechoic with a posterior acoustic shadow (Rossi et al, 1996). The pull-back technique can be used to create multiple thermal lesions along the major electrode axis (Rossi et al, 2000). At the end of the procedure, the electrode is withdrawn, but the generator remains on during this phase; this way, the electrode tract itself also undergoes coagulation, which diminishes the risks of bleeding and tumor seeding.

This technique can be used for HCCs up to 3.5 cm in diameter and for CRC liver METs with diameters of 2.5 cm or less. For larger tumors, other treatment strategies have been adopted. For HCC nodules whose diameters exceed 3.5 cm, RFA has been performed with a multiple-insertion technique (Livraghi et al, 2000), an expandable triple-spiral electrode (Rossi et al, 2006), clusters of cooled electrodes (Cheng et al, 2008), and combination of RFA with other techniques (Murakami et al, 2007). As discussed above, a larger volume of necrotic tissue can also be achieved by preablation embolization of the tumor with gelatin sponge particles. Some operators perform selective transarterial chemoembolization (TACE; see Chapter 83) of larger tumors after RFA debulking. The rationale of this approach is that the amount of embolic agent will be greater in the tumor tissue if its volume was previously reduced with RFA.

Complications

RFA is a safe procedure with very low rates of death and major complications. Tables 85A.2, 85A.3, and 85A.4 show the post-RFA complication rates observed in HCC or MET series reported by our group and others. Mortality rates ranged from 0% to 3.7%, whereas major complication rates were reported in 0% to 22%. Most of the adverse outcomes reported occurred in the initial clinical experiences, and fatal and nonfatal complications have become progressively less common with the increasing experience of the investigators. Indeed, in reports published during the last 5 years, mortality rates are consistently close to 0%, and major complication rates range from 0% to 10%. The complications described include abdominal hemorrhage, hepatic abscess, pleural effusion, hepatic infarction, bronchobiliary fistula, bile peritonitis, biloma, hemobilia, thrombosis of vessels in the hepatic venous system, skin burn, and perforation of the stomach, intestine, or diaphragm. Table 85A.4 shows the complications observed by our group over the last 10 years. This series includes 706 patients with 859 HCC nodules and no procedure-related deaths, which is consistent with previous reports. Less than 1% of the procedures were associated with major complications, a percentage similar of those reported after percutaneous injection therapies. The most serious adverse effect in our series involved shearing of a branch of the hepatic artery; however, all cases were promptly detected by Doppler US studies and controlled by selective embolization of the damaged vessel. Our patients receive neither general anesthesia nor sedation, and the most frequent complication is therefore mild to moderate pain during the procedure that occurs in about 30% of all patients. The pain is easily managed with intravenous analgesia and disappears entirely shortly after the procedure. Use of local, rather than general, anesthesia has several advantages, and this approach is now used by most operators. For one thing, it simplifies the procedure and reduces the cost. More importantly perhaps, it reduces the risk of extrahepatic complications such as perforations of intestinal loops, diaphragm, and gallbladder. The frequency of these events obviously depends on the operator's skill and experience, but conscious patients can report severe pain, which almost inevitably reflects incorrect electrode placement; indeed, a conscious

Table 85A.2

Complications Reported After Radiofrequency Ablation of Hepatocellular Carcinoma

First Author, Year	Patients/Sessions	Mortality Rate, n (%)	COMPLICATIONS, N (%)	
			Major	Minor
Livraghi, 2000	114 P	1 (0.8)	1 (0.8)	5 (4.4)
Bowles, 2001	99 S	1 (1)	7 (7)	10 (10)
Mulier, 2002	3670 P	20 (0.5)	327 (8.9)	–
Livraghi, 2003b	2320 P	6 (0.3)	50 (2.2)	110 (4.7)
Mazzaferro, 2004	50 P	0 (0)	4 (8)	10 (20)
Curley, 2004	608 P	3 (0.5)	33 (8.6)* 15 (2.4)†	–
Buscarini, 2004	166 P	0 (0)	7 (4.6)	3 (1.9)
Tateishi, 2005	1000 S	0 (0)	40 (4)	17 (1.7)
Giorgio, 2005	336 P	1 (0.3)	2 (0.6)	–
Khan, 2007	228 P	0 (0)	8 (5.4)	–
Chen, 2008	172 S	0 (0)	9 (5.2)	–
Brunello, 2008	70 P	0 (0)	2 (2.9)	8 (11.4)
Livraghi, 2008	218 P	0 (0)	4 (1.8)	–
Kim, 2008	133 P	2 (1.5)	9 (6.8)	8 (6)
Laspas, 2009	322 S	0 (0)	0 (0)	9 (2.8)
Kong, 2009	255 P	0 (0)	35 (10)	–

*Early complication
†Late complication
P, patients; S, sessions

patient can provide important feedback that can prevent major organ damage.

A 12% seeding rate was reported by a Spanish group during their initial experience with RFA (Llovet et al, 2001). The results contrast with those of other studies, and they may be a reflection of poor technique. Seeding along the electrode tract is virtually impossible, if the electrode is activated before and during each withdrawal. If the recommendations made in the Technique section are followed, the electrode tract itself undergoes coagulation, produced by the gases that develop during the procedure or by the heat generated by the activated electrode during its withdrawal. Our group, in fact, has observed only two cases of subcutaneous tumor seeding after a total of 1921 RFA sessions, and in both cases, it is impossible to say whether the seeding was actually caused by the RFA or by previous US-guided biopsies.

When RFA is performed during or after TAE, other complications are also possible (Rossi et al, 2000). Sporadic cases have been reported of chemical cholecystitis and intimal dissection of the hepatic artery. All patients experience transient increases in serum aminotransferase levels, but baseline values are

Table 85A.3

Complications Reported After Radiofrequency Ablation of Liver Metastases

First Author, Year	Patients/Sessions	Mortality Rate, n (%)	COMPLICATIONS, N (%)	
			Major	Minor
Rossi, 1996	11 P	–	0 (0)	0 (0)
Solbiati, 1997	29 P	–	1 (3.5)	5 (17)
Livraghi, 1997	15 P	–	0 (0)	3 (20)
Lencioni, 1998	29 P	–	0 (0)	8 (27)
Jiao, 1999	27 P	1 (3.7)	6 (22)	–
Gillams, 2000	69 P	1 (1.6)	2 (3.2)	8 (12)
Solbiati, 2001	162 S	0 (0)	1 (0.6)	7 (4.3)
Livraghi, 2003b	88 P	0 (0)	1 (1.1)	2 (2.2)
Knudsen, 2009	36 P	0 (0)	4 (11)	–
Gillams, 2009	617 S	0 (0)	29 (4.7)	–

P, patients; S, sessions

Table 85A.4

Complications in Patients with Hepatocellular Carcinoma after 1921 Radiofrequency Ablation Sessions

Complication	Number (%)
Major	
Hemoperitoneum	6 (0.3)
Hemothorax requiring drainage	2 (0.1)
Self-limiting hemobilia	1 (0.05)
Subcutaneous seeding*	2 (0.1)
Skin burn	1 (0.05)
TOTAL	12 (0.6)
Minor	
Postoperative pain	18 (0.9)
Self-limiting pleural effusion	32 (1.6)
Transient worsening of liver function	54 (2.8)
Low-grade fever	76 (3.9)
TOTAL	180 (9.3)

*It is not possible to define the origin of seeding (radiofrequency ablation vs. ultrasound-guided biopsy).

generally restored within a week. Some patients also display transient declines in liver function reflected by CTP scores, but these changes rarely last more than 2 weeks.

Local Tumor Control

Histologic examination of whole livers from transplant recipients who had previously been treated with RFA shows that more than 80% of HCCs measuring less than 3 cm are completely destroyed with a single RF electrode insertion (Mazzaferro et al, 2004). Complete response rates ranging from 95% to 98% have been documented in several studies; however, in numerous series of cirrhotic patients with small HCCs treated with RFA, the local recurrence rates range from 0% to 45%, as shown in Table 85A.5. In our series of 859 HCC nodules with maximum diameters of 3.5 cm, the overall local recurrence rate after a 10-year follow-up was 15.7%. The recurrence rate was 5.2% for nodules up to 2 cm in diameter, 12.7% for those with diameters of 2.1 to 3 cm, and 21% for those measuring 3.1 to 3.5 cm; however, in more than 70% of these cases, complete and persistent ablation of the recurrent disease was achieved with a single additional "clean-up" RFA session. This brought the overall local control rate close to 94%, obtained with one treatment in 82% of the cases and with two treatments in 12%.

As shown in Tables 85A.5 and 85A.6, similar complete response rates have been reported for RFA of CRC liver METs, but the recurrence rates in these cases are higher, ranging between 8% and 40%. These results are probably due in part to the use of RFA to treat METs that are too large for this type of ablation. Given the characteristics of metastatic tissue discussed above, percutaneous RFA with curative intent should probably be reserved for METs with diameters no larger than 2.5 cm. If larger METs are treated with this method, local recurrence must be expected in more than 30% of the cases.

Long-Term Results in Hepatocellular Carcinoma Patients

The long-term results reported after RFA treatment of HCCs are summarized in Tables 85A.5 and 85A.6. In our own RFA series, cumulative disease-free and overall survival was similar to those observed by others after RFA, percutaneous injection therapy, or surgical resection. Meaningful comparison of the mortality data and survival curves reported after surgical and nonsurgical treatment of HCC is virtually impossible, because only perfunctory descriptions are provided of recurrences occurring after the initial treatment. Most reports simply do not mention the characteristics of first recurrences (location, extension, etc.), how this recurrence was managed (with the same method used to treat the original tumor or with one or more other techniques), or the outcome of the treatment; even fewer details are provided on subsequent episodes of recurrence. Comparison of results reported for surgical and nonsurgical series is further complicated by the fact that cases of tumor understaging and/or positive resection margins are generally excluded from analyses of survival in surgical series, whereas cases of this type—understaged disease, tumors with persistent viability after two treatments—are usually included in the nonsurgical series (Hanazaki et al, 2000; Helling & Woodall, 2007; McCormack et al, 2005; Shimozawa & Hanazaki, 2004; Torzilli et al, 1999).

Randomized controlled studies have demonstrated that RFA is superior to chemical ablation methods in terms of both local tumor control and survival (Bouza et al, 2009; Brunello et al, 2008; Orlando et al, 2009). These findings suggest that, when possible, RFA should be the first choice for nonsurgical ablation

Table 85A.5

Local Recurrence and Survival in Patients Treated with Radiofrequency Ablation for Hepatocellular Carcinoma

			SURVIVAL (%)				
First Author, Year	No. Patients	Local Recurrence (%)	Median (mo)	1 Year	2 Years	3 Years	5 Years
Rossi, 1996	39	–	44	94	–	68	40
Curley, 2000	110	4 (3.6)	–	–	71.8	–	–
Bowles, 2001	328	30 (9)	24	75	50	–	–
Lencioni, 2003	187	–	57	97	–	71	48
Mazzaferro, 2004	50	27 (45)	–	95.0	–	83.0	–
Xu, 2004	78	10 (12.8)	32	75.6	58.5	50	–
Tateishi, 2005	319	–	–	94.7	86.1	77.7	54.3
Lu, 2005	67	14 (21)	–	71.7	47.2	37.6	24.2
Raut, 2005	194	9 (4.6)	–	84.5	–	68.1	55.4
Machi, 2005	65	11 (16.9)	40	78	55	48	39.9
Cabassa, 2006	68	7 (5)	23	94.4	–	65	43.1
Lu, 2006	105	0 (0)	–	93.5	87.1	87.1	–
Ng, 2006	52	6 (11)	–	86	75	–	–
Khan, 2007	228	12 (13)	–	91	–	71	–
Kim, 2008	192	13 (6.7)	60	92.3	79.9	72.6	46.5
Howard, 2008	189	52 (28)	–	–	–	–	–
Salmi, 2008	25	3 (12)	–	92	–	72	64
Laspas, 2009	282	62 (22)		94.8	86.6	73.1	51.1
Kong, 2009	255		21	63.1	43.3	35.7	–
Yin, 2009	109	24 (22)	–	75.8	–	30.9	15.4

Table 85A.6

Local Recurrences and Survival in Patients Treated with Radiofrequency Ablation for Liver Metastases

				SURVIVAL (%)				
First Author, Year	No. Patients	Primary Tumor	Local Recurrence, n (%)	Median (mo)	1 Year	2 Years	3 Years	5 Years
Rossi, 1996	13	M	6 (55)	–	91	–	–	–
Lencioni, 1998	41	M	5 (12)	–	93	–	–	–
Solbiati, 1997	101	CRC	25 (25)	–	92	56	–	–
Jiao, 1999	17	CRC	9 (33)	–	78	–*	–	–
Gillams, 2000	69	CRC	–	33	90	60	34	22†
Solbiati, 2001	179	CRC	70 (3)	36	93	69	46	–
Oshowo, 2003	6	CRC	2 (33)	–	–	69	–	–
Kosari, 2002	143	M	11 (8)	–	–	–	–	–
Livraghi, 2003b	88	CRC	35 (40)	–	–	–	–	–
Park, 2008	30	CRC	7 (23)	36	–	–	–	–
Otto, 2010	28	CRC	9 (32)	–	–	67	–	–
Knudsen, 2009	36	CRC	–	39	–	–	–	34
Gillams, 2009	123	CRC	–	36	–	–	49	24

*18 months
†48 months
CRC, colorectal cancer; M, miscellaneous

of HCCs. RFA was also directly compared with surgical resection in two randomized clinical trials, and neither revealed any significant differences between the local tumor control or survival rates associated with the two approaches (Chen et al, 2006; Lu et al, 2006).

Recently, HCC nodules with diameters larger than 3 cm have been treated with a cluster of cooled RF needle electrodes and a multiple-insertion technique (Goldberg, 1998a). Complete responses were observed in 61% of the nodules up to 5.0 cm in diameter and in 24% of larger nodules. These results were to be expected, because tumor volume increases exponentially with its diameter, and larger diameters are also associated with higher frequencies of daughter nodules, capsule infiltration, and neoplastic thrombosis of the portal vessels close to the tumor. Better results have been obtained with more conventional RFA electrodes during gelatin-sponge occlusion of the hepatic artery flow (see Physical Principles below). A complete response rate of 82% was achieved with this approach in 62 HCC nodules, with a mean diameter of 5.6 cm. The local recurrence rate was 19%, and the overall intrahepatic recurrence rate was 45% at 1 year (Rossi et al, 2000). RFA is now recognized as a potentially curative treatment for HCC nodules up to 3 cm in diameter, and some investigators maintain that it should be considered the treatment of choice for these cases (Choi et al, 2007; Livraghi et al, 2008; Shiina, 2009).

Long-Term Results in Patients with Metastases

Table 85A.6 shows the long-term results of RFA for resectable and unresectable CRC liver METs. Survival rates range from 33% to 46% at 3 years and from 22% to 30% at 5 years (Abdalla et al, 2004). These rates are worse than those reported after surgical resection, but it is important to recall that surgery is used in a more select population with fewer risk factors for mortality. RFA can now be considered an approach capable of improving survival in patients with limited but inoperable metastatic liver disease (Otto et al, 2010; Seidenfeld et al, 2002). RFA alone or combined with resection has also proved to be superior to other nonsurgical therapies in patients with multiple liver METs (Abdalla et al, 2004). Finally, some investigators suggest that RFA can be used as a part of a "test of time" approach. Use of RFA as the first option for limited hepatic METs would reduce the need for surgical resections by producing complete and persistent tumor necrosis in some patients. In others, RFA would be followed by new intrahepatic and/or extrahepatic METs, which means that surgery would have been a useless ordeal for the patient. And in a few, post-RFA recurrence will be limited to local regrowth at the site of the ablated MET, and in these cases, surgical resection may prove worthwhile (Livraghi et al, 2003a).

Microwave Ablation (See Chapter 85D)

The most extensive evaluations of MWA have come from Japan and China, although the method is now being studied in Western countries as well.

Physical Principles

The term *microwave* (MW) refers to electromagnetic radiation with frequencies ranging from 900 to 2450 MHz. MW radiation is emitted by the tip of a bipolar antenna electrode placed within the tissue. Microwaves cause rapid vibration and rotation of water molecules within the tissue, which immediately generates frictional heat that persists for the duration of energy delivery. The uniform distribution of this heat in all directions results in coagulative necrosis, and charring near the tip of electrode limits further heat diffusion in the tissue. The thermal lesions produced are spherical to elliptical in shape. Their diameters vary with the power delivered, the electrode caliber, and exposure time. With a 14-gauge electrode, a power output of 60 W, and an exposure time of 120 seconds, the maximum and minimum diameters of the thermal lesions were 2.4 ± 0.4 cm (length) and 1.6 ± 0.3 cm (width). Corresponding diameters

achieved with 30 minutes at 40 W were 3.6 cm (length) and 2.6 cm (width) (Seki et al, 1994).

Technique

The technique of MWA is quite similar to that described above for RFA (Seki et al, 1994). Percutaneous MWA is usually performed as an inpatient procedure after an overnight fast. General anesthesia or deep sedation is induced, and a thin (14- to 16-gauge) MW antenna is advanced directly into the tumor nodule under US guidance. The antenna is connected to the MW generator, which is activated to deliver 60 to 90 W of power. Delivery times vary from 2 to 30 minutes, depending on tumor size. In general, tumors less than 2 cm in diameter can be ablated with one or (more commonly) two electrode insertions; for larger tumors, multiple insertions are necessary. The same precautions described for RFA apply to MWA. The changes revealed by US consist of the appearance around the tip of the electrode of a hyperechoic area with a posterior acoustic shadow. This zone increases in size with exposure time and ultimately involves the entire tumor. The hyperechogenicity diminishes rapidly after the generator is switched off and disappears completely within 8 hours of the procedure.

Complications

The complications reported after MWA are quite similar to those listed above for RFA. Table 85A.7 shows the mortality and complication rates observed in the various published series. Mortality ranged from 0% to 8.3%, and complication rates from 2.6% to 14% were reported.

Local Tumor Control

MWA can produce complete tumor necrosis. Histologic examination revealed no viable tumor in 180 (92.3%) of 192 treated HCC nodules that were biopsied after MWA and in 5 (90%) of 6 HCC nodules that were surgically resected after MWA (Seki et al, 1999). None of these nodules were more than 3 cm in diameter. For HCCs of this size, the complete ablation rate is reportedly quite good, more than 90%, but it is significantly lower for larger tumors. The local recurrence rates reported by several investigators after MWA of hepatic tumors ranged from 2% to 37%, as shown in Table 85A.8.

Table 85A.7

Complications Reported after Microwave Ablation

First Author, Year	Patients/ Sessions	Mortality Rate, n (%)	COMPLICATIONS, N (%)	
			Major	Minor
Shimada, 1998*	42 P	–	6 (14.2)	–
Shibata, 2000†	14 P	0 (0)	2 (14)	–
Dong, 2003*	234 P	0 (0)	0 (0)	167 (71.36)
Aramaki, 2004*	24 P	2 (8.3)	–	–
Lu, 2005*	49 P	0 (0)	4 (8.2)	–
Iannitti, 2007‡	87 P	0 (0)	14 (16)	–
Ohmoto, 2009*	49 P	–	6 (14)	28 (56)
Zhang, 2008‡	160 P	0 (0)	23 (14)	–
Liang, 2009‡	3697 S	0 (0)	30 (2.6)	–
Martin, 2010‡	100 P	0 (0)	29 (29)	–

*Hepatocellular carcinoma
†Metastases from colorectal cancer
‡Miscellaneous
P, patients; S, sessions

Table 85A.8

Local Recurrence and Survival of Hepatocellular Carcinoma Patients Treated by Microwave Ablation

First Author, Year	No. Patients	Local Recurrence, n (%)	SURVIVAL (%)				
			Median (mo)	1 Year	2 Years	3 Years	5 Years
Sato, 1996†	19	2 (10)	–	–	–	–	–
Beppu, 1998§	124	17 (14)	–	–	–	63	43
Seki, 1999†	25	2 (8)	–	–	–	90	70
Shibata, 2000‡	14	0 (0.0)	27	71	57	14	–
Dong, 2003†	234	17 (7.3)	–	92.7	81.6	72.8	56.7
Aramaki, 2004†	24	1 (1.4)	–	–	–	–	–
Xu, 2004†	112	8 (7.1)	32	75.6	58.5	50.5	–
Ikai, 2004†	1751	–	–	94.2	84	72.9	44.1
Lu, 2005†	49	11 (11.8)	27	81.6	61.2	50.5	36.8*
Seki, 2005†	68	8 (12)	–	97	–	81	43
Liang, 2009†	288	23 (8)	–	93	82	72	51
Tanaka, 2006†	16	6 (37.5)	–	80	–	51	17*
Iannitti, 2007§	87	6 (2.7)	–	–	–	–	–
Ohmoto, 2009†	49	6 (13)		89	70	49	39*
Martin, 2010§	100	2 (2)	27	–	–	–	–

*4 years
†Hepatocellular carcinoma
‡Metastases from colorectal cancer
§Miscellaneous

Long-Term Results

Several clinical studies have investigated the usefulness of MWA in the treatment of HCC. The long-term results observed in these studies are summarized in Table 85A.8. The overall survival rates 3 years after the procedure ranged from 50.5% to 90%, and at 5 years from 17% to 70%. The Fifteenth Nationwide Follow-up Survey conducted by the Liver Cancer Study Group of Japan found 1-, 2-, 3, and 5-year survival rates of 94.2%, 84%, 72.9%, and 44.1%, respectively, in 1751 patients whose HCC had been treated with MWA (Ikai et al, 2004). The effectiveness of MWA and that of RFA have also been compared in randomized trials (Ohmoto et al, 2009; Shibata et al, 2002). No statistically significant differences were observed between the two treatment methods in terms of local efficacy, but RFA tended to be associated with slightly better local recurrence and complication rates; however, since RFA was introduced in 1999, use of MWA has steadily decreased, even in centers where it was once widely used (Shiina et al, 2002).

Limited data have been reported so far concerning the long-term results of MWA of liver METs (see Table 85A.8). Some investigators have reported promising results in their initial experience with several types of primary tumors (Abe et al, 2005; Liang et al, 2003). In another randomized study comparing MWA and surgical resection in patients with multiple CRC liver METs, no statistically significant differences were observed in the survival rates of the two groups (Tanaka et al, 2006).

Collectively, the data cited above indicate that MWA is an effective method for the treatment of hepatic tumors. Its major limitation is the relatively small size of the thermal lesions it produces. To ablate most tumors, multiple overlapping lesions must be created; because this requires multiple electrode insertions, it is unlikely that percutaneous MWA will be widely used to treat hepatic tumors, unless equipment and electrodes can be modified to produce a larger zone of coagulative necrosis with small caliber electrodes.

Laser Thermal Ablation (See Chapter 85D)

Physical Principles

Laser light, which has a wavelength of 800 to 1064 nm, is delivered to the tissue through the tip of a bare, flexible, quartz laser fiber (300 to 600 μm in diameter) where it is scattered, reflected, and absorbed to varying degrees, depending on its specific wavelength and the specific optical properties of the tissue. The production of heat stems from interaction between the photons of low-intensity laser energy and molecular chromophores—hemoglobin, myoglobin, bilirubin, the cytochrome pigments in mitochondria, and so on—structures ubiquitous in human tissues. This distinguishes laser thermal ablation (LTA) from RFA and MWA, which produce heat by inducing ionic and molecular friction, but the results are the same: lethal thermal injury. Temperatures between 45° C and 55° C ultimately lead to cell death if the heating is persistent. In contrast, temperatures that exceed 60° C cause immediate and irreversible cellular death with protein denaturation, breakage of chemical bonds in DNA and RNA molecules, and loss of integrity in the lipid layers (Head & Dodd, 2004; Izzo, 2002).

Use of high-power laser energy results in vaporization and rapid tissue charring around the tip of the fiber. Although temperatures near the light-emitting portion of the laser fiber can range from 300° C to 1000° C, the presence of coagulated tissue around the tip drastically reduces the optical penetration of the light into adjacent tissues and thereby limits heat diffusion. As a consequence of overheating and charring, the areas of thermal necrosis produced with LTA are often less than 1 cm in diameter. If low-power laser energy is used, tissue heating occurs slowly, which decreases vaporization and tissue carbonization around the tip of the laser fiber. This approach produces a zone of radiant and conductive tissue heating that enlarges progressively, and the area of thermal necrosis ranges from 1.0 to 1.5 cm in diameter (Germer et al, 1998).

Obviously, the relatively small volume of LTA thermal lesions limits the clinical applicability of this thermal ablation technique. To overcome this problem, a variety of strategies have been proposed. The use of sapphire-tipped laser fibers significantly reduces the occurrence of carbonization at the fiber tip, but it does not significantly increase the size of the thermal lesions (Vogl et al, 2002). The use of interstitial fibers, quartz fibers with flat or cylindrical diffusers at the tip, reduces tissue carbonization and produces thermal lesions ranging from 2.3 to 5 cm in diameter (Khan, 2008). Cooled laser application sheaths, designed to reduce temperatures around the laser fiber tip, allow the use of higher power output without carbonization and produce larger thermal lesions (Vogl et al, 2002); however, diffusers increase the caliber of the laser fiber, and water-cooled sheaths require insertion of a coaxial dilation system introduced through an 18-gauge puncture. The beam-splitting multiple-fiber LTA device offers further improvement in thermal lesion size. Most of these systems use four parallel fibers positioned 1.5 to 2 cm from each other. The simultaneous activation of all four fibers produces a thermal lesion that is larger than the sum of the individual lesions produced by each fiber, because killing temperatures are also reached in the overlapping peripheral zones. This laser device can produce thermal lesions from 4 to 7 cm in diameter; however, positioning the multiple fibers in the tumor nodule is a highly complex procedure that requires training and a great deal of practice. In addition, even for skilled investigators, it is almost impossible to place the fiber tips correctly within the three-dimensional space, and in most cases, the thermal lesion produced will be irregularly shaped.

Technique

Like other thermal ablation methods, LTA can be performed percutaneously, laparoscopically, or during open surgery. The percutaneous technique is identical to those described above for RFA and MWA, and US is the technique most commonly used to insert the Chiba or Chiba-like needle into the tumor. When the needle tip is in the correct position, the laser fiber is passed through the needle and advanced, until its tip lies about 1 cm beyond that of the needle. Laser energy is then delivered for 6 to 10 minutes.

The appearance of the thermal lesions on US is the same as that described for other methods of thermal ablation. The technique used with the beam-splitting multiple-fiber laser device is basically the same, but it involves the placement four Chiba-like needles as guides for the four laser fibers. With single and multifiber techniques, the pullback technique can be used to create multiple lesions (Pacella et al, 2009).

Unlike other thermal ablation methods, LTA can be performed under the guidance of MRI. This approach allows real-time monitoring of the temperatures reached in the tissue undergoing ablation. Several MRI sequences have been evaluated for this purpose (Botnar, 1998; Matsumoto et al, 1994; Vogl et al, 1995). The simplest and most widely used is the T1-weighted

Table 85A.9

Complications Reported After Laser Thermal Ablation

First Author, Year	Patients/ Sessions	Mortality Rate, n (%)	COMPLICATIONS, N (%)	
			Major	Minor
Pacella, 2001*	117 S	–	0 (0)	3 (2.6)
Vogl, 2002‡	2132 S	3 (0.1)	42 (2)	967 (45.4)
Vogl, 2004†	1555 S	2 (0.2)	29 (1.5)	
Christophi, 2004†	80 P	0 (0)	13 (16)	
Pacella, 2006*	148 P	1 (0.7)	1 (0.7)	–
Ferrari, 2007*	81 P	0 (0)	0 (0)	–
Arienti, 2008*	1004 S	4 (0.8)	15 (1.5)	62 (6.2)
Pacella, 2009*	432 P	1 (0.2)	7 (1.6)	424 (98.1)

*Hepatocellular carcinoma
†Metastases from colorectal cancer
‡Miscellaneous
P, patients; S, sessions

sequence. The T1 values of a tissue decreases linearly with increasing temperatures (up to about 55° C). However, conventional MRI significantly limits access to the patient, so percutaneous insertion and placement of laser fibers is often done under US or CT guidance, and the patient is then transferred into the MRI scanner to monitor the treatment. This limitation may be overcome by the use of open MRI systems, which are becoming more and more common (Izzo, 2002).

Complications

The complications reported after LTA are also quite similar to those observed after the other percutaneous methods of thermal ablation. Table 85A.9 shows the LTA mortality and complication rates reported by several investigators. Mortality ranged between 0% and 0.8%, and complication rates were between 0% and 2%.

Local Tumor Control

LTA has been shown to be effective in producing complete ablation of tumor nodules, and as expected the probability of success depends on the size of the tumor. Increasing size is associated with decreasing rates of complete ablation; therefore all three major methods for thermal ablation can produce complete ablation in more than 90% of HCC nodules, as long as their diameters do not exceed 3 cm. As shown in Table 85A.10, the local recurrence rates reported by several investigators vary widely after LTA of hepatic tumors, from 2% to 37% (Eichler et al, 2001).

Long-Term Results

The long-term results of LTA of HCC and METs are summarized in Table 85A.10. In terms of survival, the best results were those of Vogl and coworkers (2004), who reported 3- and 5-year survival rates of 49% and 33% after LTA treatment of liver METs; however, the wide variability of the results and the limited number of reports make these data of limited value. Some investigators have reported promising 3- and 5-year survival rates after LTA of HCC (61% and 34%, respectively). On the whole, LTA is an effective method for treating hepatic tumors, but it has two major limitations: First, the small size of the thermal lesions obtained with a single laser fiber reduces the applicability of the technique and necessitates multiple treatment sessions to ablate most tumors. Second, the multiple-fiber technique is a much more complex procedure that requires a high degree of skill and experience. It also tends to produce irregularly shaped thermal lesions, therefore LTA technology needs to be improved before it gains worldwide use. At present, the available data on local recurrences and long-term survival are inadequate to allow any meaningful conclusions on the future of LTA.

Cryoablation (see Chapter 85B)

Physical Principles

Cryoablation kills tumor cells by the induction of hypothermia rather than hyperthermia. The mechanisms underlying the cellular damage produced by cryoablation depend on the freezing rate. Rapid cooling near the cryoprobe tip produces an ice ball. Water molecules are trapped within the cells and are transformed into ice crystals, which aggregate and cause cell death.

Technique

Cryoablation has been practiced during open surgery for more than 40 years. Recently, needle-like cryoprobes 3 mm in caliber

Table 85A.10

Local Recurrence and Survival After Laser Thermal Ablation

First Author, Year	No. Patients	Local Recurrence	SURVIVAL (%)				
			Median (mo)	1 Year	2 Years	3 Years	5 Years
Pacella, 2001†	74	5 (6)	–	99	95	68	15
Eichler, 2001†	39	1 (2.5)	53	–	–	–	–
Vogl, 2004‡	603	71 (18)	46	86	64	49	33
Christophi, 2004‡	80	26 (33)	35	–	–	48.3	6.7
Pacella, 2006†	148	18 (15)	39	89	75	52	27
Ferrari, 2007†	81	8 (10)	–	88.6	70.4	56.6	22.9
Pacella, 2009†	432	67 (20)*	47	–	–	61	34

*Local and nonlocal recurrences
†Hepatocellular carcinoma
‡Metastases from colorectal cancer

Table 85A.11

Complications Reported After Cryoablation

First Author, Year	Patients/Sessions	Mortality Rate, n (%)	COMPLICATIONS, N (%)	
			Major	Minor
Weaver, 1995†	47 P	2 (4)	11 (23)	47 (100)
Sarantou, 1998‡	335 P	5 (1.5)	16 (4.8)	
Seifert, 1999‡	2173 P	33 (1.5)	21 (1)	77 (3.5)
Adam, 2002‡	31 P	1 (3.2)	9 (29)	
Mala, 2004†	24 S	0 (0)	10 (42)	
Jungraithmay, 2005	19 P	0 (0)	4 (21)	7 (36.9)
Xu, 2008†	326 P	0 (0)	5 (1.5)	—
Zhou, 2009*	124 P	1 (0.8)	29 (23.4)	—

*Hepatocellular carcinoma
†Metastases from colorectal cancer
‡Miscellaneous
P, patients; S, sessions

have been developed that can be used for percutaneous tumor ablation, which is generally performed under US guidance (Mala, 2006); general anesthesia is typically used, because the procedure lasts longer than 30 minutes. The tip of the cryoprobe is placed in the deepest part of the tumor under US guidance, and the freeze-thaw cycle begins. On US, the ice ball appears as an increasing hyperechoic rim with a posterior acoustic shadow. Multiple cryoprobes must be inserted to ablate tumors larger than 3 cm in diameter. In this way, ablation areas larger than 5 cm in diameter can be created (Bilchik et al, 2000).

Complications

Cryoablation is associated with a higher rate of complications than other thermal ablation techniques (Seifert & Morris, 1999). One event that is peculiar to this type of ablation is cracking of the liver parenchyma, resulting in hemorrhage. Another typical complication is a syndrome known as *cryoshock*, which involves pulmonary, renal, and coagulation abnormalities in a variety of combinations (Head & Dodd, 2004). The severity varies, and the syndrome may include diffuse intravascular coagulopathy. Severe hypothermia can occur with either intraoperative or percutaneous cryoablation, and this can be lethal when the tumor being treated is large (Sarantou et al, 1998). Other complications are similar to those reported for the other thermal ablative methods. Table 85A.11 shows the mortality and complication rates reported by several investigators after cryoablation of hepatic tumors; they range from 0% to 4% and from 1.5 % to 29%, respectively.

Local Tumor Control

Cryoablation can completely destroy hepatic tumors, but the complete response rates, as shown in Table 85A.12, are lower than those reported for RFA or MWA. Local recurrence rates

Table 85A.12

Local Recurrence and Survival After Cryoablation

First Author, Year	No. Patients	Local Recurrence	SURVIVAL (%)				
			Median (mo)	1 Year	2 Years	3 Years	5 Years
Weaver, 1995‡	140	—	22	—	—	—	—
Seifert, 1999†	116	38 (33)	26	—	56	—	—
Zhou, 1998*	235	—	—	63	—	40	27
Ruers, 2001†	30	3 (9)	32	76	61	—	—
Sheen, 2002‡	57	—	22	—	—	14	—
Adam, 2002‡	31	16 (53)	—	73	—	—	—
Seifert, 2004‡	77	15 (20)	28	—	—	44	—
Kerkar, 2004‡	98	5 (5)	33	81	62	48	28
Mala, 2004†	19	8 (44)	—	—	—	—	—
Jungraithmay, 2005‡	19	10 (58)	21	62	—	16	5
Xu, 2008†	326	21 (6.4)	29	78	62	41	23
Zhou, 2009*	124	—	31	75	56	37	—

*Hepatocellular carcinoma
†Metastases from colorectal cancer
‡Miscellaneous

(6.4% to 58%) also seem to be higher than those observed after RFA.

Long-Term Results

In several centers, cryoablation has been used to destroy liver tumors, for the most part liver metastases from CRC. Only limited initial experiences have been reported for HCC, but for these tumors, RFA has surpassed cryoablation in terms of local tumor control (Adam et al, 2002). The long-term results documented in several studies are shown in Table 85A.12, but these data are characterized by a degree of variability that precludes any meaningful assessment of the efficacy of cryoablation.

The major drawbacks of cryoablation are the large caliber of the cryoprobes, which are not suitable for percutaneous insertion, and the long exposure times required to ablate even small tumors. These aspects need to be substantially improved before cryoablation can compete with the other thermal ablation methods.

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CHAPTER 86

Regional chemotherapy for liver tumors

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OVERVIEW

The liver is an organ with a rich blood supply, therefore it serves as the destination of metastases for many tumors. As the portal vein drains the entire gastrointestinal (GI) tract, malignancies arising from these organs frequently produce liver metastases. Because of the dual blood supply and the large volume of blood flow in the liver, extraabdominal tumors—such as bronchogenic carcinoma, breast cancer, and malignant melanoma—spread hematogenously and also metastasize to the liver with some frequency. This chapter focuses on the use of intraarterial chemotherapy and associated surgical issues for the treatment of liver metastases from colorectal cancer (CRC), which is the third most common malignancy in the United States, with 141,210 new cases and 49,388 deaths in 2009. Additionally, because CRC often presents with or develops isolated spread to the liver, most major studies of hepatic intraarterial chemotherapy address liver metastases deriving from CRC. The use of systemic therapy is discussed briefly to put in perspective the relative response rates and survival with intrahepatic therapy.

SYSTEMIC CHEMOTHERAPY

Responses to systemic chemotherapy (SYS) vary with the type of tumor; for example, patients with liver metastases from a breast primary may have high response rates with SYS (Harris et al, 1997), in contrast to metastases from a gastric or pancreatic primary tumor. Despite 20% response rates and median survivals less than 1 year, fluoropyrimidines represented the standard of care for metastatic CRC for decades (Thirion et al, 2004). More recently, patients with metastatic colon carcinoma have had response rates greater than 30%. With the development of newer drugs, such as irinotecan and oxaliplatin, response rates have increased to 35% to 40% with median survivals of 15 to 19 months (Goldberg et al, 2002; Saltz et al, 2000). The use of targeted agents, such as bevacizumab and cetuximab (Cunningham et al, 2004), has further improved outcomes, and bevacizumab demonstrated overall survival of 20 months (Hurwitz et al, 2004). Many chemotherapy trials do not differentiate patients with liver-only metastases to show how these patients respond to chemotherapy. In tumors with high response rates, such as breast carcinoma, a reasonable response to SYS is found even in patients with liver metastases, although the response is lower with liver metastases than with soft-tissue metastases (George & Hoogstraten, 1978). In patients with CRC, the liver is the most common site of dissemination, and 60% of patients (Daly & Kemeny, 1986) develop liver metastases during the course of their disease.

RATIONALE FOR HEPATIC ARTERIAL CHEMOTHERAPY

The rationale for hepatic arterial infusion (HAI) is based upon anatomic and pharmacologic principles.

1. Liver metastases are perfused almost exclusively by the hepatic artery, whereas normal hepatocytes derive their blood supply from the portal vein and the hepatic artery (Breedis & Young, 1954). After injection of floxuridine (FUDR) into either the hepatic artery or the portal vein, mean liver concentrations of the drug do not differ based on the route of injection; however, mean tumor FUDR levels are significantly increased (15-fold) when the drug is injected via the hepatic artery (Sigurdson et al, 1987).
2. The use of drugs that are largely extracted by the liver during first-pass metabolism results in high local concentrations of drug with minimal systemic toxicity. Ensminger and colleagues (1978) showed that 94% to 99% of FUDR is extracted by the liver during the first pass compared with 19% to 55% of 5-fluorouracil (5-FU). FUDR is therefore an ideal drug for hepatic arterial infusion (HAI), with a 400-fold increase in hepatic exposure with FUDR. The pharmacologic advantage of various chemotherapeutic agents for HAI is summarized in Table 86.1 (Ensminger & Gyves, 1983).
3. Drugs with a steep dose-response curve are more useful when given by the intrahepatic route, because small increases in the concentration of administered drug result in a large improvement in response. FUDR follows linear kinetics and is not saturated at high dose rates.
4. Drugs with a high total body clearance are more useful for hepatic infusion. The area under the concentration-versus-time curve is a function not only of drug clearance but also of hepatic arterial flow. Because hepatic arterial blood flow has a high regional exchange rate (100 to 1500 mL/min), drugs with a high clearance rate are needed (Collins, 1984). If a drug is not cleared rapidly, recirculation through the systemic circulation mitigates the advantage of intraarterial therapy over systemic therapy (Collins, 1986).
5. Another rationale for hepatic arterial chemotherapy, especially for patients with metastatic CRC, is the concept of a stepwise pattern of metastatic progression (Weiss, 1989; Weiss et al, 1986). This theory states that hematogenous spread occurs first via the portal vein to the liver, then from

Table 86.1

Estimated Increase in Hepatic Exposure for Drugs Given by Hepatic Arterial Infusion

Estimated Increase by Drug	Half-Life (min)	Hepatic Arterial Exposure
Fluorouracil	10	5- to 10-fold
Floxuridine	10	100- to 400-fold
Bis-chloroethyl-nitrosourea	5	6- to 7-fold
Mitomycin C	10	6- to 8-fold
Cisplatin	20 to 30	4- to 7-fold
Doxorubicin	60	2-fold
Dichloromethotrexate	—	6- to 8-fold

the liver to the lungs, and then to other organs. Aggressive treatment, either resection or hepatic infusion, of metastases confined to the liver yields prolonged survival for some patients.

The development of an implantable infusion pump allowed for the safe administration of hepatic arterial chemotherapy in the outpatient setting (Blackshear et al, 1972). Early trials using an implantable pump and continuous FUDR therapy produced a median response rate of 47% (Johnson & Rivkin, 1985) and a median survival of 17 months (Weiss et al, 1983). To further show that HAI had a therapeutic benefit, several randomized studies were conducted.

FIRST-LINE THERAPY IN UNRESECTABLE LIVER METASTASES

One of the first randomized trials was conducted at Memorial Sloan-Kettering Cancer Center (MSKCC) (Kemeny et al, 1987). Before randomization, patients were stratified for extent of liver involvement by tumor and baseline lactate dehydrogenase level, two factors that have been shown to be important prognostic indicators of survival (Table 86.2; Kemeny & Braun, 1983; Kemeny et al, 1989). This prospective randomized trial compared HAI with SYS using the same chemotherapeutic agent (FUDR), drug schedule (a 14-day continuous infusion), and method of administration (internal pump) in both groups.

Of the 99 evaluable patients, two complete responses and 23 partial responses (53%) were observed in the group receiving HAI, and 10 partial responses (21%) were reported in the SYS group ($P = .001$). Of the patients randomized to SYS, 31 (60%) crossed over to HAI after tumor progression, and 25% of these patients went on to a partial response after the crossover, and 60% had a decrease in carcinoembryonic antigen (CEA) levels.

Toxicity differed between the two groups. An increase in hepatic enzymes and serum bilirubin levels occurred in the HAI group. In the SYS group, diarrhea occurred in 70% of patients, and 9% required admission for intravenous hydration. Mucositis occurred in 10% of patients receiving SYS.

The median survival for the HAI and SYS groups was 17 and 12 months, respectively ($P = .424$). The interpretation of survival in this study is difficult because 60% of the patients in the systemic group crossed over. The patients who did not cross over usually had clots of the hepatic arterial system and had a median survival of only 8 months compared with 18 months for the patients who crossed over to hepatic infusion ($P = .04$). An analysis of baseline characteristics in the crossover and noncrossover groups revealed no significant differences.

Two subsequent European randomized trials using HAI therapy in this setting have been published. The first was conducted by the Medical Research Council (MRC) and European Organization for the Research and Treatment of Cancer (EORTC) groups, which compared HAI 5-FU/leucovorin (LV) with intravenous 5-FU/LV. Crossover from the intravenous to the HAI arm was not allowed. Of 290 patients randomized, only 66% on the HAI arms received treatment. Response rates were 22% for HAI and 19% for intravenous

Table 86.2

Randomized Studies of Hepatic Arterial Infusion (HAI) vs. Systemic Chemotherapy (SYS) for Unresectable Hepatic Metastases

		HAI		SYS		
Group (Reference)	No. Patients	Drug	Response (%)	Drug	Response (%)	*P* Value
MSKCC (Kemeny et al, 1987)	162	FUDR	50	FUDR	20	.001
NCI (Chang et al, 1987)	143	FUDR	42	FUDR	10	.0001
NCOG (Hohn et al, 1989)	64	FUDR	62	FUDR	17	.003
City of Hope (Wagman et al, 1990)	41	FUDR	55	FU	20	—
Mayo Clinic (Martin et al, 1990)	69	FUDR	48	FU	12	.02
French (Rougier et al, 1992)*	163	FUDR	44	FU	—	—
HAPT (Allen-Mersch et al, 1994)	100	FUDR	—	FU or BSC		
German (Lorenz & Muller, 2000)	168	FUDR	43	FU/leucovorin	22	.009
EORTC (Kerr et al, 2003)	290	FU/leucovorin	22†	FU/leucovorin	19	—
CALGB (Kemeny et al, 2006)	135	FUDR/dexamethasone	47	FU/leucovorin	24	.012

*Patients receieved SYS only when they became symptomatic (not all receieved SYS in HAPT).

†Responses calculated at single time point (12 weeks).

BSC, best supportive care; CALGB, Cancer and Leukemia Group B; EORTC, European Organization for the Research and Treatment of Cancer; FUDR, fluorodeoxyuridine; FU, follow-up; HAPT, Hepatic Artery Pump Trial; MSKCC, Memorial Sloan-Kettering Cancer Center; NCI, National Cancer Institute; NCOG, Northern California Oncology Group.

Table 86.3

Summary of 1- and 2-Year Survival in Randomized Trials Comparing Hepatic Arterial Infusion (HAI) and Systemic Chemotherapy (SYS)

	SURVIVAL (% ALIVE)				SURVIVAL (% ALIVE)			
	1 Year		2 Years		1 Year		2 Years	
Group (Reference)	HAI	SYS	HAI	SYS	Crossover	No Crossover	Crossover	No Crossover
MSKCC (Kemeny et al, 1987)	60	50	25	20	60	28	25	14
NCOG (Hohn et al, 1989)	60	42	30	20	78	42	40	17
NCI* (Chang et al, 1987)	85	60	44	13	—	—	—	—
France (Rougier et al, 1992)	61	44	22	10	—	—	—	—
CALGB (Kemeny et al, 2006)	—	—	51	35	—	—	—	—
Mean	66	49	34	20	69	35	37	15

*Excludes patients with metastasis to hepatic lymph nodes

CALBG, Cancer and Leukemia Group B; MSKCC, Memorial Sloan-Kettering Cancer Center; NCI, National Cancer Institute; NCOG, Northern California Oncology Group.

5-FU/LV. This trial used subcutaneous ports rather than implantable pumps and had significant catheter-related problems (36% of HAI patients) (Kerr et al, 2003). The median survival was 14.7 months and 14.8 months in the HAI and SYS groups, respectively ($P = .79$).

The second trial was by a German cooperative group that randomized 168 patients with unresectable colorectal liver metastases to HAI of FUDR, HAI of 5-FU/LV, or intravenous 5-FU/LV (Lorenz & Muller, 2000). Response rates were higher in the two HAI arms, with no significant differences in time to progression, the primary end point, or overall survival (OS) between the arms. Only 70% of patients on the HAI arms actually received assigned treatment. The study also used ports instead of pumps.

The Cancer and Leukemia Group B (CALGB) (Kemeny et al, 2006) completed trial 9481, which compared systemic 5-FU/LV via the Mayo Clinic regimen, considered standard of care at the time of trial design, with HAI of FUDR, LV, and dexamethasone, a regimen that had produced high response rates (78%) and lower toxicity (3% biliary sclerosis) in a phase II study (Kemeny et al, 1994). An earlier trial randomized patients to HAI of FUDR with or without dexamethasone, which demonstrated less biliary toxicity and a trend toward median OS (23 months vs. 15 months, respectively, $P = .06$) in the dexamethasone-containing arm (Kemeny et al, 1992). In CALGB 9481, no crossover was permitted, and a total of 134 patients were randomized. Most patients (70%) had greater than 30% liver involvement, synchronous metastases (78%), and were chemotherapy naive (97%). Response rates were higher in the HAI group (47% vs. 24%; $P = .012$), although time to progression was not significantly different (5.3 months vs. 6.8 months; $P = .8$); time to hepatic progression was better in the HAI arm (9.8 months vs. 7.3 months; $P = .017$) and in the systemic arm (7.7 months vs. 14.8 months; $P = .029$). Median OS was significantly better in the HAI arm (24.4 months vs. 20 months; $P = .0034$; Kemeny et al, 2006). Resource use, quality of life, and molecular markers of prognosis, such as thymidylate synthase (TS) and p21 gene expression, were examined prospectively in this study, and final analysis of these factors were presented. At 3- and 6-month follow-up, physical functioning was improved in the HAI group. TS levels correlated with survival in HAI patients (24 months if TS >4, 14 months if TS ≤4), but these differences were not significant ($P = .17$).

A total of 10 randomized phase III trials have been done, most of which demonstrate a higher response rate with HAI versus SYS in patients with hepatic metastases from CRC (see Table 86.2). Whether this increase in response rate translates into increased survival is controversial. Several factors complicate this issue. Importantly, most of the trials contain relatively few patients; therefore the power to observe differences in survival rates is low. Also, because of early successes with intrahepatic infusion, some of these studies allowed patients in the systemic arm to cross over to intrahepatic therapy after tumor progression on systemic therapy. This crossover may have negated any difference in survival between the two groups. The studies show a survival advantage for those who received subsequent HAI, with a mean 1-year survival of 69% for the patients who had crossed over from SYS to HAI versus 35% for the patients who did not cross over (Table 86.3). Additionally, some trials included patients with extrahepatic disease, complicating survival analyses in the absence of systemic treatment. Other factors to consider are that some patients randomized to HAI did not receive it but were included in the survival analysis, and an absence of modern toxicity-based dose-titration schema may have resulted in fewer cycles of treatment.

The European studies are difficult to interpret, because in the first two studies, the SYS group received SYS only when they became symptomatic. The two new European studies used ports instead of pumps, which resulted in more technical complications.

Two meta-analyses of the original seven trials were conducted and included more than 600 patients. The Meta-Analysis Group in Cancer (MAGIC, 1996) confirmed the increased response rates seen with HAI over SYS (41% vs. 14%); however, survival differences were deemed only statistically significant in the trials that included a control group treated only when symptoms arose. With the statistical methodology used, the authors were unable to include the data from Hohn and colleagues (1989); however, a second meta-analysis published the same year did incorporate the results from that study and found an absolute survival difference of 12.5% at 1 year ($P = .002$) and 7.5% at 2 years ($P = .026$) in favor of HAI (Harmantas et al, 1996). The authors omitted the trial by Allen-Mersch and colleagues (1994) given the fact that most patients in the SYS arm of that study received best supportive care only. Furthermore, they analyzed their results to show that, when

omitting the data from Rougier and colleagues (1992)—because, like the study from Allen-Mersh and others (1994), only half of the patients in the SYS arm received chemotherapy—survival was only statistically significantly higher at the 1-year time point. Nonetheless, factoring only those six studies without crossover, the survival differences at 1 and 2 years were accentuated, and actually both significantly favor of HAI.

As mentioned above, CALGB 9481 permitted no crossover, and with the incorporation of dexamethasone, it demonstrated survival with HAI that compares well to published results with modern SYS regimens; however, a recent and well-orchestrated third meta-analysis that accounted for the design flaws discussed above examined all 10 randomized trials to date and failed to demonstrate a survival benefit with HAI (Mocellin et al, 2007). This report and the published commentary that followed demonstrated that, although there may be no clear survival benefit in using HAI instead of SYS, combining HAI and SYS has led to high response rates with acceptable toxicity profiles.

Subsequent sections of the chapter discuss how newer management principles, such as the incorporation of dexamethasone for toxicity abrogation and the use of combination HAI and SYS, may improve overall outcomes. This underscores the need to examine response and OS data in the context of modern treatment paradigms.

TOXICITY OF INTRAHEPATIC THERAPY

Table 86.4 summarizes the GI toxicities noted by investigators using the implantable pump. The side effects of SYS are almost never observed with HAI, and myelosuppression does not occur with intrahepatic FUDR (Kemeny et al, 1984). Although intrahepatic mitomycin C or bis-chloroethyl-nitrosourea may depress platelet counts, the absolute depression and frequency of depression are less than with systemic administration. Nausea, vomiting, and diarrhea do not occur with HAI of FUDR. If diarrhea does occur, shunting of the chemotherapeutic agent to the bowel should be suspected (Gluck et al, 1985).

The most common problems with HAI are ulcer disease and hepatic toxicity (Hohn et al, 1985; Kemeny et al, 1984). Severe ulcer disease results from inadvertent perfusion of the stomach and duodenum with drug via small, unligated branches from the hepatic artery, but this can be prevented by meticulous dissection at the time of pump placement (Hohn et al, 1985); however, even without radiologically visible perfusion of the stomach or duodenum, mild gastritis and duodenitis can occur. This toxicity can be reduced by careful dose reductions when any GI symptoms arise. Hepatobiliary toxicity is the most problematic toxicity seen with HAI. Although some evidence of hepatocellular necrosis and cholestasis has been found on liver biopsy specimens (Doria et al, 1986), most studies point to a combined ischemic and inflammatory effect on the bile ducts as the most important cause of this toxicity. The bile ducts are particularly sensitive to HAI; this is because the bile ducts derive their blood supply almost exclusively from the hepatic artery, similar to hepatic tumors (Northover & Terblanche, 1979).

In patients with severe toxicity, endoscopic retrograde cholangiopancreatography (ERCP) shows lesions resembling primary sclerosing cholangitis (Kemeny et al, 1985). Because the ducts are sclerotic and nondilated, ultrasound usually is not helpful. In some patients, the strictures are more focal, and they are usually worse at the bifurcation, and drainage procedures by endoscopic or by percutaneous transhepatic intubation may be helpful. Duct obstruction from metastases should be excluded first by computed tomography (CT) of the liver.

Close monitoring of liver function tests is necessary to avoid biliary sclerosis. If the serum bilirubin becomes elevated, no further treatment should be given until the bilirubin returns to normal, and then treatment should proceed with only a small test dose (0.05 mg/kg/day). In patients who cannot tolerate even a low dose for 2 weeks, it may be possible to continue treatment by giving the FUDR infusion for 1 week rather than the usual 2 weeks. At MSKCC, we modify treatment as outlined in Table 86.5.

In older trials, cholecystitis occurred in 33% of patients receiving HAI (Kemeny et al, 1986a). In more recent series, the gallbladder was removed at the time of catheter placement to prevent this complication and to avoid the confusion of these symptoms with other hepatic side effects of chemotherapy.

SURGICAL TECHNIQUE

Hepatic Artery Pump Placement

The arterial anatomy of the liver varies (Table 86.6), and a normal anatomy is present in only about two thirds of patients

Table 86.4

Hepatic Arterial Floxuridine Infusion with Internal Pump: Toxicity

Reference	No. Patients	Gastritis (%)	Ulcer (%)	AST (%)	Bilirubin (%)	Diarrhea (%)	Biliary Sclerosis (%)
Niederhuber et al, 1984	70	56	8	32	24	–	–
Balch & Urist, 1986	50	–	6	23	23	0	–
Kemeny et al, 1984	41	29	29	71	22	0	5
Shepard et al, 1985	53	–	20	49	24	–	–
Cohen et al, 1983	50	–	40	10	25	–	–
Weiss et al, 1983	17	50	11	80	23	23	–
Schwartz et al, 1985	23	53	–	77	20	10	–
Johnson et al, 1985	40	–	8	50	13	0	5
Kemeny et al, 1985	31	17	6	47	–	8	19
Hohn et al, 1989	61	35	2	0	78	11	29

AST, aspartate aminotransferase

Table 86.5

Dose Modification of HAI of FUDR for Hepatic Toxicity

	Aspartate Aminotransferase		FUDR (%)
Ref value	≤50 U/L	>50 U/L	—
Current value	0 to <3 × ref	0 to <2 × ref	100
	3 to <4 × ref	2 to <3 × ref	80
	4 to <5 × ref	3 to <4 × ref	50
	≥5 × ref	≥4 × ref	Hold
If held, restart when:	<4 × ref	<3 × ref	50% off last dose
	Alkaline Phosphatase		**FUDR**
Ref value (ref)	≤90 U/L	>90 U/L	—
Current value	0 to <1.5 × ref	0 to <1.2 × ref	100
	1.5 to >2 × ref	1.2 to 1.5 × ref	80
	≥2 × ref	≥1.5 × ref	Hold
If held, restart when:	<1.5 × ref	<1.2 × ref	25% off last dose
	Total Bilirubin		**FUDR**
Ref value	≤1.2 mg/dL	>1.2 md/dL	—
Current value	0 to <1.5 × ref	0 to <1.2 × ref	100
	1.5 to <2 × ref	1.2 to <1.5 × ref	50
	≥2 × ref	≥1.5 × ref	Hold
If held, restart when:	<1.5 × ref	<1.2 × ref	25% off last dose

Reference value is obtained on the day patient received the last FUDR dose. Current value is obtained at pump emptying or on the day of planned treatment, whichever is higher.

FUDR, fluorodeoxyuridine; HAI, hepatic arterial infusion; Ref, reference.

(Allen et al, 2002; see Chapter 1B). Before consideration of pump placement, it is imperative to carry out a careful review of the arteriogram with the radiologist and formulate a plan for the management of aberrant anatomy. In the past, direct arteriography was required, but excellent definition now can be ascertained from CT angiography. In most cases, a pump with a single catheter is adequate to provide access to the entire hepatic arterial inflow. It is best not to place the catheter directly into the hepatic artery, which risks thrombosis of the vessel; instead, it should be placed into an accessible side branch. The gastroduodenal artery (GDA) is the preferred conduit for the catheter and provides the most reliable method of catheter implantation (Allen et al, 2002). As previously mentioned, cholecystectomy should be performed to prevent chemotherapy-induced cholecystitis. Numerous incisions have been employed for this operation with success, including an upper midline incision, right subcostal incision, or limited right subcostal hockey-stick incision. Preoperative intravenous antibiotics close to the time of incision are imperative.

For patients with unresectable disease, a staging laparoscopy is advisable to rule out occult extrahepatic disease, which in our experience occurs in approximately one third of patients (Grobmyer et al, 2004). A thorough examination of the abdomen is performed at laparoscopy and at laparotomy to look for extrahepatic disease. The most common sites of extrahepatic metastases are the peritoneum and portal lymph nodes; therefore a biopsy should be done if the lymph nodes look suspicious, because their involvement generally would preclude the use of the pump. The extent of liver involvement should be assessed and documented. Any radiographically occult hepatic tumors should be noted, and the potential for future resection should be specifically addressed in the operative note.

Standard Hepatic Arterial Anatomy

A standard cholecystectomy is performed, and the hepatic artery and its branches are circumferentially dissected. The common hepatic artery and the GDA are palpable superior to the body of the pancreas and the first portion of the duodenum. The GDA runs parallel to and lies immediately to the left of the common bile duct, and it is advisable to start by dissecting the common hepatic artery to minimize the risk of injuring the bile duct. The right gastric artery is ligated and divided. The distal common hepatic artery, the entire GDA, and the proximal proper hepatic artery are dissected away from their attachments. It is important to mobilize the full length of the extrapancreatic GDA to facilitate insertion of the catheter. Suprapyloric side branches of the GDA are often encountered and must be ligated. Frequently, branches to the pancreas and duodenum arise from many of these dissected vessels, and it is essential to identify and ligate these branches to avoid perfusion of the pancreas, stomach, or duodenum. The common hepatic artery is mobilized 1 cm proximally, and the proper hepatic artery is mobilized about 2 cm distally from the origin of the GDA. Branches to the retroperitoneum from the right or left hepatic artery are common and should be ligated. Review of preoperative angiography to look specifically for these branches

Table 86.6

Summary of Reported Prevalence (%) of Hepatic Arterial Anatomic Variants

	Daly et al, 1984	Michels, 1966	Kemeny et al, 1986b	Curley et al, 1993	Allen et al, 2002
Anatomy	(n = 200)	(n = 200)	(n = 100)	(n = 180)	(n = 265)
Normal	70	55	50	63	63
Variant gastroduodenal artery	6	—	9	9	11
Accessory right hepatic artery	4	7	4	1	1
Replaced right hepatic artery	6	12	16	12	6
Accessory left hepatic artery	3.5	8	1	2	10
Replaced left hepatic artery	4	10	16	11	4
Other	5	2.5	1	2	5

From Allen PJ, et al, 2002: The management of variant arterial anatomy during hepatic arterial infusion pump placement. Ann Surg Oncol 9:875-880.

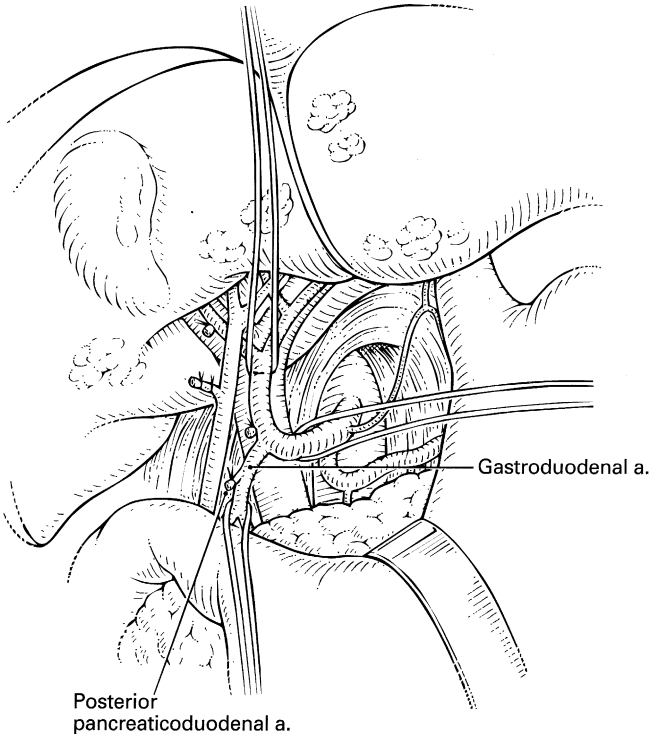


FIGURE 86.1. The common hepatic, proper hepatic, and gastroduodenal arteries are completely mobilized. All branches to the stomach, duodenum, or pancreas are identified and ligated.

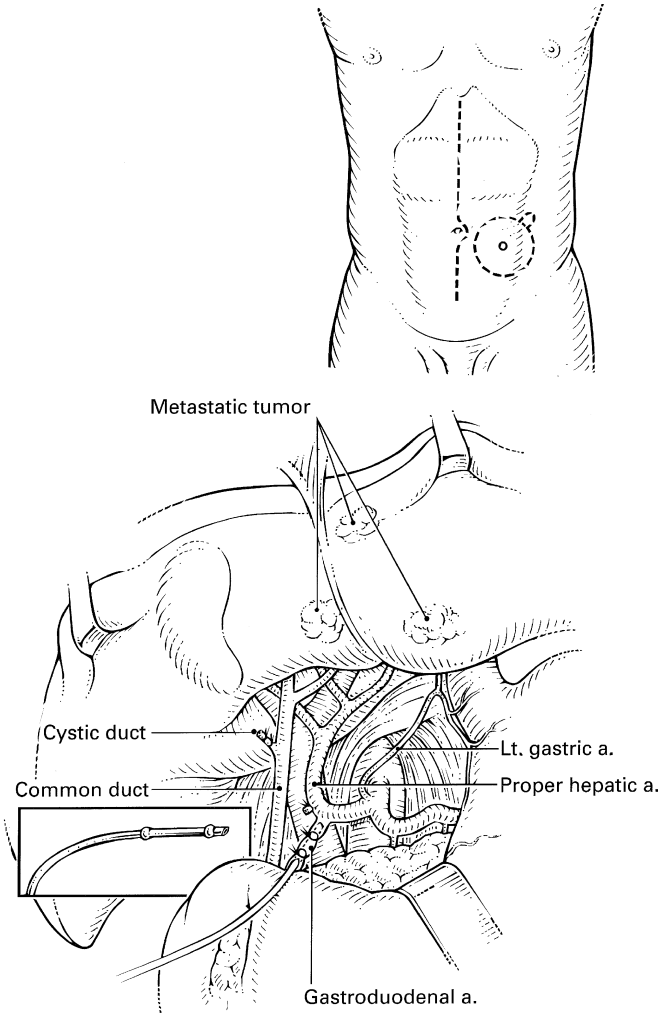


FIGURE 86.2. The infusion pump ideally is placed in the left lower quadrant, away from the liver, to avoid artifacts on subsequent computed tomographic scans. With normal anatomy, the catheter is placed in the gastroduodenal artery and secured with nonabsorbable ties, the right gastric artery is ligated, and the gallbladder is removed.

is important, because they are often found in retrospect. At this point, a complete circumferential dissection of the common hepatic artery, GDA, and proper hepatic artery should be ensured such that no vessels to the pancreas, stomach, or duodenum remain (Fig. 86.1). The GDA should be temporarily occluded with palpation of the proper hepatic artery to rule out retrograde flow to the liver through the GDA secondary to celiac stenosis. No attempt at dissection of the common bile duct is necessary, because this risks devascularization and ischemic stricturing.

The pump pocket should be created in the lower abdomen so that the pump lies below the waist and avoids contact with the iliac spine and the edge of the ribs. In obese patients, placing the pump over the ribs should be considered, because this may help in locating and accessing the pump. The pump and catheter should be handled carefully, avoiding contact with the patient's skin. The catheter is trimmed at a level just beyond the last tying ring and is tunneled into the abdominal cavity. The pump is secured to the abdominal fascia with nonabsorbable sutures; the catheter should be positioned behind the pump to prevent injury by a needle. The GDA is ligated with a nonabsorbable tie at its most distal point, and vascular control of the common and proper hepatic arteries is achieved with vascular clamps or vessel loops. Isolated vascular control of the GDA at its orifice also can be used to avoid occlusion of the hepatic artery.

An arteriotomy is made in the distal GDA, and the catheter is inserted up to, but not beyond, the junction with the hepatic artery (Fig. 86.2). If the catheter protrudes into the common hepatic artery, turbulence of blood flow can lead to thrombosis of the vessel. Failure to pass the catheter to the junction leaves a short segment of the GDA exposed to full concentrations of FUDR without the diluting effect of blood flow, potentially resulting in sclerosis, thrombosis, or late dislodgment. When positioned, the catheter should be secured two or three times with nonabsorbable ties proximal to the tying rings on the catheter. Perfusion of both lobes of the liver and lack of extrahepatic perfusion is confirmed by infusing 2 to 3 mL of half-strength fluorescein through the pump and visualizing it with a Woods lamp. Half-strength methylene blue injection is an alternative method of ensuring proper perfusion. After the perfusion test, the catheter is flushed with heparinized saline, and the wounds are closed. Antibiotic coverage should be continued for 2 to 3 days postoperatively because of the seriousness of a pump infection. Any sign of erythema indicates a wound infection postoperatively and should be treated immediately and aggressively.

Aberrant Hepatic Arterial Anatomy (See Chapter 1B)

As discussed earlier, aberrant hepatic arterial anatomy is common, and numerous variations occur. Each anatomic

situation is specifically addressed here, but first, general principles in managing variant anatomy are discussed. In analyses of our extensive experience with this operation, the factor most consistently associated with catheter-related complications and decreased durability of the catheter is cannulation of a vessel other than the GDA. The overall preferred technique is placement of the catheter in the GDA with ligation of the isolated variant vessel. This method relies on intrahepatic collateral development and cross-perfusion to the liver fed by the ligated vessel. Although concerns have been raised over incomplete hepatic perfusion with this technique, it is rare; in our published experience with this operation for variant anatomy, incomplete hepatic perfusion occurred once in 52 cases. This cross-perfusion sometimes can take 4 weeks to occur, and early perfusion scans may be abnormal initially; however, these should be rechecked in a few weeks to assess for the cross-perfusion, because most normalize (Allen et al, 2002; Curley et al, 1993). The only exception to this rule may be patients with central tumors so large that they impede cross-collateralization. Lastly, although cross-perfusion after ligation of aberrant vessels is highly reliable, it has not been proven that this results in equal blood flow for chemotherapy delivery.

Aberrant Origin of the Gastroduodenal Artery

The GDA can arise from the right or left hepatic artery, or there can be a trifurcation in which the GDA, right hepatic artery, and left hepatic artery all arise simultaneously from the common hepatic artery; this anomaly occurs 6% to 11% of the time (Allen et al, 2002). In general, it is preferable to place the catheter into the GDA and ligate vessels that are not receiving catheter-directed flow, because this is the technique associated with the lowest rate of catheter-related complications (Allen et al, 2002, 2005). In the case of a trifurcation, the catheter should be placed in the GDA, and perfusion should be tested with fluoroscein or methylene blue. If bilobar perfusion is adequate, ligation of vessels is unnecessary. If no perfusion of one lobe of the liver is seen at testing, the hepatic artery to that lobe should be ligated, most commonly the left hepatic artery, thereby relying on cross-perfusion of the left liver.

The hepatic arterial tree also may be accessed through the splenic artery just to the left of the celiac axis. The catheter is placed in the splenic artery and maneuvered across the celiac axis to lie freely in the hepatic artery, ending proximal to the bifurcation. The GDA and the right gastric artery are ligated, and the catheter is secured doubly in the splenic artery. This technique is technically difficult, as it requires extensive dissection of the celiac axis and manipulation of the catheter across the celiac artery branches; it is also associated with more complications, including thrombosis and extrahepatic perfusion, and it is therefore rarely used. Another option is retrograde cannulation of the common hepatic artery through the GDA with an attached short, stiff, small-gauge catheter; however, this technique is also associated with a higher rate of complications, including arterial dissection and thrombosis, and it should be used rarely if ever.

Accessory Left Hepatic Artery

An accessory left hepatic artery arises from the left gastric artery, crosses the gastrohepatic ligament, enters the liver at the base of the umbilical fissure, and typically supplies segments II and III. The native left hepatic artery, which arises from the proper hepatic artery, also supplies the left liver, typically segment IV in this situation. This abnormality is present in 2% to 10% of cases. The simplest, safest, and most reliable option is to ligate the accessory left hepatic artery and place the pump catheter in the GDA, because cross-perfusion is highly reliable. Another option is to use two catheters (or pumps), one in the GDA and one in the accessory left hepatic artery, although this technique is cumbersome and is generally not used.

Accessory Right Hepatic Artery

Accessory right hepatic arteries arise from the superior mesenteric artery and run in the portacaval space to supply a portion of the right lobe of the liver. This abnormality is present 1% to 7% of patients. Accessory and replaced right hepatic arteries rarely have side branches adequate for cannulation. The preferred technique in this situation is placement of the catheter in the GDA and ligation of the accessory vessel, because cross-perfusion is reliable. Placing a second catheter directly in the accessory vessel is another option but is generally unnecessary and not advised.

Replaced Left Hepatic Artery

A replaced left hepatic artery arises from the left gastric artery and supplies the left liver; no native left hepatic artery is found, an abnormality present in 4% to 16% of patients. Once again, the preferred technique is to place the catheter in the GDA and ligate the replaced left hepatic artery. Initial reports on this specific situation suggested rates of incomplete cross-perfusion of 40% (Cohen et al, 1987). More recent reports, including our experience, show that incomplete cross-perfusion is uncommon in this situation and occurred in only 1 of 10 of our patients at last analysis (Allen et al, 2002; Curley et al, 1993). Other techniques, such as placing catheters in the GDA and in a branch of the replaced left hepatic artery, can be considered in patients with bulky disease in the left liver or in those with a large central tumor that may impede cross-perfusion.

Replaced Right Hepatic Artery

A replaced right hepatic artery originates from the superior mesenteric artery, runs in the portacaval space, and supplies the whole right liver. No branches to the right liver originate from the proper hepatic artery, an anatomic situation that occurs 6% to 16% of the time. If the surgeon ligates the replaced right hepatic artery, cross-perfusion from the left hepatic artery occurs almost uniformly (Allen et al, 2002; Cohen et al, 1987; Curley et al, 1993). The catheter should be placed in the GDA, and the replaced right hepatic artery should be ligated. Other techniques have been described, such as placing a second catheter in the replaced right hepatic artery, either directly through a small arteriotomy, as there are no significant side branches from this vessel, or using a vascular graft, but these are rarely if ever indicated. This technique requires that the catheter be trimmed flush just beyond the tying ring and that it be placed such that the ring lies just inside the vessel, and the arteriotomy is closed over the ring.

PUMP PLACEMENT AFTER MAJOR HEPATECTOMY

In the event that a pump is being placed for adjuvant therapy after hepatectomy, the specific anatomy to the remnant liver must be considered. In general, the best results are obtained if the catheter is placed in the GDA. In the presence of replaced

or accessory vessels to the remnant liver, the surgeon must consider the condition of that remnant (i.e., steatosis, congestion) and the potential risk of ligating the arterial supply or risking thrombosis by directly cannulating the vessel to the remnant. One option that is often available after a hemihepatectomy is to use the stump of the artery to the resected liver as a conduit for the catheter, if the anatomy allows this. If the arterial anatomy is normal, or a trifurcation is present at the GDA, there is generally no issue, and the catheter is placed routinely in the GDA. When a variation of the origin of the GDA is present (i.e., off of the right or left hepatic artery), care must be taken to preserve the origin such that the catheter can be placed. For a remnant right lobe, an accessory right hepatic artery generally can be ligated, unless major concerns about the condition of the remnant are an issue. In the case of a remnant right lobe and a replaced right hepatic artery, it is generally not recommended to place a pump, because it would require direct cannulation of that artery, risking thrombosis, injury, and a higher rate of catheter-related complications in general. For a remnant left lobe, an accessory left artery generally can be ligated. If the remnant left lobe is fed solely by a replaced left hepatic artery, a pump can be placed, but this requires dissection of the left gastric artery and a suitable side branch for the catheter. Special care must be taken to ensure that all branches to the stomach have been properly ligated to prevent extrahepatic perfusion.

POSTOPERATIVE ASSESSMENT

After surgery and before administering chemotherapy, the distribution of arterial perfusion is assessed by a radionuclide pump flow study (see Chapter 15). A baseline technetium 99m (^{99m}Tc)-sulfur colloid scan is obtained to identify the liver contour. Pump perfusion is assessed by infusing ^{99m}Tc-labeled macroaggregated albumin (MAA) through the bolus port of the pump and into the hepatic artery. When the MAA scan produces an image that matches the sulfur colloid liver scan, the pump is perfusing the entire liver as intended. Perfusion of extrahepatic tissues produces ^{99m}Tc signals outside the liver image (Fig. 86.3). Incomplete perfusion of the liver produces an incomplete image on the MAA scan. Misperfusion is discovered in 5% to 7% of cases and often can be corrected by surgical or angiographic intervention to occlude additional hepatic vessels missed at operation (Campbell et al, 1993). If no additional vessels are seen on angiography for embolization, it is worth repeating the scan in a few weeks to allow sufficient time for intrahepatic collaterals and cross-perfusion to develop (Allen et al, 2002).

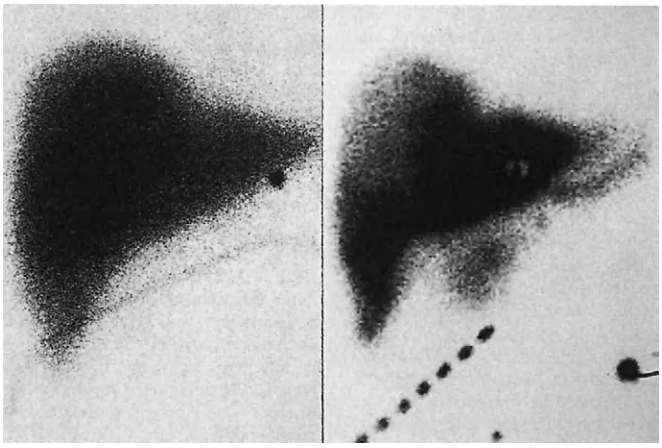


FIGURE 86.3. The liver-spleen technetium 99m–sulfur colloid scan on the left shows the normal liver. The macroaggregated albumin (MAA) scan on the right shows extrahepatic perfusion to the duodenum and head of the pancreas.

TECHNICAL COMPLICATIONS OF HEPATIC ARTERY INFUSION PUMP PLACEMENT

Surgical and technical complications of pump placement occur, and the spectrum and frequency of these complications must be understood by the surgeon, the medical oncologist, and the patient before initiating treatment. To assess the risks of insertion and the use of an implantable pump for hepatic artery chemotherapy, we reviewed the charts of all patients who underwent pump insertion for unresectable metastases over a 15-year period (1986 to 2001) at MSKCC (Allen et al, 2005). During this period, 544 infusion pumps were inserted by several different surgeons for HAI of FUDR alone or in combination with other drugs for patients with isolated unresectable colorectal hepatic metastases. Variant arterial anatomy was present in 205 patients (38%), most of which (82%) involved a single vessel. A colectomy was performed in addition to the pump placement in 136 patients (25%).

Operative mortality was low, and five patients died within 30 days of the operation (0.9% mortality rate). Early in this series, two deaths were from hepatic failure secondary to extensive metastatic disease within the liver. We now exclude patients with extensive (>70%) liver replacement from pump placement because of this risk. Generalized operative morbidity unrelated to the pump itself occurred in approximately 25% of patients in our series. The most common complications were prolonged ileus, wound complications, atelectasis, and abscesses.

Pump-related morbidity occurred in 120 patients (22%) and is summarized in Table 86.7. Most of these complications (63%) occurred more than 30 days after pump placement. The most common complications (51%) were related to the hepatic arterial system and included thrombosis, hemorrhage, or perfusion abnormalities. Early (<30 days) pump-related morbidity occurred in only 8% of cases, and all of the catheter-related complications occurred after 30 days. Overall, the pumps were salvaged from these complications 45% of the time; however, salvage was much more common with early complications (70% if <30 days) than with late complications (30% if >30 days). In a multivariate analysis, surgeon experience and the use of any vessel other than the GDA were independently associated with pump-related morbidity and pump survival. Pump failure was generally low—5% at 6 months, 9% at 1 year, 16% at 2 years, and 26% at 3 years—and HAI was discontinued for pump-related complications in only 9% of cases. The performance of a concomitant colorectal resection was not associated with a higher rate of complications.

Extrahepatic Perfusion

Small branches of the hepatic artery to the stomach, duodenum, and pancreas can be missed on preoperative angiography. If small vessels are not divided and ligated, perfusion of the bowel with FUDR produces severe pain and GI ulceration; if the pancreas is perfused, severe pancreatitis will ensue. These

Table 86.7

Postoperative Pump-Related Complications and Salvage Rates in 544 Hepatic Artery Infusion Pump Placements

		EARLY (<30 DAYS)		LATE (>30 DAYS)	
Type of Complication	**Total (N)**	**n**	**% Salvaged**	**n**	**% Salvaged**
Pump malfunction	6	6	100	—	—
Pocket Infection	14	4	50	10	40
Hematoma	1	1	100	—	—
Pump migration	4	1	100	3	33
Catheter occlusion	11	—	—	11	36
Dislodgment	18	—	—	18	11
Erosion	4	—	—	4	0
Arterial hemorrhage	1	1	100	—	—
Thrombosis	33	13	31	20	30
Extrahepatic perfusion	16	9	100	7	57
Incomplete perfusion	12	9	78	3	67
Overall	120	44	70	76	30

From Allen PJ, et al, 2005: Technical complications and durability of hepatic artery infusion pumps for unresectable colorectal liver metastases: an institutional experience of 544 consecutive cases. J Am Coll Surg 201:57-65.

complications are potentially lethal, and extrahepatic perfusion should be identified and corrected before starting chemotherapy whenever possible.

If extrahepatic perfusion is seen on the ^{99m}Tc MAA scan, the next step is to perform an angiogram by bolus injection through the pump; the angiogram usually shows the vessel responsible for the extrahepatic perfusion. This occasionally is unsuccessful, and a transfemoral celiac or superior mesenteric artery study is needed to identify the problem (Fig. 86.4). More recently, we have proceeded directly to transfemoral angiograms for assessment of patients in whom the perfusion scan shows obvious extrahepatic perfusion. This approach simplifies the process, because one procedure can diagnose the problem and potentially treat it. In our review of 544 cases, 9 patients (2%) were found to have extrahepatic perfusion on the postoperative scan. The cause was identified arteriographically, and in 7 cases, it was corrected with transarterial embolization or surgical ligation; these patients went on to receive HAI without complication (Allen et al, 2005).



FIGURE 86.4. A transfemoral celiac angiogram shows a vessel arising from the gastroduodenal artery (GDA), which had not been ligated. At operation, this vessel was found to be arising from the posterior aspect of the GDA.

Incomplete Hepatic Perfusion

In nine cases (2%), the postoperative ^{99m}Tc MAA scan showed incomplete perfusion of the liver. The causes included failure to ligate a replaced or accessory hepatic artery and failure to achieve cross-perfusion after ligation of an accessory artery (one case). In every case, the anatomic problem was identified by a side port or transfemoral angiogram. Overall, seven of the nine cases were corrected with embolization or surgical ligation of the accessory vessel, and chemotherapy was administered uneventfully. In the instance of incomplete crossover perfusion, collateral flow to the remaining liver developed over time. A repeat MAA scan in 4 weeks confirmed the development of collateral blood flow.

Gastroduodenal Ulcers

In rare instances, the ^{99m}Tc MAA scan fails to identify subtle extrahepatic perfusion. The most frequent anomaly is a small branch to the lesser curve of the stomach. Early in our experience, we treated three patients who were clinically shown to have extrahepatic perfusion that was not apparent on ^{99m}Tc MAA scan, even in retrospect. The patients developed severe epigastric pain during the first course of chemotherapy, and endoscopy showed large ulcers in the stomach or duodenum. These patients do not respond to standard antiulcer therapy, because the cause is not acid hypersecretion but loss of mucosa in the area perfused with FUDR. The diagnosis is confirmed by angiography, and treatment requires angiography or laparotomy for identification and ligation of the vessel. When the

offending vessel has been occluded, and the ulcer has healed, chemotherapy can be given safely. If a patient develops unexplained epigastric pain during infusional chemotherapy, the pump should be emptied immediately and refilled with heparinized saline until the cause of the pain can be elucidated.

Arterial or Catheter Thrombosis

Complete dissection and thrombosis of the hepatic artery intraoperatively has been described during pump insertion, but this condition is rare. In our series, 13 cases (2%) of acute postoperative arterial thrombosis were noted, but the technical problem leading to thrombosis was uncertain in most of these cases. Of these 13 cases of early thrombosis, 31% were salvaged with anticoagulation or lytic therapy. We also observed that delayed thrombosis of the hepatic artery (20 cases) was more common than acute thrombosis (13 cases). The vasculitis caused by infusional chemotherapy is thought to contribute to late arterial thrombosis. Often, arterial thrombosis manifests as extrahepatic perfusion on ^{99m}Tc MAA scan (Fig. 86.5). Catheter thrombosis was seen only as a late complication, and it occurred in 11 cases (2%) and was more likely to be related to technical errors, such as not filling the pump frequently or allowing back bleeding into the catheter during side-port manipulation.

Infectious Complications

Infectious complications associated with any major operation—including pneumonia, urinary tract infections, and wound infections—may occur after laparotomy and pump placement. Because a foreign body is inserted during this operation, particular care must be directed against wound or pump-pocket infections. Technical precautions must be taken in the operating room to limit bacterial contamination of the pump. Postoperatively, any sign of pump-pocket erythema should be treated early and aggressively with parenteral antibiotics.

We have not seen an increased incidence of complications in patients undergoing pump insertion combined with colectomy. It is preferable to place the pump first, close the pump pocket, exclude the catheter from the rest of the procedure, and then proceed with the colectomy. In this way, the instruments and

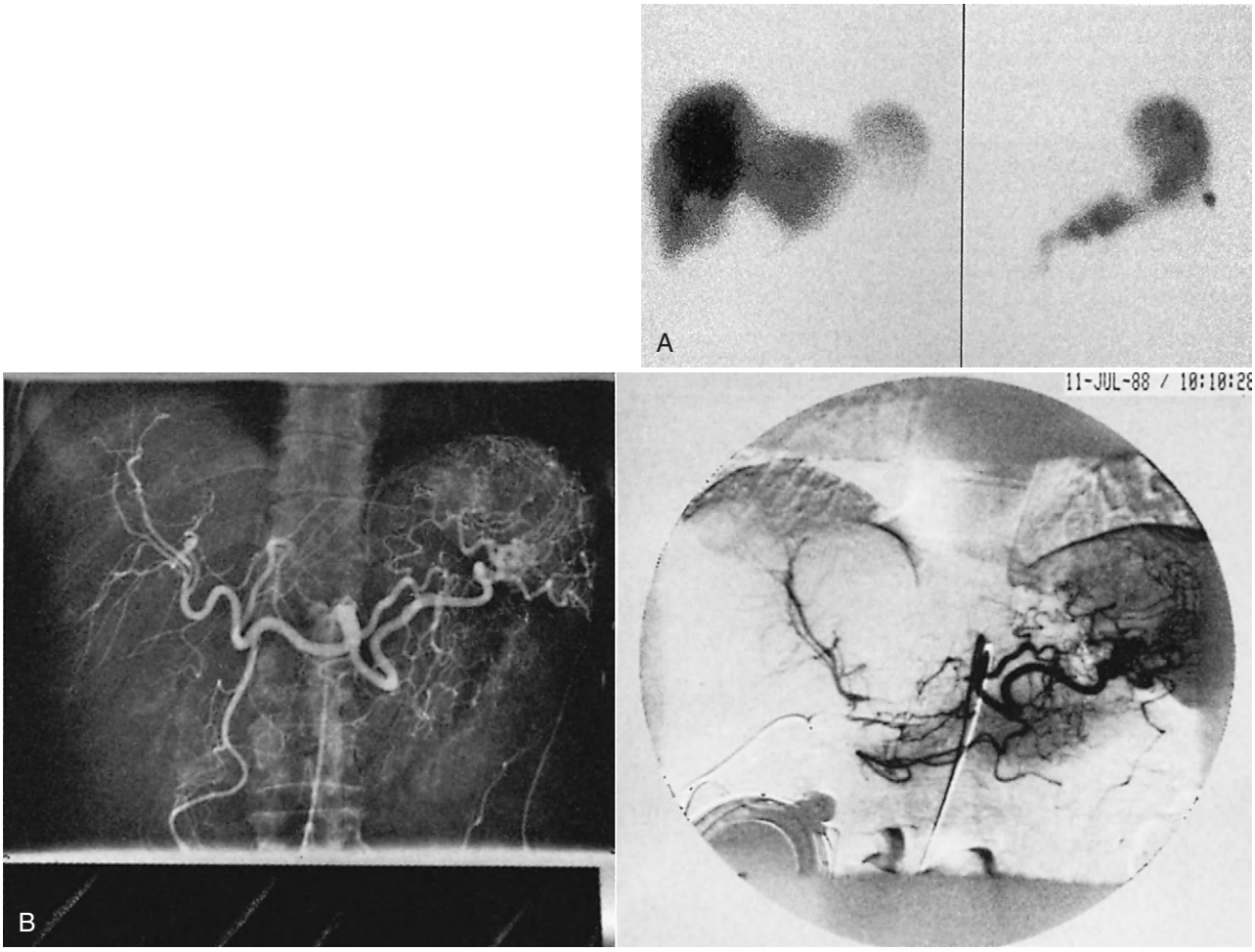


FIGURE 86.5. A, When hepatic artery thrombosis occurs, the macroaggregated albumin scan (*right*) shows an absence of perfusion of the liver together with perfusion of the spleen, stomach, and pancreas. **B,** Arteriogram before operation shows normal patent vessels (*left*), but postoperative arteriography (*right*) confirms that the artery is thrombosed. The first sign of hepatic artery thrombosis may be abdominal pain occurring with chemotherapy owing to perfusion of the stomach and pancreas. If severe pain occurs during chemotherapy, the first step should be to empty the pump and replace the chemotherapy with heparinized saline.

the wound have not been contaminated by the open bowel. Because this approach violates the principle of treating the primary problem first, the surgeon may choose to mobilize the bowel initially. In this manner, the colectomy can be performed rapidly and safely should the patient have difficulties during the procedure.

Hemorrhagic Complications

Two patients developed bleeding complications postoperatively. In one case, the patient developed severe abdominal pain when the pump was injected for the initial ^{99m}Tc MAA scan. On the flow scan, extrahepatic extravasation of ^{99m}Tc was seen. At laparotomy, bleeding from a suprapyloric branch that had been inadequately clipped during the operation was observed. A second patient developed bleeding into the pump pocket that resulted in a hematoma. Both complications were salvaged, and the pumps were used successfully.

LAPAROSCOPIC PLACEMENT OF HEPATIC ARTERIAL INFUSION PUMPS

The necessity of a laparotomy to place HAI pumps has been and remains a hurdle for pump chemotherapy. Because a major operation is mandated, many oncologists and patients have been deterred, and minimally invasive methods of pump implantation are attractive. HAI pump placement requires substantial skill, sophisticated knowledge of upper GI anatomy, and experience, making this operation technically challenging and difficult to perform laparoscopically.

The technique of laparoscopic HAI pump placement should mimic the open operation. Review of the preoperative angiogram is crucial, and management of aberrant anatomy must be planned for in advance. A right subcostal port is placed for retraction of the liver, and a three-port working triangle is created in the left upper quadrant, aiming at the porta hepatis. The dissection and isolation of the vessels is exactly the same as in the open operation. Ultrasonic dissectors are helpful to divide the often dense lymphatics and keep bleeding to a minimum. Branches to the stomach, duodenum, and pancreas can be clipped or divided with the ultrasonic dissector; because controlling torn branches can be difficult, patience is crucial.

When the anatomy is dissected, the pump pocket is made in the right abdominal wall, and the catheter is placed into the peritoneal cavity under laparoscopic visualization. The distal GDA is ligated, and ties are left long for countertraction. Laparoscopic bulldogs are used for vascular isolation; two can be placed on the common hepatic artery and proper hepatic artery each, or a single clamp can be placed just at the orifice of the GDA. A tie is left around the GDA in anticipation of tying the catheter in, and a laparoscopic No. 11 blade is used to create an arteriotomy. Using countertraction on the GDA, the catheter is placed into the GDA, up to the orifice, and tied into place. The clamps are carefully removed, and hemostasis is ensured; this is followed by intraoperative dye injection to confirm bilobar hepatic perfusion and absence of extrahepatic flow.

Published experience with laparoscopic placement of HAI pumps is largely limited to small cases series (Cheng et al, 2003, 2004; Feliciotti et al, 1996; Urbach & Hansen, 2000; Urbach et al, 2001). The largest series to date was published by Cheng and colleagues and describes their experience in 38 patients (Cheng et al, 2004), of whom 24 had additional radiofrequency ablation (RFA), 2 had a laparosopic partial hepatectomy, and 1 was converted to laparotomy. The median time in the operating room was 5.5 hours, and the overall results were excellent: only one postoperative cardiac-related mortality was reported but no pump-related morbidity, and the median hospital stay was 3 days.

When this chapter was submitted for the previous edition of this text, we had attempted laparoscopic pump placement in 13 cases over a 2-year period; of these, five were converted for minor bleeding, severe chronic cholecystitis, bowel injury, dense adhesions, and a small GDA that could not be cannulated at open operation. Eight cases were completed laparoscopically with no significant moribidy, no pump-related complications, and a median hospital stay of 3.5 days (unpublished data). With limited experience, it seems that laparoscopic HAI pump placement is feasible and safe. It is crucial, however, that these cases are attempted by surgeons experienced in laparoscopic surgery and open pump placement.

NONOPERATIVE PLACEMENT OF HEPATIC ARTERIAL INFUSION PUMPS

HAI pump placement can be done safely by laparotomy with an acceptable morbidity. Poor overall prognosis and the requirement for a laparotomy have deterred many surgeons and oncologists from using this modality, however. Robotic-assisted laparoscopic pump placement has recently been described (Hellan & Pigazzi, 2008) that carries the potential to improve on perioperative outcomes but warrants surgical expertise with new technology. Several groups have worked on alternate placement methods to eliminate the laparotomy "hurdle."

Percutaneous techniques to catheterize the hepatic artery for delivery of intrahepatic chemotherapy have been developed using a variety of peripheral arteries for access (Table 86.8). Most of these techniques have been abandoned or are used only by a few specialized groups for the following reasons:

1. The insertion is technically difficult and sometimes cumbersome. The technique described by Arai and colleagues (Arai, 1988; Arai et al, 1997; Inaba et al, 1998) requires embolization of the GDA to anchor the catheter. The tip of the catheter remains anchored in the GDA, while perfusion is achieved through a sidehole in the catheter.
2. The insertion site is in a mobile part of the body, such as the arm or the leg, resulting in risk of catheter dislocation or migration (Oberfield et al, 1979).

Table 86.8

Peripheral Arteries Used for Catheter Placement in the Hepatic Artery

Artery	References
Femoral artery	Matsumada et al, 1997
Brachial artery	Cohen et al, 1980
Axillary artery	Arai, 1988; Cohen et al, 1983
Subclavian artery	Arai, 1988; Arai et al, 1997; Inaba et al, 1998
Hypogastric artery	Arai et al, 1997, 1988; Inaba et al, 1998
Intercostal artery	Castaing et al, 1998; Saldinger & Sandhu, 2004

3. The artery used for access is "essential" for limb perfusion, and any thrombotic complication is a potentially limb-threatening complication (see Table 86.8).

Castaing and colleagues (1998) tried to address these shortfalls by using an intercostal artery as conduit. A cutdown is performed over the tenth left rib. The intercostal artery is catheterized and the catheter is advanced, under fluoroscopic control, across the aorta into the ostium of the celiac axis and ultimately into the proper hepatic artery, just beyond the takeoff of the GDA. The catheter is connected to an implantable port located in the left upper quadrant. The study included 35 patients with metastatic lesions to the liver, mainly from CRC, and 30 patients (86%) underwent a successful placement. Placement was not feasible in five patients because of an unsuitable artery. No procedure-associated deaths were reported, no thrombotic complications in either the aorta or the hepatic artery resulted, and no dislocations or migrations of the catheter occurred. Follow-up was brief because most of these patients died from their disease, although all of the patients had not responded to previous standard treatments and had advanced disease at the time of catheter placement.

This method has clear advantages because of its simplicity and the fact that the catheter is attached to an immobile part of the body, thus preventing catheter motion. Catheter patency was less than 50% at 4 months, likely as a result of a lack of continuous flow. Also, the catheter used in Castaing's study has not been approved by the FDA for prolonged indwelling use; their method is therefore not applicable in the United States.

Our group modified Castaing's method to address these points (Saldinger & Sandhu, 2004). A peripherally inserted 3-Fr central catheter was chosen as the indwelling arterial catheter (Arrow International, Reading, PA). We used a 15-mL Codman 3000 constant-flow implantable pump for access and drug delivery (Codman, Raynham, MA). The pump catheter and arterial catheter were connected via a special connector (Arrow International, Walpole, MA; Fig. 86.6). Our method uses largely the same techniques as described by Castaing, but with a few differences:



FIGURE 86.6. The indwelling arterial catheter is tunneled from the insertion site at the eleventh rib to the left upper quadrant, where it is connected to the catheter of the infusion pump via a connector. The pump is placed into a pocket in the subcutaneous tissue.

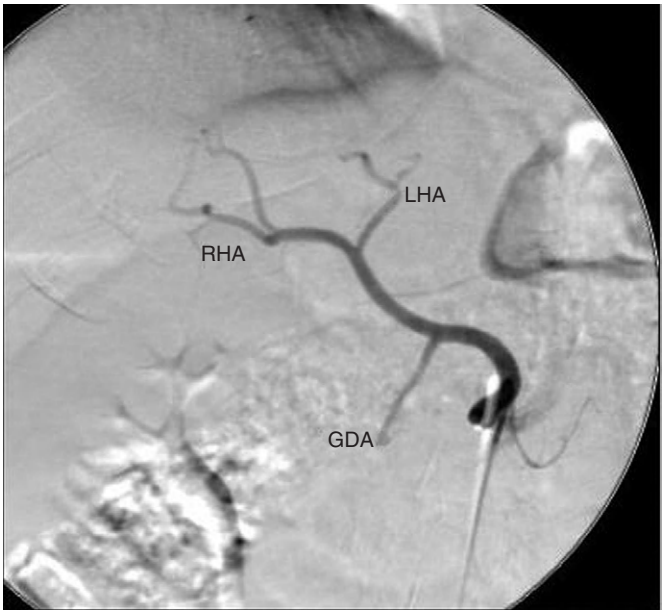


FIGURE 86.7. Transfemoral celiac arteriogram mapping the hepatic arterial anatomy. GDA, gastroduodenal artery; LHA, left hepatic artery; RHA, right hepatic artery.

1. A preoperative angiogram is obtained for mapping of the hepatic vessels (Fig. 86.7). The angiogram is saved and used during the procedure as a guide. Accessory hepatic arteries are embolized to optimize pump perfusion, and if the distance between the GDA and the hepatic bifurcation is deemed too short, the GDA is embolized; that is, if it poses a risk for nondelivery of the target drug.
2. The intercostal artery is accessed by micropuncture, followed by introduction of a sheath. This sheath allows repeated introduction of wires, should the situation require it. A guidewire is introduced and placed into the hepatic artery (Fig. 86.8). The 3-Fr catheter is advanced into the hepatic artery, the wire is withdrawn, and the catheter is secured (Fig. 86.9). An on-table angiogram is obtained through the catheter to confirm proper placement. We confirm catheter placement and exclude extrahepatic perfusion the next day with a perfusion scan. The pump is filled the same day with chemotherapy.

This procedure was performed successfully in four patients with metastatic colon cancer to the liver as part of a feasibility study. All patients had failed at least two chemotherapeutic regimens and were unresectable; no perioperative deaths or complications were reported. The catheters remained patent until the patient's death from progression of disease at 1, 3, 6, and 7 months. The nonoperative placement of HAI pumps is a safe method and has all the advantages of minimally invasive procedures. Its role in the armamentarium of therapies to treat metastatic CRC to the liver depends largely on the role of intraarterial chemotherapy for liver tumors.

APPROACHES TO DECREASE HEPATIC TOXICITY

New approaches to decrease the hepatic toxicity induced by HAI of FUDR have been studied. Because portal triad

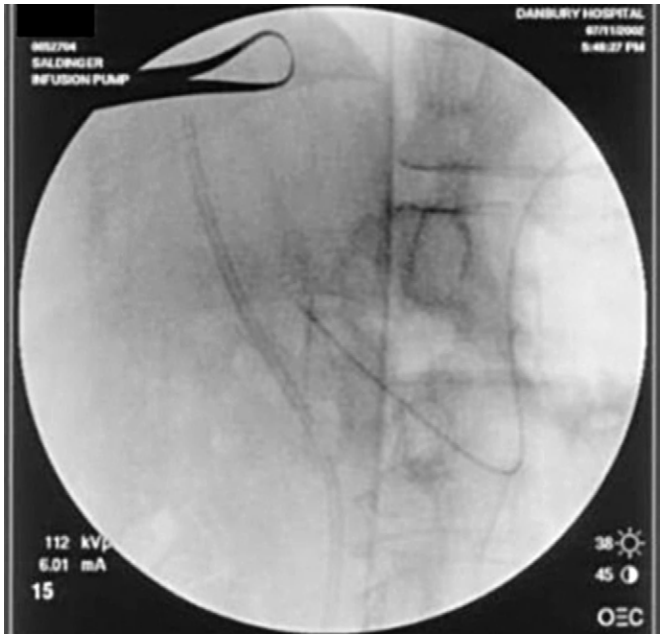


FIGURE 86.8. Fluoroscopic control of guidewire placement. Note the course of the wire: its entrance into the aorta and exit into the celiac axis, and finally the hepatic artery, is outlined.

inflammation may lead to ischemia and stricturing of the bile ducts, the hepatic arterial administration of dexamethasone decreases biliary toxicity. As previously mentioned, a prospective double-blind randomized study of intrahepatic FUDR with dexamethasone versus FUDR alone was conducted at MSKCC (Kemeny et al, 1992). The response rate in 49 evaluable patients was 71% for those who received FUDR plus dexamethasone versus 40% for those given FUDR alone ($P = .03$). Survival also favored the FUDR-dexamethasone group: 23 months versus 15 months for FUDR alone ($P = .06$). In addition, a trend was noted toward decreased bilirubin elevation in patients receiving FUDR plus dexamethasone compared with the group receiving FUDR alone (9% vs. 30%; $P = .07$).

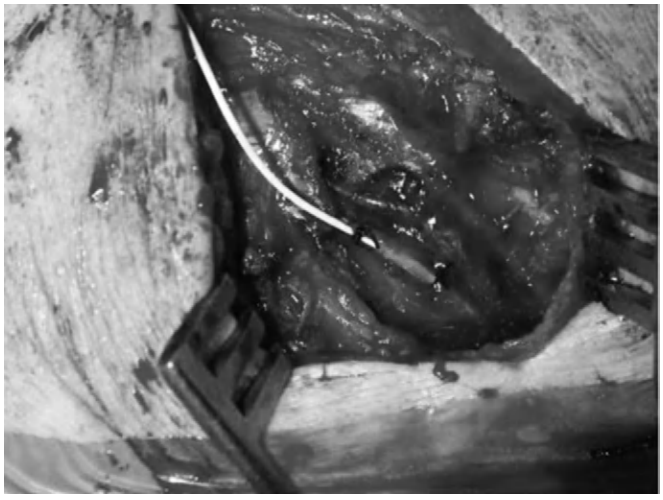


FIGURE 86.9. A 3-Fr catheter secured to the intercostal artery. The inferior border of the eleventh rib has been exposed, allowing exposure of the intercostal artery and vein.

A second method to decrease hepatic toxicity is the use of circadian modification of hepatic intraarterial FUDR infusion. In a retrospective nonrandomized study (Hrushesky et al, 1990), a comparison of constant (flat) infusion versus circadian-modified HAI of FUDR was conducted in 50 patients. Over nine courses of treatment, the patients with circadian-modified infusion tolerated almost twice the daily dose of FUDR. Circadian-modified infusion resulted in 46% of patients having no hepatic toxicity versus 16% after flat FUDR infusion. The authors did not present information on response rates achieved in both groups.

Another approach to decrease toxicity from HAI is to alternate intraarterial FUDR with intraarterial 5-FU. A weekly intraarterial bolus of 5-FU has similar activity to intraarterial FUDR and does not cause hepatobiliary toxicity; however, it frequently produces treatment-limiting systemic toxicity or arteritis with the pharmacokinetic differences previously discussed. Stagg and colleagues (1991) used an alternating regimen of HAI of FUDR and HAI of 5-FU, with a response rate of 51% and median survival of 22.4 months. In contrast to the experience with single-agent HAI of FUDR, no patient had treatment terminated because of drug toxicity. Another report described 57 CRC patients with unresectable liver metastases treated with an alternating HAI schedule of FUDR and 5-FU (Davidson et al, 1996), of which 2 patients (3.5%) developed biliary sclerosis, and 12 (21.1%) had mild transient liver function abnormalities.

METHODS TO INCREASE RESPONSE RATE

Based on the fact that systemic combination chemotherapy regimens are more effective than single agents, the potential benefit of multidrug HAI has been evaluated. In an early study using mitomycin C, bis-chloroethyl-nitrosourea, and FUDR, Cohen and associates (1985) produced a 69% partial response rate. In a randomized trial at MSKCC comparing this three-drug regimen with FUDR alone (Kemeny et al, 1993), the response rates were 45% for the three-drug regimen and 32% for FUDR alone in the 67 patients who entered this trial. The median survivals from the initiation of HAI were 18.9 months and 14.9 months. Other trials using FUDR and LV have produced response rates up to 62% (Hohn et al, 1989).

METHODS TO TREAT EXTRAHEPATIC DISEASE: COMBINED HEPATIC ARTERIAL INFUSION AND SYSTEMIC CHEMOTHERAPY

Extrahepatic disease develops in 40% to 70% of patients who undergo HAI. Such metastases can occur even when the patient's hepatic tumors are responding. In many patients, extrahepatic disease is the cause of death. Safi and colleagues (1989) studied whether concomitant SYS reduces the development of extrahepatic metastases in patients who receive HAI. Ninety-five patients were randomized to intraarterial FUDR (0.2 mg/kg/day for 14 of 28 days) or a combination of intraarterial FUDR (0.21 mg/kg/day) and intravenous FUDR (0.09 mg/kg/day) given concurrently for 14 of 28 days (intraarterial/intravenous). The response rates were 60% for both arms of the study; however, the incidence of extrahepatic disease was

Table 86.9

Results of Hepatic Arterial Infusion Combined with Systemic Chemotherapy in the Second-Line Setting

Drug	No. Patients	Response (%)	Median Survival from Pump Placement (mo)
FUDR + dexamethasone + sideport mitomycin C (Kemeny et al, 2005b)	37	70	20
FUDR + dexamethasone + SYS CPT-11 (Kemeny et al, 2001)	56	74	20
FUDR + dexamethasone + SYS oxaliplatin + CPT-11 (Kemeny et al, 2005a)	21	90	28
FUDR + dexamethasone + SYS oxaliplatin + FU/leucovorin (Kemeny et al, 2005a)	15	87	22

CPT-11, irinotecan; FU, follow-up; FUDR, fluorodeoxyglucose; SYS, systemic chemotherapy

significantly less in patients who received the intraarterial/intravenous treatment (56%) compared with intraarterial treatment (79%; $P < .01$). No significant difference in survival was found between the two groups ($P = .08$). The results of this trial, as well as the development of improved SYS regimens, have underscored the need for further study of combined systemic/intraarterial regimens. Results of some of these studies are presented in Table 86.9, and SYS irinotecan and oxaliplatin are discussed in detail below.

Irinotecan is a topoisomerase I inhibitor with proven efficacy in first-line and second-line treatment of metastatic CRC. The activity of irinotecan is not inhibited by high thymidylate synthase activity (Saltz et al, 1998); combining systemic irinotecan with HAI therapy may therefore result in improved control of extrahepatic disease. In a Phase I study at MSKCC, 46 patients with unresectable liver metastases, 8 of whom underwent cryosurgery, received HAI of FUDR/dexamethasone and systemic irinotecan in escalating doses; all 38 patients who did not undergo cryosurgery were previously treated, and 16 had prior therapy with irinotecan. The regimen was well tolerated, with dose-limiting toxicities of diarrhea and myelosuppression. The response rate was 74%, median time to progression was 8.1 months, and 13 of 16 patients who had previously received irinotecan had partial responses (Kemeny et al, 2001).

Another nonrandomized study used HAI of FUDR with systemic irinotecan as "adjuvant" therapy after cytoreduction (therefore not "true adjuvant") of unresectable hepatic CRC metastases. The cytoreduction was defined as using cryosurgery, RFA, partial resection, or some combination to treat all identifiable sites of disease. Seventy-one patients received "adjuvant" therapy and were compared with a historic control group that received cytoreduction alone. Time to progression was 19 months versus 10 months, and median survival was 30.6 months versus 20 months, for HAI versus control groups (Bilchik et al, 2000). A Japanese group examined HAI of 5-FU and SYS irinotecan in previously treated patients and demonstrated response rates of 76.5%, with median OS of 20 months (Shiatra et al, 2006).

Oxaliplatin is a cytotoxic agent with a mechanism of action similar to that of other platinum derivatives, but it has a different spectrum of activity and toxicity. When combined with 5-FU/LV, clinical response rates have been greater than 50%, with median survival of 16.2 months in untreated patients with metastatic CRC (de Gramont et al, 2000; Tournigand et al, 2004). Preliminary studies using systemic oxaliplatin-based regimens combined with HAI of FUDR demonstrated the feasibility and safety of this approach and revealed promising early results (Pancera et al, 2002). In a two-grouped MSKCC Phase I study, 36 patients with unresectable hepatic metastases, 89% of whom were previously treated, received HAI of FUDR/dexamethasone and SYS oxaliplatin plus either SYS irinotecan or SYS 5-FU/LV. Both regimens were well tolerated, and response rates for the two groups were 90% and 88% (see Table 86.9; Kemeny et al, 2005a). This high response rate for second-line therapy with HAI plus SYS, as well as conversion to resectability, was demonstrated in a recent MSKCC pooled analysis of phase I data in 49 patients with unresectable liver metastases from CRC (Kemeny et al, 2009a). Patients received HAI of FUDR/dexamethasone, SYS irinotecan, and SYS oxaliplatin, and 98% had bilobar disease, whereas 85% had tumors bordering vasculature. A partial or complete response was reported in 92% (84% partial, 8% complete), and 47% of patients were resectable, three with pathologic complete responses. With a median follow-up of 26 months from time of pump placement, OS was 51 months for untreated patients: all 23 responded to treatment, and 57% had resection. OS was 35 months for previously treated patients: 85% responded to treatment, and 38% had resection. This revealed that even in heavily pretreated patients with significant hepatic metastasis, HAI of FUDR can increase response and resection rates when combined with modern SYS. Future randomized trials are needed to assess the impact that HAI specifically has in these outcomes.

ADJUVANT TREATMENT AFTER LIVER RESECTION OF COLORECTAL METASTASES

The rationale for the use of adjuvant chemotherapy after resection of liver metastases from CRC is based on the observation that, although some patients have long-term disease-free survival (DFS) after resection, many patients' disease recurs. Recurrence may be solely in the liver, it may be extrahepatic and intrahepatic, or it may be solely extrahepatic. An effective adjuvant treatment may have a substantial impact on recurrence and survival. The use of SYS without HAI has been formally tested in this setting, but only to a limited extent, with one randomized study (Portier et al, 2006) that met its primary end point of 5-year DFS—33.5% for the chemotherapy group and 26.7% for the control group ($P = .028$)—but failed to show a survival benefit with 6 months of adjuvant 5-FU/folinic acid. Because this trial and another Phase III study (EORTC) both closed early because of slow accrual, their results were pooled and reported together (Mitry et al, 2009), demonstrating both a lack of DFS and OS statistical significance for 5-FU adjuvant therapy in this setting. When adjusting for poor characteristics

Table 86.10

Randomized Trials of Adjuvant Hepatic Arterial Infusion After Resection of Liver Metastases

	MSKCC, 1999		Intergroup, 2002		German, 1998*		Greek, 2001	
Arms	**HAI + SYS**	**SYS**	**HAI + SYS**	**Control**	**HAI (Port)**	**Control**	**HAI + SYS**	**SYS**
n	74	82	53	56	113	113	62	60
Median time to progression (mo)	37.4†	17.2	37‡	18‡	20*	12.6*	60%‖	20%‖
Median time to hepatic progression (mo)	Not reached†	42.7	Not reached	20.2	44.8*	23.3*	85%¶	50%¶
Median overall survival (mo)	72.2	59.3	63.7	49.7	44.8	39.7		
2-Year overall survival	86%†	72%	62%	53%	62%‡	65%‡	92%	75%
5-Year overall survival	57%§	48%§	55%§	37.5%§	—	—	73%	60%

*Results are for treated patients.
†Statistically significant difference ($P < .05$) compared with control group.
‡Not reported, but calculated based on Kaplan-Meier curves published in original citations.
§Updated results.
‖5-Year disease-free survival.
¶Hepatic disease-free survival.
HAI, hepatic artery infusion; MSKCC, Memorial Sloan-Kettering Cancer Center; SYS, systemic chemotherapy.

Modified from Cohen AD, Kemeny NE, 2003: An update on hepatic arterial infusional chemotherapy for colorectal cancer. Oncologist 8:553-566.

in a multivariate analysis, however, an increase in DFS was reported for the group treated with chemotherapy. In EORTC 40983, reversible complications occurred in 25% of the patients receiving perioperative 5-FU plus leucovorin and oxaliplatin (FOLFOX) compared with 16% in the surgery-alone group (P =.04) (Nordlinger et al, 2008). The Japanese are conducting a multicenter randomized Phase II/III trial of adjuvant modified FOLFOX versus hepatic metastasectomy alone (Kanemitsu et al, 2009).

Because combining HAI and SYS may be useful in decreasing recurrence, four relatively large randomized trials have been conducted in this group of patients (Table 86.10). In the MSKCC study (Kemeny et al, 1999), 156 patients with resected hepatic metastases were randomized to 6 months of systemic 5-FU/LV or systemic 5-FU/LV plus HAI with FUDR. Primary end points were 2-year overall and progression-free survival. Forty percent of patients received prior adjuvant chemotherapy after resection of their primary CRC, and 15% had received prior chemotherapy as treatment for metastatic disease. Randomization was performed intraoperatively after complete resection of metastases, and patients were stratified based on number of metastases and prior treatment history. Of enrolled patients, 92% received treatment as assigned; 2-year survival was 86% in the combined therapy group versus 72% for those who received systemic therapy alone (P = .03), with median survivals of 72.2 months and 59.3 months, respectively. In an updated analysis, 10-year survival was 41% in the HAI plus SYS group, with 27% alive in the SYS-alone group still alive (Fig. 86.10; Kemeny & Gonen, 2005). Two-year hepatic progression-free survival was 90% for the combined group and 60% for the monotherapy group ($P < .001$). Updated hepatic progression-free survival at 10 years was 70% and 40%, respectively (P = .0001; Fig. 86.11), and overall progression-free survival was 40% and 20%, respectively, at 10 years (P = .001). If patients with poor clinical risk scores are considered (Fong et al, 1999), their survival is still improved with HAI compared with SYS alone (Fig. 86.12).

Toxicity was increased in the combined group, and 39% of patients required hospitalization for diarrhea, neutropenia, mucositis, or small bowel obstruction compared with 22% in the monotherapy group (P = .02). Elevated bilirubin was seen in 18% of patients in the combined group. In most patients, the bilirubin returned to normal, but 6% of patients required biliary stents. In the control group, 2% had an elevation in bilirubin, and 2% required biliary stents. No significant difference was found among the groups in therapy-related deaths (one combined, two monotherapy).

The intergroup study (Kemeny et al, 2002) randomized 109 patients to resection alone or resection followed by four cycles of HAI with FUDR and infusional systemic 5-FU, followed by eight more cycles of systemic 5-FU. Patients with more than three liver metastases or extrahepatic disease at laparotomy were taken off the study; only 80 of 109 patients were actually included in the study, which was designed to examine the effect of adjuvant therapy on DFS. When patients were analyzed as treated (n = 75), the 4-year DFS (46% vs. 25%; P = .04) and 4-year hepatic DFS (67% vs. 43%; P = .03) favored

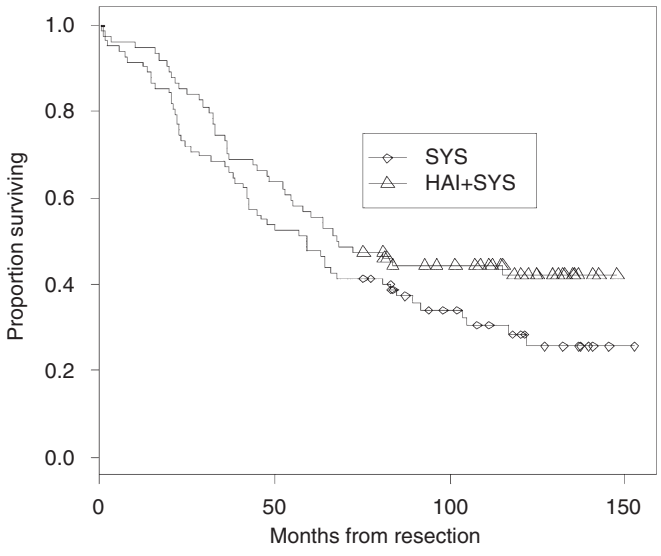


FIGURE 86.10. Updated overall survival from the Memorial Sloan-Kettering Cancer Center trial comparing adjuvant systemic therapy (*SYS*) with hepatic arterial infusion (*HAI*) plus SYS.

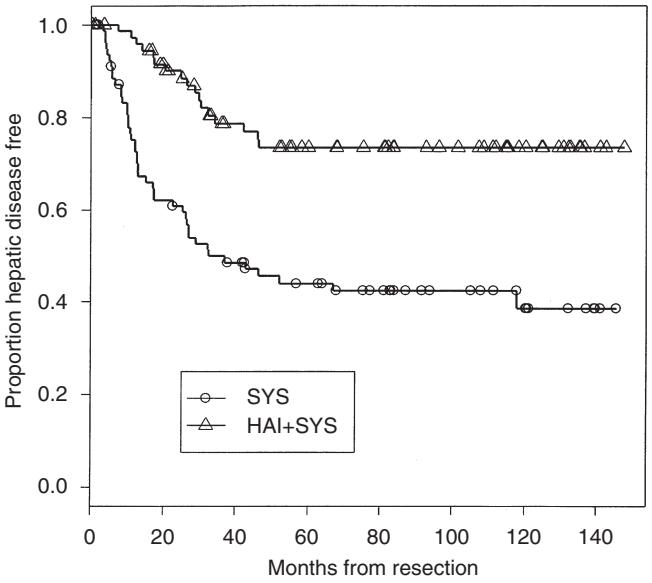


FIGURE 86.11. Updated hepatic disease-free survival from the Memorial Sloan-Kettering Cancer Center trial comparing adjuvant systemic therapy (*SYS*) with hepatic arterial infusion (*HAI*) plus SYS.

HAI over the control groups. Based on an intention-to-treat analysis, no difference was reported in median or 4-year OS between the groups. Currently, the 5-year survival is 55% versus 37.5% favoring adjuvant therapy (Kemeny M, 2005); however, this study was not designed to look at OS.

In the German cooperative multicenter study (Lorenz et al, 1998), 226 patients were randomized to resection alone or resection plus 6 months of HAI with 5-FU/LV given as a 5-day continuous infusion every 28 days. The study was terminated early, because an interim analysis suggested a very low chance of showing a survival benefit with adjuvant therapy. The impact of HAI in this study is difficult to assess because only 74% of patients assigned to HAI received this treatment, and only 30% completed it. No difference in time to progression, time to hepatic progression, and median OS was noted in an intention-to-treat analysis. When patients were analyzed "as treated," time to hepatic progression (45 months vs. 23 months) and time to progression or death (20 months vs. 12.6 months) were improved in the HAI arm. Grade 3 or 4 toxicity—including stomatitis, nausea, and vomiting—was noted in 63% of patients who received adjuvant therapy. These findings reflect significant systemic absorption of 5-FU when given via HAI.

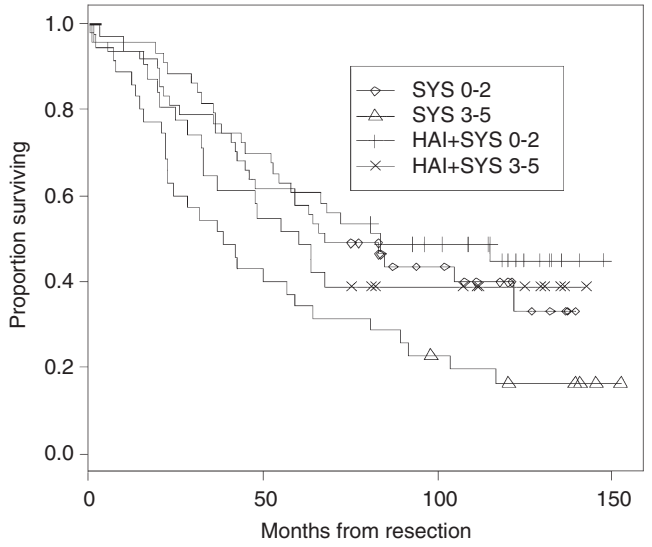


FIGURE 86.12. Survival stratified by clinical risk score. A score ranging from 0 to 5 was calculated by adding 1 point for the following clinical variables: tumor size >5 cm, tumor number >1, serum CEA >200 ng/mL, node-positive primary tumor, and disease-free interval >12 months (Fong et al, 1999). SYS, systemic therapy; HAI, hepatic arterial infusion.

A study conducted in Greece on 122 patients used mitomycin C, 5-FU, and interleukin (IL)-2 by both HAI and the intravenous (IV) route versus the IV route alone. The 2-year survival was 92% versus 75%, and 5-year survival was 73% versus 60% for the HAI plus SYS group versus the SYS-alone group, respectively. DFS was significantly longer for the HAI plus SYS group: 60% at 5 years versus 20% for the intravenous group ($P = .0012$); hepatic DFS was 85% versus 50% ($P = .0001$; Lygidakis et al, 2001).

The two American studies showed a reduction in hepatic and extrahepatic recurrence for combined HAI plus systemic therapy after surgical resection. Of the two European studies, one showed a significant increase in survival and DFS, whereas the other did not. In the MSKCC study, 2-year survival after liver resection was significantly improved with combined therapy: 86% compared with 72% with systemic therapy alone. Historic 2-year survivals (Chang et al, 1987; Fegiz et al, 1991; Jamison et al, 1997; Scheele et al, 1990) for patients treated with resection alone range from 55% to 70%.

Nonrandomized studies of modern chemotherapy regimens combined with HAI of FUDR in the post–liver metastasis resection (adjuvant) setting have been conducted and suggest improved outcomes. Phase I and II trials of adjuvant SYS irinotecan combined with FUDR/dexamethasone in 96 patients showed a 2-year survival of 89% at a median follow-up of 26 months. The dose-limiting toxicities were diarrhea and neutropenia, and all 27 patients treated at the maximum-tolerated dose were alive at publication (Kemeny et al, 2003). A phase I trial of adjuvant HAI of FUDR/dexamethasone with escalating doses of SYS oxaliplatin/5-FU/LV in 35 patients revealed 4-year survival and progression-free survival of 88% and 50%, respectively, at a median follow-up of 43 months. Dose-limiting toxicities of diarrhea and elevated bilirubin were each 8.5% (Kemeny et al, 2009b).

A multivariate analysis performed as a part of a recent review of over 1000 patients showed that post–liver metastasis resection HAI was one of the significant factors to improve survival. Median OS was 50 months in those who did not receive HAI and 68 months in those who did ($P = .0001$) (Ito et al, 2008). Another MSKCC retrospective review described 612 patients who underwent liver resection from 1985 to 1994. The 10-year OS was 38% for patients who received HAI of FUDR and 15% for those who did not ($P < .0001$) (Tomlinson et al, 2007). Finally, colleagues at our institution retrospectively compared outcomes from 125 metastatic CRC patients who received postoperative SYS (FOLFOX or 5-FU plus leucovorin and irinotecan [FOLFIRI]) with HAI to 125 similar patients who received only SYS. The 5-year hepatic progression-free survival was 75% in the HAI group and 52% in the SYS group ($P = .0005$) with

a median follow-up of 43 months; OS at 5 years was 72% and 52%, respectively (House et al, 2011). These data underscore the need for randomized studies of modern HAI plus SYS compared with modern SYS alone.

NEOADJUVANT HEPATIC ARTERIAL INFUSION

Neoadjuvant treatment is a strategy increasingly used in solid-tumor oncology, given the multifaceted rationale that it may enable downsizing and subsequent resectability of tumor burden, and more systemic treatment may be tolerated, or given at all, than in postoperative settings, where complications may limit or preclude administration of chemotherapy. In addition, neoadjuvant HAI may prevent unnecessary operations in patients who have clinically and biologically declared themselves to have inoperable metastatic disease. In the context of converting CRC patients with unresectable liver metastases to operable candidates, some neoadjuvant approaches have been discussed above. Combining SYS with HAI agents besides FUDR has been studied in the neoadjuvant setting. Numerous reports have been made that HAI of oxaliplatin, for instance, has shown benefit in response and resectability rates when combined with SYS 5-FU (Boige et al, 2008; Del Freo et al, 2006; Ducreux et al, 2005).

HEPATIC ARTERIAL INFUSION FOR NONCOLORECTAL LIVER METASTASES AND PRIMARY LIVER CANCER (SEE CHAPTERS 50A, 80, AND 81C)

Although liver metastases from noncolorectal carcinoma are less commonly treated with regional therapy, HAI chemotherapy has been used in cases of breast cancer, HCC, melanoma (Melichar et al, 2009), bronchogenic carcinoma, and pancreas cancer. Studies in breast cancer have employed numerous HAI agents including FUDR, mitomycin/FU/doxorubin, vinblastine/cisplatin, and cyclophosphamide/etoposide. One trial of 15 patients undergoing systemic chemotherapy for refractory metastatic breast cancer tested HAI of FUDR and mitomycin and demonstrated a partial response rate of 53% and OS of 18 months after HAI was begun (Maral et al, 1985). FUDR alone and in combination with various cytotoxic agents has also been evaluated in HCC (see Chapter 80), including treatment with mitomycin/interferon/FUDR (Atiq el al, 1992) and LV/doxorubicin/cisplatin/FUDR (Patt el al, 1994) in 27 patients. In the latter, response rates were 41% to 54%, and median OS was 15 months.

More recent experience with HAI for HCC and intrahepatic cholangiocarcinoma (ICC; see Chapter 50A) at MSKCC was published, and it demonstrates the correlative and predictive utility of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) in 34 patients with unresectable disease treated with HAI of FUDR/dexamethasone. Partial responses were seen in 47%, with median OS of 30 months (Jarnagin et al, 2009). One patient in this study responded sufficiently to undergo resection and was found to have had a complete pathologic response. The median duration of response was 1 year, and median time to progression was 7 months. Median follow-up at time of publication was 35 months, and 1- and 2-year survival was 88% and 67%, respectively. Therapy was well tolerated, and DCE-MRI data showed that pretreatment and posttreatment tumor perfusion and permeability parameters correlated with median survival, therefore these may serve as a biomarker of treatment outcome.

CONCLUSION

HAI offers several advantages. From a pharmacologic standpoint, HAI is more effective than SYS, because higher drug levels are achieved at the sites of metastatic disease. Using agents with high hepatic extraction virtually eliminates the systemic toxicity observed with standard systemic therapy. The 50% to 70% response rate obtained in trials of intrahepatic FUDR therapy has not been matched by any systemic therapy to date. The addition of leucovorin or dexamethasone to FUDR has increased both response rate and survival. Most randomized HAI studies do not clearly evaluate the issue of survival, mainly because a crossover was allowed in some, whereas patients with positive portal nodes were included in the HAI-treated groups in other studies. In addition, severe toxicity may occur with HAI or SYS. Although HAI therapy may produce GI or hepatic toxicity, this is minimized with proper surgical technique during pump placement, with close monitoring of liver function tests, and with HAI of dexamethasone.

Because the liver is often the initial site of metastatic disease in patients with colorectal carcinoma, early intensive therapy with surgical resection, HAI, or both at a time when the tumor burden is small may prevent the progression of metastases to other sites. Although HAI therapy is applicable only to selected patients with hepatic metastases, it may be the best therapy available.

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CHAPTER 87

Systemic chemotherapy for hepatic colorectal cancer: impact on surgical management

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OVERVIEW

The liver is the most common site of metastases from colorectal cancer (CRC). Approximately half of all patients with CRC will develop liver metastases at some point during their disease (Ekberg et al, 1987; Steele & Ravikumar, 1989), and half of these will be seen with synchronous liver metastases at the time of diagnosis (Bengmark & Hafstrom, 1969). Resection remains the best treatment for patients with resectable colorectal liver metastases (CLM; see Chapter 81A). Early studies reported 5-year survival rates of 25% to 48% following complete resection of the liver metastases (Adson et al, 1984; Fong et al, 1997; Sugihara et al, 1993) in an era when the only active chemotherapeutic agent used in the United States was the antimetabolite 5-fluorouracil (5-FU). With the single-agent regimen of 5-FU, or 5-FU plus leucovorin (LV), tumor response was seen in only 10% to 20% of those treated, which provided an overall survival of approximately a year in patients who were not candidates for an operation (Meta-Analysis Group in Cancer [MAGIC], 1998; Thirion et al, 2004). Substantial improvements in both response and survival have been reported with the use of the two "modern" cytotoxic agents, irinotecan and oxaliplatin.

Newer chemotherapeutic regimens that combine continuously infused 5-FU and LV with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) yield overall response rates over 50% and provide a doubling of survival time in patients with unresectable disease (de Gramont et al, 2000; Tournigand et al, 2004). The integration of molecularly targeted agents, such as bevacizumab (monoclonal antibody to vascular endothelial growth factor) and cetuximab (antiepidermal growth factor receptor), into treatment strategies has further increased response rates to an impressive 70% (Folprecht et al, 2010). By combining surgery with these newer chemotherapeutic agents and regimens, 5-year survival rates approaching 60% have been reported following hepatic resection of CLM (Abdalla et al, 2004; Choti et al, 2002; Fernandez et al, 2004).

As the efficacy of systemic chemotherapy is increasing, the number of patients who potentially benefit from adjuvant and neoadjuvant chemotherapy is also growing. Traditional dogma of offering hepatic resection to only those patients with four or fewer lesions confined to one side of the liver no longer applies. Planning the right therapeutic approaches for individual patients is becoming more complex, and it requires a close multidisciplinary collaboration between surgical and medical oncologists. This chapter will discuss the current data on the role of systemic chemotherapy in a multidisciplinary approach in the treatment of metastatic CRC, and it will focus on the implications of surgical management.

CHEMOTHERAPEUTIC AGENTS

Fluoropyrimidines

The fluoropyrimidine 5-FU has remained the backbone of systemic chemotherapy for metastatic CRC for decades. This drug inhibits thymidylate synthase, thereby lowering production of the pyrimidine thymidine for DNA synthesis. It has been used synergistically with leucovorin (folate) either in a daily bolus administration in repeated cycles of 5 days (Mayo Clinic regimen) or on a biweekly infusional schedule (de Gramont regimen). By meta-analysis, continuous infusional administration of 5-FU/LV provides an improved response rate (24% vs. 14% with bolus; $P = .002$) and decreased grade 3 to 4 toxicity (4% vs. 31% with bolus; $P < .001$) compared with bolus therapy (MAGIC, 1998; de Gramont et al, 1997). Capecitabine is the orally administered prodrug of 5-FU, which has lower toxicity and provides similar survival rates compared with an intravenous 5-FU/LV regimen (Hoff et al, 2001).

Irinotecan

Irinotecan (CPT-11) is a topoisomerase I inhibitor, which prevents DNA unwinding and results in failure of DNA replication, DNA strand breaks, and cell death. In a randomized trial that evaluated irinotecan in patients with unresectable metastatic CRC, survival after irinotecan alone was equivalent to that of patients treated with standard bolus 5-FU/LV, but the combination of irinotecan and 5-FU/LV improved overall survival by 2.2 months over 5-FU/LV alone (14.8 vs. 12.6 months; $P = .04$) (Saltz et al, 2000). Subsequently, the combination of irinotecan with 5-FU/LV administered in continuous infusion (FOLFIRI) was associated with further improvement in survival (17.4 vs. 14.1 months; $P = .03$) (Douillard et al, 2000).

Oxaliplatin

Oxaliplatin is a platinum compound that alkylates DNA strands, thereby inhibiting DNA transcription and replication, resulting in cell death. Although already in use in Europe, oxaliplatin received U.S. Food and Drug Administration (FDA) approval in 2002. Oxaliplatin is commonly used in combination with

continuous infusional 5-FU/LV (FOLFOX). Different drug doses and timed regimens—FOLFOX4, FOLFOX6, and FOLFOX7—have been evaluated, but no data support the superiority of any one over another in terms of patient survival. In a national effort, the intergroup N9741 trial (Goldberg et al, 2004) showed that FOLFOX treatment was associated with a 4.5-month improvement in median overall survival compared with continuous infusion of 5-FU/LV alone (19.5 vs. 15 months; $P = .001$). As no trial has found a difference in efficacy between FOLFOX and FOLFIRI regimens, both remain first-line treatment options for systemic chemotherapy treatment of unresectable metastatic CRC. FOLFOX is used primarily over FOLFIRI because of potentially debilitating diarrhea associated with the latter.

MOLECULAR TARGETED AGENTS

The monoclonal antibodies bevacizumab and cetuximab have emerged as useful adjuncts to systemic chemotherapy for metastatic CRC. Bevacizumab targets and effectively neutralizes circulating vascular endothelial growth factor (VEGF), and several mechanisms of action have been proposed. VEGF is one of the key growth factors required for development and stabilization of new blood vessels that supply tumor growth. Bevacizumab decreases microvascular density and integrity and reduces interstitial tumor pressure in vivo, potentially increasing local delivery of other concurrently administered cytotoxic drugs (Jain, 2001; Willett et al, 2004).

In 2004 Hurwitz and colleagues demonstrated a benefit of adding bevacizumab to systemic chemotherapy for metastatic CRC. In a randomized controlled double-blinded trial, they compared bolus 5-FU/LV plus irinotecan in conjunction with either bevacizumab (n = 402) or placebo (n = 411). Patients in the bevacizumab group had a near 5-month improvement in median survival compared with the placebo group (20.3 vs. 15.6 months; $P < .001$), and they had an increase in median progression-free survival (10.6 vs. 6.5 months; $P = < .001$). Although generally well tolerated, the toxicity seen in the bevacizumab group was that of increased gastrointestinal perforation (1.5% of patients) and major thrombotic events (2.5%). In addition, treatment with bevacizumab prior to surgery may be associated with increased wound infections and dehiscences, attributable to inhibition of neovascularization of the healing wound (Scappaticci et al, 2005); however, following hepatic resection for CLM, this phenomenon was not observed in a prospective Phase II trial, in which bevacizumab had been discontinued for 5 weeks (Gruenberger et al, 2008). The current recommendation is still to wait at least 28 days from cessation of bevacizumab to proceed with surgery, but many surgeons prefer to wait 6 weeks.

Cetuximab and the newer drug panitumumab are two recombinant chimeric monoclonal antibodies, which bind to the epidermal growth factor receptor (EGFR). Cetuximab is sometimes used as first-line therapy of unresectable metastatic colon cancer. By competitively blocking the transmembrane tyrosine kinase EGFR, these agents inhibit cell growth, induce apoptosis, and decrease matrix metalloproteinase and VEGF production; however, the effectiveness of both of these drugs seems to be significantly dependent on the wild-type phenotype of *KRAS*, as this protein is part of the downstream signal-transduction pathway of EGFR. Results from the CRYSTAL study showed that for patients with wild-type *KRAS*, the addition of cetuximab to FOLFIRI as first-line treatment for CLM increased the response rate to 59% compared with 43% using FOLFIRI alone ($P = .003$). A slight increase in progression-free survival was found (9.9 vs. 8.7 months; $P = .017$), a benefit not seen among patients with *KRAS* mutations (Van Cutsem et al, 2008). The OPUS study was constructed similarly and assessed the addition of cetuximab to FOLFOX, and it also showed benefits for the *KRAS* wild-type subgroup (61% vs. 37%; $P = .011$) but not for patients with *KRAS* mutations (Bokemeyer et al, 2009). Based on these results, the American Society of Clinical Oncology published a consensus statement that patients who have tumors with *KRAS* mutations in codon 12 or 13 were unaffected by EGFR inhibition, and they recommended that anti-EGFR drugs not be used as part of the treatment regimen for this patient population (Allegra et al, 2009).

The colorectal liver metastases (CELIM) study randomized patients with unresectable colorectal liver metastases to receive FOLFOX plus cetuximab or FOLFIRI plus cetuximab in a nonblinded fashion. Response rates for the 53 patients in each arm were similar (68% and 57%; P = not significant [NS]). When analyzed for *KRAS* mutation, an impressive overall response rate of 70% was found for the entire group (Folprecht et al, 2010). Following a median of eight cycles, complete resection was achieved in 41 patients (34%), suggesting that this regimen was useful for converting unresectable cases to resectable ones. In a secondary analysis, 68 patients were included in a retrospective reevaluation by seven experienced hepatobiliary surgeons. Twenty-two patients (32%) were considered to be resectable based on initial staging imaging studies, which increased to 41 patients (60%) based on restaging studies after chemotherapy ($P = .001$).

In summary, the array of chemotherapeutic and molecular targeted agents available to treat CRC and CLM is growing. As such, patients who were not typically considered candidates for liver-directed surgery for CLM are now sometimes considered for potentially curative resection. The following sections will illustrate how the availability of active medical therapy is changing the landscape of surgical therapy for CLM.

CONVERSION THERAPY

One possible use of chemotherapy for patients with initially unresectable CLM is for downsizing tumors to the point where they become amenable to a complete resection. This treatment strategy is commonly referred to as *conversion therapy,* as opposed to *neoadjuvant therapy,* which is designated to those patients with resectable disease at initial presentation.

The first retrospective reports from France (Adam et al, 2001; Bismuth et al, 1996; Giacchetti et al, 1999) were updated in 2004 with a series of 1439 patients who underwent resection of colorectal liver metastases between 1988 and 1999. Among these, 1104 patients were described who were initially considered to have unresectable disease based on large tumor size, poor tumor location, multinodularity, or presence of extrahepatic disease. After receiving an average of 10 cycles of systemic chemotherapy (5-FU and chronomodulated oxaliplatin), 138 patients (12.5%) demonstrated enough response to become anatomically resectable, but within the median follow-up time of 49 months, 111 (80%) recurred. Recurrence was limited to the liver in 29%. Five-year overall and disease-free survival were 33% and 22%, both of which were lower than for those patients

Table 87.1

Outcome Associated with Resection Following Conversion Chemotherapy of Initially Unresectable Colorectal Liver Metastases

Reference	n	Chemotherapy Agents	Metastases Confined to Liver	Resection Rate, n (%)	R0 Rate, n (%)	Median PFS (mo)	Median OS (mo)
Zelek et al, 2003	31	5-FU/LV, IRI, HAI	Yes	11 (35)	9 (82)	20.2*	NR
Baize et al, 2006	39	5-FU/LV, OX	Yes	11 (28)	—	14	60
Pozzo et al, 2004	40	5-FU/LV, IRI	No	16 (40)	13 (81)	14.3	NR
Barone et al, 2007	40	5-FU/LV, IRI	Yes	13 (33)	13 (100)	52.5*	NR
Alberts et al, 2005	42	5-FU/LV, OX	Yes	17 (40)	14 (82)	19	NR
Tournigand et al, 2004	109	5-FU/LV,OX, IRI	No	10 (9)	8 (80)	—	47
Masi et al, 2009	196	5-FU/LV, OX	No	47 (24)	37 (79)	18*	40*
Tournigand et al, 2006	309	5-FU/LV, OX	No	35 (11)	29 (83)	—	39

*In patients with R0 resection

OS, overall survival; PFS, progression-free survival; NR, not reached; 5-FU, 5-fluorouracil; LV, leucovorin; OX, oxaliplatin; IRI, irinotecan; HAI, hepatic artery infusion

considered resectable prior to chemotherapy (48% and 30%, respectively; $P = .01$). The authors identified four preoperative factors independently associated with shorter survival: a rectal primary, three or more metastases, maximum tumor size greater than 10 cm, and a carbohydrate antigen (CA) 19-9 greater than 100 U/L. Mean adjusted 5-year survival rates—according to the presence of 0, 1, 2, 3, or 4 of these factors—were 59%, 30%, 7%, 0%, and 0%, respectively (Adam et al, 2004a).

Since those first retrospective reports, prospective trials have provided additional data concerning outcomes of conversion chemotherapy, but few studies report on long-term outcome after resection (Table 87.1). Resectability rates following preoperative chemotherapy for 20 patients presenting with unresectable CLM have been reported as high as 80% (Mentha et al, 2006). Subsequent reports with larger sample sizes provide more modest results with respect to conversion to resectability after chemotherapy (15% to 24%) (Masi et al, 2009; Tournigand et al, 2006). Variability in chemotherapy type, duration, and timing with respect to resection and a lack of standard definitions of resectability make comparison between studies impossible.

Two recent prospective studies compared long-term outcomes between primary resection and secondary resection following systemic therapy. Capussotti and colleagues (2006) found no statistical difference in overall survival after resection in 34 patients who were converted to resectable, compared with 116 patients who underwent immediate partial hepatectomy (median survival 41 vs. 50 months, respectively; P = NS). At a median follow-up of 35 months, a 94% recurrence rate was observed in the conversion group compared with 66% in the immediate-resection cohort ($P = .001$). Disease-free survival was 9 months in the converted group compared with 37 months in the immediate-surgery group ($P = .001$). These authors also noted that extrahepatic recurrence after resection was greater in patients who were converted from unresectable to resectable (Capussotti et al, 2006).

The second study by Nuzzo and colleagues (2007) compared the outcomes of 60 initially resectable patients to that of a cohort of 15 patients with initially unresectable CLM who underwent complete resection following conversion chemotherapy. This study also found no significant difference in overall survival between initially resectable and unresectable patients with a mean survival of 46 and 47 months, respectively (P = NS). At a median follow-up of 34 months, disease recurrence rates were higher in initially unresectable patients (53%) compared with those of the primarily resectable comparison group (28%), and 3-year disease-free survival rates were 31% and 58%, respectively ($P = .04$) (Nuzzo et al, 2007).

In summary, conversion chemotherapy is a reasonable strategy for managing CLM in motivated patients with good performance status; however, this group of patients must understand that the benefit of resection following conversion is lower than if they had presented with resectable disease at the outset. Furthermore, attempting to compare results among studies illustrates the need for standardized chemotherapy regimens and common definitions of resectability.

COMBINING SYSTEMIC THERAPY WITH SURGERY

Preoperative Versus Postoperative Chemotherapy

Although developments in systemic therapy for CRC over the past decade have resulted in objective improvements for patients with advanced, unresectable disease, less is known regarding the benefits of systemic therapy for patients with primary, resectable CLM. Few clinical trials have investigated the role of systemic chemotherapy in the preoperative and/or adjuvant setting.

The use of adjuvant chemotherapy in patients who have undergone resection of colorectal liver metastases has the theoretic benefit of decreased recurrence rates from addressing potential micrometastases before they become too large to treat medically. Early evidence of the effect of systemic chemotherapy on resected patients was published by Figueras and colleagues in 2001. They reported on a series of 235 patients who underwent partial hepatectomy with curative intent. Of 180 patients considered for adjuvant treatment with six cycles of 5-FU, only 99 were actually treated, and several patients received oxaliplatin in addition. Patients receiving adjuvant therapy had an improved 5-year survival rate of 53%, compared with 25% for those intended to receive therapy but denied

treatment, or for those who declined for other reasons ($P <$ .001). Multivariate analysis revealed adjuvant chemotherapy as an independent predictor of survival (Figueras et al, 2001). Selection bias in this report limits interpretation of the results.

The largest retrospective multicenter study from Parks and colleagues (2007) included 247 patients treated with adjuvant 5-FU–based chemotherapy following resection of CLM and 518 patients who received no adjuvant treatment. They found an increase in overall survival with the use of adjuvant chemotherapy with a 47-month median survival and a 5-year survival of 37% compared with 36 months and 31%, respectively, for patients who did not receive chemotherapy ($P = .007$). Stratifying patients according to the clinical risk scores (Fong et al, 1999), they noted that patients who received adjuvant chemotherapy had improved survival in each category (range, 1.3- to 2.0-fold) (Parks et al, 2007).

Subsequently, Portier and colleagues (2006) conducted a multicenter, randomized, controlled trial that compared surgery combined with adjuvant 5-FU/LV to surgery alone. After recruiting 173 patients who had undergone R0 resection, this trial was aborted early because of low accrual rates. Although the study was underpowered, the investigators reported their results. At a median follow-up of 87 months, they demonstrated an improved 5-year disease-free survival rate in the adjuvant chemotherapy group compared with that of the surgery-alone group (33.5% vs. 26.7%; $P = .028$); they also found a nonsignificant trend toward increased 5-year overall survival (51.1% vs. 41.9%; $P = .13$). Recently, Mitry and colleagues (2008) pooled the results of this trial with another trial reported in abstract form to overcome the lack of statistical power. By combining patients, they were able to increase the study population to 278, of which 138 (50%) received six cycles of adjuvant 5-FU/LV following complete resection. In this combined dataset, a trend toward improved median progression-free survival was noted (27.9 months vs. 18.8 months; $P = .058$) and a trend toward increased overall survival (62.2 months vs. 47 months; $P = .095$) for the adjuvant chemotherapy group. Treatment with adjuvant chemotherapy was independently associated with improved disease-free and overall survival by multivariate analysis.

Regarding newer systemic regimens, some data are available from Phase II studies. Mackay and colleagues reported a multicenter Phase II study of 29 patients treated with six 21-day cycles of irinotecan (after receiving 5-FU) following resection of metachronous CLM. This study found an estimated median relapse-free survival time of 45.2 months, with acceptable toxicity.

Although these data suggest a benefit for adjuvant systemic therapy following hepatic resection for patients with CLM, other investigators have raised the possibility of using a preoperative approach, as has been championed in the treatment of rectal cancer (Bosset et al, 2005; Sauer et al, 2004). The rationale and theoretic benefits of preoperative chemotherapy include the ability to 1) treat micrometastatic disease prior to exposing patients to the regional growth factors that attend surgery following partial hepatectomy; 2) downsize tumors; 3) ensure that patients will get some systemic therapy, as complications after partial hepatectomy may preclude this; and 4) identify those patients who have aggressive tumor biology with disease progression while on systemic therapy, who would not likely have benefited from surgical resection. On the other hand, the risks of preoperative chemotherapy include liver toxicity, increased risk of disease progression or development of new metastatic sites, and selection of more resistant cell clones (Kemeny, 2007).

The best data have been published by the European Organization for Research and Treatment of Cancer (EORTC). Their prospective randomized controlled trail enrolled 364 patients and compared a group who received perioperative FOLFOX and surgery to a group who received surgery alone. A median of six cycles were given prior to and following resection, and all patients had four or fewer lesions and were deemed resectable prior to enrollment. This trial demonstrated a 7.3% progression-free survival benefit, from 28.1% (95.66% confidence interval [CI], 21.3 to 35.5) to 35.4% (CI, 28.1 to 42.7; hazard ratio [HR], 0.79 [0.62 to 1.02]; $P = .06$) for patients receiving chemotherapy along with surgery (Nordlinger et al, 2008). Only 63% of patients (115 of 151) in the chemotherapy group actually received chemotherapy following surgery, of which only 70% (n = 80) received all six cycles. Thirty-six patients did not receive postoperative chemotherapy, mainly because of patient refusal, perioperative complications, toxic effects of preoperative chemotherapy, or disease progression. Overall, the results of this study support the hypothesis that chemotherapy is beneficial for some patients undergoing partial hepatectomy for CLM, but it does not address the question of whether treating patient with preoperative chemotherapy impacts prognosis.

The existing retrospective studies that compare survival after resection of CLM with and without preoperative chemotherapy typically include patients who also received adjuvant chemotherapy. To date none of these studies demonstrates a significant benefit from preoperative chemotherapy (Table 87.2).

In summary, the combination of systemic therapy plus hepatic resection is superior to resection alone for resectable patients with CLM; however, prospective randomized trials are needed to determine whether administering systemic therapy prior to, following, or both prior to and following hepatic resection for CLM provides superior outcomes.

IN VIVO RESPONSE TO SYSTEMIC TREATMENT

It seems clear that chemotherapy improves the results of resection, but it remains unclear whether such therapy is optimally given before or after surgery. One of the potential benefits of administering chemotherapy prior to hepatic resection for CLM is to assess in vivo response of disease. Adam and colleagues (2004b) investigated the response to chemotherapy as a predictor of long-term outcome in 131 patients after potentially curative resection of multiple liver metastases (≥4). After a median of nine courses of 5-FU/LV with either irinotecan or oxaliplatin, they observed objective tumor response in 58 patients (44%), stable disease in 39 (30%), and tumor progression in 34 (26%). Response to chemotherapy correlated with overall survival following hepatectomy at 37%, 30%, and 8%, respectively, at 5 years ($P < .001$). In another recent retrospective analysis of 88 patients treated with preoperative oxaliplatin or irinotecan-based chemotherapy regimens followed by partial hepatectomy for resectable CLM, Chiappa and colleagues (2009) also noted that response to chemotherapy on restaging was associated with a significantly improved 5-year survival compared with that of nonresponders (71% vs. 15 %; $P = .026$).

Two studies from Memorial Sloan-Kettering Cancer Center (MSKCC) addressed the question of chemoresponsiveness of

Table 87.2

Studies Comparing Long-Term Outcome After Resection of Colorectal Liver Metastases in Patients with and Without Preoperative Chemotherapy

				DISEASE-FREE SURVIVAL AFTER RESECTION							OVERALL SURVIVAL AFTER RESECTION						
		Patients (N)		3 Years (%)		5 Years (%)		Median (mo)			3 Years (%)		5 Years (%)		Median (mo)		
Reference	Chemotherapy Agents	PCT	No PCT	PCT	No PCT	PCT	No PCT	PCT	No PCT	*P* Value	PCT	No PCT	PCT	No PCT	PCT	No PCT	*P* Value
Tanaka et al, 2003	5-FU/LV, OX	48	23	–	–	–	–	25	34	NS	38.5	30.4	–	–	–	–	NS
Hewes et al, 2007	5-FU/LV, OX	42	45	–	–	–	–	–	–	–	62	80	–	–	–	–	0.04
Malik et al, 2007	5-FU/LV, OX, IRI	84	84	–	–	17	32	22	16	NS	–	–	49	40	47	37	NS
Nordlinger et al, 2008*	5-FU/LV, OX	151	152	42	33	–	–	–	–	0.025	–	–	–	–	–	–	–
Scoggins et al, 2009	5-FU/LV, OX, IRI	112	74	–	–	–	–	40	56	NS	–	–	–	–	56	65	NS
Lubezky et al, 2009	5-FU/LV, OX, IRI	37	19	50	49	–	–	–	–	NS	70	84	–	–	–	–	NS
Boostrom et al, 2009	5-FU/LV, OX, IRI	44	55	20	32	20	32	13	14	NS	62	63	51	45	70	44	NS

*Prospective, randomized, controlled trial

PCT, preoperative chemotherapy; 5-FU, 5-fluorouracil; LV, leucovorin; OX, oxaliplatin; IRI, irinotecan; NS, not significant

CLM and survival in patients who had staged resections. Allen and colleagues (2003) found that the 46 patients who did not progress on chemotherapy administered prior to hepatic resection saw a 5-year survival benefit over that of the 54 patients who did not receive chemotherapy (85% vs. 35%; $P = .03$). The results of this analysis suggest that a clinical response to chemotherapy can identify a subset of patients with biologically favorable tumors, and treating clinicians can select them for more aggressive therapy. In a separate study by Gallagher and colleagues (2009) of 111 patients from MSKCC who underwent hepatic resection after preoperative chemotherapy, no differences were seen in median overall survival among patients who responded, had stable disease, or showed progression of disease (58 months vs. 65 months vs. 61 months; $P = .98$); however, it should be noted that the protocol for this evaluation was to proceed with hepatectomy at the first clinical sign of progression, as opposed to proceeding with resection at the first sign of response.

It remains unclear what the optimal duration of preoperative chemotherapy should be and when to proceed with hepatic resection; however, more surgeons are advocating proceeding with hepatic resection at the first signs of tumor response to avoid extended exposure of the liver to cytotoxic chemotherapy (see Chapter 65). To address this question, White and colleagues (2008) reviewed data for 35 patients with CLM who received FOLFOX with or without bevacizumab and evaluated radiologic tumor changes at 2-month intervals after the start of treatment; they found that the mean cumulative tumor reduction among responders (n = 30) was 39% at 2 months, and it increased to 56% at 4 months ($P < .01$) after commencing therapy. Importantly, no significant incremental tumor size reduction occurred between 4 and 6 months. Although this study was constructed to assess the time of maximal response in initially unresectable patients, these data suggest that 4 months of preoperative therapy may be sufficient to achieve the maximal tumor response in potentially resectable patients.

In summary, close multidisciplinary observation and communication are essential to avoid overtreating patients during preoperative chemotherapy for CLM. Borderline resectable and higher risk patients may benefit from in vivo response testing to systemic treatment.

Complete Response

As a result of increased effectiveness of systemic chemotherapy, it is now more common for tumors to demonstrate a complete radiographic response. This creates a new set of issues for managing patients with CLM following conversion or preoperative chemotherapy. The question remains whether these lesions are undetectable but still present and therefore likely to grow back. Elias and colleagues (2004) reported on 11 patients in whom at least one liver metastasis disappeared on imaging and could not be localized at laparotomy. Local recurrence was seen in three of these patients (27%), with a median follow-up time of 31.1 months. Few conclusions can be drawn from this initial report, given the small sample size, but the result from this analysis suggests that a durable response is possible in a majority of patients following complete radiographic resolution.

Subsequently, Benoist and colleagues (2006) reported on 66 liver metastases that disappeared radiographically following chemotherapy, which represented 20% of all lesions in the cohort. At the time of exploration, 31 lesions (47%) could not be identified, even with intraoperative ultrasonography, and they were consequentially not removed. By 1 year of follow-up, 23 (74%) of these lesions recurred. Of the other 35 liver lesions (53%) identified and removed at surgery, 32 (91%) contained viable disease, suggesting that tumors are still present, even when they disappear on imaging. Thus 55 of the original 66 lesions (83%) either harbored residual viable disease or returned following complete radiographic response.

Even more compelling is the question of a complete histologic response and how it impacts patient survival. In a study from the M.D. Anderson Cancer Center (MDACC), 305 patients received a median of five cycles of oxaliplatin- and irinotecan-based chemotherapy, with or without bevacizumab, prior to hepatic resection, and they were then stratified according to histopathologic response (Blazer et al, 2008). Complete response with no residual histologic evidence of tumor was observed in 9%, a major response (1% to 49% residual cells) was seen in 36%, and a minor response (≥50% residual cancer cells) was seen in 55% of tumors in the resection specimen. The 5-year survival rates for these three groups were 75%, 56%, and 33%, respectively ($P < .05$), and pathologic response to preoperative chemotherapy was independently associated with improved survival on multivariate analysis.

Adam and colleagues (2008b) found that only 4% of patients had a complete pathologic response in a series of 767 patients who underwent liver resection after preoperative chemotherapy for CLM. This cohort involved a heterogeneous group of patients with initially resectable and unresectable disease, including some patients with extrahepatic disease. As with the Blazer study, patients with a complete pathologic response (n = 29) had an excellent 5-year survival that reached 76% compared with 45% for patients without (n = 738; $P = .004$). A complete radiographic response was reported in only two patients when reviewed by a radiologist; interestingly, neither of these patients had complete pathologic response.

A report by Chun and colleagues (2009) assessed the association of morphologic radiologic response with pathologic response. A total of 234 lesions were examined from 50 patients who underwent hepatic resection after treatment with bevacizumab. In the cohort that had an "optimal" morphologic radiologic response, the median number of residual tumor cells was 20%, and the median survival was not yet reached by the time of the study's conclusion. In contrast, patients who had an "incomplete or absent" response had 50% to 70% residual tumor cells on pathologic assessment and had a shorter median survival (31 months; $P = .03$). This report represents an early assessment of the correlation between radiographic and histologic findings and how they correlate with patient outcome.

These data suggest that all original sites of metastases should be addressed surgically or with ablative therapy if possible, even if they are no longer present on restaging imaging, as they are likely to harbor viable malignant cells that may progress at some point. Identifying hepatic metastases after a complete radiologic response remains a technical challenge that can be overcome by use of a simple coil-marking technique described by Zalinski and colleagues (2009). This is especially valuable in steatotic, chemotherapy-treated livers, given the muted contrast between the lesions and the liver background as a result of impaired perfusion (Peppercorn et al, 1998). Medical oncologists are urged to refer potential resection candidates to surgeons prior to starting chemotherapy, and surgeons are urged to review available imaging obtained prior to preoperative chemotherapy.

CHEMOTHERAPY-INDUCED LIVER DAMAGE (SEE CHAPTER 65)

With increased use of preoperative chemotherapy, treating physicians are becoming more aware of the toxic effects of chemotherapy on liver parenchyma and how these changes affect postoperative outcome (Fong & Bentrem, 2006; Zorzi et al, 2007). Investigators have shown a wide spectrum of histopathologic changes to the underlying liver parenchyma in resection specimens (see Chapter 65 for a detailed description). Prolonged use of 5-FU and irinotecan-based chemotherapy has been associated with fatty liver changes ranging from mild forms of steatosis to more severe forms of steatohepatitis with additional necroinflammatory components (Peppercorn et al, 1998; Vauthey et al, 2006). Oxaliplatin-based regimens have been associated with venoocclusive injuries, termed *sinusoidal obstruction syndrome* (SOS) (Rubbia-Brandt et al, 2004). Although the association between chemotherapy and histopathologic changes has been well documented, the impact of chemotherapy-associated hepatotoxicity on surgical management of colorectal liver metastases remains somewhat ill defined.

From the transplant literature, we know that hepatic steatosis can impair liver function and postoperative regeneration. In a study of 485 patients undergoing liver resections for neoplasms (325 steatotic livers, 160 matched controls), steatosis was found to be an independent predictor of postoperative complications on multivariate analysis ($P < .01$) (Kooby et al, 2003). Overall and infective complication rates of 62% and 43% for the marked steatosis group (n = 102) were significantly higher than in the control group, at 35% and 14%, respectively ($P < .01$). The association between steatosis and previous exposure to chemotherapy was noted. Vauthey and colleagues (2006) systematically analyzed hepatic injury in 158 patients treated with varying preoperative chemotherapy regimens for metastatic CRC and correlated them to postoperative outcomes after hepatic resection. This study distinguished steatosis and steatohepatitis as separate pathologic findings and demonstrated that steatohepatitis induced by irinotecan-based chemotherapy was associated with an increase in 90-day mortality following major hepatectomy for CLM (14.7% vs. 1.4%, no steatohepatitis; $P = .001$). Furthermore, patients with steatohepatitis have a higher risk of death from postoperative liver failure compared with all other patients (6% vs. 1%; $P = .01$).

Karoui and colleagues (2006) reported that chemotherapy was significantly associated with sinusoidal dilation ($P = .005$), present in 49% of patients in the chemotherapy group (two thirds receiving oxaliplatin) compared with 14% in controls. Furthermore, significantly greater postoperative morbidity after major hepatectomy was found in the chemotherapy group compared with the control group (38% vs. 14%; $P = .03$), which was mostly attributed to the high incidence of transient liver failure in the chemotherapy group (11% vs. 0% in controls; P = NS). The addition of bevacizumab to oxaliplatin-based chemotherapy may have a protective effect on sinusoidal injury. Ribero and colleagues (2007) found that the addition of bevacizumab to oxaliplatin-based chemotherapy reduced the incidence of sinusoidal dilation of any grade by half (27% vs. 54%) and lowered severe, grade 2 to 3 sinusoidal dilation (8% vs. 28%) to about a third of reviewed pathologic specimens.

Although multiple studies support that patients with damaged livers have higher perioperative morbidity and mortality rates compared to those with healthy livers, others that directly compare perioperative outcome with and without preoperative chemotherapy for CLM have not been able to demonstrate this phenomenon (Pawlik et al, 2007; Scoggins et al, 2009). The reason for this discrepancy likely lies in factors of timing and dose of preoperative chemotherapy treatments and extent of hepatic resection. Both prolonged chemotherapy treatments and short intervals between the cessation of chemotherapy have been found to be associated with significantly increased morbidity (Aloia et al, 2006; Welsh et al, 2007). Although the optimal regimen and duration of systemic chemotherapy are still being assessed, dialogue between treating medical and surgical oncologists regarding the timing of surgery is critical. Theoretically, a longer interval may provide the liver time to recover from any reversible hepatotoxic effect of chemotherapy. On the other hand, a longer interval prior to hepatic resection may result in progression of disease. With this in mind, most surgeons will proceed with resection between 3 and 6 weeks after the last dose of chemotherapy.

MANAGEMENT OF SYNCHRONOUS LIVER METASTASES

Synchronously diagnosed CRC liver metastases pose additional challenges regarding the timing, sequence, and method of treatment. The traditional approach would be resection of the colorectal primary followed by a course of adjuvant chemotherapy and hepatic resection in the absence of interval disease progression; however, in the era of more active chemotherapy, this approach remains most applicable for patients with unresectable liver metastases, with the hope of conversion to secondarily resectable status. Alternative treatment pathways have also been proposed for patients with initially resectable synchronous liver disease (Fig. 87.1). The first issue specific to this patient subset is the question of whether the bowel or liver should be addressed first, or if they should both be removed at the same time.

In recent years, two large studies have confirmed previous smaller reports that simultaneous colon and hepatic resections are safe and may demonstrate benefits of reduced morbidity and mortality compared with staged procedures (Martin et al, 2003; Reddy et al, 2007). In the earlier report, by Martin and colleagues (2003), simultaneous resections were more likely performed for right colon primaries and for smaller and fewer liver metastases, and they resulted in similar rates of major complications (27% vs. 25%; P = NS) and mortality (4% vs. 4%; P = NS) for patients undergoing major hepatic resections between the groups. Reddy and colleagues (2007) found similar morbidity between simultaneous and staged minor hepatectomy (overall 36% and 38%; P = NS), but a significantly higher rate of severe morbidity (36.1 vs. 17.6%; $P = .05$) and mortality (8.3 vs. 0%; $P = .007$) was reported after simultaneous major hepatic resection. Long-term outcomes are similar among simultaneous and staged hepatic resections for synchronous CLM, and more than one study has shown that timing of hepatic resection does not affect long-term outcome (Minagawa et al, 2006; Tanaka et al, 2004).

Another more recent report by de Haas and colleagues (2010) confirms the safety of simultaneous resection, but it suggests that this strategy is an independent predictor of earlier tumor recurrence compared with the delayed hepatectomy approach. The authors compared outcomes from 55 patients who had simultaneous hepatic and colorectal resections to 173 patients who had the staged approach. The morbidity rate was

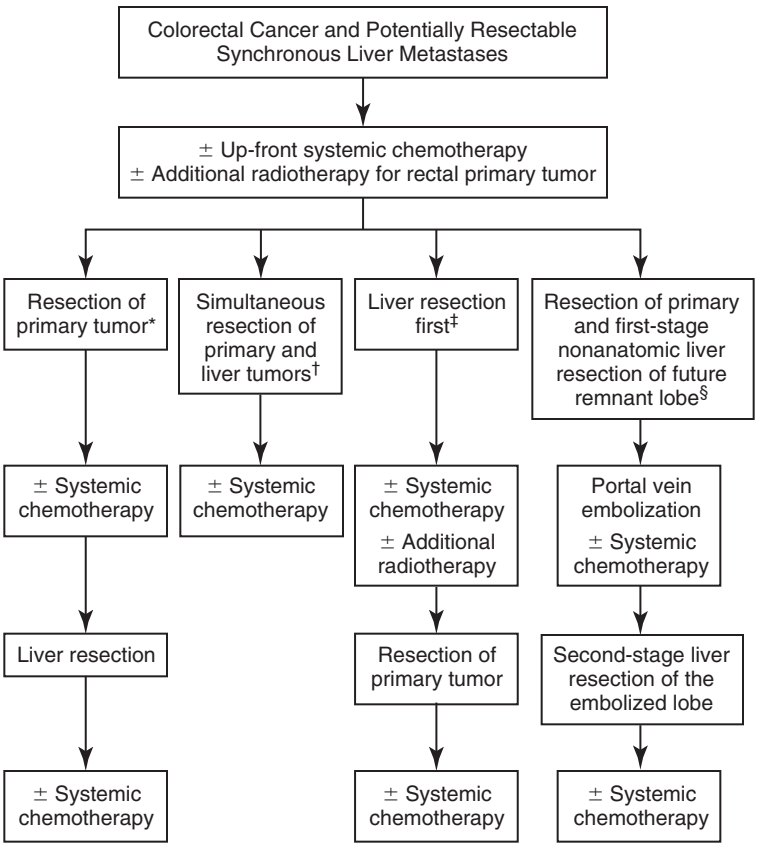


FIGURE 87.1. Treatment pathways for colorectal cancer patients with synchronous liver metastases. *Primary goal in patients with obstructing or bleeding tumors. †Preferred for cases of minor hepatectomy or for selected cases of major hepatectomy. ‡Option for advanced local disease and initially resectable liver disease. §Option for selected patients with limited bilobar disease.

actually lower in the simultaneous group (11% vs. 25%; P = .015), but more recurrences were observed in the simultaneous group at 3 years (85% vs. 64%; P = .002).

The "liver first" approach has been introduced as alternative treatment strategy for patients with advanced CRC with synchronous liver metastases. Patients receive chemotherapy before the liver resection and then undergo resection of the colorectal primary at a later date. This approach resulted from the improved efficacy of chemotherapy and focuses on delivering chemotherapy to the liver without potential delays as a result of prolonged recoveries from colon surgery. This idea is based on the belief that the liver is the component that will ultimately limit survival. Secondly, authors have raised concerns of enhanced metastatic tumor growth after removal of the primary tumor (Demicheli et al, 2008). Published reports of this approach are limited to small case series. Mentha and colleagues (2008) have recently updated their initial series and reported 35 patients, of which 30 completed the pathway. With a clinical risk score of 3 or higher, the reported 5-year survival of 31%, with a median survival of 44 months, is encouraging. Limitations of this approach include risks of secondary obstruction, disease progression, and chemotherapy-induced liver damage.

The role of preoperative chemotherapy in patients with resectable synchronous liver metastases remains a subject of debate. Despite the theoretic benefits of preoperative chemotherapy, data on the actual survival benefits are equivocal. In a study of 151 patients initially evaluated at MSKCC, Fahy and colleagues (2009) reported an overall disease-specific survival of 26.7 months after diagnosis of synchronous colon cancer. Both liver resection and preoperative chemotherapy were treatment modalities significantly associated with survival, but most patients received some sort of postresection therapy. Reddy and colleagues (2009) specifically addressed timing of chemotherapy in their large multiinstitutional study of 499 patients undergoing resection for synchronous CLM. Postoperative chemotherapy alone was independently associated with recurrence-free survival, if given for 6 months or longer (HR, 0.75; P = .04), and with overall survival, if administered for 2 months or longer (HR, 0.59; P = .001). Preoperative chemotherapy alone was not associated with improved survival, but patients with perioperative chemotherapy had similar outcomes to patients who received postoperative chemotherapy alone, thus given the lack of level 1 evidence, the available data do not support use of prehepatectomy chemotherapy uniformly in all resectable synchronous CLM.

Among selected patients prehepatectomy therapy may be useful. Tanaka and colleagues (2003) found that prehepatectomy chemotherapy was associated with improved survival (5-year survival of 39% vs. 52%; P = .04) in a group of 71 patients with bilateral multiple, mostly synchronous CLM. Interestingly, the authors also noted a lower rate of major hepatectomy in their patients who received prehepatectomy chemotherapy (81% vs. 100%; P = .027). Given the fact that patients who received preoperative chemotherapy had unresectable

extensive bilobar disease, this is one of the few studies that indicate the possibility for smaller resection after effective treatment; however, no studies directly compare extent of resection to the originally planned procedure before chemotherapy.

In rectal cancer patients, the potential need for locoregional radiotherapy further complicates the matter. Neoadjuvant chemosensitizing radiation has proven to lower local relapse rates to less than 10% (range, 6% to 8%) in locally advanced rectal cancer (T3 to T4) in several prospective randomized trials (Roh et al, 2009; Sauer et al, 2004). This outcome is extremely valuable, because surgical salvage options are slim and are generally associated with poor quality of life and poor survival (Salo et al, 1999); however, this treatment modality has not proven to be beneficial in terms of overall survival, and its role in patients with stage IV disease is unclear. Several potential approaches to integrating neoadjuvant chemoradiation exist in this stage of disease, and the question is in what sequence neoadjuvant chemotherapy, radiation, or chemoradiation should be given. This decision naturally is dictated by the toxicity of such extensive therapy and based on the needs of the individual patient. Although simultaneous resection can theoretically be achieved through one long midline incision, most surgeons recommend a staged procedure with initial resection of the rectal primary (Reddy et al, 2007). Early reports of the liver-first approach have also been published from a European Center (Verhoef et al, 2009). Of 22 patients with advanced local rectal primaries and synchronous liver metastases in this series, 16 patients (73%) completed the full treatment protocol, and all were alive after a median of 19 months. Morbidity of this approach was equivalent to that seen with the rectum-first approach and simultaneous resections in a second small case series (van der Pool et al, 2010).

EXTRAHEPATIC DISEASE

The presence of extrahepatic disease in the setting of CLM has traditionally been considered a contraindication for hepatic resection. With better systemic chemotherapy, survival has improved in all stages of disease, and surgeons have become more aggressive in considering resection in patients who were not candidates in the past. Several centers have published their experience with liver resection in patients with concomitant extrahepatic disease. Carpizo and colleagues (2009) reported the outcome of 127 patients with extrahepatic disease, which comprised 9% of all patients undergoing liver resection at MSKCC between 1997 and 2007. Overall survival of 47% and 26% at 3 and 5 years was significantly inferior to the 67% and 49% ($P < .001$) observed in patients without extrahepatic disease. Importantly, the survival observed in patients with extrahepatic disease in this study is similar to that observed for patients with only liver disease resected during the 1980s and 1990s.

It is noteworthy that recurrence was observed in 95% of patients in this group with median follow-up of 24 months. This included both local extrahepatic invasion and distant metastatic sites including lung, ovaries, peritoneum, and regional hepatic lymph nodes. Although this study found that patients with perihepatic lymph node metastases had worse survival than those with lung and ovarian metastases, with a median survival of 26, 45, and 82 months, respectively ($P < .05$). The incidence of occult microscopic lymph node involvement ranged from 2% to as high as 28% (Beckurts et al, 1997), likely because of the fact that hepatic lymph node dissection is not commonly performed. Adam and colleagues (2008a) found regional lymph node metastases in 6% of 763 patients undergoing hepatic resection for CLM and reported a predicted 5-year survival that was significantly inferior compared with that of patients without nodal involvement (18% vs. 53%; $P = .001$). The authors pointed out that all patients who survived 5 years had lymph node metastases in the hepatoduodenal ligament, and no long-term survivors were among those with celiac or retroperitoneal lymph node metastases.

Jaeck and colleagues (2002) prospectively performed systematic portal lymphadenectomy on 160 patients and examined differences in survival of different subsites; overall, metastatic lymph nodes were found in 17 patients (11%), with a 3-year survival of 19%. Similarly, this study distinguished between hepatoduodenal ligament nodes (zone 1) and celiac/common hepatic artery nodes (zone 2) and found a substantially worse survival for patients with zone 2 compared with zone 1 lymph node involvement (0% 1-year vs. 38% 3-year survival). The same group recently updated their results of 45 patients with regional lymph node involvement (Oussoultzoglou et al, 2009). After a change in multimodal treatment strategies, the vast majority received modern oxaliplatin- or irinotecan-based chemotherapy, with or without bevacizumab or cetuximab, and the surgical approach shifted toward a more aggressive lymphadenectomy. With a median follow up of 26 months, 3-year overall survival was increased to 29.7%, and 5-year survival of 17.3% was reported. Interestingly, no significant survival difference was found among patients with zone 1 and 2 nodal involvement, with a median survival of 19 and 20 months ($P = .44$), respectively. Elevated carcinoembryonic antigen (CEA) greater than 200 μg/L was found in 82% of patients and was found to be the only preoperative factor independently associated with overall survival (odds ratio [OR], 7.1; $P < .001$).

Given recent data, lymphadenectomy can provide a chance for long term-survival in selected patients with extrahepatic disease, and that may outweigh any additional associated morbidity. Data regarding resections of distant sites of extrahepatic disease are limited, and the surgical approach must be considered on a patient-by-patient basis.

PORTAL VEIN EMBOLIZATION AND CHEMOTHERAPY

Preoperative portal vein embolization (PVE) is used to promote compensatory hypertrophy in patients whose future liver remnant (FLR) may be insufficient to support them during the recovery phase following major hepatic resection. Techniques, indications, and results of PVE are outlined in Chapter 93; they will only be discussed briefly here, as they may be affected by concurrent systemic chemotherapy or underlying chemotherapy-induced liver damage.

PVE increases the safety of hepatectomy for patients with marginal hepatic reserve. The average increase of the estimated FLR is between 8% and 16% at 2 to 4 weeks after PVE, depending on the measurement technique and underlying liver disease (Covey et al, 2005; Madoff et al, 2003; Vauthey et al, 2000). Long-term survival has been found to be comparable for patients with and without PVE before major hepatic resection for CLM, at 40% and 38% at 5 years (Azoulay et al, 2000).

Given the cytotoxic nature of chemotherapeutic agents and their ability to hinder cell proliferation, the question arises whether liver regeneration and hypertrophy are altered by concurrent chemotherapy. In particular, the inhibition of vascular endothelial growth factor (VEGF), as targeted by bevacizumab, has been shown to impair liver regeneration in animal models after partial hepatectomy (Bockhorn et al, 2007). One of the first reports to address this issue was from Goéré and colleagues (2006) in France. Data from 10 patients who had no chemotherapy between static portal embolization and surgery were compared with data from another 10 patients who had continuous chemotherapy. No significant difference was observed in FLR growth between the groups, but the sample size was small. Covey and colleagues (2008) further addressed this question in a study of 100 patients undergoing PVE before resection of CLM, 43 of whom received concurrent chemotherapy of various regimens. This study found no statistically significant difference in liver growth between the patients who had concurrent chemotherapy treatment and those who did not (22% vs. 26%; P = NS). Confirming results were presented by Zorzi and colleagues (2008), who showed no difference in FLR growth after PVE in patients treated without chemotherapy, those treated with systemic chemotherapy, and those treated with chemotherapy that included bevacizumab (10.1% vs. 8.8% vs. 6.8%; P = NS). More recently, one paper suggested that a bevacizumab-containing chemotherapy regimen impairs FLR hypertrophy after PVE (Aussilhou et al, 2009). The authors found a significantly smaller increase in FLR in the bevacizumab-treated group (n = 13) compared with the group that did not receive bevacizumab (n = 27) in their regimens (561 + 171 cm^3 vs. 667 + 213 cm^3; P = .031). Based on existing data, administration of systemic therapy appears to be acceptable around the time of PVE, but it may be prudent to avoid bevacizumab in these patients.

Data regarding the impact of chemotherapy-induced liver injuries on liver regeneration after PVE are scant. A recent study showed that steatosis was associated with significantly lower hypertrophy volume and hypertrophy ratios after right PVE in 35 patients after hemihepatectomy (Tanaka et al, 2010). Based on existing data, it appears safe to consider PVE in patients who receive chemotherapy prior to hepatic resection; however, the actual benefit of PVE for this set of patients still remains unclear. Our recommendation is to limit the use of PVE to patients who will undergo major hepatic resection with an FLR less than 25%. Further data on PVE in patients with CLM are needed.

TWO-STAGE HEPATECTOMY

Two-stage hepatectomy is a relatively new strategy to expand the criteria of resectability. Using this approach, complete resection is feasible in selected patients with bilateral CLM. PVE or portal vein ligation is often required after the first resection to promote hypertrophy of the FLR and to ensure sufficient liver remnant. In the first description by Adam and colleagues (2000), the authors proposed to remove as many tumor sites as possible during the first operation, followed by a course of chemotherapy, with or without PVE, and second-stage resection to clear the remaining liver. Among 13 patients who had both resections, reported 3-year survival was 35%. This strategy was then modified by Jaeck and colleagues (2004) because of concerns of accelerated tumor growth during the regeneration period after major hepatectomy and PVE. The new strategy is to initially remove tumor in the FLR, clear one side of the liver in a usually smaller operation prior to PVE, and resect the remaining tumor-bearing liver in a second operation.

Success rates and long-term outcome of patients who have both hepatic resections largely depend on patient selection and utilization of modern chemotherapy. The literature reports success rates from 69% to 92% (Adam et al, 2000; Jaeck et al, 2004; Tanaka et al, 2007; Wicherts et al, 2008), but perioperative morbidity and mortality rates are uniformly higher after the second hepatectomy. In the largest series of 41 patients who underwent two-stage hepatectomy, the cumulative morbidity was 79%, with an overall morbidity of 20% and 59% and mortality of 0% and 7% after the first- and second-stage hepatectomy, respectively (Wicherts et al, 2008).

The best long-term results were presented in a study by Chun and colleagues (2007) from the MDACC. In this study, all patients received a course of modern oxaliplatin- or irinotecan-based chemotherapy preoperatively, and 81% received additional chemotherapy postoperatively. With a median follow-up of 25 months, they reported an astonishing 3-year overall and disease-free survival of 86% and 51%, respectively, which was favorable when compared with patients who had a one-stage hepatectomy. Although this series presents a well-selected patient population, it demonstrates that in combination with modern chemotherapy, two-stage hepatectomy offers a chance of long-term survival for patients who would otherwise not be candidates for resection.

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CHAPTER 88

Advances in systemic therapy for hepatocellular carcinoma

Ghassan K. Abou-Alfa and Leonard B. Saltz

OVERVIEW

Hepatocellular carcinoma (HCC) is the fifth most common solid tumor and the third most common cause of cancer death worldwide (Abou-Alfa, 2008; see Chapter 80). Its incidence mirrors that of chronic liver injury, most commonly the result of viral infection by both hepatitis B and C (see Chapter 64). Other etiologies that lead to chronic liver injury and cirrhosis include alcohol abuse; nonalcoholic steatohepatitis, commonly associated with morbid obesity and diabetes; and other metabolic diseases, such as hemochromatosis. The highest incidence of HCC remains in Southeast Asia and sub-Saharan Africa (McGlynn et al, 2001); however, concern continues about the rising incidence of HCC in North America (El-Serag & Mason, 1999). A threefold increase in the age-adjusted rates for HCC associated with hepatitis C virus (HCV) infection has been observed, from 2.3 per 100,000 between 1993 and 1995 to 7.0 per 100,000 between 1996 and 1998; this is most likely explained by the increased incidence of HCV in North America during that period.

Many chemotherapeutic agents have been demonstrated to produce occasional responses in some patients with HCC, yet none has shown a clear impact on survival. The advent of novel therapeutics and their impact on survival in patients with HCC have changed the platform of managing advanced HCC and have opened opportunities to look into other therapeutic indications, such as adjuvant therapy.

HEPATOCELLULAR CARCINOMA AND CIRRHOSIS: TWO DISEASES IN ONE (SEE CHAPTER 70)

Both cirrhosis and the tumor itself impact the HCC patient's overall survival (OS), thus the cirrhosis status of patients with liver cancer must be evaluated. A scoring system was originally developed by Child (1964) that consisted of three parameters: jaundice (bilirubin), ascites, and encephalopathy. This scoring system was later updated by Pugh et al (1973), who added an assessment of hepatic synthetic function by evaluating serum albumin levels and prothrombin time (PT) (Table 88.1; see Chapters 2 and 70B). This combined score is known as the *Child-Turcotte-Pugh (CTP) score,* and it remains the most commonly used scoring system for liver cirrhosis. The pitfall of this classification is its lack of any parameters that relate to the cancer itself, as it was developed in patients who have cirrhosis but no cancer. As such, it is unlikely to be the best predictor of outcome in patients with HCC.

Okuda and colleagues (1985) recognized the need for an HCC staging system that incorporated factors related to both the cirrhosis and the tumor itself and developed what is known as the *Okuda staging system,* which encompasses four variables: 1) albumin, 2) bilirubin, 3) ascites, and 4) tumor size as a percentage of the size of the liver (greater or less than 50%). The Okuda staging system served as a platform for more advanced and sophisticated prospective scoring systems that used the Cox proportional hazard regression model. The Cancer of the Liver Italian Program (CLIP) developed a scoring system in patients with HCC, with mainly HCV as an etiology (CLIP, 1998, 2000), that found the independent prognostic variables for patients with HCC to be the CTP score plus three additional variables that relate to the tumor itself: tumor morphology, as assessed by the number of lesions and extent of disease in the liver; presence or absence of portal vein thrombosis; and α-fetoprotein (AFP) level (Table 88.2). Patients with a high score (4 to 6) were shown to have a median survival of only 3.2 months.

In contrast to the CLIP scoring system, the Chinese University Prognostic Index (CUPI), another scoring system based on multivariate analysis, was developed mainly in patients with hepatitis B virus (HBV)-associated HCC (Leung et al, 2002). This prognostic index identified bilirubin, alkaline phosphatase, and the presence or absence of ascites, in addition to tumor stage based on the tumor-node-metastasis (TNM) staging and AFP levels, as the most important predictors of outcome. In addition, a clinical assessment parameter of presence or absence of symptoms at presentation was incorporated (Table 88.3). An important aspect of the CUPI index is that different weights are attributed to the different parameters. The median survival of the highest risk group was close to 1 month. Other scoring systems include the Groupe d'Étude et de Traitement du Carcinome Hépatocellulaire (GETCH) staging system (Chevret et al, 1999), the Japan Integrated Staging (JIS) Score (Kudo et al, 2003), and the Barcelona Clinic Liver Cancer (BCLC) classification system (Llovet et al, 1999).

The BCLC system was developed with the aim of fine tuning the differences between patients with early stage disease, something the Okuda staging system fails to do; however, by the same token, the BCLC staging system had limited permutations for patients with advanced disease and grouped patients with unresectable disease—with Okuda stage I or II or CTP class A or B—in the same category as advanced disease.

In a retrospective analysis of patients with advanced HCC seen by medical oncologists at Memorial Sloan-Kettering Cancer Center (MSKCC) over a period of 5 years, we attempted to identify which of these eight scoring systems would be most valuable in this specific clinical setting (Huitzil-Melendez et al,

Table 88.1

Child-Turcotte-Pugh Scoring System

	POINTS		
Parameter	**1**	**2**	**3**
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Bilirubin (mg/dL)	<2	2-3	>3
Ascites	Absent	Slight	Moderate
Encephalopathy	None	I-II	III-IV
Prothrombin time (INR)	<1.7	1.8-2.3	>2.3
Score	A	B	C
Points	5-6	7-9	10-15

INR, international normalized ratio

Table 88.2

Cancer of the Liver Italian Program (CLIP) Scoring System

	SCORE				
Parameter	**0**		**1**		**2**
Child-Turcotte-Pugh class	A		B		C
Tumor morphology	Uninodular, extension ≤50%		Multinodular, extension ≤50%		Massive or extension >50%
Portal vein thrombosis	No		Yes		
α-Fetoprotein (ng/dL)	<400		≥400		
Score	0	1	2	3	4-6

2010). By using a concordance index, the GETCH, CLIP, and CUPI were found to be the most informative staging systems in predicting survival in patients with advanced HCC. The BCLC system did not score well in this exercise, which studied a specific niche of patients with advanced HCC, all of whom fell within the single basket of category C of BCLC; therefore it lacks any discriminatory value. Other groups have independently come to the same conclusion regarding the BCLC system (Collette et al, 2007).

ROLE OF CHEMOTHERAPY IN HEPATOCELLULAR CARCINOMA

Almost all classes of chemotherapy have been studied in advanced HCC (Nerenstone et al, 1988). Doxorubicin is one of the most studied drugs in this disease, partly as a result of what has thus far been an irreproducible response rate of 79%, originally reported by Olweny and colleagues (1975). It should be noted that this early report from the mid-1970s did not use modern computerized tomography (CT) or magnetic resonance imaging (MRI) methods available and used routinely today. The majority of "responses" were determined either on the basis of physical examinations of the liver or using a colloidal gold liver scan, measuring techniques that would not be acceptable as evidence of a response in clinical trials by current standards. Many subsequent attempts to try to reproduce this high response rate have been made, both with doxorubicin as a single agent (Barbare et al, 1984; Chlebowski et al, 1984; Ihde et al, 1977; Johnson et al, 1978; Sciarrino et al, 1985; Vogel, 1977; Williams & Melia, 1980) and in combination with other chemotherapeutic agents (Choi et al, 1984; Falkson et al, 1978, 1984; Melia et al, 1983; Olweny et al, 1980), but to no avail.

Other older and newer chemotherapeutic agents have also been studied in HCC, including cisplatin (Falkson et al, 1987), etoposide (Melia et al, 1983), mitoxantrone (Falkson et al, 1987), vinblastine (Damrongsak et al, 1973), capecitabine (Patt et al, 2004), gemcitabine (Kubicka et al, 2001), irinotecan (O'Reilly et al, 2001), and paclitaxel (Chao et al, 1998), all with reported dismal response rates and no impact on survival.

Although several combination chemotherapy agents have shown improved response rates, the impact on survival was not noticeable in most cases (Baker et al, 1977; Bobbio-Pallavicini et al, 1997; Porta et al, 1995). As a single agent, interferon α-2b in a trial by the Gastrointestinal Tumor Study Group (GITSG, 1990) showed a limited response rate of only 7%. This disappointingly low response, in addition to increased toxicity as a result of high doses of interferon, led to testing lower doses in combination with chemotherapy. Despite a reported high response rate of 31% in some trials (Ji et al, 1996; Patt et al, 1993), favorable results have not been reproducible (Kardinal et al, 1993; Stuart et al, 1996).

Nevertheless, the preliminary indication of some activity for interferon set the platform for a more intense combination

Table 88.3

Chinese University Prognostic Index (CUPI) Scoring System

Parameter	**Weight (CUPI Score)**					
Bilirubin (mg/dL)	<1.9	0	1.9-2.8	3	≥2.9	4
Ascites	Present	3				
Alkaline phosphatase	≥200 IU/L	3				
TNM stage	I and II	−3	IIIa and IIIb	−1	IVa and IVb	0
AFP (ng/mL)	≥500	2				
Disease symptoms on presentation	None	−4				
Risk group	Low		Intermediate		High	
Score	−7 to 1		2-7		8-12	

AFP, α-fetoprotein; TNM, tumor-node-metastasis

of cisplatin, interferon, doxorubicin, and 5-fluorouracil (5-FU), which became commonly known as PIAF (Patt et al, 1999). PIAF was subsequently modified and tested in the outpatient setting (Leung et al, 1999), and a Phase II trial of 50 patients showed a response rate of 26%. More importantly, nine patients (18%) had their tumor resected after therapy, and of these resected patients, four had a pathologic complete response noted in the resected tumor. Considerable hematologic toxicity was reported in this 50-patient cohort, and two treatment-related deaths resulted from neutropenic fever. It is important to note that this study was conducted before granulocyte-stimulating factors were commonly used for similar intense chemotherapeutic regimens.

These data led to a randomized Phase III trial of doxorubicin versus a combination, PIAF (Yeo et al, 2005). This trial showed the same 21% response rate for PIAF versus 10% for single-agent doxorubicin; however, the study failed to show any survival advantage in favor of the PIAF combination (8.7 vs. 6.8 months; $P = .83$). Despite this trial having a negative outcome for the primary end point, it did provide several important and useful pieces of information: First, as noted above, it identified what can realistically be considered the true response rate—by current standards of response definition and determination—of doxorubicin in HCC, and that response rate is 10%. Furthermore, although the study failed to provide support for use of PIAF as a routine palliative therapy for advanced disease, it might be considered as a conversion therapy in very carefully selected patients with potentially resectable tumors.

Some of the generally disappointing results are explained by the genetic makeup of HCC, which comprises highly resistant clones of cancer cells (DeVita & Abou-Alfa, 2000). The HCC cells carry a high genetic mutation load, which makes them less amenable to the destructive actions of chemotherapy. HCC cells usually contain a high level of dihydropyrimidine dehydrogenase (DPD), which potentially makes them relatively resistant to 5-FU (Jiang, 1993). HCC cells also overexpress the multidrug resistance gene *MDR1* (Chenivesse, 1997) and the gene product P-glycoprotein (P-gp) (Soini et al, 1996). This may help explain the resistance of HCC to paclitaxel (Chao et al, 1998), but it would not necessarily explain the PIAF pathologic response (Leung et al, 1999), the witness to the efficacy that chemotherapy can exert onto HCC, contrary to all attestations that it cannot; this concept will be revisited as part of its evaluation in combination with biologic therapy (Abou-Alfa, 2008).

Several attempts at overcoming this resistance by developing novel cytotoxic agents have been made, although not with any appreciable success. T138067 is an antimicrotubular non–P-gp substrate (Shan et al, 1999; Venook et al, 2004) that showed a modest 9% response in chemotherapy naïve patients (Leung et al, 2002); however, a randomized Phase II/III trial of T138067 versus doxorubicin in patients with advanced HCC was prematurely closed because of lack of survival benefit (Posey et al, 2005). Nolatrexed dihydrochloride is a nonclassic lipophilic inhibitor of thymidylate synthase that is not catabolized by dihydropyrimidine dehydrogenase. It lacks a glutamate side chain and thus has reduced potential transport-associated resistance (Webber et al, 1993). Nolatrexed was studied in two different clinical trials; however, results were disappointing, with an 8% response rate in a Phase II North American study (Stuart, 1999) and no responses in a randomized Phase II study in Hong Kong (Mok et al, 1999). Despite those disappointing results, a randomized Phase III trial that evaluated nolatrexed versus doxorubicin in patients with unresectable HCC was performed. It showed a median OS of 5.6 months for nolatrexed versus 8 months for doxorubicin ($P = .0068$) (Gish et al, 2007). It is unclear whether nolatrexed conferred a negative survival effect or was simply inactive.

A novel modality of administering floxuridine (FUDR) and dexamethasone via hepatic arterial infusion (HAI) was also studied in HCC (Jarnagin et al, 2009). Among eight patients studied, the response rate was 25%, and the hepatic progression-free survival (PFS) was 9.4 months. Interestingly, patients in the same study with cholangiocarcinoma fared better, with a 53.8% response rate and 11.6 months hepatic PFS. HAI is discussed in detail in Chapter 86.

In summary, no chemotherapy agent or combination of agents has so far shown any impact on survival in patients with HCC. With the advent of novel targeted agents came a pressing need to have them evaluated in the setting of HCC; however, chemotherapy is not necessarily forgotten, as the potential of combining it with targeted therapies may carry a certain promise in HCC given the success of such a strategy in multiple other solid-tumor models.

NOVEL BIOLOGIC THERAPIES IN HEPATOCELLULAR CARCINOMA

The advent of novel targeted therapeutics and the lack of a consistent standard of care for advanced HCC has led to interest in identifying and evaluating relevant targets in HCC along the signal transduction pathways (Huitzil-Melendez et al, 2009; Fig. 88.1).

Epidermal Growth Factor Receptor, c-MET, and Insulin Growth Factor Receptor

The epidermal growth factor receptor (EGFR) is one of the most thoroughly studied therapeutic targets. Several authors have reported no difference in expression of EGFR between HCC and noncancerous diseased liver tissues (Harada et al, 1999; Kira et al, 1997), whereas others have reported overexpression in 17% of HCC cases (Kiss et al, 1997). Erlotinib, an

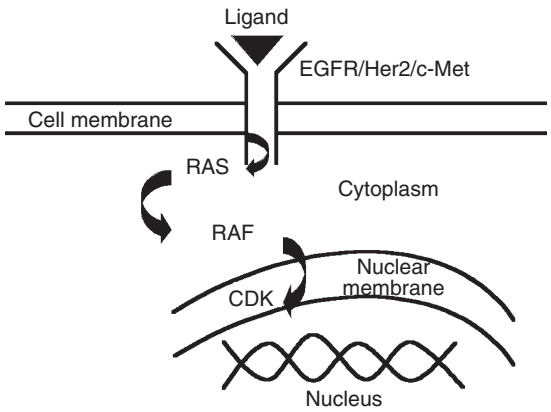


FIGURE 88.1. Potential targets for hepatocellula carcinoma therapy along the signal transduction pathway. CDK, cyclin-dependent kinase; c-Met, mesenchymal epithelial transition factor; EGFR, epidermal growth factor receptor; Her2, human epidermal growth factor receptor-2; RAF, rapidly growing fibrosarcoma (serine/threonine protein kinase); RAS, rat sarcoma (guanosine triphosphate–binding protein).

EGFR-specific receptor tyrosine kinase inhibitor, was tested in HCC as part of a Phase II trial of 38 patients with advanced HCC (Philip et al, 2005). Close to half of the patients had prior therapy, and 71% of all patients had class A cirrhosis. The primary end point was PFS at 6 months, using Response Evaluation Criteria in Solid Tumors (RECIST), and this end point was reached in 12 (32%) of 38 patients, with a median PFS of 3.8 months. In addition, three partial responses (8%) were reported, and median OS was 13 months. Similar to the experience with other tumors, immunohistochemical staining of EFGR expression was not associated with outcome. The most frequent grade 3 and 4 toxicities were skin rash (13%), diarrhea (8%), and fatigue (8%).

Despite having some preclinical activity in HCC (Huether et al, 2005), cetuximab has not been tested in HCC. Lapatinib, an oral agent with dual inhibition of EGFR and tyrosine kinase 1 and 2 (Her2/Neu), has been studied in HCC (Ramanathan et al, 2009) despite the rare expression of Her2/Neu in human HCC tissues (Hsu et al, 2002) and with disappointing results. In a Phase II trial, 40 patients with advanced HCC were treated with lapatinib, and the response rate was 5%, PFS was 2.3 months (95% confidence interval [CI], 1.7 to 5.6), and median survival was 6.2 months. Both fall short of other reported data in the literature, and EGFR genotyping indicates that HCC patients with less than 20 repeats have the worst PFS.

Another potential target is the hepatocyte growth factor (HGF) and its receptor c-Met, which were found to be overexpressed in 33% and 20% of human HCC tissues, respectively (Kiss et al, 1997). In another study, c-Met was found to be overexpressed preferentially in early stage resected HCC, with no association with outcome as measured by OS (Huitzil-Melendez et al, 2009). Certain c-Met inhibitors are already being studied in HCC, such as ARQ 197, which was already evaluated in a Phase I study (Garcia et al, 2007).

Insulin growth factors (IGFs) are reported to be a strong mitogen of HCC, exerting their effect through the IGF1 receptor (Pollak, 2005). IGF1 receptor inhibitors are currently under study in HCC. In conclusion, the data shown so far do not provide enough support for the routine use of any of the single-agent EGFR, c-Met, or IGF receptor inhibitors in the management of HCC.

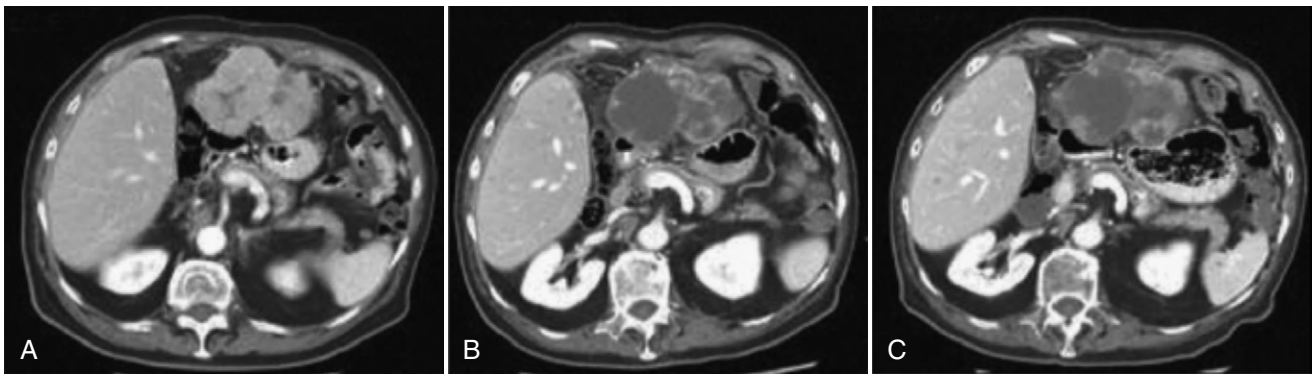
Sorafenib

Sorafenib is a novel molecular targeted agent that inhibits the serine/threonine kinase Raf-1 in vitro in addition to the pro-angiogenic (vascular endothelial growth factor receptor [VEGFR]-1, -2, and -3; platelet-derived growth factor receptor [PDGFR]-β); and tumorigenic receptor tyrosine kinases (RTKs; RET, Flt-3, and c-Kit) (Wilhelm et al, 2004). Sorafenib has been studied extensively in HCC and has now been approved by regulatory agencies worldwide as a standard therapy for unresectable HCC.

HCC is a highly vascular solid tumor with high expression of VEGF, which plays a major role in HCC development and potentiates its metastatic capability in preclinical models (Yoshiji et al, 2004). Proangiogenic platelet-derived growth factor receptor-β (PDGFR-β) also contributes to this increased metastatic potential (Zhang et al, 2005).

Anti–VEGFR-1, -2, and -3 and PDGFR-β sorafenib are the most studied antiangiogenic drugs in HCC so far; although an initial Phase II trial evaluating response to sorafenib in patients with advanced HCC showed no significant response rate (2%) (Abou-Alfa et al, 2006), 34% of patients had stable disease of a minimum 4 months' duration. This was commensurate with a median time to progression (TTP) of 4.2 months and median OS of 9.2 months, both of which compare favorably to historic controls (Yeo et al, 2005). The main grade 3 and 4 toxicities were fatigue (9.5%), diarrhea (8%), and hand-foot skin reaction (5.1%), known also as *hand-foot syndrome*. The high rate of stable disease was associated with an observed phenomenon of central tumor necrosis in many patients in the study whose tumors were evaluated using triphasic CT scans inclusive of an arterial phase (Fig. 88.2). This central tumor necrosis was quantified, and the volume was assessed using a computer algorithm for semiautomated delineation of tumors (Zhao et al, 2006). It was later found that the ratio of the percentage of the described tumor necrosis over the tumor volume correlated with objective response (Abou-Alfa, 2008). This phenomenon is still pending validation and is currently the subject of many prospective correlative studies of ongoing HCC clinical trials.

The suggested improved outcome noted in this Phase II study led to a large, double-blinded, randomized Phase III trial evaluating sorafenib versus placebo in patients with advanced



Volume (cm^3)	295	341	285
Necrosis (%)	2.1	53.1	51.0

FIGURE 88.2. A representative example of baseline and serial follow-up scans demonstrating tumor necrosis in a hepatocellular carcinoma patient. *(From Abou-Alfa GK, et al, 2006: A phase II study of sorafenib in patients with advanced hepatocellular carcinoma. J Clin Oncol 24[26]:4293-4300.)*

HCC and class A cirrhosis (Llovet et al, 2008) with two primary end points of OS and time to symptomatic progression (TTSP) using the FHSI8-TSP instrument. This Phase III study, known for short as the *SHARP trial* (Sorafenib HCC Assessment Randomized Protocol), demonstrated a survival of 10.7 months in the sorafenib group versus 7.9 months in the placebo group ($P < .001$, hazard ratio [HR], 0.69). The second primary end point in evaluating TTSP showed no difference between the two arms ($P = .77$). This observation is limited by the poor understanding of the validity of the FHS18-TSP instrument in this setting. Add to the fact that a large number of the patients in this study—including 17% with locally advanced tumor, BCLC B patients—had an excellent performance status and lacked any symptoms that the FHS18-TSP instrument would otherwise depend on for its measurements. The toxicity profile was similar to that noted in the Phase II study, with 8% grade 3 to 4 diarrhea and hand-foot syndrome. Rare bleeding events were observed (<1%) that would still force a word of caution considering the antiangiogenic nature of sorafenib, which is true also for other agents in its class, such as bevacizumab and sunitinib, that may cause fatal hemorrhage (Siegel et al, 2008; Faivre et al, 2009).

A second randomized Phase III study to evaluate sorafenib in patients with advanced HCC and class A cirrhosis was conducted in the Asia-Pacific geographical area (Cheng et al, 2009). The study had eligibility criteria similar to the SHARP trial but had two differences in the design: 1) the study had a 2:1 randomization, typically to help encourage accrual, and 2) it did not have a predefined primary end point but rather looked at several. Similar to the SHARP trial, the Asia-Pacific study showed an improvement in survival in favor of sorafenib (6.5 months) versus placebo (4.2 months); however, this statistically significant improvement ($P = .014$) was not of the same magnitude as that of the SHARP trial, despite similar HRs—0.68 and 0.69, respectively—in the Asia-Pacific and SHARP studies. In an attempt to explain the difference in magnitude of the OS, it was argued that in the Asia-Pacific study, patients were more ill at the time of accrual (Abou-Alfa et al, 2009) and had more extensive disease at a more advanced stage. This observation may partly explain the difference in magnitude of benefit from sorafenib between those two populations, and it may suggest, in view of the similar HRs, that the benefit for sorafenib was expressed on the survival curve at two different times in the natural history of the disease: earlier in the SHARP trial and later in the Asia-Pacific study.

In a subgroup analysis of the SHARP trial, it was noted that sorafenib-treated patients with HCV-based HCC (n = 93) had a median survival advantage of 14 months compared with the entire sorafenib-treated group, whose survival was only 10.7 months (Bolondi, 2008); this suggests a possible positive influence of HCV status on the efficacy of sorafenib. The placebo-controlled HCV group did not have any added survival advantage over the placebo population of the study, thus proving the lack of any advantage brought on by the HCV itself. Of note, in HCV infection, the virus core proteins result in high basal activity of Raf-1, which leads to a sustained response to EGFR by hepatocytes and results in an increased possibility of neoplastic transformation (Giambartolomei et al, 2001). A similar observation was noted in a retrospective analysis of the Phase II trial that evaluated sorafenib in patients with advanced HCC (Abou-Alfa et al, 2006). In this analysis, it was noted that patients who were infected with HCV but not HBV (n = 13) had a longer time to progression of 6.5 months, compared with 4 months ($P = .05$) for the patients infected with HBV (n = 33; Huitzil et al, 2008). A similar trend was noted in survival advantage ($P = .29$) for the HCV patients (12.4 months) versus HBV patients (7.3 months), with 73% of those accrued in the Asia-Pacific study found to have HBV as an underlying etiology for their HCC, versus only 18% of patients in the SHARP trial; this may offer another explanation, or at least a complementary one, for this difference in the outcome magnitude between the two studies. Of note, the outcome of the 18% of patients with HBV in the SHARP trial for unspecified reasons is still not reported; however, this observation does undermine the antiangiogenic effect of sorafenib, which continues to be indicated for all patients with unresectable HCC irrespective of the etiology of their cancer.

Patients with unresectable HCC and CTP class A cirrhosis who are eligible for sorafenib based on the SHARP trial encompass no more than half of the patients seen by medical oncologists (Huitzil, 2010). The safety and efficacy of sorafenib in patients with class B or C cirrhosis, who make up the other half, remain a subject of discussion. In the Phase II study that evaluated sorafenib in HCC (Abou-Alfa et al, 2006), 28% of patients had class B cirrhosis and pharmacokinetic profiles that included area under the curve (AUC) and maximun drug concentration (Cmax) comparable to patients with class A disease. The class B patients had more frequent worsening of liver function, including elevated total serum bilirubin, worsening ascites, and encephalopathy (Abou-Alfa, 2008). Considering the lack of a control arm, these data cannot help determine whether this deterioration in liver function is part of the expected natural history of class B disease, a result of sorafenib, or a combination of these. The elevated total bilirubin may also be due to sorafenib's inhibitory effect of uridine diphosphate-glucouronosyl-transferase-1 polypeptide-1 (UGT1A1) and decreased bilirubin glucuronidation; because the study did not collect direct bilirubin measurements, this distinction cannot be made. Median TTP for class A patients was 21 weeks (95% CI, 16 to 25 weeks), and it was 13 weeks for class B patients (95% CI, 9 to 18 weeks); median OS was 41 weeks (95% CI, 36.6 to 63.6 weeks) and 14 weeks (95% CI, 11.6 to 25.7 weeks), respectively. In a phase I study that evaluated two different doses of sorafenib in Japanese patients with advanced HCC (Furuse et al, 2008), geometric means of $AUC_{0\text{-}12}$ and Cmax were slightly lower in patients with class B cirrhosis compared with class A disease despite the lack of any substantial differences in the incidence of adverse events between the two groups.

One additional study evaluated sorafenib in 150 patients with different types of tumors in cohorts of different levels of liver dysfunction, and their results offer some guidance on the use of sorafenib in such patients (Miller et al, 2009). Among all the cohorts with higher than normal total bilirubin, the most commonly reported drug-limiting toxicity (DLT) among patients was further elevation of bilirubin. The study suggested sorafenib doses of 400 mg PO twice per day for bilirubin up to 1.5 times the upper limit of normal (ULN) and 200 mg PO twice per day, or 400 mg PO daily, for bilirubin 1.5 to 3 times the ULN; it was recommended that sorafenib be avoided for patients whose bilirubin is above three times the ULN. These recommendations may at least be used as a guideline, until more data become available regarding the safety and efficacy of sorafenib in patients with HCC and class B or C cirrhosis; this would require a randomized study that allows assessment of the natural history of the disease, and ways of evaluating worsening

cirrhosis, in noninvasive ways that are also more predictive than measuring bilirubin levels.

Bevacizumab, an anti-VEGF, has been studied extensively in patients with advanced HCC. Bevacizumab was studied as a single agent in 46 patients with advanced HCC at doses of 5 mg/kg and 10 mg/kg (Siegel et al, 2008). Median PFS was 6.9 months, and median survival was 12.4 months. Grade 3 to 5 hemorrhage occurred in 11% of patients, including one death secondary to a variceal bleed. In the initial phase of this study with 18 patients accrued, 4 had to discontinue therapy because of serious adverse events, including one transient ischemic attack and three serious esophageal bleeding events. The study was thus modified to identify and manage esophageal varices prior to enrollment (Schwartz et al, 2005). Another study that evaluated single-agent bevacizumab in HCC showed similar results (Malka et al, 2007). Among 24 patients evaluable for response, 3 had a partial response and 13 had stable disease.

Sunitinib, a multitargeted receptor tyrosine kinase inhibitor, was evaluated as a single agent in patients with advanced HCC as part of a Phase II study (Zhu, 2009). Of 34 patients treated with sunitinib at a 37.5 mg daily dose, 50% of patients had stable disease, with a median PFS of 3.9 months and an OS of 9.8 months. The most common grade 3 and 4 adverse events included hematologic toxicities, fatigue, and transaminase elevation; in addition, two deaths were reported and attributed to worsening disease and liver failure. A second well-conducted study evaluated sunitinib at a higher dose of 50 mg/day in 37 patients with advanced HCC; however, it did not move to a planned second stage because of a low response rate of 2.7% in the first stage of the study (Faivre et al, 2009). In addition, four deaths were reported that were interpreted as possibly drug related; these included events of hepatic encephalopathy, hematologic toxicities, and a variceal bleed. Despite those findings, enthusiasm continues regarding the potential therapeutic value of sunitinib, which is being studied as part of a Phase III clinical trial to evaluate sunitinib versus sorafenib in patients with advanced HCC.

Brivanib, a dual inhibitor of VEGF and fibroblast growth factor (FGF), was also studied in HCC. In a study that evaluated brivanib as first- and second-line therapy in 96 patients with advanced HCC, limited responses were reported, and OS was 10 months in the treatment-naïve cohort and was not reached in the second-line cohort (Raoul et al, 2009). Although the OS compared favorably to the historic control, PFS was only 2.7 months in the treatment-naïve group, and TTP was only 2 months in the second-line group; however, the drug was well tolerated in the second-line setting (Finn et al, 2009). Another drug recently studied in advanced HCC is ABT-869, a VEGF and PDGF inhibitor. In a recently reported Phase II study of 44 patients, of whom 38 had class A and 6 had class B liver dysfunction, the class A patient outcome was equivalent to historic controls, with a median OS of 9.7 months and TTP of 5.4 months. Despite this similarity in outcome, and with the lack of any apparent advantage over sorafenib (Llovet et al, 2008), both brivanib and ABT-869 are currently being evaluated in large randomized Phase III trials against sorafenib.

Combination Therapy Studies with Antiangiogenics

Bevacizumab is the antiangiogenic most studied in combination with various other agents. Several Phase II studies have evaluated bevacizumab in combination with chemotherapy. Gemcitabine and oxaliplatin plus bevacizumab were examined in a Phase II trial in 30 previously treated HCC patients (Zhu et al, 2006). The objective response rate was 20%, and 27% of patients had stable disease; median PFS was 5.3 months, and median OS was 9.6 months. The most common grade 3 and 4 toxicities included leucopenia and neutropenia, elevation of transaminases, hypertension, and fatigue.

Another Phase II study evaluated the combination of bevacizumab, oxaliplatin, and capecitabine in 30 patients with advanced HCC (Sun et al, 2007). Partial response was noted in 13.3% of the patients, and 76.7% had stable disease. Median PFS and median OS were 4.5 and 10.6 months, respectively. Toxicity was not trivial: 33% of the patients sustained grade 2 or 3 peripheral neuropathy, and 11% experienced grade 2 or 3 hand-foot syndrome. In addition, three bleeding events, one gastrointestinal perforation, and two variceal hemorrhages were reported. Bevacizumab plus capecitabine only was also studied in 25 patients with advanced HCC and yielded parallel results (Hsu et al, 2007), with median PFS of 4.1 months and OS of 10.7 months. The most common treatment-related grade 3 toxicity was hand-foot syndrome, and one gastric ulcer hemorrhage was reported.

Bevacizumab was also studied in combination with erlotinib in 40 patients with HCC and class A or B cirrhosis and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. Bevacizumab was administered at a dose of 10 mg/kg every 2 weeks, and erlotinib was given PO daily at 150 mg (Thomas, 2009). The primary end point at 16 weeks for PFS was 62.5%, with median PFS of 39 weeks; median OS was 68 weeks, and the response rate was 25%. The most common grade 3 or 4 drug-related toxicities were fatigue (20%), hypertension (15%), diarrhea (10%), elevated transaminase levels (10%), and gastrointestinal hemorrhage (12.5%). A randomized Phase II study of erlotinib, bevacizumab, and sorafenib was also started.

Sorafenib has also been evaluated in combination with biologic therapy and chemotherapy in two separate studies: despite the almost inexistent data (Duran et al, 2007) on the combination in HCC, one ongoing randomized Phase III study was initiated to evaluate sorafenib plus erlotinib versus sorafenib alone in patients with advanced HCC; the other study was a randomized Phase II study that evaluated doxorubicin plus sorafenib and doxorubicin plus placebo in 96 patients with advanced HCC and class A cirrhosis (Abou-Alfa, 2008). The primary end point, median TTP, was 9 months for the doxorubicin-sorafenib arm and 5 months for the doxorubicin-placebo arm. An exploratory comparison of OS between the two arms showed a significant difference of 13.7 months in favor of doxorubicin and sorafenib versus 6.5 months for doxorubicin and placebo ($P = .0049$; HR, 0.45). In both arms of this study, grade 3 and 4 toxicities included fatigue (15%) and neutropenia (50%). In the combination arm, sorafenib-related toxicities included grade 3 and 4 diarrhea (11%) and grade 3 and 4 hand-foot syndrome (9%). In addition, more left ventricular dysfunction was reported in the doxorubicin-sorafenib arm, observed in 19% of the cases (all grades), most of which were subclinical and caught solely on a Multiple Gated Acquisition test (MUGA) or echocardiography evaluation, with only 2% clinical grades 3 or 4.

A potential synergistic effect between doxorubicin and sorafenib is suggested that may explain the improved outcome as well as the increased cardiac function. Anthracyclines such as doxorubicin depend on Ask-1 to exert their apoptotic effect. In

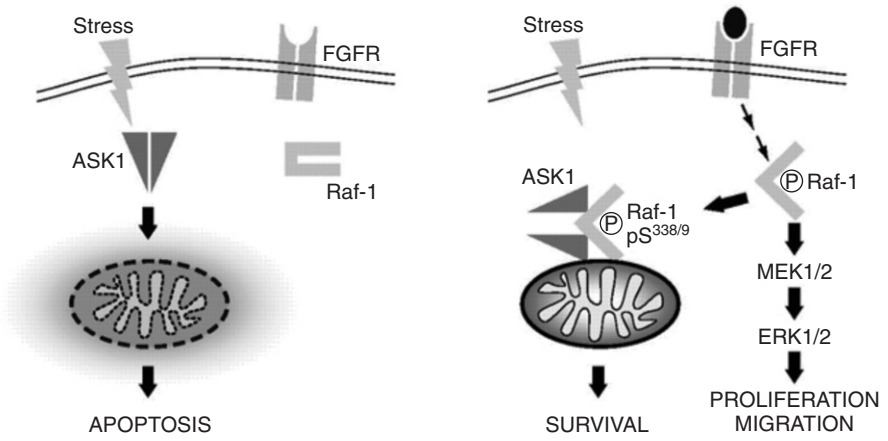


FIGURE 88.3. A model depicting the role of Raf-1 in regulation of ASK1-mediated apoptosis. At the mitochondria, bFGF-mediated activation of Raf-1 promotes a complex between Raf-1 and ASK1, leading to inhibition of ASK1 kinase activity and prevention of stress-mediated apoptosis. ASK1, apoptosis signal-regulating kinase-1; ERK, extracellular signal-regulated kinase; FGFR, fibroblast growth factor receptor; MEK, mitogen-activated protein kinase/ERK kinase; Raf-1, rapidly growing fibrosarcoma (protein). *(From Alavi AS, et al, 2007: Chemoresistance of endothelial cells induced by basic fibroblast growth factor depends on Raf-1–mediated inhibition of the proapoptotic kinase, ASK1. Cancer Res 67[6]:2766-2772.)*

cancer cells, a basal fibroblast growth factor (bFGF)-mediated activation of Raf-1, a target of sorafenib, may promote a complex between Raf-1 and ASK1 at the mitochondrial level that leads to inhibition of Ask-1 kinase activity and prevention of stress-mediated apoptosis of anthracyclines. Inhibiting RAF kinase activity with sorafenib may release Ask-1 and restore the apoptotic activity of doxorubicin (Alavi et al, 2007; Fig. 88.3). A large, randomized, Phase III trial was recently initiated to evaluate the combination of sorafenib and doxorubicin versus sorafenib alone, and it will answer the question regarding the potential synergy between sorafenib and doxorubicin.

Second-Line Therapies

With the advent of sorafenib as a first-line agent in the treatment of HCC, efforts to study second-line treatments have already been noticed. Brivanib has already been tested in the second-line setting (Finn et al, 2009; Raoul et al, 2009), and it is currently being evaluated against placebo in a large, randomized Phase III trial.

ASSESSMENT OF RADIOLOGIC RESPONSE IN HEPATOCELLULAR CARCINOMA

In contrast to early clinical trials conducted in the 1970s, in which assessment of response was mainly dependent on clinical evaluation, the advent of radiologic technologies, such as contrast-enhanced computed tomography (CT) and triphasic CT scanning (see Chapter 16) and magnetic resonance imaging (MRI; see Chapter 17), have helped improve our ability to assess disease extent and tumor response to therapy in a more objective manner. Despite these improved imaging modalities, HCC remains one of the most difficult tumors to evaluate radiologically; this is due in part to the infiltrative nature of these tumors, their poor margination, and their hypervascularity, all of which make it hard to define their exact margins. In addition, there is growing recognition that response can also be assessed through dynamic measures, such as necrosis and blood flow to the tumor.

In the Phase II trial that evaluated sorafenib in patients with advanced HCC, tumor necrosis was noted in the absence of actual tumor regression (Abou-Alfa et al, 2006). This was associated with declines in AFP in several patients and in improvement of symptoms. A subanalysis to evaluate the correlation between tumor necrosis and response followed (Abou-Alfa, 2008). Triphasic CT scans of 12 patients from the study were evaluated; 5 patients were found to have stable disease or stable disease with necrosis, and 7 progressed on therapy. Median survival was based on a landmark analysis computed from the date of the last CT scan to the date of death or last follow-up to ensure that all probability estimates and statistical tests were conditional on the response status of patients at the landmark time (Anderson et al, 1983). The landmark analysis-based median survival was 4.8 months among responders and 3.1 months among nonresponders. The ratio of tumor necrosis and volume (TN/V) was significantly associated with response, with responders having greater increases in the TN/V relative to baseline compared with nonresponders ($P = .02$). TN/V was not significantly associated with OS and surely needs to be further evaluated prospectively as part of a large clinical trial.

Dynamic contrast-enhanced MRI (DCE-MRI) has been shown to be useful in studying the pathophysiology of tumors (Taylor, 1999; Yuh, 1999) and possibly response (Morgan et al, 2003). In view of the antiangiogenic activity of drugs like sorafenib in HCC, this technology could be helpful in assessing parameters of interest, such as microvascular density, vascular permeability, and the extravascular extracellular space (Knopp et al, 1999). DCE-MRI has also been investigated as an early indicator of response or failure of an agent. Several studies have shown that successful therapies result in early changes (within 48 hours) in DCE-MRI contrast-enhancement parameters, which may prove to be a more accurate early indication of response (Barentsz et al, 1998; Brasch et al, 1997; Pham et al, 1998). In the Phase II study evaluating sunitinib in 34 patients with advanced HCC (Zhu, 2009), DCE-MRI was performed and showed a sunitinib-related rapid decrease in vessel leakiness, and this effect was more pronounced in patients with delayed progression. In the randomized Phase II study that evaluated doxorubicin plus sorafenib and doxorubicin plus placebo in patients with advanced HCC (Abou-Alfa, 2008), DCE-MRI scans obtained on six patients showed no significant association between response and changes in k_{ep}, $K^{trans,}$ and AFP, but a trend toward significant association was observed between response and AUC180 ($P = .07$; Abou-Alfa et al, 2009). DCE-MRI as a surrogate of response needs to be better evaluated as part of a large clinical study.

NEOADJUVANT AND CONVERSION THERAPY

In some instances, surgical resection of a large, localized primary HCC tumor might be feasible, if disease regression was

achieved. Conversion therapy as a concept may render some unresectable tumors surgically approachable (see Chapter 87); it may also contribute to better outcome by possibly eradicating microscopic local and systemic disease, in contrast to neoadjuvant therapy, which is potentially given to patients considered resectable a priori. Different modalities have been studied in the context of conversion therapy for HCC, but none thus far has been shown to add any survival benefit over surgery alone. Bridging to transplant may be considered under the same umbrella, in view of its goal of maintaining or reducing a tumor size to fit within the transplant (Milan) criteria (Mazzaferro, 1996).

Transarterial chemoembolization (TACE) has been evaluated in multiple randomized studies. A randomized trial of one to five TACE applications prior to surgery (n = 24) versus surgery alone (n = 28) did not offer a benefit as neoadjuvant therapy (Wu et al, 1995). TACE had no effect on 33% of the patients who had the intervention, and they either remained with stable disease or had progression. No difference was found between the two groups in operative morbidity or mortality rates and pathologic staging. The disease-free survival (DFS) rate in the two groups was similar, but the incidence of extrahepatic cancer recurrence was higher in the neoadjuvant group (57% vs. 23%; $P = .03$), and 5-year survival was also significantly worse in the TACE group (30% vs. 60%; $P = .01$).

The experience with transarterial embolization (TAE, without chemotherapy) has not been any different. In a study that randomized 97 patients to TAE plus surgery versus surgery alone, DFS did not differ between the two groups (39 vs. 31.1 months) despite an increased rate of necrosis in the TAE group (Yamasaki et al, 1996).

The experience with yttrium-90 TheraSpheres (MDS Nordion, Kanata, Canada) in the treatment of locally advanced HCC continues to expand (Salem et al, 2002; see Chapter 84A). A new study to evaluate sorafenib with or without ^{90}Y in patients awaiting transplant is underway. In addition, limited experience has been gained with immunoembolization (Lygidakis & Tsiliakos, 1996), radiation (Tang et al, 1995), and chemoradiation (Sitzmann & Abrams, 1993); however, none of these techniques have so far been shown to confer a survival advantage when administered in the neoadjuvant setting.

Chemotherapy-based clinical trials in the conversion therapy setting have lagged because of the discouraging response rates seen in the advanced disease setting. This has changed somewhat with the advent of the more intense chemoimmunotherapeutic combination of cisplatin, interferon, doxorubicin, and 5-FU, also known as PIAF (Patt et al, 1999). In the Phase II study discussed above of 50 patients with unresectable HCC, 13 (26%) had a partial response (Leung et al, 1999). Of those 13 patients, 9 (18%) underwent surgical resection, and 4 had a pathologic complete response, meaning no viable tumor was evident at surgery. Unfortunately, PIAF did not stand up to a randomized Phase III trial (Yeo et al, 2005) against doxorubicin in the advanced disease setting, and it is important to recall that the PIAF combination carries substantial treatment-related morbidity and mortality. The majority of those patients who had excellent performance status had grade 3 or higher hematologic toxicity, and two deaths occurred secondary to neutropenic sepsis. The role of PIAF may therefore be limited to those very thoroughly reviewed cases in a multidisciplinary clinic or conference, where conversion therapy may be valuable to a patient with a potentially resectable tumor.

ADJUVANT THERAPY

Regardless of surgical techniques, which have improved in the last decade, a high number of patients with resected HCC will have recurrence of their disease (Ziparo et al, 2002). In a recent series, the recurrence rate after surgical resection was 55% after 26 months' follow-up (Cha et al, 2003). The experience with liver transplantation has been better, with lower recurrence rates; however, these are nonrandomized comparisons, and transplant patients are more carefully selected and in general have a lower volume of disease (Mazzaferro, 1996). Although liver transplantation eliminates the cirrhotic fertile ground for recurrence (Nissen et al, 2004), it unfortunately cannot be the answer for every patient with HCC, not only because of the limited supply of organs but also because of its limited efficacy in anything other than small tumors; thus the question of whether adjuvant therapy reduces the risk of recurrence after surgical resection remains an important and pressing one.

With the lack of a standard, active systemic chemotherapy for advanced disease, chemotherapy has never been seriously considered in the adjuvant setting. One very small, randomized study investigated oral carmofur (1-hexylcarbamoyl-5-fluorouracil) versus no therapy (Yamamoto et al, 1996). The study randomized and stratified 67 patients based on their Liver Cancer Study Group of Japan (LCSGJ) staging (LCSGJ, 1994). The regimen was poorly tolerated and offered no survival advantage for either stage I or II disease. DFS for the stage I patients showed a tangible advantage of 60% versus 30% at 3 years and 50% versus 20% at 5 years ($P = .04$). This trial was suspended prematurely, because 56% of the treated patients had unacceptable side effects.

Hepatic arterial chemotherapy, with or without systemic chemotherapy, has also been utilized in the adjuvant setting in HCC. An underpowered randomized study that combined hepatic arterial epirubicin and systemic epirubicin and carmofur versus no further therapy (Ono et al, 1997) showed no survival or DFS benefit. Side effects again led to the discontinuation of therapy in 21% of randomized patients. In addition, a randomized trial of hepatic artery epirubicin versus the same plus oral tegafur showed no difference in survival or rate of recurrence between the two groups (Kohno, 2004), and no description of any difference in side effects between the two arms was reported.

TAE, both bland and with chemotherapy, was studied in the adjuvant setting. An improvement in DFS was reported in a randomized study of a bolus hepatic arterial infusion (HAI) of Lipiodol containing doxorubicin and mitomycin C versus no adjuvant therapy after surgical resection (32% vs. 12% at 3 years; $P = .02$) (Izumi et al, 1994); however, no survival advantage was reported. Another trial randomized patients to a hepatic artery emulsion of iodized oil and cisplatin and intravenous epirubicin (Lai et al, 1998). This trial showed a worse DFS in the treatment group at 3 years (18% vs. 48%; $P = .04$). A third study of TACE versus no further therapy after surgical resection was able to show a survival advantage in patients defined at risk for residual tumor and thus recurrence (Ren et al, 2004). These risk factors included tumor diameter more than 5 cm, multiple nodules, and vascular invasion; 5-year survival was 44.36% in the adjuvant TACE group versus 37.40% in the control group ($P = .0216$).

More promising data in the adjuvant setting comes from the use of transarterial ^{131}I-Lipiodol (Lau et al, 1999). In a randomized phase II trial evaluating transarterial ^{131}I-Lipiodol versus

no adjuvant therapy after surgical resection, an improvement was seen in DFS in the adjuvant therapy arm of 74% versus 36% in the control arm (P = .037). In addition, 3-year OS improved and was reported in 85% of the treatment group versus 46% of the control group (P = .039). A recent update showed the actuarial 5-year DFS in the treatment and control groups to be 61.9% and 31.8%, respectively (P = .0397), and the actuarial 5-year OS in the treatment and control groups was 66.7% and 36.4%, respectively (P = .0433); however, 7 years after randomization, the DFS and OS benefits lost their statistical significance (Lau et al, 2008). It should be noted that ^{131}I-Lipiodol is not available in the United States.

Immune modulators have also been tested in the adjuvant setting, including an attempt at infusing autologous lymphocytes cultured with interleukin (IL)-2 and antibodies to CD-3 versus no therapy (Takayama et al, 2000), HAI of doxorubicin and IL-2 plus an infusion of lymphokine-activated killer (LAK) cells versus HAI of doxorubicin (Kawata et al, 1995), oral acyclic retinoids versus placebo (Muto et al, 1996), and interferon-α versus no therapy (Kubo, 2001). None of those studies reported a survival advantage with the exception of the retinoid study, which did on further follow-up and 2 years after the study was originally reported (Muto et al, 1999); in addition, 6-year survival was 74% in the acyclic retinoid group versus 46% in the placebo group (P = .04).

Active immunization has also been evaluated in the adjuvant setting for HCC. An HCC vaccine consisting of autologous formalin-fixed tumor tissue fragments, biodegradable microparticles containing human granulocyte macrophage colony-stimulating factor and human IL-2, and tuberculin (autologous formalin-fixed tumor [AFTV]) was tested in a small, randomized trial (Kuang et al, 2004). Nineteen patients received three intradermal vaccinations at 2-week intervals beginning 4 to 6 weeks after hepatic resection, and 22 patients received no further therapy after surgical resection. In a median follow-up of 15 months, the risk of recurrence in the vaccinated patients was reduced by 81% (P = .003). Vaccination significantly prolonged OS by 89% (P = .01). AFTV was most effective in preventing recurrence in patients with small tumors; in addition, 12 vaccinated patients showed a positive delayed-type hypersensitivity response, and 92% of those patients were recurrence-free at the end of the trial. Adverse effects were limited to grade 1 or 2 skin toxicities, such as erythema, dry desquamation, and pruritus. Again, this is a very small trial that is intriguing, but larger confirmatory data are required before the merits of this approach can be fully assessed.

A more aggressive approach was attempted in a very small pilot study of five patients who, after undergoing orthotopic liver transplantation (OLT) for HCC, received a nonmyeloablative preparative regimen of fludarabine combined with total-body irradiation or cyclophosphamide followed byallogeneic peripheral blood stem cell transplant (PBSCT), which was performed 16 to 135 days after OLT with human leukocyte antigen-matched donors (Soderdahl et al, 2003). The aim of the study was to see whether a stable mixed-donor chimerism could be sustained, which was observed in one of two patients with HCC in the study. Chimerism analysis 36 days after PBSCT showed 100% donor T cells and 90% donor myeloid cells in peripheral blood. The patient was reportedly doing well, albeit after only 10 months follow-up after OLT. Sorafenib is also being evaluated in the adjuvant setting.

It is clear that investigators have utilized almost every therapeutic modality to attempt to reduce the risk of recurrence of HCC after surgical resection or transplantation. Although some rare positive outcomes have been reported, most were either part of very small series or lacked the statistical power to show true evidence of a survival advantage. Until these issues and many others, such as the molecular predictors of recurrence, are answered or identified, no standard adjuvant therapy can be recommended for resected HCC; therefore adjuvant treatment outside of a clinical trial cannot be supported by available data at this time.

CONCLUSION

The incidence of HCC is on the rise, especially in developed countries, mainly as a result of an increased incidence of hepatitis C. Trying to treat HCC means that both the underlying cirrhosis and the cancer must be addressed. A thorough understanding of the cirrhosis is imperative as part of understanding the status of the disease and to help identify the appropriate therapies that a physician might recommend.

In the case of advanced HCC, sorafenib has shown an improvement in survival and thus can be considered an appropriate standard treatment. Other novel therapies and combinations of biologics and chemotherapies continue to be evaluated in advanced HCC.

Finding a better therapy for advanced HCC does not mean only developing better therapeutics, it also means finding a better way to assess the disease. The infiltrative nature of HCC, poor margination, and hypervascularity limits the use and benefit of the standard radiologic techniques, such as CT and MRI. Newer modalities that evaluate the necrosis and dynamic aspects of the cancer are in development and parallel the investigation of novel biologics in the treatment of HCC.

Thus far, neoadjuvant and adjuvant therapies have failed to be proven effective in HCC. Systemic therapy is a critical component of the managing of patients with advanced HCC.

References are available at expertconsult.com.

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CHAPTER 89

Isolated hepatic perfusion for extensive liver cancer

James Pingpank Jr.

OVERVIEW

Each year, isolated hepatic metastases from a variety of primary malignancies pose a significant clinical dilemma for tens of thousands of patients. For a small percentage of patients, surgical resection or ablation is effective in controlling clinically apparent disease, but for many patients with colorectal, gastrointestinal, or neuroendocrine tumors or ocular melanoma, the number of tumors and volume of affected liver render resection and/or ablation incapable of meaningful disease control (see Chapter 81). In more selected circumstances, metastases arising from tumors of the breast, skin, and soft tissue can be present solely as hepatic disease, with patient quality of life and survival dictated by the ability to control liver-based disease.

Since the 1950s, strategies designed to focus chemotherapy solely upon liver metastases have been investigated by a number of researchers at a limited number of institutions around the world, with sequential improvements in safety and efficacy observed with advances in surgical and catheter-based technology. Isolated hepatic perfusion (IHP) has been developed under a series of clinical trials within institutions with experience in regional therapies to the liver, limb, and lung, approaches that share a common goal of intensifying focused treatment to the cancer-bearing region of the body, while minimizing systemic drug exposure and toxicity. Regional isolation of drug delivery allows for unaffected tissue to be spared from drug exposure, and potential associated toxicity, via complete separation of the regional and systemic circulation; thus dose escalation of therapeutic agents is limited largely by the tissue tolerance of the perfused organ or limb. For agents with a sharp dose-response curve, such as melphalan, improved efficacy manifested via increases in tumor response can be observed as the absence of bone marrow and gastrointestinal visceral exposure to the drug, allowing dose escalation into more clinically relevant dose levels.

Based on its unique vascular anatomy (see Chapter 1B), the liver is a favorable site for delivery of regional therapy (see Chapter 86), as complete control of circulatory inflow and outflow can be readily obtained. Additionally, established tumors in liver derive the majority of blood flow from the arterial tree, and the portal vein is maintained as the primary source of nutrient flow to the hepatic parenchyma, allowing intra-arterial delivery to effectively concentrate drug within tumor-bearing areas of the liver. Animal models demonstrate that nearly 100% of blood delivered to tumors arises from the arterial circulation versus 25% for normal liver (Breedis & Young, 1954; Ridge et al, 1986). The ability to obtain complete vascular isolation also permits the delivery of clinically relevant levels of hyperthermic and/or biologic agents that would otherwise be too toxic or technically impractical to deliver. For patients with multiple hepatic metastases, the likelihood of additional subclinical disease being present within the liver increases with greater tumor volume, and thus the ability to treat the entire diseased organ through regional perfusion strategies allows the targeting of micrometastatic disease within the diseased organ.

The initial report detailing the clinical use of IHP was published in 1961 by Robert Ausman from the Roswell Park Cancer Center, describing his experience with both a porcine treatment model along with five treated patients (Ausman, 1961). In this brief report, evidence of antitumor efficacy was seen in two patients after a 60-minute perfusion with melphalan. Over the ensuing 2 decades, additional small series examined the utility of prolonged hyperthermic perfusions (Skibba & Quebbeman, 1986) without drug, as well as normothermic perfusions utilizing melphalan (Hafström et al, 1990) or mitomycin-C and 5-fluorouracil (5-FU) (Aigner et al, 1988), and were described by Skibba (Medical College of Wisconsin) and multiple European groups, respectively. The absence of long-term follow-up and the presence of significant toxicity prevented widespread adoption of this approach, until interest in the field of regional therapy was reignited by Leinhard and colleagues' 1992 publication that detailed the successful delivery of a combination of melphalan, tumor necrosis factor (TNF), and interferon-α via hyperthermic isolated limb perfusion in a group of 29 patients with advanced extremity sarcoma or melanoma. Clinical results demonstrated a 90% complete response rate for patients with in-transit melanoma along with an 80% limb salvage rate for patients with advanced sarcoma. Of equal or greater significance was the demonstration that meticulous surgical technique could result in very effective vascular isolation with a resultant decrease in out-of-field drug exposure and associated toxicity. When this increased attention to circuit integrity and leak monitoring was applied to patients undergoing IHP, a similar decrease in systemic toxicity permitted more widespread investigation of this clinical approach.

Within the United States, a significant effort in the development and refinement of vascular isolation-perfusion techniques was initiated by Drs. Douglas Fraker and Richard Alexander within the Surgery Branch of the National Cancer Institute (NCI) (Alexander et al, 1998, 1999).

SURGICAL TECHNIQUE

Preoperative evaluation of patients thought suitable for IHP should include an assessment of the patients' overall cardiovascular risk factors, the extent of both intrahepatic and extrahepatic tumor malignancy, and an assessment of the liver functional status (see Chapter 2). Standard preoperative cardiac

clearance should include a treadmill stress test, as the induction of venovenous stress can lead to the induction of atrial fibrillation in patients so disposed. Hepatic reserve is important to assess, as the dose-limiting toxicity observed in Phase I trials was liver based, and it was seen in patients with more than 50% of hepatic replacement with tumor or a serum bilirubin level higher than 3 mg/dL. For patients with colorectal cancer and a significant chemotherapy history that includes either oxaliplatin and/or irinotecan, a biopsy assessment of the uninvolved hepatic parenchyma must be done to rule out extensive portal inflammation, hepatic congestion, and steatohepatitis (see Chapter 65). Patients who have had extensive portal of hepatic venous dissection associated with major hepatectomy should be approached with caution.

IHP is performed under general anesthesia via an upper midline incision, with a right flank transverse extension once extrahepatic disease is ruled out. In patients in whom the primary tumor remains in situ, a full midline incision is indicated. The presence of extrahepatic disease other than periportal lymphadenopathy or primary tumor amenable to complete resection is a contraindication to perfusion.

Preparation of the liver for perfusion includes completion of a cholecystectomy and full mobilization the liver (Alexander, 2005; Libutti et al, 2000). All lateral attachments are taken down so that the vena cava is fully visualized, and all retroperitoneal venous tributaries are taken down to ensure there will be no leak of chemotherapy from the isolated segment of the retrohepatic inferior vena cava (IVC). The duodenum is mobilized, and the IVC is mobilized from the renal veins to the hepatic veins. The right adrenal vein is suture ligated and divided, but both phrenic veins are preserved. The hepatic artery is identified, and the gastroduodenal artery (GDA) is mobilized from its origin for a length of 2 cm to serve as the arterial inflow catheterization site. Nodal tissue in the porta hepatis is dissected to allow clamping of the portal structures, with the hepatic artery clamp proximal to the takeoff of the GDA. Minor accessory right and left hepatic vessels may be ligated, but replaced or accessory arteries of a significant size are prepared for cannulation along with the GDA.

After completion of dissection, the patient is heparinized to an activated clotting time longer than 400 seconds. An external venovenous bypass circuit is established by placing a cannula into the left femoral vein and advancing it into the infrarenal IVC and then advancing a second cannula through the internal jugular vein into the superior vena cava (SVC). This allows maintenance of the systemic circulation by actively shunting IVC blood during treatment. Once the venous bypass has been established, the intrahepatic (IHP) circuit is constructed (see Fig. 89.1), and the GDA is ligated distally. The inflow perfusion cannula is positioned in the proximal GDA; once it has been secured, a cross clamp is placed across the entire porta hepatis, including the common hepatic artery, bile duct, and portal vein. The perfusion outflow cannula is inserted into the retrohepatic IVC via a percutaneous cannulation of the right femoral vein, and a tourniquet is placed around the cannula at the level of the suprarenal infrahepatic IVC. The suprahepatic IVC is then cross clamped, completing the vascular isolation of the liver, and perfusion is initiated; the perfusate consists of approximately 500 mL Ringer's lactate to which 2 U packed red blood cells are added.

Once perfusion is initiated, flow through the isolated circuit is maintained between 400 and 600 mL/min. The routine use of leak monitors has been abandoned, as detectable leak is rare in the presence of a stable circuit reservoir (Barker et al, 1995). Temperature probes are placed into the anatomic right and left lobes of the liver, and the perfusate is heated to maintain hepatic

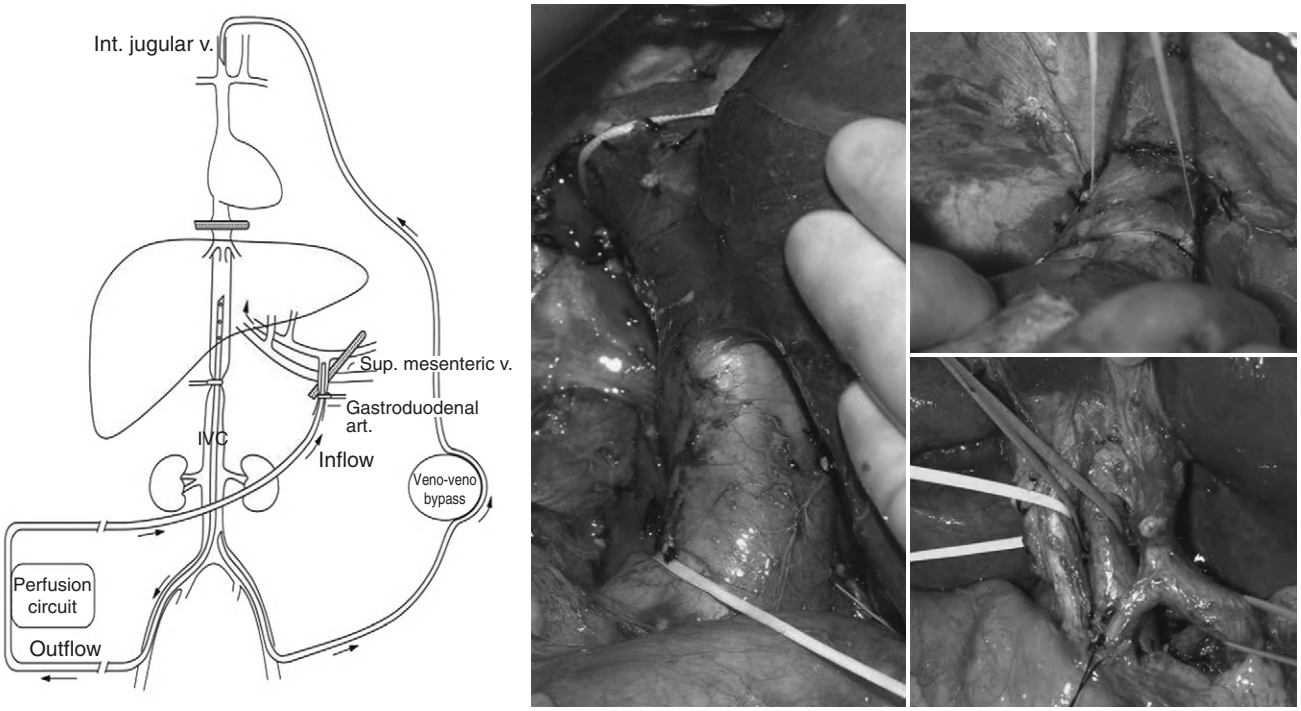


FIGURE 89.1. Schematic of the intrahepatic perfusion circuit, detailing both the hepatic perfusion circuit and the venovenous bypass circuit. The procedure is associated with an extensive dissection of the retrohepatic and suprahepatic inferior vena cava (*IVC*) and a full portal dissection. art., artery; v., vein.

hyperthermia of 40° C. Once hyperthermia is obtained, and perfusion parameters are stable, melphalan (1.5 mg/kg ideal body weight) is administered into the arterial limb of the isolated perfusion circuit over 5 minutes. The liver is perfused for 1 hour, after which time the circuit is flushed with 2000 mL saline and 500 mL colloid to flush all chemotherapy from the hepatic vasculature. The portal and suprahepatic IVC clamps are removed to allow native blood flow to be restored. The GDA is either suture ligated or a hepatic arterial infusion pump is placed. The venovenous bypass circuit is halted, and both the femoral vein and right internal jugular vein catheters are removed; anticoagulation is reversed with protamine and 2 U fresh frozen plasma.

Postoperative care focuses on the maintenance of normal coagulation profiles and standard fluid resuscitation (see Chapter 22). Heparin should be avoided, as high levels of heparin-induced antibodies are common (Masucci et al, 1999); this phenomenon is rare but can lead to devastating consequences, if heparin is administered in the early postoperative setting.

Pharmacokinetic analyses performed during early phase IHP trials have demonstrated that complete vascular isolation is routinely achieved with no detectable levels of melphalan in the systemic circulation (Lans et al, 2001). A small amount of systemic drug observed in the immediate postperfusion period has been addressed by unclamping the portal clamp for 10 seconds during the washout phase, facilitating clearing of the portal circulation. A transient significant elevation of aspartate and alanine transaminases was universally observed but was self-limited and resolved within 7 days. Biliary congestion and cholestatic jaundice is rare when proper patient selection is maintained with regard to underlying liver disease and tumor volume. Overall operative mortality rate is 4% across single-institution experiences (Alexander, 2005), and operative times and blood loss have decreased with the implementation of less invasive catheterization techniques, with operative times of less than 5 hours and mean operative blood loss less than 500 mL. An additional 500 mL of blood loss results from the removal of melphalan-contaminated hepatic circuit blood. Recent dose-escalation studies performed by Zeh and Bartlett at the University of Pittsburgh have demonstrated effective isolation and safety utilizing both 5-FU and oxaliplatin (Colville et al, 2010).

RESULTS

Colorectal Cancer (See Chapters 81A and 86)

The greatest volume of data regarding clinical effectiveness of IHP can be found for patients with metastatic colorectal cancer treated at two institutions: the Surgery Branch of the NCI in Bethesda, MD, and the Leiden Medical Center in the Netherlands. In a series of 154 patients reported by Van Iersel and colleagues (2008), 105 patients were deemed eligible for IHP at laparotomy. A 50% response rate with a median survival of 11.4 months was reported in treated patients, with improved survival associated with the delivery of adjuvant systemic chemotherapy. The primary site of progressive disease was intrahepatic, either in isolation (68%) or associated with other systemic progression (18%).

Alexander and colleagues (2005, 2009) reported a series of 120 patients treated with melphalan-based IHP over an 11-year period ending in 2005 at the NCI in Bethesda. The majority of patients received melphalan alone (n = 69) or in combination with TNF (n = 41), with an additional 10 patients receiving TNF alone. The latter small cohort of patients did not appear to show any clinically meaningful benefit from IHP. Overall, this was a heavily pretreated patient group: 74 patients had received systemic or liver-directed therapy for their metastatic disease. A median overall survival (OS) of 17.4 months was achieved, with a 2-year survival rate of 34% and an overall response rate of 61%. Five treatment-related mortalities were reported, but three of these events were associated with the Phase I dose-escalation portion of the program. A multivariate analysis of factors associated with hepatic progression-free and OS demonstrated that a preoperative carcinoembryonic antigen (CEA) level less than 30 and the ability to successfully administer postoperative hepatic arterial embolization (HAI) therapy with fluorodeoxyuridine (FUDR) (see Chapter 86) were associated with significant gains in both outcomes. Of interest, neither response rate nor duration of survival was impacted negatively with a history of previous chemotherapy, contrary to observations made in other second-line approaches.

Recently, Zeh and colleagues (2009) published a Phase I dose-escalation trial that examined the use of oxaliplatin administered via the IHP circuit, with dosing based upon ideal body weight. Dose-limiting hepatic venoocclusive disease was noted at 60 mg/m^2, establishing the maximally tolerated dose of 40 mg/m^2, at which minimal hepatic toxicity was observed (Zeh et al, 2009). Although only 10 patients were included in this report, the assessment of overall response at 6 months was 66% based on Response Evaluation Criteria in Solid Tumors (RECIST). An additional Phase I trial examining dose escalation of 5-FU paired with fixed-dose oxaliplatin is ongoing (Table 89.1).

Ocular Melanoma (See Chapter 81C)

Ocular melanoma has the unique ability to metastasize to the liver in the absence of clinically apparent extrahepatic disease, with liver failure being a significant source of mortality in this patient population. Of the approximately 4000 patients who have ocular melanoma develop on an annual basis in the United States, nearly 50% will develop metastatic disease; in 80%, the liver will be the sole or life-limiting site of spread. The group from the surgery branch at the NCI reported an overall response rate of 62%, including a 10% complete response in 29 patients treated with melphalan alone via the IHP circuit (Alexander et al, 2003). OS for all treated patients was 12 months, with a median progression-free survival (PFS) of 8 months. In those patients who achieved a response by RECIST criteria, the median duration of response was 10 months, with the majority of patients (66%) experiencing hepatic progression as the initial site of progressive disease. Transient, self-limited grade 3 or 4 toxicity was observed in noted in 19 patients, with no treatment mortalities; however, patient-selection criteria limited treatment to individuals with less than 50% hepatic replacement with tumor, and elevations in preoperative lactate dehydrogenase were observed as a strong predictor of poor outcome.

Several European groups reported similar experiences in cohorts of patients with metastatic ocular melanoma, including Noter and colleagues (2004) and Rizell and colleagues (2008); both supported the results of Alexander and others. Noter and colleagues at the Leiden University Medical Center treated 8 patients with a fixed dose of 200 mg melphalan for 60 minutes;

Table 89.1

Patient and Treatment Characteristics of 120 Patients with Metastatic Colorectal Cancer Undergoing Intrahepatic Perfusion

Number of patients	120
Age in years (range)	52 (22-74)
Female/male	41 : 79
Tumor Characteristics	
Number of metastatic lesions, median (range)	8 (1 to 50)
Percentage of liver replaced by tumor, median (range)	20% (5% to 75%)
Preoperative CEA Level	
Normal	14
High, stable	15
High, increasing	81
Unknown	10
Type of Liver Metastases	
Synchronous	79
Metachronous	41
Prior Chemotherapy	
Chemotherapy for established liver tumors (5-FU/LV and CPT-11 or HAI)	74
Chemotherapy as adjuvant (5-FU/LV, at least 4 cycles)	20
None	26
Perfusion and Operative Data, Median (Range)	
Total melphalan (mg) dosed at 1.5 mg/kg	105 (69-160)
Tumor necrosis factor dose (mg)	1 (0.3-2.0)
Perfusion flow rate (mL/min)	800 (550-1350)
Perfusion pressure (mm Hg)	145 (70-255)
Bypass flow rate (mL/min)	1888 (1300-2520)
Central liver temperature (°C)	40 (39-40.8)
Estimated blood loss (L)	2.0 (0.5-5.0)

CEA, carcinoembryonic antigen; FU/LV, fluorouracil/leucovorin; CPT-11, irinotecan; HAI, hepatic arterial infusion

From Alexander HR Jr, et al, 2009: Analysis of factors associated with outcome in patients undergoing isolated hepatic perfusion for unresectable liver metastases from colorectal center. Ann Surg Oncol 16:1852-1859.

they reported a 50% response rate and median progression-free and OS of 6.7 and 9.9 months, respectively, and 2-year survival was 37.5%. A larger series of 27 patients, with a response rate of 71% and a median OS of 12.6 months, was reported by Rizell. Multiple series consistently report recurrent liver disease to be the greatest threat to patient survival, even after significant treatment responses.

Hepatocellular Carcinoma (See Chapters 80, 86, and 88)

Ku and colleagues (1998) from Kobe, Japan, reported long-term IHP with 60 to 150 mg/m^2 doxorubicin in 28 consecutive patients with multiple advanced HCC. In this group of stage IV patients, the main tumor diameter averaged 7.4 cm, and 17 of 28 patients had macroscopic vascular invasion to the portal vein. The overall response rate was 63% with 5 complete remissions and 12 partial responses. The OS rate was 67% and 39% at 1 and 5 years, respectively. A similar tumor response rate of 64% has been reproduced by the current updating series with 79 patients (Ku et al, 2003), which represents the largest single-institution experience with IHP. In this expanded series, with a mortality rate of 4%, the 1- and 5-year survival rates of stage IVa patients were 81% and 20%, respectively.

The Kobe group also reported results of repetitive IHP combined with reductive hepatectomy for 25 patients with multiple advanced HCCs (Ku et al, 2004) previously deemed to be unresectable. This dual-treatment strategy of surgical resection plus IHP is based on several oncologic advantages: First, a large HCC frequently accompanies feeding arteries from adjacent organs, and these collateral arteries are eliminated at the time of surgical resection. Second, reductive hepatectomy results in decreasing the vascular bed of the liver, which is theoretically beneficial to IHP, because the relative dose rate to the residual tumors is increased. Third, in HCC patients with tumor thrombi in the portal trunk, a life-threatening sequence of events, such as massive ascites, variceal hemorrhage, and eventual hepatic failure, frequently occurs. Such urgent situations could be prevented by the first-stage surgery. In a series of 35 patients with multiple advanced HCCs, the complete response rate was 46% with a partial response rate of 36%; in patients with the disease confined to the liver, the 5-year survival rate reached 51% (Ku et al, 2004).

Other Histologies

Phase II trials examining the utility of IHP for patients with advanced gastrointestinal neuroendocrine tumors (see Chapter 81B) and primary hepatobiliary tumors (see Chapter 50) were reported by the NCI group. Grover and colleagues (2004) described a group of 13 patients who were treated with melphalan (n = 10), melphalan plus TNF (n = 2), or TNF alone (n = 1). A single treatment-associated mortality was observed, along with a response of 50% and a median OS of 48 months. Nine patients with either HCC or cholangiocarcinoma were treated under the same conditions. Baseline tumor volume was significant, with a median percent hepatic replacement of 41%. Overall response rate (all positive response) was 66%, with median PFS and OS of 7.7 and 16.3 months, respectively (Feldman et al, 2004).

PERCUTANEOUS HEPATIC PERFUSION

The greatest weakness of IHP technology is the inability to repeat the procedure secondary to extensive surgical scarring around the IVC, made more acute by the observation that intrahepatic recurrence is common even after significant clinical responses. First reports of a less invasive technique of liver perfusion were published by Curley and colleagues (1993, 1994); utilizing percutaneously catheters and hepatic venous filtration, 80% of doxorubicin administered via the hepatic artery was effectively filtered from the hepatic venous circulation. Ravikumar and colleagues (1994) reported a similar series of 28 patients who underwent 58 treatments with either 5-FU or doxorubicin, but neither series established a clear utility for the technology, and further studies were not completed.

A systematic examination of a refined percutaneous hepatic perfusion (PHP) system was initiated at the Surgery Branch of the NCI in 2001 that utilized melphalan in a formal dose-escalation protocol with results published in 2005. The PHP system uses a double-balloon IVC catheter system (Delcath

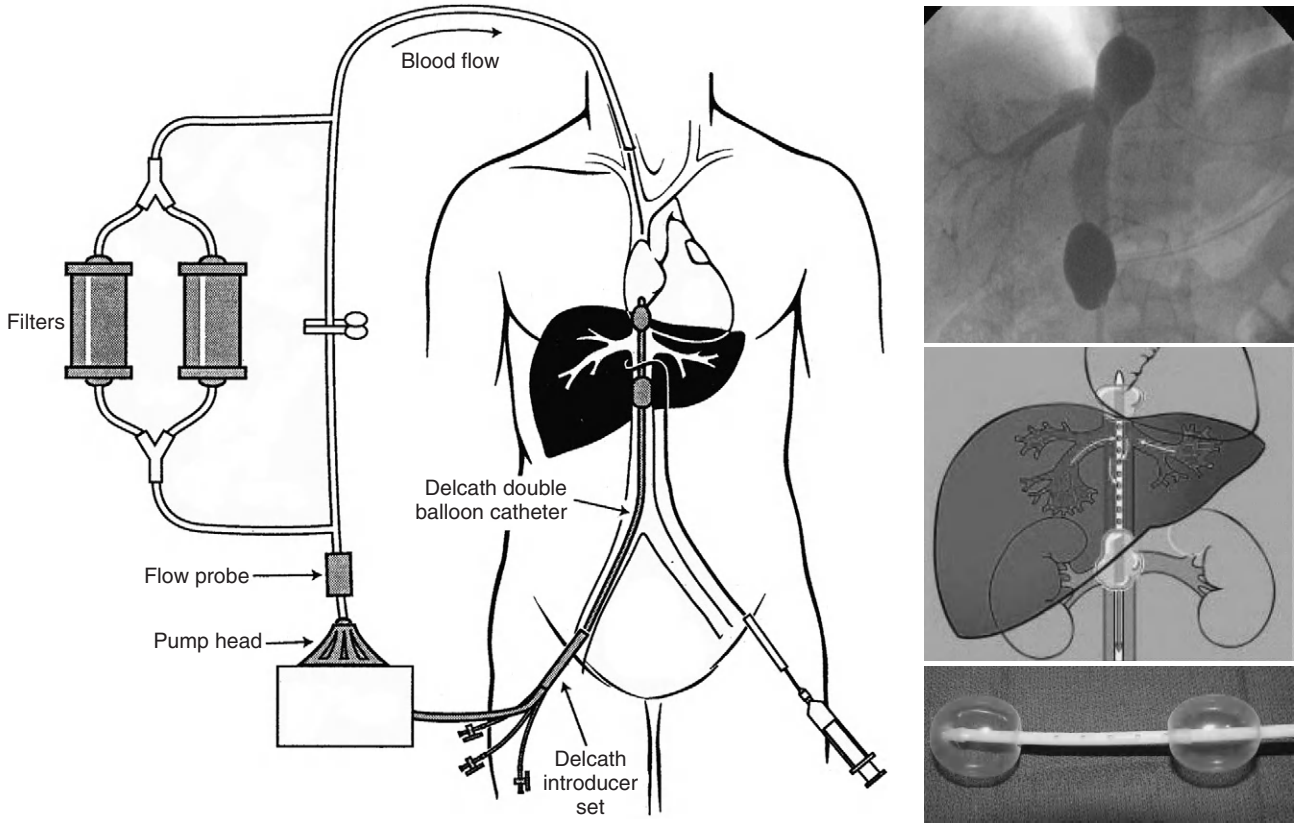


FIGURE 89.2. Schematic of the percutaneous hepatic perfusion circuit with inflow from a catheter introduced via the femoral artery. The double-balloon catheter is pictured, along with a radiograph depicting the catheter with both balloons deployed; isolation of the retrohepatic vena cava and hepatic veins is shown. *(From Pingpank JF, et al, 2005: Phase I study of hepatic arterial melphalan infusion and hepatic venous hemofiltration using percutaneously placed catheters in patients with unresectable hepatic malignancies. J Clin Oncol 23:3465-3474.)*

Systems, New York, NY) to isolate hepatic venous outflow and allow high-dose infusion of chemotherapy to the liver (Fig. 89.2). The main component of the system is a 16-Fr polyethylene double-balloon catheter with one large lumen and three accessory lumina. The two low-pressure occlusion balloons are inflated independently through separate lumina. The cephalic balloon blocks the IVC superior to the hepatic veins, and the caudal balloon obstructs the IVC inferior to the hepatic veins, allowing complete isolation of hepatic venous outflow. The span between the two occlusion balloons consists of a fenestrated segment that feeds into the large, central lumen, which exits the catheter from the proximal end. The additional lumen enters the catheter at a point inferior to the caudal balloon and exits at the distal tip; it serves as a channel for a guidewire and also allows some blood flow from the infrarenal IVC to the right atrium. During the procedure, melphalan is infused through a catheter percutaneously inserted into the hepatic artery. The melphalan perfuses the liver and exits the organ through the hepatic veins. Hepatic venous effluent is collected using the occlusion balloon catheter, and melphalan-dosed blood from the central lumen is pumped through an extracorporeal circuit that consists of a centrifugal pump and hemoperfusion drug-filtration cartridges. Melphalan flowing through the circuit is filtered with two activated-carbon filter cartridges arranged in parallel, and filtered blood is returned to systemic circulation via a venous return sheath inserted into the internal jugular vein. Treatments are administered with patients under general anesthesia (Figs. 89.3 and 89.4)

The completed Phase I study reported 28 patients who underwent 74 treatments (Pingpank et al, 2005). Twelve patients were treated in an initial feasibility cohort at 2.0 mg/kg prior to a 16-patient dose escalation to 3.5 mg/kg, after which dose-limiting bone marrow toxicity was observed in 2 of 6 treated patients. Maximum tolerated dose (MTD) was established at 3.0 mg/kg for a total of four planned treatments per patient. Examination of the venous filtration system revealed a consistent 78.5% melphalan extraction. At the MTD, grades 3 and 4 hepatic and hematologic complications, neutropenia and thrombocytopenia, were observed in 19% and 66% of treated patients, respectively. An overall response rate of 30% was reported across multiple tumor types and at all dose levels, with a 50% response rate noted in the 10 patients with metastatic ocular melanoma.

Two subsequent trials have been reported, including a Phase II cohort of 23 patients with metastatic gastrointestinal neuroendocrine tumors. The overall response rate was 79% in the 19 evaluable patients, with median hepatic PFS and OS of 39 and 40 months, respectively (Pingpank et al, 2008). A recently completed Phase III random-assignment trial that compared PHP with melphalan to standard of care for patients with hepatic metastatic melanoma has been reported. The primary end point of this trial was hepatic PFS, and 93 patients were randomized

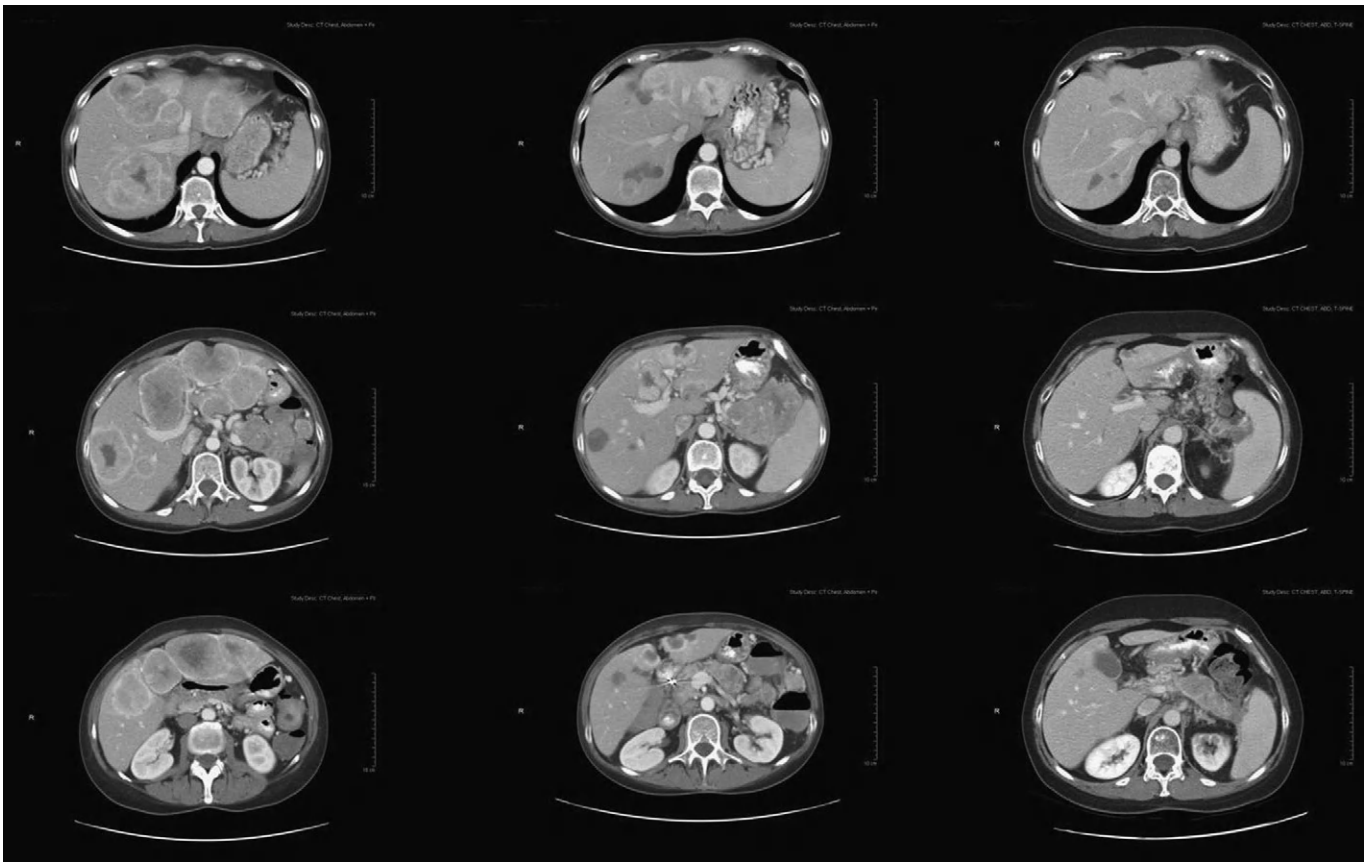
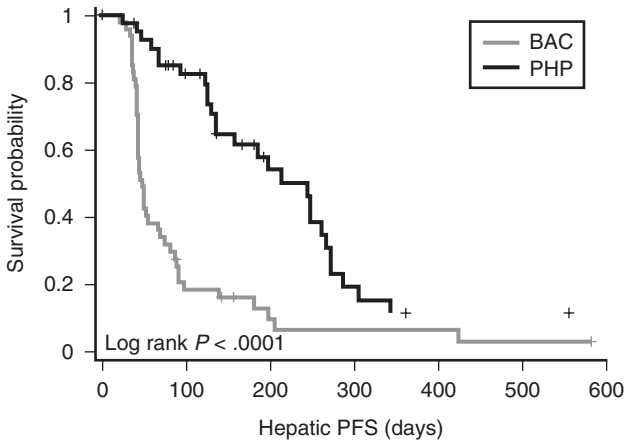


FIGURE 89.3. Response to percutaneous hepatic perfusion. Computed tomographic scans before and after treatment of a patient with multiple hypervascular hepatic metastases from a pancreatic neuroendocrine tumor. *(From Pingpank JF, et al, 2008: High-dose intra-arterial melphalan delivered via percutaneous hepatic perfusion [PHP] for patients with unresectable hepatic metastases from primary neuroendocrine tumors. Proc AHPBA, March.)*



	No. of subjects	Event	Censored	Median Survival (95% CI)
BAC	49	88% (43)	12% (6)	49.0 (43.0 68.0)
PHP	44	61% (27)	39% (17)	245.0 (136.0 267.0)

FIGURE 89.4. Kaplan-Meier assessment of hepatic progression-free survival (*PFS*). The primary end point in the phase III percutaneous hepatic infusion trial versus standard of care was hepatic PFS. BAC, best alternative care; CI, confidence interval; PHP, percutaneous hepatic perfusion. *(From Pingpank JF, et al, 2010: A phase III random assignment trial comparing percutaneous hepatic perfusion with melphalan [PHP-mel] to standard of care for patients with hepatic metastases from metastatic ocular or cutaneous melanoma. Proc ASCO [LBA #8512].)*

at 10 institutions, with 27 of 49 patients crossing over from the standard-of-care arm at hepatic progression. Median hepatic (245 days vs. 49 days; $P < .001$; hazard ratio [HR] .301) and overall (186 days vs. 46 days; $P < .001$; HR, 0.404) PFS were significantly improved on the experimental (PHP) arm of the study. OS was not significantly improved, in part because of the high crossover rate. Overall response rate was 34.1% (15 of 44) for PHP vs. 2.0 % (1 of 49) for best alternative care (BAC) ($P < .001$) (Pingpank et al, 2010).

CONCLUSION

Regional hepatic perfusion with high-dose melphalan provides an important clinical benefit for patients with diffuse hepatic metastases of ocular melanoma not amenable to surgical resection. Both IHP and PHP are well tolerated and effective. Careful patient selection and proper use of appropriate systemic chemotherapy is very important for these patients. The characteristics of the nonspecific alkylating agent melphalan make it an ideal candidate for these systems, as incremental dose-escalation provides meaningful increases in drug efficacy. The use of additional drugs with known therapeutic benefit against colorectal and primary biliary malignancies, such as 5-FU and oxalipatin, is the rational next step in the development of these treatment modalities, and this is underway at a limited number of centers.

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CHAPTER 90A

Hepatic resection: general considerations

Jacques Belghiti and William R. Jarnagin

OVERVIEW

Over a comparatively short period, partial hepatectomy has been transformed from a high-risk, resource-intensive procedure to one that is now performed routinely, often removing a large amount of liver tissue and/or combined with resection of other organs, with the expectation of an uncomplicated postoperative course and recovery in most patients. Although reports of hepatic resection date back to antiquity (see the Introduction to this text), it was Lortat-Jacob's report of an elective right hepatectomy for malignancy in 1952 that ushered in the modern era of hepatobiliary surgery, suddenly creating new possibilities to treat a wide range of disorders (Lortat-Jacob & Robert, 1952); however, from that point forward, the initial experience with hepatic resection was far from promising. In 1977, James Foster and Berman published a multiinstitutional summary of hepatic resection surgery in the United States composed of 168 resections performed over the preceding 14 years. This report documented a marked and unacceptably high operative mortality rate, which was due primarily to two often related factors: inability to control hemorrhage in the operating room and postoperative liver failure (Foster & Berman, 1977).

Since that time, progressive advances in many different areas have led to the improvement in outcome required for hepatic resection to take its place as a mainstream procedure. These advances have come on several fronts, and it is therefore difficult to single out one for special mention. Perhaps the most noteworthy gain has been a greater appreciation of the segmental anatomy of the liver and the willingness and ability of surgeons to pursue resections based on anatomic principles (see Chapters 1B, 90B, and 92). This particular element has had a profound effect, not only improving the results of major resections but spurring greater use of parenchyma-sparing sublobar resections, such as posterior or anterior sectoral hepatectomy or central hepatectomy, rather than right or extended right hepatectomy, respectively. Equally important, this change fundamentally altered the approach to patients who require bilobar resections.

A number of studies have documented this trend over time, and it has been associated with, and is probably responsible for, decreases in blood loss and transfusion rates, reductions in hospital stays, and decreases in operative mortality (Fan et al, 1999; Jarnagin et al, 2002; Belghiti et al, 2000).

Practice changes in other areas, including intraoperative and perioperative management and patient selection, have clearly contributed to the overall improvement in outcomes (see Chapter 22). The use of low central venous pressure (CVP) anesthesia, now widely used, represented a notable change in the previous standard practice of fluid loading prior to resection. Despite concerns of possible risks of air embolization or disturbance of renal function, both unfounded, low-CVP anesthetic management has been shown to reduce blood loss during the resection because of decreased filling pressures and reduced distension of the hepatic veins, and it does so with no significant untoward effects (Cunningham et al, 1994; Melendez et al, 1998).

Beyond the technical aspects of partial hepatectomy, a greater understanding of the impact of resection on the natural history of many diseases, combined with a clearer delineation of perioperative risk, have allowed a much more informed patient-selection process, one that has increasingly targeted resection more effectively to those patients most likely to benefit (see Chapters 49 and 50 and 79 through 81). Additionally, the quality and quantity of the future liver remnant has assumed great importance in patient selection for operations (see Chapter 93). Both of these issues have represented particularly critical developments for patients with hepatic colorectal metastases, for whom the advent of more active chemotherapeutic agents has led to more frequent treatment prior to operation. The latter development has greatly altered the landscape of this disease by allowing many more patients, particularly those with very advanced lesions previously considered surgically

unapproachable, to undergo potentially curative surgery (Adam et al, 2000; Masi et al, 2009); however, while enhancing the results of resection, such therapy has the potential to cause significant hepatotoxicity and increase the risk of postoperative liver failure (see Chapters 65 and 87; Vauthey et al, 2006). In an effort to mitigate the risks in heavily pretreated patients and those with fibrosis or cirrhosis, preoperative portal vein embolization, first introduced 30 years ago, has been used with increasing frequency and has emerged as a powerful tool for inducing hypertrophy of the future liver remnant (see Chapter 93; Makuuchi et al, 1984).

This changing treatment paradigm in patients with hepatic colorectal metastases, with chemotherapy playing an increasingly prominent role, has yet to evolve in other malignant diseases; however, as more effective drugs emerge, it is more than likely that similar changes in practice will be seen in other tumor types. An example of note is biliary tract cancer: recent publication of the results of the ABC-02 trial holds some promise for better results with chemotherapy treatment (Valle et al, 2010).

Advances in imaging technology deserve special mention, as patient selection is continually refined. Whereas radiologic evaluation once required invasive investigations in many cases, it can now provide complete, noninvasive assessment of the liver, including the biliary tree, the arterial and venous anatomy, and the intrahepatic and extrahepatic disease extent in the case of malignant disease (see Chapters 13, 16, and 17). Indeed, for certain tumors, classic imaging findings are now considered pathognomonic and have supplanted the need for a biopsy. Specific examples in this regard include liver hemangiomata and focal nodular hyperplasia (see Chapter 17) and the guidelines for the diagnosis of hepatocellular carcinoma (Bruix & Sherman, 2005). Going forward, advances in imaging technology likely to influence the practice of hepatic resectional surgery include computer-aided reconstruction, functional imaging, and intraoperative navigation (Cherqui & Belghiti, 2009; Chopra et al, 2010).

Technical progress in other areas, particularly with devices such as vascular staplers and those used to transect the liver parenchyma (see Chapter 90B), is often hailed as a significant advance; however, although their value should not be dismissed, they cannot overcome poorly conceived or poorly executed operations, and their relative contribution, compared to the enhancements in other aspects, is modest at best.

Advances in imaging have also played a major role in postoperative management, particularly in diagnosing and treating postoperative complications. Over the past several years, the marked reduction in operative mortality after hepatic resection has seemingly occurred with little obvious change in morbidity (see Chapter 25). This observation suggests an overall improvement in the ability to salvage patients who experience significant complications. The ready availability of high-quality imaging and a heightened sense of awareness of the perioperative problems that may occur have led to earlier detection of complications. These changes, combined with the ability to manage many problems percutaneously or endoscopically, rather than operatively, have clearly had a major impact on perioperative outcome.

CONCLUSION

This chapter has detailed the contemporary approach to hepatic resection for a wide variety of diseases and indications (see Chapters 90B, 90C, and 90F), including the technical aspects of partial hepatectomy for living-donor transplantation (see Chapter 90D), and advances in minimally invasive approaches (see Chapter 90E) in particular, which represents a remarkable evolution in hepatic surgery; continued technical progress will certainly bring laparoscopic and robotic approaches to resection further into the mainstream. The descriptions herein reflect the current state of the art, built upon the collective contributions of many pioneering surgeons over the past several decades and continuing to the present. The techniques and approaches discussed include, to some degree, the biases of the authors; however, the overriding theme is always adherence to best principles of hepatic resection surgery, and alternative viewpoints must be considered where appropriate.

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CHAPTER 91A

Vascular isolation

Jacques Belghiti and O. Scatton

OVERVIEW

Bleeding and subsequent blood transfusions remain important causes of death and morbidity with hepatectomies. Evidence also shows that blood transfusion may be associated with an increased risk of recurrence of malignancy through impairment of the patient's immune response (Asahara et al, 1999; Tung-Ping Poon et al, 2000). Vascular clamping, irrespective of its modality, minimizes the risk of bleeding during liver resection. Liver cell injury induced by ischemia and reperfusion is the major drawback of clamping. Overall, normal liver tolerates up to an hour of warm ischemia, but diseased liver with fibrosis, steatosis, inflammation, and vascular or biliary disease requires much shorter periods of ischemia. Indeed, the vast majority of liver resections are performed in such diseased livers, including resections of hepatocellular carcinoma (HCC) (see Chapters 70 and 81A) and of liver metastases, which are more often performed after chemotherapy and can induce parenchymal changes (chemotherapy-associated steatohepatitis, sinusoidal obstruction syndrome) (see Chapters 65 and 81A).

With technical improvements in liver surgery, patients with various underlying liver conditions—such as fibrosis, steatosis, or chemotherapy-induced injury—are undergoing complex and extensive liver resections (Belghiti et al, 2000; Poon et al, 2002). In this regard, pedicular intermittent clamping, which alternates short periods of clamping with intervals of restoration of blood flow, has been shown to be the best tolerated clamping modality, especially in patients with diseased liver parenchyma (Belghiti et al, 1999; Man et al, 1997). Although a real advantage in clinical practice was not demonstrated (Gurusamy et al, 2009), ischemic preconditioning that initiates a short period of clamping and restoration of blood flow followed by continuous clamping is an attractive concept (Clavien et al, 2000). On the other hand, better understanding of vascular anatomy, particularly of the venous tributaries; better anesthesiologic management with perioperative low filling (restrictive fluid administration); and the development of modern tools of transection and coagulation, such as the ultrasonic dissector associated with bipolar coagulation, have made possible even major liver resection without vascular clamping or transfusion. Therefore if vascular clamping must be applied, balancing its efficacy to control bleeding with the potential side effects of ischemic liver injury is vital.

This chapter describes techniques, benefits, drawbacks, and hemodynamic monitoring of vascular control of the most appropriate technique for each patient's requirements.

ANATOMIC BASIS FOR VASCULAR CONTROL

The liver receives a dual vascular inflow that provides approximately one quarter of the total cardiac output, or a blood flow of 1500 mL/min. The portal vein provides 75% of the total hepatic blood flow, and the hepatic artery provides the remaining 25%. The portal vein originates behind the neck of the pancreas at the confluence of the superior mesenteric and splenic veins, and it courses posterior to the bile duct and hepatic artery in the free edge of the lesser omentum. At the hilum of the liver, the vein divides into a shorter, more vertically oriented right branch and longer, horizontally oriented left branch. The right portal branch may be absent when the right anterior and posterior sectorial veins originate directly from the trunk of the portal vein, thus the right portal branch can be more difficult to dissect and control than the left portal branch.

The hepatic artery is highly variable, but it most commonly arises as a branch of the celiac axis and enters the hepatoduodenal ligament after providing the right gastric and gastroduodenal arteries; the right and left branches usually lie on a plane posterior to the bile ducts at the hilum of the liver. In fact, this classic branching pattern is found in only 50% of patients. The accessory or replaced arteries pertinent to vascular clamping include a left artery, which can arise from the left gastric artery (25% to 30%), and a right artery, which can arise from the superior mesenteric artery (17% to 20%).

Three large hepatic veins lie posterosuperior to the liver just below the diaphragm and form the major drainage of the liver (Fig. 91A.1). The right hepatic vein is a short, wide trunk formed by the convergence of an anterior trunk situated in the right portal fissure, which drains mainly segments V and VI, and a posterior trunk, which drains mainly segment VII. The right hepatic vein also drains part of segment VIII. The middle hepatic vein is situated in the plane of principal portal fissure; it drains the entire central sector and receives the veins from segments V and VIII at its right border and the veins of segment IV at its left border, thus forming the major drainage vein of segment IV and part of segments V and VIII. The left hepatic vein arises from the confluence of the segment II and III veins. It often receives drainage from the posterior part of segment IV, and it terminates as a short common trunk with the middle hepatic vein in the majority. In 10% to 20% of cases, a significant right inferior hepatic vein may be found (>5 mm diameter), which mainly drains segment VI. In addition to these, there are two groups of accessory hepatic veins, the right and the left. The right accessory veins drain the posterior part of the dorsal sector. On the left, they are formed by the veins of the caudate lobe. In half of the cases, a large solitary vein terminates in the inferior vena cava (IVC); in the other half, two or three veins are present, and they end in a staged fashion in the left border of the IVC. These anatomic variations are important in the context of vascular clamping, as the presence of large drainage veins can result in the inability to achieve complete vascular control during the clamping procedure (see Chapter 1B).

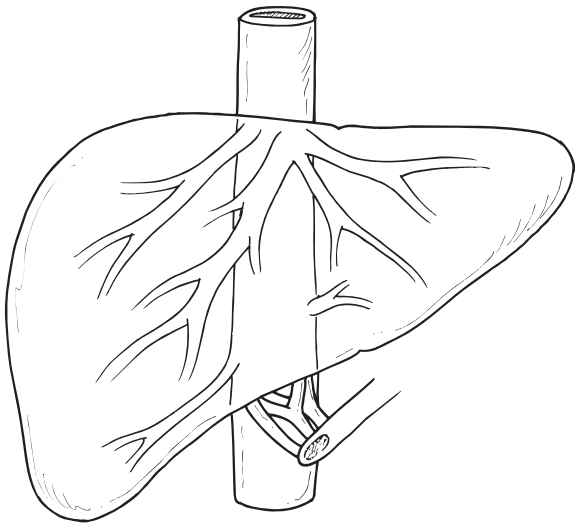


FIGURE 91A.1. Venous drainage of the liver depicting the major hepatic veins and their tributaries.

HEMODYNAMIC RESPONSE TO DIFFERENT TYPES OF CLAMPING

Hemodynamic changes are proportional to the type and extent of vascular interruption. These changes are also related to several factors, including the level of anesthesia, quantity and rapidity of bleeding, vascular filling, and spontaneous adaptation of the circulatory system to the reduction of venous return. Pedicular clamping is nearly always well tolerated, but the addition of caval clamping is more likely to be followed by major hemodynamic consequences (Table 91A.1).

Hemodynamic Response to Pedicle Clamping

The pedicular clamping, which leads to a moderate decrease in cardiac preload with a 5% decrease in pulmonary artery pressure and a 10% decrease in cardiac index, is paradoxically associated with a 10% increase in mean arterial pressure because of a sympathetic reflex after arterial clamping that induces a significant increase in systemic vascular resistance (Delva et al, 1987). Therefore isolated pedicle clamping is usually well tolerated and does not require specific anesthetic management. During the period of declamping, blood pressure is restored to normal or even shows an increase from the baseline; however, it is a frequently observed phenomenon that, as the cycle of clamping and declamping progresses, declamping causes more significant hypotension. This phenomenon, which can be observed when the cumulative period of clamping lasts 1 hour, may be attributed to a reperfusion-like syndrome as a result of the long-term ischemia of liver parenchyma and splanchnic release of toxic vasodilators; therefore it is recommended to increase the duration of declamping during each cycle, if the cumulative duration is prolonged more than 1 hour, especially in patients with diseased liver (Imamura et al, 2003).

Hemodynamic Consequences and Limitations of Hepatic Vascular Exclusion

The hemodynamic consequences of the addition of total caval clamping to pedicular clamping is more profound (see Table 91A.1). Hepatic vascular exclusion (HVE), which leads to a severe decrease in cardiac preload with 25% decrease in pulmonary artery pressure and 40% to 50% decrease in cardiac index, is associated with a 10% decrease in mean arterial blood pressure despite a 50% increase in heart rate and a very significant increase in systemic vascular resistance. Reduced venous return produces a marked reduction in left ventricular and diastolic volume that could be precisely monitored by transesophageal echocardiography (Eyraud et al, 2002). The sequence of HVE includes initial inflow occlusion followed by infrahepatic caval clamping and then suprahepatic caval clamping. The compensatory cardiac response to maintain blood pressure requires approximately 5 minutes and is facilitated by "preloading" the patient with intravenous fluids. A fall in mean arterial pressure less than 80 mm Hg suggests intolerance to HVE and should lead to consideration of caval declamping. Ventricular dimensions could be monitored by transesophageal echocardiography (Eyraud et al, 2002).

Causes of hemodynamic intolerance to HVE include 1) inadequate fluid loading, 2) hepatic congestion as a result of persistent inflow (see below), and 3) inadequate cardiovascular response. Insufficient fluid loading is likely to occur in case of fluid restriction and unexpected need for caval occlusion without adequate preparation of the patient. In addition, the 10% of patients who cannot increase their cardiac output are difficult to identify preoperatively.

ANESTHETIC CONSIDERATIONS (SEE CHAPTER 22)

Liver surgery requires continuous collaboration and communication among experienced surgeons and anesthesiologists. Historically, liver resections were associated with significant hemorrhage; hence, anesthesiologists tend to overload patients with intravenous fluids to minimize the hemodynamic consequences of blood loss. This approach has paradoxically

Table 91A.1

Hemodynamic Changes Observed During Various Methods of Clamping

Clamping Technique	Portal Pressure	Caval Artery Pressure	Pulmonary Index	Cardiac Resistance	Vascular Pressure	Arterial Procedure
Pedicle clamping	Severe increase	No change	Slight decrease	Slight decrease	Moderate increase	Slight increase
HVE	Severe increase	Moderate increase	Moderate decrease	Moderate decrease	Severe increase	Slight decrease
HVE with preservation of caval flow	Severe increase	No change	Moderate decrease	Slight decrease	Moderate increase	No change

HVE, hepatic vascular exclusion

aggravated operative blood loss even during pedicular clamping as a consequence of backflow bleeding from the hepatic veins, and this is increased by increased filling. One of the main advances in the past decade was the ability of anesthesiologists to maintain a low central venous pressure (CVP) during hepatectomy.

Low Central Venous Pressure Anesthesia and Limited Filling

The CVP directly influences the occurrence of back bleeding during liver inflow occlusion. In a retrospective study, Smyrniotis and colleagues (2004) showed that the Pringle maneuver at a CVP of 6 mm Hg or more is associated with greater blood loss than the maneuver performed at a CVP of 5 mm Hg or less. Thus the concept of low CVP anesthesia during hepatectomy has emerged. Maintaining a low CVP during hepatic transection reduces the distension of hepatic veins and thus significantly decreases bleeding (Jones et al, 1998). It also avoids vena caval distension and thus facilitates safe dissection of the retrohepatic vena cava and major hepatic veins. As the blood loss resulting from a vascular injury is proportional to the pressure gradient across the vessel wall and to the fourth power of the radius of the injury, lowering the CVP to one fifth will decrease the blood loss by a factor greater than 5 (Melendez et al, 1998).

Low CVP during liver transection is consistently associated with reduced blood loss (Chen et al, 2000; Cunningham et al, 1994; Eid et al, 2005; Jones et al, 1998; Melendez et al, 1998; Wang et al, 2006). Moreover, in retrospective studies, low CVP tends to be associated with lower postoperative morbidity and reduction of hospital stay (Chen et al, 2000; Smyrniotis et al, 2004).

The potential drawbacks of low CVP anesthesia include perioperative occurrence of air embolism, requirement for pressor agents, and postoperative renal dysfunction. The incidence of gas embolism varies according to the approach and the surgical technique used for parenchymal transection. During a laparoscopic approach, transesophageal echocardiography detects, in nearly all cases, small volumes of air embolism (Schmandra et al, 2002, 2004). During liver resection using ultrasonic devices, air embolism was detected in all the patients who underwent liver resection with an ultrasonic surgical dissector (Koo et al, 2005). Although in the previous study, nearly half of the patients had air embolism filling more than half the right heart diameter, the incidence of clinically relevant accidents is rarely defined. Zhou and colleagues (2008) found an incidence of three cases in 110 liver resections performed with inflow occlusion, and liver surgery complicated by gas embolism accounted for 4% of the patients treated in a referral center for hyperbaric treatment (Bessereau et al, 2010).

Gas embolism usually originates in the venous system from hepatic vein injury through the parenchymal resection stump. Venous gas embolism can lead to arterial paradoxical embolism favored by a patent foramen ovale or intrapulmonary arteriovenous pulmonary shunting (Lee et al, 2002). During hepatic surgery, gas embolism is usually recognized by a sudden drop in end-tidal expiratory carbon dioxide, followed by a subsequent drop in arterial blood pressure or sudden cardiac arrest (Adachi et al, 2006). Arterial systemic embolism can cause arterial ischemia in cerebral, myocardial, spinal, or limb circulation (Lee et al, 2002). Gas embolism is considered a medical emergency, and treatment includes interruption of the embolic procedure, an attempt to extract intravascular gas, external cardiac massage, and immediate oxygenation. Despite an absence of high-level evidence, hyperbaric oxygen therapy is recommended in case of cardiac arrest or in any patient with an unexpected neurologic abnormality following a risky procedure (Blanc et al, 2002; Trytko & Bennett, 2008). But it should be kept in mind that hyperbaric therapy can be limited by the location of hyperbaric chambers, necessitating the transfer of critically ill patients; the ability of those chambers to be used to care for critically ill patients during the therapy; and the risk of hyperoxic seizures and barotrauma (Bessereau et al, 2010; Edsell & Kirk-Bayley, 2009).

The risk of postoperative renal failure linked to low-CVP anesthesia has been suggested in the setting of liver transplantation (Schroeder & Kuo, 2008). During liver resection, the incidence of postoperative renal dysfunction related to low intraoperative volemia has not been clearly established (Melendez et al, 1998). The ability of patients to tolerate fluid restriction in terms of renal function with improved recovery has led some authors to use a restrictive fluid policy in liver surgery. It has been shown in living donor resection that CVP monitoring did not reduce blood loss when a low-infusion policy was routinely applied (Niemann et al, 2007).

Maintaining Low Venous Backflow (See Chapter 22)

The anesthesiologist can maintain a low venous backflow by several methods. Fluid restriction during induction and liver transection is the most commonly used method. Intravenous fluids are given at a rate of 0.5 to 1 mL/kg/h, until the hepatic resection is complete. The patient is brought back to normovolemia at the end of surgery, and hemostasis is ensured. Other methods commonly used are the use of anesthetic gases such as isoflurane, which has systemic vasodilatory properties and results in minimal cardiac depression (Gatecel et al, 2003), and the use of certain drugs that produce vasodilatory effects. Although low tidal volume ventilation was considered to reduce the backflow bleeding, no evidence is available to support that this maneuver reduces the quantity of blood lost during the hepatic transection phase (Hasegawa et al, 2002). The surgeon can decrease the backflow bleeding by partially or totally clamping the infrahepatic IVC. This technique, which decreases venous return, has been shown to have no deleterious effect on renal function, even with a clamping time of up to an hour (Otsubo et al, 2004). The ideal tool for hemodynamic monitoring under these circumstances remains to be determined, although transesophageal echocardiography and pulmonary artery catheterization can be used (Eyraud et al, 2002). Intraoperative monitoring of fluid responsiveness could also be implemented noninvasively, using respiratory variations in arterial pulse pressure or monitoring of peripheral venous pressure (Choi et al, 2007; Solus-Biguenet et al, 2006). In experienced centers, CVP monitoring did not show any significant advantage (Niemann et al, 2007).

Special Considerations During Hepatic Vascular Exclusion

Application of vascular isolation techniques mandates a high level of anesthetic expertise. Intraoperative management of patients undergoing vascular exclusion should include the use

of pulmonary artery catheterization and occasionally of transesophageal echocardiography. When a major hepatectomy performed under HVE is planned, anesthetic management is adjusted to anticipate the reduction in venous return, sudden decrease in cardiac output, and increase in afterload. Volume expansion is usually required for patients undergoing HVE. This is achieved by rapid infusion of 500 mL of colloids before cross clamping of the vena cava. In patients who do not tolerate caval cross clamping, even after volume expansion, vasopressor agents such as noradrenaline are added (Redai et al, 2004). Persistent hypotension and/or low cardiac index, which can occur in 10% to 20% of patients, should be considered intolerance to HVE and is an indication to unclamp the vena cava or to consider the use of venovenous bypass (Redai et al, 2004).

SURGICAL ASPECTS OF VASCULAR CLAMPING

The easiest procedure to reduce bleeding during liver resection is inflow control. Pedicular clamping, which controls the inflow, has little hemodynamic consequence and offers the greatest efficiency in association with low filling. Continuous clamping, which increases ischemic injury of the liver parenchyma, induces splanchnic congestion as well. Intermittent clamping has supplanted the use of continuous pedicular clamping to overcome these two drawbacks; however, patients with large tumors involving the caval-hepatic confluence may require additional outflow vascular control.

Inflow Vascular Clamping

The hepatic pedicle clamping (Pringle maneuver), which interrupts the arterial and portal venous inflow to the liver, is a standard in hepatic surgery. According to the Cochrane database, in elective resection, intermittent portal triad clamping seems better than continuous clamping, especially in patients with diseased parenchyma; therefore intermittent triad clamping could be recommended as the gold standard method of clamping (Gurusamy et al, 2007).

Total Inflow Control

Inflow control implies an encircling of the hepatic pedicle (Fig. 91A.2). Adhesions to the gallbladder are freed, and the lesser omentum is opened at the level of the pars flacida, taking care to avoid injury to the right gastric pedicle. A finger or a blunt dissector may thereafter be easily passed through the foramen of Winslow, and the hepatoduodenal ligament is encircled with tape. Clamping is easily achieved by a vascular clamp or tourniquet, which should be closed until the pulse in the hepatic artery distal to the clamp is stopped; excessive closure should be avoided, as it may otherwise result in arterial or biliary injury. Care should be taken to avoid lymph nodes of the hepatoduodenal ligament, as these may be large in cirrhotic patients or in patients with a long-standing cholestasis. A search for a left hepatic artery originating from the left gastric artery is mandatory to prevent persistent bleeding during parenchymal transection. When a left hepatic artery exists, simultaneous occlusion of this vessel should be performed to complete the vascular inflow control.

In patients who have undergone previous abdominal surgery, dense adhesions may lie between the right lateral and posterior aspects of the hepatoduodenal ligament, and the portal vein in particular, and the anterior surface of the IVC and segment I. Adhesions may form between the duodenum, greater omentum, and the anterior aspect of the hepatoduodenal ligament. All these adhesions should be lysed prior to pedicular clamping to avoid accidental injury to the vena cava or the duodenum. A safe approach is to expose the IVC in its retropancreatic portion by a Kocher maneuver and to progress cranially.

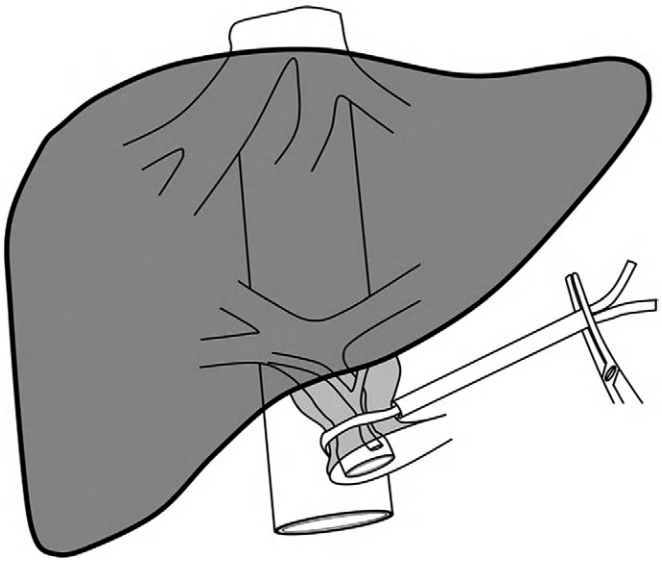


FIGURE 91A.2. Hepatic pedicle clamping (Pringle maneuver) occludes the arterial and portal inflow of the liver.

Continuous Clamping

Continuous clamping implies interruption of inflow continuously during the hepatic transection phase without intermittent release to allow reperfusion. Although conceptually very efficient to control bleeding, it is used less frequently, as it is not universally effective and has several disadvantages (Table 91A.2). The efficacy is limited by its inability to control the backflow bleeding, which is increased if the CVP is high or the patient has large hepatic tumors that compress hepatic veins associated with multiple venous collaterals.

Disadvantages of continuous clamping include splanchnic congestion and prolonged parenchymal ischemia. The splanchnic congestion and fluid sequestration in the visceral compartment cause bowel edema, which takes a long time to subside, leading to difficulties in the closure of the abdominal cavity at the end of the operation and to prolonged postoperative ileus. A difficult closure of the abdomen can lead to abdominal compartment syndrome with subsequent effects on the intraabdominal organs (Moore et al, 2004). Development of edema will be detrimental to bowel anastomoses, especially in the context of synchronous hepatic resections for colorectal malignancies (Elias et al, 1995). Continuous clamping has been shown to induce hyperamylasemia, and it can lead to clinically significant pancreatitis in some patients (Miyagawa et al, 1994, 1996). Interruption of splenic venous return without arterial interruption poses a risk for spontaneous splenic rupture during prolonged continuous clamping (Emree et al, 1993). Continuous clamping causes prolonged ischemia to the liver. Normal liver can tolerate inflow occlusion under normothermic conditions

Table 91A.2

Comparison of Relative Technical Difficulty, Control of Blood Loss, and Physiologic Tolerance for Various Clamping Techniques

Clamping Technique	Technical Difficulty	Hemodynamic Tolerance	Hepatic Tolerance	Prevention of Bleeding	Contraindications	Complications
No clamping	—	Most	Most	Least	—	Bleeding requiring transfusion
Intermittent hepatic pedicle clamping	Least	Most	Intermediate	Intermeidate	—	—
Continuous hepatic pedicle clamping	Least	Most	Least	Intermediate	Diseased liver	Splanchnic congestion
Hepatic pedicle and infrahepatic IVC clamping	Least	Intermediate	Intermediate*	Intermediate	Low CVP	—
Partial pedicle clamping	Intermediate	Most	Most	Most	Pedicular involvement	—
HVE (classic)	Intermediate	Least	Least	Least	Diseased liver; cardiac disease	Splanchnic congestion; renal dysfunction
Intermittent HVE with preservation of caval flow	Most	Intermediate	Intermediate	Most	Juxtacaval tumors	—

*Intermittent
CVP, central venous pressure; IVC, inferior vena cava; HVE, hepatic vascular exclusion

for up to 60 minutes (Delva et al, 1989; Huguet et al, 1992), but diseased livers are much less tolerant of extended ischemia, so continuous clamping cannot be applied to diseased livers for very long. Moreover, restoration of blood flow after prolonged clamping can cause reperfusion syndrome characterized by hemodynamic disturbances as a result of the release of toxic metabolites and vasodilators from the liver and the splanchnic bed (Kim, 2003; Kim et al, 2002). Intermittent clamping has been introduced to overcome these drawbacks of continuous clamping.

Intermittent Clamping

Intermittent inflow occlusion with intervals of reperfusion reduces the consequences of splanchnic congestion and decreases the ischemic injury to the liver parenchyma. After a short period of pedicular clamping, ranging from 10 to 20 minutes, the inflow is restored for 5 to 10 minutes, according to the duration of the transection, underlying liver status, and surgeon preference (Imamura et al, 2003). Classically, each cycle comprises 15 minutes of clamping followed by 5 minutes of reperfusion (Belghiti et al, 1999; Capussotti et al, 2003; Hardy et al, 1995; Man et al, 1997; Takayama et al, 1998). Although a randomized, controlled trial (RCT) that compared the short-term outcome of hepatectomy using intermittent clamping with an ischemic interval of 15 minutes instead of 30 minutes, with 5 minutes of reperfusion, showed no significant difference (Esaki et al, 2006), most authors favor 10 to 15 minutes of clamping.

Genuine intermittent clamping requires a true period of unclamping, which implies that the surgeon should not continue transection during the period of unclamping. This interval, during which the surgeon applies gentle compression to the transected surface, can be used to reexamine the adequacy of the transection line with respect to the vascularization and the oncologic margin. The period of revascularization gives the surgeon an opportunity to visualize the healthy color of the remnant liver. Intraoperative ultrasonography (US) can be performed to confirm the adequacy of inflow and outflow of the remnant liver and to examine the progress and direction of transection in relation to tumor margin.

Intermittent pedicle clamping, the most commonly used vascular clamping modality, has gained wide acceptance, as it is technically simple, effective in control of hemorrhage, and is well tolerated, above all, by diseased liver. Intermittent clamping of a diseased liver has no significant deleterious effects, even if the cumulative clamping time is up to 1 hour (Takayama et al, 1998). Two randomized, controlled studies compared continuous versus intermittent portal triad clamping and found that, although significantly more bleeding was noted in the intermittent group during parenchymal transection, no statistical difference was reported in the total operative blood loss (Belghiti et al, 1999; Capussoti et al, 2003). The most important result, however, was the better tolerance of diseased liver to intermittent clamping (Belghiti et al, 1999); thus the application of intermittent clamping in normal livers has prolonged the total clamping duration by up to 3 hours, which allows surgeons to perform even complex hepatic resections with minimal blood loss (Sakamoto et al, 1999).

The wide safety margin of intermittent pedicle clamping has served to promote its safe use in donor hepatectomy in living donor liver transplantation (LDLT). This has not jeopardized donor safety, nor has it compromised graft function (Imamura et al, 2002, 2004). The use of intermittent clamping enables a bloodless resection, thus it adds to donor safety, suggesting that surgeons should not hesitate to use this technique during surgery for live donation (Imamura et al, 2002, 2004). The better tolerance of intermittent ischemia has stimulated investigators to further explore the possible benefits of preconditioning.

Preconditioning

A newer perspective on inflow vascular clamping has emerged from study of the biologic response to ischemia and reperfusion (Clavien et al, 2000; Hardy et al, 1996). A period of ischemia followed by reperfusion of the liver not only protects the liver from the negative effects of any subsequent period of ischemia, but it may also protect distant organs from the systemic effects of organ ischemia; recognition of this phenomenon led to a study of this technique in humans. Clavien and colleagues (2000) revealed that an initial period of ischemia (10 minutes) followed by reperfusion (10 minutes) protects the liver against subsequent prolonged ischemia, and the authors postulated that some of the benefits of intermittent clamping may actually result from the impact of the first clamp-unclamp sequence as a preconditioning treatment.

In addition, preconditioning followed by continuous clamping may have the advantage of avoidance of blood loss during the unclamped period, although no major differences have been shown in terms of blood loss between the continuous versus intermittent clamping approaches. In a prospective randomized study, the authors showed that this protective strategy against hepatic ischemia was shown to be efficient, especially in the presence of steatosis (Clavien et al, 2003); however, the beneficial effect of preconditioning was shown only for 30 minutes of continuous clamping and only for a small volume of liver resection.

Although the theoretic advantage of a hepatoprotective effect of preconditioning is definitely attractive, in practice this procedure has not been shown to have significant advantages over intermittent clamping. An RCT that compared ischemic preconditioning versus continuous clamping (Chouker et al, 2004) showed improved cardiovascular stability by lowering the need for catecholamines after liver reperfusion. In contrast, a third RCT (Azoulay et al, 2006) did not confirm a beneficial effect of ischemic preconditioning. Furthermore, the application of ischemic preconditioning in the setting of liver transplantation has not been shown to be beneficial compared with conventional liver-harvesting methods for deceased or living donors (Azoulay et al, 2005; Koneru et al, 2005). In addition, a recent Cochrane analysis found no statistically significant difference in mortality rate, liver failure, blood loss, or hemodynamic changes (Gurusamy et al, 2007).

Pharmacologic preconditioning is a promising field, as a variety of substances have been proven effective in animal experiments, although very few concepts have made the transition to being applied to humans. In one RCT (Beck-Schimmer et al, 2008), 64 patients undergoing liver surgery with inflow occlusion were randomized to 30 minutes of intraoperative preconditioning with sevoflurane or anesthesia with propofol. Thirty minutes before inflow occlusion, propofol was replaced by sevoflurane in the preconditioning group, and it was found that preconditioning with sevoflurane significantly reduced postoperative aspartate aminotransferase and alanine transaminase levels. Furthermore, the overall incidence of postoperative complications and the number of major events was reduced, and this beneficial effect was stronger in patients with hepatic steatosis.

Topical Hypothermia

As hepatic inflow occlusion carries a serious risk of ischemic injury to the remnant liver, induction of hypothermia was proposed to reduce the injury, particularly in patients with underlying liver disease (Kim et al, 1994, 2004). The adverse hemodynamic effects of systemic hypothermia has led some authors to use topical cooling by placing ice packs or ice slush on the liver surface (Imakita et al, 2000; Yamanaka et al, 1998); using such techniques, ischemic time could be prolonged for more than an hour in diseased livers, especially if the hepatic core temperature fell below 30° C (Kim et al, 2004).

Selective Inflow Control

Selective inflow control selectively interrupts the arterial and portal venous inflow to the hemiliver to be resected. The advantages of this procedure include 1) clear demarcation of the limits of resection, 2) absence of ischemic injury of the remnant liver, 3) absence of splanchnic congestion, and 4) hemodynamic disturbances. Selective inflow control was specifically devised for segmental and subsegmental resections for small hepatocellular carcinomas in diseased liver (Shimamura et al, 1986; Castaing et al, 1989). Additional clamping of the ipsilateral hepatic vein can also be performed along with this procedure for better vascular control (Makuuchi et al, 1987; Fig. 91A.3) With the wider use of intermittent clamping, selective clamping techniques have not gained wide acceptance, as this is more technically demanding and has no obvious beneficial effects compared with genuine intermittent clamping. In a prospective controlled study that included patients who underwent minor resection, both techniques were associated with similar blood loss and postoperative complications (Figueras et al, 2005); however, induction of lesser cytolysis was observed in those in the cirrhotic group who underwent selective clamping.

TECHNICAL ASPECTS. After encircling the pedicle and performing cholecystectomy, the portal vein is approached

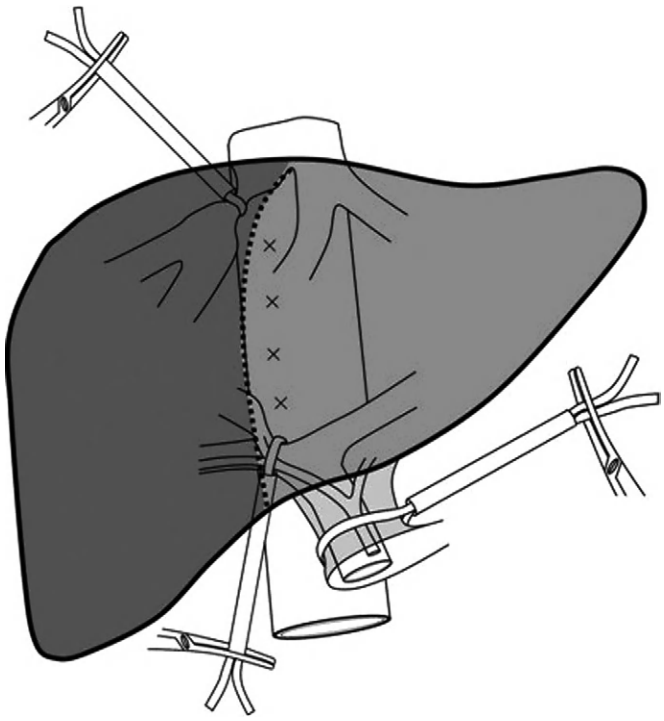


FIGURE 91A.3. Hemihepatic vascular clamping interrupts the inflow and outflow of the hemiliver to be resected.

posterolaterally from the right to avoid devascularization of the common bile duct. Care must be taken to avoid inadvertent injury to a right hepatic artery arising from the superior mesenteric artery. The main portal vein is dissected caudally to cranially on its anterior surface up to the bifurcation. During the dissection of its posterior surface, the consistent branch from the right posterior face of the right portal vein to the paracaval portion of the caudate lobe is ligated. After isolation and retraction of the right branch of the hepatic artery, the portal bifurcation is identified. The posterior passage of the curved dissector in the bifurcation is facilitated by a slight caudal traction of the main portal trunk. The bifurcation of the portal vein is usually accessed from the right side; however, when the caudate lobe is preserved, the dissection of the left branch of the portal vein should be accessed from the left side of the portal pedicle, with attention to one or two small portal branches to the left part of the caudate lobe. The right or left branch of the hepatic artery is identified and encircled. We do not advocate extrahepatic biliary dissection before parenchymal transection because of the risk for biliary injury. The branches of the portal vein and hepatic artery supplying the liver to be resected can be cross-clamped or ligated.

Segmental selective clamping can be useful for delineating the territory of some tumors, but this requires difficult segmental or subsegmental resection. Sectoral territories can be delineated by extraparenchymal pedicular control of the respective sectors. Isolated control of single segments is more difficult and requires balloon occlusion of the portal flow. Under US guidance, the portal branch is punctured, followed by introduction of a balloon catheter. Inflation of the balloon, along with pedicular arterial clamping, can delineate the portal territory; the injection of methylene blue into the portal catheter can allow more precise identification of the territory of interest.

Inflow and Outflow Vascular Control

Hepatic Vascular Exclusion

HVE combines total inflow and outflow vascular occlusion of the liver. Total isolation of the liver from the systemic circulation is intended during resection of large tumors adjacent to or involving the major hepatic veins and/or the IVC. This procedure can also be considered when significant backflow bleeding occurs as a result of persistently elevated CVP despite efficient hepatic pedicle clamping (e.g., in a patient with tricuspid insufficiency). This procedure, which requires prolonged continuous clamping, cannot be tolerated in patients with diseased liver and can cause significant hemodynamic disturbance in some patients (see Table 91A.2).

Effective HVE requires complete mobilization of the liver from its ligamentous attachments and from all surrounding adhesions. The IVC is completely freed from the retroperitoneum, which requires the ligation of the right adrenal vein. The IVC is mobilized above and below the liver and is encircled. The hepatoduodenal ligament is encircled as described above, and a careful search is made for accessory or replaced hepatic arteries (Fig. 91A.4). Clamps are applied in the following order: 1) hepatoduodenal ligament, 2) infrahepatic IVC, and 3) suprahepatic IVC. Once the surgeon and the anesthesiologist agree that clamping will be tolerated, clamps are reapplied for up to 60 minutes in patients with a normal liver. After completion of the parenchymal transection, prior to removing the clamps, the clamp on the infrahepatic vena cava can be partially released to flush air that might have been trapped and to test for caval integrity. The clamps are then removed in reverse order of placement.

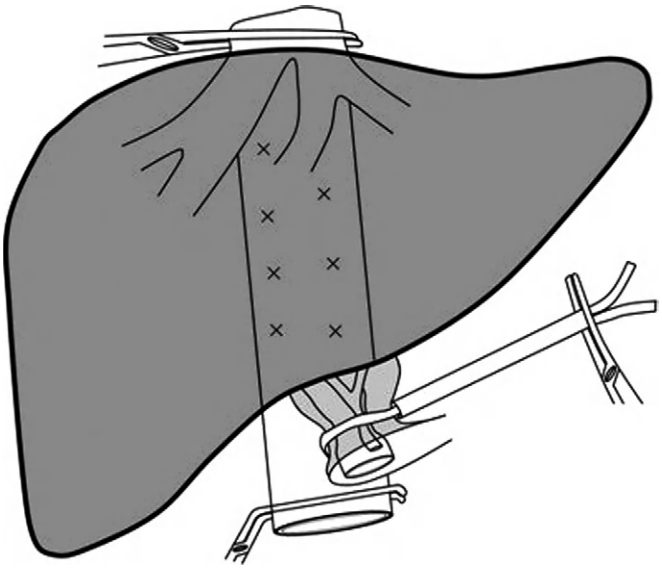


FIGURE 91A.4. Hepatic vascular exclusion.

Inadequate HVE technique will result in progressive congestion of the liver as a result of 1) inadequate clamping of the portal pedicle or the IVC, 2) persistent arterial inflow through an unrecognized left hepatic artery or through hypervascular perihepatic adhesions, 3) persistent entry of venous blood into the excluded retrohepatic IVC via anatomic (right adrenal) or pathologic veins (tumor adhesions). Patients with huge tumors with diaphragmatic and peritoneal adhesions, the best candidates for HVE, can experience hepatic congestion after suprahepatic caval clamping. This congestion reveals itself by an increase in liver size and a change in color and consistency of the liver, which is always associated with hemodynamic intolerance that immediately reverses after release of the suprahepatic clamp; this is because flow through retrocaval veins may fill the liver, when every connection from the cava to the liver is not controlled.

Supracaval declamping provides the path of least resistance for blood from the liver to flow toward the heart rather than backward into the surgical field. Although concomitant supraceliac aortic clamping has been proposed in this situation, the technique has not been widely adopted. Three randomized studies (Belghiti et al, 1996; Chen et al, 2006; Smyrniotis et al, 2002) compared total vascular exclusion (TVE) with portal pedicle clamping or selective vascular exclusion and showed that both techniques were effective in bleeding control. No statistically significant difference was reported in the operative blood loss, number of patients transfused, or number of units transfused (Gurusamy et al, 2007), and no difference in mortality was found between the two groups; however, TVE was associated with significant decrease in mean arterial pressure and mean pulmonary arterial pressure. Postoperative serum creatinine level and length of hospital stay were significantly greater in the TVE group (Gurusamy et al, 2007). Finally, TVE requires prolonged continuous clamping that can be poorly tolerated in patients with diseased liver.

Two refinements have been proposed to overcome these drawbacks: 1) HVE with preservation of caval flow to minimize the hemodynamic impact and 2) hypothermic perfusion to decrease parenchymal injury related to prolonged warm ischemia.

Hepatic Vascular Exclusion with Caval Flow Preservation

Better understanding of intrahepatic anatomy and advances in surgical techniques allow many liver surgeons to safely expose and control the three main hepatic veins. In the absence of tumor involvement of the hepatocaval junction, HVE with caval flow preservation can be considered. The association of inflow occlusion (hepatic pedicle clamping) and outflow occlusion by extraparenchymal clamping of the three main hepatic veins (Fig. 91A.5) enables complete vascular isolation without interruption of the IVC flow (Cherqui et al, 1999; Elias et al, 1995); however, this attractive procedure is restricted to patients without tumor involvement of the hepatocaval junction. In addition, the presence of large veins draining the caudate lobe may render this procedure ineffective. Caudate lobe veins are not isolated in this technique and can communicate intraparenchymally with other major veins, causing persistent backflow bleeding. The technical sequence of HVE with preserved caval flow includes total pedicular clamping with subsequent clamping of the three major hepatic veins at their confluence with the IVC. This clamping procedure can be applied either continuously or intermittently.

Extrahepatic control of the right hepatic vein (RHV) requires a complete mobilization of the right liver. Division of the falciform ligament is extended cranially to the upper peritoneal folds of the right and left triangular ligaments. The gutter between the liver, the RHV, and the middle hepatic vein (MHV) is dissected free to the anterior surface of the IVC. At this stage, dissection of a major hepatic vein from above is considered very hazardous and should not be attempted.

After mobilization of the right lobe, and upon complete exposure of the right and anterior side of the IVC, the liver is retracted medially and upward. The right half of the IVC is dissected caudally to cranially with ligation of short and small retrohepatic veins. When a significant right inferior hepatic vein is present, it is either encircled or ligated and then divided according to the type of resection. Before reaching the RHV level, the IVC ligament is encountered, which is dissected and divided between clamps; because it contains small veins, it should be closed with a running suture. Only after this has been completed should the RHV be encircled and taped, which is achieved easily by placement of a clamp that passes on the anterior surface of the IVC toward the space between the RHV and MHV. To facilitate the subsequent parenchymal dissection, a tape is inserted behind the RHV and is passed along the anterior surface of the IVC (Fig. 91A.6), and the right liver is released to lie in its anatomic position. The tape that elevates the precaval space, the so-called hanging maneuver, facilitates subsequent division and hemostasis of the parenchyma (Belghiti et al, 2001).

Extrahepatic control of the middle and left hepatic veins requires exposure of left border of the IVC. The left upper aspect of the IVC is exposed by division of the peritoneal reflection above the caudate lobe, and the ligamentum venosum is ligated and divided to expose the junction of left hepatic vein (LHV) and the IVC (Majno et al, 2002). When the left phrenic vein drains directly into the LHV, the former is ligated and divided. A dissector is inserted from above in the previously dissected gutter between the right and middle hepatic veins and is passed in close contact with the anterior surface of the IVC beneath the MHV. The common trunk is then encircled with a tape. When the confluence of the middle and left hepatic veins

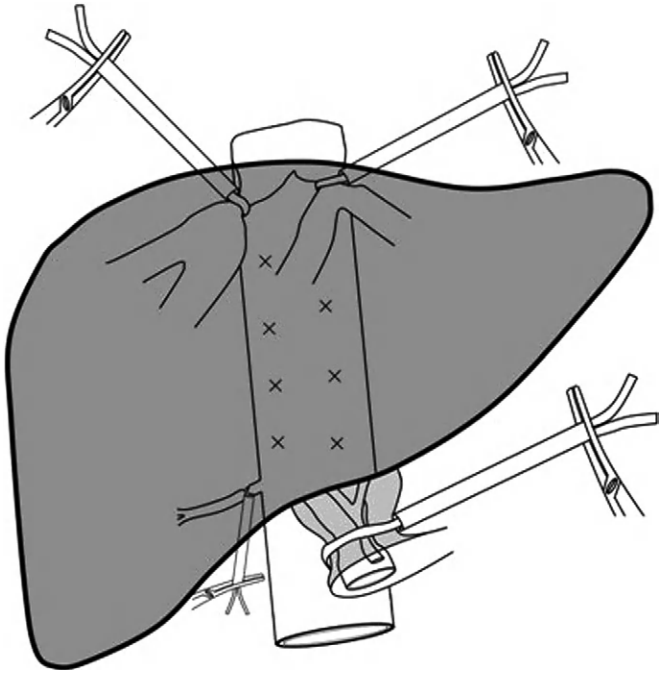


FIGURE 91A.5. Hepatic vascular exclusion (HVE) with preservation of caval flow enables isolation of the liver from the systemic circulation, thereby avoiding the hemodynamic disturbances of HVE as the vena caval flow is maintained.

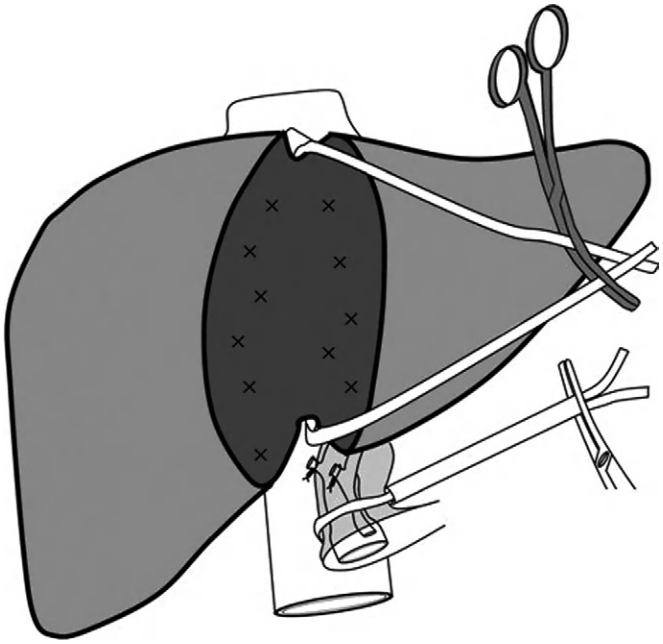


FIGURE 91A.6. Liver-hanging maneuver helps to guide the direction of transection.

is extrahepatic, it is possible to separately encircle these two vessels; otherwise the common trunk of the middle and left hepatic veins can be encircled as a unit.

Hepatic Vascular Exclusion with Hypothermia

Initially described by Fortner and colleagues (1974), this technique has been reevaluated by Azoulay and others, especially when HVE was longer than 60 minutes in duration (Azoulay et al, 2005). Compared with standard HVE, this group showed that hypothermic perfusion of the liver was associated with better postoperative liver and renal functions and less morbidity, especially in patients who required more than 60 minutes of HVE, although the technique requires systematic venovenous bypass for all patients. In the study, cooling was performed using 4 to 8 L of University of Wisconsin solution chilled to 4° C, perfused through the PV, and let out through an incision above the inferior caval clamp. To expedite the process, surface cooling using cold packs, ice, or cold water may be used. Intraparenchymal temperature should ideally be monitored using a fine needle, and the objective is to range between 14° C and 18° C. This renewed attractive procedure is applicable in difficult and complex liver resection in patients with diseased liver, and it should be added to the armamentarium of modern surgery.

Isolated Caval Clamping

Infrahepatic Caval Clamping

The major impact of caval pressure on blood loss during liver resection has led some surgeons to propose isolated IVC clamping to decrease the CVP (Fig. 91A.7; Abdalla et al, 2004; Otsubo et al, 2004). This technique is simple and is usually hemodynamically well tolerated, and it can decrease the CVP by approximately 4 cm of H_2O and can be used alone, when the liver resection is performed without pedicular clamping or along with pedicular clamping. When it is used in fluid-loaded patients, the hemodynamic impact on arterial pressure and postoperative renal function is minimal (Otsubo et al, 2004); therefore surgeons should consider this method, especially when the anesthesiologist cannot maintain a low CVP.

Isolated Total Caval Clamping

Clamping of the infrahepatic vena cava before liver transection can be considered in patients with a persistently high CVP (Otsubo et al, 2004). When a suprahepatic venous trunk is not involved by a tumor that otherwise involves the vena cava, total caval clamping below the hepatic veins associated with clamping of the vena cava but above renal veins maintains hemodynamic stability (Varma et al, 2007). This technique of caval clamping is indicated in patients with tumors in contact with the vena cava or near the cavohepatic junction, which necessitates en bloc resection of the IVC or cavohepatic junction. In this maneuver, the vena cava alone is clamped, leaving the inflow and outflow of the remnant liver intact; this procedure requires the control of the infrahepatic vena cava and of the uninvolved venous trunk.

The initial phase of the procedure consists of parenchymal transection by an anterior approach, usually under intermittent clamping after ligation of the hepatic pedicle to the tumor-bearing hemiliver. When the parenchymal transection reaches the anterior surface of the vena cava, the tape that encircled the uninvolved venous trunk is passed behind the suprahepatic IVC. The IVC is clamped at the site of this caval tape after clamping the infrahepatic vena cava. Thus the vena cava is isolated while hepatic flow is maintained through the remnant liver (Fig. 91A.8). The maintenance of the flow to the suprahepatic vein through the "liver shunt" avoids splanchnic congestion, hemodynamic disturbances, and liver ischemia. Total caval clamping without liver ischemia allows comfortable caval resection and reconstruction. This procedure, which is especially indicated, is efficient when the caudate lobe is involved and resected, which further reduces the indication of HVE to exceptional patients.

Nonclamping Technique

The ideal alternative to clamping would be to perform hepatectomy without clamping and without significant blood loss.

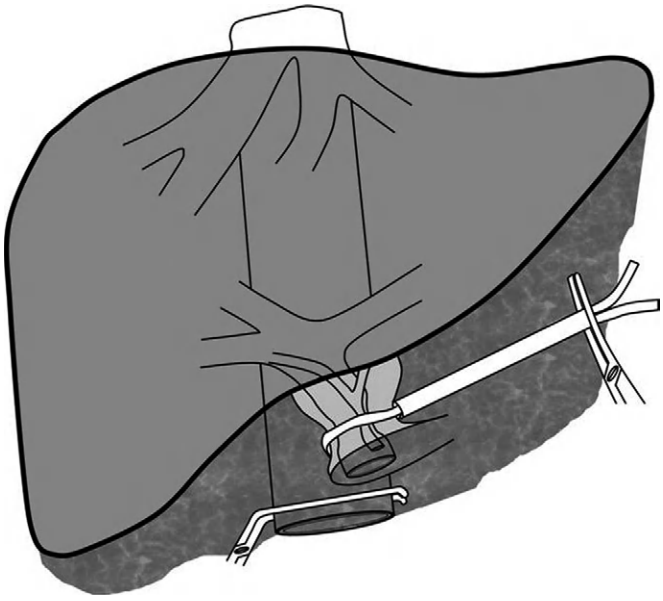


FIGURE 91A.7. Isolated infrahepatic vena caval clamping is performed to reduce a persistently elevated central venous pressure.

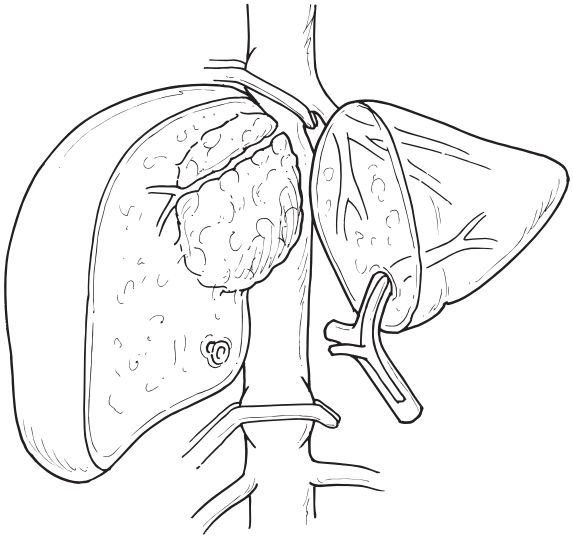


FIGURE 91A.8. The vena cava is isolated while the hepatic flow is maintained through the remnant liver.

This ideal approach is considered by many surgeons faced with major resection on underlying diseased parenchyma, living donor harvesting, and combined digestive operation to avoid splanchnic congestion on bowel anastomoses.

Several conditions should be satisfied to perform a hepatectomy without clamping: 1) fluid must be restricted, 2) completely preserved remnant liver venous drainage should be assessed preoperatively with CT scan and intraoperatively by Doppler US, and 3) the surgeon should possess modern tools of parenchymal transection. Bleeding from the transection surface is minimized when the remnant liver has a patent venous drainage; therefore a nonclamping technique should be considered essentially in major anatomic resections that preserve complete venous drainage of the remnant liver. Nonclamping increases liver transection time, which can be reduced by the use of several technical refinements that include use of an ultrasonic dissector, bipolar scissors, or water-irrigated bipolar forceps. As minimizing blood loss remains the major objective, the pedicle should be controlled and clamped if the blood loss approaches 20 mL/kg (Scatton et al, 2004). A recent randomized trial has shown that major liver resection can be performed without clamping (Capussotti et al, 2006).

CONCLUSIONS

Living donor liver resection is the best illustration that major hepatectomy can be performed without clamping and without transfusion. This reflects the progress and improvements in technique that have been achieved during the past decade. Minimizing blood loss, however, is not well tolerated in patients with diseased liver and requires the use of vascular clamping, especially in complex liver resections. Each vascular occlusion technique, which should be defined with the anesthesiologist, has a place in major and minor hepatic resection surgery, based on the tumor location, presence of associated underlying liver disease, patient cardiovascular status, and experience of the operating surgeon; however, intermittent pedicle clamping remains the procedure of choice.

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CHAPTER 92

Segment-oriented anatomic liver resections

Charbel Sandroussi and Paul D. Greig

OVERVIEW

Decreased intraoperative blood loss and preservation of parenchyma are key contributors in recent advances in liver surgery that have resulted in reduced morbidity and mortality in liver resection. The understanding of the segmental anatomy of the liver has been pivotal in the evolution of a safe liver surgery (Scheele et al, 1995). Segmental liver resection offers maximum preservation of liver parenchyma with minimal blood loss and without compromising oncologic safety (Agrawal & Belghiti, 2011; Billingsley et al, 1998; Bismuth et al, 1988; Machado et al, 2003; Polk et al, 1995). The ability to resect one or more segments, rather than the entire lobe, allows parenchymal preservation in patients with diseased parenchyma or in re-resection patients with limited residual volume. Segmental vascular inflow control facilitates the resection by precisely mapping the transection plane. In addition, anatomic resections that involve the removal of a hepatic segment confined by tumor-bearing portal tributaries for the eradication of intrahepatic metastases in the vicinity of the primary tumor represent an oncologic approach to liver resection for some malignant tumors (Agrawal & Belghiti, 2011; Liau et al, 2004).

ANATOMY AND TERMINOLOGY

The current understanding of the segmental anatomy of the liver has come from the original 1952 descriptions of Claude Couinaud (1952a, 1952b, 1956). Based on his analysis of vascular and biliary casts of the liver, Couinaud determined that the human liver consists of eight segments, each with its own portal triad—vein, hepatic artery, and hepatic duct—and hepatic venous outflow. Subsequently it has been shown that each segment can be resected independently (Bismuth et al, 1982). These segments have evolved to become the standard for hepatic nomenclature. This so-called Brisbane terminology (Pang, 2002) eliminates confusing lobes and sectors used in the American, European, and Japanese descriptions of liver anatomy. The terms *hemiliver* (first-order division), *section* (second-order division), and *segment* (third-order division) are not interchangeable; these provide universal terminology for better communication among liver surgeons.

The first-order divisions are *right liver* (segments V through VIII) and *left liver* (segments I through IV), or *hemiliver,* the boundary of which lies along the Cantlie line marked by the path of the middle hepatic vein (MHV), from the middle of the gallbladder fossa to its termination in the inferior vena cava (IVC) (Fig. 92.1). The second-order division into liver sections is based upon hepatic arterial supply and biliary drainage. The sections are derived from the primary divisions of the major right and left portal triads. The right hemiliver is divided into sections known as the *right anterior* (segments V and VIII) and *right posterior* (segments VI and VII), separated by the right hepatic vein (RHV). The left hemiliver is divided into *left lateral* (segments II and III) and *left medial* (segments IVa and IVb) sections by the umbilical fissure and falciform ligament. Together segments II and III are often erroneously referred to as the *left lateral segment.*

The third-order division, segments I through VIII, is defined by hepatic arterial supply and biliary drainage. The axial plane is at the level of the intersection of the hepatic veins and the axial plane of the bifurcation of the portal vein (Table 92.1 and Fig. 92.2). When considering a segmental resection, it is important to identify the common anomalies that may determine resectability. The biliary and arterial anomalies are the most common: about 30% of patients have a major arterial anomaly, and up to 50% have nonstandard biliary anatomy.

PATIENT SELECTION

A liver resection based on the segmental anatomy should be the first consideration for any liver resection. Excluding the fenestration of liver cysts or small "wedge excisions" of superficial lesions, an understanding of the patient's segmental liver anatomy is essential to a safe, controlled resection. This technique is applicable for all types of livers and indications for resection (Hasegawa et al, 2005).

Achieving balance between parenchymal sparing and radical oncologic clearance is of the utmost importance in hepatocellular carcinoma (HCC) patients with cirrhosis. Segmental liver resection forms a bridge between major hepatectomy and nonanatomic resection to preserve maximum liver volume and prevent postoperative liver failure (Agrawal & Belghiti, 2011; Wakai et al, 2007). Replacement with nonanatomic resection should be done only when the anatomy is unsuitable, or when the residual liver would be at high risk for complications. Segmental liver resection is preferred in patients who have colorectal metastasis with multifocal lesions and are undergoing preoperative chemotherapy, which is frequently associated with steatosis and hepatic cirrhosis (DeMatteo et al, 2000).

PREOPERATIVE PLANNING

Variable anatomy from patient to patient confounds the preoperative planning of liver resection. Seldom does any patient have the classic vascular anatomy as depicted by the idealized diagrams. The planning of a segment-based resection must be individualized for the specific anomalies, and their relationship to the plane of transection is particularly important. The assessment of suitability of the operation requires a precise mapping with attention to vascular and biliary anomalies. Resection has been facilitated by the precision digital imaging provided by

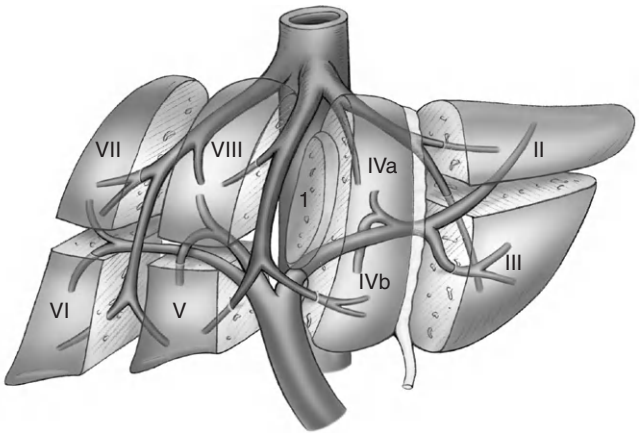


FIGURE 92.1. Diagram depicting the relationships of the eight liver segments with the major hepatic veins and portal veins of the idealized liver.

Table 92.1

Description of the Anatomic Boundaries of Each Segment

Segment	Vertical Boundary	Horizontal Boundary	Other
I	Middle of the IVC		Posterior to PV
II	Left of the left PV (falciform)	Cephalad to the left HV	
III	Left of the left PV (falciform)	Caudate to the left HV	
IVa	Right of the left PV (falciform) Left of the middle HV	Cephalad to the bifurcation of the PV	
IVb	Right of the left PV (falciform) Left of the middle HV	Caudate to the bifurcation of the PV	
V	Right of the middle HV Anterior to the right HV	Caudate to the bifurcation of the PV	
VI	Posterior to the right HV	Caudate to the bifurcation of the PV	
VII	Posterior to the right HV	Cephalad to the bifurcation of the PV	
VIII	Right of the middle HV Anterior to the right HV	Cephalad to the bifurcation of the PV	

HV, hepatic vein; IVC, inferior vena cava; PV, portal vein

computerized tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US), allowing the surgeon an interpretation of intrahepatic vascular and biliary anatomy, facilitated by the ability to manipulate the images using widely available software. With the appropriate protocol for arterial and venous enhancement, the third- and fourth-level vascular structures can be accurately defined. Furthermore, the ability to easily scroll through reconstructions in the axial, coronal, or sagittal planes allows the surgeon to analyze and define the anatomy. More advanced, three-dimensional reconstructions of the liver allow the surgeon to dynamically view the anatomy by rotating the liver along a vertical axis, centered on the IVC, or along a horizontal axis, through the bifurcation of the porta. Based on the segments involved by the disease process, their relationship with the segmental hepatic venous outflow and portal venous inflow, which is representative of the arterial and biliary triad structures, can be determined. One technique for planning is to first determine which hepatic veins require resection or

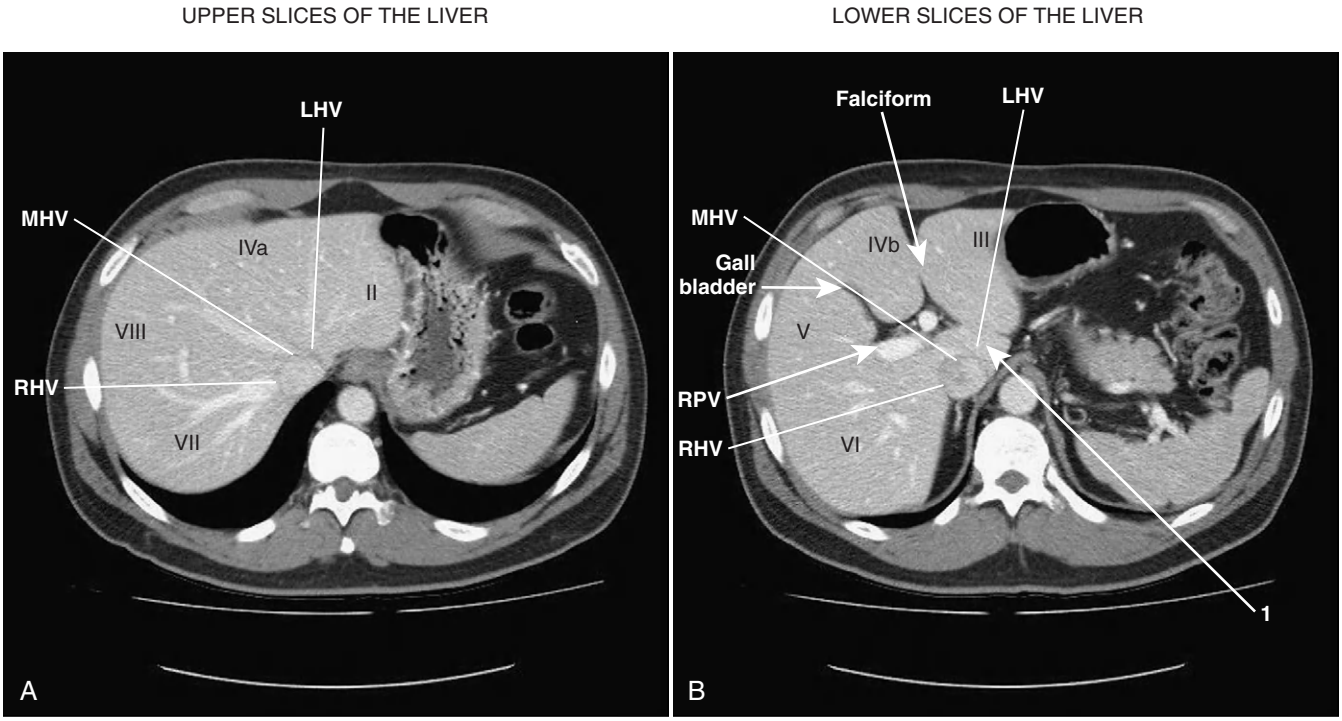


FIGURE 92.2. A, Axial computed tomographic (CT) scan image through the upper liver, demonstrating the anatomic boundaries of segments I, II, IVa, VIII, and VII. **B,** Axial CT scan image through the lower liver, demonstrating the anatomic boundaries of segments I, III, IVb, V, and VI. LHV, left hepatic vein; MHV, middle hepatic vein; RHV, right hepatic vein; RPV, right portal vein.

preservation, and at what level for an adequate margin, and then to consider the portal triads that need to be included as a basis for the segmental resection.

For a donor right hepatectomy, the presence of single or multiple right portal veins, hepatic arteries, and hepatic ducts impacts the suitability of the donor graft. For example, the presence of the segment V and VIII portal pedicle, arising from the left portal pedicle, and the size of the hepatic veins of segments V and VIII could influence the decision to include the MHV with the graft.

Other technology is being developed, and more sophisticated software is available, that will facilitate the preoperative planning of liver resection. These easily manipulated, three-dimensional reconstructions create a virtual reproduction of the liver that can be used to determine the proposed plane of transection, taking into account the minimum resection margin and residual liver volume. Some facilities that use such technology include the University of Toronto and the University of Illinois at Chicago. The MeVIS imaging system (MeVisLab, Bremen, Germany) is widely used. Some of these systems have been extended to facilitate real-time, image-guided resection by coupling the preoperative images of the virtual liver to a real-time liver and instrument tracking system. Systems being investigated include those under development by Pathfinder Therapeutics (Nashville, TN) and the Medical University of Graz, Austria. These advances offer significant potential for increased precision of preoperative planning for segment-oriented liver resections and intraoperative application to facilitate image-guided surgery.

GENERAL OPERATIVE PRINCIPLES

Preoperative Assessment and Anesthesia

The preoperative assessment and preparation of the patient for a liver resection have been described in Chapter 2. Comorbidities should be identified and optimized. Careful assessment of liver function is important, particularly in those with intrinsic liver disease. Preoperative decompression of an obstructed biliary tree should be considered for improving postoperative liver function (Belghiti & Ogata, 2005). Volumetric analysis should be performed in patients with potentially marginal residual liver size and function. Preoperative portal vein embolization (PVE) may facilitate the safety of a complex or extended liver resection by inducing regeneration of the potential contralateral remnant liver segments (Abulkhir et al, 2008). Particular attention should be paid to the reduction of the central venous pressure during transection to reduce blood loss, and measures to prevent hypothermia are also important. The appropriate prophylaxis of infections and venous thromboembolism is required.

Exposure and Mobilization

For a segment-oriented liver resection, open operative exposure can be achieved through a variety of incisions. The most common incisions include the right subcostal with midline extension cephalad (hockey stick) or its modification (J-shaped), or a bilateral subcostal incision with midline extension cephalad ("Mercedes" incision) or without (chevron incision). For access to the infrahepatic IVC, right kidney, duodenum, and retroperitoneum, a midabdominal transverse incision to the umbilicus with midline extension offers generous exposure. A long midline incision may be used for selected liver resections; a right thoracoabdominal incision is seldom required.

One principle to consider in selecting the appropriate incision is whether exposure of the suprahepatic IVC and the origin of any of the hepatic veins is needed. If so, an incision that extends cephalad to the right of the xiphoid process to the junction with the costal margin is valuable. This can usually be achieved without resection of the xiphoid process. Adequate exposure of the liver, including the porta and suprahepatic structures, is facilitated by a retractor fixed to the operating table, which provides for substantial cephalad and somewhat anterior retraction of the costal margins, especially the right. Suitable retractors are the Omni-Tract (Omni-Tract Surgical, St. Paul, MN), the Iron Intern (Automated Medical Products, Edison, NJ), and similar retractors made by various other manufacturers, such as the Bookwalter (Codman, Raynham, MA) and Thompson retractors (Thompson Surgical Instruments, Traverse City, MI).

After the laparotomy and general inspection, the liver is mobilized by transection of the obliterated umbilical vein and division of the falciform ligament, as it triangulates onto the IVC, to identify the origins of the hepatic veins and, in particular, the right middle groove and the left middle groove, if it is extrahepatic. Mobilization of the left and/or right lobes may be performed either before or after pedicular dissection. Left liver mobilization requires division of the left triangular ligament, and a laparotomy pad or sponge placed posterior to segment II can be valuable in protecting the cardia of the stomach and spleen, especially in a patient with a very long left lateral section that wraps over the spleen.

During the division of the lesser omentum (gastrohepatic ligament), attention should be given to the presence of an anomalous left hepatic artery, arising from the left gastric artery. Right liver mobilization requires division of the right triangular ("rookie") ligament; division of the anterior layer of the coronary ligament, as it reflects from the diaphragm onto segment VIII; and the posterior layer of the coronary ligament that reflects onto segment VI. The liver is mobilized off the right hemidiaphragm, thereby exposing the bare area of segments VI and VII. The right adrenal gland is separated from segment VI (a densely adherent adrenal gland may be divided and oversewn), and the retrohepatic IVC is identified.

Intraoperative Assessment

Intraoperative assessment of the liver requires correlation of the findings of inspection and palpation of the mobilized liver with those of the preoperative imaging. Intraoperative US has been advocated to localize the lesion and further stage the proposed remnant liver (Makuuchi et al, 1991); however, with the increased precision of preoperative imaging, intraoperative ultrasound (IOUS) seldom alters the procedure (Jarnagin et al, 2001). IOUS of the liver may be valuable to identify venous tumor thrombus and to assess the proposed plane of transection and its relationship with major hepatic veins and portal triads.

Recently, systematic segmentectomy and subsegmentectomy by IOUS-guided finger compression has been described (Torzilli et al, 2010). This technique can be applied in each segment of liver, as long as the thickness of the parenchyma and the anatomy of liver are suitable. IOUS-guided finger compression of the vascular pedicle feeding the tumor at the level

closest to it results in a demarcation area, allowing oncologic resection.

Transection Techniques

There are at least two distinct philosophies of liver transection, which result in distinct surgical techniques and surgical styles. The first is that blood loss from the transected liver is minimized by speed, external compression, vascular occlusion (outflow and/or inflow) (Bismuth et al, 1989; Stephen et al, 1996), and the use of surgical interventions to stop bleeding using cautery, sutures, and tissue glues. The second is that blood loss is best minimized by prevention of injury to vascular structures, using transection techniques that dissect out structures from the surrounding parenchyma as understood and anticipated by preoperative imaging and planning. Use of the Cavitron Ultrasonic Surgical Aspirator (CUSA; Valleylab, Boulder, CO), which reduces blood loss better than the clamp-crushing technique (Fan et al, 1996), has become the standard technique of liver transection even in cirrhotic liver (Takayama et al, 2001).

More recently, a third technique has been described that reflects a philosophy of prevention of bleeding that uses destructive hemostatic control of the parenchyma before transection (Ayav et al, 2007; Curro et al, 2008). We prefer the second approach, although clamp crushing, the conventional method of liver transection, is still used in some centers (Imamura et al, 2003; Jarnagin et al, 2002; Lin, 1974). Surgical techniques that facilitate a precise, controlled transection of liver parenchyma and allow the dissection of intrahepatic structures are the Helix Hydro-Jet dissector (ERBE USA, Marietta, GA) (Baer et al, 1991) and the CUSA dissector (Little & Hollands, 1991). Each provides selective destruction of liver parenchyma with relative sparing of denser fibrotic tissue, such as hepatic veins and portal triads. Inflow and outflow vascular occlusion may be added to these techniques for better hemostasis. Because no evidence clearly supports the superiority of any one technique (Clavien et al, 2003), the transection method for any particular operation should be dependent on local expertise.

Techniques that achieve destructive control of the parenchyma and any crossing structures before division include linear cutting staplers, in-line radiofrequency ablation (Habib; Angiodynamics, Latham, NY), and bipolar cautery (Gyrus, Gyrus ACMI, Southborough, MA; and LigaSure, Covidien, Boulder, CO). In-line radiofrequency ablation (RFA) allows surgeons to perform minor and major hepatectomies with minimal blood loss, low blood transfusion requirement, and reduced mortality and morbidity (Ayav et al, 2008); however, this device is seldom used in tertiary reference centers because of concerns about the preservation of venous drainage of the remnant liver and the risk of postoperative bile leak and necrosis (Kim et al, 2003; Lupo et al, 2007). The role of this technology is probably limited to segmental or wedge excision because of the potential risk of bile duct injury, when using this instrument near the liver hilum, and its inability to control bleeding from large venous branches.

Pretransection vascular control is used by many surgeons with oncologic, anatomic delimitation and hemostasis (Bismuth et al, 1989; Stephen et al, 1996). Early occlusion of the hepatic venous outflow of any resected segments may reduce the risk of venous tumor emboli. Occlusion of the hepatic artery (HA) and portal vein (PV) to those segments being resected facilitates the procedure by defining the line of division between ischemic segments to be removed and the well-perfused remnant liver for reduction of blood loss. Pretransection occlusion of the inflow of the segments to be resected before outflow results in better hemostasis. Occlusion of the inflow to sectors of the right hemiliver (VI and VII and V and VIII) or to the segments of the left lobe (II, III, IVa, and IVb) can be performed either by dissection and division of the artery and vein outside the liver, leaving the transection of the hepatic duct and remaining hilar plate for later in the procedure (Figueras et al, 2003), or by the glissonian technique (Launois & Jamieson, 1992), in which the sectoral or segmental pedicle is encircled, using either an anterior or posterior intrahepatic approach; this is done by incising the reflection of the Glisson capsule onto the portal structures to drop the hilar plate off the liver parenchyma, thereby encircling the pedicle. The duct, artery, and vein can be transected en masse either by suture or with a linear stapler.

PROCEDURES

Monosegment and Bisegment Resections

Segment I Resection

Segment I lies behind the posterior aspect of the portal bifurcation and receives inflow predominantly from the left PV and HA. The biliary drainage of segment I is variable, and the segment I bile duct runs in the hilar plate and enters the posterior aspect of either the left or right hepatic duct. Posteriorly, segment I rests on the IVC, and most of its outflow is directly into the IVC via a series of fragile veins. Tumors arising in the caudate lobe are closely related to the posterior aspect of the left and middle hepatic veins. This "critical oncologic margin" is a decisive factor in the choice between an isolated caudate resection or a left hepatectomy, with or without the MHV, including the caudate lobe.

DIRECT APPROACH. The falciform ligament is dissected in a cephalad direction, until the anterior and left surface of the suprahepatic vena cava has been isolated. The left hepatic vein (LHV) is identified, and the left triangular ligament is divided from left to right; as the dissection is carried medially, care should be taken to avoid injury to any low-entering phrenic veins and the LHV. The fissure for the ligamentum venosum, the *caudate groove,* is identified by retracting segments II and III to the right, and the hepatogastric ligament is incised.

For large tumors the right lobe should be mobilized to fully expose the caudate lobe from the right side as well. The resection can usually be performed from the left, although some large tumors may require an anterior approach. Peritoneal reflection onto the IVC in the lesser sac is incised, which allows some retraction of segment I, and occasionally the left side of the IVC is exposed through some or all of its length. The small bridge of liver between segments I and VI is also divided. To obtain further mobility and reduce the chances of a traction injury to the hepatic veins, the ligamentum venosum is ligated and divided in the superior aspect of its fissure, as it enters the posterior aspect of the left or middle vein. The inflow is then ligated as it emerges from the posterior aspect of the PV and HA. Often two distinct, paired PV branches enter segment I.

The dissection of segment I from the IVC then continues in a cephalad direction, dividing several thin-walled veins that drain segment I into the IVC. It must be noted that a large

predominant vein of segment I is often present 1 to 2 cm below the MHV and LHV confluence. Some of the venous branches between segments VI and VII and the IVC may be divided to provide adequate mobilization of the caudate off the IVC. Once segment I is mobilized, the thin parenchymal bridge between the caudate groove and the posterior transection line is divided. Usually, very few vascular structures are found in this plane, although the segment I duct and hilar plate tissue should be anticipated anteriorly. During parenchymal transection, the fissure for the ligamentum venosum is sometimes encountered and may need to be divided again. Dissection continues to its completion at the apex of segment I beneath the confluence of the hepatic veins.

ANTERIOR APPROACH. For very large tumors in segment I, an anterior approach may be used. A full mobilization of the liver off the IVC up to the inferior aspects of the left, middle, and right hepatic veins is performed by dividing the branches that drain segments I, VI, and VII directly into the IVC. Following division of the HAs and PVs to the caudate lobe, a vertical parenchymal transection plane through the Cantlie line to the left of the MHV partitions the right and left livers. The second parenchymal transection plane is made from the fissure of the ligamentum venosum, posterior to the plane of the left and middle hepatic veins and horizontally toward the vertical cut edge of the liver. The caudate duct is divided as it enters either the left or right hepatic ducts. At the conclusion of the resection, the remaining segments II and III should be resuspended by reapproximating the falciform ligament.

Segment III or III Resection

Given the discrepancy between portal venous supply and biliary drainage, and also given the difficulty of preserving left hepatic venous drainage, the combined segment II and III resection (left lateral sectionectomy; Fig. 92.3) is safer and more feasible than isolated resection of segments II or III. When either of these segmentectomies is being planned, the plane of resection is by either side of the LHV (left and posterior for segment II resection, right and anterior for segment III). The inflow is approached on the left side of the falciform ligament by incising the peritoneal reflection onto the liver and identifying either the

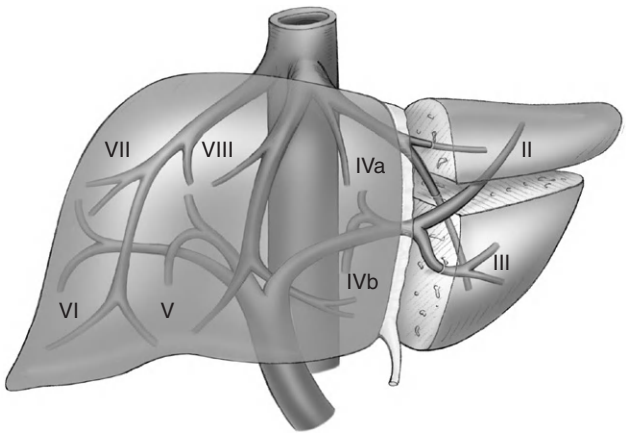


FIGURE 92.3. Diagram of the planes of transection for resection of segments II and III or segments IV, V, VI, VII, VIII (extended right hepatectomy).

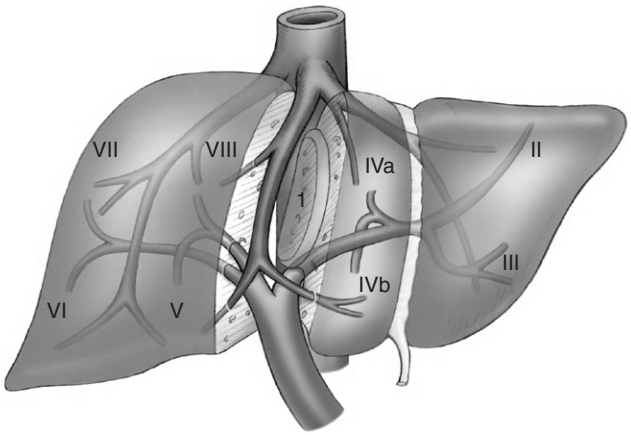


FIGURE 92.4. Diagram of the planes of transection for a right or left hepatectomy (hemihepatectomy).

segment II or III portal pedicles. Once the inflow is divided, the line of parenchymal transection becomes prominent between the ischemic segment to be resected and the normally perfused residual segment.

Combined Resection of Segments II and III: Left Lateral Sectionectomy

The left lateral section is mobilized by division of the falciform ligament and the left triangular ligament (Fig. 92.4). The extrahepatic portion of the left hepatic vein can be lengthened by dividing the fibrous tissue to the left of the IVC down to the level of the fissure for the ligamentum venosum, which is then ligated and divided as it enters the posterior aspect of the LHV; this allows encircling of this vein if the joining with the MHV is not intraparenchymal. Otherwise, the isolation of the LHV is delayed until completion of the parenchymal transection.

The inflow to segments II and III is usually isolated during transection of the parenchyma to the left of the falciform ligament. Occasionally, pedicles to segments II and III could be identified and encircled outside the liver in the left side of the portoumbilical fissure. The plane of parenchymal transection follows the falciform ligament. As the liver is divided, the portal structures to segments II and III will become apparent, and these can be electively ligated and divided. Once this is done, and the parenchyma surrounding the LHV has been dissected, the vein can also be ligated and divided.

The transection is completed by dividing the parenchyma anterior to the caudate lobe, in the fissure for the ligamentum venosum. The blood supply to the caudate emerges from the PV and left HA at the level of the portoumbilical fissure, and these should be identified and preserved before the parenchymal transection.

Segment IV Resection

Isolated resection of segment IV or IVa alone is very uncommon. This segment is limited posteriorly by the hilar plate and IVC, on the right by the falciform ligament and the left PV, and on the left by the MHV. Inflow and biliary drainage to segment IV comes from left to right from the left-sided portal structures in the base of the falciform ligament (the "comeback" branches from the left portal vein). Sometimes, aberrant right anterior and posterior sectoral ducts cross in this position; these should

be avoided during resection. Outflow from segment IV is predominantly to the MHV, but occasionally a separate draining vein (scissural vein) goes directly to the suprahepatic IVC or to the terminal part of the LHV or MHV.

Once the falciform ligament has been divided, with identification of the termination of the HVs, the arterial and venous inflow can be divided. By incising the peritoneal reflection on the right of the falciform ligament, the segment IVa and IVb pedicles can be isolated, encircled, and divided; the lines of transection become demarcated on the surface of the liver along the Cantlie line.

The resection continues at the base of segment IV off the anterior surface of the hilar plate. Care must be taken to avoid excessive use of cautery in the hilar plate, as the bile duct bifurcation and left hepatic duct lie immediately behind this area. Parenchymal transection commences on the right side of the falciform ligament with identification of portal pedicles to segments IVa and IVb. These may arise from a common trunk, and occasionally there are more than two, which is usually appreciable on preoperative imaging.

Transection continues superiorly to the level of the suprahepatic IVC to the junction of the LHV and MHV. The LHV and MHV commonly join within the liver at this point prior to insertion into the IVC, and in this case, the dissection terminates inferior to this point. Care should be taken to identify significant venous tributaries from segment IV into the left hepatic vein, which may not be appreciated on preoperative imaging. The dissection of the right side is along the Cantlie line to the left of the MHV. Several tributaries to the middle hepatic vein, the IVa and IVb veins, will need to be identified and ligated. Once the medial border of the hilar dissection has been reached, the parenchymal transection is done in a transverse plane to complete the separation of segment IV.

Segment V or VIII Resection

These two segments compose the right anterior sector. The bifurcation of the right portal pedicle into anterior and posterior pedicles is intrahepatic, and primary ligation of these pedicles is difficult, especially for segment VIII; therefore some parenchymal transection along the Cantlie line toward the pedicle is required before its division to allow demarcation of either segment V or VIII. The segment V pedicle emerges anteriorly and runs anteroinferiorly, and the segment VIII pedicle emerges posteriorly and runs superiorly. The horizontal plane of transection for an isolated segment V or VIII resection runs through the liver at the level of the bifurcation of the portal vein, with segment V below and segment VIII above this line. The medial and lateral limits of the resection are the middle and right hepatic veins, respectively.

Segment V Resection

Isolated segment V resection begins with division of the liver on the undersurface up the center of the gallbladder fossa and anteriorly along the Cantlie line halfway up toward the IVC. Then the parenchyma is divided in a plane to the left of the RHV, which extends on the undersurface of the liver along the incisura dextra to the free edge and anteriorly halfway toward the IVC. This posterior plane is quite coronal and usually results in a large exposed area of parenchyma. The resection is completed by connecting the two vertical transection lines by division of the parenchyma horizontally from anterior to posterior immediately below the level of division of the portal vein.

Segment VIII Resection

Isolated segment VIII resection is a very challenging procedure, because no external demarcation of this segment is apparent. The initial landmark is the Cantlie line with a parenchymal transection in the right side of the MHV. The segment VIII pedicle, which corresponds to the ascending division of the right anterior sectoral pedicle, can be isolated either at this point, after division of the liver, or by dividing the liver between segments IV and V in the horizontal plane along the level of the portal bifurcation. This latter maneuver is useful, as it allows for demarcation of the right-sided resection margin, which is on the left side of the RHV. This horizontal transection should follow the coronal plane of the RHV, which requires IOUS guidance.

The parenchymal division of the right-sided resection margin continues superiorly; using the termination of the RHV as a landmark, there is often only 1 to 2 cm of liver at the upper margin of the transection between the RHV and MHV. Care must be taken during the right-sided parenchymal division to adhere to the correct transection plane, as this plane takes about a 45-degree angle from the vertical. This allows resection of all the liver in segment VIII, while avoiding injury to the RHV. The segment VIII resection is completed by separating the remaining parenchyma off the deep attachment to the IVC, although this should have been mostly completed during mobilization.

Combined Resection of Segments V and VIII

The combined resection of segments V and VIII requires the division of the right anterior sectoral portal triad with left-sided parenchymal division along the Cantlie line along the right side of the MHV; the right-sided parenchymal division is in the coronal plane of the left side of the RHV. The anterior sectoral pedicle may be encircled from outside the liver, either anteriorly or posteriorly, and it is divided en masse with a linear cutting stapler, or it may be identified during the parenchymal transection along the Cantlie line at the base. Early division of the inflow provides demarcation of the ischemic parenchyma, which facilitates identification of the planes of parenchymal transection.

Segment VI or VII Resection

The right posterior sectoral pedicle can be identified in the incisura dextra of Ganz, which corresponds to the horizontal fissure lateral to the gallbladder fossa. The segment VI/VII branch of the right HA can usually be isolated extraparenchymally; however, the segment VI/VII portal branch, which corresponds to the posterior division of the right portal branch, is more difficult to isolate. Therefore the pedicle for an isolated resection of segment VI or VII is usually approached within the liver during parenchymal transection (Fig. 92.5). A resection of segment VI or VII requires complete mobilization of the right lobe of the liver with division of the segment VI and VII hepatic veins, when present, to the IVC.

Segment VI Resection

Isolated segment VI resection (Figs. 92.5 and 92.6) commences with an oblique transection line along the incisura dextra in the inferior surface of the liver and anteriorly halfway toward the IVC, following the posterior side of the RHV. The horizontal plane of resection is at the level of the PV bifurcation. The descending branches of the right posterior sectoral portal triad are encountered about two thirds of the way through the dissection. The resection is completed by taking a horizontal

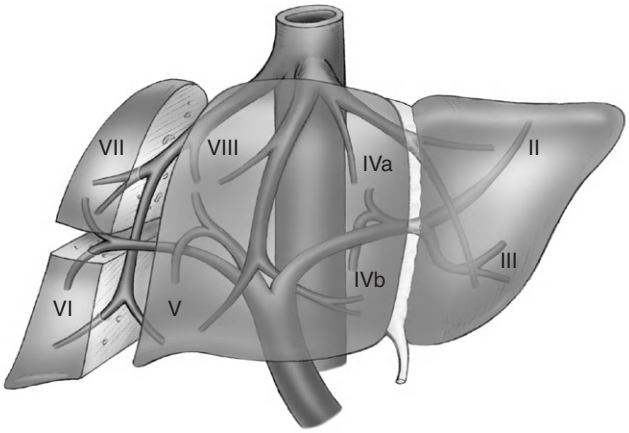


FIGURE 92.5. Diagram of the planes of transection for resection of segments VI and VII or segments II, III, IV, V, and VIII (extended left hepatectomy).

transection plane through the posterior surface of the liver lateral to the right hepatic vein.

Segment VII Resection

An isolated segment VII resection (see Fig. 92.5) commences with the horizontal transection line just above the bifurcation of the portal vein; this line is congruous with the horizontal resection line for a segment VI resection. The resection continues medially to the lateral margin of the RHV. During the horizontal resection, the ascending right posterior sectoral branches can be isolated and divided, which will allow for demarcation of the medial aspect of the resection. The vertical transection line runs obliquely through the liver lateral and posterior to the RHV.

Combined Resection of Segments VI and VII

This right posterior sectorectomy (see Fig. 92.5) is a procedure often considered as an alternative to a right hepatectomy, especially in patients with diseased parenchyma. Identification of the right posterior sectoral pedicle may be possible from outside the liver. Early division of the inflow facilitates the identification of the transection margins. Otherwise, the segment VI and VII HA and PV may be divided separately, leaving the transection of the VI and VII duct and plate for later, during the parenchymal transection. The plane of transection posterior to the RHV is coronal and results in a relatively large surface area of cut parenchyma, which requires specific attention for hemostasis and biliostasis.

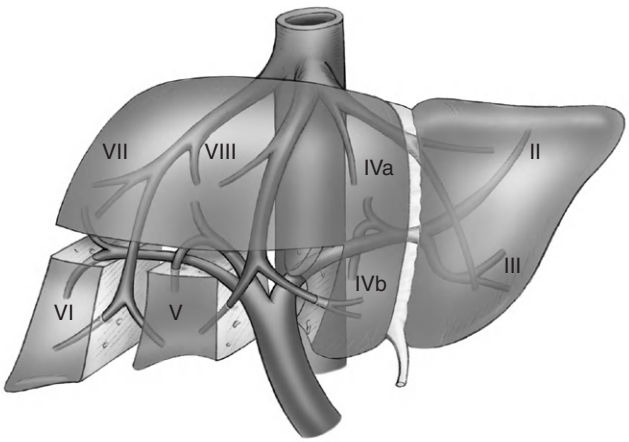


FIGURE 92.6. Diagram of the planes of transection for resection of segments V and VI.

Combined Resection of Segments V and VI

Resection of these two segments is very commonly performed. The vertical plane of transection is along the Cantlie line on the right side of the MHV from the edge of the liver to halfway up toward the IVC (see Fig. 92.6). The horizontal plane of transection is at the level of the PV. The portal pedicles to segments V and VI are usually divided during the parenchymal transection, which requires full mobilization of the right lobe of the liver from the diaphragm with division of segment VI and most, if not all, of the segment VII hepatic veins on the anterior surface of the IVC. The transection starts in the middle of the gallbladder fossa and extends along the Cantlie line up to the level of the right portal pedicle. Then with a dissection to the left, the horizontal plane of transection is developed from the top of the vertical plane. The segment V portal pedicle may be identified at the base and divided, followed by division of the segment VI pedicle posteriorly. From right to left, the horizontal dissection plane reaches the RHV.

Three or More Segmental Resections

Resection of Segments V Through VIII: Right Hepatectomy

Right hepatectomy is a very well-standardized procedure, consisting of resection of liver parenchyma on the right side of the Cantlie line in the right side of the MHV (see Fig. 92.4). The inclusion of the MHV corresponds to an extended right hepatectomy. Inflow and outflow control prior to transection may be appropriate and can be accomplished in many ways, and parenchymal resection can be performed with or without an intermittent Pringle maneuver. Mobilization commences by dividing the falciform ligament as it triangulates onto the IVC. The right middle groove, between the right hepatic and middle hepatic veins, is developed taking care not to injure a small tributary that may empty directly into the IVC from segment VIII.

Dissection of the porta hepatis commences with a cholecystectomy. A glissonian approach to the right portal pedicle may be performed by dividing the capsule that reflects onto the porta anteriorly and posteriorly, hugging the sheath as it is dropped off the parenchyma. Once encircled, the pedicle may be divided en masse with an Endo GIA (Covidien) stapler. Alternately, the inflow HA and PV may be dissected and divided individually. The peritoneum posterior and lateral to the portal structures is incised, and the RHA or its branches can be identified and divided. The peritoneum along the PV is incised, and the PV is mobilized off the back of the bile duct to clearly identify the bifurcation and origin of the left PV. The dissection continues cephalad along the anterior surface of the right PV. A small branch off the posterolateral aspect of the right PV to segment VI should be identified and divided to provide sufficient length for transection. The right PV is then encircled, taking care to divide any small branches that arise from the bifurcation, and it is divided with a vascular stapler. The liver should demarcate along the Cantlie line.

The right liver is mobilized by dividing the coronary ligament then exposing the bare area of the liver by dissecting the diaphragm and adrenal off the liver to expose the IVC. Rotation of the liver along the axis of the IVC facilitates this dissection.

Division of the left triangular ligament may make this rotation easier, especially when the liver is large, or when the patient is obese. Once the IVC has been identified, the segment VI and VII hepatic veins are ligated and divided. The retrocaval fibrous bridge between segments VII and I is divided, taking care to control any significant veins that may run through it. The RHV identified is encircled by passing a Kelly hemostat up the right middle groove between it and the MHV. The RHV is then divided with a vascular stapler, and an umbilical tape is placed in the groove of the IVC behind the liver to perform the hanging maneuver.

The parenchymal transection commences at the gallbladder fossa along the line of demarcation. The first major structure to be expected is the segment V hepatic vein, as it becomes the MHV. After division of this vein, the parenchymal transection continues along a broad front, either staying to the right side of the MHV or leaving a small amount of liver parenchyma on the surface of the vein. The hilar plate containing the right hepatic duct is approached at the base of the resection plane and may be divided prior to completion of the superior aspect of the parenchymal transection. Division of the bile duct and the hilar plate allows the parenchyma of the superior aspect of the liver to be separated and consequently reduces the risk of hepatic vein injury. Uppermost parenchymal transection is facilitated by placing some upward traction on the umbilical tape, the so-called hanging maneuver, dividing any segment VIII veins that cross over to the MHV. The dissection is completed posteriorly by dividing the glissonian capsule in the caval groove.

The right hepatectomy can be extended to include the middle hepatic vein and part of segment IV. To include the MHV, the transection begins to the left of the gallbladder fossa, and the first major structure expected is the segment IVb vein as it forms the MHV. Transection is then carried out to the left of the MHV, dividing any IVa veins that cross over to it. The MHV is encircled and divided before its junction with the LHV. Alternatively, the MHV may be identified and divided outside the liver, early after division of the RHV, by mobilizing a part of the caudate lobe off the IVC and encircling the MHV. In order to include segment IV in the resection specimen, the plane of transection is 1 cm to the right of the falciform ligament. The recurrent branches of the left portal triad to segments IVa and IVb need to be divided within the liver.

Resection of Segments II to IV: Left Hepatectomy

A left hepatectomy consists of resection of segments II, III, IVa, and IVb along the the Cantlie line to the left of the MHV (see Fig. 92.4). An extended left hepatectomy includes the MHV and/or segment I (caudate lobe). Inflow and outflow control prior to transection may be appropriate and can be accomplished in many ways, and parenchymal resection can be performed with or without an intermittent Pringle maneuver. Mobilization commences by dividing the falciform ligament as it triangulates onto the IVC. The plane between the LHV and MHV may be developed anterior to the IVC; however, the LHV and MHVs may join within the substance of the liver, and the left vein may not be able to be encircled outside the liver. To encircle the LHV, the ligamentum venosum is divided within its fissure to allow access to the posterior aspect of the LHV. Alternatively, the LHV may be divided at the end of the parenchymal transection, and control of vascular inflow may be appropriate. Using the glissonian approach, the left portal pedicle is encircled, and the pedicle may be transected en masse using an Endo GIA stapler. Alternatively, the branches of the left HA and the left PV may be divided outside the liver, leaving the left hepatic duct and plate to be divided late during the parenchymal transection.

The base of segment IV is dissected off the anterior surface of the bile duct bifurcation to allow for the transection line to be defined. The branches of the left HA are identified on the left side of the porta hepatis and are ligated. An early segment IV branch is often present, and this also should be ligated. The anterior surface of the PV can be identified and mobilized to clearly identify the origin of the right PV, and the left PV is encircled after dividing one or two of the branches to the caudate lobe. The left PV can then be ligated and divided. The parenchymal transection commences along the Cantlie line beginning to the left of the gallbladder fossa. The first major vascular structure encountered is the segment IVa vein, as it becomes the MHV. When the MHV is identified, the dissection is carried in a cephalad direction on its left side.

At the base of segment IV, the parenchymal transection should be carried to the left to minimize injury to any aberrant right hepatic ducts draining into the left hepatic duct. If the plane of transection is close to the falciform ligament, leaving the medial portion of segments IVa and IVb, the segment IVa and IVb portal pedicles that return from the left portal structures are identified and divided. The hilar plate is transected using a stapler, or it is ligated and divided. As the parenchymal transection continues cephalad, the LHV will become apparent, and it should be divided proximal to its junction with the MHV, if it was not divided outside the liver. The resection is completed by separating the parenchyma of segments II and III off the caudate lobe, ending by dividing the capsule along the caudate groove.

The left hepatectomy can be extended to include the MHV and variable amounts of segments V and VIII. Left hepatectomy extended to the right parenchyma with part or all of segments V and VIII could include parenchymal transection up to the left side of the RHV. In this procedure, also called *anterior hepatectomy,* the plane of transection is almost parallel to the operating table. The right anterior sectoral pedicle is usually ligated within the liver during the parenchymal transection. The right anterior and posterior pedicles can be orientated in many different ways, and it is important to ensure that the correct pedicle has been isolated, before anything irreversible has been done. This can be achieved by temporary pedicle clamping with a bulldog vascular clamp, assessing the delimitation of devascularized parenchyma. The anterior surface of the RHV should be cautiously dissected.

These major resections can be combined with caudate lobe and extrahepatic biliary tree resection in some cases of hilar cholangiocarcinoma. En bloc resection requires prior mobilization of the caudate off the IVC.

Resection of Segments IV, V, and VIII: Mesohepatectomy

This resection is very uncommonly performed, and it is indicated primarily for large central tumors where a formal extended right or left hepatectomy will not leave enough residual liver. The left-side plane of transection is to the right of the falciform ligament and the umbilical fissure, and the right-side plane is to the left side of the RHV (Fig. 92.7). The coronal transection plane is above the hilum and anterior to the right posterior sectoral portal pedicle.

Once the liver is mobilized completely, the RHV, MHV, and LHV are identified as they enter the IVC. After cholecystectomy, the hilar plate is dissected away from the base of

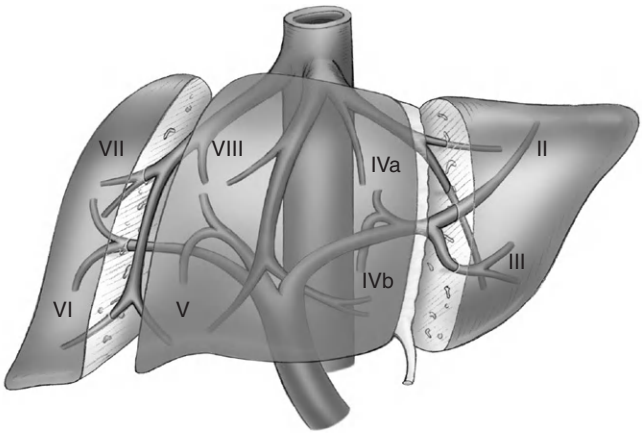


FIGURE 92.7. Diagram of the planes of transection for resection of segments IV, V, and VIII (mesohepatectomy).

segment IV by dividing the areolar tissue between the bifurcation of the common hepatic duct and the liver. Early isolation and division of the right anterior pedicle demarcates the liver and identifies the lines of transection. The inflow pedicle to IVb may be controlled outside the liver, but more commonly the IVa and IVb pedicles are taken during the parenchymal transection. The right anterior sectoral pedicle may be controlled using the glissonian extrahepatic approach, or the segment V and VIII pedicles may be ligated during the transection.

The parenchymal transection begins to the right of the falciform ligament. The portal pedicles to segments IVa and IVb are ligated and divided as they come back from the left-sided portal structures. This transection plane is carried cephalad toward the junction of the middle and left hepatic veins. Care must be taken to ensure that the LHV is not injured or inadvertently divided. The deeper portions of the left-sided dissection plane are best left until the right-sided parenchymal transection is complete. The right-sided transection plane is to the left of the RHV, angled approximately 45 degrees from the horizontal and vertical planes.

Transection begins to the right of the gallbladder fossa and is directed anteriorly toward the right middle groove and posteriorly toward the incisura dextra. Care must be taken to remain anterior to the right posterior portal pedicle and also not to injure the RHV. At the base of this transection plane, the right anterior sectoral portal pedicle or the individual segment V and VIII pedicles are divided, if they were not controlled earlier; prior to division a test clamping is valuable to ensure that the right posterior portal pedicle is not accidentally encircled. The dissection continues until the upper aspect of the left and right transection margins meet, and then the MHV is divided to complete the resection. Because of the large surface of cut liver and the proximity to the hilar plate, these resections are more prone to bleeding and bile leak.

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CHAPTER 93A

Preoperative portal vein embolization: rationale, indications, and results

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OVERVIEW

Although recent advances in surgical techniques and perioperative care have significantly improved both short- and long-term outcomes after hepatic resection (Belghiti et al, 2000; Fan et al, 1999; Grazi et al, 2001; Imamura et al, 2003; Jarnagin et al, 2002), postoperative liver volume insufficiency is still a major concern after an extensive liver resection. Both the small size of the remnant liver parenchyma after an extensive liver resection and sinusoidal injury caused by an abrupt increase in portal venous flow/pressure may be implicated in an increased rate of postoperative morbidity associated with cholestasis, ascites, and impaired synthetic function (Panis et al, 1997). These conditions all may lead to a protracted recovery and extended hospital stay and may eventually result in fatal liver failure, although rarely. This concern is even more relevant in patients with obstructive jaundice or underlying liver disease; that is, in those who not only have liver fibrosis or cirrhosis but also liver injury induced by chemotherapy, originally in patients with normal liver (see Chapters 50B, 65, 87, and 90F).

In 1982, we first carried out a preoperative portal vein embolization (PVE) for a patient with hilar bile duct carcinoma with the intention of increasing the operative safety under these circumstances (Makuuchi et al, 1984, 1990). The approach was based on the concept of the hepatic atrophy-hypertrophy complex (see Chapter 5). We attempted to initiate hypertrophy of the future liver remnant (FLR) before resection to induce atrophy in the embolized part of the liver to be resected with compensatory hypertrophy of the nonembolized FLR. Satisfactory initial outcomes led us to extend the indications for PVE to patients with metastatic liver tumors of colorectal origin (Kawasaki et al, 1994a) and for patients undergoing hepatopancreatoduodenectomy (Kawasaki et al, 1994b). Because of its technical simplicity and the consistent attainment of liver hypertrophy after the procedure, PVE has become a standard preoperative intervention worldwide, and its indications have been expanded to patients with hepatocellular carcinoma (HCC) (Aoki et al, 2004; Azoulay et al, 2000a; Lee et al, 1993; Ogata et al, 2006; Tanaka et al, 2000; Yamakado et al, 1997).

HISTORIC BACKGROUND

The concept of the hepatic atrophy-hypertrophy complex dates back to 1920, when Rous and Larimore (1920) showed that ligation of a major branch of rabbit portal vein resulted in atrophy of the ipsilateral hepatic lobe and hypertrophy of the contralateral lobe. The same phenomenon was observed in experiments involving long-term bile duct obstruction (McMaster & Rous, 1921); however, in contrast to the predictable response to portal venous occlusion, the magnitude of response to bile duct obstruction differs substantially among species (Braasch et al, 1972; Schalm et al, 1956; Steiner & Martinez Batiz, 1962; Stewart et al, 1937).

In 1975, Honjo and colleagues ligated the ipsilateral portal venous branch in patients with HCC in an effort to suppress tumor growth. Although this approach did not succeed in preventing tumor growth, it did produce marked atrophy of the occluded hemiliver. Likewise, our patients experienced an uneventful postoperative clinical course after extensive hepatectomy for hilar bile duct carcinoma involving a branch of the portal vein, causing hemiliver atrophy with corresponding hypertrophy of the contralateral hemiliver (Takayasu et al, 1986). These clinical observations led one of us (M.M.) to attempt PVE application as an adjunct procedure for major hepatectomy.

HEMODYNAMIC CONSEQUENCES

Total portal venous flow volume was thought to remain unchanged before and after PVE, because liver does not have an intrinsic ability to modulate portal flow, which is a function of extrahepatic (i.e., splanchnic and systemic) factors. This principle was confirmed in a study using a rat model of hemihepatic portal vein ligation and radioactive microsphere technique (Rocheleau et al, 1999) and in a human PVE study using Doppler ultrasound (Denys et al, 2000), proving that the same volume of portal venous flow as that prior to PVE would enter nonembolized liver segments after PVE. Portal pressure in the nonembolized hemiliver is elevated immediately after PVE by 4.9 ± 2.7 cm H_2O (Takayama et al, 1997). A similar increment was observed in patients with cirrhosis, who had higher baseline portal pressure (Aoki et al, 2004). Information on chronologic alterations in portal pressure after PVE is unavailable, but the elevation is believed to be transient, with pressure gradually returning to the baseline value in 2 to 3 weeks, as indicated by the portal flow velocity (cm/sec) changes measured by transcutaneous Doppler ultrasound (Goto et al, 1998).

Our concern that an abrupt increase in portal venous pressure after major hepatectomy may result in liver damage is one of the two reasons why we had attempted PVE. This concern seems to have been given little attention compared with a concern that a diminished liver may not meet metabolic demands after resection. We believe that incremental increases in portal venous flow/pressure observed after PVE may increase

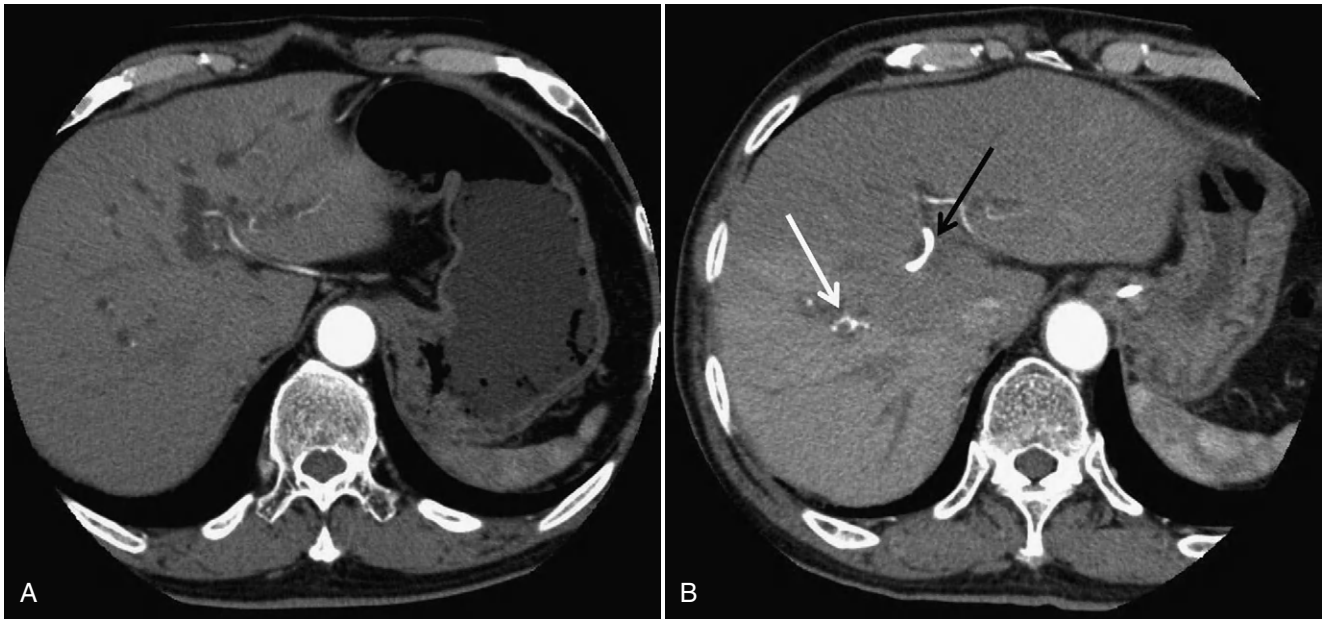


FIGURE 93A.1. Computed tomographic images of a 76-year-old man with hilar bile duct carcinoma. **A,** Before portal vein embolization (PVE). **B,** The same patient 2 weeks after PVE at the right hemiliver using gelatin sponge, thrombin, and coils (*white arrow*). The *black arrow* indicates the biliary drainage tube. Note the cessation of portal flow and attenuation difference by hepatic arterial buffer response in the right hemiliver.

tolerance in patients to high portal venous flow/pressure after extensive hepatic resection, resulting in an attenuation of liver damage after the subsequent resection (Makuuchi et al, 1991). Other recent studies on living donor liver transplantation (LDLT) have focused on portal pressure and small-for-size syndrome, and high portal pressure immediately after LDLT was reported to be associated with daily volume of ascites (Konishi et al, 2008). Attempts were made to attenuate this problem by splenic arterial ligation or portacaval shunt by some groups (Boillot et al, 2002; Man et al, 2003; Takada et al, 2004; Troisi et al, 2003, 2005).

In contrast to portal venous flow, liver is known to have an intrinsic regulatory mechanism to compensate even partially for alteration in portal flow, which is referred to as *hepatic arterial buffer response* (Lautt, 1985). In the case of PVE with hemihepatic portal vein occlusion or thrombosis of a portal branch, hepatic arterial buffer response is thought to still operate in embolized liver based on studies using dynamic computed tomography (CT) (Fig. 93A.1; Nagino et al, 1998; Wakabayashi et al, 2001), Doppler ultrasound (Denys et al, 2000; Kito et al, 2001), and three-dimensional magnetic resonance angiography (Gülberg et al, 2004), and their findings are in line with the report of a study using a rat model (Rocheleau et al, 1999); however, controversy surrounds the maintenance of hepatic arterial buffer response in nonembolized hemiliver (Denys et al, 2000; Kito et al, 2001; Rocheleau et al, 1999; Wakabayashi et al, 2001). Total liver blood flow, as estimated by a pharmacologic method, remained unchanged throughout the post-PVE period in our previous study (Shimada et al, 2002).

In summary, arterial flow in an embolized hemiliver is increased after PVE, in part to compensate for the cessation of portal flow. It is unclear whether arterial flow in the nonembolized hemiliver remains stable or decreases in response to the increment in portal flow. These factors may be a major concern when considering tumor growth in these hemilivers after PVE.

Because hepatic arterial buffer response is a partial compensation, hyperperfusion in a nonembolized hemiliver occurs after PVE, in contrast to hypoperfusion in an embolized hemiliver as expressed per gram of liver tissue. Corresponding hepatocyte regeneration in the nonembolized hemiliver occurs immediately after PVE proportional to the magnitude of the stimulus; however, little is known about when and how the atrophy-hypertrophy complex is terminated. Rocheleau and colleagues (1999) reported that, in a rat model of hemihepatic portal vein ligation, the hepatic atrophy-hypertrophy complex process (i.e., liver weight changes in the ligated and nonligated lobes) continues until total lobar flow per gram of liver tissue is restored. In Western series, planned hepatectomy after PVE had been scheduled when hypertrophy of the nonembolized liver segments seemed to reach their plateau, and full hypertrophy of the nonembolized segments was obtained 7 to 9 weeks after PVE (Azoulay et al, 2000a).

CLINICAL COURSE AFTER PORTAL VEIN CHEMOEMBOLIZATION

In contrast to transcatheter arterial chemoembolization (TACE), signs and symptoms of postembolization syndrome—such as pain, nausea, and vomiting—are minimal. Most patients experience mild fever after PVE, which subsides within 2 to 3 days. Changes in liver function, as reflected by an increased total bilirubin value and prolonged prothrombin time, are mild and transient, returning to their baseline values 2 to 3 days after PVE. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values are found to be stable in half of the patients, and in those remaining, values are mildly elevated (1.5 to 3 times the pre-PVE values) on day 1, returning to baseline values in 4 to 7 days after PVE, regardless of the embolization materials used. These findings suggest that inflammatory and necrotic reactions after PVE are minimal, if they

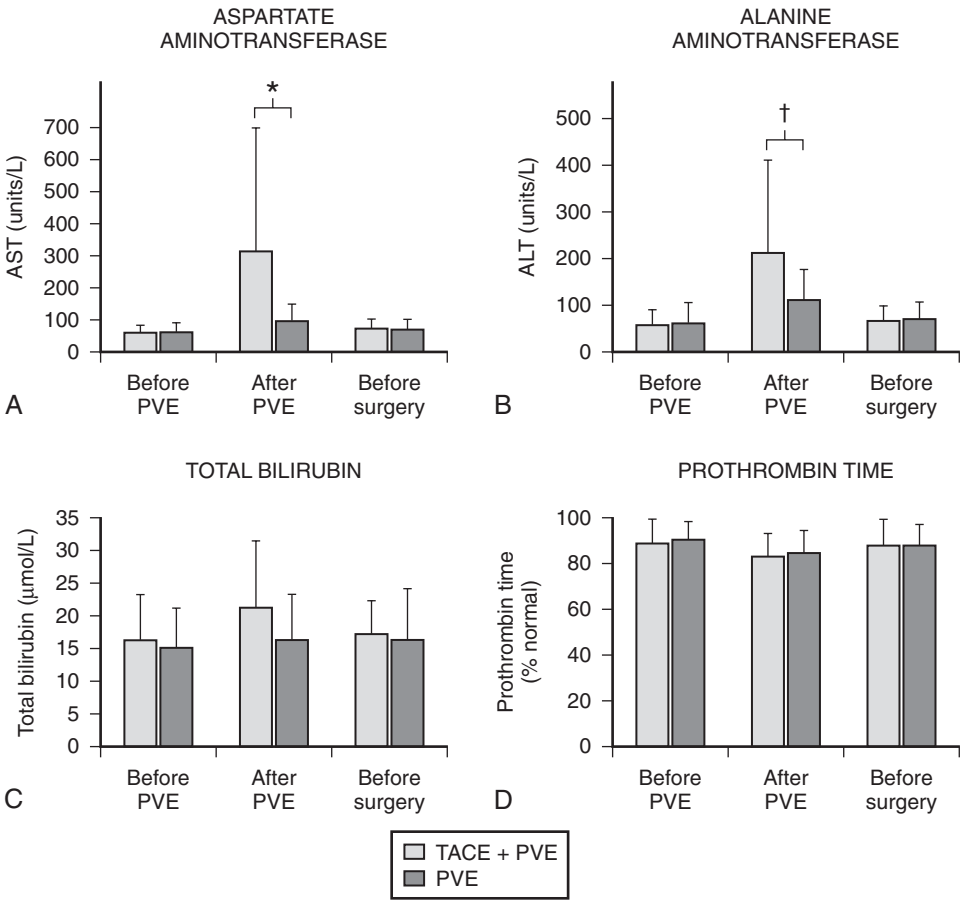


FIGURE 93A.2. Results of liver function tests before portal vein embolization (*PVE*), after PVE, and before surgery for patients who had transarterial chemoembolization (*TACE*) plus PVE and PVE alone. Values are mean (standard deviation). Peak values of (**A**) aspartate aminotransferase, (**B**) alanine aminotransferase, and (**C**) total bilirubin and (**D**) minimum value of prothrombin time were assessed before PVE, within 5 days after PVE, and within 5 days before surgery (*P = .026, †P = .031; student t test). *(From Ogata S, et al, 2006: Sequential arterial and portal vein embolizations before right hepatectomy in patients with cirrhosis and hepatocellular carcinoma. Br J Surg 93:1091-1098.)*

are present at all (Imamura et al, 1999a). The exceptions are when absolute ethanol is used for embolization (Shimamura et al, 1997), and when PVE is carried out after TACE (Aoki et al, 2004; Ogata et al, 2006). In both situations, PVE is followed by marked AST and ALT elevations, although both returned to baseline values by the time of scheduled hepatectomy (Fig. 93A.2).

Some have reported on adverse events (complications) or on morbidity rates associated with PVE (Table 93A.1). A multicenter European study of 188 patients who underwent contralateral PVE reported 24 adverse events (12.8%) (Di Stefano et al, 2005). Most adverse events were associated with the PVE technique, including complete portal thrombosis (n = 1), migration of embolic material in the main left portal vein feeding the FLR (n = 2), hemoperitoneum (n = 1), hemobilia (n = 1), rupture of a metastasis into the gallbladder (n = 1), and transient liver failure (n = 6). A recent meta-analysis documented overall morbidity rate for PVE to be 2.2% (Abulkhir et al, 2008). A summary of 37 publications involving 1088 patients showed a total of 497 minor complications and 11 major complications (see Table 93A.1).

VOLUMETRIC CONSEQUENCES OF PORTAL VEIN EMBOLIZATION

CT scan with contrast enhancement is the most commonly used method for calculating total liver volume (TLV) and FLR volume (FLRV). The nontumorous FLRV/(TLV– Tumor volume), or FLRV/TLV ratio, is a widely used parameter to determine whether PVE is necessary before hepatic resection and to assess the degree of FLR hypertrophy. Vauthey and associates (2002) proposed the use of standard liver volume (SLV), a concept first applied to clinical situations by us in 1995 (Urata et al, 1995). SLV is an alternative method for estimating TLV from a linear regression formula, correlating body surface area or body weight and TLV in healthy subjects (Urata et al, 1995; Vauthey et al, 2002). This formula is based

Table 93A.1

Complications Following Portal Vein Embolization

Details	
Complication	**Number**
Minor	
Abdominal discomfort or pain	209
Fever	250
Nausea or vomiting	26
Ileus	9
Overflow of embolization materials	2
Coil displacement	1
Major	
Liver abscess	3
Cholangitis	2
Main or left portal vein thrombosis	2
Subcapsular hematoma	2
Portal hypertension	1
Septic necrosis from hepatic artery injury	1

From Abulkhir A, et al, 2008: Preoperative portal vein embolization for major liver resection: a meta-analysis. Ann Surg 247:49-57.

on a concept that optimal liver/body mass ratio in healthy subjects is constant. We first referred to this optimal liver volume as SLV and proposed the application of SLV for recipients of LDLT and also for patients with end-stage liver disease, whose actual liver volumes are either extremely large or small in terms of ideal liver volume to be grafted, such as in cases of primary biliary cirrhosis or fulminant hepatic failure (Urata et al, 1995).

Vauthey and associates (2002) emphasized the importance of SLV as determining indications for PVE, because it may be applied to patients with pathologic liver or obstructive jaundice with dilated bile ducts and may even be calculated in patients with multiple liver metastases. Nevertheless, we adhere to the use of actual TLV for several reasons. First, SLV is a virtual volume estimated by using a formula, and different formulas are used among investigators; r^2 in the equation of Vauthey and associates (2002) is 0.49, indicating that their formula explains only half of the interindividual variations for TLV even in healthy subjects. Second, patients with extremely large or small livers in terms of SLV because of underlying liver diseases may not be candidates for liver resection even after PVE. Finally, up-to-date devices such as multislice helical CT with contrast administration allow accurate volumetric measurement by subtracting small tumor volumes and vasculobiliary structures, even to Couinaud's segment level.

PVE leads to an increment of segmental volume in nonembolized hemiliver and a decrement of segmental volume in embolized hemiliver, homogeneously maintaining a constant TLV (in most studies, TLV remained unchanged after PVE). In case of right hemiliver PVE, regeneration rate of the noncirrhotic liver was 12 cm^2/day 2 weeks after PVE (Lee et al, 1993; Nagino et al, 1995), decreasing to 11 cm^2/day at 4 weeks (Nagino et al, 1995) and then 6 cm^2/day at 32 days (De Baere et al, 1996). In cirrhotic patients, regeneration is reportedly slower, at a rate of 9 cm^2/day at 2 weeks (De Baere et al, 1996; Lee et al, 1993). In noncirrhotic and cirrhotic livers, regeneration processes are thought to be blunted by approximately 50% compared with that after hepatectomy (Yamanaka et al, 1993). Results of hypertrophy of nonembolized liver segments after PVE are summarized in Table 93A.2. In most series, hypertrophy of nonembolized liver segments in normal liver was 10% to 15%, expressed in volumetric ratio of nonembolized liver segments to TLV. The figure was smaller (5% to 10%) in diseased liver.

Various factors have been reported to affect the regeneration rate after PVE. Regeneration rate depends on embolized hemiliver volume (Imamura et al, 1999a; Yamakado et al, 1997). In other words, the greater the FLRV before PVE, the smaller the volume increase after PVE. Materials used for embolization affect the results in magnitudes of hypertrophy. Hypertrophy seemed to be modest when biologic materials such as Gelfoam and fibrin glue were used, most probably as a result of the progressive recanalization they induced. Absolute ethanol was reported to achieve the highest degree of regeneration but at the expense of marked increases in AST and ALT levels secondary to liver necrosis (Shimamura et al, 1997). Among the disorders related to background patient characteristics, diabetes, obstructive jaundice, active hepatitis, and cirrhosis have been reported to hamper the regeneration process (Imamura et al, 1999a; Nagino et al, 1995; Tanaka et al, 2000).

Table 93A.2

Hypertrophy of Nonembolized Liver Segments After Portal Vein Embolization

Reference	Number	Cancer Type	Embolizing Materials	Interval (weeks)	Volume Increase (%)
Makuuchi et al, 1991	54	32 HCC, 12 HBD, 8 CLM, other 2	Gelfoam, Urografin, gentamicin	2 to 3	14
Nagino et al, 1995	19	14 GB, 5 HBD	Fibrin glue, Lipiodol	1	11
De Baere et al, 1996	31	22 CLM, other 9	Histoacryl, Gelfoam, or coils	4-5	12
Shimamura et al, 1997	7	7 HCC	Absolute ethanol	7	27
Imamura et al, 1999a	84	49 HBD, 22 GB, 7 CLM, 5 HCC, other 1	Gelfoam, thrombin, Urografin, Lipiodol, or gentamicin	2	10
Azoulay et al, 2000a	10	10 HCC	Histoacryl, Lipiodol	9	16
Azoulay et al, 2000b	30	30 CLM	Histoacryl, Lipiodol	9	11
Wakabayashi et al, 2002	43	25 HCC, 10 CLM, 81 CC	Gelfoam	3	9
Elias et al, 2002	68	69 metastatic	Histoacryl, Lipiodol	4	13
Abdalla et al, 2002	18	9 metastatic, 9 primary (normal liver)	Polyvinyl alcohol, microcoils	3-6	8
Farges et al, 2003	27	14 HCC	Histoacryl, Lipiodol	4-8	9
		11 CC, 10 CLM, 2 others	Hostoacryl, Lipiodol	4-8	16
Aoki et al, 2004	17	17 HCC	Gelfoam, thrombin, Urografin, gentamicin	3	9
Ogata et al, 2006	36	36 HCC	Histoacryl, Lipiodol	4-8	8
Seo et al, 2007	32	32 HCC	Liquid embolic material (Embol-78)	3	0

CC, colorectal cancer; CLM, colorectal liver metastases; GB, gallbladder; HBD, hilar bile duct; HCC, hepatocellular carcinoma

HISTOLOGIC CONSEQUENCES OF PORTAL VEIN EMBOLIZATION

Human liver tissue obtained 3 weeks after PVE showed almost normal microscopic structures in the embolized and the nonembolized lobes. In the embolized lobe, dilation of sinusoids with decreased hepatocyte density and hepatocyte apoptosis were observed, especially in the pericentral area (Harada et al, 1997). Nevertheless, no signs of necrosis or inflammation were apparent, except when the embolizing material used was absolute ethanol, with tissue showing clear evidence of necrosis (Shimamura et al, 1997), or cyanoacrylate, which causes peribiliary fibrosis (De Baere et al, 1996). In contrast, microscopic findings in the nonembolized hemiliver showed hepatocyte replication as evidenced by the increased mitotic figures and other parameters of cell proliferation, such as proliferative cell nuclear antigen and Ki-67 (Harada et al, 1997; Kusaka et al, 2006), these hepatocytes were histologically characterized by basophilic cytoplasm and abundant binuclear cells, and they were small. These observations are indirect evidence of hepatocyte proliferation (Harada et al, 1997).

Concluding from the above described laboratory and volumetric data, embolized hemiliver seemed to atrophy (Fig. 93A.3) through apoptosis and subsequent cell deletion, as already suggested by Kerr and associates (1972), who coined the term *shrinkage necrosis.* Meanwhile, the volume increase in nonembolized hemiliver is explained by hyperplasia; that is, a net increase is seen in cell numbers, rather than cellular hypertrophy, such as in the case of *foie gras de canard.*

FUNCTIONAL CONSEQUENCES OF PORTAL VEIN EMBOLIZATION

Cellular hyperplasia and resulting hemiliver hypertrophy do not signify functional gain in the corresponding hemiliver, because proliferating isolated hepatocytes lose their differentiated hepatocyte-specific functions. Most previous reports that investigated liver function after PVE assessed whole liver function, including the embolized and the nonembolized lobe. Overall, functional hepatocyte number—estimated by the clearance of antipyrine, a prototype of low-extractable drug—showed similar values before and 2 weeks after PVE (Shimada et al, 2002). The adenosine triphosphate concentrations and hepatic energy reserves per gram of liver tissue assessed in the nonembolized lobe 3 weeks after PVE were similar to those of control tissue (Chijiiwa et al, 2000). Likewise, the nonembolized lobe uptake of technetium 99m-galactosyl human serum albumin (^{99m}Tc-GSA), a ligand bound to asialoglycoprotein receptors on the hepatocyte cell membrane, showed a rapid increase 1 to 2 weeks after PVE (Hirai et al, 2003; Nishiguchi et al, 2000). These findings showed the volume increase in the nonembolized lobe accompanied by a parallel increment in liver function in the corresponding lobe. Improvement in FLR function was also apparent from an increase in bilary excretion (Ijichi et al, 2001; Uesaka et al, 1996).

In a human PVE study, Uesaka and associates (1996) reported that patients with obstructive jaundice showed biliary indocyanine green (ICG) excretion from the nonembolized lobe increasing from the baseline value 10 to 16 days after PVE, and that this increment was more significant than the volume increase. Taking into account that the ICG extraction ratio in noncirrhotic liver is 0.7 to 0.8, ICG transport from hepatocyte to bile canaliculi is extremely fast, and accordingly, its biliary excretion is highly flow dependent; this result in human studies is thought to be an equivalent to that of the rat study reported by Rocheleau and colleagues (1999), and it suggests that the hepatic atrophy-hypertrophy complex process is still underway 2 weeks after PVE. Although this study is often considered to suggest that the gain in function is faster than the gain of volume after PVE, the results should appropriately be interpreted as relating to hemodynamic changes after PVE, considering the pharmacokinetic properties of ICG.



FIGURE 93A.3. Liver of a 75-year-old man with hepatitis C–related chronic hepatitis and hepatocellular carcinoma after right portal vein embolization. Left hemiliver was hypertrophied; right hemiliver was atrophied with darkened color and a wrinkled surface.

INDICATIONS

Cholangiocarcinoma

PVE is indicated most frequently for cholangiocarcinoma, because extended right hepatectomy together with caudate lobe resection is often necessary for curative resection (Kawasaki et al, 2003; Makuuchi et al, 1984, 1990; Nagino et al, 2001; Seyama et al, 2003; see Chapter 50B). Most patients have obstructive jaundice and cholestasis-induced impairment of liver function. Associated pancreatoduodenectomy is necessary in cases with widespread bile duct carcinoma of the main bile duct, as a scheduled procedure or as a result of intraoperative frozen section pathology, to obtain a negative surgical margin. These factors favor the application of PVE to achieve safe hepatic resection.

Unilateral biliary decompression of the FLR lobe is recommended before PVE to improve function in the portion of the liver to remain after hepatectomy. We favor a unilateral approach, even when the communication between the right and left bile ducts is interrupted by tumor progression, in view of the enhanced atrophy-hypertrophy process and the volume gain in the FLR lobe (Braasch et al, 1972; Kawasaki et al, 2003; Kyokane et al, 2003; Seyama et al, 2003). Our recent results also demonstrated that both hypertrophy and bilirubin clearance of the FLR were much improved by selective biliary drainage when compared with total biliary drainage (Ishizawa et al, 2007). The rate of catheter-related infection was also reported

to have increased with the number of stents (Neuhaus et al, 1999), and it is important not to carry out unnecessary cholangiography after biliary drainage until hepatectomy. When PVE by a transhepatic contralateral approach is scheduled, biliary decompression before PVE decreases the risk of portobiliary fistula, although not all agree with this approach.

Liver Metastases

Liver resection offers the only chance for cure with possible long-term survival for patients with liver metastases of colorectal origin, including bilateral metastases (Weber et al, 2000; see Chapter 81A). In patients with massive liver tumors that occupy the right liver, extended right hepatectomy does not result in a marked decrease in normally functioning hepatic mass. When similar extensive surgical procedures are indicated for small multiple metastases in the right hemiliver, for a solitary tumor located adjacent to the hilum of the liver, or for bilateral tumors, a large amount of functional hepatic mass must be removed. PVE may be performed under these circumstances to expand the operative indications to patients whose tumors would otherwise be unresectable, owing to their small FLRV, or to increase operative safety (Azoulay et al, 2000b; Elias et al, 2002; Kawasaki et al, 1994a). PVE is also recommended when major hepatectomy is planned with a simultaneous major gastrointestinal procedure, such as when hepatic metastases are removed synchronously with the primary colorectal lesion, or when liver injury is suspected from the preceding systemic or locoregional chemotherapy (Farges et al, 2003).

One major concern is whether PVE enhances tumor growth, especially in the nonembolized lobe (Elias et al, 1999; Kokudo et al, 2001). Increasing evidence suggests that PVE itself stimulates tumor growth, both in embolized and nonembolized segments of the liver, by altering the blood supply and/or inducing a network of cytokines and growth factors, although the precise mechanism and network have not been fully clarified (Fig. 93A.4; see Chapter 10). In embolized segments of the liver, the increased hepatic arterial flow induced by the occluded portal venous flow, the *hepatic arterial buffer response*, may also promote tumor growth.

In addition, various cytokines and growth factors associated with liver regeneration and hypertrophy may also have stimulatory effects on tumors in the nonembolized segments. Hepatocyte growth factor, epidermal growth factor, transforming growth factor–α, tumor necrosis factor–α, and interleukin-6 are all positive regulators of regeneration and hypertrophy, and all are candidates for tumor growth–inducing factors after PVE (Christophi et al, 2008). On the other hand, a recent animal study suggests that cytokines and growth factors associated with atrophy-hypertrophy after PVE are different from those associated with liver regeneration after a partial hepatectomy (Heinrich et al, 2006).

Clinically, long-term results were reported to be similar regardless of whether PVE was conducted (Azoulay et al, 2000b; Elias et al, 2002). However, Kokudo and colleagues (2001) reported that the disease-free survival period was significantly poorer in the PVE group than in the control group, suggesting that PVE may enhance the aggressiveness of metastatic tumors.

With this possible shortcoming in mind, several authors have proposed two-stage procedures to avoid possible tumor growth in the nonembolized FLR lobe for patients with bilobar metastases: first, the primary tumor is resected, if necessary; next, left liver limited metastasectomies are performed; then right portal vein ligation or PVE are carried out. After an interval of several weeks, (extended) right hepatectomy is performed (Jaeck et al, 2004; Kianmanesh et al, 2003a).

Currently, an increasing number of patients with colorectal liver metastases receive neoadjuvant chemotherapy; however, the liver parenchyma after neoadjuvant chemotherapy using irinotecan is often steatotic, fibrotic, and sometimes cirrhotic. Similarly, sinusoidal obstruction syndrome associated with oxaliplatin has been reported. Such hepatotoxicity is assumed to have an inhibitory effect on the hypertrophy of the nonembolized FLR. Several groups have evaluated the effect of periprocedural chemotherapy, both on tumor growth and FLR hypertrophy, with conflicting results (Aussilhou et al, 2009; Beal et al, 2006; Covey et al, 2008; Goere et al, 2006; Zorzi et al, 2008). Further investigation is necessary to draw an exclusive conclusion.

Hepatocellular Carcinoma

Hepatectomy remains the sole treatment for large HCC, and major hepatic resection is often required (see Chapter 80). Likewise, segment-oriented anatomic resection is recommended even for small HCCs to prevent postoperative recurrence (Hasegawa et al, 2005; Imamura et al, 1999b; Makuuchi et al, 1985; Regimbeau et al, 2002; see Chapter 92); however, 90% of HCC patients have impaired hepatic functional reserve because of hepatitis B or C virus–associated liver fibrosis and cirrhosis, which is the main obstacle to performing hepatic resection. Shirabe and associates (1999) reported a rise in the rate of postoperative liver failure with a smaller FLRV in HCC patients, and PVE triggered liver regeneration in 80% to 90% of HCC patients with chronic liver disease; however, the process was hampered compared with that in patients with normal livers (Aoki et al, 2004; Azoulay et al, 2000a; Farges et al, 2003; Wakabayashi et al, 2002).

We combine selective TACE with PVE before performing major hepatic resections for patients with HCC (Aoki et al, 2004; Kubota et al, 1997). This double preparation aims at 1) using TACE to prevent tumor progression during the interval between PVE and the planned hepatectomy, in view of the fact that most HCCs are hypervascular tumors fed exclusively by arterial blood flow (Fig. 93A.5); and 2) enhancing the effect of PVE by first using TACE to embolize the possible arterioportal shunt, which is frequently found in cirrhotic livers and HCC tumors. Others also advocate this double preparation (Azoulay et al, 2000a; Ogata et al, 2006; Wakabayashi et al, 2002; Yamakado et al, 1997).

In most cases, we perform PVE when liver function test results stabilize, usually 7 to 10 days after TACE. Compared with cases with PVE alone, PVE performed after TACE resulted in marked elevations of AST and ALT values, reflecting necrotic and inflammatory reactions after embolization (see Fig. 93A.2). These values returned to their baseline by the time of the planned hepatectomy. Bilirubin level remained essentially stable after PVE (Aoki et al, 2004); however, 10% to 20% of patients did not show FLR hypertrophy after PVE, and hepatectomy was abandoned. Despite a technically successful PVE, lack of hypertrophy is most likely explained as failure to increase portal flow to the FLR because of the presence or development of collateral vessels to the systemic circulation.

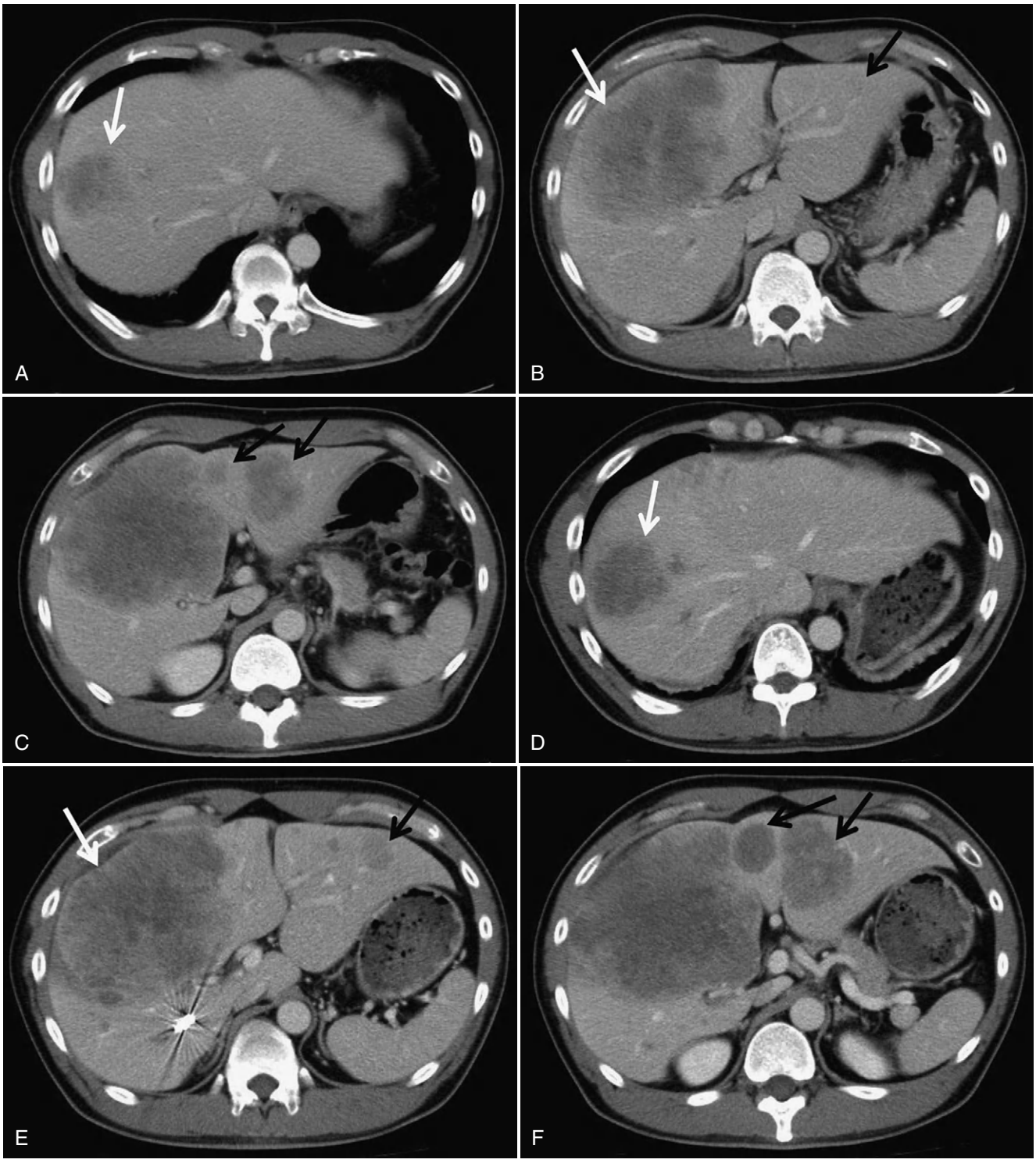


FIGURE 93A.4. Tumor growth after portal vein embolization (PVE) is shown on computed tomographic imaging of a 47-year-old man with multiple colorectal liver metastases before (**A** to **C**) and 2 weeks after (**D** to **F**) right PVE. Tumors both in the embolized segments (*white arrows*) and nonembolized segments (*black arrows*) show increases in size.

Our group and others have reported similar phenomena after embolization in patients with portal hypertension (Hasegawa et al, 2004; Nagino et al, 2002). Based on these observations, Kianmanesh and associates (2003b) used it in Child-Turcotte-Pugh class A patients. PVE preoperatively tests the capacity of injured liver to regenerate, and the absence of hypertrophy after PVE is a contraindication for major hepatic resection for these patients. Wakabayashi and associates (2002) also recognized the close relationship between the result of hypertrophy and short-term outcome. Based on their results, Farges and associates (2003) claim that, contrary to the views of Azoulay and colleagues (2000a), in most patients showing

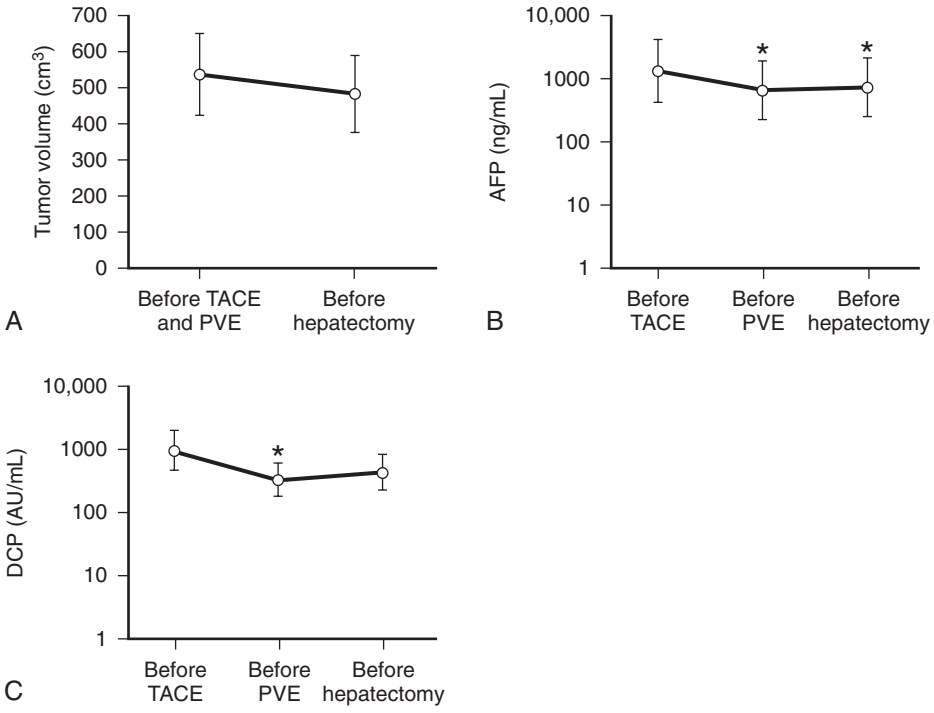


FIGURE 93A.5. Changes in (**A**) tumor volume before transarterial chemoembolization (*TACE*) and portal vein embolization (*PVE*) and before hepatectomy, and changes in (**B**) serum α-fetoprotein (*AFP*) and (**C**) plasma des-γ-carboxy prothrombin (*DCP*) before TACE, before PVE (after TACE), and before hepatectomy (after PVE), all in patients with hepatocellular carcinoma. Data are expressed as mean ± standard error of the mean, and the levels of AFP and DCP were compared after logarithmic transformation (*$P = .02$ by analysis of variance). *(From Aoki T, et al, 2004: Sequential preoperative arterial and portal venous embolizations in patients with hepatocellular carcinoma. Arch Surg 139:766-774.)*

adequate hypertrophy, the actual interval between PVE and resection can be less than 4 weeks. Our opinion is in line with Farges and colleagues (2003) because one of the aims of conducting PVE is to avoid the sudden increase of portal venous pressure after major hepatectomy, and because portal pressure is elevated immediately after PVE, it decreases gradually in 1 to 2 weeks.

In contrast to the observation that PVE may affect disease-free survival of patients with colorectal liver metastases with its stimulatory effect on the tumor (Kokudo et al, 2001), it was suggested that long-term results after right hepatectomy following PVE for HCC may be superior to right hepatectomy without PVE, although tumor-free survival was comparable between the two groups. Tanaka and associates (2000) speculated that preoperative PVE may preserve hepatic function and allow treatment of tumor recurrence, which in turn leads to better overall survival. In addition, Ogata and associates (2006) reported that, compared with PVE alone, the combination of TACE and PVE resulted in superior FLR hypertrophy and better long-term survival.

General Indications

Under what circumstances does PVE become necessary? In other words, to what extent can liver be safely resected without PVE? General indications for PVE are based on the size of the FLR, the underlying liver disease, and the extent or complexity of the hepatectomy. Intuitively, patients with liver pathology—such as fibrosis or cirrhosis, cholestasis, steatosis, and side effects of prior chemotherapy—require a larger FLRV than patients whose liver is normal. The same holds true for patients who require synchronous additional surgery, such as pancreatoduodenectomy or low anterior resection for rectal carcinoma; however, few data exist regarding the hepatic volume required to support life and prevent complications. In LDLT, the lower limit of residual liver volume or TLV that allows a patient to be a donor candidate is thought to be 30% (Fan et al, 2000; Kokudo et al, 2005). The FLRV/TLV ratio indicated for PVE is determined arbitrarily by each institution, and it ranges from 20% to 40% (Azoulay et al, 2000a, 2000b; Elias et al, 2002; Hemming et al, 2003; Imamura et al, 1999a; Kishi et al, 2009).

We advocate PVE in two situations: first, in patients with normal liver (ICG retention rate at 15 minutes [ICG R15] < 10%) if FLRV/TLV is less than 40% and, second, in patients with an injured liver (10% < ICG R15 < 20%), if FLRV/TLV is less than 50%. If ICG R15 exceeds 20%, major hepatectomy is contraindicated even after PVE (Kubota et al, 1997). Again, we think that actual TLV is more suitable for required volume estimation than the estimated TLV calculated from a formula correlating to body size, whereas Vauthey and colleagues advocate a standardized FLRV (percentage of FLRV to estimated TLV) of 20% or less (Abdalla et al, 2002).

Farges and associates (2003) reported that induction by PVE resulted in an increase of the FLRV/TLV ratio from 31% to 47% in patients with normal liver parenchyma (n = 13); however, these patients showed similar postoperative courses to those of patients who underwent hepatectomy without PVE (n = 14; FLRV/TLV = 30%) in terms of total bilirubin, prothrombin time, and hospital stay. Meanwhile, the authors obtained data to improve these parameters by conducting PVE in patients with chronic liver disease (n = 14 each; FLRV/TLV ratio increased by 9% in the PVE group) (Farges et al, 2003). Based on these findings, they recommended routine application of PVE for patients with diseased livers. On the other hand, this procedure was considered unnecessary for patients with normal liver, except in patients undergoing an extensive resection, a major synchronous surgical procedure, or for minor hepatectomies involving the FLR lobe (Belghiti, 2004; Farges et al, 2003).

Indications for PVE should be discussed, with special emphasis on its medical cost and associated complications.

Complication rates depend heavily on technical expertise; however, if these factors are considered negligible, we would favor our criteria, discussed earlier. Although fatal complications such as liver insufficiency are rare, hepatic dysfunction as assessed by prothrombin time prolongation and bilirubin elevation, overall complication rate, and mean hospital stay correlated closely with FLRV/TLV ratio (Abdalla et al, 2002; Belghiti, 2004; Shoup et al, 2003). At the same time, in LDLT, although the clinically significant complication rate did not differ among the various types of grafts, residual liver volume fraction showed a close correlation with peak prothrombin international normalized ratio and total bilirubin levels (Kokudo et al, 2005; Salamé et al, 2002).

CONCLUSION

In 2 to 4 weeks, PVE induces atrophy in the embolized hemiliver to be resected, with compensatory hypertrophy of the hemiliver to be preserved. By decreasing the risk of liver failure, complication rate, and hospital stay, PVE increases the safety of resection and expands the indication for liver resection to patients who are otherwise poor candidates for hepatectomy, owing to inadequate estimated liver size and function. PVE is of particular value for patients with chronic liver disease, including obstructive jaundice and steatosis; for patients undergoing concomitant resection of major organs; or those with bilateral liver tumors. Some variables are known to effect the atrophy-hypertrophy complex after PVE, including extent of embolization, the embolizing material used, and comorbidities such as diabetes, obstructive jaundice, active hepatitis, and cirrhosis.

Meanwhile, the effect of periprocedural chemotherapy on hypertrophy of the FLR remains to be clarified. According to published reports, the cutoff residual liver volume indicated for PVE ranges from 20% to 40%. The range is inevitable, because a randomized trial to verify which patients might be candidates for liver resection, with the lowest residual liver volume but without PVE, would be unethical. Continued prospective examination of PVE with defined end points—such as postoperative liver function, operative complications, and length of hospital stay—should in the future clarify the benefits attained by PVE.

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CHAPTER 94

Ex vivo and in situ hypothermic hepatic resection

Ian D. McGilvray and Alan W. Hemming

OVERVIEW

The limits of liver surgery are constantly evolving, propelled by advances in surgical technique and imaging. Extended right and left hepatectomies, previously considered to be pushing the boundaries of resection, have become relatively standard procedures for experienced liver surgeons. Strategies such as preoperative portal vein embolization (PVE) (see Chapter 93) to allow growth of the planned liver remnant allows even more aggressive resections to be performed with a morbidity similar to that of less extensive resections. Advances in surgical technique have been paralleled by advances in hepatic imaging, giving the liver surgeon greater ability to assess tumor position in relation to the intrahepatic vascular and biliary structures. Over the same period, liver transplantation has thrived and proliferated, and more recently the development of living donor liver transplantation (LDLT) has led to a variety of techniques that also can be applied in nontransplant liver surgery. Standard components of LDLT include resection and reconstruction of portal venous, hepatic arterial, biliary, and hepatic venous structures (see Chapters 90D and 98B). These same techniques are now more frequently being considered for the resection of hepatic tumors by surgeons experienced with liver resection and transplantation techniques.

The principal difficulty of vascular reconstruction during hepatic resection is the resulting period of hepatic ischemia. The liver can tolerate short periods of ischemia surprisingly well. During standard liver resections, the use of hepatic inflow occlusion is often used during the parenchymal transection to control excessive blood loss. The use of a combination of inflow occlusion with maintenance of low central venous pressure (CVP) allows relatively bloodless transection of the liver. Intermittent hepatic inflow occlusion for 15 minutes with 5 minutes of reperfusion at the end of each 15-minute interval can reduce the degree of liver injury (Man et al, 1997) and may be particularly useful in more complex resections.

Ischemic preconditioning seems to protect the liver from subsequent ischemic injury (Clavien et al, 2003) and is performed by applying a Pringle maneuver for 10 minutes, then reperfusing the liver for at least 10 minutes before reapplying inflow occlusion. The mechanisms by which ischemic preconditioning protects the liver from subsequent ischemia have not been fully elucidated, but even longer periods of ischemia are relatively well tolerated. The normal liver can tolerate 60 minutes or more of continuous inflow occlusion and warm ischemia (Huguet et al, 1994; Azoulay et al, 2005), but patients with cirrhosis or altered liver function from biliary obstruction or prolonged chemotherapy may tolerate significantly less ischemic insult before sustaining irreversible injury (Hannoun et al, 1996); the same may be true of older patients (Selzner et al, 2009). Even with normal liver function, the risk of irreversible liver damage following prolonged periods of continuous ischemia is significant.

Beyond inflow occlusion, tumors that involve the retrohepatic inferior vena cava (IVC) or that involve the hepatic veins at their junction with the vena cava may require total vascular isolation (see Chapter 91A). Total vascular isolation may increase the degree of ischemic injury to the liver more than inflow occlusion alone, as there is some evidence that backward diffusion of hepatic venous blood into the liver attenuates ischemic injury (Smyrniotis et al, 2003). In most cases, however, the procedure can be planned such that most of the hepatic parenchymal division is performed without total vascular exclusion, and caval clamping is reserved for the relatively short time that is required to deal with the IVC or hepatic veins.

In fact, most resections involving hepatic vascular structures can be dealt with using techniques that do not involve protective strategies, such as hypothermic perfusion of the liver. Tumors that involve hilar vessels usually can be dealt with by temporary occlusion of the hepatic artery or portal vein with relatively short ischemic times. Blood flow to the liver is maintained by the artery, if the portal vein is reconstructed, or the portal vein, if the artery is reconstructed. In the rare case that the hepatic artery *and* the portal vein require reconstruction, the reconstructions can be performed sequentially, maintaining flow through one vessel or the other.

Based on the previous information, it would seem that standard liver resection techniques can be applied to almost every liver resection, without the need to consider the use of techniques that require hypothermic perfusion; however, a minority of patients will have lesions that seem truly unresectable by any conventional technique. Lesions that are centrally placed and involve all three main hepatic veins, with or without involvement of the retrohepatic IVC, are essentially unresectable using standard liver resection techniques. These few patients who require complex reconstruction of venous outflow may benefit from ex vivo or in situ hypothermic perfusion of the liver with hepatic resection and vascular reconstruction.

History of Hypothermic Perfusion and Ex Vivo Techniques

Fortner and colleagues (1974) first described the use of hypothermic perfusion during liver resection to protect the liver from ischemic injury in a series of 29 patients. Technical improvements in liver surgery over the next 2 decades, along with the growing understanding of the liver's ability to tolerate normothermic ischemia, made the use of hypothermic perfusion

unnecessary in most cases. During the same period, liver transplantation had been applied to technically unresectable primary and secondary liver malignancy with dismal results (see Chapter 97A). Although the procedure was technically feasible, transplantation for large, unresectable primary liver tumors, and especially for metastatic lesions, resulted in the rapid recurrence of malignancy, either in the new liver or elsewhere shortly after transplantation.

In response to patients with unresectable tumors who were considered inappropriate for liver transplantation, Pichlmayr and associates (1988) developed hypothermic perfusion with ex vivo liver resection. During ex vivo liver resection, the liver is removed completely from the body and perfused with cold preservation solution on the back table. The liver resection is performed on the back table in a completely bloodless field such that reconstruction of hepatic venous outflow is performed under ideal conditions; however, the morbidity and mortality rates from this procedure are relatively high; as a result, in situ and ante situm hypothermic perfusion techniques have been explored.

In situ hypothermic perfusion is performed using standard liver resection mobilization techniques, but the liver is placed in total vascular isolation (see Chapter 91A) and cold perfused via the portal vein. In the ante situm procedure, the liver is cold-perfused via the portal vein, with the hilar structures left otherwise intact; but the suprahepatic IVC is divided, and the liver is rotated forward, allowing improved access to the area of the liver and IVC centered around the hepatic vein confluence. To a great extent, the three techniques—in situ hypothermic liver perfusion, ante situm hypothermic liver perfusion, and ex vivo liver resection—overlap, and all three mirror aspects of LDLT. The procedure and role for each technique are described below.

IN SITU HYPOTHERMIC PERFUSION

In situ hypothermic perfusion is the least technically demanding of the three techniques. In situ perfusion has been recommended (Hannoun et al, 1996) for liver resections that require total vascular isolation for periods exceeding 1 hour. More recently Azoulay and colleagues (2005) demonstrated that hypothermic perfusion of the liver is associated with better tolerance to ischemia in the setting of total vascular isolation of any duration.

The need for total vascular isolation arises when patients have tumors in close proximity to or involving the hepatic veins, retrohepatic IVC, or both. In initial descriptions, the entire hepatic parenchymal transection was performed after cold perfusion of the liver, allowing a precise dissection of the hepatic veins and IVC to occur under bloodless conditions. If caval or hepatic vein resection was required during resection of the tumor, hepatic hypothermia safely allowed the additional ischemic time to perform reconstruction of the vascular structures.

To perform in situ cold perfusion as originally described, the liver is mobilized as for total vascular isolation (see Chapter 91A) with control of the suprahepatic and infrahepatic IVC and the portal structures. The main portal vein is dissected out for insertion of a perfusion catheter. Although the portal vein can be dissected from the right of the bile duct, for in situ perfusion, it is usually easier to dissect it from the left of the bile duct after dissecting out the hepatic artery; the hepatic artery eventually requires control in any event. A sufficient length of portal vein (3 to 4 cm) is exposed to place a perfusion catheter and the portal venous cannula of venovenous bypass, if this is to be used. Most patients tolerate total vascular isolation without venovenous bypass; however, the standard use of bypass reduces the time pressures involved in these cases and reduces the gut edema associated with prolonged portal clamping. Prior to clamping, the patient is bolused with at least 5000 U of heparin intravenously. The infrahepatic cava is clamped, and the patient is placed on the caval portion of venovenous bypass.

It is generally advisable, although not absolutely necessary, to ligate and divide the right adrenal vein before clamping the infrahepatic IVC, because it otherwise has a tendency to become avulsed during some particularly inconvenient portion of the procedure. A portal clamp is placed relatively superiorly on the portal vein with bypass instituted below. The portal cannula can be inserted down toward the superior mesenteric vein after complete division of the portal vein or by dividing just the anterior wall of the portal vein and sliding the cannula down the back wall. Full venovenous bypass is started. The liver side of the portal vein is cannulated with the perfusion solution tubing, and the hepatic artery is clamped. The suprahepatic cava is clamped, and a transverse venotomy is created in the infrahepatic IVC just above the clamp. Cold perfusion of the liver is begun with preservation solution, and the effluent is suctioned from the venotomy in the infrahepatic cava (Fig. 94.1).

Preservation solution is either histidine-tryptophan-ketoglutarate (HTK) (Gubernatis et al, 1990) or University of Wisconsin (UW) solution (Kalayoglu et al, 1988). The liver resection proceeds in a bloodless field with excellent visualization of intrahepatic structures. The liver can be cooled continuously throughout the parenchymal transection by slow infusion of cooling solution (see below), or it can be cooled intermittently

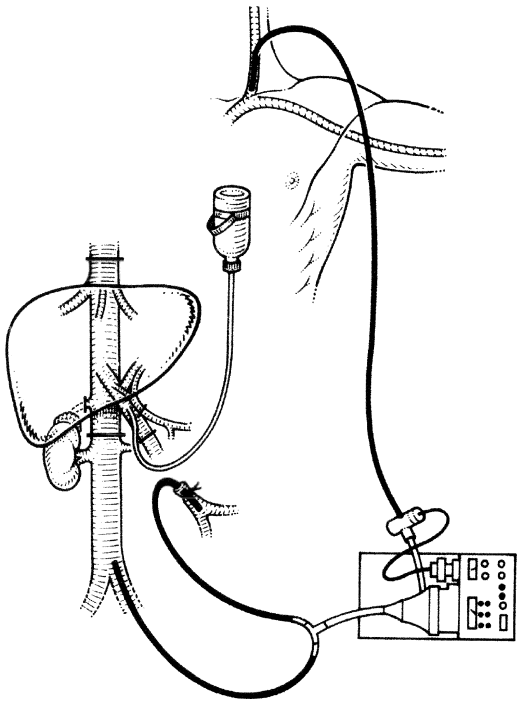


FIGURE 94.1. In situ cold perfusion. The patient is placed on venovenous bypass, and a cold perfusion solution is infused through the portal vein and vented through a venotomy in the infrahepatic inferior vena cava.

every 30 minutes by bolus infusion; at completion of the liver resection, the liver should be flushed of cold preservation solution, which can be done by flushing the portal vein with cold 5% albumin before restoring flow to the liver, or by allowing the initial 300 to 500 mL of venous effluent from the reperfused liver to be vented out the infrahepatic cava venotomy after reperfusion but before removing the suprahepatic cava clamp. Next, the portal bypass cannula is removed, and the portal vein is repaired or reanastomosed if divided. If the liver has been flushed with 5% albumin, the infrahepatic venotomy is closed, and the suprahepatic cava clamp is removed to assess hepatic venous bleeding, which should be controlled if present. Portal and hepatic arterial inflow is reestablished.

If the liver is warm-flushed with the initial blood flow through the liver, the sequence is altered slightly to prevent flushing of cold, high-potassium solution into the cardiac return. If a warm-flush technique is used, the portal vein is repaired, and the infrahepatic venotomy is closed with a running suture left loose and untied. Portal flow is established with the suprahepatic cava clamp in place. The initial 300 to 500 mL of blood is suctioned from the infrahepatic cava venotomy, the suture is secured, and the suprahepatic cava clamp is removed. We often cold flush the liver with 5% albumin, because it can be done in an unhurried fashion, and it allows sequential removal of clamps with separate assessment of hepatic venous and portal bleeding on reperfusion. The patient is decannulated from caval bypass if bypass has been used.

We rarely use in situ perfusion as just described. The advent of LDLT (see Chapters 90D and 98B) and the more frequent use of the anterior approach to liver resection (Liu et al, 2000) have improved the ability to divide the liver parenchyma and dissect along the hepatic veins without the need for extensive periods of inflow occlusion. In patients in whom a single hepatic vein or the vena cava requires reconstruction, most of the parenchymal transection can be performed without inflow occlusion under low CVP conditions. As the parenchymal transection is near completion, total vascular isolation is applied to divide and reconstruct the vascular structures only. This practice results in substantially shorter periods of hepatic ischemia and allows a different method of applying in situ cold perfusion that is simpler and generally does not require bypass.

In this technique, the liver is mobilized as for total vascular isolation. The portal vein is dissected to the right and left branches, and perfusion tubing is placed into the portal vein branch on the side of the liver to be removed (Fig. 94.2). The branch is divided, maintaining portal flow to the side of the liver to be left in but allowing access for cold perfusion. Alternatively, the anterior wall of the main portal vein can be used as a site of cannula insertion (Fig. 94.3). As much of the hepatic parenchyma as possible is divided under low CVP, maintaining hepatic perfusion until it becomes necessary to divide the hepatic veins or IVC that requires reconstruction.

At this point, the patient is volume loaded, and clamps are placed sequentially on the infrahepatic cava, the portal vein, hepatic artery, and the suprahepatic IVC. If only the hepatic vein requires reconstruction, caval flow can be maintained by controlling the offending hepatic vein by placing a clamp tangentially down onto the IVC, across the hepatic vein orifice, but only partially occluding the IVC (Fig. 94.4). The anterior wall of the IVC or hepatic vein is incised, and cold perfusion of the liver is instituted through the portal cannula. Only the side of the liver remaining in place is perfused. The vessels are transected, and the specimen is removed. The vessels, hepatic veins, or IVC can be reconstructed in a bloodless field without time pressures (Fig. 94.5). Before completing the anastomoses, the liver can be flushed with cold 5% albumin. Alternatively, the liver can be flushed with 300 to 400 mL of portal vein blood with the caval clamps still in place, whereupon the portal vein clamp is reapplied, the caval venotomy is closed, and all clamps are removed. With the shorter ischemic periods involved, we have not had to use venovenous bypass with this technique (Dubay et al, 2009; Hemming et al, 2002, 2004, 2008); even longer periods of total vascular isolation do not necessarily require venovenous bypass.

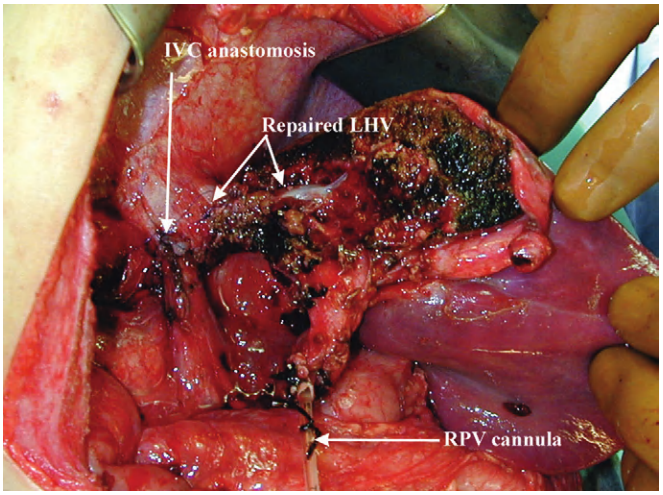


FIGURE 94.2. A portal cannula is inserted in the right portal vein (RPV) branch to allow in situ perfusion of the remaining segments II and III in an infant undergoing resection for hepatoblastoma. Cold perfusion allows resection of the inferior vena cava (IVC) and resection and repair of the medial aspect of the left hepatic vein (LHV) to be done in a controlled fashion.

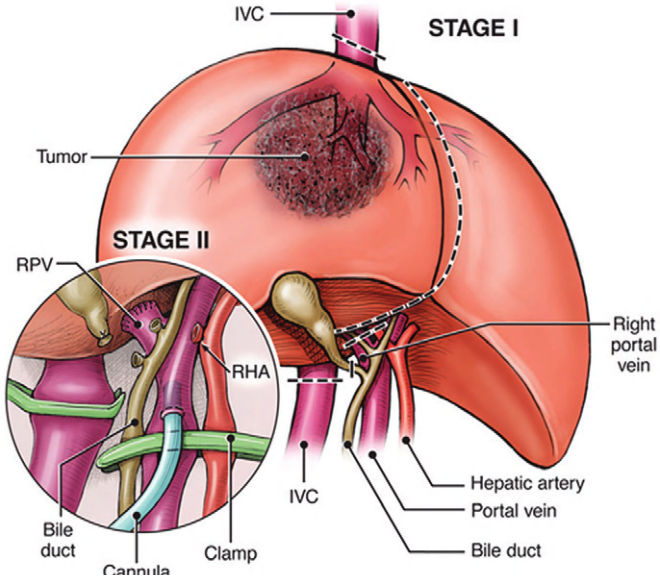


FIGURE 94.3. The anterior wall of the portal vein above the portal clamp can also be used for cannulation ad cold pefusion. IVC, inferior vena cava; RHA, right hepatic artery; RPV, right portal vein.

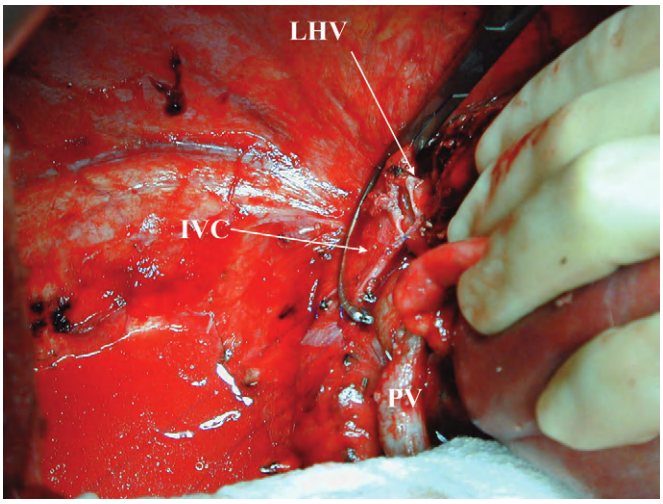


FIGURE 94.4. A vascular clamp can be placed tangentially on the inferior vena cava, occluding the implantation site of the hepatic vein but allowing maintenance of cava flow. This maneuver may allow in situ perfusion to be performed without the need for venovenous bypass. LHV, left hepatic vein.

ANTE SITUM PROCEDURE

The ante situm technique of liver resection can be used when resection of the IVC and hepatic veins is expected to be difficult, and when improved access to the hepatic veins and IVC is required. We have used this technique when combined cava and hepatic vein reconstruction is required (Azoulay et al, 2006).

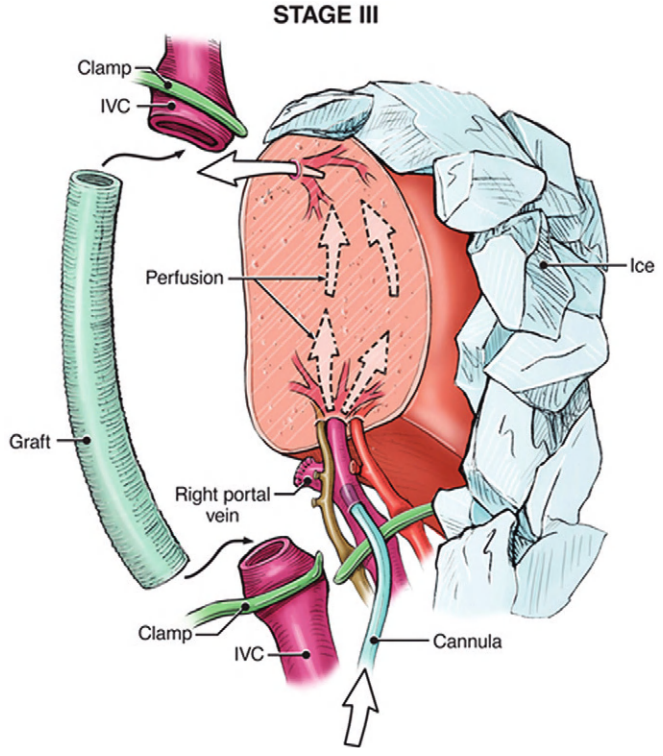


FIGURE 94.5. Continuous cold flushing of the remnant liver allows resection and reconstruction of the hepatic vasculature without time pressure. IVC, inferior vena cava.

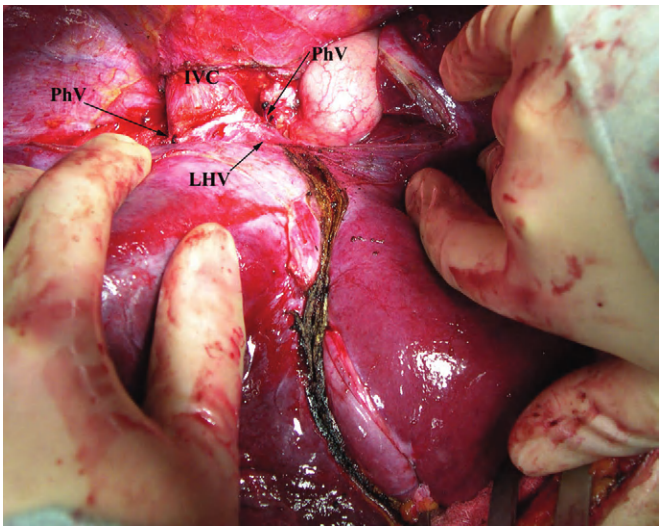


FIGURE 94.6. The phrenic veins (*Phvs*) are divided, and the suprahepatic inferior vena cava (*IVC*) is dissected away from the diaphragm to allow adequate length for placement of a suprahepatic cava clamp. This allows division of the suprahepatic vena cava with enough length to allow reanastomosis. LHV, left hepatic vein.

The ante situm technique uses the same technique as in situ cold perfusion with several caveats. The suprahepatic IVC requires more extensive dissection to achieve enough length to place a clamp on, divide, and subsequently reanastomose. Greater exposure of the suprahepatic cava can be obtained by dividing the phrenic veins and gently dissecting the IVC away from the diaphragm (Fig. 94.6). We frequently also open the pericardium directly anterior to the IVC and loop the intrapericardial vena cava; alternatively, a sternotomy provides superb exposure of the entire area (Fig. 94.7).

Control of the intrapericardial cava allows placement of the clamp on the vena cava or caudal right atrium within the pericardium as a primary option or as a secondary option in case technical difficulties arise with placement of the original suprahepatic cava clamp. We perform as much of the liver transection

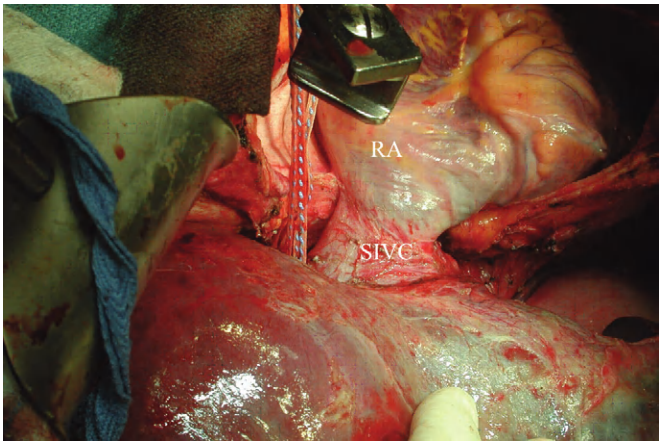


FIGURE 94.7. The addition of a median sternotomy provides excellent exposure to the suprahepatic inferior vena cava and confluence of the hepatic veins. RA, right atrium; SIVC, suprahepatic inferior vena cava.

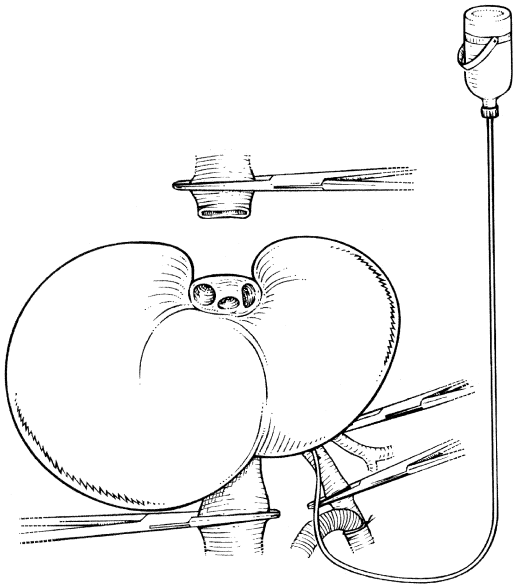


FIGURE 94.8. Ante situm cold perfusion. The suprahepatic inferior vena cava (IVC) is divided, allowing the liver to be rotated forward so the region of the hepatic vein–IVC confluence can be better visualized.

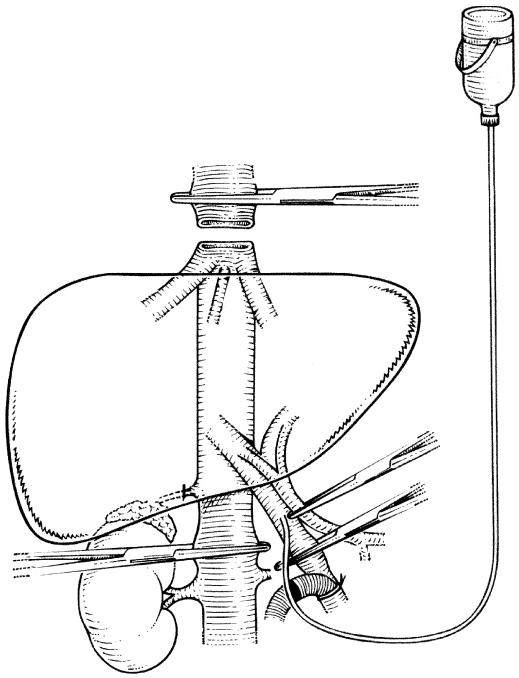


FIGURE 94.9. Venovenous bypass can be used during ante situm perfusion. If more exposure is required to the retrohepatic inferior vena cava (IVC) than is provided by dividing the suprahepatic IVC alone, the infrahepatic IVC also can be divided, allowing the liver to be rotated completely up onto the abdominal wall.

as possible without inflow occlusion before cold perfusing the liver. Venovenous bypass is generally recommended for this procedure; however, many patients tolerate caval clamping without difficulty. Institution of cold perfusion is as originally described for in situ perfusion; however, the perfusate is vented via the suprahepatic IVC as the suprahepatic cava is divided. Dividing the suprahepatic IVC allows the liver to be rotated forward and upward toward the abdominal wall, enabling greater access to the area immediately around the IVC–hepatic vein junction (the hepatocaval confluence) (Figs. 94.8 and 94.9).

If further access is required, the infrahepatic vena cava can be divided, allowing the liver to be rotated completely up onto the abdominal wall. With this technique, we have found that continuous, slow cold perfusion is required after the initial flush to prevent excessive warming of the liver. As a rule, the liver is first flushed with 1 L or so of ice-cold preservation solution wide open, with the bag suspended at shoulder height. After the initial bolus, the infusion rate is slowed to about a third of the original rate. Care is taken to suction the vented perfusate to avoid its systemic absorption.

The liver transection is completed, dividing the hepatic vein within the liver and resecting the origin of the junction of the IVC and hepatic vein en bloc with the tumor. If extension grafts are required, vascular reconstruction can be performed; the hepatic vein anastomoses, which are the most tenuous, are performed while the liver is rotated onto the abdominal wall. The liver is replaced, and the caval anastomosis is performed. The liver can be flushed with 5% albumin before reperfusion, or it can be flushed with warm portal blood, as described above.

The ante situm approach gives better access to the cava–hepatic vein junction than does simple in situ cold perfusion. The exposure is not as good as with a complete ex vivo approach. The advantage to the ante situm approach is that biliary and hepatic arterial anastomoses are not required, reducing the ischemic time to the liver and reducing the potential for complications resulting from these additional anastomoses. Currently, we use the ante situm approach when a combination of cava resection and hepatic vein reconstruction is required, and we expect to implant only a single hepatic vein orifice, whether from a single vein or one or more veins plastied together, into the cava (Figs. 94.10 through 94.12. In the few cases where the reconstruction is expected to be significantly more complex, we use a complete ex vivo approach.



FIGURE 94.10. Computed tomographic scan showing a cholangiocarcinoma centered on all three hepatic veins at the junction of the inferior vena cava. Right portal structures also were involved. A right trisegmentectomy with reconstruction of the left hepatic vein was planned.

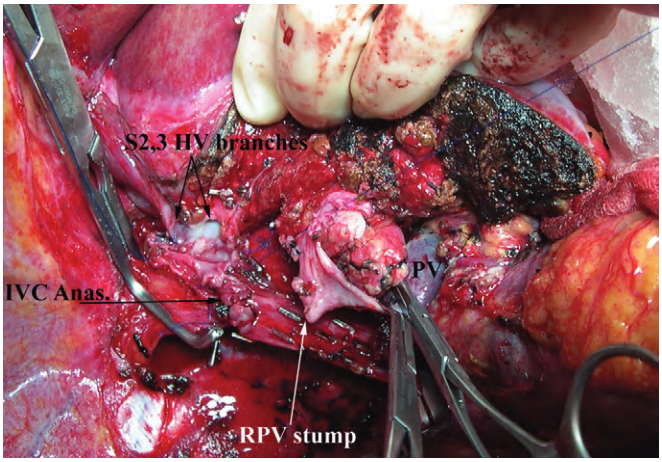


FIGURE 94.11. Parenchymal division along a right trisegmentectomy plane was performed, crossing into segments II and III superiorly. A cannula was placed in the stump of the right portal vein (*RPV*) for cold perfusion with University of Wisconsin solution. A short segment of the inferior vena cava (*IVC*) at the level of the hepatic veins and the first 3 cm of the left hepatic vein origin were resected, and the liver was rotated anteriorly. The IVC was reconstructed end to end with the left hepatic vein reimplanted above the cava anastomosis. IVC anas, IVC anastomosis; S2,3 HV, segments II and III hepatic vein branches.

EX VIVO LIVER RESECTION

Although the techniques described above can be applied to the majority of patients with difficult hepatic vein or caval reconstructions, patients who have tumors that involve the IVC and hepatic veins that require complex venous repair or patients with combined hepatic vein and hilar involvement may be candidates for ex vivo resection. During ex vivo resection, the liver is removed from the patient completely and perfused with cold preservation solution on the back table. The hepatic resection is performed in a bloodless field, and vascular reconstructions are performed before reimplanting the remnant liver into the patient.

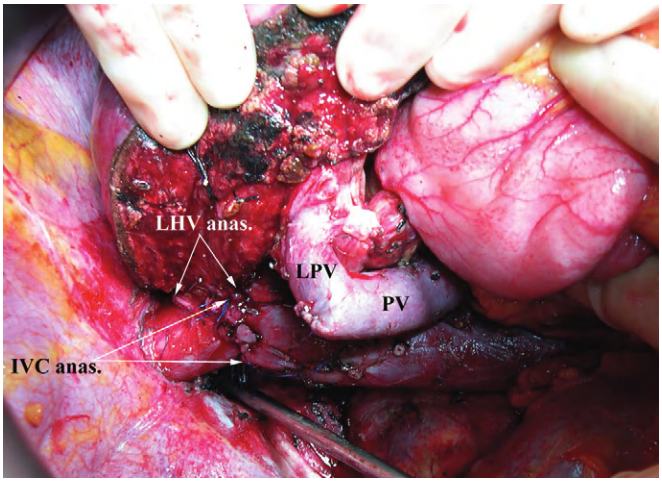


FIGURE 94.12. Reimplanted segments II and III from Figure 94.11. The left hepatic duct was reconstructed later using a Roux-en-Y limb. IVC anas., IVC anastomosis; LHV anas., left hepatic vein anastomosis; LPV, left portal vein; PV, portal vein.

Patient Selection and Preoperative Workup

In principle, any patient with liver malignancy that is unresectable by other means can be assessed for ex vivo liver surgery. In practice, almost all liver resections can be performed without the need for an ex vivo approach, whether hypothermic perfusion of the liver is required or not. Patients with tumors that involve the junction of the IVC and hepatic veins, such that complex, prolonged vascular reconstruction is required, or patients with combined vascular involvement of the hepatic veins and hilar structures, may benefit from a planned ex vivo approach.

One of the benefits of planning the ex vivo approach—or for that matter, planning any of the hypothermic perfusion techniques—is that frequently at operation, what initially was thought to be unresectable by any method short of complete removal of the liver is found to be resectable with a less complex procedure. General assessment of the patient is similar to that for liver transplantation, with particular assessment of cardiac risk factors. In patients older than 50 years of age or those with any cardiac abnormalities, a functional stress test, such as dobutamine stress echocardiogram, is performed. Any significant cardiac abnormality is a contraindication. Even mild renal dysfunction has been shown to increase the risk of standard extended hepatectomy (Melendez et al, 2001), and a creatinine level greater than 1.3 mg/dL should be considered a contraindication. Ex vivo liver resection should be attempted only in otherwise healthy, well-selected patients.

Preoperative imaging is crucial to stage the tumor and to assess its position in relation to hepatic vascular anatomy. Our current standard is triphasic spiral computed tomography (CT) with three-dimensional (3D) reconstructions, to assess the liver anatomy and tumor position, and CT of the chest and pelvis (see Chapter 16). In some instances, magnetic resonance imaging (MRI) is required, including MR angiography and MR venography, particularly when all three hepatic veins are involved, and some degree of hepatic venous obstruction is present that prevents adequate flow of contrast material into the hepatic veins during CT (see Chapter 17). With the combination of CT and MRI and the present availability of 3D reconstruction, invasive angiography is usually unnecessary. Contrast ultrasound provides a dynamic view of the relationship of the tumor to the hepatic veins and cava, and it is particularly useful for gauging extent of invasion of vascular structures by the tumor.

Remnant liver volume assessment can be performed as for extended hepatectomy. In a standard liver resection, assuming normal liver function, 25% of total liver volume (TLV) after resection is considered adequate for resection without the need for preoperative PVE (see Chapter 93A). One caveat is that patients who have undergone or are undergoing prolonged and aggressive preoperative chemotherapy may require more liver volume because of chemotherapy-induced steatohepatitis. With cold preservation and reperfusion, additional ischemic injury occurs over and above what happens during standard liver resection. We have arbitrarily chosen a projected liver remnant of 40% of TLV as a cutoff for consideration for preoperative PVE in patients who require extended hepatectomy who may need complex vascular reconstruction and cold-perfusion techniques (Hemming et al, 2003, 2008). A positron-emission tomography (PET) scan should also be considered for all patients to assess for the possibility of otherwise undetected extrahepatic disease (see Chapter 15).

Accurate imaging of the intrahepatic architecture is paramount to assess the possibilities for reconstruction. Three-dimensional imaging techniques occasionally may reveal unusual anatomy that makes vascular reconstruction unnecessary, such as the presence of a large inferior hepatic vein that makes reconstruction of the main right hepatic vein unnecessary. Alternatively, anatomy may be discovered that requires additional reconstruction, such as a large segment VI vein that drains into the middle hepatic vein (Lang et al, 2004).

Anesthesia

Anesthetic management for ex vivo liver resections is similar to that for liver transplantation (see Chapter 97B). Maintaining patient temperature is a key component of anesthesia management and includes the use of forced-air warming blankets and warming of all fluids. In addition to standard monitoring for liver resection, a Swan-Ganz catheter is inserted for hemodynamic monitoring and assessment of blood temperature in the pulmonary artery. Access for venovenous bypass, which originally was achieved by cutdowns, has been simplified by percutaneous insertion techniques.

Most cases begin with maintenance of low CVP, as would be standard for most liver resections, because most cases do not proceed to ex vivo techniques. Percutaneous catheters are placed in the internal jugular vein or subclavian vein and the femoral vein for the cava portion of the bypass circuit, when an ex vivo procedure is decided on. At that time, the patient can subsequently be volume loaded. The portal limb of the circuit is placed directly into the portal vein by the surgeon, although an alternative approach is to insert the portal cannula through the inferior mesenteric vein; this vein can then be ligated at the time of cannula removal.

In an ex vivo procedure, the anhepatic phase generally lasts from 2 to 4 hours, and attention must be paid to coagulation during this period. As for liver transplantation, we give fresh frozen plasma to meet volume requirements during this time and minimize the use of crystalloid. Glucose levels are monitored, and constant glucose infusion is required.

As with LDLT, on reperfusion of the cold autograft, the temperature of the blood in the pulmonary artery can drop precipitously. For liver transplantation and ex vivo liver resection, we continuously monitor the pulmonary artery blood temperature and manually compress the portal inflow temporarily, when the temperature decreases to less than 35° C. Portal occlusion for 10 seconds or so allows the pulmonary artery blood temperature to increase to 36° C, after which portal compression is released. The maneuver is repeated as many times as may be required over the course of reperfusion. Pulmonary artery blood temperature commonly decreases to 32° C to 33° C without portal compression on reperfusion. In our experience, avoiding this precipitous drop in pulmonary artery blood temperature seems to reduce the cardiac dysfunction that occurs on reperfusion of the liver.

Surgical Procedure

Pichlmayr and Hauss (1994) described the procedure of ex vivo liver resection in the second edition of this textbook; they appropriately described the procedure in terms similar to liver transplantation. The following description of technique is taken largely from Pichlmayr's original description in this textbook with some minor modifications by the current authors. The procedure comprises three phases: 1) assessment of resectability and removal of the liver, 2) liver resection and vascular reconstruction on the back table, and 3) reimplantation of the liver autograft. As with the preceding discussion, many of the recommendations found below are applicable to any of the three hypothermic perfusion techniques described in this chapter.

Assessment of Resectability and Removal of the Liver

An initial assessment of resectability is undertaken via laparoscopy or a limited abdominal incision to assess the presence of peritoneal disease that would preclude proceeding with resection. Even after a negative laparoscopy, we perform a limited abdominal incision and assess the abdominal cavity. It is common to have a negative laparoscopy only to find additional small lesions in the liver or elsewhere that would be a contraindication to proceeding. The incision is lengthened to some variation of a bilateral subcostal incision, with or without a midline extension. Alternatively, a midline laparotomy with a horizontal right extension can be used, and either approach can be combined with a midline sternotomy for the sake of exposure of the hepatocaval confluence.

The liver is assessed for resectability. Because the indication for ex vivo resection is generally involvement of the hepatic veins with or without cava involvement, the liver may be quite congested as a result of obstructed venous outflow. Therefore care must be taken not to injure the liver during mobilization: any small breach of the liver capsule becomes an outflow route for the obstructed venous flow, and bleeding can be torrential. Venous congestion of the liver is not a contraindication to resection, as the planned resection should relieve the venous outflow obstruction. Large tumors may restrict the ability to rotate the liver without undue tension, and in these cases, it is prudent to make an early decision regarding ex vivo resection before attempting elevation of the liver off of the IVC. A midline sternotomy can also be of use in these cases. Intraoperative ultrasound is used to assess the level of vascular involvement and to confirm vascular anatomy originally identified on preoperative imaging. If a decision is made to proceed with an ex vivo approach, the following steps are performed:

1. The hilar structures are prepared. The arterial anatomy is dissected, and an appropriate site is chosen for planned division. This usually is at the level of the common hepatic artery–gastroduodenal artery junction. If aberrant arterial anatomy is evident, an alternative site may be required, depending on the particular anatomy and the portion of the liver that remains after the resection. In most cases, to preserve small arterial communications to the biliary plate and tree, the artery is not dissected high into the hilum. If the tumor involves the hilar structures, the artery must be dissected far enough to determine that there is a usable, tumor-free portion of the respective hepatic artery branch to reconstruct. The portal vein is identified, and the common bile duct is encircled without skeletonization. A cholecystectomy is performed, and the bile duct is reflected off the portal vein, taking care to preserve its blood supply, and the neural and lymphatic tissue around the portal vein is cleared.
2. The infrahepatic IVC is dissected out down to the level of the renal veins and encircled. Planned vascular clamp placement is immediately above the renal veins, although division of the vena cava may be substantially more cephalad. The

right adrenal vein should be ligated and divided, and small caudate veins should be divided if accessible. The large size of the tumor may make access to the caudate veins difficult, in which case they can be dealt with on the back table.

3. The liver is freed from surrounding attachments. If the tumor is infiltrating the diaphragm, the portion of the diaphragm involved is resected en bloc with the tumor.
4. The suprahepatic IVC is prepared. The phrenic veins are divided bilaterally, allowing the diaphragm to be dissected away from the IVC, providing an increased length of intraabdominal IVC for subsequent clamping and reconstruction. We currently also open the pericardium directly anterior to the IVC and loop the intrapericardial IVC, or we use a midline sternotomy for the same reason. Control of the intrapericardial IVC allows placement of the clamp on the vena cava within the pericardium as a primary option for tumors that are very large, or as a secondary option in case technical difficulties arise with placement of the original suprahepatic cava clamp.
5. Clamp placement and subsequent transection lines are assessed, along with the need for vascular conduits for reconstruction, and alternatives for reconstruction are contemplated before removing the liver. Hepatic venous branches may be reconstructed using hepatic vein or portal vein segments from the side of the liver resected or from autologous vein grafts, such as superficial femoral vein, proximal left renal vein, gonadal vein, or saphenous vein panel grafts. Cryopreserved femoral vein grafts can be used for reconstruction of long segments of hepatic veins or IVC, although long-term patency is currently unclear. The IVC alternatively can be replaced with a 20-mm ringed polytetrafluoroethylene (Gore-Tex) tube graft. Planning for these eventualities should occur before placement of clamps and removal of the liver.
6. Percutaneous access of the internal jugular vein and femoral vein is achieved, the IVC is clamped, and the cava portion of the bypass is started. The portal vein is clamped just below the bifurcation, and the portal cannula is inserted down toward the superior mesenteric vein and secured. The portal vein is completely transected approximately 1.5 to 2 cm below the bifurcation, and the portal flow is added to the bypass circuit, while the liver continues to be perfused by arterial blood.
7. The liver is removed, and the bile duct is transected sharply approximately 1 to 1.5 cm below the bifurcation. To permit a duct-to-duct anastomosis on reimplantation, we do not ligate either end. The gastroduodenal artery is ligated and divided, the common hepatic artery is clamped, and the hepatic artery is transected at the takeoff of the gastroduodenal artery such that a branch patch is formed on either side of the arterial transection if possible. The suprahepatic IVC is clamped either below the diaphragm or within the pericardium, and the suprahepatic vena cava is transected, far enough away from tumor to provide an adequate oncologic margin but close enough to leave room to perform the suprahepatic cava anastomosis at the time of reimplantation. If the vena cava has been freed of its posterior attachments before clamp placement, the infrahepatic IVC is divided as cephalad as possible, and the liver is removed and placed in an ice bath. Cold perfusion through the portal vein and hepatic artery is initiated on the back table. As with any hypothermic perfusion technique, cold perfusion can be with either HTK or UW solution. If the retrohepatic IVC has not been freed up previously because of the large tumor size and difficulty with access, the liver can be cold perfused via the portal vein after the suprahepatic IVC is divided. The liver is rotated forward, as in the ante situm approach, and the retrohepatic IVC is freed of attachments. The infrahepatic IVC is divided, and the liver is removed and placed in the ice bath.
8. Bleeding is controlled, and the bypass circuit is assessed. Flows of 3 to 6 L/min would be expected on total bypass (see Fig. 94.1). The abdomen is loosely packed and covered, and attention is turned to the back table.

An alternative method can be performed in patients with complex hepatic vein involvement without IVC involvement with tumor. If access allows, the liver can be mobilized completely off of the retrohepatic IVC, until it is suspended only by the hepatic veins. The hilar structures are divided as for standard ex vivo resection, but the patient is not placed on bypass. A vascular clamp is placed partially across the IVC, occluding the hepatic vein orifices but allowing cava flow to remain uninterrupted. The hepatic veins are transected, and the liver is removed and cold flushed on the back table. A temporary portacaval shunt is constructed (Fig. 94.13) to decompressing the enteric circulation; this option avoids bypass, but it can be used only when there is no IVC involvement, and when the IVC can be preserved in situ. It is worth assessing whether the tumor can be dissected away from the IVC in most patients, because preoperative imaging can be inaccurate in determining true IVC involvement (Okada et al, 2003).

Ex Situ Liver Resection

After it is removed from the patient, the liver is placed immediately in an ice bath and perfused with preservation solution through the portal vein. We use UW solution, because it is also the preservation solution we use for LDLT; HTK solution also is a reasonable choice. After the initial 500 to 1000 mL of solution has been flushed through the liver, the effluent from the

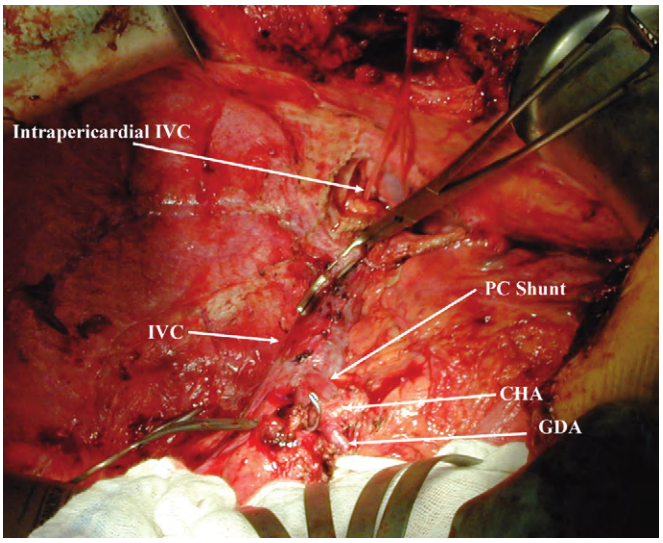


FIGURE 94.13. A temporary portacaval (*PC*) shunt is constructed, allowing a prolonged anhepatic phase without the need for venovenous bypass. The intrapericardial inferior vena cava (*IVC*) has been encircled. CHA, common hepatic artery; GDA, gastroduodenal artery.

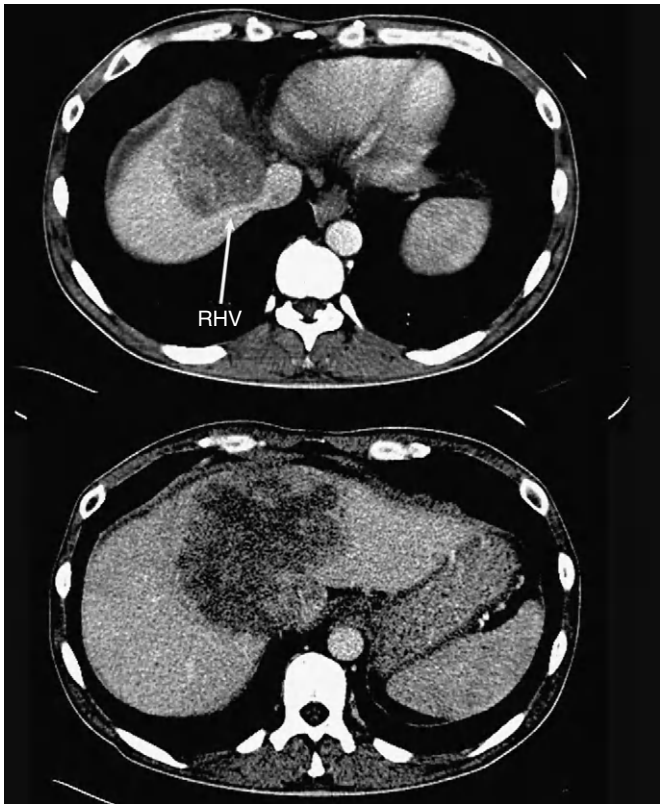


FIGURE 94.14. A single colorectal metastasis (*arrow*) involving all three hepatic veins. RHV, right hepatic vein.

IVC should be clear. The hepatic artery and biliary tree also are flushed with another 200 to 300 mL of preservation solution, the liver is immersed in cold UW solution, and the resection is performed.

Hilar structures are dissected out and divided. Great care must be taken not to divide segmental arteries that supply portions of the liver that are to remain, as their caliber is too small to reconstruct with confidence. Main segmental divisions of the portal vein usually can be repaired and reconstructed. Parenchymal transection can be performed using a variety of techniques, including ultrasonic and water-jet dissection or even sharp division with a knife. Small bile ducts and vessels are ligated or oversewn, and large hepatic veins are cut sharply and are assessed later for reconstruction (Figs. 94.14 to 94.17). The surgical tumor margin should not be compromised in order to minimize the subsequent complexity of vascular reconstruction.

A key advantage to the ex vivo approach is the ability to extend the resection to obtain negative margins, while providing the necessary time and exposure for complex reconstructions. At completion of the resection, it is helpful to flush the portal vein, hepatic artery, and bile duct with UW solution to identify leaks from the cut surface of the liver, which can be repaired before reimplantation. Fibrin glue may be sprayed on the cut surface of the liver to minimize bleeding.

Hepatic Vein and Inferior Vena Cava Reconstruction

Complex hepatic vein reconstruction, with or without IVC reconstruction, is the raison d'être for ex vivo liver resection. The hepatic veins are relatively thick-walled and straightforward to reconstruct within 2 to 3 cm of their merging with the IVC. For reconstructions of hepatic veins transected relatively close

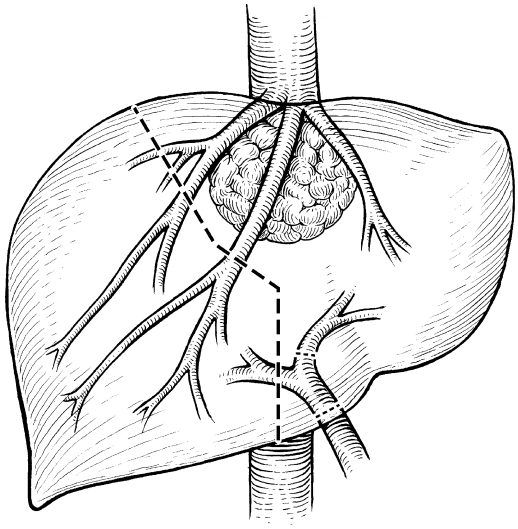


FIGURE 94.15. The planned hepatic transection line for the tumor shown in Figure 94.14. Multiple hepatic vein branches require reconstruction.

to the IVC, the liver parenchyma can be trimmed back such that direct reimplantation of the hepatic vein into the IVC or the IVC replacement can be performed.

Multiple orifices of hepatic veins can be plastied together or implanted into venous conduits (Figs. 94.18 to 94.20). The farther away from the IVC that the hepatic vein is transected, the thinner the wall of the hepatic vein, and the more difficult it is to reimplant the vein directly into the IVC. We have harvested the portal vein bifurcation, reversed it, and used it to reconstruct multiple hepatic vein branches into a single outflow vessel on several occasions (Figs. 94.21 to 94.23; Hemming & Cattral, 1999). Grafts of saphenous, superficial femoral, internal jugular, and cryopreserved vein all have been used to reconstruct hepatic veins (Dong et al, 2004; Kaneoka et al, 2000; Kishi et al, 2004;

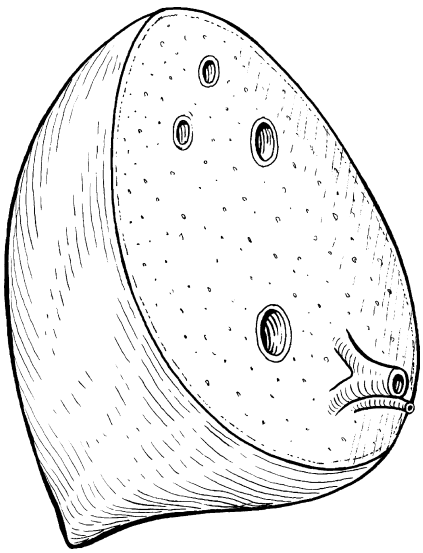


FIGURE 94.16. Back-table transection of the liver results in multiple branches of the right hepatic vein requiring reconstruction. A large segment VI branch that enters the middle hepatic vein also requires reimplantation.

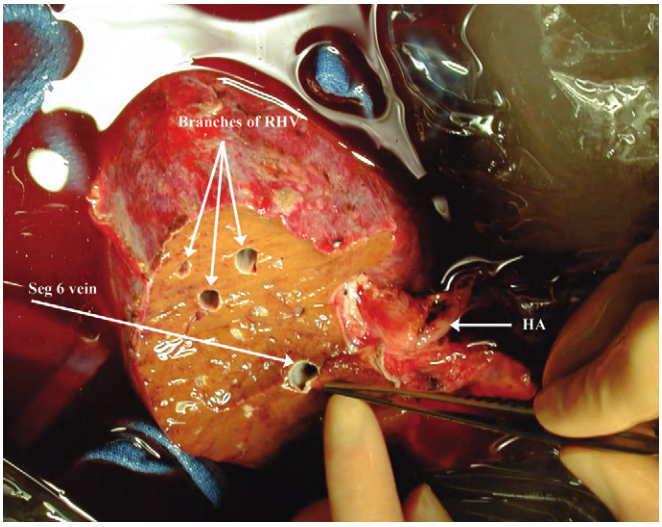


FIGURE 94.17. Completed transection on the back table. HA, hepatic artery; RHV, right hepatic vein; Seg 6, segment VI.

Kubota et al, 1997, 1998). In addition, segments of uninvolved hepatic vein from the side of the liver resected can be salvaged and used for grafts or patches.

Venous grafts should be kept as short as possible, and great care must be taken to place the grafts such that they do not kink. For extension grafts, the hepatic vein–graft anastomosis is performed first with subsequent reimplantation of the graft into the IVC. One alternative to consider prior to choosing an extension graft is whether the liver remnant can be rotated on its inflow pedicle such that the hepatic vein orifice is brought to lie directly against the caval graft; this avoids the issue of kinking of a venous extension graft.

An important issue is how to reconstruct the vena cava. If possible, it is best to reimplant the hepatic veins into native vena cava. Frequently, a large portion of the vena cava that was

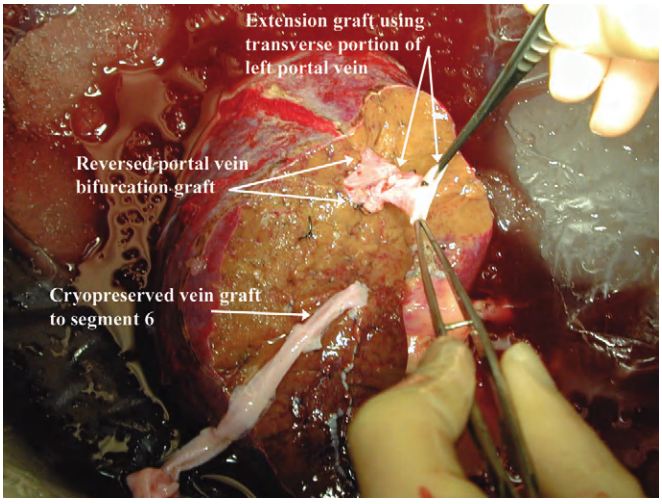


FIGURE 94.18. Joining two of the three right hepatic vein branches together and implanting the resulting two orifices into the reversed portal vein bifurcation taken from the patient's hilum allows reconstruction of the right hepatic vein branches. The transverse portion of the left portal vein is added to allow the graft to reach the inferior vena cava (IVC) without tension. A cryopreserved femoral vein graft is used to extend the segment VI vein to the IVC.

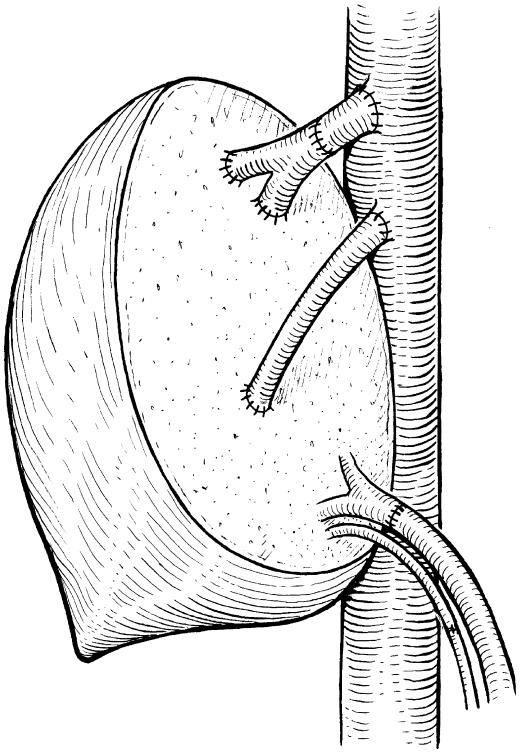


FIGURE 94.19. The prepared autograft is reimplanted into the patient as diagrammed. Reimplantation is done in similar fashion as for living donor right lobe transplantation.

removed initially with the liver can be salvaged and moved superiorly, with the hepatic veins reimplanted into this newly situated portion of IVC. A ringed 20-mm Gore-Tex tube graft can be used to make a composite cava graft with the Gore-Tex graft placed inferiorly. Alternatively, a section of the IVC remaining in the patient immediately above the renal veins can be harvested and used as the segment of IVC into which the hepatic veins are reimplanted. A ringed 20-mm Gore-Tex tube graft is used to replace the segment of IVC immediately above the renal veins. In some circumstances, it is necessary to

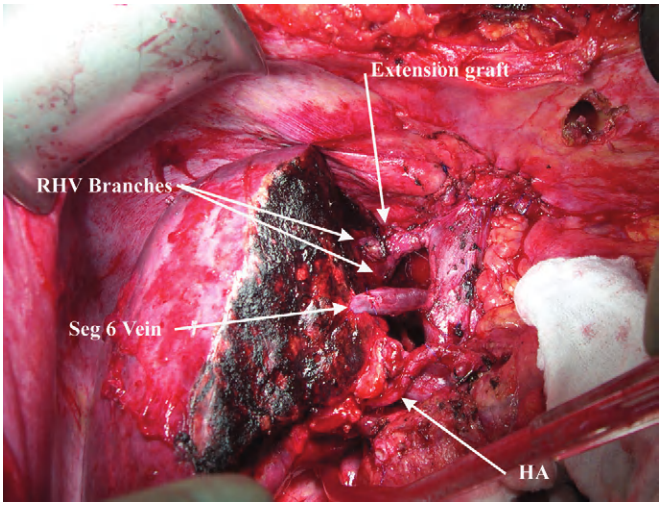


FIGURE 94.20. The reimplanted liver as in Figure 94.19. HA, hepatic artery; RHV, right hepatic vein; Seg 6, segment VI vein.

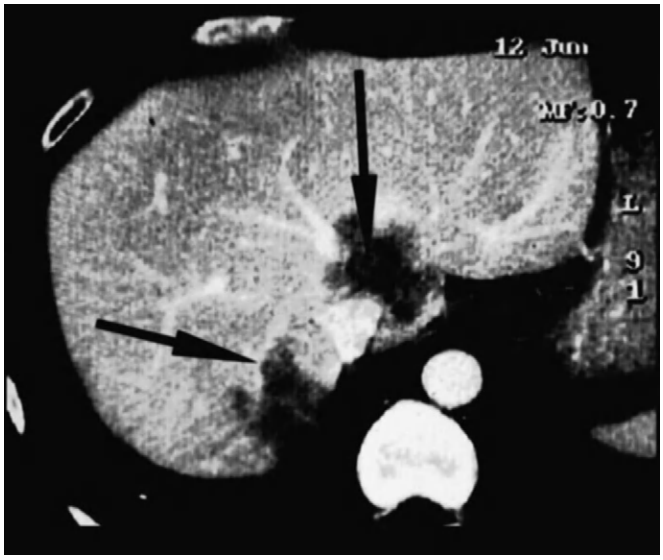


FIGURE 94.21. Computed tomographic scan showing colorectal metastases involving all three hepatic veins. *Arrows* indicate tumor.

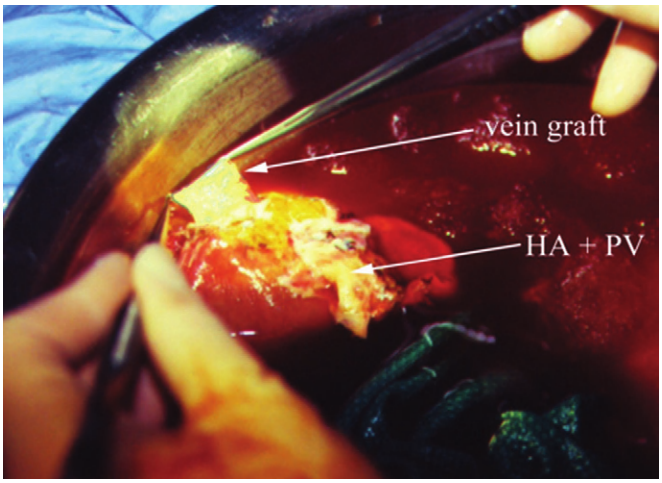


FIGURE 94.23. A reversed portal vein bifurcation (vein graft) graft taken from the patient's hilum is used to reconstruct the left hepatic vein outflow. HA, hepatic artery; PV, portal vein.

reimplant the hepatic veins directly into a relatively stiff artificial graft that is replacing the IVC (Figs. 94.24 and 94.25). In this situation, it is important to make a larger opening in the Gore-Tex than one might expect and to triangulate the anastomosis to prevent anastomotic stricturing (Lodge et al, 2000).

At completion of the back-table reconstruction, an autograft results that is similar to that of a reduced-size or split-liver allograft (Figs. 94.26 through 94.28). Total cold ischemic time is usually 2 to 4 hours, which is well within acceptable limits, when comparing cold ischemic times for split-liver or reduced-size liver transplantation.

Reimplantation

Reimplantation is similar to reduced-size liver transplantation or LDLT. The suprahepatic IVC anastomosis is performed first. If an artificial venous graft has been used to reconstruct the IVC, it is shortened such that it does not kink on implantation. When the back wall of the infrahepatic vena cava anastomosis has been completed, the portal vein is flushed with 500 mL of cold 5% albumin, which is vented through the infrahepatic cava anastomosis. The infrahepatic vena cava anastomosis is then completed. The cold rinse washes the UW solution out of the liver before reperfusion, as this solution contains high levels of potassium and adenosine, which can cause dramatic cardiac dysfunction or arrest if allowed into the circulation on reperfusion. As previously described, an alternative to cold flushing the liver before reperfusion is to leave the lower cava anastomosis open until after portal reperfusion, venting the initial 300 mL of blood before removing the suprahepatic cava clamp. Although little solid evidence supports the use of one technique over the other, we prefer the cold-flush technique only because it reduces the number of possible bleeding sites at the time of reperfusion.

After the infrahepatic cava anastomosis is performed, the portal limb of the bypass circuit is clamped and removed from the portal vein, and the portal venous anastomosis is performed. Next, the suprahepatic cava clamp is removed, and the liver is allowed to back-perfuse through the hepatic veins. Any major bleeding is controlled before reestablishing the portal flow. The portal venous clamp is removed, and the liver is reperfused. Any bleeding from the cut surface of the liver is controlled, and the patient is taken off venovenous bypass.

Finally, the arterial anastomosis is performed, and the liver is reperfused with arterial blood; total warm ischemic time ranges from 20 to 40 minutes. After hemostasis has been achieved, the biliary anastomosis is performed. In the first few ex vivo liver resections that we did, our preference was to perform a Roux-en-Y choledochojejunostomy, but our more recent cases have involved duct-to-duct anastomoses over an internal stent. This experience mirrors our larger experience with living donor right lobe transplantation.

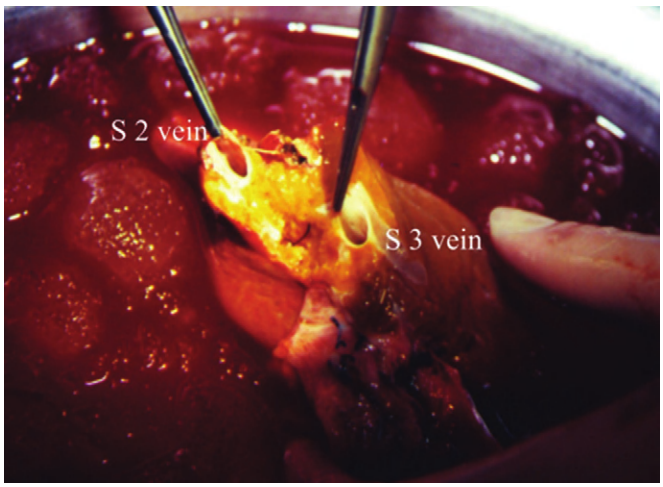


FIGURE 94.22. Remnant liver after ex vivo resection of tumor seen in Figure 94.21. S2 and S3 veins are segments II and III hepatic vein branches.

Postoperative Course

Postoperative care is similar to any major liver resection or liver transplantation. Ultrasound with Doppler assessment is performed on postoperative day 1 to assess liver blood flow. Day 1

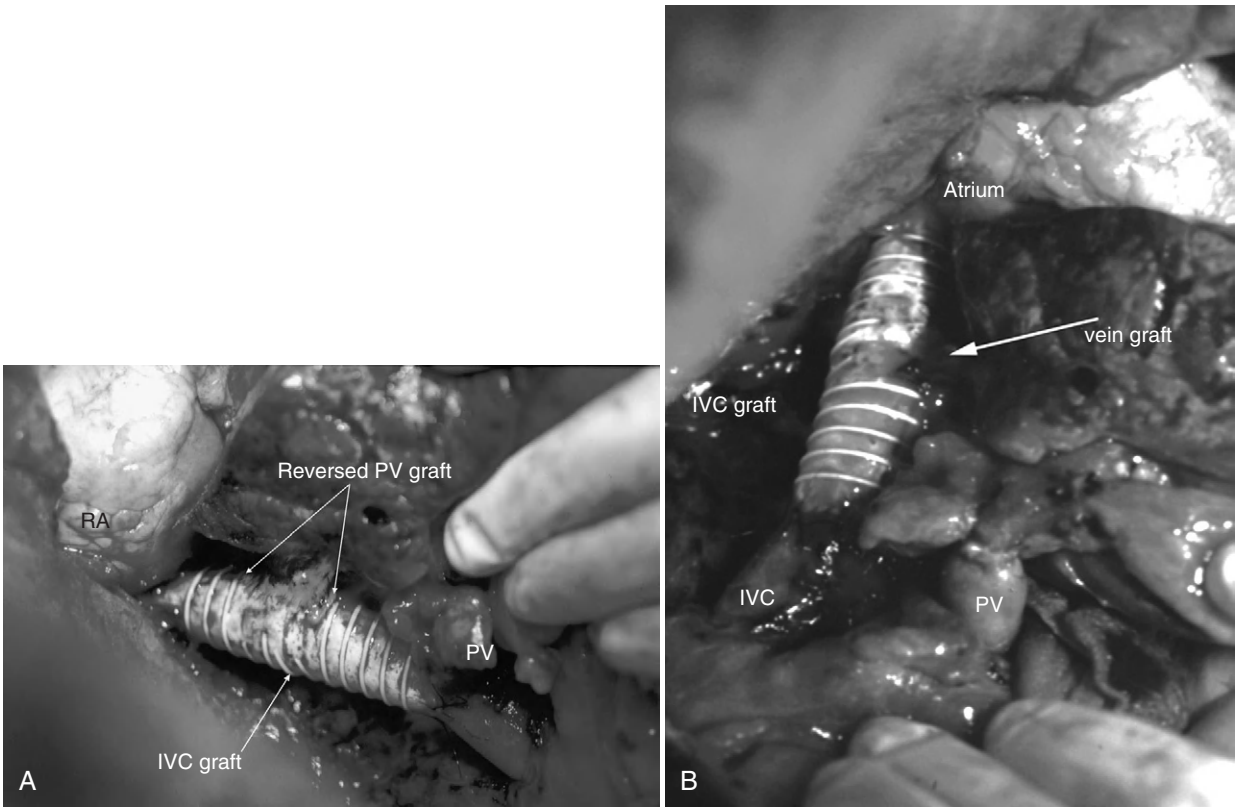


FIGURE 94.24. The reversed portal vein (*PV*) bifurcation graft has been reimplanted directly into a segment of ringed 20-mm polytetrafluoroethylene (Gore-Tex) that replaces the IVC. RA, right atrium.

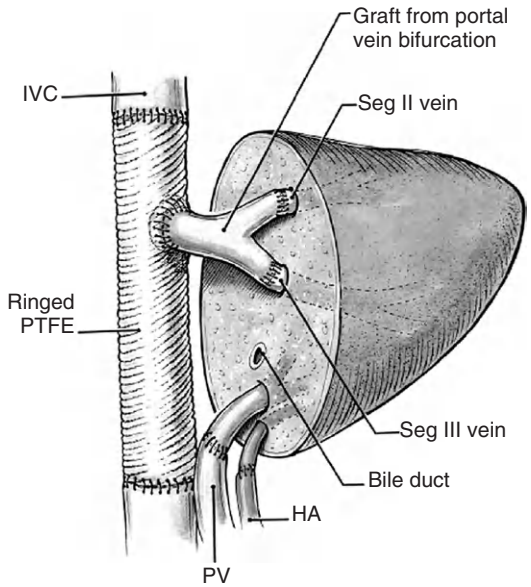


FIGURE 94.25. Diagrammatic representation of Figure 94.24. HA, hepatic artery; IVC, inferior vena cava; PTFE, polytetrafluoroethylene (Gore-Tex); PV, portal vein; Seg, segment.

transaminase levels in the 200 to 1000 IU/L range are standard but return to near normal in 1 week. Hyperbilirubinemia is common, and as might be expected, it seems to vary inversely with the size of the liver remnant. Hyperbilirubinemia by itself is not concerning, if other markers of liver function are improving.

An early sign that the autograft is functioning is the return of lactate levels to baseline in the first 12 to 24 hours after surgery. Maintenance of coagulation parameters, in particular prothrombin time or international normalized ratio (INR), suggests recovery of liver function. It is frequently necessary, however, to give fresh frozen plasma for the first few days to maintain an INR target less than 2 (Martin et al, 2003). Hypophosphatemia can occur between postoperative days 1 and 3 as the liver regenerates, and it may be so profound as to require constant intravenous replacement. Without much evidence as to its effectiveness, we have used low-dose intravenous heparin (500 U/h) perioperatively, and we attempt to maintain the hematocrit between 30% and 35%. Patients who have artificial venous caval grafts are started on low-dose aspirin before discharge. This is maintained for life, although no data confirm the need for long-term anticoagulation.

Current Role of Ex Vivo Liver Resection

The role of such an extensive procedure in advanced malignancies is open for discussion. Although 2 decades have passed since Pichlmayr and colleagues (1988) described the first ex vivo liver resection, relatively few surgeons have attempted the

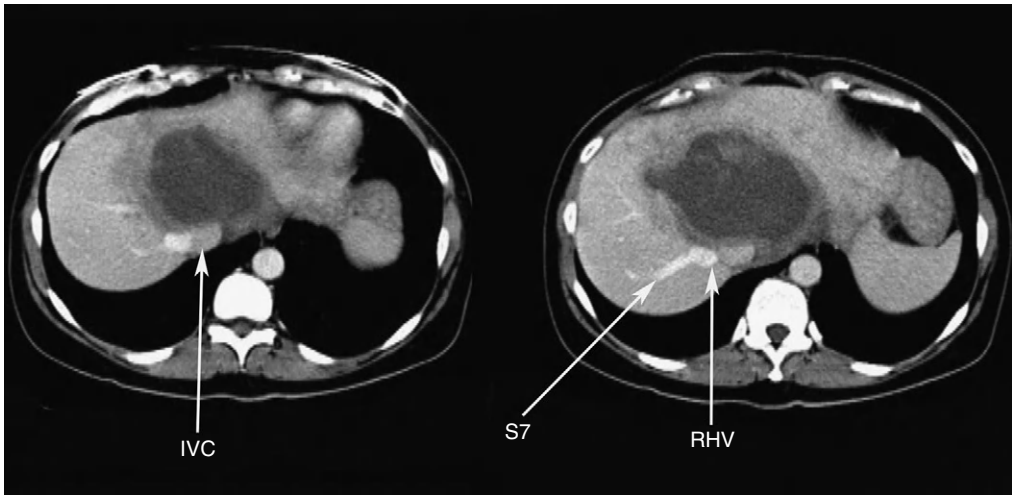


FIGURE 94.26. CT scan showing a large, centrally placed tumor. IVC, inferior vena cava; RHV, right hepatic vein; S7, segment VII hepatic vein branch.

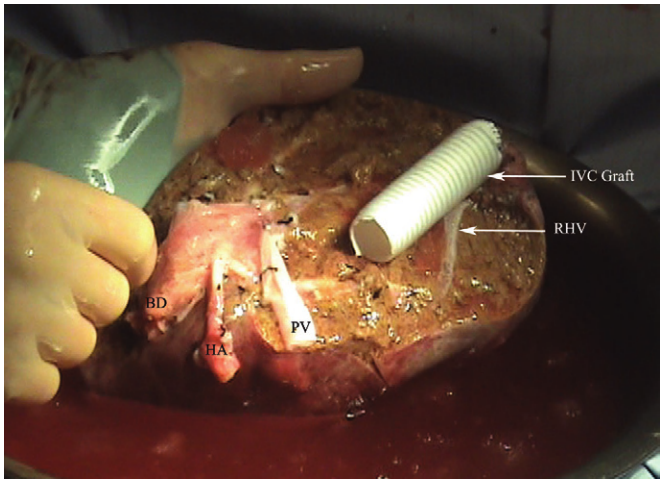


FIGURE 94.27. Ringed Gore-Tex graft has been used to reconstruct the inferior vena cava on the back table for the case in Figure 94.26. BD, bile duct; HA, hepatic artery; IVC, inferior vena cava; PV, portal vein; RHV, right hepatic vein branch.

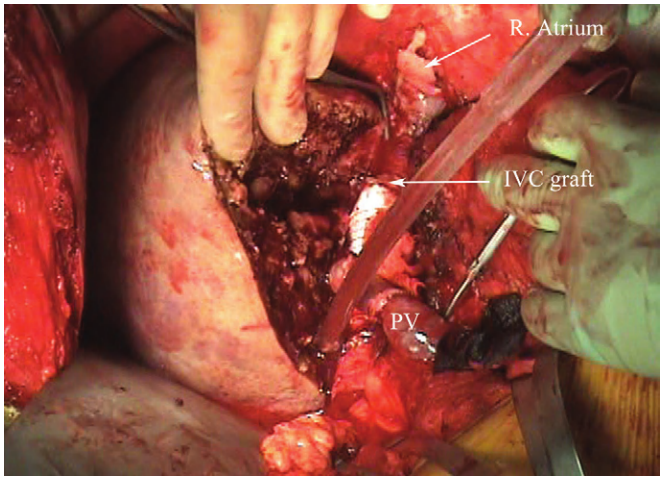


FIGURE 94.28. Case from Figure 94.26 reimplanted at time of initial perfusion through the portal vein (*PV*). IVC graft, inferior vena cava ringed Gore-Tex graft; R. Atrium, right atrium.

procedure. The largest reported series from Pichlmayr's own group consists of only 22 patients (Oldhafer et al, 2000). There are several reasons behind the lack of adoption of this technique, not least the fact that the two other hypothermic perfusion techniques described in this chapter, in situ and ante situm hepatic hypothermic perfusion, can be applied to the great majority of difficult vascular reconstructions with the important exception of tumors involving both hilar structures and the hepatic vein and/or the cava. The ex vivo technique requires a surgeon familiar with advanced techniques in liver resection and liver transplantation, which restricts the procedure to relatively few individuals. Many patients who may be candidates for ex vivo resection are deemed unresectable by competent hepatic surgeons and are not referred on. Perhaps the most compelling reason for the lack of adoption of this technique is the relatively high risk-to-benefit ratio that the procedure offers. Most of the literature on ex vivo liver resections has been case reports that describe aspects of technique, and long-term follow-up is not available. Even in well-selected patients, perioperative mortality is between 10% and 30%. By contrast, the perioperative mortality for patients undergoing in situ or ante situm hepatic hypothermic perfusion with vascular reconstruction is around 10% or less (Azoulay et al, 2005; Dubay et al, 2009; Hemming et al, 2008). Long-term survival after ex vivo liver resection is also poor: at best, the 5-year survival for ex vivo resections performed for malignancy is 15% to 30%. In Oldhafer's series (2000), the six patients who underwent ex vivo resection for colorectal metastases had a median survival of 21 months, although it might be expected that the general improvement in survival following resection for colorectal metastases seen over the last decade would apply to ex vivo liver resections as well.

Notwithstanding the considerations above, there is no doubt that the occasional patient is cured by this aggressive procedure. One patient with resection for cholangiocarcinoma in Oldhafer's series was alive and disease free at 3.5 years after resection, whereas one of our own patients who underwent ex vivo resection for HCC was alive and disease free more than 5 years after the operation (Hemming et al, 2000). It is worth noting that many patients may benefit by being considered for ex vivo liver resection, simply because a surgeon prepared to perform ex vivo resection realizes that the resection can be

done using a less aggressive technique, such as in situ cold perfusion or standard vascular reconstruction.

It is also true that liver surgery is constantly evolving, and what is considered questionable today may become a mainstream technique in the future. Even standard liver resection for malignancy was considered of dubious worth several decades ago. Improvements in surgical technique and perioperative care transformed liver resection for malignancy from a technique that many thought bordered on lunacy into an accepted therapy. Further advances in surgical technique, along with advances in adjuvant oncologic therapies, may do the same for ex vivo liver resection. Currently, it seems reasonable to consider highly selected patients for ex vivo liver resection on a case-by-case basis in centers with expertise in both hepatic resection and liver transplantation, particularly live donor liver transplantation.

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CHAPTER 95

Adjuncts to hepatic resection: ultrasound and emerging guidance systems

Guido Torzilli

OVERVIEW

Hepatic surgery performed without a parenchyma-sparing policy carries relevant risks for patient survival because of postoperative liver failure; for this reason, the application of hepatic surgery is limited (Vauthey et al, 2004). In particular, the coexistence of liver cirrhosis in most patients with hepatocellular carcinoma (HCC) has a considerable adverse effect on the surgical results (see Chapter 80), and recent series are still associated with mortality rates higher than 5% (Liu et al, 2004) and with resectability rates of 30% to 35%, which is relatively low (Sotiropoulos et al, 2006). For this reason, and for the broadening of ultrasound (US)-guided percutaneous therapies (N'Kontchou et al, 2009), the surgical treatment of HCC has surrendered its role as first choice treatment for all patients and is now reserved only for those patients with a normal bilirubin level, no signs of portal hypertension, and a single, small HCC (Bruix & Llovet, 2009).

Conversely, for colorectal cancer liver metastases (CLM), surgical treatment remains the gold standard (see Chapter 81A). The definition of *resectability* has shifted from a focus on tumor characteristics, such as tumor number and size, to determination of whether both intrahepatic and extrahepatic disease can be completely resected, and whether such an approach is appropriate from an oncologic standpoint. Therefore limiting surgery in the case of CLM has increasingly focused on the technical feasibility, although not entirely (Minagawa et al, 2000; Torzilli et al, 2009b). In this sense, progress with chemotherapeutic regimens has improved the resectability rate (Wicherts et al, 2008), although it remains generally around 15% to 25% of patients (Garcea et al, 2008). A major limit of resectability is the need for major hepatectomies, which still represents a significant factor impacting the risk of perioperative mortality and morbidity (Schroeder et al, 2006; Cucchetti et al, 2006). Portal vein embolization (PVE) was devised with the double aim of increasing the safety of major liver resection and allowing more patients to benefit from the surgical treatment (Jaeck et al, 2004; see Chapter 93). However, liver failure occurs in 33% of patients who did not undergo PVE, and it still happens in 10% of those who did (Hemming et al, 2003). As with HCC, alternative therapies have been devised for treating CLM, such as percutaneous interstitial treatment (Siperstein et al, 2007). Although these new therapies initially enabled patients otherwise excluded from the surgical program to be treated, the apparently good results obtained have generated confusion in the scientific community as to which treatment modalities should be chosen to manage these patients.

Imaging techniques have been introduced as aids for surgeons in performing liver resection. In fact, since the early 1980s, intraoperative ultrasonography (IOUS) has been used in hepatic surgery, initially in patients with liver cirrhosis (Makuuchi et al, 1980; see Chapter 21). Now liver resections can be carried out with very low mortality, even if cirrhosis is present (Imamura et al, 2003; Torzilli et al, 1999a). There are many reasons for this improvement, but a large part can be attributed to better operative technique, including IOUS. Indeed, US guidance allowing the so-called radical but conservative policy (Torzilli et al, 2005a, 2006b) makes feasible an alternative to major hepatectomies, having the aim of reducing the need for major parenchymal removal while keeping an acceptable oncologic radicality. This policy has allowed resectability rates from outpatient evaluation to hepatectomy of 68% and 69% for HCC and CLM, respectively (Torzilli et al, 2008b, 2009b). Recently, the demonstration of feasibility and efficacy of contrast-enhanced US performed intraoperatively (CE-IOUS) has furthermore stressed the relevance of IOUS guidance during liver surgery (Torzilli et al, 2007b, 2008a).

In this chapter, technical aspects of IOUS, its impact, and future perspectives of this tool during liver surgery both for staging and resection guidance are discussed.

TECHNICAL ASPECTS

Probe Selection

High-frequency (7.5 to 10 MHz) echoprobes are commonly recommended to perform IOUS, because they allow a higher spatial resolution than those that operate at lower frequencies (3.5 to 5 MHz); however, the latter are also useful, at least along the initial exploration, providing a better panoramicity that helps compensate for the lower spatial resolution (Fig. 95.1). On the other hand, it should be pointed out that often higher spatial resolution at the superficial portion of the liver is less important than the overall visibility of the deeper structures, because the most superficial portions are also those appreciable with palpation. In the latter condition, once a nodule is slightly visible at IOUS but is not palpable, especially in a cirrhotic liver, a surgical glove filled with deaerated sterile water can be positioned between the probe and the liver surface for making the lesion more visible (Fig. 95.2). Lower frequency echoprobes are also useful for allowing CE-IOUS; therefore, having both low- and high-frequency probes would be the optimal solution, and new probes with wider ranges of frequencies (3.5 to 10 MHz) are expected.

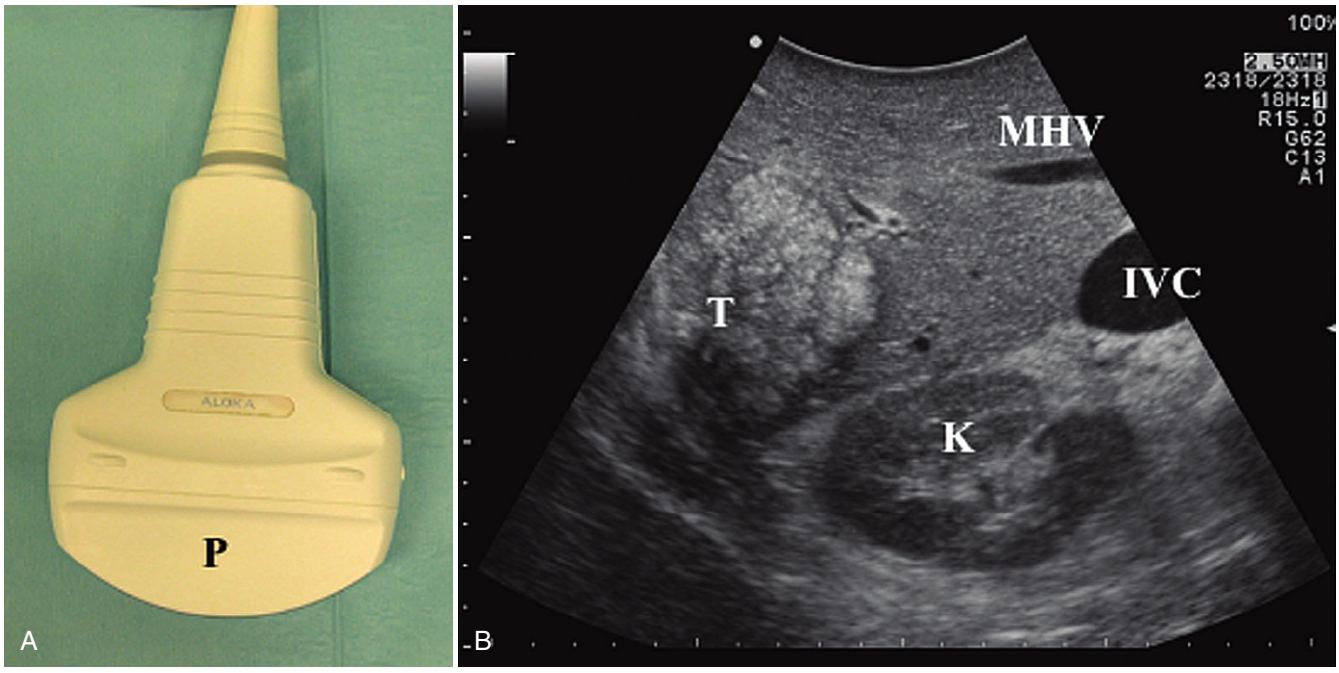


FIGURE 95.1. A, Convex probe for percutaneous exploration used intraoperatively for an initial overview. The relatively low frequency allows visualization of deep structures, although it offers some degree of spatial resolution. **B,** Appearance of a convex probe scan. In one scan, it is possible to visualize the liver with a tumor (*T*) and to recognize the middle hepatic vein (*MHV*), the retrohepatic inferior vena cava (*IVC*), and the right kidney (*K*).

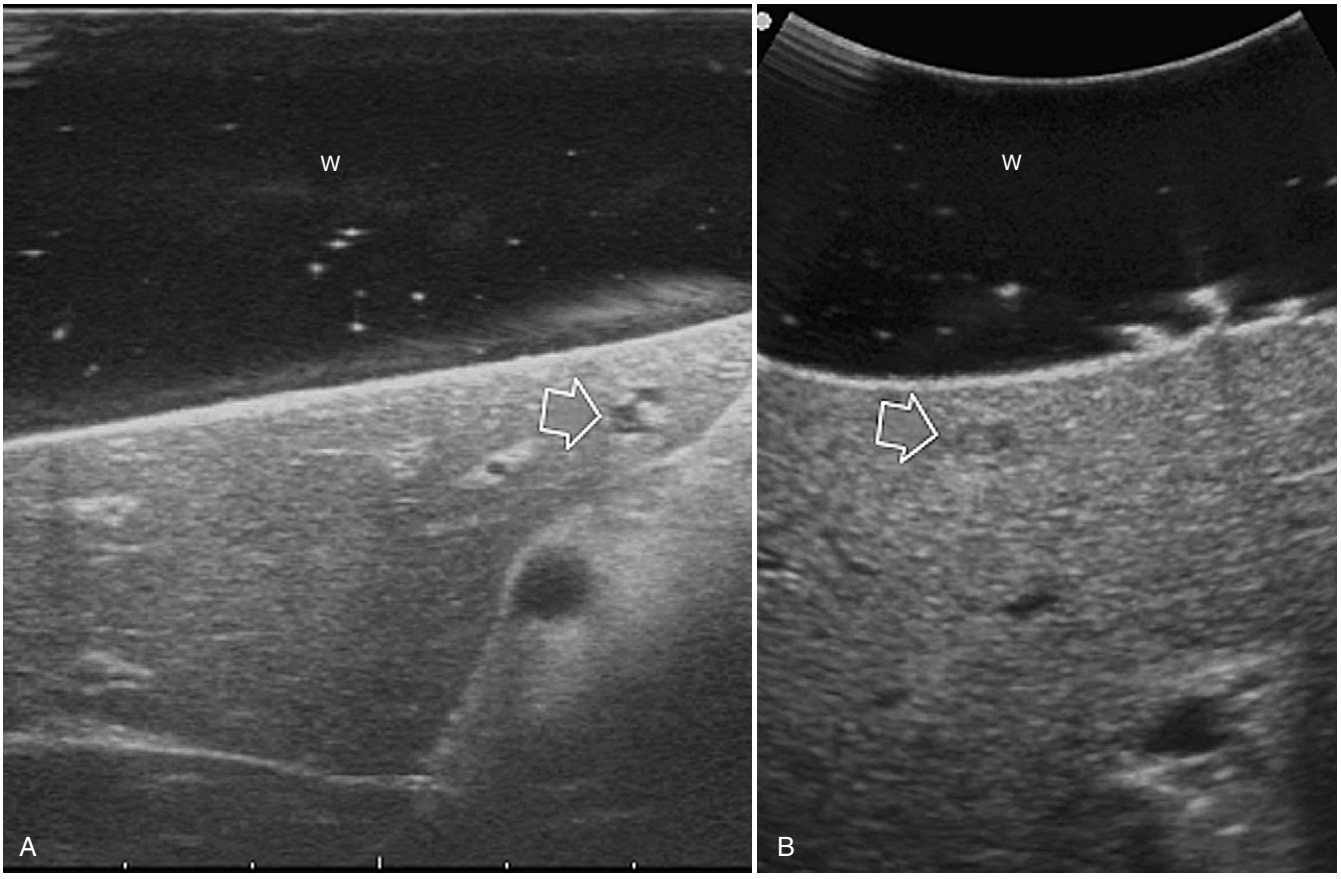


FIGURE 95.2. For better exploration of the superficial structures, a glove filled with deaerated water (*W*) is positioned in between the probe and the targeted surface. The *arrows* indicate two 1-mm lesions superficially located, a simple cyst (**A**), and a small colorectal liver metastasis (**B**).

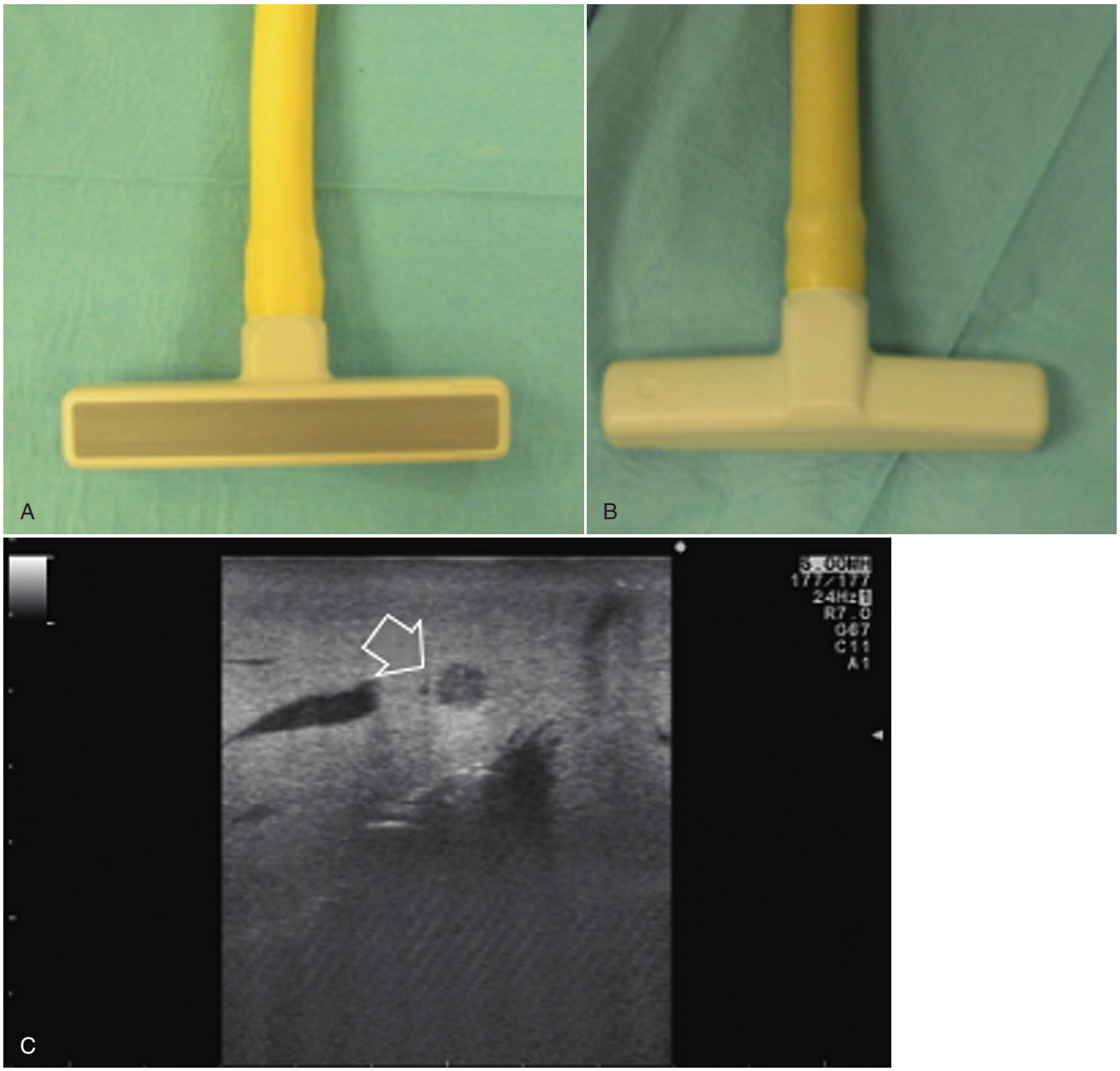


FIGURE 95.3. **A,** The scanning side of a T-shaped echoprobe. **B,** Reverse side. The scanning area is also disclosed (**C**), and a small metastatic lesion is shown (*arrow*). This high-frequency echoprobe (7.5 to 10 MHz) features high resolution but low ultrasound penetration.

Crucial points to be evaluated when selecting a probe are its shape and volume. Indeed, an optimal probe should represent the best compromise between the size, which should be smaller to facilitate handling in deep and narrow spaces; the ultrasonographic scanning window, which should be larger to enable the widest area of exploration at once; and the adherence with the surface of the target organ, which should be higher to enable adequate stability during handling and for avoiding gas interposition and artifacts that may compromise organ exploration.

The most frequently used probes are the T-shaped (Fig. 95.3), interdigital, and microconvex probes (Fig. 95.4). The microconvex probe represents the best compromise among all the aforementioned requirements. Indeed, the T-shaped probe, although it remains more stable and is associated with higher image resolution, has a lower ratio between lateral length and US scanning window than the microconvex probe. Linear transducers with enlarged scanning windows are under development that combine the stability of the linear probes and their higher image resolution with larger scanning windows and a limited volume (Fig. 95.5). When evaluating probes, another aspect that should be considered is the possibility of using them for surgical maneuvers, as described below; newer probes are being designed from this perspective (see Fig. 95.5).

Color Doppler imaging, and particularly new, more sensitive color-flow modes, are progressively assuming greater relevance in hepatic surgery. For example, e-flow intraoperative US (EF-IOUS) is useful for studying the inflow and outflow of the liver intraoperatively (Fig. 95.6), and it shows the flow modifications

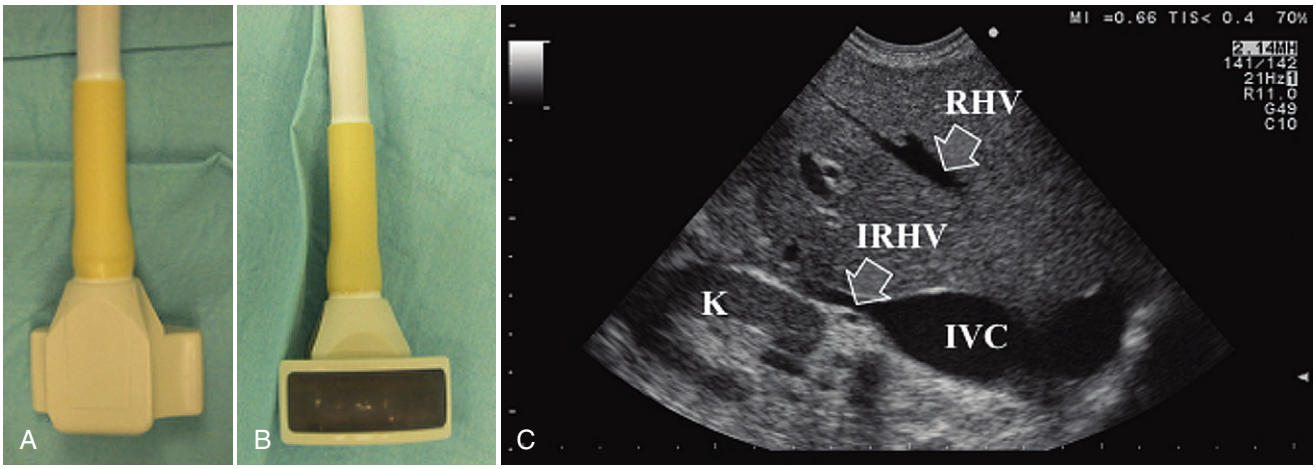


FIGURE 95.4. A, Microconvex echoprobe. **B,** Scanning side of the probe. **C,** The scanning area is shown. This wide-range frequency echoprobe (2 to 7 MHz) makes it possible in one scan to visualize the liver with a tumor, in which the right hepatic vein (*RHV*), an inferior right hepatic vein (*IRHV*), and the right kidney (*K*) are recognizable.

during surgical maneuvers; this represents crucial data for allowing surgical strategies that would not be feasible otherwise. These promising new technologies will be discussed in this chapter.

CE-IOUS is one of the latest advancements in intraoperative application of US, but dedicated probes built to carry out this diagnostic modality in direct contact with the targeted organ are few; furthermore, CE-IOUS requires high-quality digital US machines. We use the Alpha 10 (Aloka, Tokyo; Fig. 95.7), which is equipped with a convex probe working at 3- to 6-MHz frequency and at 1.88- to 3.76-MHz harmonic frequency (see Fig. 95.1). The contrast agent used, SonoVue (Bracco Imaging, Milan, Italy), consists of sulfur hexafluoride microbubbles stabilized by a phospholipid shell; the anesthesiologist injects 4.8 mL of SonoVue intravenously for exploration through a peripheral vein. The purpose of the contrast enhancement is to evaluate the lesion's vascularity, aid in the characterization of those eventually found at IOUS, and to detect new ones, taking advantage of the enhanced brightness of the liver parenchyma, especially along the delayed phases (Fig. 95.8). New liver-specific contrast agents, such as those containing perfluorobutane (Sonazoid, Daiichi Sankyo, Tokyo), will soon become commercially available for clinical use; however, initially, these are being used clinically and only in Japan. This contrast agent, which has properties similar to liver-specific contrast medium used in magnetic resonance imaging (MRI), could improve nodule differentiation (Kudo, 2007) and detection (Nakano et al, 2008).

Preparation for Liver Exploration

First of all, it must be stressed that the surgeon in charge of the surgical procedure should carry out the IOUS, rather than assistants, radiologists, or technicians. This is because obtaining and interpreting the information requires skills and a background in US imaging. But for their most profitable impact to the surgical strategy, and for allowing maneuvers guided and carried out with the echoprobe, such information must be fully comprehended by the surgeon; for that, the optimal condition would be that the US and the operation are performed by the same person.

The US machine should be positioned opposite the first operator, who should be able to simultaneously view both the screen and the operative field (Fig. 95.9). The screen must be large enough to allow optimal visibility at that distance, and lights should be positioned with caution so as not to interfere with the visibility of the US screen. An assistant familiar with the US keyboard should stay beside it, or a transparent and sterile covering pad should be available that allows the lead member of the surgical team to handle the keyboard directly (see Figs. 95.7 and 95.9).

After entering the abdominal cavity, liver mobilization, division of the round and falciform ligaments, and division of adhesions to free the anterosuperior and inferior surfaces of the liver are the steps that should precede liver exploration with IOUS (Fig. 95.10). Of course, adhesions from the tumor to other organs or structures should not be approached, as they may represent areas of tumor infiltration; in this situation, IOUS can help exclude or confirm tumor invasion, which could change the surgical strategy.

Pulling on the round ligament for traction, the liver surface is widely exposed, and following the portal branches and the hepatic veins, the liver can be entirely studied. The probe should be managed using enough pressure to ensure good contact with the liver surface but not so much as to compress the intrahepatic vascular structures and the hepatic vein in particular.

Ultrasound Liver Anatomy

Solid knowledge of the liver anatomy is required to perform IOUS properly (see Chapter 1B). For surgical anatomy, the Brisbane terminology is considered here (Pang, 2002). The three main hepatic veins are readily identified at their junction with the inferior vena cava (IVC), positioning the probe at this level and tilting it upward once the confluence of the hepatic veins into the IVC is recognized. Then, gently withdrawing the probe, the hepatic vein paths can be traced into the liver. Hepatic veins appear as echo-free zones in the liver parenchyma, and the vessel wall is invisible or appears as a thin, hyperechogenic line (Fig. 95.11A); the walls of hepatic veins can be thicker in the cirrhotic liver, and their lumens thinner, as a result of the stiffness of the diseased liver (Fig. 95.11B).

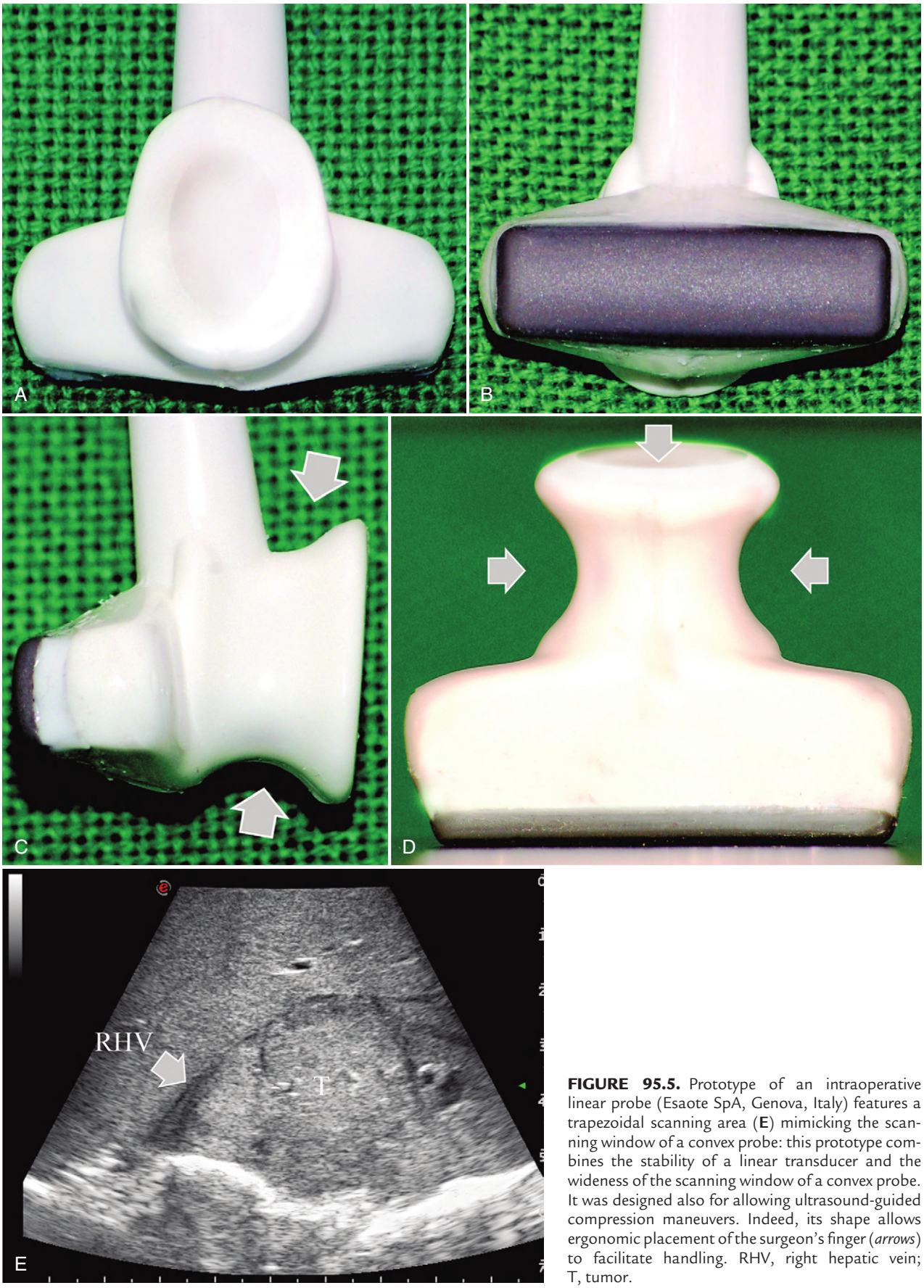


FIGURE 95.5. Prototype of an intraoperative linear probe (Esaote SpA, Genova, Italy) features a trapezoidal scanning area (**E**) mimicking the scanning window of a convex probe: this prototype combines the stability of a linear transducer and the wideness of the scanning window of a convex probe. It was designed also for allowing ultrasound-guided compression maneuvers. Indeed, its shape allows ergonomic placement of the surgeon's finger (*arrows*) to facilitate handling. RHV, right hepatic vein; T, tumor.

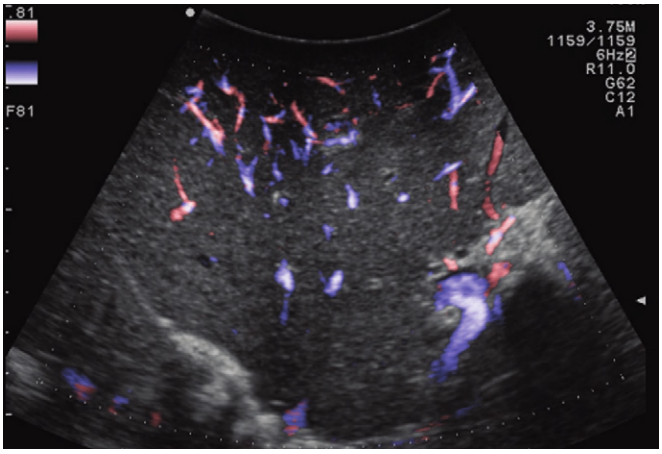


FIGURE 95.6. The appearance of the liver, once the exploration is carried out under the e-flow mode, a more sensitive modality compared with color Doppler for analyzing the blood flow. This increases the sensitivity and allows precise mapping of the slow-motion flow as shown in this picture; tiny vessels are clearly depicted.



FIGURE 95.7. An ultrasound machine with a sterile pad covering the keyboard to allow direct management by the surgical team.

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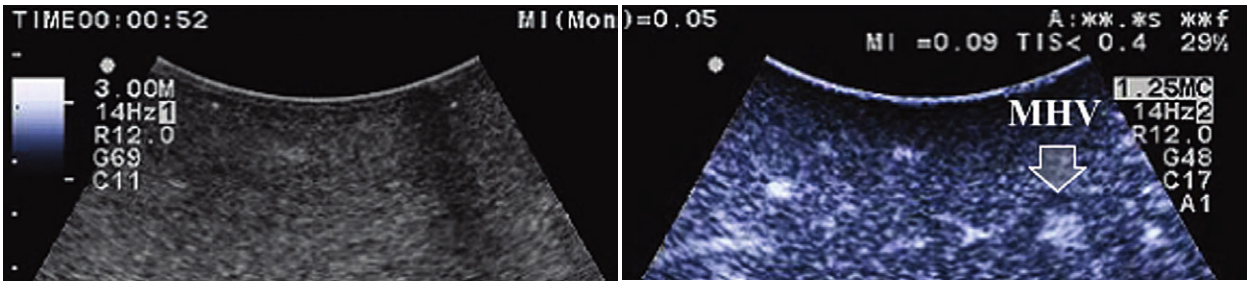


FIGURE 95.8. The appearance of the liver using contrast enhancement. **A,** B-mode conventional modality is shown on the US machine screen simultaneously with the contrast-enhanced image shown in **B. B,** Liver is shown at 52 seconds after injection of contrast (time appears in the left upper corner in **A**). The vessel and parenchymal enhancement are shown; both portal branches and hepatic veins are filled with contrast. On the upper right corner of the image, *MI* refers to the mechanical index, which should be <0.1 so as not to break the microbubbles and to allow the contrast effect of real-time enhancement at ultrasound. IVC, inferior vena cava; MHV, middle hepatic vein; P8d, portal branch to segment VIII dorsal; RHV, right hepatic vein.



FIGURE 95.9. The ultrasound machine positioned in the operative theater: the operator is facing the screen while the keyboard is managed by the first or second assistant.

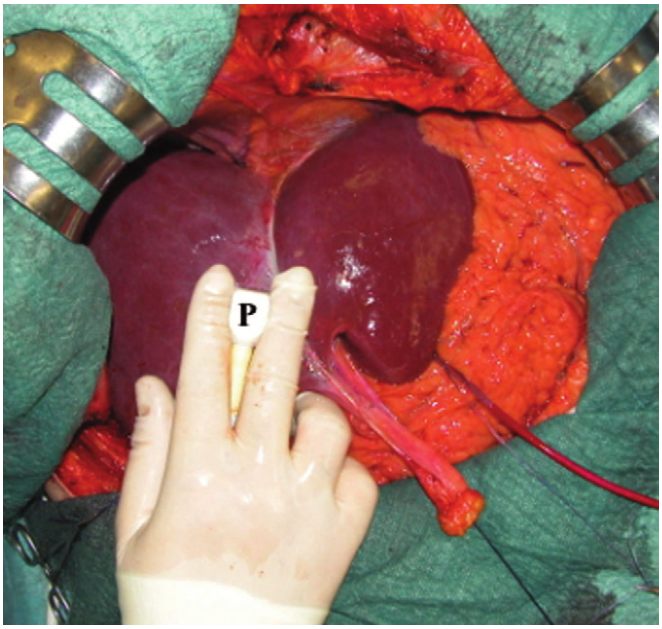


FIGURE 95.10. Liver exposed for initial exploration, once the falciform ligament has been cut; the surgeon is handling a microconvex probe (*P*).



FIGURE 95.11. A, The glissonian sheath (*GS*) and the middle hepatic vein (*MHV*) in a normal liver have a different wall thickness on intraoperative ultrasound. The GS is represented by at least two hypoechoic (black) structures, representing the artery and the portal vein; the bile duct is always seen in the case of the first- and second-order branches, which are often disclosed, particularly when dilated in the case of a more peripheral GS. **B,** In the cirrhotic liver, HVs have a thickened wall that mimics the wall of a glissonian vessel: the anatomic landmarks and the inclusion of various structures together allow their proper differentiation. Shown is an inferior right hepatic vein (*IRHV*) with a thickened wall but typically running behind the right portal branches as the right portal vein (*RPV*). IVC, inferior vena cava; LPV, left portal vein.

The portal vein branches can be followed by initially positioning the probe horizontally above the inferior portion of segment IV (see Fig. 95.10) to visualize the first-order bifurcation (Fig. 95.12), then the first-, second-, and third-order portal branches can be followed. Because of the existence of the Glisson capsule, the portal pedicles—which include portal vein branches, arteries, and bile ducts—have thicker vessel walls compared with the hepatic veins, and for this reason, they appear at IOUS as echo-free zones surrounded by a thicker hyperechogenic layer (see Fig. 95.11); furthermore, other parallel, thinner vascular structure are visible, which are the arteries (Fig. 95.13), and the bile ducts of the glissonian triad are also visible (Fig. 95.14). The newer, more sensitive color-flow modalities, such as EF-IOUS, help in this differentiation by allowing the recognition of arterial and portal elements that also lie within thin glissonian sheaths (Fig. 95.15); however, in principle, distinction between hepatic veins and portal branches should be based not only on their appearance but mainly on their anatomy. Indeed, in the cirrhotic liver, as already mentioned, the vessel wall of the hepatic vein could be thicker and not easily differentiated from a peripheral portal branch. Following the portal pedicles at the sectional, segmental, and subsegmental level, and positioning them in relation to the hepatic veins, it is possible to precisely define the location of the IOUS target in terms of sections and segments (Fig. 95.16).

The appearance of the bile ducts on IOUS is worth mentioning because of their peculiarity. Whereas normally they result as thin echo-free zones in the glissonian triad (see Fig. 95.14), once dilated, they appear as more evident echo-free zones with a serpiginous path (Fig. 95.17). The element that is difficult to recognize in the IOUS study of the bile ducts is their segmental anatomy; bifurcation of sectional and segmental ducts is closer to the hilum, compared with the portal branches

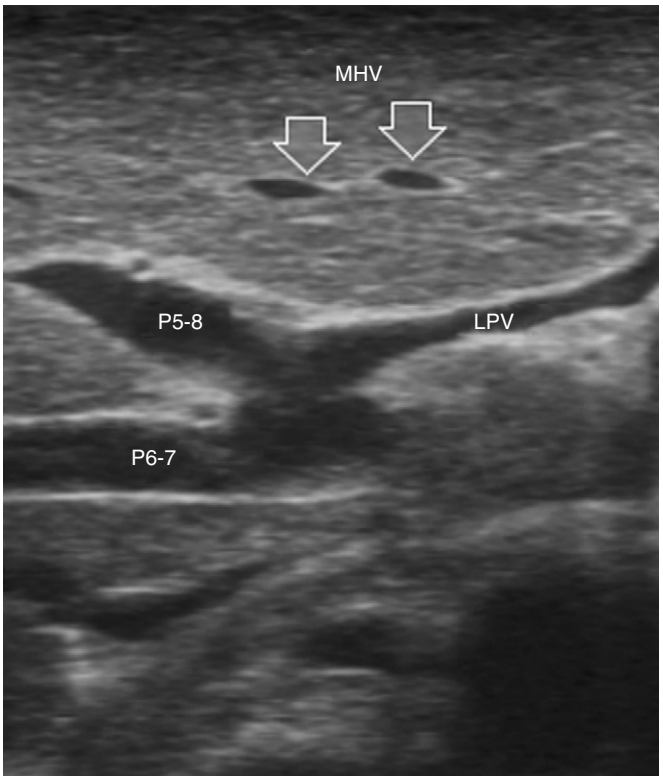


FIGURE 95.12. An atypical branching pattern of the portal branches with the portal branch to right anterior section (*P5-8*) and to the right posterior section (*P6-7*) originating separately and lacking a formal right portal vein. MHV, middle hepatic vein; LPV, left portal vein.

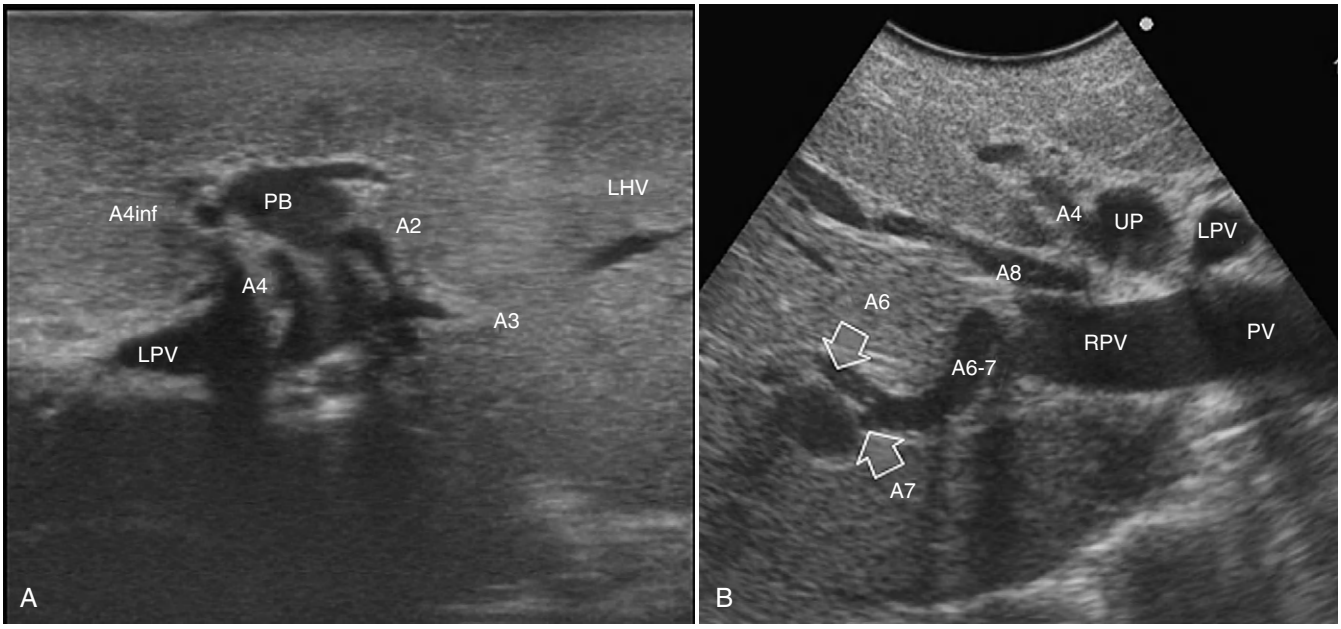


FIGURE 95.13. Arterial branching pattern in the left (**A**) and right (**B**) hemiliver. A2, arterial branch to segment II; A3, arterial branch to segment III; A4, arterial branch to segment IV; A4inf, arterial branch to segment IV inferior; A6, arterial branch to segment VI; A7, arterial branch to segment VII; A6-7, arterial branch to the right posterior section; A8, arterial branch to segment VIII; LHV, left hepatic vein; LPV, left portal vein; PB, portal branch; PV, portal vein; RPV, right portal vein; UP, umbilical portion.

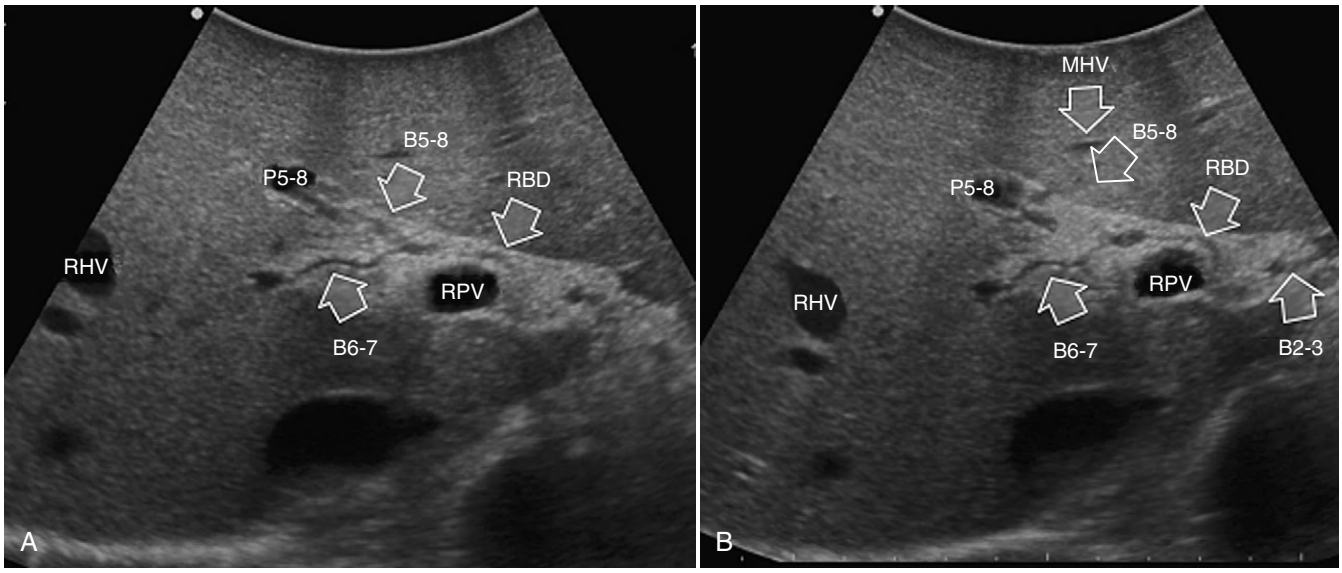


FIGURE 95.14. The biliary branching pattern in the right hemiliver and partially the left. B2-3, bile duct to segments II and III; B5-8, bile duct to right anterior section; B6-7, bile duct to right posterior section; LPV, left portal vein; MHV, middle hepatic vein; P5-8, portal branch to right anterior section; RBD, right bile duct; RHV, right hepatic vein; RPV, right portal vein.

(Fig. 95.18), and because of that, it is possible to visualize more than one segmental bile duct with one scan; however, with enough US background, IOUS can allow exact definition of the bile duct anatomy, not only in pathologic conditions but also in the normal state. This possibility also allows assessment of variations in the normal anatomy, such as confluence of the right posterior sectional bile duct into the left hepatic duct (Fig. 95.19), which is clearly critical information, particularly if a left hepatectomy is planned.

INDICATIONS

The use of IOUS in liver resections can be schematically divided into three principal phases: 1) liver exploration for staging of the disease, 2) planning of the surgical strategy, and 3) guidance of surgical maneuvers.

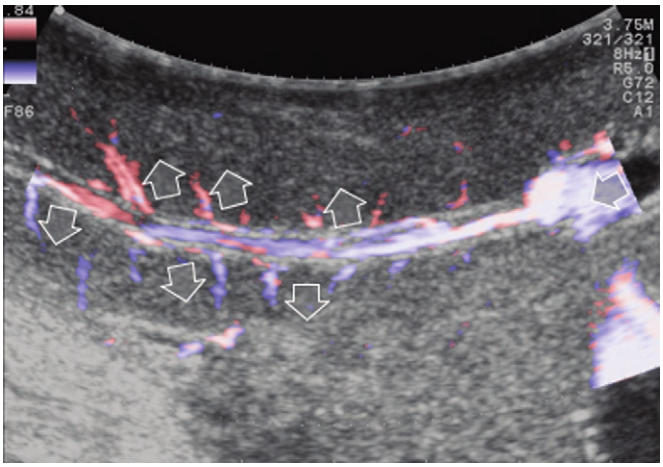


FIGURE 95.15. This image shows the capability of e-flow intraoperative ultrasound to disclose flow and its direction (*arrows*), not only in the third-order portal branches but even more peripherally.

Liver Exploration

Detection and differentiation are the two main targets of IOUS exploration of the liver. The hard and irregular surface of cirrhotic livers makes difficult the detection of small nodules by palpation; conversely, IOUS allows the detection of new lesions in around 30% of cases (Kokudo et al, 1996), although most of the nodules detected by IOUS in the cirrhotic liver are not tumors but more often are regenerative nodules. In this way, IOUS introduces the risk of overestimating tumor stage (Fig. 95.20). Indeed, except for those nodules with a mosaic pattern

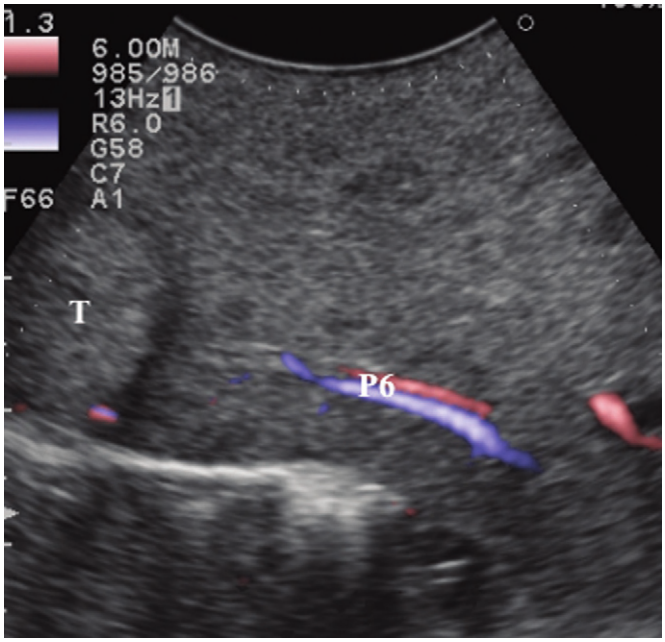


FIGURE 95.16. Tumor (*T*) fed by the portal pedicle of segment VI (*P6*).

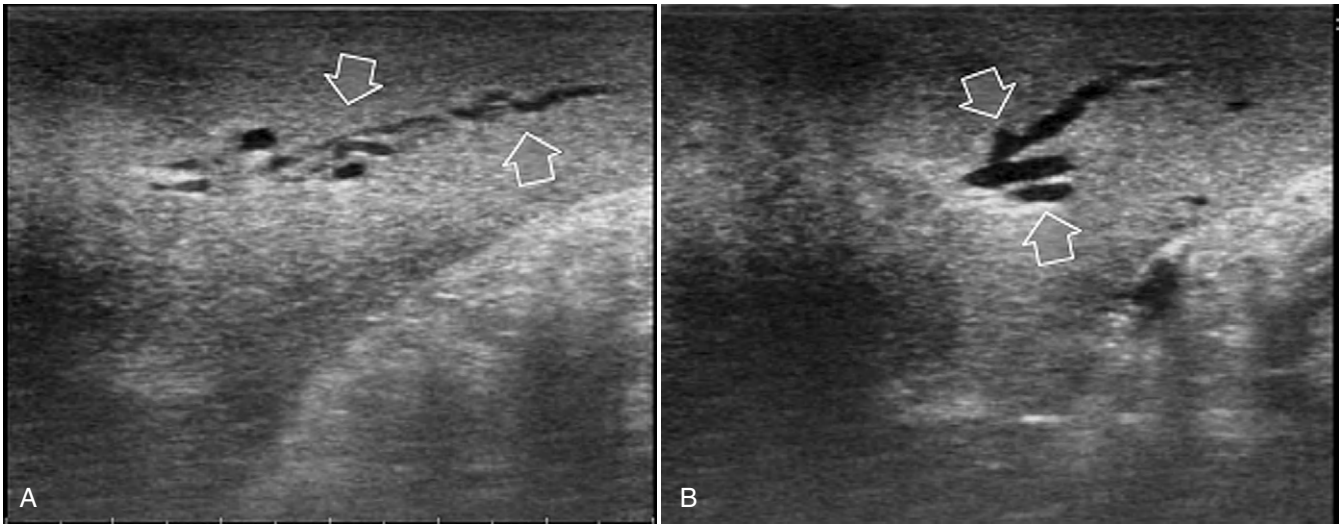


FIGURE 95.17. **A** and **B** show the dilation of segmental bile ducts, which assume a serpiginous path (*arrows*).

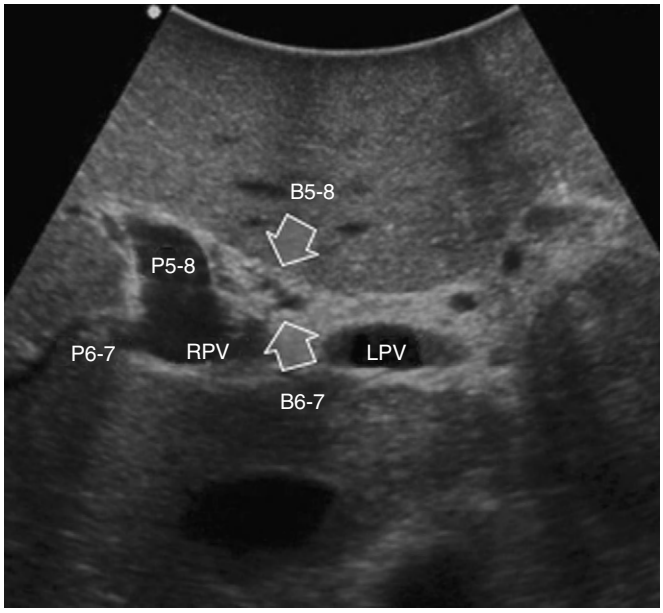


FIGURE 95.18. Centripetal branching pattern of the bile duct compared with that of the portal vein. B5-8, bile duct to right anterior section; B6-7, bile duct to right posterior section; LPV, left portal vein; P5-8, portal branch for right anterior section; P6-7, portal branch to right posterior section; RPV, right portal vein.

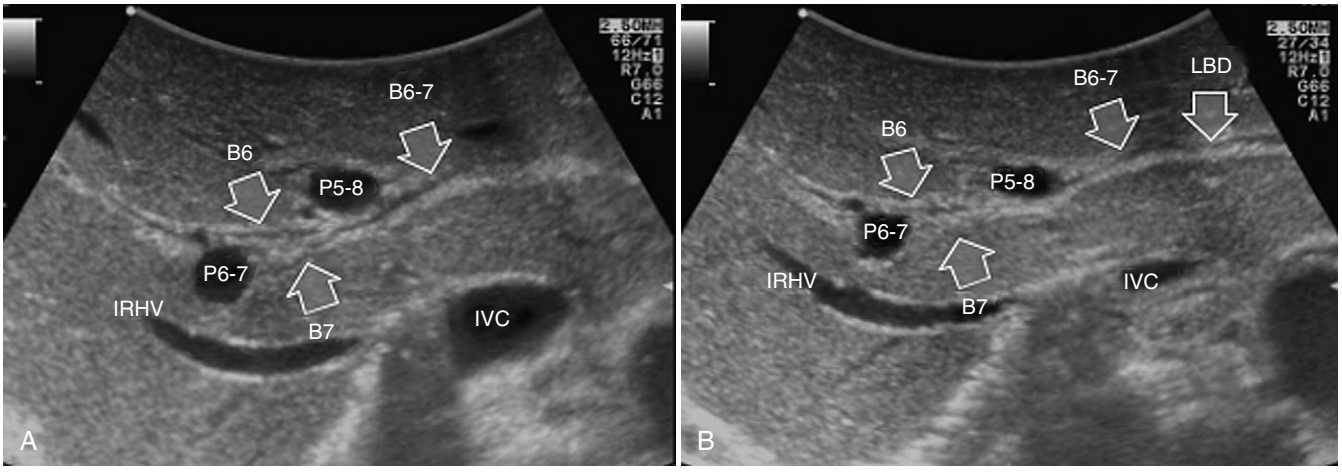


FIGURE 95.19. **A,** The confluence of the segmental bile ducts of segments VI (*B6*) and VII (*B7*) into the sectional bile duct of the right posterior section (*B6-7*); **B,** B6-7 is flowing into the left bile duct (*LBD*) as shown in this picture. IRHV, inferior right hepatic vein; IVC, inferior vena cava; P5-8, portal branch for right anterior section; P6-7, portal branch to right posterior section.

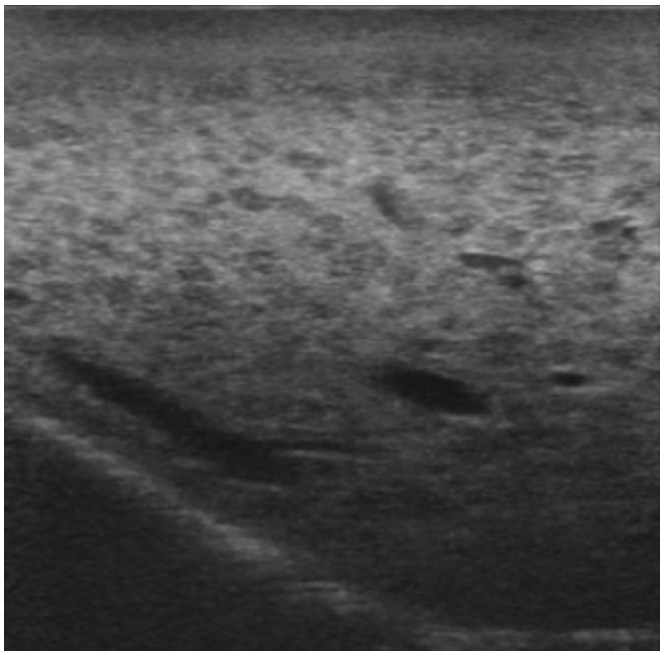


FIGURE 95.20. Cirrhotic liver with an inhomogeneous pattern as a result of the presence of an uncountable number of hypoechoic (dark) nodules.

evident on US (Fig. 95.21A), which are malignant in 84% of cases, only 24% to 30% of hypoechogenic (dark) nodules (Fig. 95.21B) and 0% to 18% of those hyperechogenic (bright) nodules (Fig. 95.21C) are neoplasms (Kokudo et al, 1996; Takigawa et al, 2001).

To overcome this problem, even biopsy seems to be inadequate. The only nodule that can be easily differentiated intraoperatively from HCC or liver metastases is the small hemangioma, often discovered primarily at IOUS (see Chapter 79); it displays a typical ultrasonographic pattern, and when compressed, it changes in size and appearance (Fig. 95.22; see Chapter 13). The problem of differentiating benign from malignant lesions on IOUS exploration becomes crucial. Some attempts are now ongoing using elastography, which should allow lesion differentiation based on tissue stiffness expressed on the IOUS screen and indicated by different colors (Fig. 95.23); however, to date, limited data are available to describe its use in this application. In the next section, it will be shown how CE-IOUS will play an increasingly important role in this context and will be even more relevant in the near future.

Rather than differentiation, in the case of CLM, their clue is their accurate detection, particularly in the event of multinodular hepatic involvement. Indeed, in patients with CLM, the detection of any tiny nodule undiscovered preoperatively becomes crucial for attempting a reduction of the still high postoperative early recurrence rate (Yoshidome et al, 2008). From 10% to 40% of patients with colon cancer have nonpalpable CLM (Agrawal et al, 2006; Machi et al, 1991); as a consequence, IOUS exploration of the liver remains crucial, and CE-IOUS seems able to enhance its role in this context.

Contrast-Enhanced Intraoperative Ultrasonography

Hepatocellular Carcinoma

CE-IOUS is now used for characterizing the new lesions of HCC eventually detected at IOUS (Torzilli et al, 2007b). The rationale is to check the vascular pattern during contrast enhancement of each new lesion. Because it is very important to identify the arterial vascularization in HCC, which can take 20 to 30 seconds, each nodule must be carefully evaluated, and this necessity demands multiple injections in the presence of multiple nodules. This requirement may be obviated by the new liver-specific contrast agents. Using these, the contrast enhancement remains visible from several minutes to even hours after injection, and CE-IOUS should become easier to use and will likely be more effective for detection of HCC.

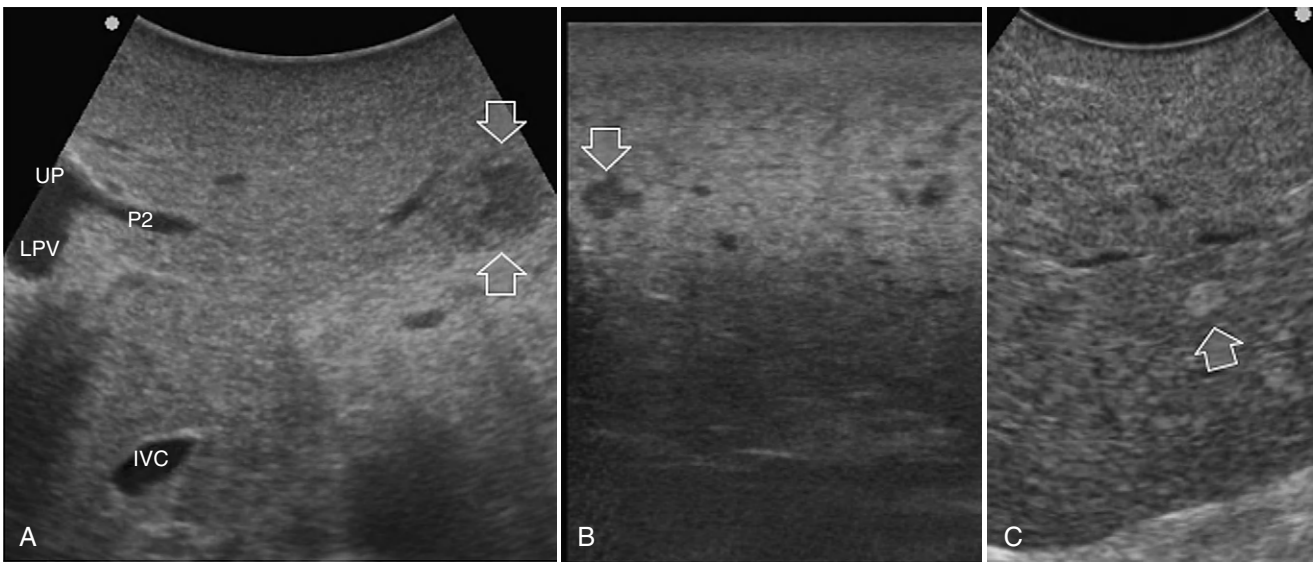


FIGURE 95.21. A, Nodule (*arrows*) with a mosaic pattern on intraoperative ultrasound (IOUS). **B,** Nodule (*arrow*) with a hypoechoic dark pattern at IOUS. **C,** Nodule (*arrow*) with a hyperechoic bright pattern at IOUS. IVC, inferior vena cava; LPV, left portal vein; UP, umbilical portion; P2, portal branch to segment II.

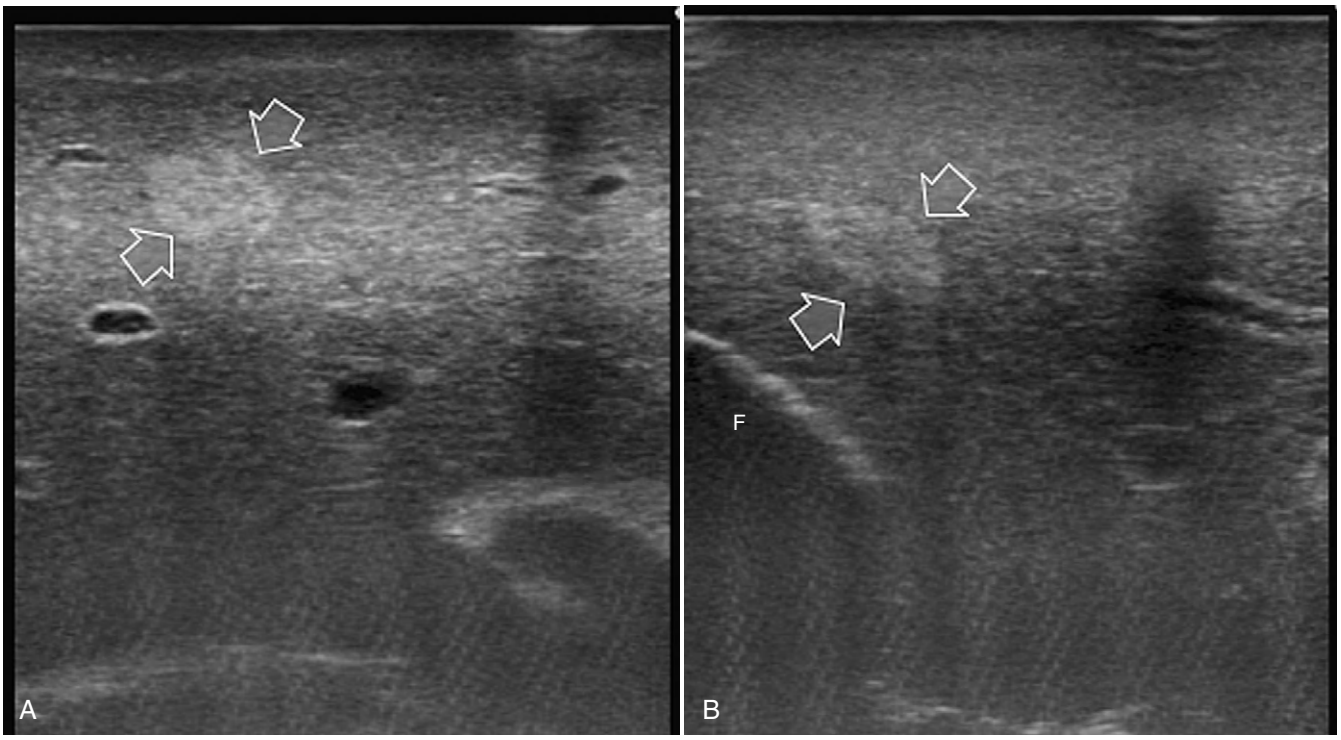


FIGURE 95.22. Test for diagnosing a hemangioma. **A,** Hemangioma (*arrows*) with hyperechoic (bright) pattern compatible with this type of lesion, although not specific enough. **B,** Once compressed under IOUS guidance, the lesion modifies its shape (*arrow*); this finding together with its echogenicity leads to the diagnosis of hemangioma. F, finger.

Tumor vascularity as a criterion for differentiating regenerative or dysplastic nodules from HCC correlates with the histologic evidence of a progressive increase in unpaired arteries from dysplastic to neoplastic nodules in a cirrhotic liver (Roncalli et al, 1999). Certainly, the pattern of vascular enhancement by itself is not sufficient for differentiating malignant from nonmalignant nodules with 100% specificity. Indeed, although percutaneous contrast-enhanced US (CE-US) provides differential diagnosis of hepatic nodules based on their vascular pattern with 95% specificity (Quaia et al, 2004), intraoperatively there is the need to differentiate lesions smaller than 1 cm. For these nodules, the vascularity as a criterion for differential diagnosis is less specific, although some improvements compared with conventional IOUS could be expected. Therefore, in the early 1990s, attempts were made to apply CE-IOUS using carbon dioxide as a contrast material, but the need for arterial catheterization made this technique too invasive (Takada et al, 1990). In my preliminary experience, CE-IOUS has provided remarkable findings, either by adding information on nodular vascularity in patients with HCC, or by detecting nodules that were not visible at IOUS, in patients with CLM (Torzilli et al, 2004).

For patients undergoing operation for HCC, my colleagues and I have introduced a classification of the enhancement pattern of lesions seen at CE-IOUS, upon which the surgical decision making is established (Fig. 95.24; Torzilli et al, 2007b). In brief, any pathologic lesion should appear as hypoechogenic at the late phases, with or without inner vessels and with or without an arterial phase, in which it is enhanced prior to the remnant liver parenchyma. Lesions with this type of appearance

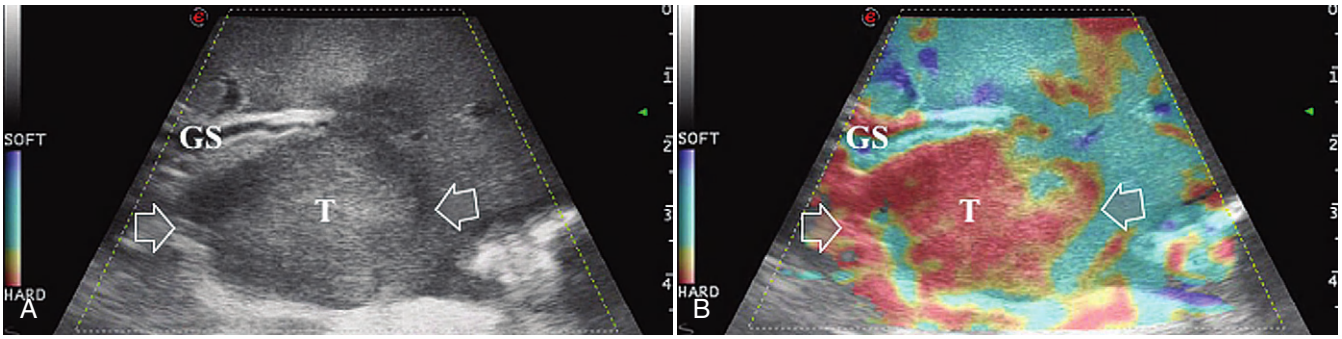


FIGURE 95.23. Potential value of elastography in estimating the tissue stiffness, relating it to a color scale disclosed on the left of each image. **A,** Tumor (*T*) as it appears at the B-mode (*arrows*). **B,** Once elastography is activated, the tumor appears brownish (*arrows*), according to its higher stiffness compared with the surrounding liver parenchyma. GS, glissonian sheath.

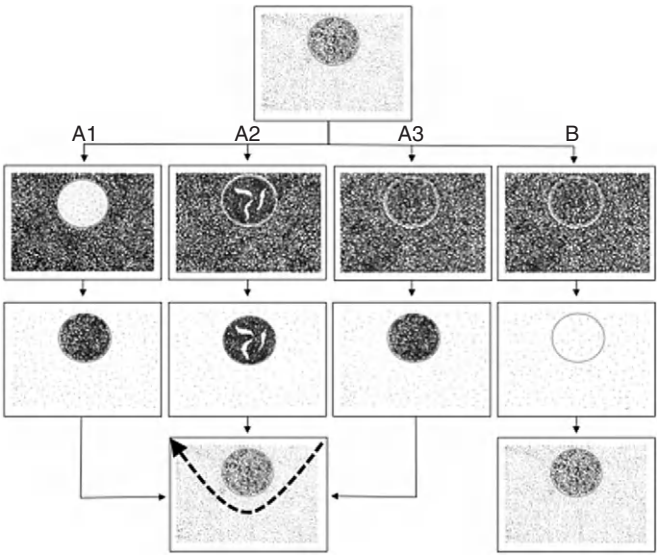


FIGURE 95.24. Classification of pattern of enhancement with contrast-enhanced intraoperative ultrasound (IOUS) of those lesions detected at IOUS and during surgery for hepatocellular carcinoma. Lesions with a class A pattern of hypervascular enhancement in early phase (*A1-A2*) or a hypoechoic pattern in the delayed phases (*A1, A3*) must be resected; inversely, lesions showing a class B pattern of enhancement (disappearance during contrast phases) are not removed.

should be removed (Fig. 95.25). Those lesions that disappear once the contrast enhances the liver are not considered neoplastic and are not removed (Fig. 95.26). With these criteria, we obtained with CE-IOUS a specificity of 69% (Torzilli et al, 2007b). This value is probably not that high, especially when compared with that reported for CE-US (Quaia et al, 2004); however, as mentioned before, the small size of the lesions targeted for CE-IOUS study could explain this discrepancy. For these tiny nodules, the neovascularity as a criterion for differentiation between malignant and benign lesions has limits that are independent from the method we use; therefore CE-IOUS can be helpful in a certain percentage of nodules but not in all, although the rate of 69% specificity is encouraging, as it means that we can provide proper information with this new technique in 7 of 10 lesions we detect at laparotomy. For those lesions remaining, even histology may be lacking, as we know no common agreement exists among Western and Eastern pathologists on the definition of early HCC and dysplastic lesions (International Consensus Group for Hepatocellular Carcinoma, 2009). New perspective may be provided by a more extensive use of the new contrast agent, for now clinically available only in Japan (Kudo, 2007). This agent (Sonozoid) has a Kupffer phase, and it adds further criteria for differentiating those nodules detected at IOUS.

Colorectal Liver Metastases

Improving detection is the main target of CE-IOUS in the case of CLM. In the 1990s, half of the patients who underwent surgery for CLM had a surgical strategy modified by IOUS findings (Kane et al, 1994). More recently, progress in preoperative imaging has reduced this rate; in fact, some authors have reported that just 4% of the operative decision making is modified by IOUS (Sahani et al, 2004). Conversely, adding CE-IOUS to IOUS exploration modified operative decision making in 38% of patients with CLM (Torzilli et al, 2008a). If this discrepancy in the rates of modified surgical strategy among series is partially the result of different surgical approaches, particularly more parenchyma-sparing procedures, then probably CE-IOUS is playing a role, too. Indeed, with CE-US, the CLM shows the so-called "black hole" effect (Fig. 95.27). The

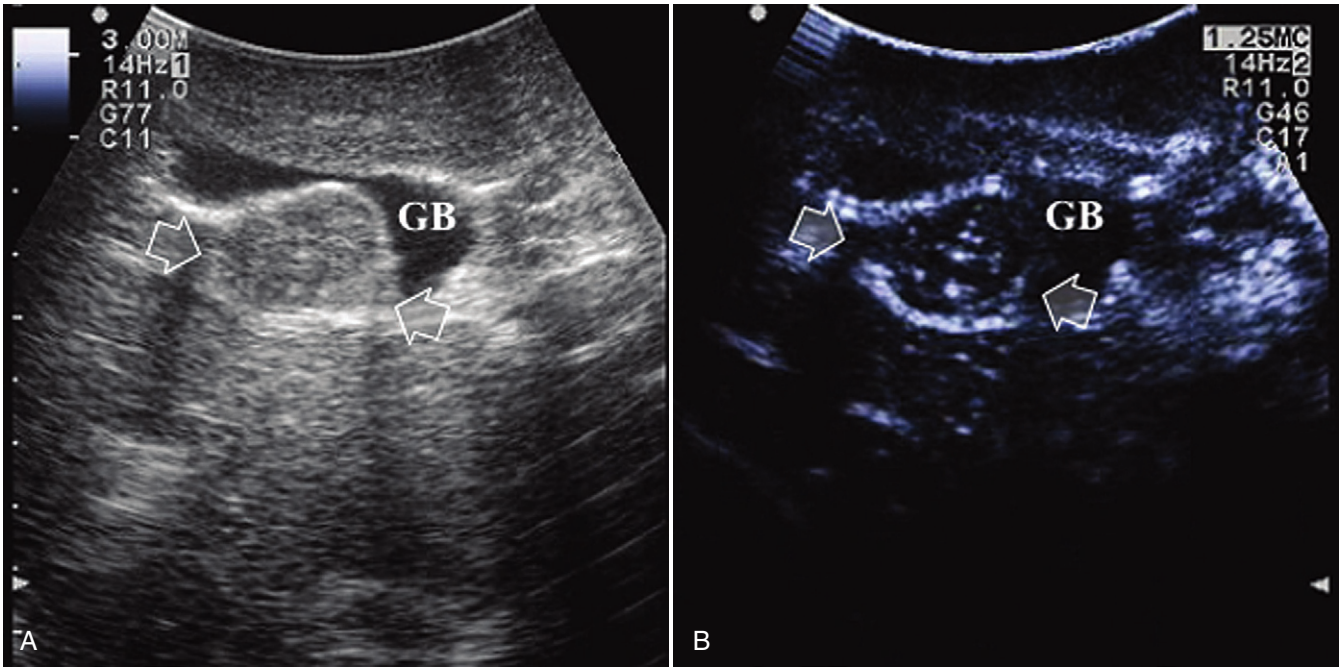


FIGURE 95.25. A, *Arrows* indicate a lesion at the level of the gallbladder (*GB*) fossa. **B,** At early enhancement, the same lesions (*arrows*) shows intranodular, hyperechoic (bright) spots, which allow its classification as an A2 nodule.

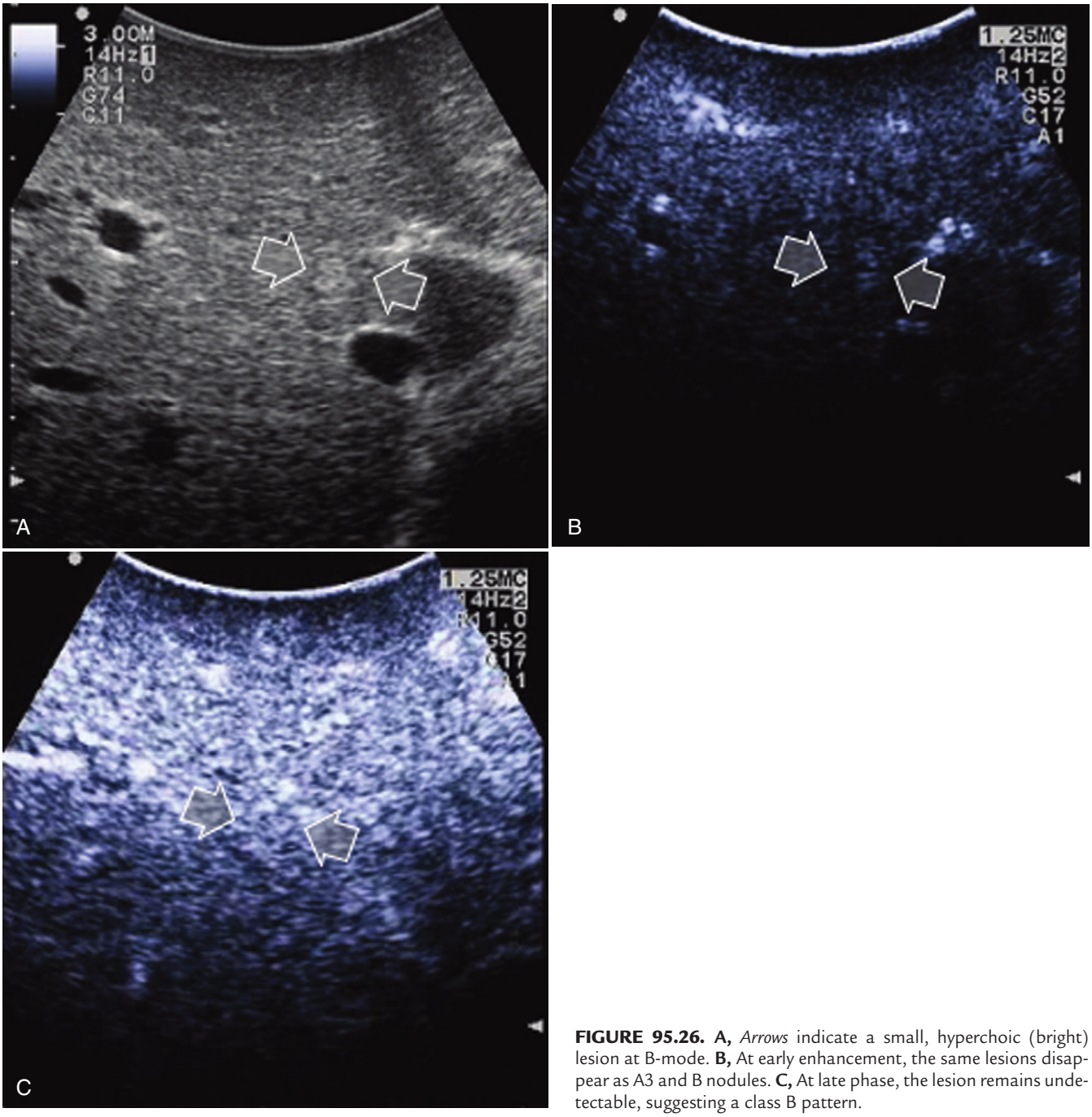


FIGURE 95.26. A, *Arrows* indicate a small, hyperchoic (bright) lesion at B-mode. **B,** At early enhancement, the same lesions disappear as A3 and B nodules. **C,** At late phase, the lesion remains undetectable, suggesting a class B pattern.

metastastic nodule in the late phase, which lasts from 2 to 5 minutes after injection, remains unenhanced and black in comparison with the surrounding enhanced liver parenchyma (Fig. 95.28). This is particularly useful in those patients who undergo surgery after chemotherapy, in whom some nodules may not be well visualized by IOUS because of the histologic rearrangements induced by the chemotherapeutic agents. CE-IOUS allows better nodule visibility and has allowed my colleagues and me to detect 9% of adjunctive nodules (Torzilli et al, 2008a); therefore CE-IOUS application resulted in an increased sensitivity, and in patients with CLM, it appears to have an important role. The only condition under which it may not help is in the event of a bright liver at IOUS (Chen et al, 2008), which correlates with the degree of fatty change and accounts for 10% of our patients (Torzilli et al, 2008a). Indeed, in these circumstances, the visibility of CLM, generally hypoechogenic, is enhanced by the brightness of the surrounding liver parenchyma, mimicking the effect of the contrast enhancement (Fig. 95.29). As a confirmation of this, we never found new sites of disease at CE-IOUS in those patients having a bright liver at IOUS.

For CLM, new perspectives could be obtained by using liver-specific contrast agents, which allow prolonged exploration. A preliminary experience of eight patients showed new lesions in two detected only at CE-IOUS (Nakano et al, 2008).

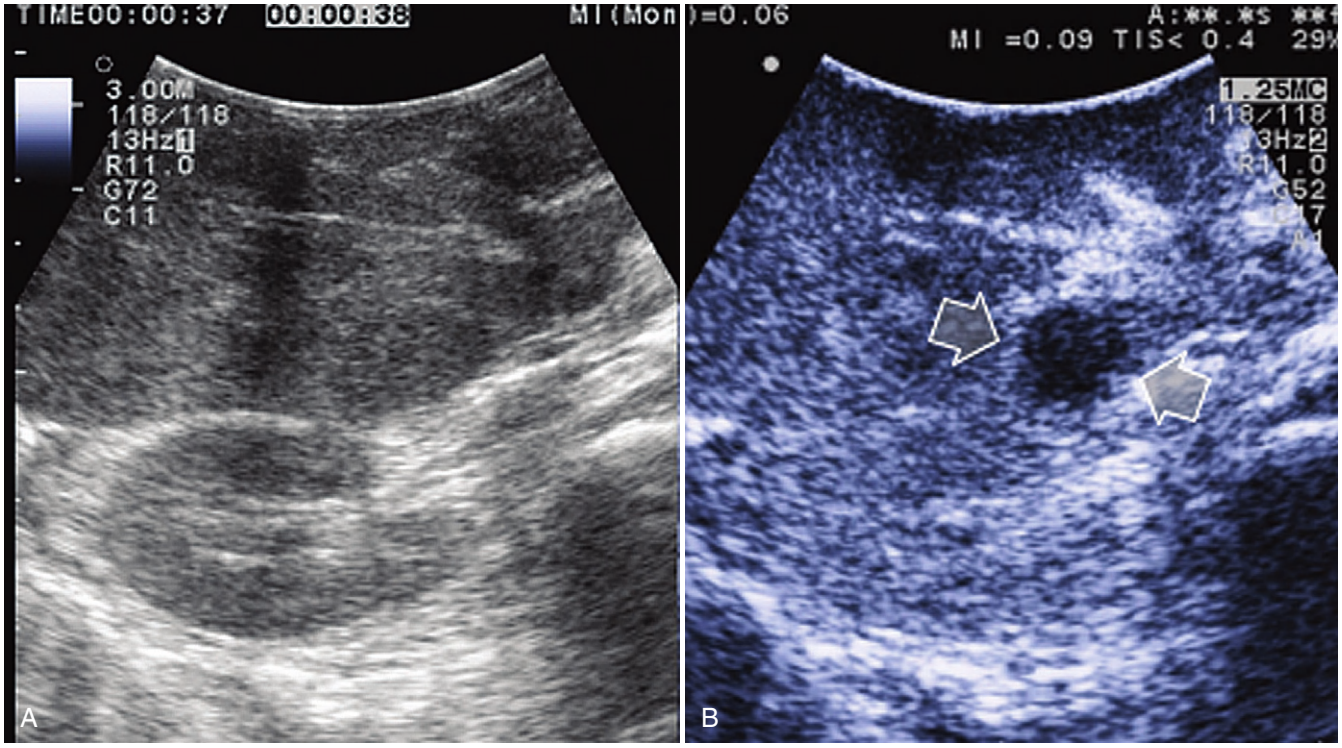


FIGURE 95.27. A, This relatively large metastatic lesion is substantially hypoechoic compared with the surrounding liver parenchyma. **B,** At 37 seconds after injection of the contrast agent (time is shown in the upper right corner), the lesion is clearly visible (*arrows*), showing the so-called "black hole" effect.

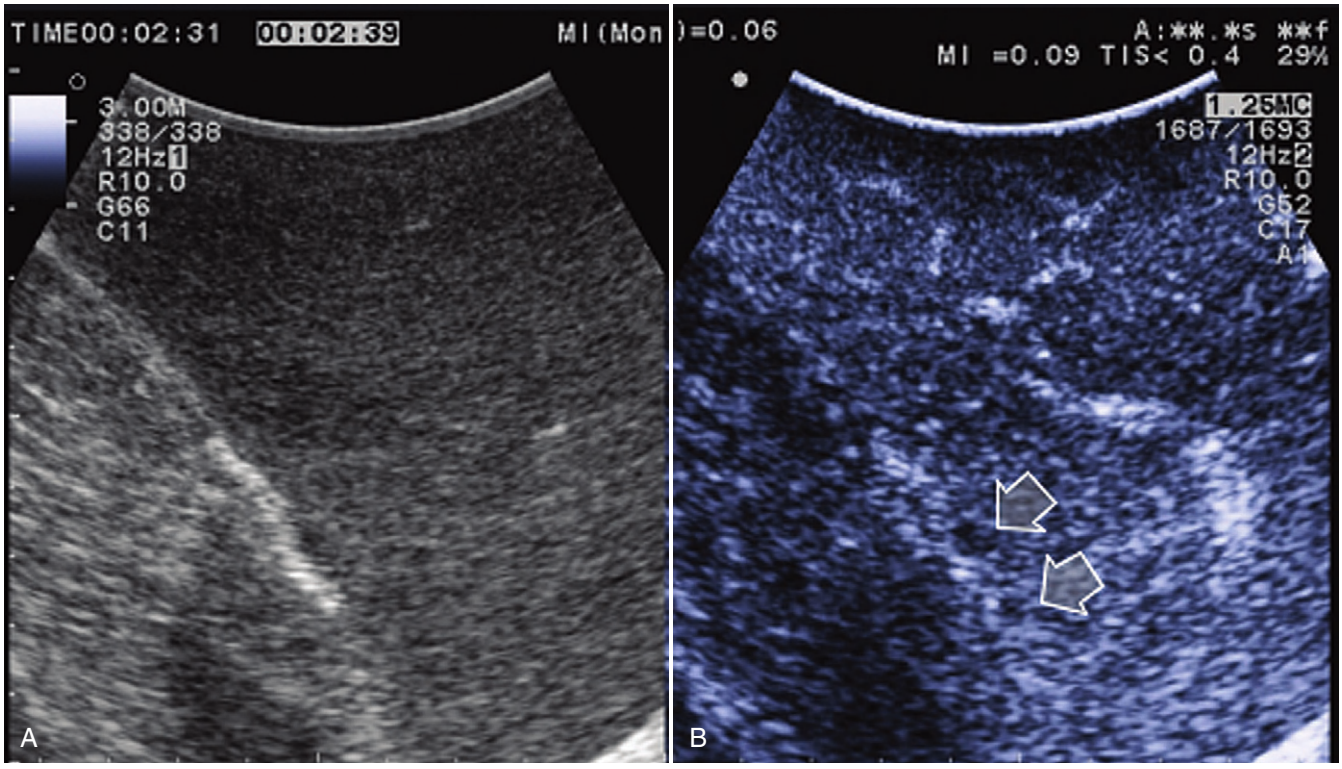


FIGURE 95.28. A, Two small metastatic lesions cannot really be visualized in intraoperative ultrasound. **B,** At 2 minutes and 39 seconds after injection of the contrast agent (time is shown in the upper right corner), the lesions (*arrows*) are clearly visible, showing the so-called "black hole" effect.



FIGURE 95.29. Clear visibility of two hypoechoic masses (*arrows*) in a so-called bright (fatty) liver.

Care should be used in CLM patients who also have coexisting liver cysts, which may appear similar to the CLM along the delayed phases of contrast enhancement; however, the cysts should have been already mapped based on the preoperative imaging and should have been identified at exploration with conventional IOUS. Therefore, any new "black hole" detected in the liver in locations other than where cysts were eventually detected should be considered suspicious for malignancy. Liver cyst features at unenhanced IOUS have an anechoic content and a posterior enhanced echo (Fig. 95.30; see Chapter 13), and it must be taken into account that the anechoic pattern could be mimicked by tiny CLM (Fig. 95.31).

Other Intraoperative Techniques

Recently, imaging using indocyanine green (ICG) as a fluorescent source has been proposed (Ishizawa et al, 2009; Gotoh et al, 2009). Used in many centers to assess liver function, ICG is injected intravenously approximately 3 days before surgery and during laparotomy, and the liver is explored to detect any sign of fluorescence on its surface by means of a fluorescent imaging system that comprises a control unit and a camera. Once removed, the specimen is explored to detect undisclosed fluorescent areas. With this device, Ishizawa and colleagues (2009) disclosed 13 of 91 lesions with only an ICG fluorescent-imaging technique, obtaining a sensitivity of 100% for HCC and 93% for CLM. Although in a smaller series that included only patients with HCC, Gotoh and colleagues (2009) similarly showed that all the new lesions detected in the examined patients were visible only because of the ICG fluorescent-imaging technique.

These promising results should certainly stimulate further investigation. Furthermore, it is noteworthy that the ICG staining pattern is different compared with the histology and tumor differentiation. Indeed, CLM and poorly differentiated HCC retain ICG at the periphery, but well-differentiated HCC is fully and diffusely stained. Certainly, the main limitation of this technique is that it can be applied only to those lesions superficially located, both on the liver surgery and on the cut surface once the specimen has been removed. Indeed, the near infrared light penetrates human tissue at a depth of 5 to 10 mm.

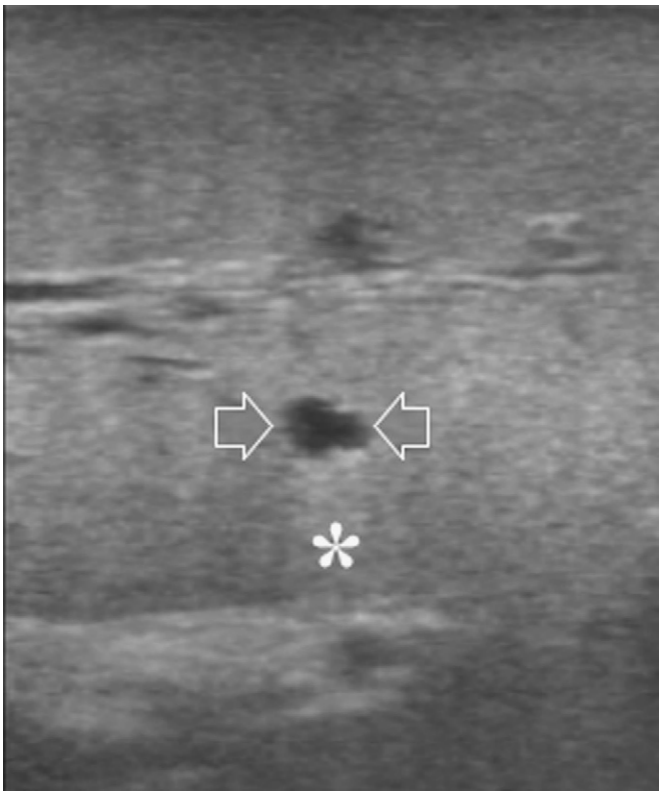


FIGURE 95.30. A small, simple hepatic cyst (*arrows*) with its typical posterior echo (*asterisk*) and the echo-free (*black*) content.

Planning of the Surgical Strategy

IOUS exploration of the liver could have a significant impact on the surgical strategy. More recently, impact of IOUS on the operative decision making, when compared with that of preoperative imaging techniques, is reported to be around 4% to 7% (Cerwenka et al, 2003; Jarnagin et al, 2001). The problem of

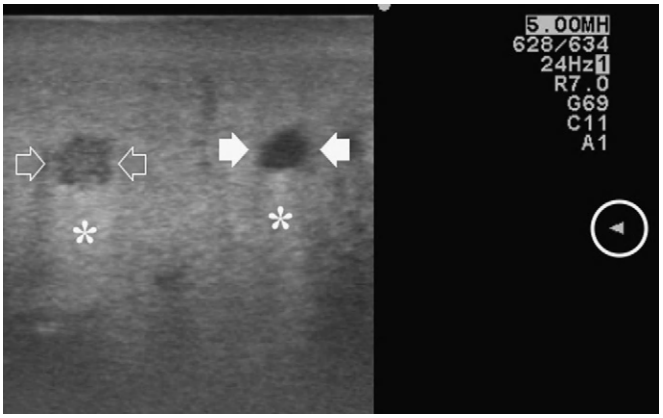


FIGURE 95.31. A small, simple hepatic cyst (*white arrows*) and a small metastasis (*transparent arrows*); both have a typical posterior echo (*asterisk*), but while the cyst is echo free (*black*), the metastasis is not. Once the focus of the ultrasound probe (*circled*) is not properly regulated (much deeper than at the level of the two lesions), the cyst may mimic the hypoechogenicity of the metastases; this represents a known artifact that should be avoided.

the impact of IOUS on the operative decision making depends on two main factors: the surgical policy of each specific team and the type of tumor. Indeed, the relatively low rates reported (Cerwenka et al, 2003; Jarnagin et al, 2001) are also influenced by the surgeon's resection policy; when a considerable number of patients undergo major hepatectomies, new nodules detected by IOUS in the same hemiliver would still be resected, and the surgical strategy would not be modified.

Recently, it was shown that major hepatectomies are carried out in a minority of patients, even in extremely complex presentations (Torzilli et al, 2009b), simply because of the extensive use of IOUS guidance for achieving parenchyma-sparing resections; from this perspective, detection of new nodules is more likely to change the surgical strategy.

IOUS allows an accurate three-dimensional reconstruction of the relationship between the tumor, the portal branches, and the hepatic veins, which is a fundamental step in defining the proper surgical strategy. Definition of tumor-vessel relationships is relevant for planning the type of resection (Torzilli et al, 2008c, 2010a). IOUS allows the surgeon to easily recognize whether an HCC is separated by some normal parenchyma from the vessel, or if it is in contact with the vessel without invading its wall, or conversely whether the HCC is invading the vessel wall or is determining the proximal bile duct dilation, or if it is associated with a tumor thrombus. Similarly, definition of the relationship between a CLM and intrahepatic vascular structures is precisely defined by IOUS; once the vessel wall is found to be intact, the circumferential extent of the contact is relevant for planning a resection that spares the vessel in contact with the CLM (Torzilli et al, 2009b). Based on these features, the decision whether the vessel should be resected is considered, and a precise surgical strategy can be pursued.

Tumor in Contact with a Glissonian Pedicle

The glissonian pedicle may be spared when in contact with an encapsulated HCC with integrity of the vessel wall appreciable at IOUS without any sign of bile duct dilation (Fig. 95.32). Similarly, the pedicle can be spared when it is in contact with a CLM, the integrity of the vessel wall is confirmed, bile duct dilation is ruled out, and the contact extent is less than one third of the pedicle circumference (Fig. 95.33). In the presence of bile duct dilation, tumor thrombus, invasion of the vessel wall, and for CLM, contact wider than one third of pedicle circumference, the pedicle must be divided (Fig. 95.34). In these conditions, extension of the hepatectomy is required for complete tumor clearance.

Tumor in Contact with a Hepatic Vein

The hepatic vein may be spared when in contact with an encapsulated HCC with integrity of the vessel wall appreciable at IOUS (Fig. 95.35). Initially for the CLM, its contact was considered an indication for hepatic vein resection; however, the vein may be spared when it is in contact with a CLM, but at IOUS, the integrity of the vessel wall is confirmed, and the contact extension is less than two thirds of the vein circumference (Figs. 95.36 and 95.37). In the presence of tumor thrombus, invasion of the vessel wall, and contact wider than two thirds of the vein circumference in CLM, the hepatic vein must

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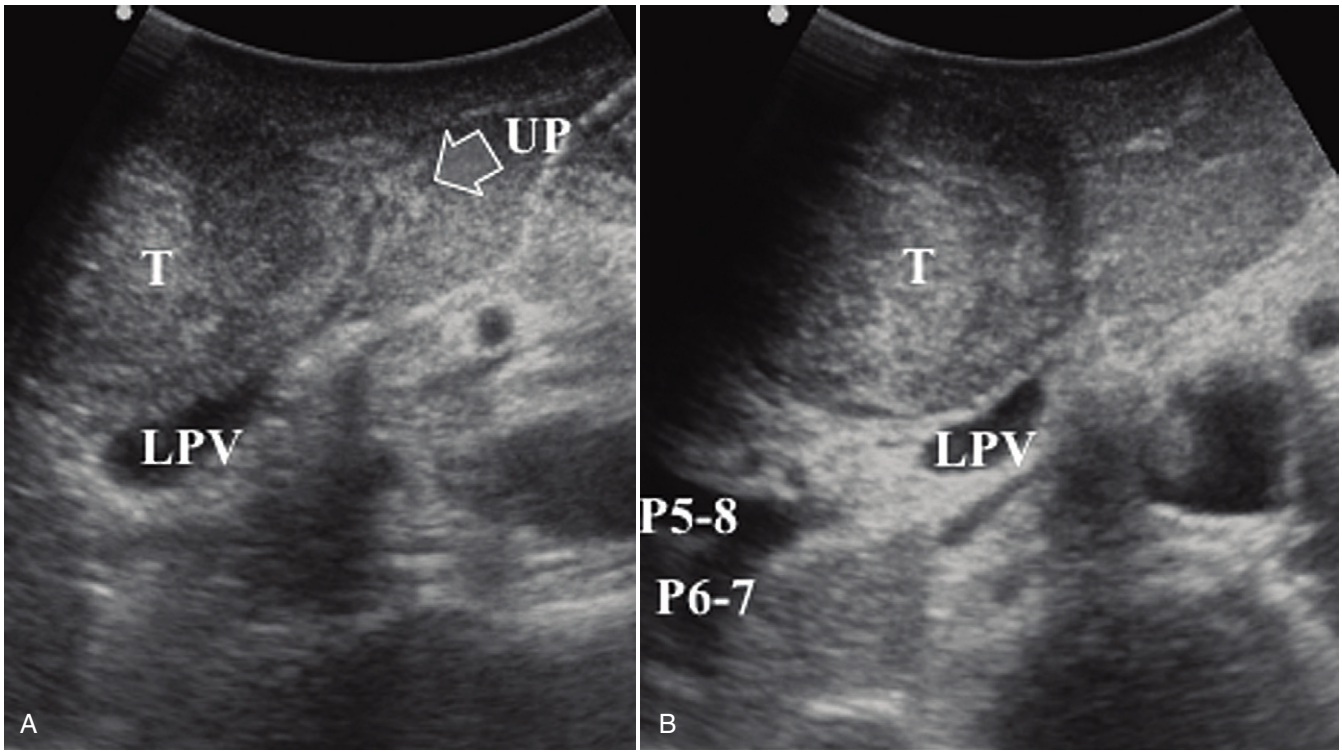
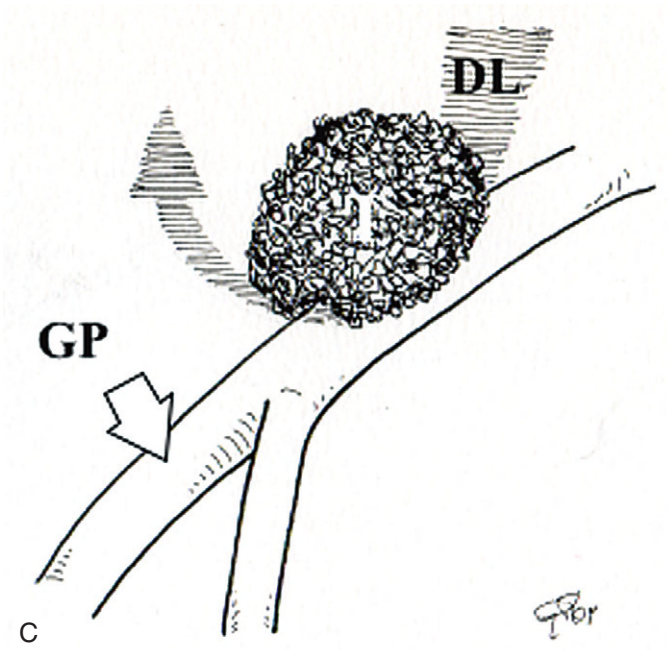
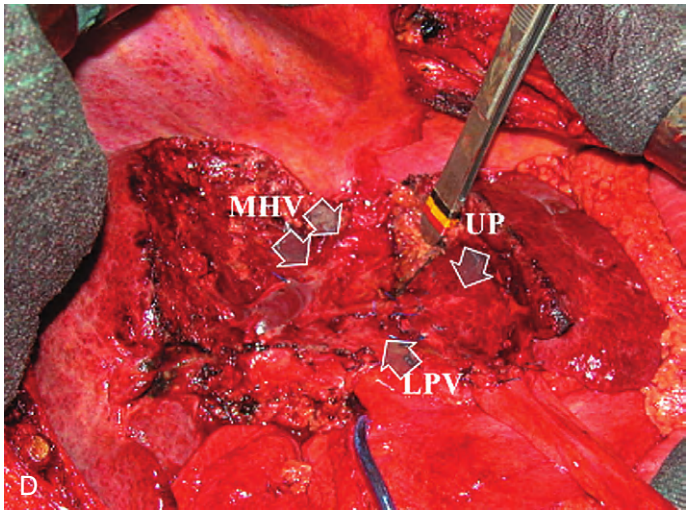


FIGURE 95.32. A, Appearance on intraoperative ultrasound of a hepatocellular carcinoma (*T*) located in segment IV, in extensive contact with the left portal vein (*LPV*) and the umbilical portion (*UP*). **B,** This image better discloses the relationship of the tumor with the LPV. Bile duct dilation is not evident in either figure.

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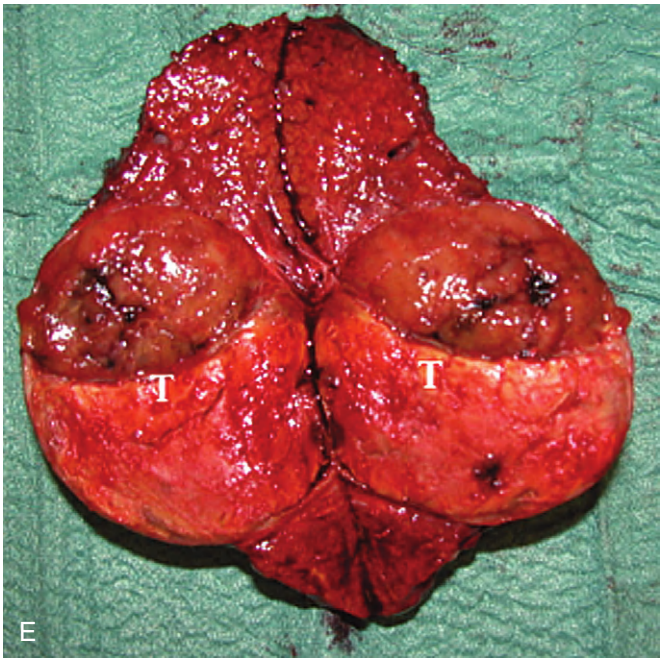
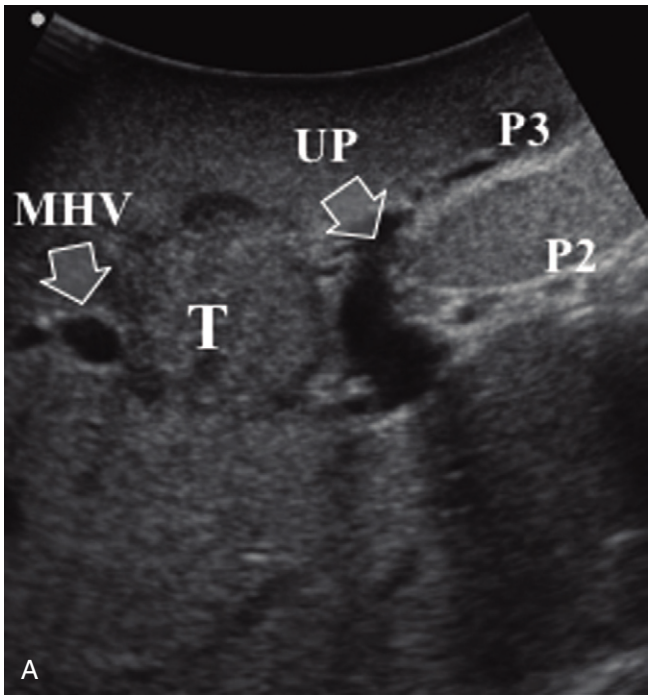
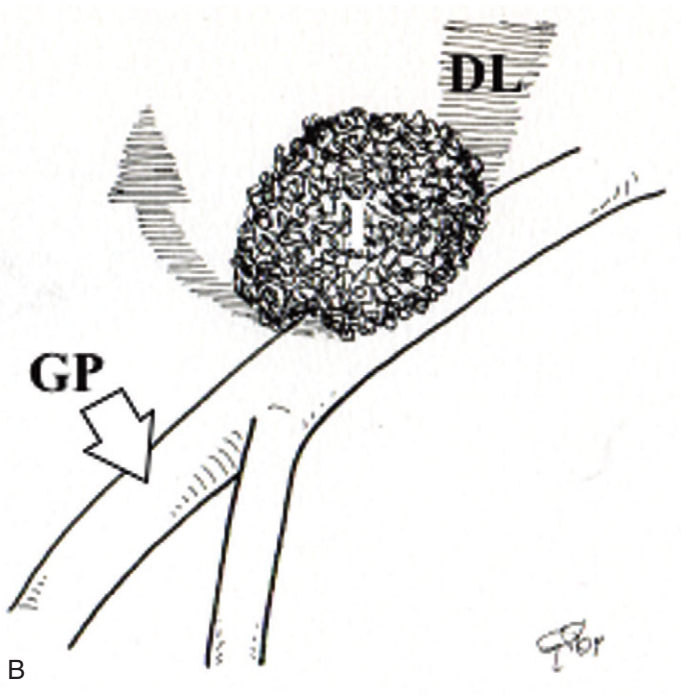


FIGURE 95.32, cont'd C, Schematically, this lesion could be classified as shown; a detachment of the tumor from the glissonian pedicle (*GP*) would be feasible, planning the drawn dissection line (*DL*). **D,** Note the cut surface at the end of the resection, which consisted of a segment IV full segmentectomy with complete exposure of the middle hepatic vein (*MHV*), the LPV, and the UP. **E,** The specimen shows an encapsulated hepatocellular carcinoma (*T*) with a typical mosaic pattern. P5-8, portal branch for right anterior section; P6-7, portal branch to right posterior section.





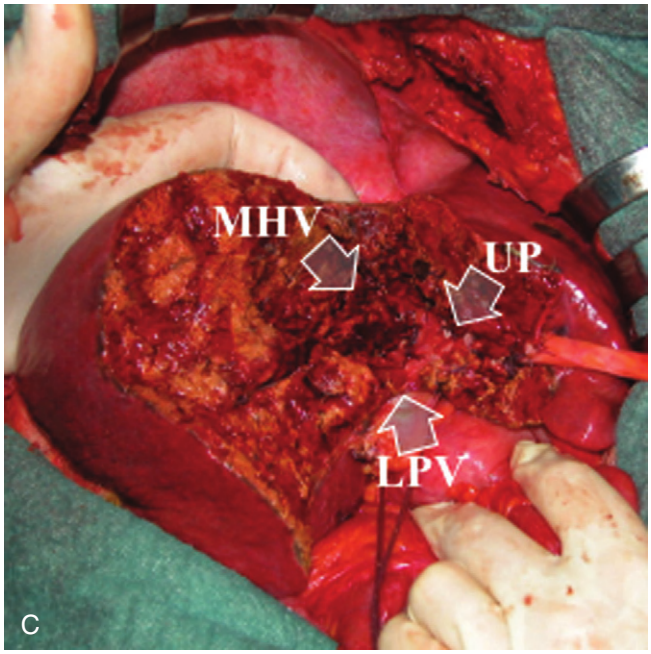
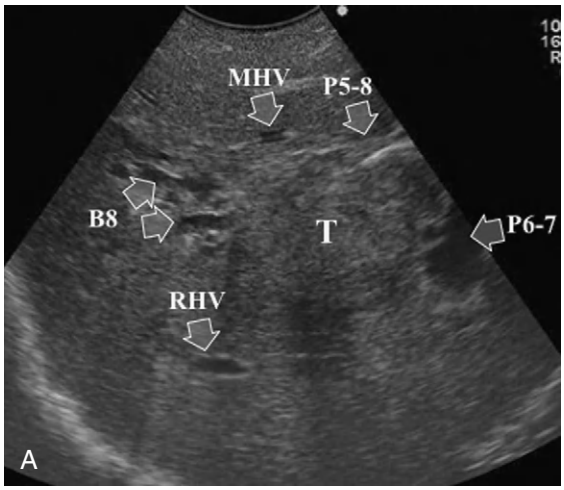
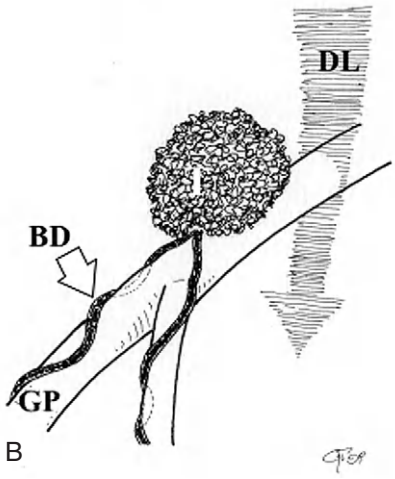
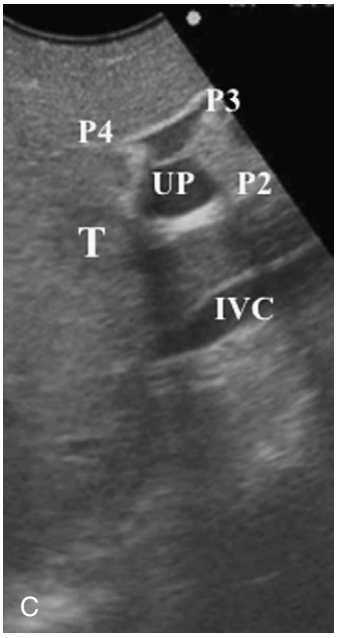
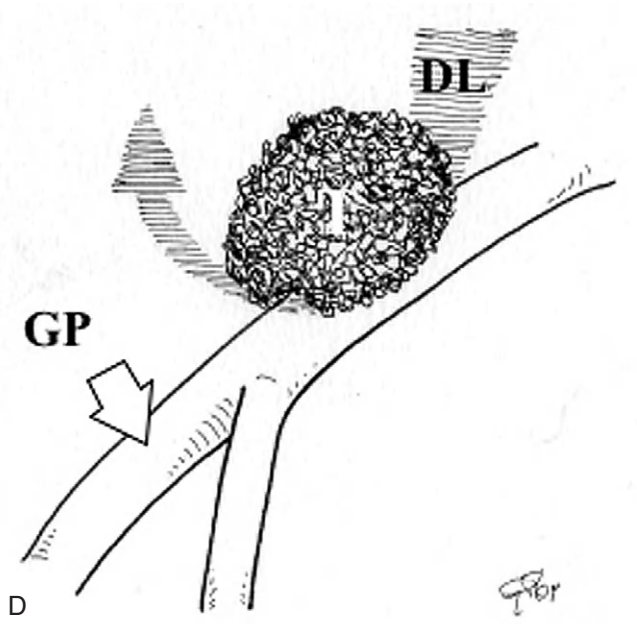


FIGURE 95.33. A, Appearance on intraoperative ultrasound of a colorectal liver metastasis (*T*) located in segment IV, in contact with the umbilical portion (*UP*) and with the middle hepatic vein (*MHV*). **B,** Schematic classification of the lesion. Detachment of the tumor from the glissonian pedicle (*GP*) and the hepatic vein (*HV*) would be suitable, therefore the drawn dissection line (*DL*) should be feasible. **C,** Cut surface at the end of the resection, which consisted of a segment IV partial resection with exposure of the left portal vein (*LPV*), the MHV, and the UP. P2, portal branch to segment II; P3, portal branch to segment III.









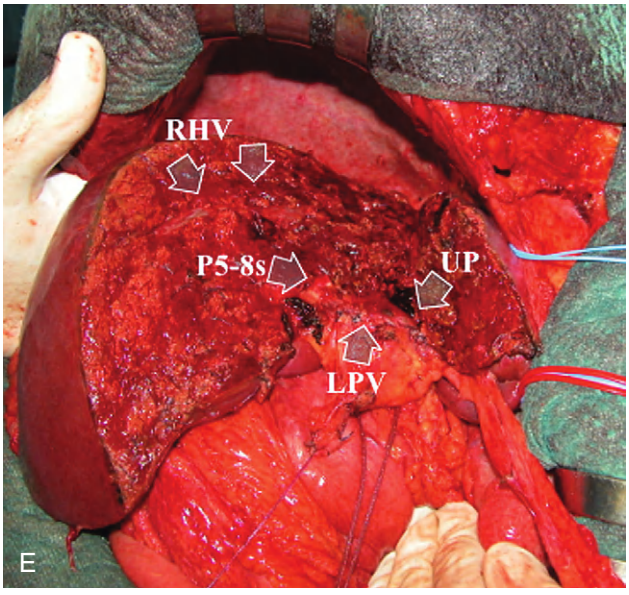


FIGURE 95.34. A, Appearance on intraoperative ultrasound of a colorectal liver metastasis (*T*) located in segment VIII, invading the portal branch of the right anterior section (*P5-8*) and causing dilation of the segmental portal branches of segment VIII (*B8*). **B,** Detachment of the tumor from the glissonian pedicle (*GP*) would not be suitable because of bile duct (*BD*) dilation. A suitable dissection line (*DL*) should include the GP. **C,** Relationship of the other lesion (*T*), which is located posterosuperiorly to the umbilical portion (*UP*) and in contact with it. **D,** Schematically, this lesion could be classified as shown, and as a consequence, a detachment of the tumor from the GP would be feasible, planning the drawn DL. **E,** Cut surface at the end of the resection, which consisted of a right anterior sectionectomy extended to segment IV, with the exposure of the right hepatic vein (*RHV*), left portal vein (*LPV*), and the UP. IVC, inferior vena cava; MHV, middle hepatic vein; P2, portal branch to segment II; P3, portal branch to segment III; P4, portal branch to segment IV; P6-7, portal branch to segments VI and VII.

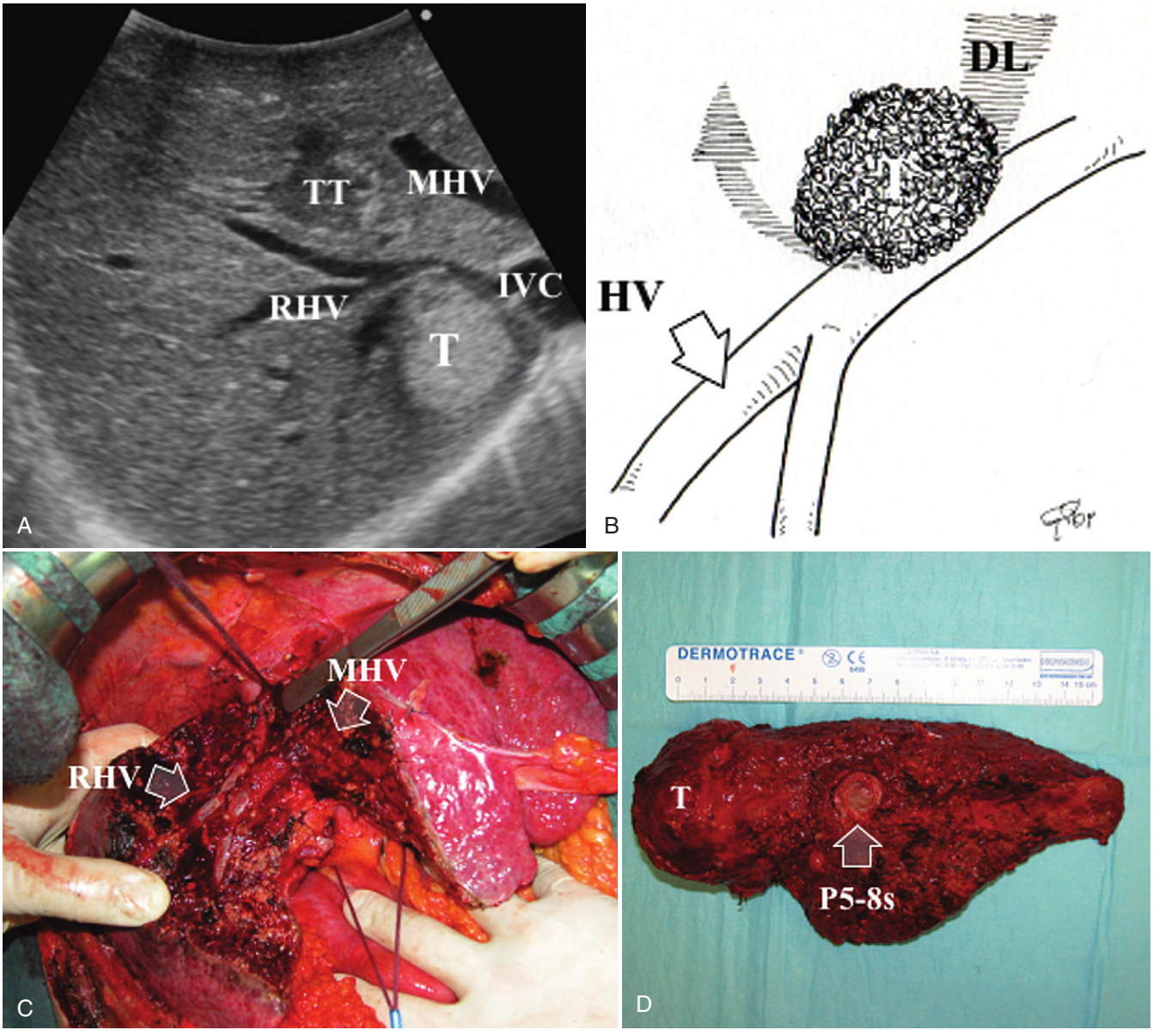


FIGURE 95.35. A, Intraoperative ultrasound appearance of a hepatocellular carcinoma (HCC) is located in the dorsal portion of segment VIII, in extensive contact with the right hepatic vein (*RHV*) and causing a tumor thrombus (*TT*) in the portal branch feeding the right anterior section. **B,** Detachment of the tumor from the hepatic vein (*HV*) would be feasible with the drawn dissection line (*DL*). **C,** Cut surface at the end of the resection, which consisted of a right anterior sectionectomy with complete exposure of the right hepatic vein (*RHV*). **D,** Specimen showing an encapsulated HCC (*T*) exposed on the cut surface and the stump of the sectional portal branch (*P5-8s*) occupied by the tumor thrombus. IVC, inferior vena cava; MHV, middle hepatic vein.

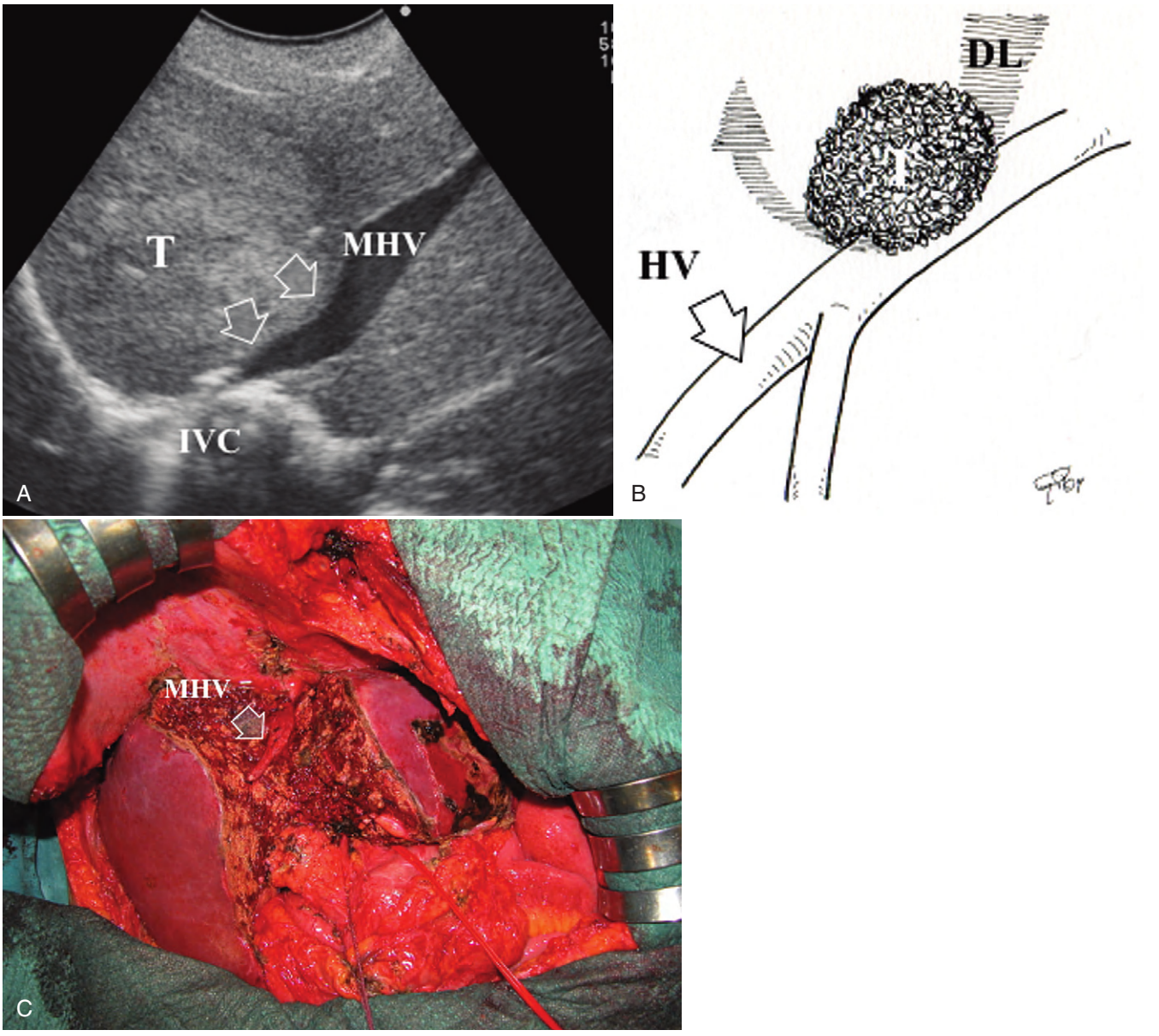


FIGURE 95.36. **A,** Intraoperative ultrasound appearance of a colorectal liver metastasis (*T*) located in segments IV (superior) and VIII ventral in extensive contact (*arrows*) with the middle hepatic vein (*MHV*). **B,** Schematically this lesion could be classified as shown, and detachment of the tumor from the hepatic vein (*HV*) would be feasible with the drawn dissection line (*DL*). **C,** Cut surface at the end of the resection; another lesion was present in segment IV inferior and necessitated a segment IV full segmentectomy extended to segment VIII ventral with complete exposure of the MHV. IVC, inferior vena cava.

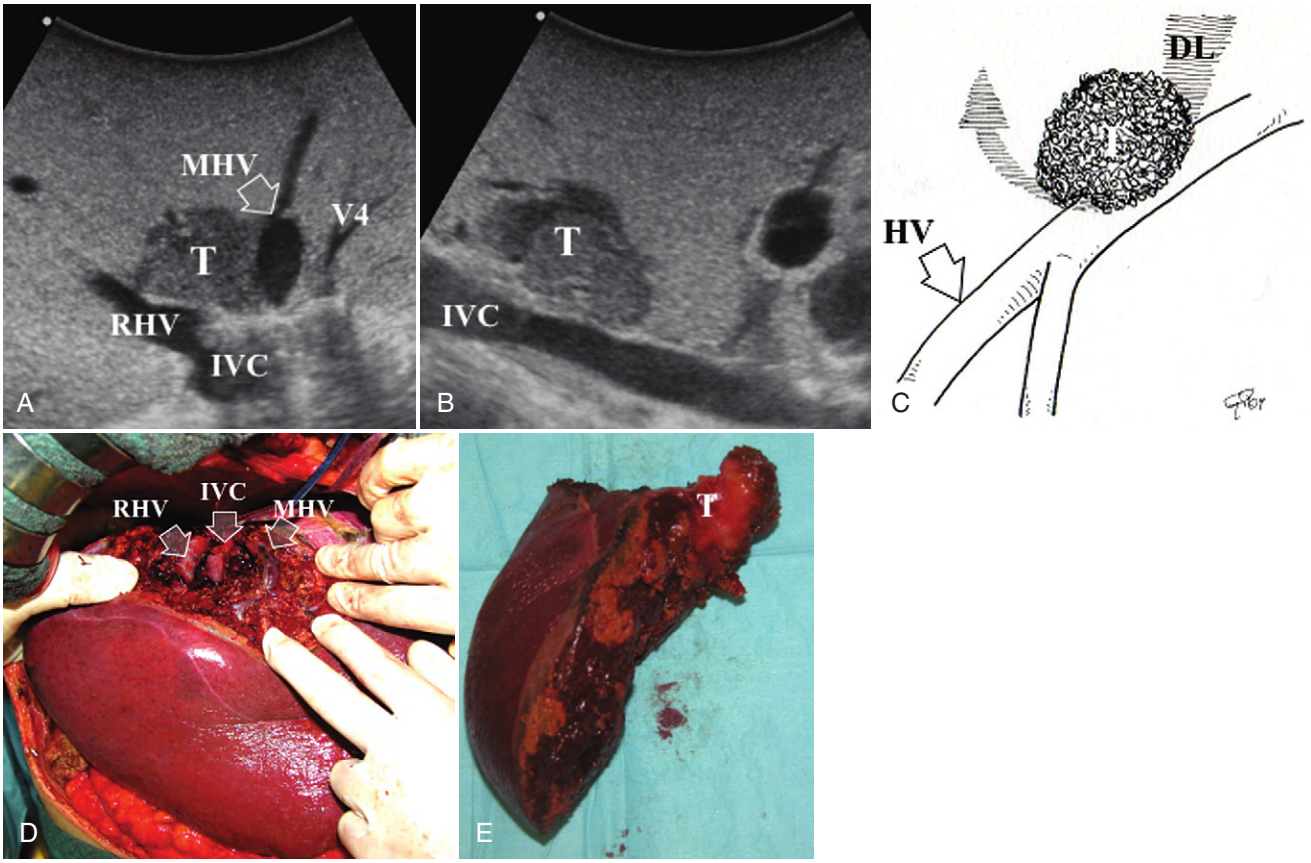


FIGURE 95.37. A, Intraoperative ultrasound appearance of a colorectal liver metastasis (*T*) located in segment VIII, segment I (paracaval), and in extensive contact with the right hepatic vein (*RHV*), the middle hepatic vein (*MHV*), and the inferior vena cava (*IVC*). **B,** Relationship of the tumor with the IVC is shown. **C,** Schematically this lesion could be classified as shown, and as a consequence, a detachment of the tumor from the hepatic vein (*HV*) would be feasible, planning the drawn dissection line (*DL*). **D,** Cut surface at the end of the resection, which consisted of a segment VIII partial resection extended to segment I (paracaval) with complete exposure of the IVC, MHV, and RHV. **E,** Specimen showing a metastases (*T*) exposed on the cut surface. V4, scissural vein.

be divided (Fig. 95.38). In this condition, extension of the hepatectomy is not compulsorily considered, even if the hepatic vein is invaded at its caval confluence (the last 4 cm). Indeed, in this condition, an extension of the resection to the liver parenchyma theoretically drained by the hepatic vein to be resected is considered only if one of the following US signs is missing:

- Presence of accessory hepatic veins at IOUS as an inferior right hepatic vein in the presence of an invasion at the caval confluence of the right hepatic vein (Fig. 95.39)
- EF-IOUS showing hepatopetal blood flow in the feeding portal branch (Fig. 95.40), once the hepatic vein to be resected is clamped (Torzilli et al, 2006b) by means of encirclement, or more simply by vein compression at its extrahepatic route using a fingertip (Torzilli et al, 2007a)
- Communicating veins connecting adjacent hepatic veins (Fig. 95.41), these being more easily detectable using EF-IOUS to disclose their presence (Torzilli et al, 2010c).

Adopting these criteria, we have been able to minimize the rate of major hepatectomy and to devise new procedures.

Systematic Extended Right Posterior Sectionectomy

Systematic extended right posterior sectionectomy (SERPS) is a surgical technique that allows the systematic sparing of part of the right anterior section (see Fig. 95.38, C and D) in the presence of tumors with the presentation shown in Figure 95.42 (Torzilli et al, 2008c).

Eligibility Criteria

Patients suitable for SERPS are those with tumors showing one of three conditions:

1. Invasion of the right hepatic vein (RHV) is evident within 4 cm of the hepatocaval confluence, with other lesions involving segment VI and eventually segment VII (Fig. 95.42A).
2. Invasion of the RHV within 4 cm of the hepatocaval confluence is evident, without other lesions involving segment VI, without an inferior RHV (IRHV), and with hepatofugal portal blood flow at color-flow IOUS in the portal branch to segment VI (P6) when the RHV is clamped if not already

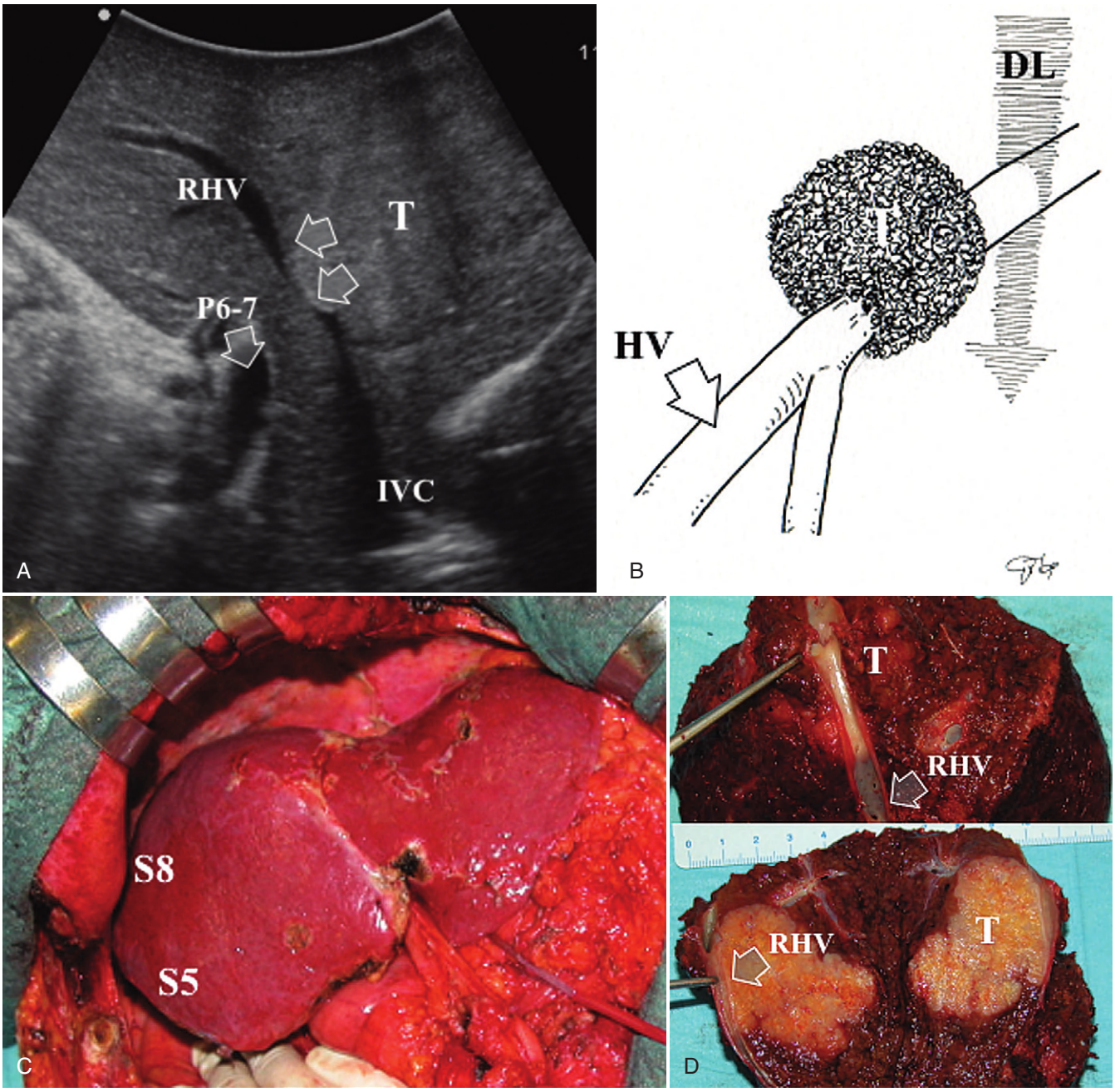


FIGURE 95.38. **A,** Intraoperative ultrasound appearance of a colorectal liver metastasis (*T*) located in segments VII and VIII and invading the wall of the right hepatic vein (*RHV*). **B,** Detachment of the tumor from the hepatic vein (*HV*) would not be feasible; the drawn dissection line (*DL*) is shown. **C,** Remnant liver at the end of the resection, a systematic extended right posterior sectionectomy sacrificing the RHV but almost completely sparing segments V (*S5*) and VIII (*S8*). **D,** Specimen showing a metastasis (*T*), not detachable from the RHV, which it contacts for more than two thirds of its circumference. IVC, inferior vena cava; P6-7, portal branch for right posterior section.

occluded (Fig. 95.42B). In the event an IRHV is present, or, if not, when the flow direction in P6 remains hepatopetal, resection of segments VII and VIII together with the RHV is carried out (Makuuchi et al, 1987) rather than SERPS; therefore SERPS is applied as an alternative to resection of segments VII and VIII in those patients who do not have proper outflow for segment VI once the RHV is divided.

3. Contact with the right anterior glissonian sheath and a relationship with the right posterior section is evident, with at least one of the following features: contact with the right posterior section determining proximal bile duct dilation, vessel wall invasion, or, for CLM, contact wider than one third of the pedicle circumference (Fig. 95.42C).

Procedure

In the first two conditions, extension to the right anterior section is tailored to guarantee the complete removal of the tumor, and a dissection line is drawn on the left side of the RHV, which is also resected (see Fig. 95.42, A and B); flow direction in the right anterior portal branch at EF-IOUS is estimated as previously described, once the RHV is clamped, if it is not occluded (Fig. 95.43). The right anterior pedicle is not necessarily

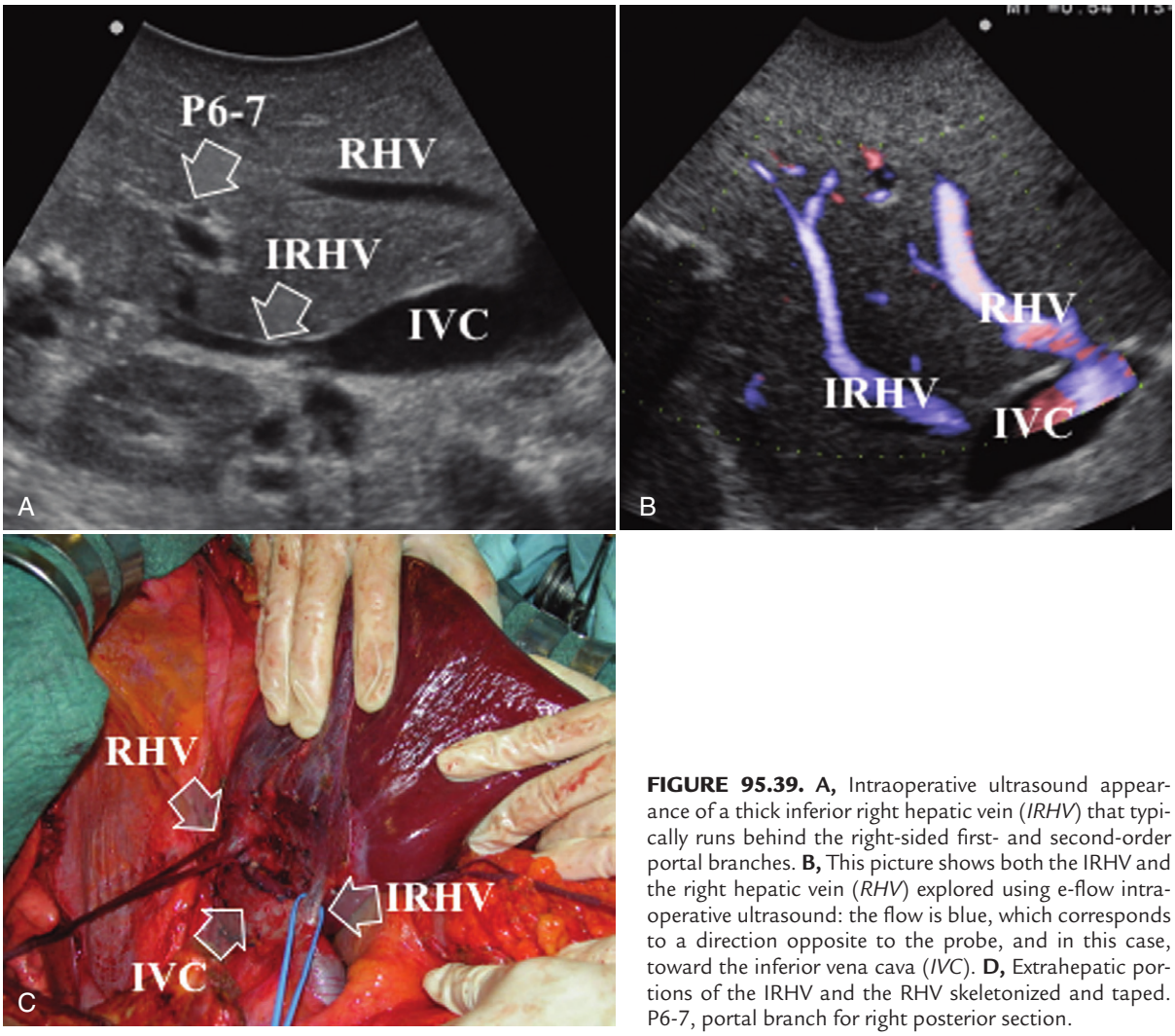


FIGURE 95.39. A, Intraoperative ultrasound appearance of a thick inferior right hepatic vein (*IRHV*) that typically runs behind the right-sided first- and second-order portal branches. **B,** This picture shows both the IRHV and the right hepatic vein (*RHV*) explored using e-flow intraoperative ultrasound: the flow is blue, which corresponds to a direction opposite to the probe, and in this case, toward the inferior vena cava (*IVC*). **D,** Extrahepatic portions of the IRHV and the RHV skeletonized and taped. P6-7, portal branch for right posterior section.

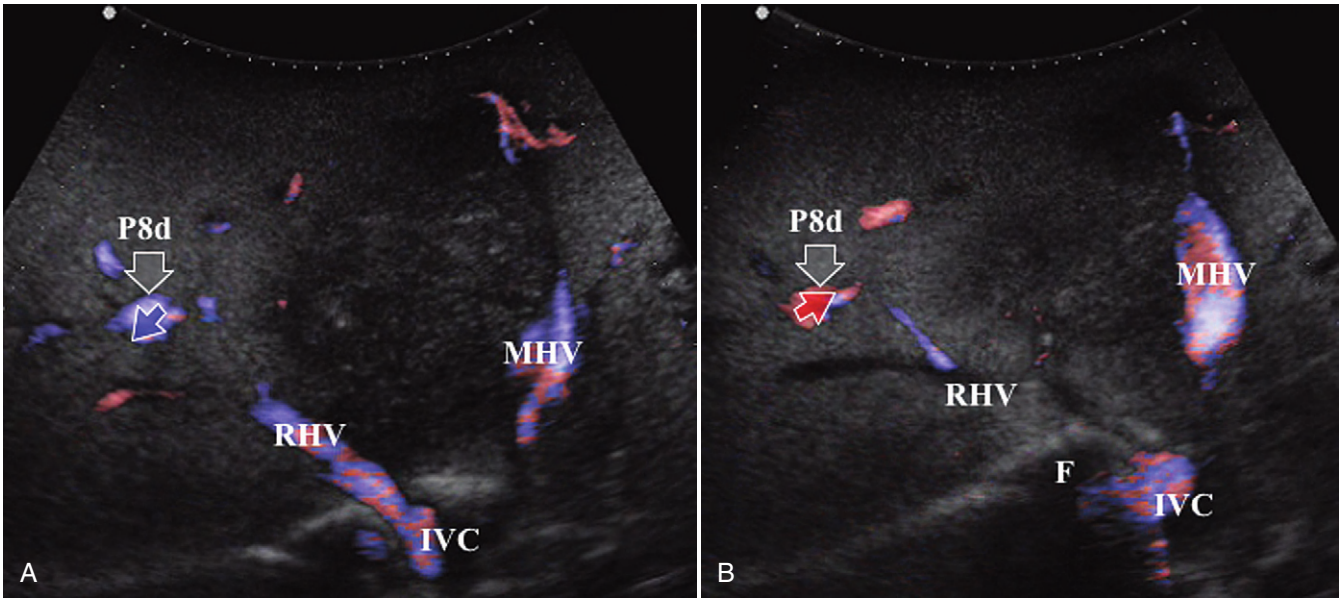


FIGURE 95.40. A, Hepatopetal flow direction (*arrow*) at e-flow intraoperative ultrasound of the portal branch to the dorsal portion of segment VIII (*P8d*). **B,** When finger compression (*F*) is applied to the right hepatic vein (*RHV*) at its caval confluence, the flow direction in P8d becomes hepatofugal (*arrow*). MHV, middle hepatic vein; IVC, inferior vena cava; T, tumor.

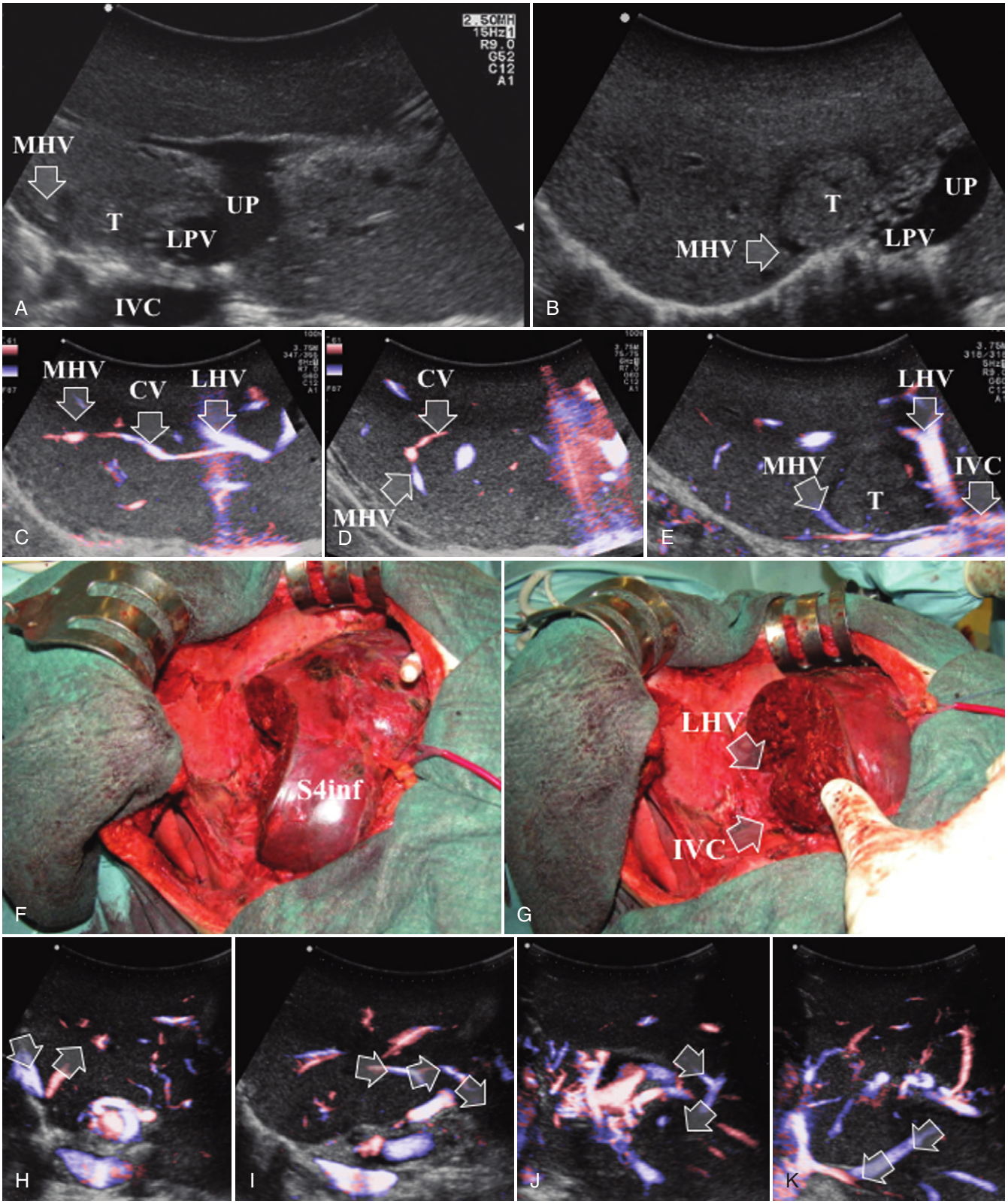


FIGURE 95.41. **A,** Intraoperative ultrasound (IOUS) appearance of a colorectal liver metastasis (*T*) located in segment IV superior in a patient who had previously had a right hepatectomy. The lesion is invading the middle hepatic vein (*MHV, arrow*) at its caval confluence and is in contact with, staying beside and above, the left portal branch (*LPV*). **B,** Another IOUS scan showing the saggital view of the same lesion with further disclosure of its relationship with the umbilical portion (*UP*), LPV, and MHV. **C,** In the same patient, EF-IOUS discloses a communicating vein (*CV*) between the left hepatic vein (*LHV*) and the MHV. **D,** The confluence of the CV into the MHV. **E,** The LHV and MHV are shown at e-flow IOUS, flowing into the inferior vena cava (*IVC*). **F,** Preserved segment IV inferior (*S4inf*). **G,** LHV flowing into the IVC after resection. **H** to **K,** Hepatic vein drainage of the S4inf at EF-IOUS (*arrows*), passing through the MHV stump and the CV (**H**), the CV (**I**), the CV and the LHV (**J**), and the LHV (**K**).

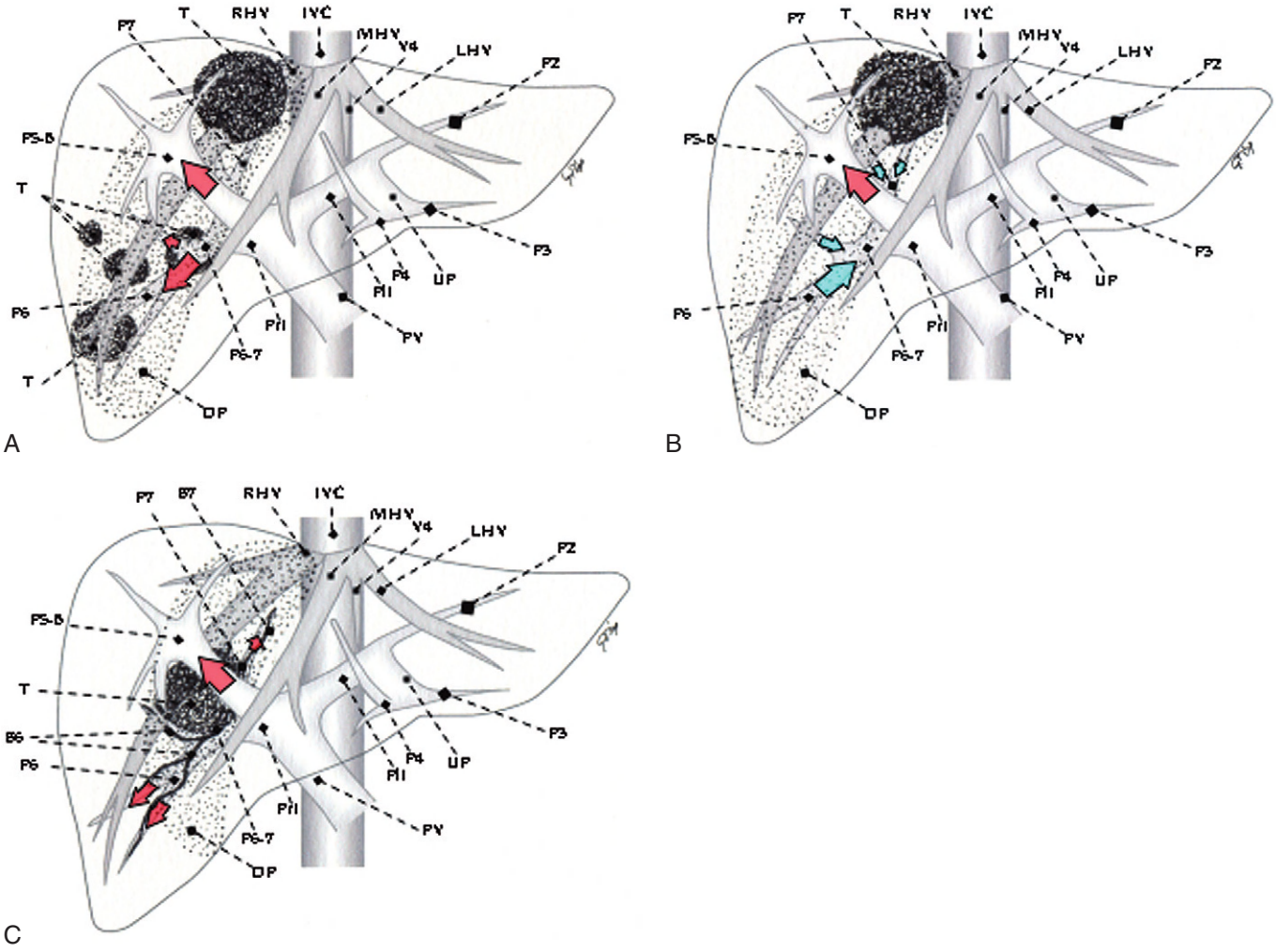


FIGURE 95.42. Eligibility criteria for systematic extended right posterior sectionectomy (SERPS). In all circumstances, at e-flow intraoperative ultrasound hepatopetal portal blood flow (*arrows*) has to be evident in the main portal branch to the right anterior section (*P5-8*), once the right hepatic vein (*RHV*) is clamped, if not already occluded. **A,** Presence of vascular invasion of the RHV at the hepatocaval confluence (within 4 cm) with tumor (*T*) in segment VI. **B,** Presence of vascular invasion of the RHV at the hepatocaval confluence (within 4 cm) without tumor in segment VI and without accessory veins and/or with hepatofugal portal blood flow (*arrow*) in the portal branch to segment VI (*P6*), once the RHV is clamped, if not already occluded. **C,** Presence of vascular invasion of the right posterior portal branch (*P6-7*) or biliary dilation of sectional branches (*B6 and B7*), with tumor (*T*) in contact with the P5-8 without signs of biliary dilation in the right anterior section. DP, dissection plane; IVC, inferior vena cava; UP, umbilical portion; P2, P3, P4, P5, P6, and P7 are portal pedicles to their respective segments. Prt, right portal vein; Plt, left portal vein; LHV, left hepatic vein; MHV, middle hepatic vein; V4, scissural vein.

exposed on the liver cut surface. In the third condition, the extension of the resection into the right anterior section is tailored to preserve most of the parenchyma of segment VIII, the tract of the RHV at the hepatocaval confluence, and the left portion of segment V without division of the right anterior pedicle, which is exposed on the cut surface (see Fig. 95.42C).

Minimesohepatectomy

This procedure represents an alternative to the conventional mesohepatectomy in patients with tumors invading the middle hepatic vein (MHV) at its caval confluence; it consists of a limited resection, including the tract of the invaded vein without its reconstruction, sparing part of segment IV, and/or of the right anterior section as shown in Figure 95.44 and as described in the next section (Torzilli et al, 2010a).

Eligibility Criteria

Patients suitable for minimesohepatectomy (MMH) are those with tumors having macroscopic signs of vascular invasion on preoperative imaging and IOUS, showing the MHV within 4 cm of the hepatocaval confluence.

Procedure

Once the anterior surface of the hepatocaval confluence is exposed, a space between the RHV and MHV extrahepatic tracts, just before their caval confluence, is obtained by dissection to accommodate the surgeon's fingertip. If not already occluded, finger compression is then applied to the MHV at its caval confluence, verifying at EF-IOUS the disappearance of blood flow in the MHV or its inversion. For planning an MMH, at least one of these three findings should be confirmed during

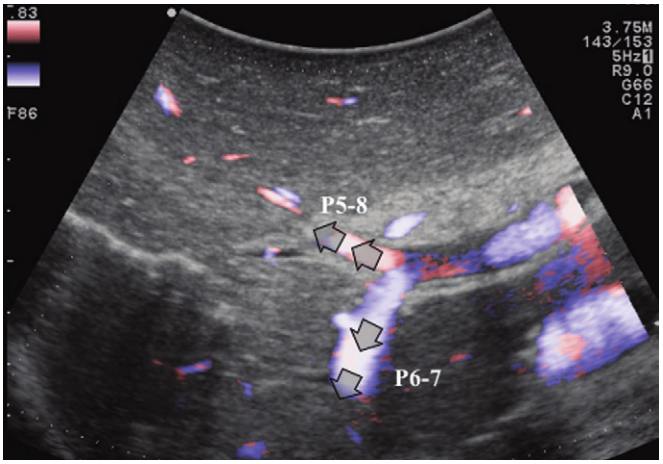


FIGURE 95.43. Direction of hepatopetal blood flow (*arrows*) into the right-sided sectional portal branches (*P5-8* and *P6-7*), as it appears at e-flow intraoperative ultrasound.

a finger compression clamping test of MHV or in the event of its occlusion:

1. Reversal flow on EF-IOUS in the peripheral portion of the MHV, which suggests drainage through collateral circulation in the RHV/left hepatic vein (LHV), depending on the side of the MHV branch with reversal flow (Fig. 95.45)
2. Detectable communicating veins on EF-IOUS between the MHV and RHV and/or LHV and/or IVC (Fig. 95.46; as mentioned, this last feature could be also visible without compressing the vein)

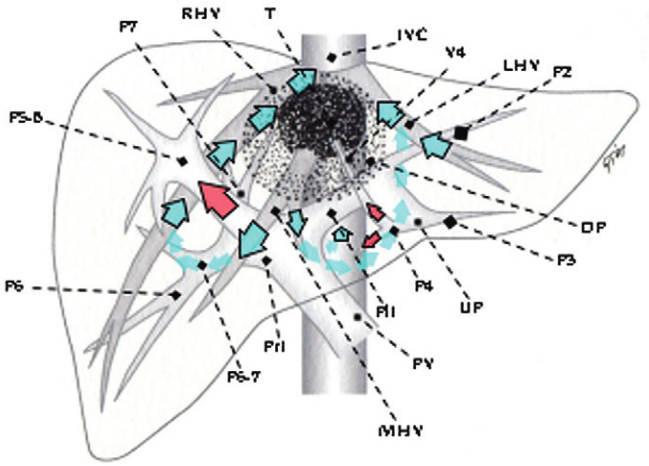


FIGURE 95.44. Eligibility criteria for minimesohepatectomy (MMH). At least one of the three signs should be present: 1) reversal of blood flow into the middle hepatic vein (*MHV*) once it is clamped at its caval confluence if not already occluded; 2) hepatopetal blood flow into portal branches to right anterior section (*P5-8*) and to segment IV (P4; if subsegmental branches show hepatofugal blood flow, that area should be included in the resection area); 3) evidence of communicating veins between the MHV and the left hepatic vein (*LHV*) and/or right hepatic vein (*RHV*). DS, dissection plane; IVC, inferior vena cava; UP, umbilical portion; P2, P3, P4, P5, P6, and P7, portal pedicles to their respective segments; P6-7, portal branch to right posterior section; Prt, right portal vein; Plt, left portal vein; V4, scissural vein.

3. Hepatopetal flow in segments V through VIII and/or the segment IV inferior portal branches (Fig. 95.47A)

If none of these findings is confirmed, and especially if hepatofugal flow direction in portal branches to segments V and/or VII and/or IV inferior is detected (Fig. 95.47B), hepatectomy should be extended to the area fed by those portal branches.

The posterior wall of the MHV, or of the tumor involving the paracaval portion, is used as a deep landmark for delimiting the resection area (Fig. 95.48). A crucial point for proper performance of the MMH in the presence of a communicating vein is to delineate a dissection plane that does not interrupt the communicating vein (see Fig. 95.48I).

RESECTION GUIDANCE

Mobilization of the Liver (See Chapter 90)

Although for liver exploration with IOUS, any approach would be suitable to allow most of the IOUS-guided parenchyma-sparing procedures described here, adequate preparation of the surgical field is essential, which implies adequate incision and liver mobilization. A J-shaped laparotomy is usually performed, and a J-shaped thoracophrenolaparotomy is carried out when the tumor is located in the paracaval portion or at the hepatocaval confluence; control of the hepatic veins at this level could prove difficult with an abdominal incision only.

For right-sided segmentectomies, subsegmentectomies, or sectionectomies, the bare area is dissected, and the right hemiliver is mobilized, until the surgeon's nondominant hand is positioned behind the hemiliver to sustain it and is passing over the resection area established by means of IOUS (Fig. 95.49). A slight mobilization of the right hemiliver, just dividing the triangular ligament and partially or completely dividing the bare area, will be accomplished for lesions located in segments V, VI, and the inferior portion of section VII (Fig. 95.50). Conversely, the right side of the retrohepatic IVC is reached for lesions located in the dorsal portions of segments VII and VIII (Fig. 95.51). If the lesion is located in the superior portion of segment VII or the dorsal portion of section VIII—that is, close to the hepatocaval confluence, in the last 4 cm—but it is not in contact with the hepatic veins and an anatomic segmental approach is not required, the hepatocaval ligament is not divided, and only the space between the RHV and the MHV is dissected to allow fingertip insertion. The caval confluence of the RHV is recognized, following the trajectory of the right inferior phrenic vein, which flows near the RHV at this level and which is a constant landmark (Fig. 95.52; Torzilli et al, 2006a).

If the lesion is still right-sided but makes contact with an HV at its caval confluence, or if it involves the paracaval portion of segment I or an anatomic segmental approach with hepatic vein exposure is not required, liver mobilization includes division of the retrohepatic caval ligament and exposure of the retrohepatic IVC; this proceeds until the area to be resected is under control of the surgeon's nondominant hand, with the surgeon's fingertip reaching over the most distal portion of the planned dissection plane, including the complete detachment (Figs. 95.52 and 95.53).

For segment II and III segmentectomies or subsegmentectomies, the left triangular ligament and the left coronary ligament are divided, and with the surgeon's nondominant hand, the left lobe is handled. For lesions located in the superior portion of

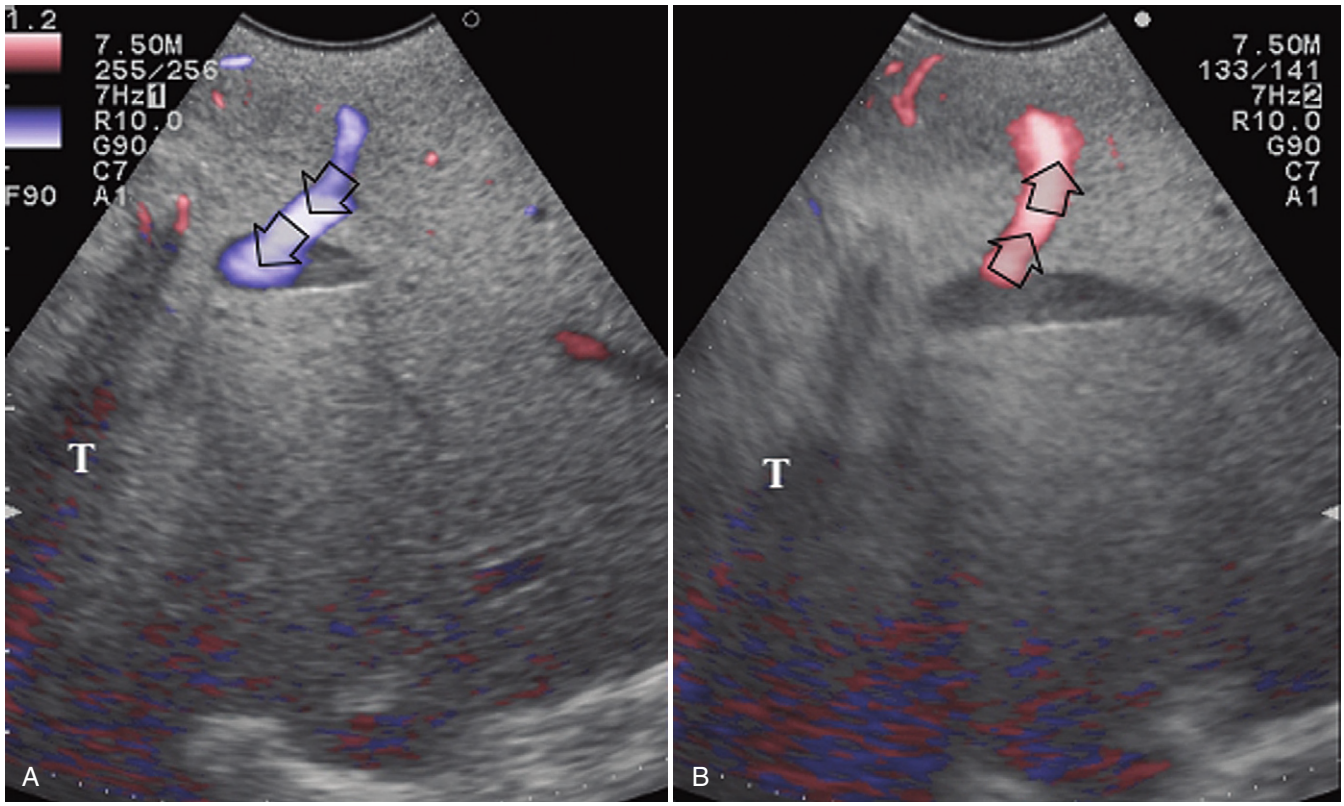


FIGURE 95.45. E-flow IOUS appearance of direction of blood flow into the middle hepatic vein (MHV) toward the inferior vena cava (*arrows*), before clamping of the MHV (**A**), and reversed after MHV clamping (**B**). T, tumor.

segment IV at the hepatocaval junction without contact with the LHV and/or MHV, the mobilization combines those described for lesions at segments VII (inferior) and those in the left lobe. In case of contact with hepatic veins, their selective encirclement at the caval confluence and eventually the exposure of the retrohepatic IVC are carried out.

Anatomic Resections (See Chapters 90 and 92)

Selection of an anatomic resection for CLM may not be relevant for long-term prognosis (Sarpel et al, 2009), and its use for HCC is still controversial (Cho et al, 2007; Eguchi et al, 2008; Kaibori et al, 2006; Regimbeau et al, 2002; Tanaka et al, 2008; Wakai et al, 2007); indeed, for the latter, no studies have been done that compare anatomic and nonanatomic resections in a truly randomized fashion; however, many reports show the long-term benefits of the anatomic approach (Cho et al, 2007; Eguchi et al, 2008; Kaibori et al, 2006; Regimbeau et al, 2002; Ueno et al, 2008; Wakai et al, 2007), and significant selection bias likely influences the reliability of the results (Hasegawa et al, 2005). The rationale for anatomic resection for HCC is based on its pattern of intrahepatic dissemination from the main lesion through the portal branches. As a consequence, the resected specimen should include at least the portal area perfusing the area of the liver that includes the lesion. Indeed, the superiority of the anatomic resection seems more evident in those subgroups with a single HCC larger than 2 cm in diameter (Eguchi et al, 2008) or with extranodular growth (Ueno et al, 2008), which should be those with higher risk of satellites and microvascular invasion.

Whether technical requirements for accomplishing truly anatomic sectionectomies and formal major hepatectomies are more uniformly accepted, the agreement on the requirements for defining a subsegmental resection as a genuine anatomic one is still unclear. Indeed, the recognition and demarcation of the segmental area to be removed in a fully anatomic fashion is still subject to debate. The only certainty is that the portal area feeding the tumor cannot be recognized visually on the liver surface if it is not associated with an interventional procedure for its precise disclosure. Almost all the proposed techniques require US guidance, especially in a cirrhotic liver, where there are generally wide variations and abnormalities in the extension of the segmental areas. The first procedure described in this was the systematic segmentectomy devised in early 1980s (Makuuchi et al, 1980), which consists of puncture of the portal branch feeding the tumor and subsequent injection of dye (Fig. 95.54); more recently, alternatives to this approach have been devised. In the following paragraphs, details concerning US-guided techniques and others for segmental and sectional resection will be provided.

Segmentectomies (See Chapter 92)

Puncture of the Portal Branch

The portal branch feeding the tumor to be resected is punctured under IOUS guidance, using a freehand technique or with a proper device, and 3 to 5 mL of indigo-carmine dye is injected into the vessel (see Fig. 95.54A). The stained area becomes evident on the liver surface, it is marked with

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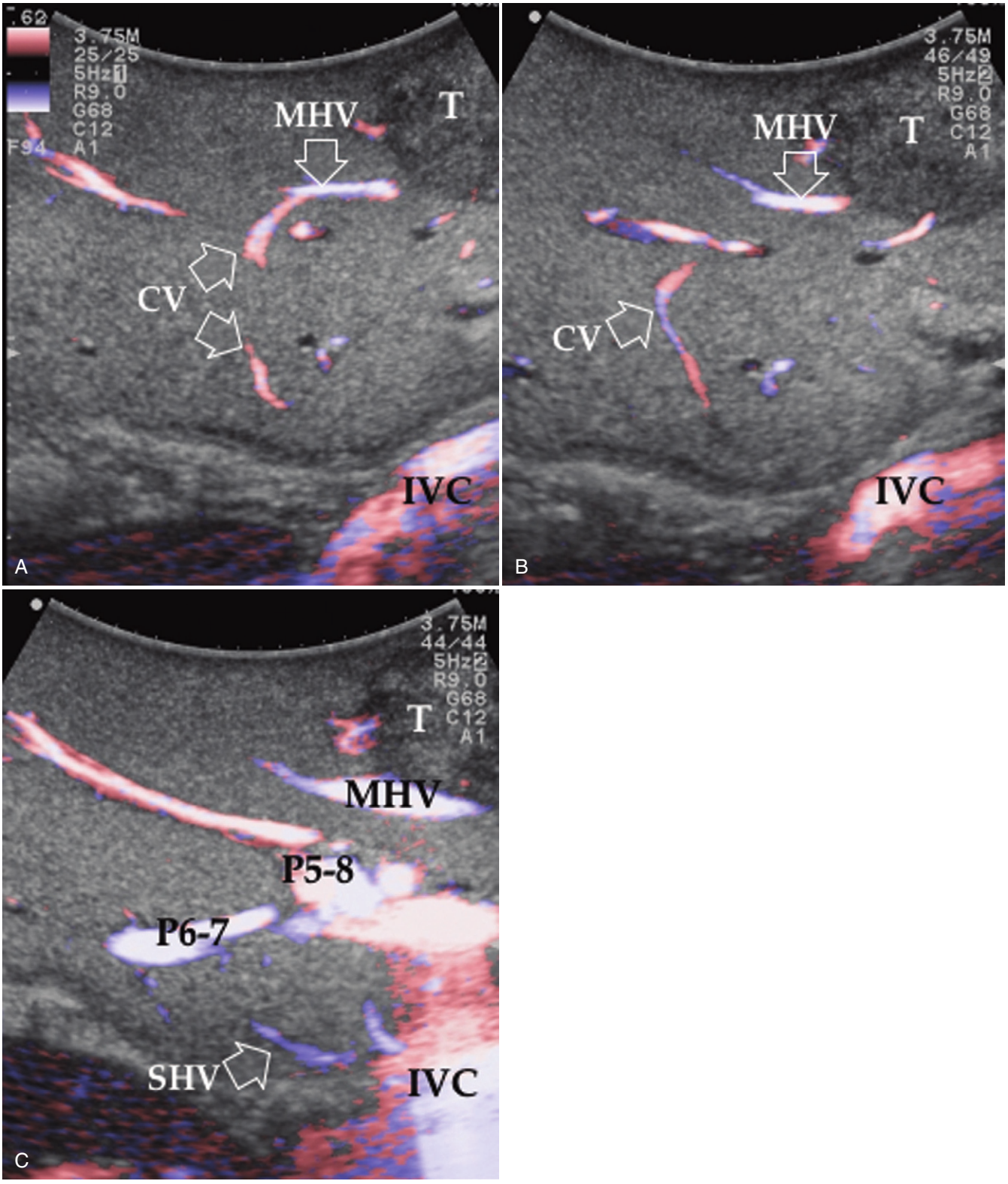


FIGURE 95.46. **A** and **B,** E-flow intraoperative ultrasound demonstration of a communicating vein (*CV*) connecting the middle hepatic vein (*MHV*) to a short hepatic vein (*SHV*) flowing into the inferior vena cava (**C**). P5-8, portal branch to right anterior section; P6-7, portal branch to right posterior section; T, tumor.

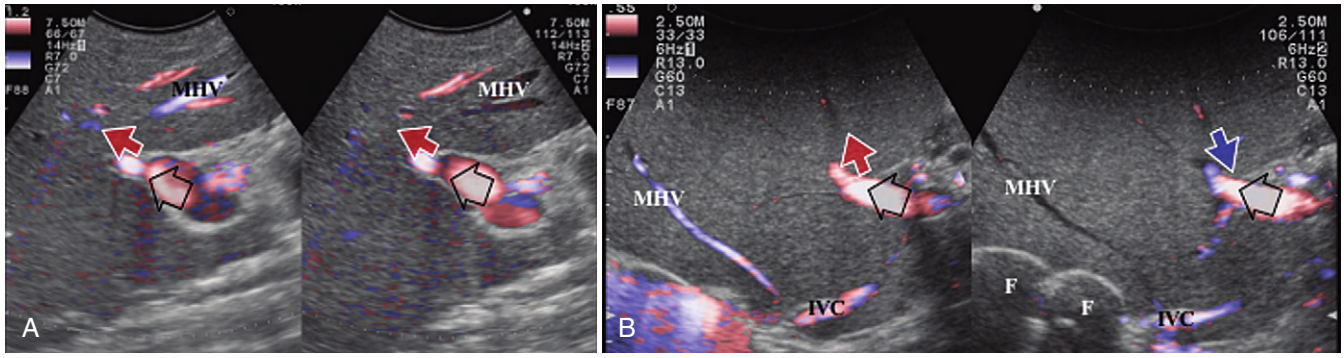


FIGURE 95.47. **A,** EF-IOUS view of the portal branch feeding the right anterior portal branch, keeping a hepatopetal blood flow (*white arrow*) before (*left*) and during (*right*) clamping of the middle hepatic vein (MHV), which has a colored lumen before but not during clamping. **B,** E-flow intraoperative ultrasound of the portal branch feeding the right anterior portal branch hepatopetal blood flow is shown (*white arrow*) before clamping of the MHV (*left*), and hepatofugal blood flow is shown in one of its branches (*white arrow, right*) during clamping of the MHV, which has a colored lumen before but not during clamping. F, finger-tips clamping the MHV by means of finger compression; IVC, inferior vena cava.

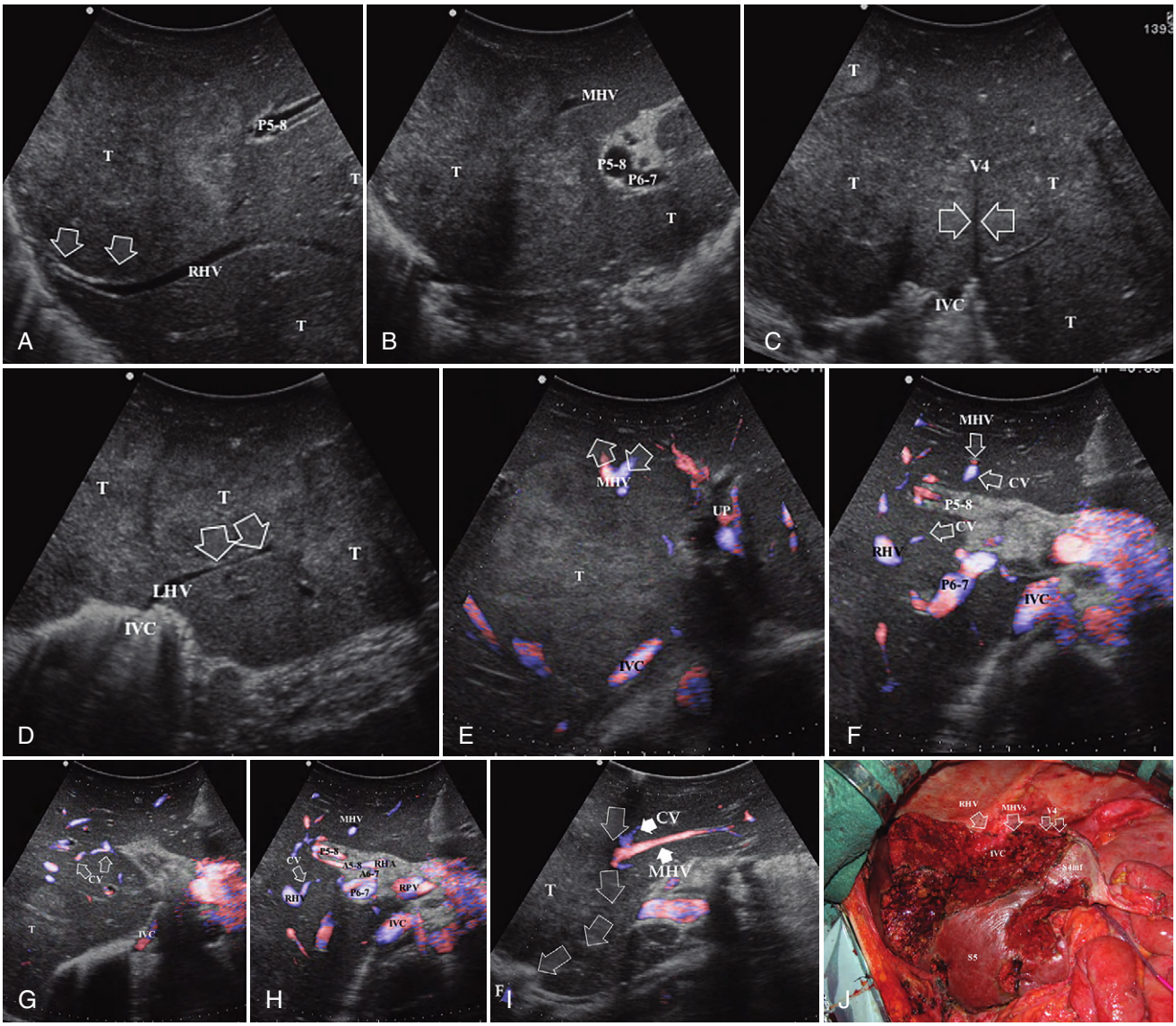


FIGURE 95.48. Surgical treatment of a patient with multiple, bilobar, large colorectal liver metastases (CLM) with a complex vascular relationship, seen with the aid of intraoperative ultrasound (IOUS) and e-flow (EF)-IOUS guidance, accomplishing a mini-mesohepatectomy (MMH) among the various resections carried out simultaneously. **A,** IOUS appearance of a CLM. The tumor (*T*) is in contact with the right hepatic vein (*RHV; arrows*) and is invading a portal branch to the right anterior section (*P5-8*): this patient had multiple bilobar CLM, and another lesion (*T*) is visible in this picture. **B,** Invasion of the middle hepatic vein (*MHV*) is well disclosed. **C,** Several lesions are disclosed (*T*), and two of them are compressing the scissural vein (*V4, arrows*) . **D,** Contact (*arrows*) between one lesion (*T*) and the left hepatic vein (*LHV*) at its caval confluence: the LHV more peripherally is invaded by tumors. **E,** The MHV shows reversal blood flow at EF-IOUS (*arrows*). **F,** A communicating vein (*CV*) originating from the MHV. **G,** Other portions of the CV. **H,** The CV flowing into the RHV. **I,** The dissection plan to be followed (*transparent arrows*) to avoid the division of the origin of the CV from the MHV. **J,** The liver after removal of 15 CLMs by means of segment II and III resection, MMH, and other atypical resections. IVC, inferior vena cava; MHVs, MHV stump; P6-7, portal branch to right posterior section.

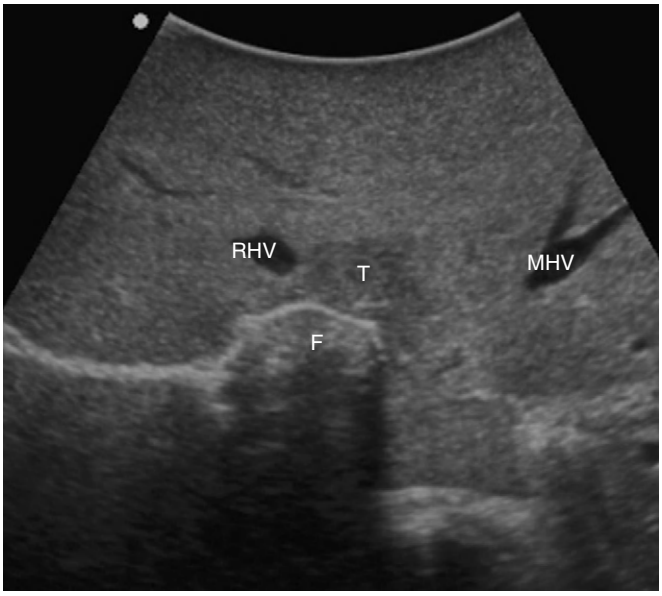


FIGURE 95.49. Intraoperative ultrasound shows the surgeon's fingertip (*F*) which can be positioned over the left edge of the tumor (*T*), located in the paracaval portion of segment I. This means that the mobilization is probably almost completed. MHV, middle hepatic vein; RHV, right hepatic vein.

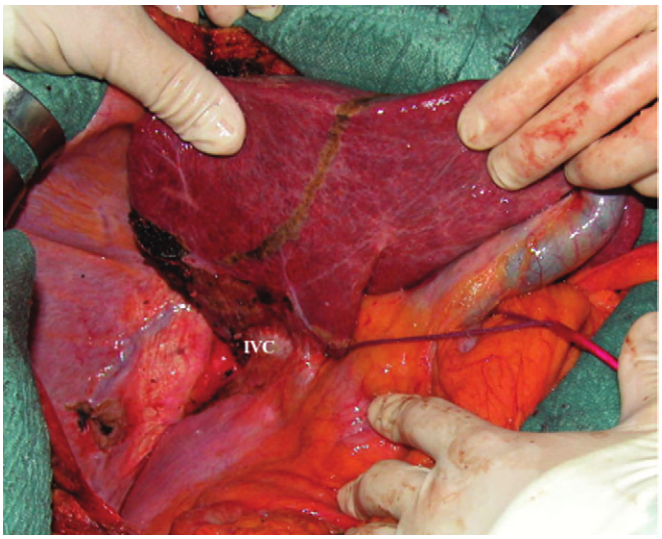


FIGURE 95.50. Mobilization of the right hemiliver just showing the inferior portion of the right-sided anterolateral aspect of the retrohepatic inferior vena cava (*IVC*).

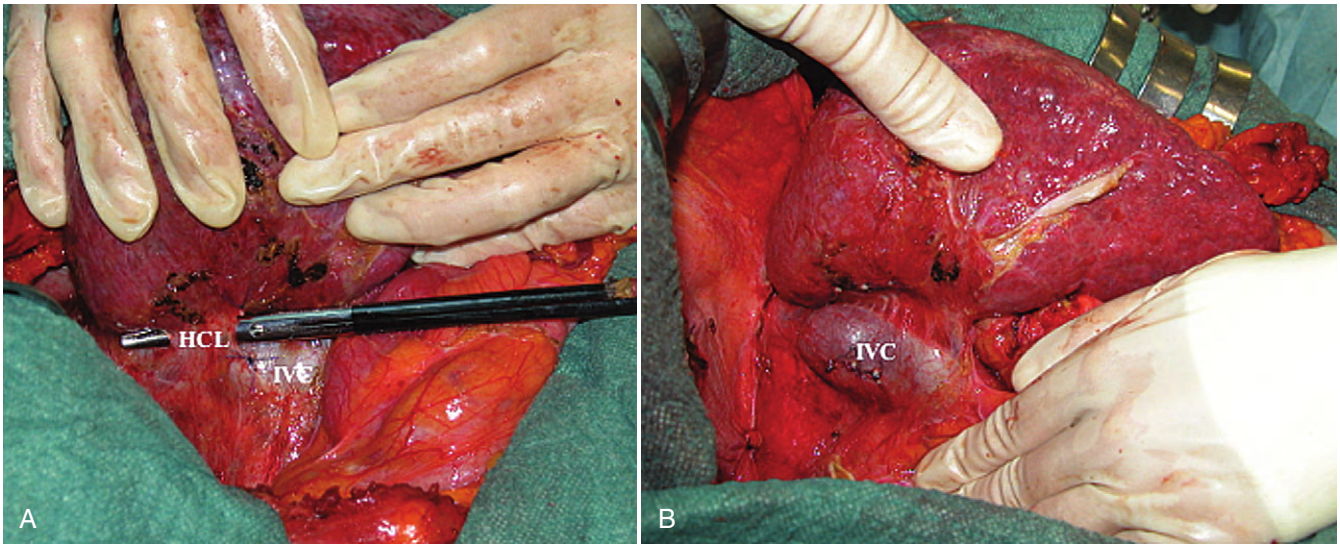


FIGURE 95.51. **A,** Dissection of the hepatocaval ligament (*HCL*) from the inferior vena cava (*IVC*) with a scissors. **B,** This pattern of mobilization allows exposure of the right-sided anterolateral aspect of the retrohepatic IVC.

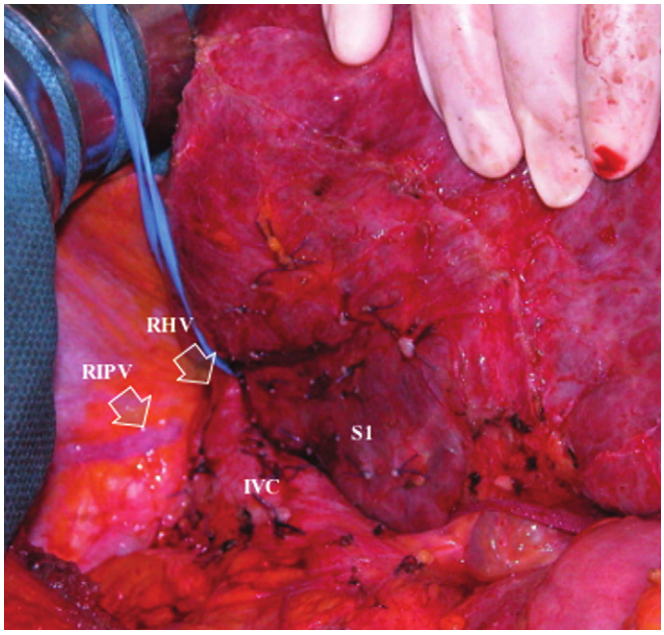


FIGURE 95.52. Full mobilization of the liver from the retrohepatic inferior vena cava (*IVC*) and the right inferior phrenic vein (*RIPV*), which has a trajectory indicating the confluence of the right hepatic vein (*RHV*) into the IVC. S1, segment I.

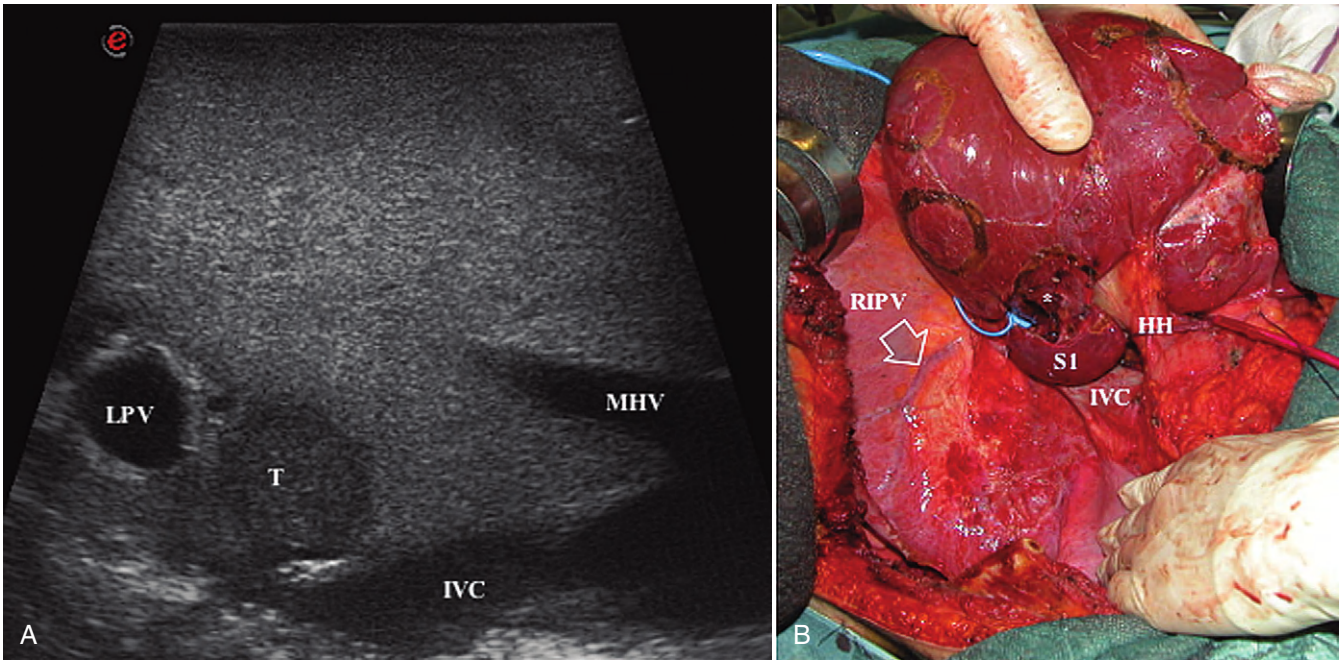


FIGURE 95.53. A, Intraoperative ultrasound image of a lesion (*T*) located in the paracaval portion of segment I. **B,** For its removal by means of a limited resection (*asterisk*), full mobilization of the liver from the retrohepatic inferior vena cava (*IVC*) is carried out. LPV, left portal vein; HH, hepatic hilum; MHV, middle hepatic vein; RIPV, right inferior phrenic vein; S1, segment I.

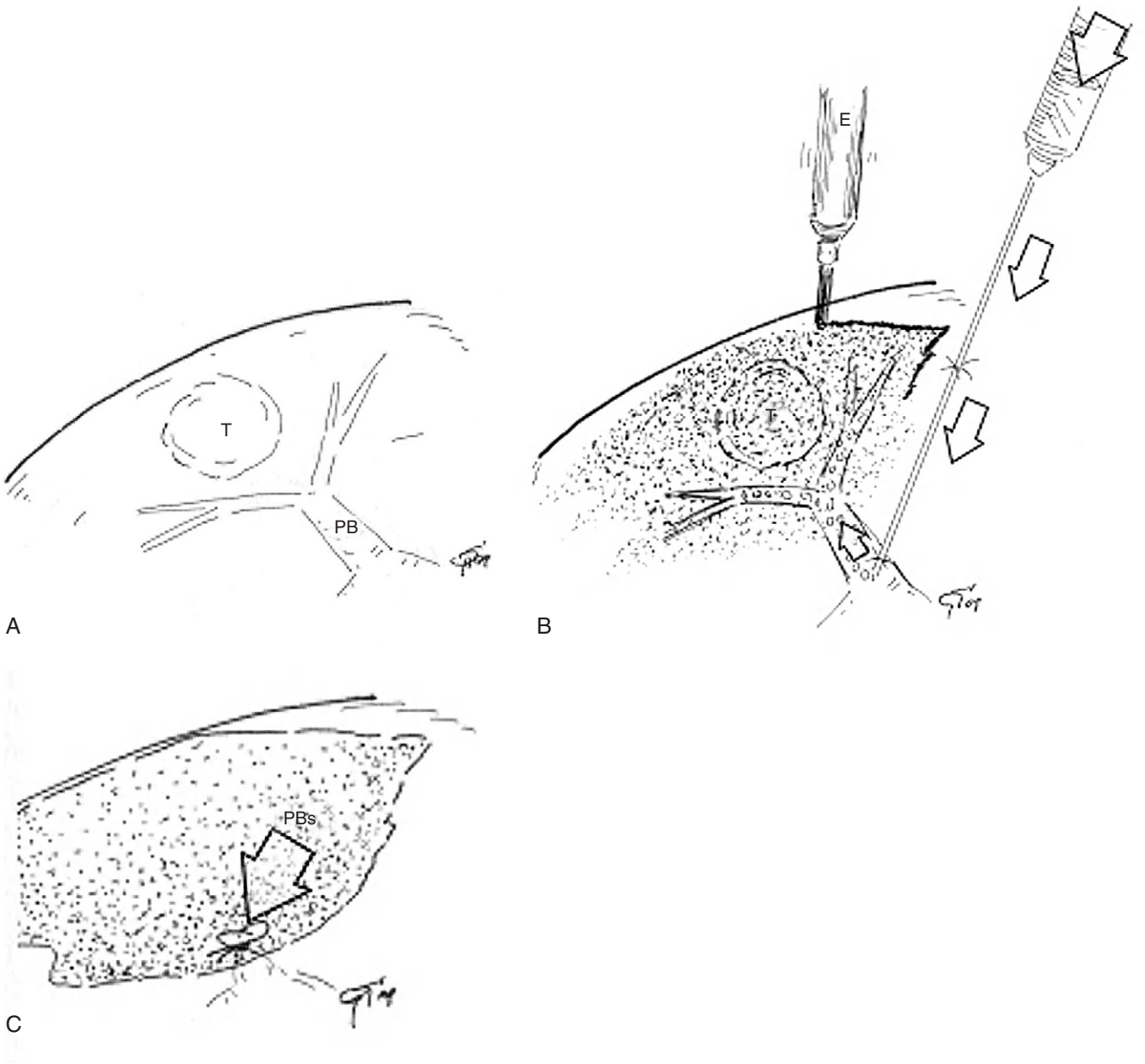


FIGURE 95.54. **A,** For a systematic subsegmentectomy, the feeding portal branch (*PB*) is identified and punctured for injecting dye, resulting in coloring of the subsegmental area. **B,** This is marked with electrocautery (*E*). **C,** Resection is carried out with the PB stump (*PBs*) visible at the end on the cut surface.

electrocautery (see Fig. 95.54B), and the resection can be accomplished fully anatomically (see Fig. 95.54C). If the nodule is located between two adjacent segments, the two portal branches afferent to the area must be punctured and injected. In this case, the deepest and most dorsal vessel must be punctured first to prevent the air bubbles contained in the dye from disturbing the US detection and puncture of the other branch. The portal branch is punctured 1 to 2 cm distally from its origin to avoid dye reflux; the direction and velocity of the infusion are controlled by IOUS. To prolong the staining, the hepatic artery at the hilum is clamped before portal branch puncture. When there are numerous and thin vessels that should be punctured, or in the case of tumor thrombus in the segmental portal branch of the segment that should be removed, the dye is injected in the portal branches afferent to the adjacent segment; this is the so-called counterstaining technique (Takayama et al, 1991).

This technique remains the most precise method for segmental and subsegmental anatomic demarcation. Its main drawback, other than the level of skill required for puncturing very small vessels, is the fact that if the ink regurgitates or is injected into the wrong portal branch, it could be difficult to identify the proper area to be removed.

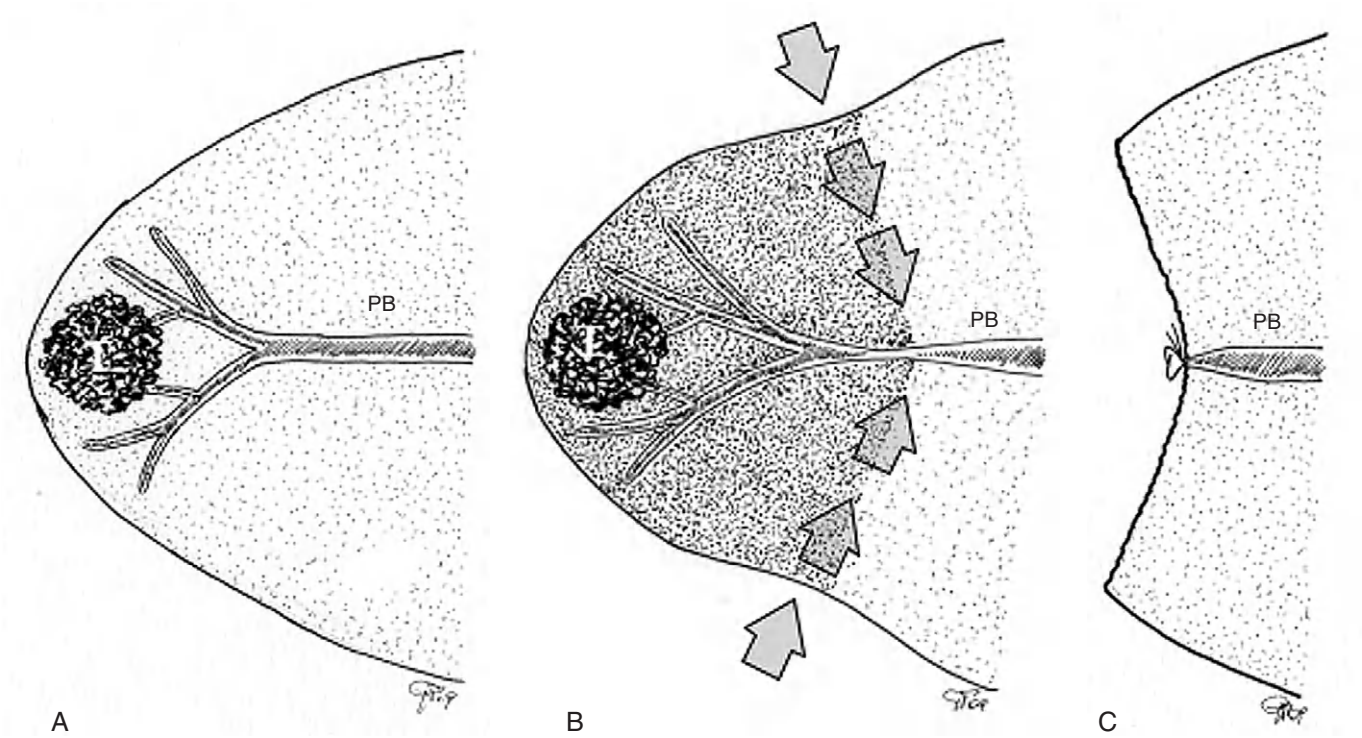


FIGURE 95.55. For subsegmentectomy by means of compression, the feeding portal branch (*PB*) is identified (**A**) and compressed at the point targeted by intraoperative ultrasound, resulting in discoloring of the subsegmental area, which is marked with electrocautery (**B**) and selectively removed (**C**).

Compression of the Portal Branch

Initially used for tumors located in the left hemiliver (Torzilli & Makuuchi, 2004), more recently it has been successfully extended in its application to any segmental location (Torzilli et al, 2010b, 2011a) and even to a sectional portion of the liver (Torzilli et al, 2009a). Conceptually, the procedure could be summarized as shown in Figure 95.55. In practice, once the feeding portal branch is identified at IOUS (Figs. 95.56A and 95.57A), it is compressed using the IOUS probe on one side of the liver and the finger on the opposite side (Figs. 95.56B and 95.57B), confirming the proper compression by IOUS real-time control (Figs. 95.56C and 95.57C); in this way, it is possible to induce a transient ischemia of the portion of the liver distally to the compression site. This portion can be marked with electrocautery, the compression is released (Figs. 95.56D and 95.57D), and the resection is carried out (Figs. 95.56E and 95.57E). This technique is simple, fast, noninvasive, and reversible, with the possibility of modifying the site of compression if necessary.

Furthermore, the compression can be used in a countercompression perspective, borrowing from the technique proposed by Takayama and colleagues (1991) of defining the adjacent segmental margins. Indeed for segments such as segment I and the superior portion of segment IV, for which direct compression of the feeding portal branch is difficult, compressing the adjacent segmental branch allows the definition of their segmental margins (Torzilli et al, 2010b; Fig. 95.58). Similarly, as is described later, this technique can be applied to disclose the margin of the right anterior section of the liver by compressing the glissonian pedicles to the right posterior section and to the left hemiliver, respectively (Torzilli et al, 2009a).

More recently, for segment VIII as a whole—and selectively for its subsegmental dorsal and ventral branches—contrary to what had appeared at the first experiences with right-sided compression of the portal branches (Torzilli et al, 2010b), direct compression of their respective feeding portal branches has been demonstrated as feasible (Torzilli et al, 2011a).

Hooking of the Portal Branch

The segmental portal branches to segment IV are generally divided into two groups: those for the superior and those for the inferior portion, but the commonest branching pattern can be recognized in only half of the patients (Onishi et al, 2000). Instead of puncture under IOUS guidance, these branches can be approached by dissecting the umbilical portion. Once exposed the vessel can be encircled with a suture and pulled, under IOUS control, to verify that it is the branch to the inferior portion of segment IV. The proper portal branch can then be ligated and divided, and the discolored area that appears on the liver surface should correspond to the inferior portion of segment IV, which can be marked with electrocautery; this is a peculiar application of the so-called hooking technique (Torzilli & Makuuchi, 2001). Furthermore, the superior portion of subsegment IV could be resected by clamping the portal branch to the inferior portion, as it is identified with the hooking

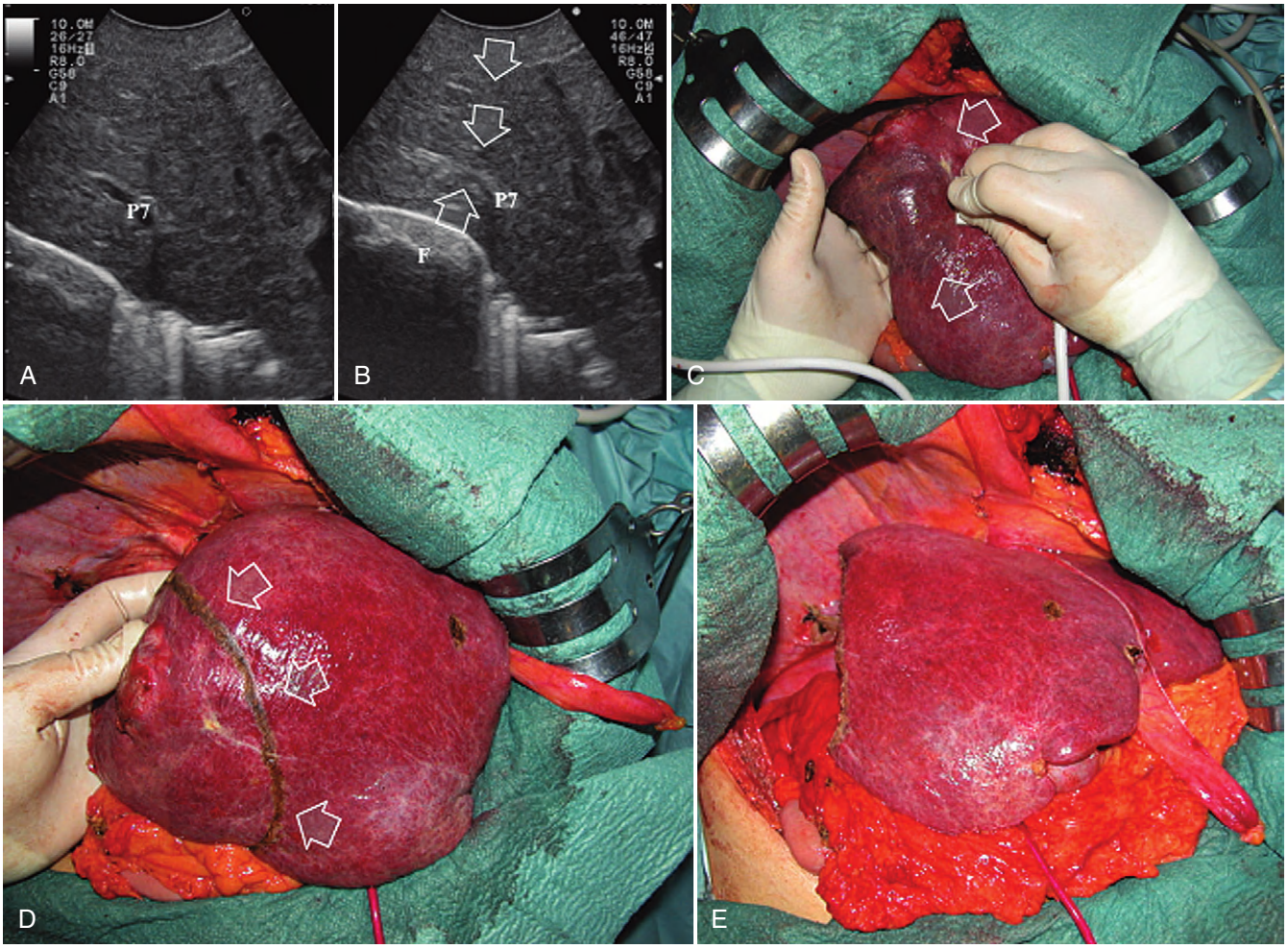


FIGURE 95.56. **A,** This intraoperative ultrasound (IOUS) scan shows the portal branch (*P7*) feeding the tumor in segment VII. **B,** Once identified under IOUS guidance, P7 compression is carried out (*arrows*) by means of the probe and the surgeon's finger (*F*) positioned on the opposite side. **C,** Compression results in discoloration of the subsegmental portion to be removed (*arrows*). **D,** The area is marked with electrocautery (*arrows*). **E,** The liver after subsegmental resection.

technique; the discolored inferior subsegment IV caudally, the plane that includes the MHV laterally, as seen on IOUS, and that marked by the falciform ligament medially delimit the area to be resected.

Other Techniques

Other methods have been proposed, such as a balloon catheter inserted transhepatically to occlude the feeding portal branch (Shimamura et al, 1986), or, more recently, the portal branch is accessed through the mesenteric vein (Ou et al, 2007). For segment VIII resection, Mazziotti and colleagues (2000) proposed the division of the liver along the main portal fissure and a subsequent intraparenchymal approach to the segment VIII glissonian pedicle. Other authors have recently suggested ablation of the feeding portal and arterial branches (Curro et al, 2009; Lupo et al, 2003; Santambrogio et al, 2008). All these alternative techniques are made less attractive by their invasive nature, and in some circumstances (Curro et al, 2009; Lupo et al, 2003; Santambrogio et al, 2008), for their irreversible damage to the target, which could imply compulsory extension of the resection area, should the first targeted vessel be incorrectly identified. This extension of the resection area, although accidental, is exactly what anatomic segmental resection seeks to avoid.

Sectionectomies (See Chapter 92)

Right Posterior Sectionectomy

As for segmentectomies, the demarcation of the sectional area to be removed is advocated. Among methods proposed for obtaining this demarcation, extrahepatic isolation of the right-sided sectional pedicles consists of careful and meticulous skeletonization of each sectional arterial and portal branch (Makuuchi et al, 1993). Alternatively, the three glissonian pedicles in their surrounding fibrous sheath could be encircled as a whole with or without the use of a hepatotomy incision (Takasaki et al, 1990). As an alternative to these established techniques, the compression technique could be applied (Torzilli et al, 2011b). The hepatic pedicle is encircled with a tourniquet but not dissected.

At IOUS, the portal pedicle for the right posterior section (segments VI and VII) is identified as well as the branches for segments VI and VII (Fig. 95.59A); the level targeted for

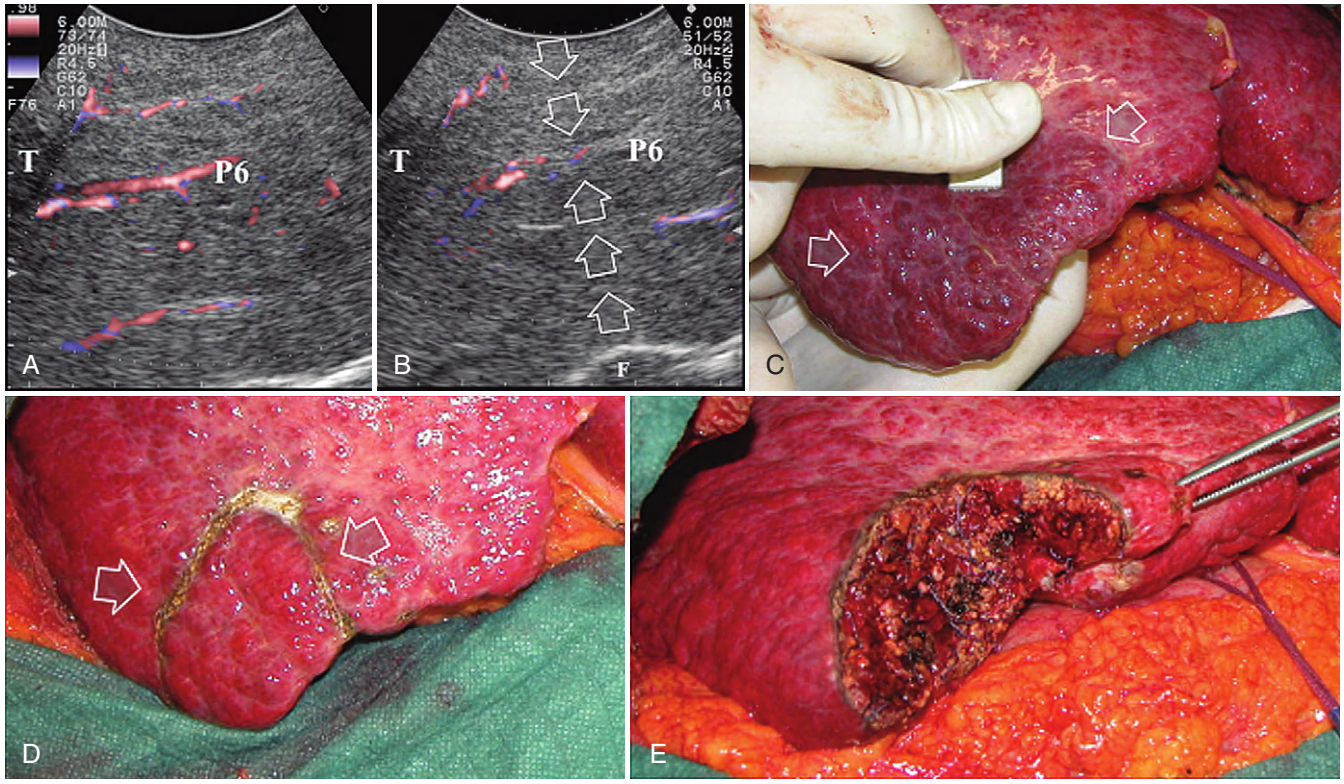


FIGURE 95.57. **A,** This intraoperative ultrasound (IOUS) scan shows the portal branch (*P6*) feeding the tumor in segment VII. **B,** Once identified under IOUS guidance, P6 compression is carried out (*arrows*) with the probe and the surgeon's finger (*F*) positioned on the opposite side. **C,** Compression results in discoloration of the subsegmental portion to be removed (*arrows*). **D,** The area is marked with electrocautery (*arrows*). **E,** The liver after subsegmental resection, which is particularly limited but anatomic.

compression is then identified (Fig. 95.59B). The surgeon's nondominant hand is put behind the right hemiliver, and the probe is positioned with the dominant hand to show the sectional portal branch at the level of interest, which corresponds to the most distal portion of the vessel in relation to its origin but proximal to the tumor to be removed.

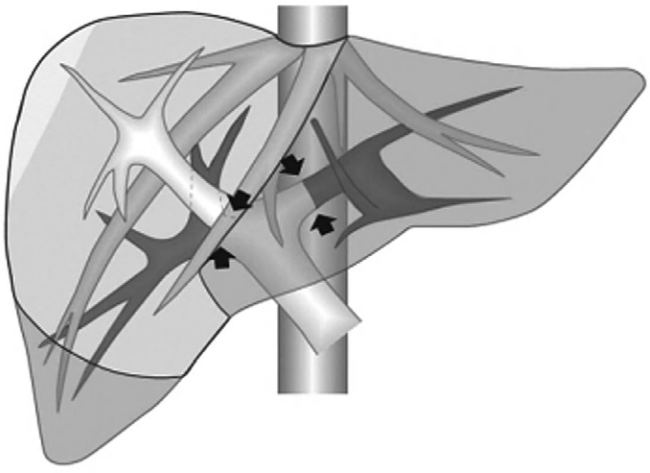


FIGURE 95.58. Countercompression sites for disclosing the right anterior section. Once marked, a right anterior sectionectomy is performed. *Dark gray areas* are those discolored by finger compression at the sites shown by the arrows. The *light gray area* is the right anterior section to be removed.

The surgeon next uses the fingertips of the nondominant hand and the IOUS probe as instruments to compress the liver bilaterally at the targeted position, resulting in compression of the sectional portal branch in the previously identified tract. When there is not a common sectional pedicle to segments VI and VII, compression is applied to the respective segmental portal pedicle as previously described. This maneuver is constantly monitored in real time by IOUS by means of the probe used for compression, and compression is maintained until the surface of the right posterior section lateral to the compression site starts to discolor (Fig. 95.59C); at this time the assistant marks the discolored area with the electrocautery device, and the compression is released (Fig. 95.59D). In this way, a three-dimensional plane has been drawn on the liver surface that passes through portal branch at the level of compression; liver resection is now carried out following that plane (Fig. 95.59E).

Right Anterior Sectionectomy

Similarly, as for the right posterior section, the hilar dissection and the encirclement of the sectional glissonian pedicles are the most commonly adopted techniques for defining the resection area in a fully anatomic manner. More recently, the countercompression technique has been applied for this purpose (Torzilli et al, 2009a). The portal pedicle feeding the right posterior section (segments VI and VII) is identified at IOUS, and the level targeted for compression is then detected just after its origin from the right portal branch (Fig. 95.60A). Demarcation of the right posterior section is carried out as described in

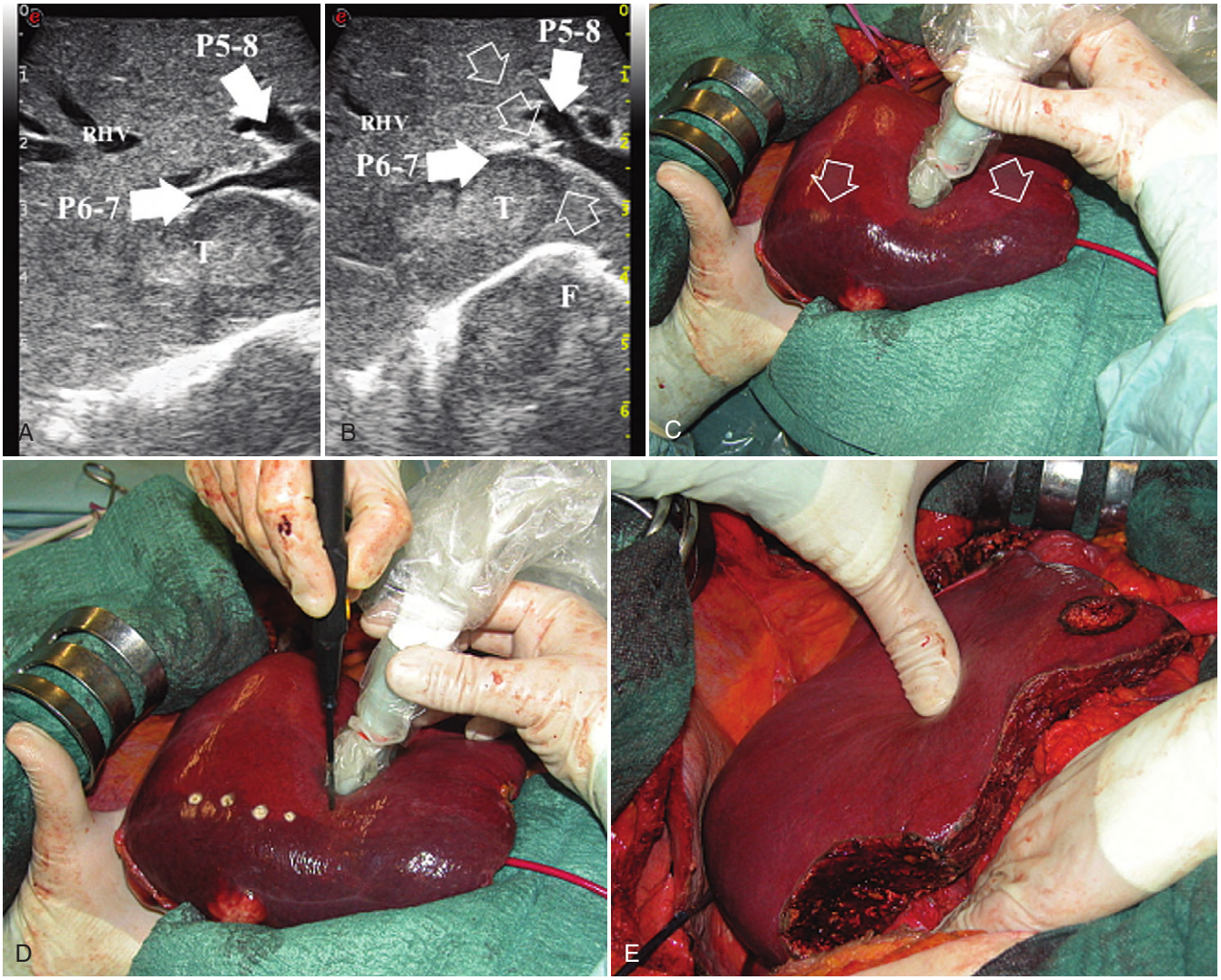


FIGURE 95.59. **A,** This intraoperative ultrasound (IOUS) scan shows the sectional portal branches for the anterior (*P5-8*) and posterior (*P6-7*) sections. **B,** To disclose the margins of the right posterior section in the eventuality of a right posterior sectionectomy, under IOUS guidance, P6-7 compression is carried out (*arrows*) with the probe and the surgeon's finger (*F*) positioned on the opposite side. **C,** Compression results in discoloration of the right posterior section to be removed (*arrows*). **D,** The area is marked with electrocautery. **E,** The liver at the end of the right posterior sectionectomy.

the previous paragraph (Fig. 95.60, B and C). Similarly, the left portal vein (LPV) is identified at IOUS, and the level targeted for compression is then identified just past its origin from the main portal vein (Fig. 95.61A); the LPV compression is carried out and is released once the Cantlie line becomes evident by left hemiliver discoloration (Fig. 95.61, B and C), and it is demarcated with the electrocautery. Once the right anterior section is defined, resection can be carried out.

Limited Resections

Selection of an anatomic or nonanatomic resection for HCC, although a controversial issue (Cho et al, 2007; Eguchi et al, 2008; Kaibori et al, 2006; Regimbeau et al, 2002; Tanaka et al, 2008; Wakai et al, 2007), is leaning in favor of the anatomic approach (Eguchi et al, 2008; Hasegawa et al, 2005; Ueno et al, 2008). Conversely, limited resection is commonly accepted as an oncologically proper approach for CLM (Sarpel et al, 2009). For limited resections, IOUS guidance plays a fundamental role; indeed, although there is no need for identifying the area of the liver fed by the portal branch to be ligated, once the tumor is identified, the surgeon can mark the border of the lesion and that of the area to be removed on the surface of the liver with the electrocautery under IOUS control. To carry out this maneuver, the flat and thin tip of the electrocautery device is positioned between the probe and the liver surface. This results in a shadow on the IOUS image that runs deeply just below the electrocautery (Fig. 95.62, A to D). In this way, it is possible to define the position of the electrocautery device with the tumor edge and consequently to mark the nodule profile on the liver surface with electrocautery and to select the safer edge for the incision. The adequacy of the marked edge can be further checked with IOUS, as the air trapped between the probe and the irregular surface of the demarcation line

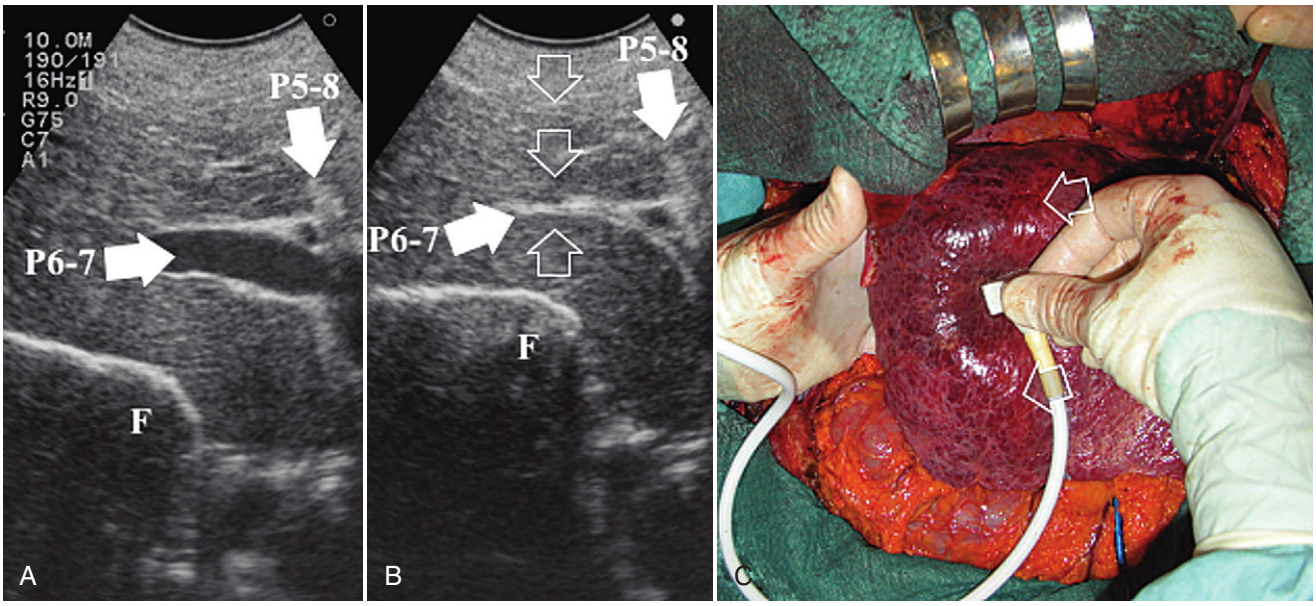


FIGURE 95.60. A, This intraoperative ultrasound (IOUS) scan shows the sectional portal branches for the anterior (*P5-8*) and posterior (*P6-7*) sections. **B,** To disclose the margins between the right posterior and right anterior sections, P6-7 compression is carried out (*open arrows*) under IOUS guidance using the probe and the surgeon's finger (*F*) positioned on the opposite side. **C,** Compression results in discoloration of the right posterior section (*arrows*).

drawn with the electrocautery on the liver surface can be visualized at IOUS, having a similar aspect compared with the images that result with the electrocautery (Fig. 95.63).

Additionally, with the probe positioned on the liver surface at the site of the resection margin previously drawn, the surgeon uses a fingertip to push at the opposite edge of the resection area (see Fig. 95.62A), and the profile of the resection area is visualized at IOUS. As a consequence, structures between the fingertip and the tumor edge can be precisely estimated, the resection area can be marked on the liver surface, and the dissection plane is visualized (see Fig. 95.62B). The main target to be obtained once the resection area is drawn on the liver surface is that of achieving at the end of the dissection the flattest and most regular cut surface (see Fig. 95.62E).

Liver Parenchyma Dissection

The main advantage provided by the resection guidance accomplished with the aid of IOUS is the modification of the traditional way to dissect the liver tissue, which was done on vertical planes to avoid the tumor exposure on the cut surface. IOUS allows the surgeon to follow the dissection plane in real time, to see it constantly in relation to the tumor edge, and then to modify its direction when needed: this is because it is possible to visualize the dissection plane on the IOUS image, which appears as an echogenic line as a result of the entrapment of air bubbles and clots between facing cut surfaces (Fig. 95.64). If the dissection plane is not clearly visible, it can be better visualized by inserting plain gauze (Fig. 95.65) or a specifically devised silicone gauze between facing surfaces. These techniques allow the surgeon to keep the proper dissection plane, and early recognition of an improper dissection plane permits its modification and avoids a possible tumor seeding. In this way, it is possible to carry out a rounded trajectory of the dissection plane around the tumor, avoiding its seeding and allowing the surgeon to spare important vascular structures; this results in more conservative but radical treatments and in a lower rate of major hepatectomies.

The artifacts that may show up on IOUS sometimes mask structures critical to the dissection plan, such as portal branches, which should be ligated or conversely respected. For this reason, to better visualize the targeted point where the portal branch should be divided, the so-called hooking technique has been devised (Torzilli et al, 1999b). When the glissonian sheath is exposed and skeletonized, it is encircled with a stitch. Under US control, the stitch hooking the exposed vessel is then gently pulled up, which stretches the portal branch slightly; this traction point is demonstrated clearly by IOUS (Fig. 95.66, A and B). If the exposed portal branch is not clearly visible because it has collapsed, the portal triad is unclamped. If the target site is correct, the portal branch is ligated and divided, and resection is completed under IOUS guidance; conversely, if the exposed vessel was not the targeted one, it is spared, and useless sacrifice of further liver parenchyma is avoided.

A practical example in which the hooking technique is used is during ventral or dorsal subsegmentectomy of segment VIII. The portal trunk to this segment may show bifurcation in its dorsal branch and ventral trunk near the origin of the portal vessel to segment V. In this situation, there is the risk of ligating and dividing the portal branch of segment V, instead of the planned subsegmental branch of segment VIII, and necrosis of segment V may occur. Under IOUS control, the hooking technique enables the identification of the branch, which was encircled, and then the surgeon can decide with certainty whether to ligate it.

This technique is also useful in case of tumor thrombus in major portal branches (Torzilli et al, 2005b). In this situation, once the portal branch is skeletonized, it is encircled with a stitch; then the stitch is gently pulled up under IOUS control, and this traction stretches the portal branch slightly, and the traction point is demonstrated clearly by IOUS (Fig. 95.67). If

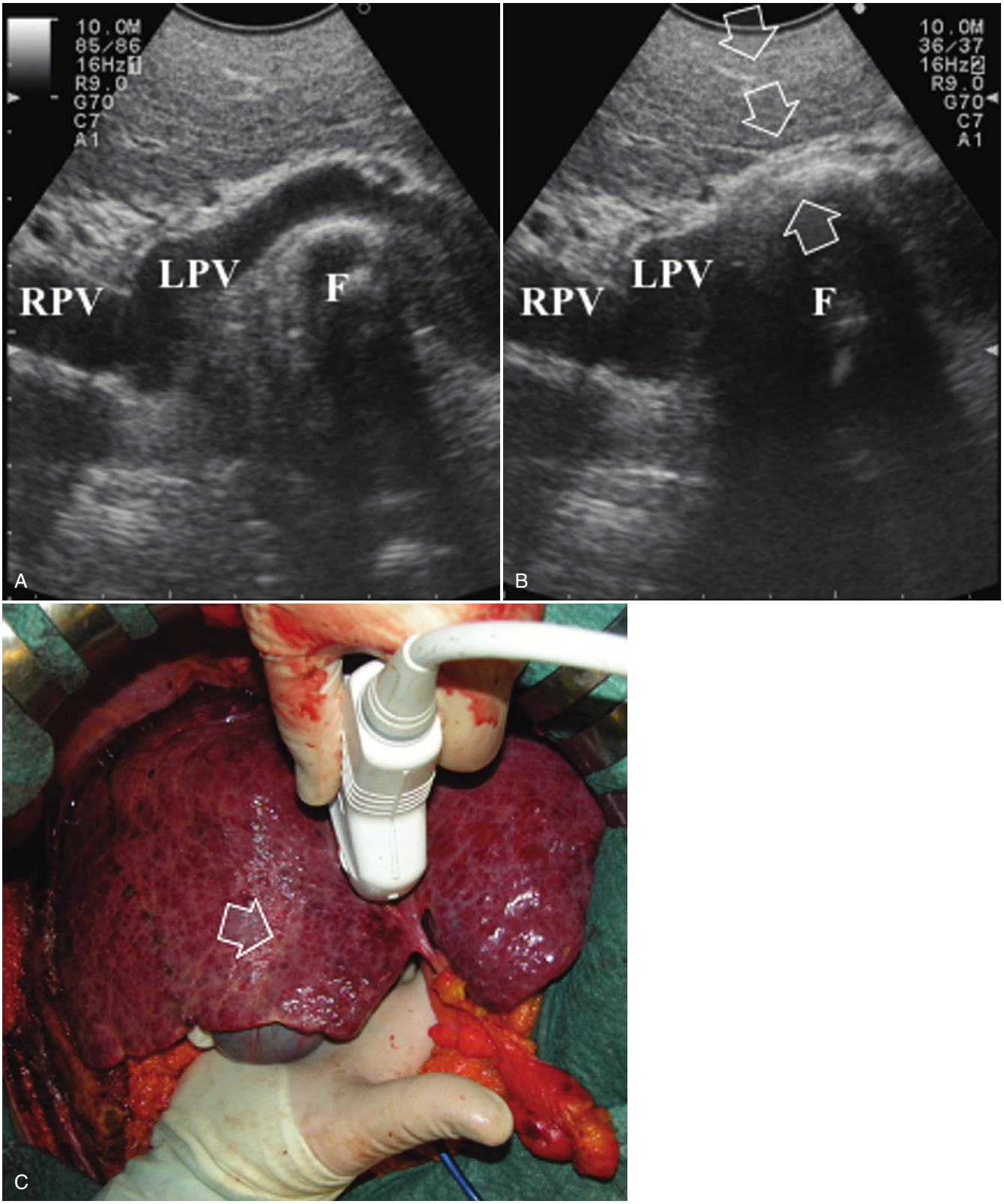


FIGURE 95.61. **A,** This intraoperative ultrasound (IOUS) scan shows the right portal vein (*RPV*) and left portal vein (*LPV*) and allows the proper positioning of the surgeon's finger (*F*) behind the LPV. **B,** To disclose the margins between the left and right hemilivers, under IOUS guidance, LPV compression is carried out (*arrows*) using the probe and the surgeon's finger (*F*) previously positioned. **C,** Compression results in discoloration of the left hemiliver (*arrows*).

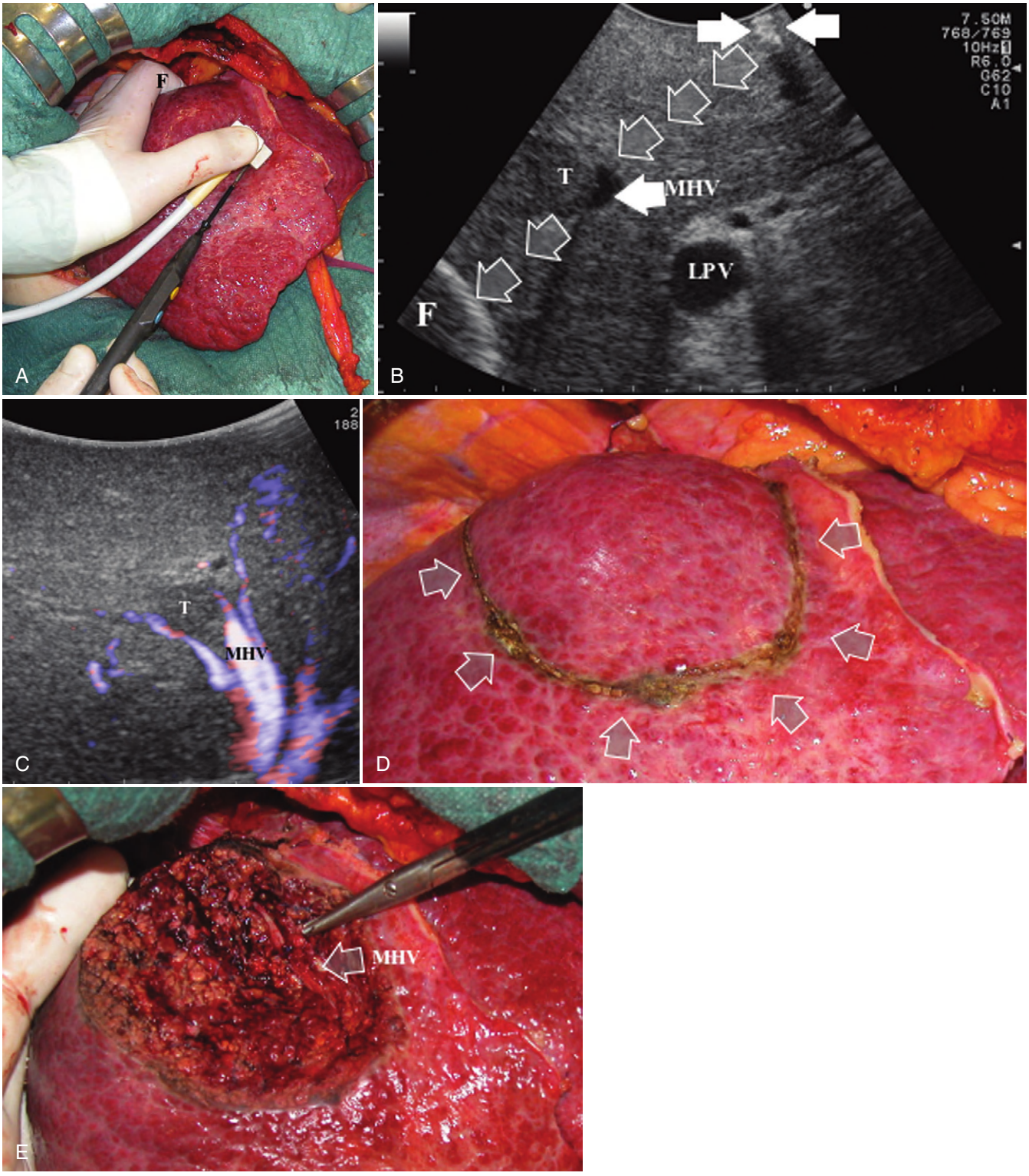


FIGURE 95.62. **A,** The electrocautery positioned between the probe, liver surface, and surgeon's finger (*F*) at the opposite edge of the resective area. **B,** Both the shadow generated by the electrocautery (*white arrows*) and the profile of the surgeon's finger (*F*) are visualized, and the surgeon can draw an ideal dissection plane (*transparent arrows*) that can be followed once the resection area is marked using these landmarks. **C,** This e-flow intraoperative ultrasound image confirms that the lesion (*T*) is in contact with the middle hepatic vein (*MHV*). **D,** The resected area is marked on the liver surface (*arrows*). **E,** Cut surface of the limited resection with exposure of the tract of the MHV, which was in contact with the lesion.

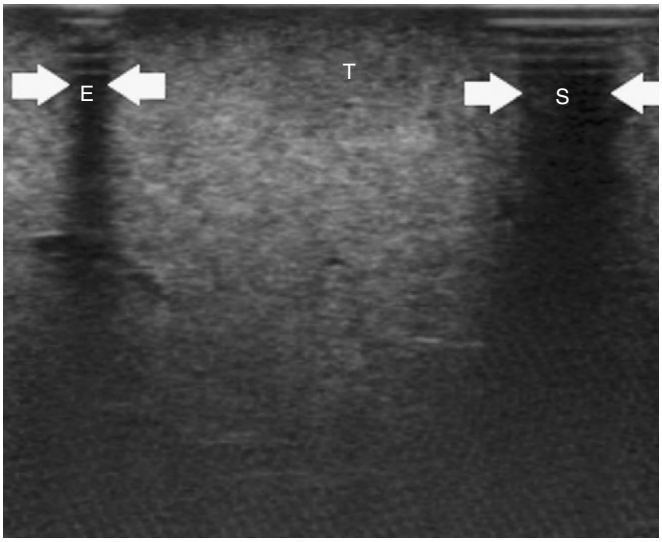


FIGURE 95.63. Intraoperative ultrasound shows both the electrocautery (*E*) and the scar (*S*). A vertical shadow is generated that allows verification of the proper margins of resection in relation to the tumor (*T*) location.

the traction point is not at the level of the tumor thrombus, it is possible to ligate the portal branch and proceed with the liver resection, being sure that thrombus will not migrate because of surgical manipulation.

During liver dissection, the backflow bleeding from the hepatic veins is an important source of blood loss, and it is one of the most important factors in determining the short- and long-term outcome; therefore limiting the backflow bleeding from the hepatic veins is a priority in liver resections. A US-guided technique has been recently described for backflow bleeding control from the RHV during right-sided liver resection (Torzilli et al, 2007a). The technique is very simple and is now applied to every hepatic vein. Once the hepatocaval confluence is exposed anteriorly (Fig. 95.68, A to C), dissection proceeds until the surgeon's fingertip is able to compress the targeted hepatic vein at its caval confluence; the effectiveness of this maneuver is checked by EF-IOUS (Fig. 95.68D to E).

Alternative Methods for Liver Dissection Guidance

In recent years, tracking systems that combine the position of the dissecting instruments and the three-dimensional (3D) liver reconstruction, based on software elaboration of the preoperative CT or MRI or the 3D US images themselves, have been proposed for dissection guidance (Chopra et al, 2008). This approach is mainly used to offer real-time and continuous guidance of the liver dissection, rather than the one warranted by IOUS guidance, which can be done repeatedly but is not providing information anyway, if dissection is not interrupted for the US check; however, up to now, data provided by a few groups are not consistent enough to disclose a real advantage of an approach that on the other hand seems rather complex. A free line between the tracking system and the trackers allocated on the US probe and the dissecting instrument used must be maintained; otherwise, data registration for navigation is interrupted. In this context, tracking systems may be optical, for which a free line of sight must be maintained between the instruments, or they may be electromagnetic, which makes them sensitive to disturbances originated by the surgical instruments.

In one of the few experiences reported, the lack of communication between elements connected via an infrared-based optical line was responsible for the failure of the navigation in 4% of those treated (Beller et al, 2007). Another problem concerning the use of these navigation systems is in the reduction of precision, once the dissection gets deeper into the liver, as a result of organ shifting and deformation that make data less reliable. This represents the major limitation of this approach, because it seems to fail to provide information exactly when more data may be needed. Indeed, with neurologic or head and neck surgery, for example, the targets are fixed, and results seem more consistent with the objectives (Hamada et al, 2005; Hohlweg-Majert et al, 2005); whereas in abdominal surgery, the mobility of the viscera do not facilitate the fixing of targets. More recently, a further modification has been introduced in the original setting in which an electromagnetic sensor is inserted into the liver under US guidance, close to the tumor to be removed (Beller et al, 2009), with the purpose of overcoming the problem of decreased navigating precision as the instrument gets deeper into the liver; however, some concerns may be raised by the further complexity of the method proposed.

Some authors are trying to overcome the problem of organ shifting and deformation during surgical maneuvers with a framework that makes feasible the updating of the 3D preoperative models with the new intraoperative data (Dagon et al, 2008). This allows us to foresee that, in the future, improvements in technology may be able to overcome the difficulties brought about by organ deformation and shifting; however, the need for adjunctive instruments in the surgical theatre—and the use and related costs of 3D US, which is somewhat more complex to interpret than two-dimensional US, even if the technical drawbacks are resolved—make unclear the advantages of the implementation of these technologies compared with the use of US guidance as it has been described here. Indeed, in expert hands, US guidance provides suitable results in terms of enhanced conservation of parenchyma in the various hepatectomies, while at the same time maintaining and somewhat improving the oncologic radicality; therefore US guidance should be considered the gold standard in terms of "navigated" liver surgery.

Postresectional Control

After nodule removal, two possibilities for specimen handling are offered by IOUS: one is the "water bath" technique, which consists of real-time control of the proper resection of the targeted nodule, verifying its complete inclusion in the specimen removed from the liver (Makuuchi, 1987; Fig. 95.69); the second is done checking the cut surface, which is refilled with saline to avoid the artifacts generated by the residual air bubbles and clots (Fig. 95.70).

In those patients in whom major resections are needed, color Doppler IOUS allows the proper positioning of the remnant liver, until the inflow and outflow are proper in terms of velocity and waveform on color Doppler US (Ogata et al, 2005; Fig. 95.71).

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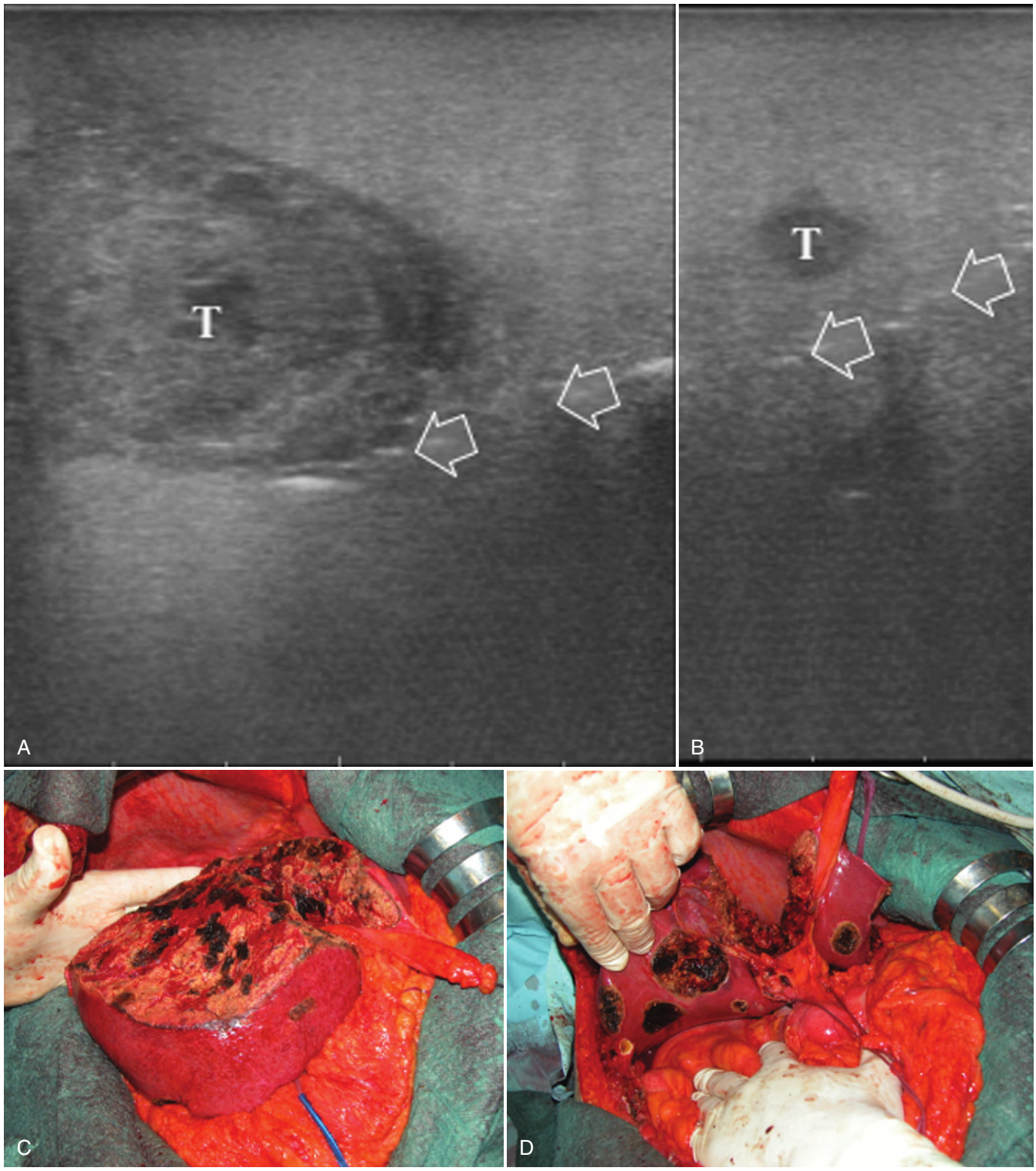


FIGURE 95.64. A and **B,** The dissection lines can be well visualized (*arrows*), and in both situations run under the tumors (*T*). Their visibility at intraoperative ultrasound is due to the artifacts generated by the clots and gas bubbles trapped between the facing cut surfaces. **C** and **D,** Resection area after the dissection, with removal of a total of 33 lesions.

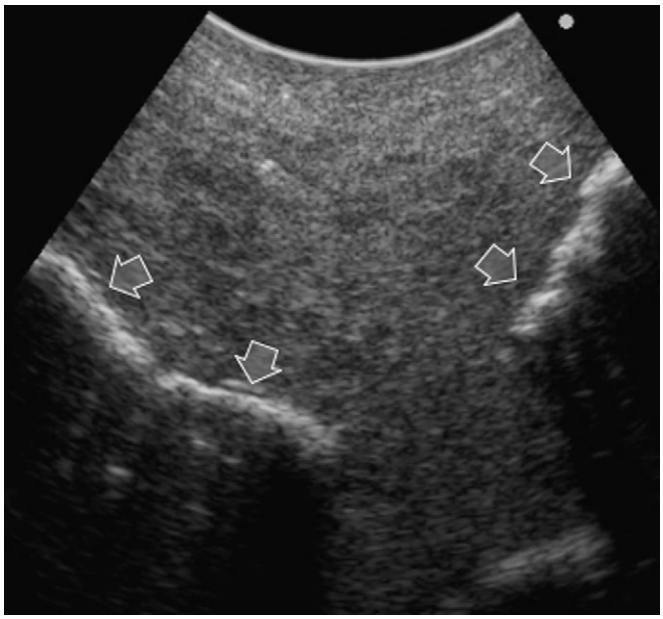


FIGURE 95.65. Dissection lines (*arrows*) highlighted by the interposition of gauzes between the cut surfaces. Their visibility is enhanced, but the shadows cast by the gauzes do not allow visualization of the parenchyma under the dissection lines.

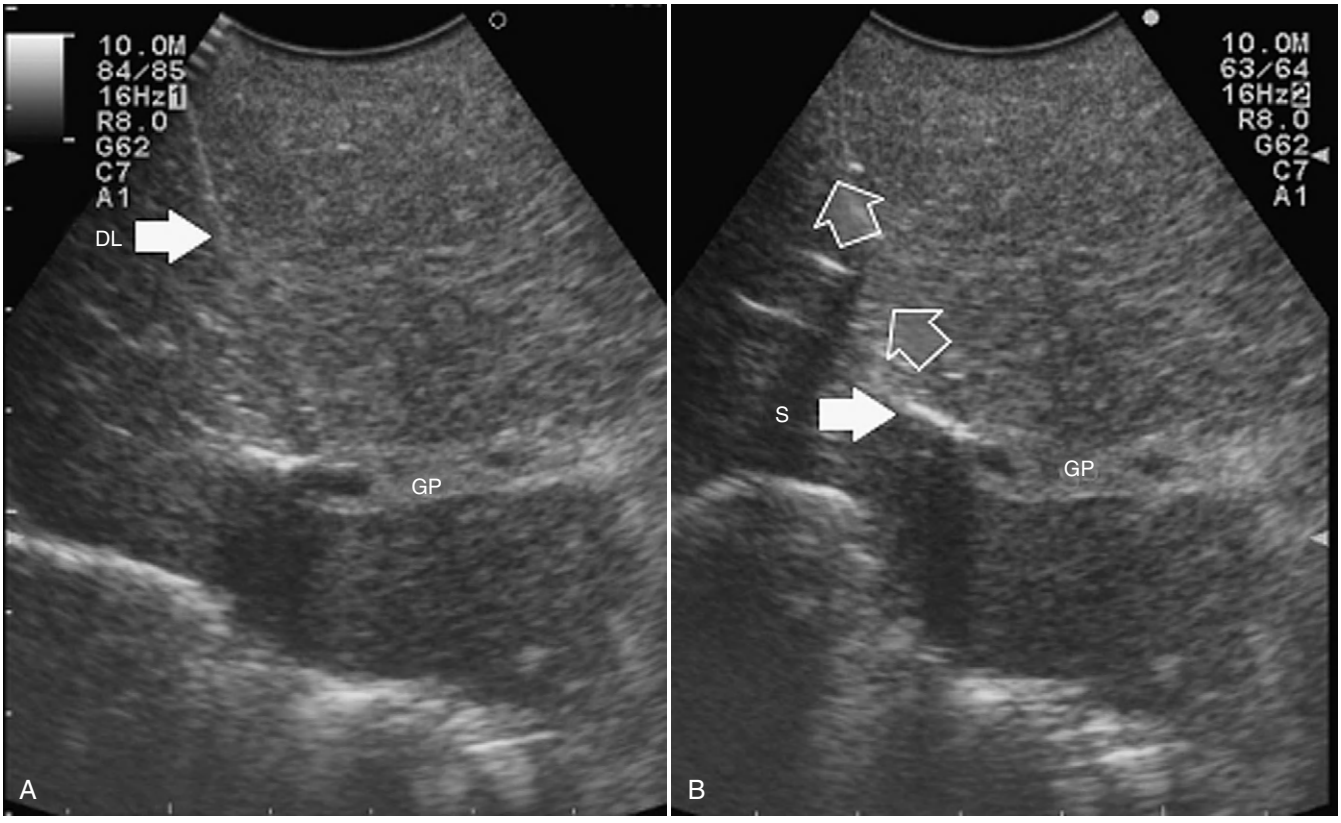


FIGURE 95.66. **A,** The dissection line (*DL*) reaches a glissonian pedicle (*GP*). **B,** Once traction is applied (*transparent arrows*) to the vessel previously encircled with a stitch, modification of the GP confirms that this is the same one visualized at intraoperative ultrasound; the hyperechoic (bright) spot (*solid arrow*) corresponds to the stitch (*S*).

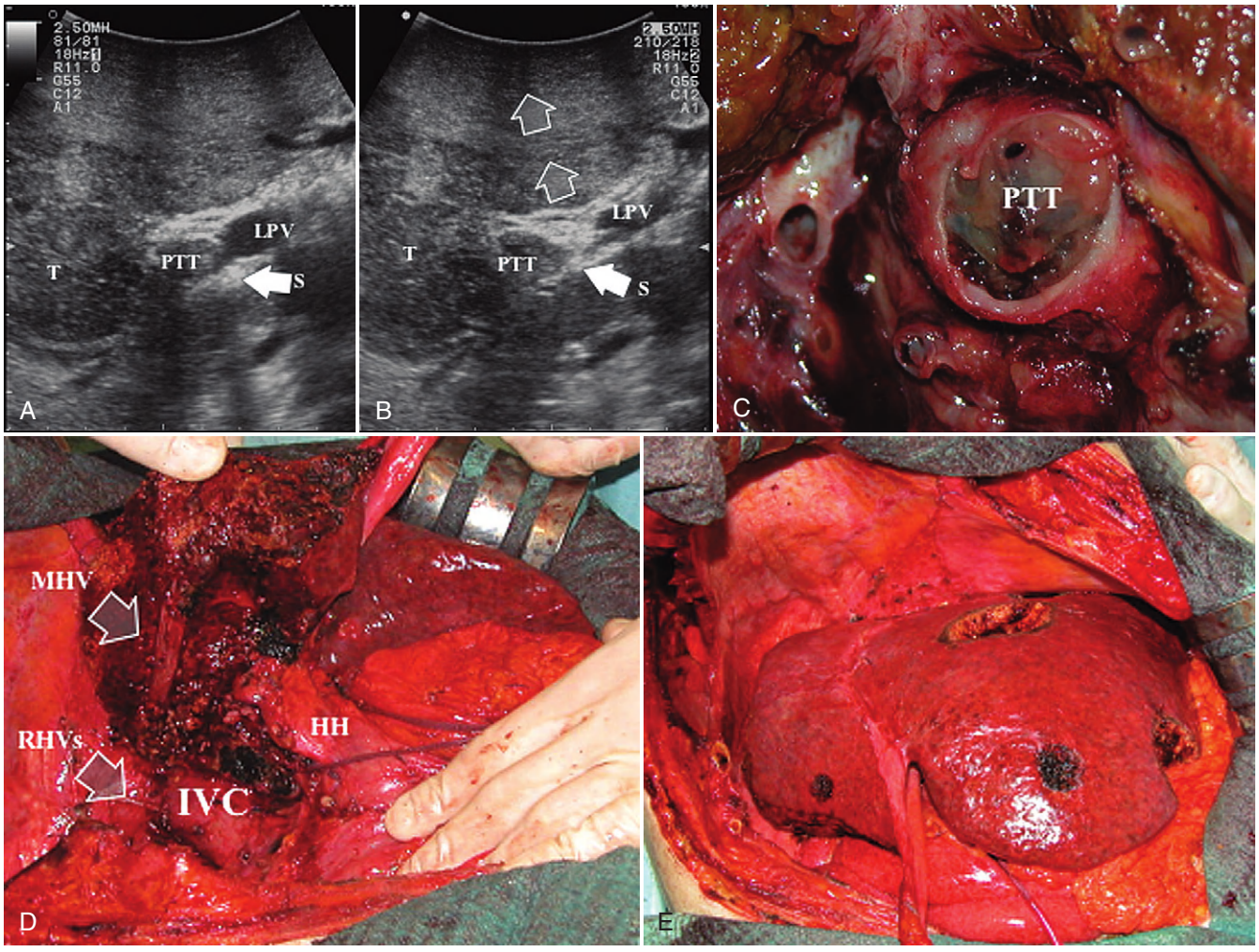


FIGURE 95.67. **A,** The tumor thrombus (*PTT*) in the right portal vein, which has been encircled with a stitch (*S, arrow*). **B,** Once traction (*transparent arrows*) is applied to the stitch (*S, arrow*), the PTT is moved backward into the portal branch, which indicates that the vein can be ligated at the level of traction. **C,** The integrity of the PTT is verified on the specimen. **D,** Cut surface of the liver after right hepatectomy partially extended to segment IV (inferior). **E,** Remnant liver after extended right hepatectomy and multiple limited resection in the left hemiliver. HH, hepatic hilum; IVC, inferior vena cava; LPV, left portal vein; MHV, middle hepatic vein; RHVs, right hepatic vein stump; T, tumor.

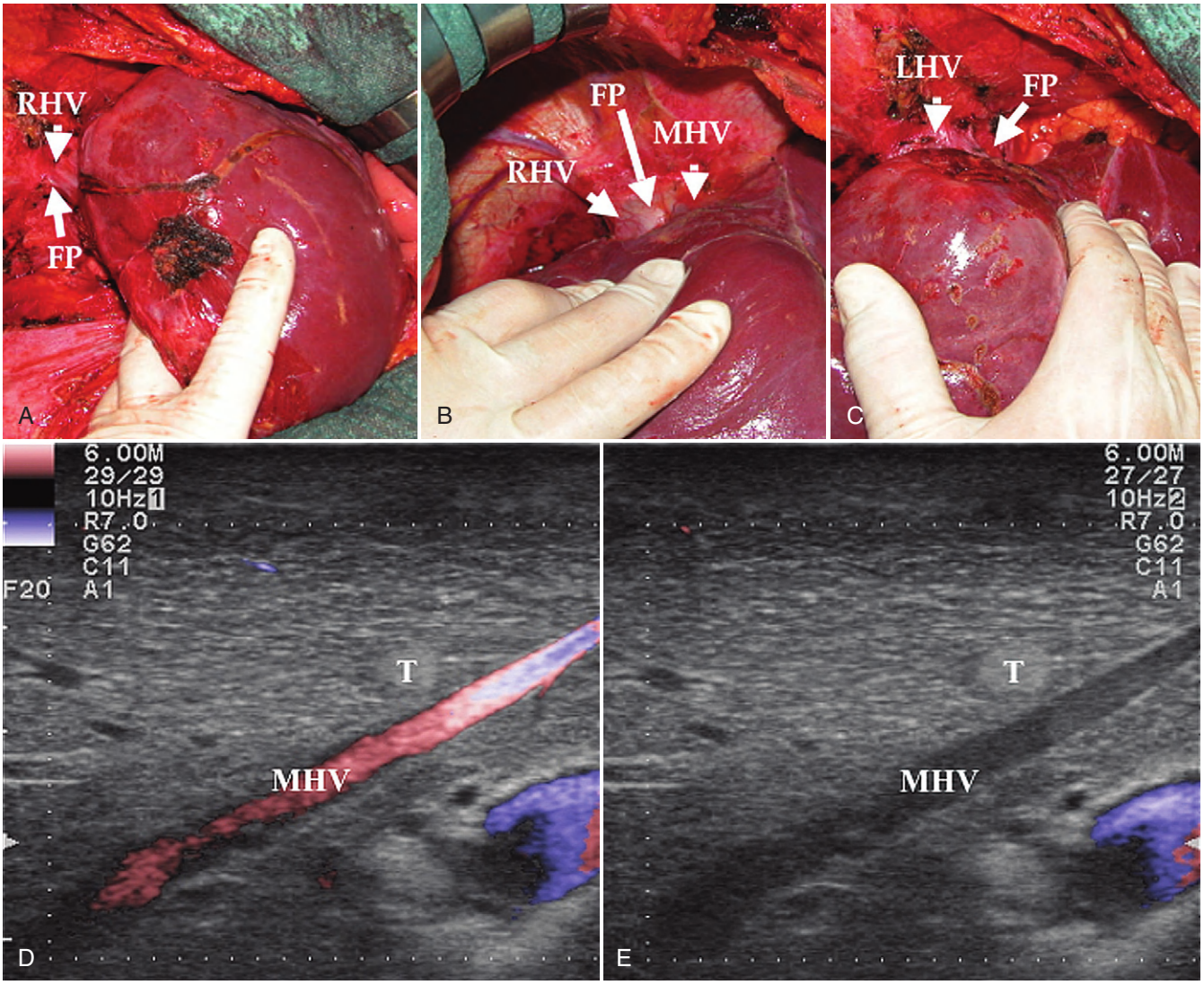


FIGURE 95.68. **A,** Hepatocaval confluence preparation for intraoperative ultrasound-guided compression maneuvers on the right hepatic vein (*RHV*). **B,** The middle hepatic vein (*MHV*). **C,** The left hepatic vein (*LHV*). Once the vein to be compressed is monitored (**D**), the compression results in the disappearance of the color flow inside the compressed vein (**E**). FP, fingertip position; T, tumor.

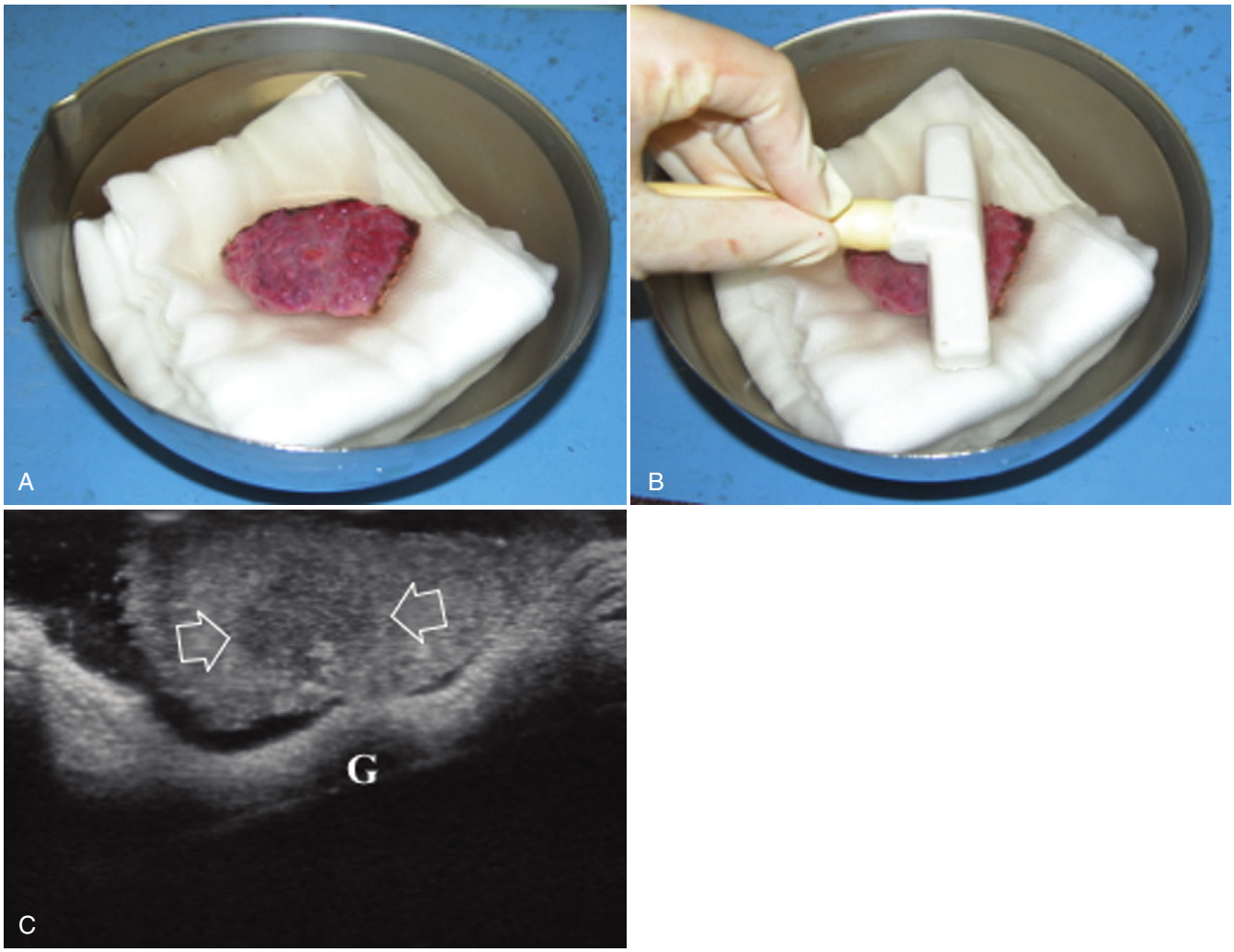


FIGURE 95.69. **A** and **B,** The water-bath technique for checking the surgical specimen. **C,** Inclusion of the targeted nodule, as it is confirmed at intraoperative ultrasound (*arrows*). G, gauzes.

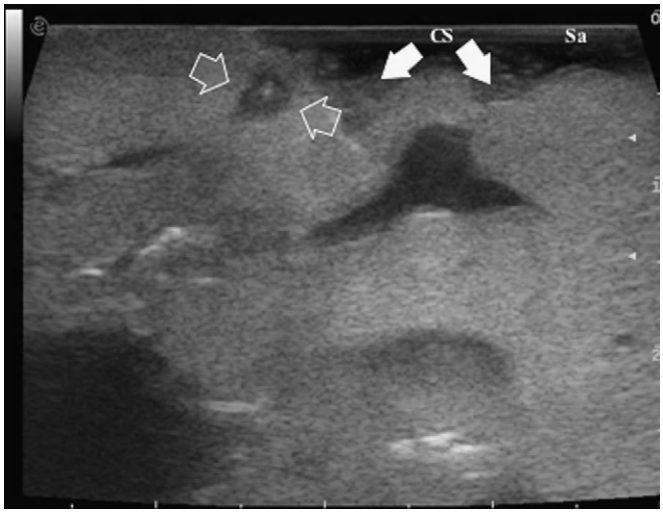


FIGURE 95.70. If the inclusion in the specimen is not confirmed, the cut surface (*CS*) filled with saline (*Sa*) is reexplored with intraoperative ultrasound, and the lesion (*arrows*) is identified and removed.

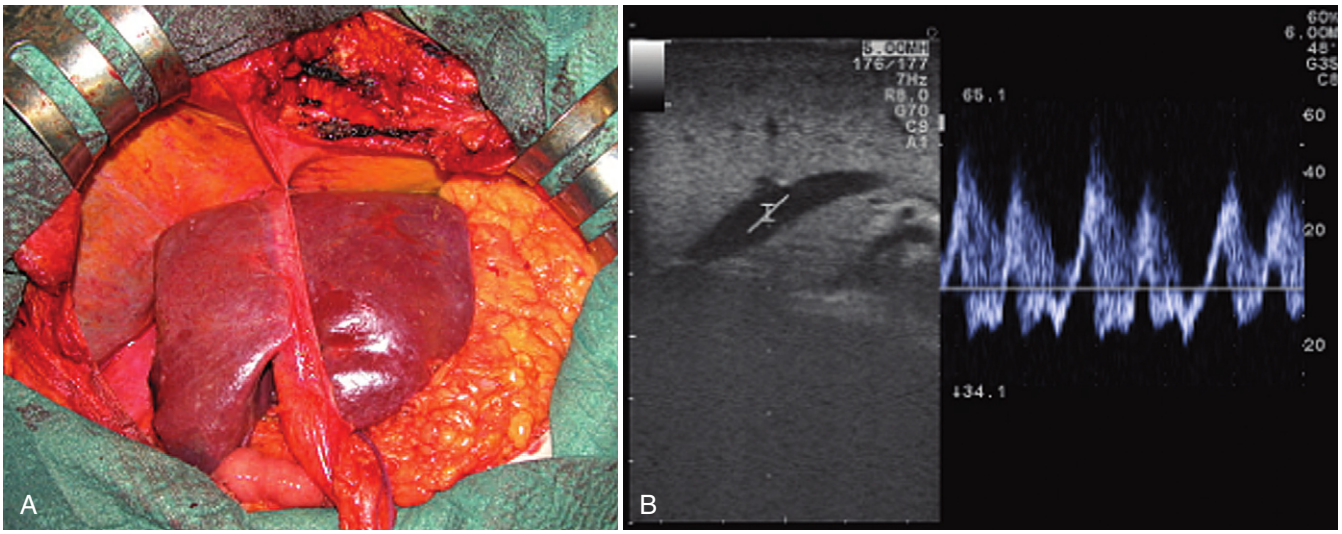


FIGURE 95.71. If a right hepatectomy is carried out (**A**), the proper repositioning of the remnant liver is performed using color Doppler to see whether the proper outflow is obtained with a triphasic wave pattern as shown (**B**).

CONCLUSIONS

IOUS is still the best method for staging the involvement of liver by tumor. The role played by CE-IOUS in this context seems relevant to enhancing sensitivity and specificity of IOUS, although this to be better evaluated. IOUS is certainly the best method for the surgeon to use to understand the liver anatomy and the relationships between tumors and intrahepatic vessels. This information is crucial for planning the resection, and in this sense, IOUS probably has the most important role in guiding the surgeon's hand in real time during the liver parenchyma dissection.

The aforementioned methods for performing an IOUS-guided resection guarantee, whenever possible, both anatomic and limited resection with a radical intent; this has consequences for both the effectiveness of the surgical treatment and for its safety. Procedures that are not guided by IOUS lead to dangerous and somewhat useless major resection or, inversely, to incomplete operations. IOUS tumor vessel classification and the related surgical policy has proven that in selected patients, it is possible to get close to the tumor burden without increasing the risk of incomplete removal and, as a consequence, of local recurrence or tumor seeding (Torzilli et al, 2005a); therefore new oncologic concepts are introduced.

For HCC, tumor exposure of the cut surface is not in contradiction with a fully anatomic resection, if it respects the oncologic requirements for this kind of tumor (see Figs. 95.32 and 95.35), and descriptions of several experiences are confirming this (Torzilli et al, 2008b; Matsui et al, 2007; Ochiai et al, 1999). Similarly, in the case of CLM, getting closer to the tumor burden under IOUS guidance, even exposing the tumor, is not only not in contradiction to the concept of radical surgery, at least in conditions otherwise not suitable to any other approach, but also does not increase the risk of local recurrence and allows survivals similar to those obtained by more conventional procedures (de Haas et al, 2008; Kokudo et al, 2002; Minagawa et al, 2000; Pawlik et al, 2005; Torzilli et al, 2009b).

In practice, this evidence suggests that with IOUS guidance, it is possible to perform conservative but radical hepatectomies, even in complex presentations, and then to enlarge the surgical indications. With this approach, the rate of major hepatectomies has been limited to about 8% in patients with tumors involving one or more hepatic veins close to their caval confluence, without performing any vascular reconstruction (Torzilli et al, 2006b); it has been limited to 4% in patients with multiple bilobar CLM, with removal of up to 49 lesions at once (Torzilli et al, 2009b).

Limitation of major hepatectomy allows resection of advanced HCC, with a less than 1% mortality rate and improved long-term outcome (Torzilli et al, 2008b). New US-guided operations have contributed to achieving these results, thus allowing technical solutions otherwise not feasible (Torzilli et al, 2008c, 2010a). Just because this approach reduces the rate of major hepatectomies, the real need could be debated for interventions such as preoperative PVE, which are adopted to prevent liver failure after removal of significant amounts of liver parenchyma (Torzilli et al, 2009c); however, this approach to liver resection, which allows the combination of widened indications and a high standard of safety, demands large incisions with extensive mobilization and complex dissection planes. These requirements run counter to the trend to use smaller incisions, such as with the anterior approach, with or without the hanging maneuver (Liu et al, 2006; Ogata et al, 2007), and in laparoscopic hepatic surgery, in which the complex IOUS-guided maneuvers described herein, and the required complex dissection planes, would be difficult to realize, at least with the same level of safety.

In spite of this, IOUS-guided liver surgery should be considered a minimally invasive procedure whose main target is the sparing of liver parenchyma, and its absolute safety is paradigmatic of what has been just affirmed. Mostly because of that, surgery can still be considered the treatment of choice for most liver tumors, in spite of the development and progresses in other local treatments, such as ablation therapies and intravascular procedures. Furthermore, this use of US

intraoperatively for expanding the indications for tumor removal is paradoxically in opposition to the trend of introducing US for guiding intraoperative tumor ablation. As a matter of fact, stressing the use of IOUS for guidance, it is possible to expand indications for HCC and CLM without risking the recurrence rates observed after ablation, even when performed intraoperatively (Abdalla et al, 2004; N'Kontchou et al, 2009; Torzilli et al, 2008b, 2009b).

From this standpoint, having IOUS in the surgeon's technical background, every effort should be focused on maximizing the capability of enhancing the hepatic surgeon's resective power, rather than for allowing ablation technique, which from the perspective of a simple alternative is undoubtedly an oncologically suboptimal shortcut. This use of US will probably improve with further improvements in contrast agents and new color-flow modalities, which up to now have shown more potential. Conversely, such potentials can be anticipated and will no doubt be consolidated by the technical evolution and consequent diffusion of the navigation systems, which for now have proven too costly and are limited in number to those centers involved in relevant clinical trials.

For all these reasons, IOUS should be in the armamentarium of every hepatic surgeon, and in this sense, the present and future challenge should be to train young surgeons in the use of US-guided technique in the course of their educational process. Only with this perspective can an effective diffusion of US technologies in the practice of hepatic surgery be definitely and fully established.

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SECTION I
General

CHAPTER 96

Liver and pancreas transplantation immunobiology

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MAINTENANCE MINIMIZATION, IMMUNOSUPPRESSANT WITHDRAWAL, AND TOLERANCE

Allotransplantation, the transfer of tissues between genetically nonidentical individuals, has been shown to provide relief from incurable liver diseases and type 1 diabetes; however, unless some modification of the recipient immune system is made, transplanted organs are invariably destroyed through a process broadly known as *rejection*.

Over the past 5 decades, the ability to manipulate the immune response has become increasingly selective and less morbid. Through a general understanding of alloimmunity and the unique properties of the liver and pancreas, transplantation results have steadily improved (U.S. Organ Procurement and Transplantation Network, 2009). This chapter provides an overview of the principles governing immune management of liver and pancreatic transplant recipients, highlighting agents and strategies generally available for clinical use.

GENERAL CONSIDERATIONS: SPECIFICITY AND CONTEXT

Allograft rejection is mediated by the elements of physiologic immunity but stems from a nonphysiologic practice: transplantation. As with most immune responses, rejection requires a specific recognition event and a context that signifies that this recognition warrants a response.

Immune recognition is mediated through one of two types of lymphocyte receptors, the T-cell receptor and/or immunoglobulin. Immune specificity is dictated by the ability of these receptors to bind a suitably complementary epitope. A cluster of highly polymorphic genes on chromosome 6, known as the *major histocompatibility complex* (MHC; or human leukocyte antigen [HLA] in humans), governs the recognition of cell-based antigens. Proteins produced from polymorphic genes have the same basic structure but differ in detail. The role of these molecules differs between physiologic and transplant immunity, as will be described below.

The context of an immune response is governed through another set of receptors known as *costimulation receptors*. Broadly speaking, these receptors provide signals that determine whether antigen recognition should evoke an immune response and whether that response should be aggressive or attenuating; these receptors are also involved in the mechanisms of response termination, ensuring that immune responses are contained within physiologic parameters. By separating the signals for specificity and appropriateness, the immune response to pathogens and allografts can be tightly regulated and finely manipulated.

Typically, the ligands for costimulation receptors are most prominently expressed on professional antigen-presenting cells (APCs), the role of which is to initiate and sustain an immune response. The interactions between APCs and lymphocytes usually take place in lymphoid organs, such as the spleen or lymph nodes. The requirement for APCs and the necessity for secondary lymphoid organs provide additional opportunity for regulation and lessen the chance for autoimmune responses.

PHYSIOLOGIC IMMUNITY

The immune system developed to protect the body from pathogens, not to mediate transplant rejection. Although alloimmunity and physiologic immunity differ, it is critical to understand the components of alloimmunity in their physiologic roles.

The immune system is typically divided into two complementary arms, *innate* and *acquired*. The innate immune system recognizes general motifs that universally represent pathologic states, such as ischemia, necrosis, trauma, and nonhuman cell surfaces (Dempsey et al, 1996; Fearon & Locksley, 1996; Matzinger, 1994, 2001). The acquired immune system distinguishes specific pathogens through antigen presentation and recognition. Both systems interact to maintain overall

homeostasis. Typically, innate responses localize acquired responses to sites of pathologic processes and are less overtly regulated. In contrast, acquired immune responses lead to carefully regulated destruction of antigen-expressing tissue. The regulatory checks on acquired immunity prevent autoimmunity and uncontrolled lymphocyte proliferation. It is important to recognize that the acquired immune system is tailored for the individual based on each person's unique MHC makeup. Evolutionarily, this diversity reduces the chance that any single pathogen can evade all individuals within a population; however, this also means that one person's acquired immune response may not respond appropriately when placed in the context of another person's MHC.

Innate Immunity

Receptors of innate immunity are cell bound on macrophages, neutrophils, and natural killer cells, and they circulate freely in the form of complement (Dempsey et al, 1996; Fearon & Locksley, 1996; Wright et al, 1990). Innate immunity is limited in specificity, and it retains broad reactivity to lipopolysaccharide (LPS) and components of pathogenic organisms. Importantly, the receptors of innate immunity are conserved between individuals and, in general, function similarly in physiologic and transplant situations. Once activated, the innate immune system initiates cytolytic pathways and recruits the acquired immune response.

The complement cascade is the primary mediator of cytolysis, and the byproducts of complement, along with phagocytic cells, signal initiation of acquired immunity (Baldwin et al, 2010; Wasowska et al, 2007). Platelets also have been increasingly recognized as serving an innate immune role through the release of chemotactic proteins and other immunostimulatory molecules (Kirk et al, 2009). Professional APCs not only engulf cells coated with complement but also those bearing foreign carbohydrate moieties (Hart, 1997).

Toll-like receptors (TLRs) have also been recognized as important for innate APC activation. This highly conserved family of receptors binds to pathogen-associated molecular pattern motifs commonly expressed on invading pathogenic organisms (Akira & Takeda, 2004). Engulfed cells are processed by the APC into protein fragments and are expressed on the cell surface bound to MHC molecules. Subsequently, T cells that are specific for these peptides can recognize their cognate antigens and become activated. Interestingly, the TLRs expressed in the liver differ from those expressed in the periphery and tend to be less responsive to ambient LPS (Hart, 1997). This is likely an adaptation to portal bacteremia and is thought to make the liver more tolerant of minor perturbations that would evoke an innate response in other organs.

Acquired Immunity

Specific recognition is the hallmark of the acquired immune system. The lymphocyte receptors (T-cell receptor and antibody) have evolved to distinguish an extremely diverse group of antigens. Furthermore, antigen recognition induces physiologic changes in the recognizing cell that lowers its threshold for subsequent encounters and leads to the phenomenon of *immunologic memory,* the more rapid response to subsequent antigen encounters (Ahmed & Gray, 1996). T-cell receptors (TCRs) bind peptide antigens that have been processed and presented in combination with MHC, and B-cell immunoglobulins bind antigens in their native conformation at a site remote from the B cell.

Cellular Immunity

Formation of the TCR is fundamental to understanding its function (Cooper, 1987; Davis & Bjorkman, 1988). T cells are formed in the bone marrow and fetal liver and migrate to the thymus during development. After entering the thymus, T cells undergo rearrangement of the DNA that encodes the TCR (Gill & Gulley, 1994). Each gene rearrangement results in generation of a TCR with specificity restricted to one epitope or structurally similar epitopes. The sum of all random TCR gene rearrangements generates TCRs with approximately 10^9 specificities, essentially all possible combinations of MHC and peptide antigen; if these T cells were released into the periphery, they would mediate fatal autoimmunity. Accordingly, thymic selection eliminates those cells likely to evoke autoimmunity (Bevan, 1997; Kappler et al, 1987).

The initial phase of thymic selection is the interaction of developing T cells with the MHC that expresses cortical thymic epithelium. These T cells express the accessory cell surface markers CD4 and CD8, which allow for stronger binding of TCR to MHC. If binding does not occur to the self MHC available on the thymic epithelium, the cells are eliminated, as they would be unable to interact with self cells and thus would be nonfunctional in the periphery. This process is known as *positive selection.*

Thus all surviving T cells bind to self MHC. The developing T cells then move into the thymic medulla, where either CD4 or CD8 expression is lost. If binding to the self MHC in the medulla results in a high-affinity interaction, these T cells are also eliminated, a process known as *negative selection.* Therefore, the majority of cells released from the thymus bind to self MHC without becoming activated; however, autoreactive cells occasionally escape thymic selection and serve as the etiology of diseases such as sclerosing cholangitis (see Chapter 41), autoimmune hepatitis (see Chapter 97A), and type 1 diabetes (see Chapter 101); thus additional regulation is required to prevent autoimmunity. In fact, a single interaction of TCR and antigen-bearing MHC is inadequate to trigger T-cell activation; rather, approximately 8000 TCR-MHC interactions over a period of several hours are needed to initiate activation (Kumagai et al, 1987; Rothenberg, 1996; Viola & Lanzavecchia, 1996), which further limits the likelihood of autoimmunity. Costimulatory molecules markedly alter this need for redundancy, and we discuss this below.

Immune responses are also regulated by accessory cell surface molecules that limit the types of cells with which a T cell can interact (Leahy et al, 1992; Saizawa et al, 1987). Parenchymal cells of the body express class I MHC and display internal cellular peptides within the binding groove of this molecule. T cells charged with destruction of diseased or infected parenchymal cells express CD8 that stabilizes TCR ligation with class I MHC. These cells are termed *cytotoxic T cells.* CD8+ T-cell killing can occur through either Ca^{2+}-dependent secretory mechanisms or Ca^{2+}-independent direct cell-contact mechanisms (Berke, 1995).

Hematopoietic cells express class I and class II MHC. Class II MHC displays peptide fragments that have been phagocytized from the extracellular space (Germain, 1994; Monaco,

1993). CD4 stabilizes the TCR–class II MHC interaction. CD4+ cells interact with dendritic cells, macrophages, and in some cases activated endothelial cells that display antigen. In addition, the resting sinusoidal endothelial cells of the liver have the ability to present antigen to T cells, making the liver an organ with considerable ability to evoke or suppress an immune response (Knolle & Gerken, 2000). The interaction between CD4+ T cells and APCs produces APCs that have the ability to martial CD8+ T cells (Lanzavecchia, 1998; Ridge et al, 1998). This process is mediated through upregulation of APC cell surface molecules known as *costimulation receptors,* thus APCs initiate an immune response but require CD4+ T cells to activate the primary effector arm of the acquired immune system—the CD8+ T cells.

An additional subset of T cells, regulatory T cells (T_{reg}), further control promiscuous immune responses. Regulatory T cells have the ability to suppress cytokine secretion, adhesion molecule expression, and costimulatory signaling. The most extensively studied population of T_{reg} cells express CD4 and CD25, the high-affinity α-chain of the interleukin (IL)-2 receptor (Wood & Sakaguchi, 2003). Animal models have suggested that these cells play a critical role in controlling immune activation (Baecher-Allan et al, 2001; Wood & Sakaguchi, 2003). The prevailing evidence suggests that T_{reg} is responsive to established inflammation, rather than serving a prophylactic role in preventing inflammation; however, harnessing the power of T_{reg} to quell counteradaptive immune responses such as rejection is an ongoing area of research in autoimmunity and alloimmunity.

Humoral Immunity

B cells recognize antigen in its native, unprocessed form (Cambier et al, 1994). When antigen binds to two cell surface antibodies, the antibodies are brought together in a process known as *cross-linking,* which stimulates B-cell proliferation and differentiation into an antibody-secreting plasma cell. The activation threshold for a resting B cell is relatively high, as it is for T cells. As with TCR recognition, costimulation can lower this threshold substantially (Tedder et al, 1994). B cells also have the ability to internalize antigen bound to surface immunoglobulins and process them for presentation to T cells along with costimulation molecules (Lederman et al, 1992).

Antibody structure is determined in the bone marrow through mechanisms similar to those that govern the generation of TCR diversity in the thymus (Gill & Gulley, 1994; Hozumi & Tanegawa, 1976). Five different heavy-chain loci (μ, γ, α, ε, and δ) on chromosome 14 and two different light-chain loci (κ and λ) on chromosome 2—each with V, D and/or J, and C regions—are brought together randomly by the RAG-1 and RAG-2 apparatus to form a functional antigen receptor (Kim et al, 2000). The basic antibody structure consists of two identical heavy chains and two identical light chains. The type of heavy chain used dictates the immunoglobulin (Ig) type: IgM, IgG, IgA, IgE, or IgD. The overall structure of the antibody results in two identical antigen-binding sites and a common region, the Fc portion. Bound antibody triggers activation of the complement cascade (Baldwin et al, 1995). In addition, most phagocytic cells have receptors for the Fc portion of IgG, allowing them to actively engulf antibody-coated cells.

Unlike the TCR, B-cell immunoglobulin loci undergo alteration after B-cell stimulation to improve the functionality of the secreted antibody. *Isotype switching* is the process of shifting from the initial heavy-chain IgM to one of four types to improve function and specialization. IgG is the most significant soluble mediator of opsonization and is the dominant antibody produced in response to alloantigen. IgA is important in mucosal immunity, IgE is involved in mast cell–mediated immunity, and IgD is primarily cell bound. After a B cell is activated, the specific D and J regions of the used heavy- and light-chain genes undergo random alterations of the antigen binding site. The resultant B cell clones have altered antigen affinity, hence the term *affinity maturation* (Griffiths et al, 1984); those clones that have higher affinity for the target antigen have a selective survival advantage and form the basis for a more vigorous response on reexposure to the antigen.

Mediators of Context: Costimulation and Cytokines

Isolated TCR binding with an MHC-peptide complex or antibody ligation with an antigen is not usually sufficient for lymphocyte activation. Receptor-ligand pairs on T and B cells and APCs, known as *costimulation receptors,* determine the character of the T-cell response (Fig. 96.1; Allison & Krummel, 1995; Chambers & Allison, 1997; Crawford et al, 2006). The type of costimulatory signal received by the lymphocyte determines whether the cell will become activated, remain quiescent, die, or become resistant to subsequent immune stimulation.

The biology of T-cell costimulation is substantially more developed than that of B cell costimulation. Examples of T-cell costimulation receptors include CD28 and CTLA4 (CD152). CD28 promotes T-cell activation and leads to the expression of CTLA4 that then promotes downregulation of the T-cell response; thus activation typically begets deactivation. The B7 molecules, CD80 and CD86, are the ligands for CD28 and CTLA-4 on professional APCs. Although B7 can bind to either receptor, their affinity for CTLA-4 is much greater; when B7 is in limited supply, the higher affinity interaction with CTLA-4 predominates. Because B7 molecules are not expressed by normal tissues, CD8+ T-cell interaction with class I self MHC does not elicit a proliferative response, rather it reinforces quiescence of autoreactive T-cell clones; thus in the absence of activated APCs, presenting antigen in the context of high concentrations of costimulatory molecules on the cell surface, T-cell activity is typically suppressed.

Although the mechanisms of costimulation have not been completely elucidated, it is known that binding of CD28 allows more efficient T-cell signal transduction. Through CD28-B7 interactions, the number of binding events required to trigger activation of a T-cell decrease from 8000 to 1500 (Rothenberg, 1996; Viola & Lanzavecchia, 1996). In contrast, when CTLA-4 binds B7, the T cell becomes incapable of producing IL-2 during the encounter and even in subsequent interactions (Blair et al, 1998). The CD19-CD21 complex provides comparable control of antigen receptor binding for B cells (Tedder et al, 1994).

Additionally, costimulation is mediated through another pair of receptors: CD40 found on dendritic cells, endothelium, B cells and other APCs, and CD154 on T cells and platelets (Armitage et al, 1992a, 1992b; Clark & Ledbetter, 1986; Noelle et al, 1992; Henn et al, 1998). The ability of APCs to stimulate a cytotoxic T-cell response is markedly augmented by the effects of CD40 binding. Following CD40 ligation, activating cytokines are released, and B7 molecules are upregulated (Bennett

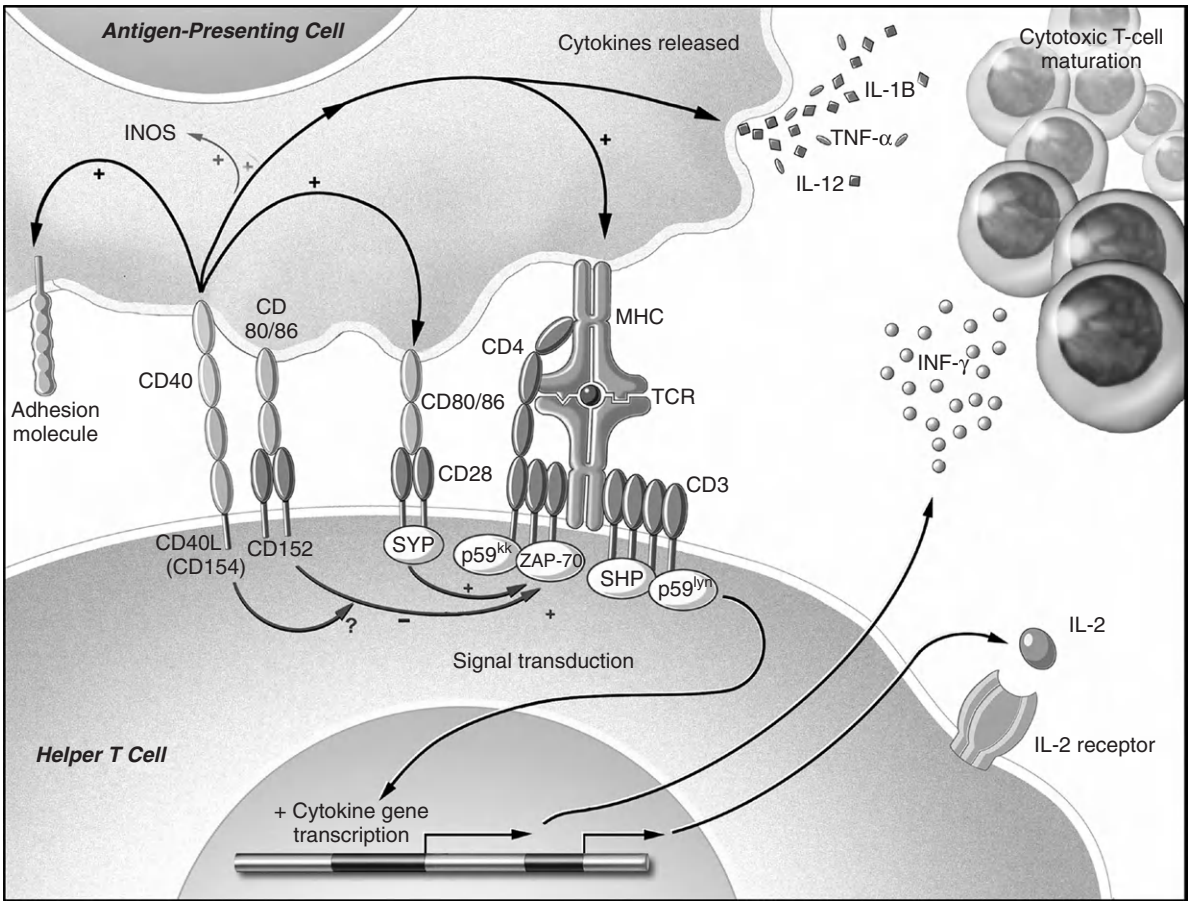


FIGURE 96.1. T-cell interactions with an antigen-presenting cell (*APC*). The T-cell receptor (*TCR*) is bound to class II major histocompatability complex (*MHC*) with the CD4 accessory molecule stabilizing the interaction. Depicted are selected costimulatory molecule interactions and the resultant effects on cytokine secretion and signal transduction. For example, CD40 ligation on the APC results in the induction of many critical APC functions, including increased MHC and B7 expression and cytokine secretion. Increased B7 expression allows CD28-positive regulation to override the negative regulation of CD152 (CTLA-4). This potentiates TCR signal transduction through CD3 and results in interferon (*IFN*)-γ and interleukin (*IL*)-2 synthesis. IFN-γ, along with APC-secreted cytokines, promotes cytotoxic T-cell maturation. IL-2 promotes T-cell proliferation in an autocrine fashion. INOS, inducible nitric oxide synthetase; TNF, tumor necrosis factor.

et al, 1998; Schoenberger et al, 1998). CD154 is upregulated after TCR ligation and provides positive feedback to the APC. In addition, CD154 is found in and released by activated platelets at sites of endothelial injury (Henn et al, 1998); therefore sites of trauma that recruit platelets create an environment of activating costimulatory molecules, thereby bridging the innate and acquired immune systems (Czapiga et al, 2004).

Direct cell-cell contact is not the only means by which immune cells communicate. Soluble mediators of communication known as *cytokines,* or *interleukins,* are polypeptides that are released from many cells; they can either activate or suppress adjacent cells (Arai et al, 1990), and the pattern of cytokine expression is thought to influence the resultant type of T-cell response (Mosmann et al, 1986; Mosmann, 1991). Once activated, T cells have been described by one of two cytokine-secretion phenotypes (see Chapter 10): cytotoxic T-cell responses are characterized by expression of interleukin (IL)-2, IL-12, IL-15, and interferon (IFN)-γ and are known as *Th1 cells;* T cells that promote humoral or eosinophilic responses are characterized by secretion of IL-4, IL-5, IL-10, and IL-13 and are known as *Th2 cells.*

In addition to cytokines, other soluble mediators of inflammation are capable of promoting increased blood flow and improved exposure of an area of injury to innate and acquired immune elements. It has been recently suggested that the APCs of the liver are more efficient in generating Th2 responses and that this may be a mechanism by which liver allografts avoid late cellular rejection.

TRANSPLANT IMMUNITY

T-cell responses to allogeneic organs are largely the result of nonphysiologic TCR-MHC interactions. T cells are initially selected to bind to self MHC and are then eliminated, if that binding event leads to activation; however, this sequence of events does not preclude the survival of cells that, through chance, bind to the MHC molecules of another individual, one with inappropriate affinity. The discrepancies between self TCR selection and allo-MHC interactions are the basis for most transplant recognition. This nonphysiologic recognition provides the opportunity for a detrimental immune response but does not mandate it in the absence of additional contextual

requirements for immunity-like costimulation; thus alloimmunity is more likely than autoimmunity but is not mandated in the absence of costimulation, innate immunity, and other factors that elicit a physiologic immune response.

Most of the significant sequence polymorphism of MHC is located in the areas of the molecule that interact with the TCR, and individual variation in the sequence at the MHC-TCR interface defines alloreactivity. The lack of recipient T-cell thymic education with donor MHC leads to a nonphysiologically high frequency of alloreactive peripheral T cells. Many of these cells are crossreactive with antigen encountered during prior viral exposures, or even with autoantigens, as in the case of autoimmune disease. This is known as *heterologous immunity,* and it results in a situation whereby recipients have allospecific memory without having been exposed to the alloantigen (Adams et al, 2003). Thus a person's immune response to a donor is the product of the individual's MHC makeup and past immune exposures. This can lead to vigorous early rejection in apparently nonsensitized recipients.

T cells recognize alloantigen via their TCR in two distinct ways: either directly, by binding to donor MHC on transplanted tissues in the presence of donor costimulation, or indirectly, through self APC that has phagocytized and processed alloantigens to be presented, bound to self MHC and costimulation (Rogers & Lechler, 2001). In the case of transplanted organs, surgical trauma and ischemia exacerbate the potential for T-cell activation by causing class I and class II MHC upregulation (Gerritsen & Bloor, 1993). In addition, adhesion molecules and costimulation molecules are upregulated perioperatively (Takada et al, 1997; Hoffmann et al, 2002).

Initial T-cell binding to donor cells is nonspecific, mediated by adhesion molecules upregulated during donor cell activation (Fuggle & Koo, 1998). CD40 on donor APCs and endothelial cells is important in mediating cell activation in this setting via CD154 on T cells and activated platelets (Henn et al, 1998). Following nonspecific adhesion, MHC recognition occurs in the relatively high costimulation environment induced by surgical trauma and ischemia (Takada et al, 1997). Once alloreactive T cells are activated, they secrete cytokines, including IL-2 and IFN-γ, and they stimulate APCs to secrete IL-12 (Arai et al, 1990; Kirk et al, 1995; Krams et al, 1992). The resultant cytokine milieu recruits more T cells to the site of injury and potentiates clonal expansion. Secretory and cell contact–dependent mechanisms, perforin/granzyme and Fas mechanisms, respectively, are involved in T-cell cytotoxicity within the graft, resulting in graft destruction (Strehlau et al, 1997). Although acute rejection is the result of T-cell activation, antibody responses accompany many episodes. Cellular and soluble components of immunity mediate multiple distinct clinical rejection syndromes through cytokine mediated toxicity, cellular cytotoxicity, and direct effects of antibody and complement.

Clinical Rejection Syndromes

Hyperacute Rejection

Hyperacute rejection (HAR) is caused by donor-specific antibody that exists at the time of transplantation as a result of prior exposure to donor antigens or to antigens with crossreactivity. It develops precipitously within minutes to hours after graft reperfusion. Typically, HAR is avoided by confirming ABO compatibility and performing a crossmatch using techniques that detect donor-specific antibodies. When clinically relevant donor-specific antibodies are detected, graft survival is significantly decreased for most organ types (Noreen et al, 2003); however, the liver has long been regarded as relatively resistant to HAR, and crossmatching is often done only retrospectively (Neumann et al, 2001). Actually, the rates of acute rejection and long-term liver survival are similar among groups with a positive or negative crossmatch; this does not hold true for ABO-incompatible liver allografts (Egawa et al, 2004).

The role of antibody in liver transplantation remains an area of investigation at present. Unfortunately, the pancreas does not have similar resistance to HAR, and a positive crossmatch represents an absolute contraindication to pancreas transplantation. Although high titer antibodies mediate rapid graft injury, chronic exposure to lower titer antibody results in indolent graft damage, particularly in the case of the pancreas. The role of chronic alloantibody in liver transplantation remains controversial but likely mediates some degree of graft injury over time. Autoantibody directed against nonpolymorphic determinants of a graft is increasingly being recognized as detrimental in pancreas transplantation with recurrent β cell–specific autoimmunity responsible for at least some late graft loss after pancreas transplantation (Vendrame et al, 2010). Recurrent autoimmunity is also relevant in autoimmune hepatitis (Hytiroglou et al, 2009).

Acute Rejection

Acute rejection is most common between 4 days and 6 months after transplantation, and rejection that occurs during this time is considered *early acute rejection;* acute rejection after 6 months is considered *late acute rejection.* Liver allografts undergo acute rejection at a rate of approximately 24% to 47% (Fisher et al, 2004; Neuhaus et al, 2002; Wiesner et al, 2001), whereas pancreas allografts in the modern era (post 1995) undergo acute rejection at a rate of approximately 15% to 30%. These differences reflect a tendency toward less immunosuppression in liver patients, because the liver tolerates rejection better, perhaps because damaged parenchyma can regenerate. Also, liver rejection is more easily diagnosed than pancreas rejection through biopsy and serum enzyme measurements.

In both organs, acute rejection evolves over a period of days to weeks. After activation by either direct or indirect allorecognition, T cells infiltrate the allograft and initiate organ destruction through cytolysis and endothelial and ductular damage. Much of the acute graft dysfunction is likely mediated through the effects of macrophage-derived inflammatory cytokines that hinder parenchymal function without necessarily causing cell death (Girlanda et al, 2008), thus prompt treatment has the potential to quell the rejection prior to direct T-cell–mediated cytotoxicity. Usually acute liver allograft rejection is also accompanied by graft and peripheral eosinophilia (Barnes et al, 2003).

Early detection of acute rejection is critical to facilitate intervention prior to permanent T-cell–mediated parenchymal damage; therefore unexplained hepatic dysfunction should prompt a graft biopsy. In the case of pancreas allografts, usually no direct biochemical evidence of rejection is present. If the transplantation was performed with a kidney, rejection of the kidney precedes or signals concomitant pancreas rejection in approximately 80% of patients. In transplantations of pancreas alone, fever, abdominal pain, allograft tenderness, and elevations in serum amylase or lipase may be signs of rejection; however, many rejections occur without early symptoms (Stratta

et al, 1996). Hyperglycemia is a late complication in pancreas rejection, because acinar cells reject prior to β cells.

Prompt recognition of acute rejection is imperative, because prolonged rejection allows for recruitment of multiple arms of the immune system and consequently results in decreased efficacy of antirejection therapies directed against T-cell responses. T-cell–specific therapies can resolve acute rejection episodes in most cases, and steroids are the first-line agent in most centers. Typically, early acute rejection episodes have a negative impact on the long-term survival of an allograft, although the liver is relatively resistant to this effect (Dousset et al, 1998). In fact, even late acute rejection in liver transplantation has not been shown to influence long-term graft function (Junge et al, 2005). This greatly contrasts both early and late acute rejection episodes in pancreas transplantation, which have repeatedly been shown to be deleterious to long-term graft survival (Reddy et al, 2001; Tesi et al, 1994).

Chronic Graft Loss

The causes of chronic graft loss remain poorly characterized (Libby & Pober, 2001). Although called *chronic rejection*, it likely has nonimmune components and immune origins. Evolving over the course of months to years, chronic graft dysfunction remains resistant to conventional immunosuppressive therapies; regardless of the transplanted organ, it develops as fibrosis with modest lymphocytic infiltration. Monocytic and dendritic cell infiltrates predominate, and destruction of epithelial and endothelial structures is progressive.

Many aspects of chronic graft loss relate to the events surrounding transplantation, such as ischemic injury. In the liver, chronic graft loss manifests as *ductopenia*, or *vanishing bile duct syndrome* (Inomata & Tanaka, 2001), typically defined as a condition wherein less than 50% of portal triads contain bile ducts (Demetris et al, 1998). The rate of chronic graft loss is far slower for liver grafts than for other organs, likely because of the ability of the liver to regenerate following subtle injury. As the technical challenges of pancreas transplantation have been corralled, more grafts are being lost to chronic rejection (Humar et al, 2003), a significant portion of which may be related to recurrent autoimmune diabetes.

IMMUNOSUPPRESSION

To date, no single agent has been discovered that effectively prevents allograft rejection, although liver transplant recipients can often be weaned over time to a single-drug regimen. Similarly, all manipulations that limit rejection also increase susceptibility to infection and malignancy. No immunosuppressant is allograft specific; therefore the rational selection of immunosuppressants involves using multiple synergistic agents to prevent rejection without simultaneously crippling the recipient's defenses. Characteristically, liver allografts typically require less immunosuppression than other organs (Ramos et al, 1995). This has been proposed to be a function of the APCs in the liver, the sheer size and antigenic load of the liver, and its regenerative capacity. Indeed, recent evidence indicates that 10% to 20% of liver transplant recipients can eventually be withdrawn from all immunosuppressive drugs over a period of years (Martinez-Llordella et al, 2008). Importantly, no immunosuppressive regimen has clearly established itself as superior, and the therapies chosen remain variable from one center to another.

The immune system is most prone to reject an allograft perioperatively because of the surgical and ischemic injury associated with transplantation; therefore the most intense immunosuppression is given during the weeks that follow transplantation. A period of rigorous immunosuppression at the time of transplant is known as *induction therapy* (Kirk, 2006), which typically consists of T-cell–depleting strategies that, while effective, are too toxic to be administered long term. Maintenance immunosuppression is less potent but can be given chronically to prevent acute rejection for the life of the transplant recipient. Finally, agents used to halt ongoing rejection are known as *rescue agents*. The sites of action of various immunosuppressive agents are illustrated in Figure 96.2.

Corticosteroids

Corticosteroids have been a mainstay of transplant immunosuppression for over 40 years (Starzl et al, 1963). At low doses, glucocorticosteroids, typically prednisone or methylprednisolone, are used as maintenance immunosuppression; at higher doses, they can be used as rescue therapy. Although steroids are ineffective as monotherapy to prevent rejection, they have been effectively combined with other agents to improve graft survival. Unfortunately, the desirable immunosuppressive effects of steroids are counterbalanced by their contribution to transplant morbidity; therefore many ongoing efforts have sought to minimize or eliminate glucocorticosteroid use for maintenance immunosuppression. Many centers now rapidly wean liver allograft recipients off steroids, whereas most pancreas programs rely on low-dose steroids indefinitely, although steroid-free regimens are increasingly being used (Singh & Stratta, 2008; Tanchanco et al, 2008; Vessal et al, 2007).

The immunosuppressive mechanism of glucocorticosteroids was elucidated long after its clinical introduction (Auphan et al, 1995; Scheinman et al, 1995). After nonspecific cytoplasmic uptake, steroids bind to an intracellular receptor, enter the nucleus as a receptor-ligand pair, and increase the transcription of several genes, notably *IκBα*. This protein binds to and inactivates NFκB, an important transcription factor of T-cell and APC activation and cytokine production.

The NFκB pathway is an important amplification step in the T-cell and APC response, and blockade of this pathway results in diverse effects. Steroids decrease IL-1, tumor necrosis factor (TNF)-α, and IFN-γ transcription and also decrease MHC upregulation. Inhibition of phospholipase A_2 results in blockade of the entire arachidonic acid cascade, and steroids mute the entire inflammatory process and decrease the costimulatory environment; steroids also promote apoptosis of activated T cells and limit the signal transduction of many innate immune receptors, such as the TLRs.

Antiproliferative Agents

Azathioprine

The antimetabolite azathioprine (AZA) was the first immunosuppressant used in organ transplantation (Calne & Murray, 1961; Hitchings et al, 1950). AZA undergoes hepatic conversion to 6-mercaptopurine (6-MP) and then to 6-thio-inosine-monophosphate (6-tIMP). These derivatives alkylate DNA precursors and inhibit DNA synthesis. In addition, they can introduce chromosomal breaks and interfere with DNA repair mechanisms, and the ultimate effect is to deplete the cell of

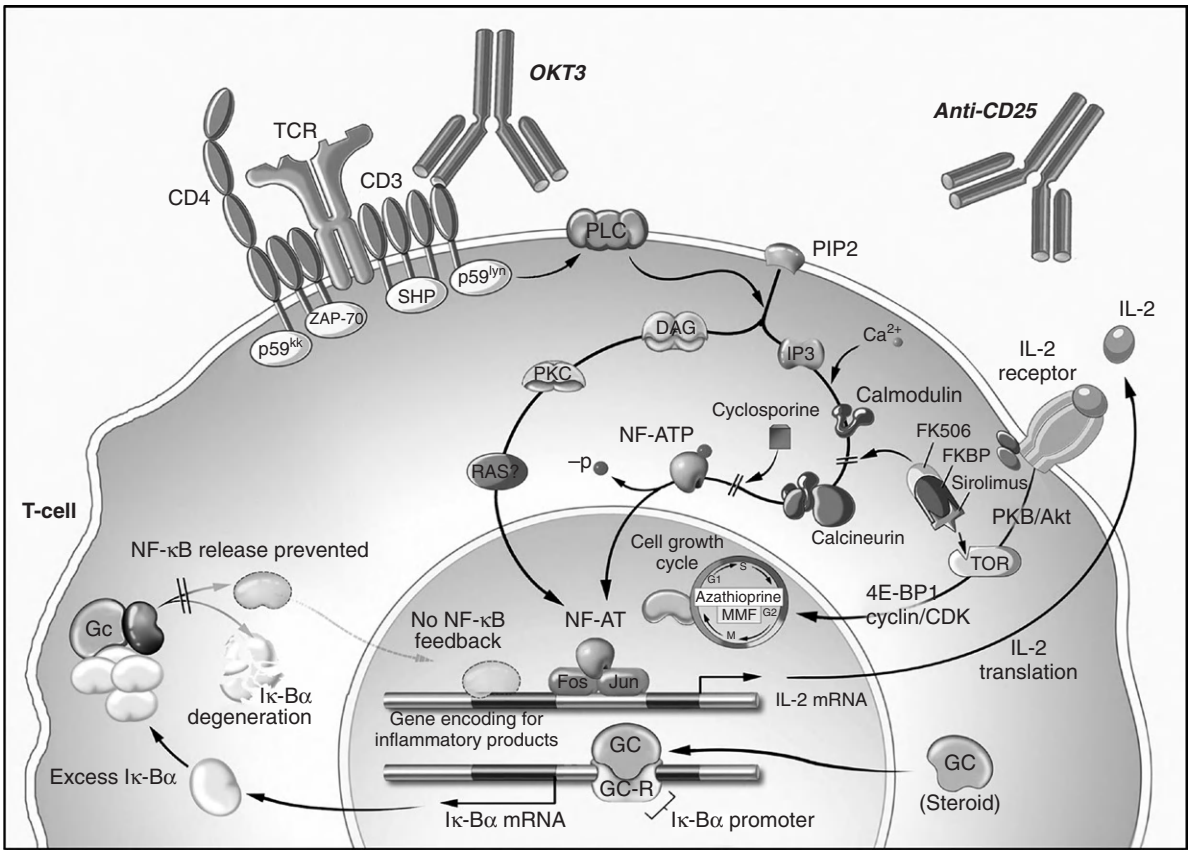


FIGURE 96.2. T-cell receptor (*TCR*) signal transduction and the sites of action of various immunosuppressants. TCR signal transduction proceeds through Ca^{2+}-dependent dephosphorylation of the nuclear factor of activated T cells (NF-*AT*), which enters the nucleus and, in conjunction nuclear factor (*NF*) κB, facilitates cytokine gene expression. Cyclosporine and tacrolimus (*FK506*) both inhibit signal transduction by blocking the ability of the calcineurin-calmodulin complex to potentiate NF of activated T cells (*AT*) dephosphorylation. The autocrine activity of interleukin (*IL*)-2 facilitates entry into the cell cycle and cell division. Sirolimus inhibits IL-2 receptor signal transduction by blocking the interactions of macrolide binding protein (*FKBP*). Mycophenolate (*MMF*) and azathioprine prevent cell cycling by altering nucleic acid metabolism. Steroids upregulate IκBα synthesis and inhibit the ability of NFκB to enter the nucleus. Monoclonal antibodies bind T-cell surface molecules and alter key interactions necessary for T-cell function. CD, Cluster of differentiation; CDK, cyclin-dependent kinase; 4E-BP1, 4E binding protein 1; IκBα, inhibitor of kappa light polypeptide gene enhancer in B cells, kinase alpha; OKT3, muromonab CD3; PIP_2, phosphatidylinositol diphosphate; PKC, protein kinase C; PKB/AKT, protein kinase B/AKT; PLC, phospholipase C; TOR, target of rapamycin.

adenosine. AZA works on all rapidly dividing cells, not only on lymphocytes; consequently, bone marrow, hepatic, and gastrointestinal toxicity are limiting factors. As monotherapy, AZA is ineffective and is rarely found in modern immunosuppressive regimens.

Mycophenolate Mofetil

Since 1995, mycophenolate mofetil (MMF) has been an approved immunosuppressant for use in adults (Platz et al, 1991). MMF is a morpholinoethyl ester of mycophenolic acid (MPA), a noncompetitive, reversible inhibitor of inosine monophosphate (IMP) dehydrogenase with improved bioavailability. MMF prevents a critical step in RNA and DNA synthesis by blocking guanosine monophosphate (GMP) formation from IMP by IMP dehydrogenase. In all cells except lymphocytes, there exists a "salvage pathway" for GMP formation. This crucial difference is exploited by MMF to produce a relatively lymphocyte-specific immunosuppressant. MMF blocks the proliferation of T and B cells and inhibits the formation of donor-specific antibody. Its introduction dramatically improved the success of pancreas transplantation; therefore it is used as an adjuvant immunosuppressive agent in most pancreas centers.

In liver transplantation, the use of MMF has continued to gain favor, because it allows a reduction in calcineurin inhibitors, the cornerstone of most immunosuppressive regimens. Presumably, this reduction mitigates the deleterious effects on renal function of calcineurin inhibitors in hepatic and pancreatic transplant recipients (Biselli et al, 2009). MMF combined with low-dose calcineurin inhibitors and corticosteroids have also been proven useful in decreasing episodes of acute rejection (Farkas et al, 2009). Its chronic use is typical in pancreas transplantation, and it plays at least a temporary role in most liver transplant regimens.

Calcineurin Inhibitors

Cyclosporine

Cyclosporine A (CyA) is a cyclic endecapeptide isolated from the fungus *Tolypocladium inflatum gams* (Borel et al, 1976; Kahan, 1994). Its introduction revolutionized transplantation and made extrarenal transplantation a viable reality. The mechanism of action of this T-cell–specific immunosuppressant is mediated through cyclophilin (Cn) binding. The CyA-Cn complex binds to the calcineurin-calmodulin complex and

prevents phosphorylation and activation of NF-AT, a transcription regulating factor. Blockade of NF-AT prevents IL-2 gene transcription. In addition, transforming growth factor (TGF)-α transcription is unregulated, and other genes critical for T-cell activation are altered (Khanna et al, 1996; Kirk et al, 1997). These and other effects may be responsible for the toxicity of CyA. Primarily, CyA blocks TCR signal transduction but does not inhibit costimulatory signaling (June et al, 1987). The effects of CyA can be overcome with high levels of IL-2, therefore once IL-2 is present in the graft, as in the case of ongoing rejection, CyA is rendered ineffective. Consequently, CyA is a maintenance immunosuppressant that has no role in rescue therapy.

CyA nephrotoxicity is a constant consideration in its use. Through a TGF-α mediated mechanism, CyA decreases renal blood flow by up to 30% (Khanna et al, 1996; Kirk et al, 1997). Increased transcription of endothelin also activates the renin-angiotensin pathway, leading to hypertension; the vascular effects of CyA may also delay resolution of hepatorenal syndrome; and CyA may lead to neurologic side effects, hypertrichosis, and malignancy (Hojo et al, 1999). In addition, metabolism of CyA through cytochrome P450 enzymes leads to multiple drug interactions.

Tacrolimus

Kino and colleagues (1987) first demonstrated the immunosuppressant effects of tacrolimus in 1987, and it has become the mainstay of most liver and pancreas transplant regimens. Tacrolimus is a macrolide antibiotic produced by *Streptomyces tsukubaensis*. Like CyA, tacrolimus blocks NF-AT activation and its downstream effects (Fruman et al, 1992). The intracellular target of tacrolimus is known as *FK-binding protein* (FK-BP). Similar to CyA, tacrolimus increases TGF-α transcription and therefore carries with it the benefits and toxicities of this cytokine (Khanna et al, 1996; Kirk et al, 1997). Although it is 100 times more potent than CyA in preventing IL-2 and IFN-γ transcription, its toxicities limit the dose to approximately 1% of CyA. In addition to its use as a maintenance agent, tacrolimus has been shown to have efficacy at high doses in reversing liver rejection episodes (Starzl et al, 1989).

As compared to CyA, tacrolimus has more pronounced neurologic side effects, such as mental status changes and tremors. Tacrolimus use also results in a higher rate of posttransplant type 2 diabetes, although it has fewer cosmetic side effects. Tacrolimus has been shown to be superior to CyA in preventing acute episodes of rejection, reducing the number of steroid-resistant acute rejections, and improving long-term graft and patient survival. For these reasons it has replaced cyclosporine as the first-line calcineurin inhibitor used in both liver and pancreas transplantation in most centers (Haddad et al, 2006). Because tacrolimus is metabolized by cytochrome P450 enzymes, drug interaction concerns are similar to those with CyA. In recent years, many liver transplant recipients have been successfully weaned to monotherapy tacrolimus, but this trend has not been seen in pancreas transplantation.

There is no doubt that calcineurin inhibitor therapy represents the current standard of care in solid-organ transplantation. Nevertheless, the improved outcomes have come at a considerable cost. The powerful immunosuppressive properties of these drugs have certainly revolutionized and improved both allograft and patient survival, and they have made liver and pancreas transplantation viable, long-term therapeutic options. They have also brought with them a host of side effects that have necessitated an entire field dedicated to their minimization or elimination.

mTOR Inhibitors

Sirolimus and Everolimus

Sirolimus and everolimus are macrolide antibiotics developed from *Streptomyces hygroscopicus* (Baker et al, 1978; Martel et al, 1977; Sehgal et al, 1975). Similar to tacrolimus, these agents bind to immunophilin FKBP12, also known as the *mammalian target of rapamycin* (mTOR). Unlike tacrolimus, these agents do not affect calcineurin activity (Dumont et al, 1990a, 1990b; Molnar-Kimber 1996). The primary effect of mTOR inhibitors is to inhibit IL-2 receptor signal transduction and not to block NF-AT nuclear translocation; therefore T cells are rendered incompetent against the proliferative effects of exogenous IL-2 (Kuo et al, 1992) but are still capable of IL-2 gene transcription.

The primary toxicities of mTOR inhibitors are hypercholesterolemia, hypertriglyceridemia, poor wound healing, thrombocytopenia, and oral ulcers. Currently, sirolimus carries an FDA black-box warning against its use in liver transplantation in the first 28 days postoperatively because of increased risk of hepatic artery thrombosis, thus its use in liver transplantation is limited to conversion regimens. In addition, sirolimus may have a direct hepatotoxic effect (Neff et al, 2004).

The principal manner in which mTOR inhibitors are being used is as an adjunct or alternative to calcineurin inhibitors, and mTOR inhibitors have been developed in recent years as antiproliferative agents for use in oncologic indications. As such, its use in patients transplanted for the treatment of hepatic malignancies is being investigated (Schnitzbauer et al, 2010; Toso et al, 2010; Vivarelli et al, 2010).

Antilymphocyte Agents

Antilymphocyte agents are commonly used in pancreas transplantation during the induction phase of immunosuppression (Niemeyer et al, 2002; Stratta et al, 2003). Their use in liver transplantation is sparse owing to the reduced immunogenic phenotype typical of liver grafts.

Antilymphocyte/Antithymocyte Globulin

A polyclonal antilymphocyte globulin (ALG) is produced by inoculating an animal, such as a horse or rabbit, with human lymphocytes and then collecting the serum and purifying the resultant IgG. This preparation contains antibodies of multiple epitope specificities directed against lymphocyte and other cell antigens (Gaber et al, 1998; Merion et al, 1998). In the United States, the common immunogen is thymocytes, and the resultant polyclonal antibody is rabbit antithymocyte globulin (RATG). These agents promote T-cell depletion through opsonization and complement-mediated lysis (Merion et al, 1998). They also have multiple nondepletional effects that inhibit T-cell activation and function, such as crosslinking costimulation and adhesion molecules and blocking TCR signal transduction through internalization of other cell surface receptors.

ALG and RATG can be used as induction and rescue agents. The primary function of these agents is to reduce the number of primary effector cells below the threshold required for acute rejection and to allow for slow repopulation after the immediate posttransplant period. Although RATG is generally

well tolerated, side effects include thrombocytopenia, increased viral disease, and transient cytokine release.

OKT3

Unlike polyclonal antibody preparations, monoclonal antibodies have single-target epitope specificity. Muromonab-CD3, better known as OKT3 (Orthoclone OKT3; Ortho Pharmaceuticals, Raritan, NJ), is a murine antibody directed against the CD3 signal transduction subunit of the TCR; it was the first monoclonal antibody approved for any use (Ortho Multicenter Transplant Study Group, 1985; Wilde & Goa, 1996). OKT3 mediates its effects by binding to CD3 and causing internalization of the TCR complex, thereby preventing antigen recognition (Marano et al, 1989; Wilde & Goa, 1996). Additionally, OKT3 opsonizes T cells, causing their activation and degranulation. This exhausts the cell, making it ineffective as an effector, but it also leads to OKT3's primary side effect: cytokine release syndrome (Chatenoud et al, 1990). Cytokine release can result in profound hypotension, pulmonary edema, and cardiac depression. Because of the relatively toxic side effect profile and the availability of other agents that accomplish the same purpose, OKT3 is no longer manufactured.

Anti–IL-2 Receptor α-Chain Monoclonal Antibodies

The high affinity α-subunit of the IL-2 receptor (CD25) has been the target of two monoclonal antibodies, daclizumab and basiliximab. CD25 is required for clonal naïve T-cell expansion and is therefore an attractive target for specific elimination of activated T cells (Goebel et al, 2000). Unlike OKT3, binding of the target epitope does not result in cytokine release, thus administration is generally well tolerated, although the antirejection effect is similarly modest. Daclizumab has recently been discontinued for use in the United States and Europe, and simulect is used in approximately a third of all pancreas and liver transplant centers.

Costimulation Blockade

As detailed earlier in this chapter, T cells not only require presentation of peptides in the context of self MHC, they require a second signal or costimulatory interaction to produce an effective and appropriate immune response. This is particularly true of naïve T cells that have never encountered antigen before. Both the CD154-CD40 and the CD28-CD80/86 pathways have been targeted in solid-organ transplantation with agents specifically designed to prevent these potentiating signals. Although promising in nonhuman primate trials, a drug targeting the CD154-CD40 pathway was abandoned after thromboembolic complications were reported. Although intense research continues pursuant to this pathway, the development of CD28-CD80/86 specific agents has advanced to the clinic.

Recently the development of belatacept, a high-affinity fusion protein specific for the B7 molecules CD80 and CD86, has been shown to be a viable costimulatory antagonist for use in renal transplant (Durrbach et al, 2010; Vincenti et al, 2010). It has also been shown to be an effective replacement for calcineurin inhibitors in selected patients and thus may find a role in liver and pancreas transplantation. Currently, trials are underway to investigate belatacept in liver and pancreas transplantation in combination with, and compared with, calcineurin inhibitor–based immunosuppression.

MAINTENANCE MINIMIZATION, IMMUNOSUPPRESSANT WITHDRAWAL, AND TOLERANCE

The benefit of organ replacement with transplantation carries with it the burden of chronic maintenance immunosuppression. Recently, numerous efforts have been made to decrease the amount of immunosuppression given to transplant recipients. The basic strategies being pursued in clinical and preclinical trials include minimization of maintenance immunosuppression through aggressive induction protocols, withdrawal of immunosuppression after the initial posttransplant period, and experimental strategies to facilitate immunologic tolerance.

The strategy of using depletional agents such as RATG to reduce the requirement for maintenance immunosuppression is gaining traction. Recently, another monoclonal depleting antibody has been investigated in liver transplantation. Alemtuzumab, a CD52-specific antibody, rapidly depletes T cells and, to a lesser degree, B cells and monocytes from the circulation and from secondary lymphoid organs. It is approved for the treatment of lymphoid malignancies and has been investigated off label in transplantation. Recently, it has been used with low-dose tacrolimus to prevent rejection in liver transplant recipients (Marcos et al, 2004; Tzakis et al, 2004). Similar efforts have been made using antithymocyte globulin induction therapy (Tchervenkov et al, 2004). Alemtuzumab depletion has also been used in pancreas (Kaufman et al, 2006), and this strategy has been used effectively in kidney transplantation (Calne et al, 1998; Kirk et al, 2003; Knechtle et al, 2003).

Steroid withdrawal is the goal for many transplant clinicians wishing to spare their patients from the numerous side effects associated with glucocorticosteroid dependence. Steroid withdrawal can be achieved in approximately 85% of liver transplant recipients at 3 months without a significant increase in acute rejection rates (Reding, 2000). Although attempts to withdraw steroids in patients receiving pancreas transplants have been less successful, with appropriate patient selection, up to 70% of pancreas transplant patients may be amenable to steroid withdrawal (Humar et al, 2000).

A modest percentage of liver transplant recipients can be completely withdrawn from all immunosuppressive agents (Benitez et al, 2009; Lee et al, 2009; Martinez-Llordella et al, 2007; Mazariegos et al, 1997). Although the periods of follow-up among withdrawal reports are highly variable, and the long-term incidence of chronic rejection and graft loss has not been defined, some recipients clearly are capable of spontaneously accepting liver allografts. The challenge remains to establish criteria for appropriate withdrawal from immunosuppression and to identify those individuals in whom drug withdrawal is a safe strategy. At present, the best predictor of successful drug withdrawal is long-term rejection-free survival on low-dose immunosuppression. Liver transplant recipients on single-drug therapy for more than 10 years are 10 times more likely to be withdrawn successfully compared with patients in the first 3 years after transplantation.

It is possible that signatures of recipient gene expression or other biologic parameters can identify a protolerant signature in liver transplantation patients (Martinez-Llordella et al, 2007). The majority of these targets are associated with NK and $\gamma\delta TCR^+$ T cells, which could be used to predict which liver

transplant patients might be successfully withdrawn from immune-modulating medications; however, no evidence suggests that pancreas transplant recipients can be withdrawn from immunosuppression.

The "holy grail" of transplantation is tolerance. From its conception (Billingham et al, 1953), *acquired allospecific tolerance* has been defined as the ability to maintain a functional allograft and an intact immune response without the need for any therapeutic drugs. Numerous strategies have been attempted in reaching this goal, but to date, all prospective attempts to create broadly applicable, reliable, and durable tolerance in humans have failed. Although the reasons are numerous and still in the process of being elucidated, the pursuit of tolerance will bring all the benefits of organ replacement therapy and eliminate its toxicity, namely chronic immunosuppression. Ongoing strategies include the manipulation of costimulation signals, depletional approaches, and techniques designed to induce mixed chimerism, a state in which elements of both the donor and recipient immune systems persist in one individual (Cosimi & Sachs, 2004; Harlan & Kirk 1999; Kirk, 2003).

Many have speculated that liver recipients are more likely to be rendered tolerant than other allograft recipients, and indeed the emerging results from immunosuppressive withdrawal trials suggest this to be the case. Reasons cited include the unique APCs in the liver (see Chapter 9), the liver's regenerative capacity, its shear antigenic bulk, and it tendency to seed the recipient's body with donor hematopoietic cells, perhaps overwhelming the recipient immune system into a state of clonal exhaustion (Starzl, 1998). Tolerance attempts in liver transplantation are likely to proceed in the coming years, and their results will be anticipated. In contrast, the pancreas has been considered an immunogenic organ with little capacity to regenerate or deal with immune insults. As such, pancreas allograft tolerance will be much less likely to be achieved in the near future with the current strategies available.

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SECTION II Indications

CHAPTER 97A

Liver transplantation: indications and general considerations

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OVERVIEW

The first human orthotopic liver transplantation was carried out by Starzl in 1963. In the subsequent 2 decades, only a relatively small number of grafts were placed, usually in moribund patients with end-stage disease, and survival results were disappointing; however, with increasing experience and confidence, results began to improve, and more patients were grafted. A major increase has been seen in both the number of transplant centers and the number of patients grafted. In both Europe and the United States, more than 6000 procedures are performed annually. Results are such that many centers are currently reporting 1-year survival rates in excess of 90% in elective cases.

It is difficult to identify any one cause for the increase in success. The contribution of better surgical and anesthetic techniques, improved postoperative care, and availability of better immunosuppressive agents have all contributed to the improvements in survival (see Chapter 97B). In addition, understanding of both indications and contraindications for the procedure have improved such that major surgery is not carried out in patients with virtually no chance of surviving, and patients are referred for transplantation at a stage when they are likely to have the greatest chance of success.

Increasing success of liver transplantation and the reduction in contraindications has meant that the number of potential recipients is increasing, while the number of donors in many countries is either remaining static or else actually falling. The increasing discrepancy between supply and demand means that the mortality of patients awaiting transplantation is increasing; patients who wait longer are sicker, and their chances of survival decreases, while resource utilization increases. Attempts to increase the donor pool by use of split livers, organs from selected non–heart-beating donors, and from living donors combined with a better understanding of the contraindications to grafts have had a significant impact but have not been sufficient to meet the need.

In North America and in some European countries, the method of allocation has been changed to one based on the patient's prognosis, such as the Model for End-Stage Liver Disease (MELD), with livers allocated to individuals based primarily on the likelihood of the recipient dying while awaiting transplantation. Use of this system has resulted in a major reduction in the mortality of patients awaiting liver transplantation without an appreciable effect on outcome after transplantation.

GENERAL INDICATIONS

In general, the indications for transplantation are relatively easy to define, although the application of these principles is often far more difficult. The two broad indications for grafting are a less than 1-year estimated survival of liver disease and a quality of life deemed unacceptable by the patient. The main contraindications to liver transplantation are numerous, and although some are relative, some are absolute.

Absolute Contraindications to Transplantation

- The patient is not fit enough to withstand surgery, for example, because of advanced cardiac or pulmonary disease.
- The patient is unlikely to survive the procedure, such as with active sepsis.
- Survival after transplantation may be too short to justify the risks of transplantation, as in the case of metastatic disease.
- Active alcoholism and substance misuse is present, evident by noncompliance with medical advice ascertained on psychiatrist or psychologist evaluation.
- The postoperative quality of life may be unacceptable to the patient, for example, as with severe, intractable depression.
- Surgery is technically impossible, as in patients with extensive venous thromboses.
- The patient does not wish to undergo the operation.

Relative Contraindications to Transplantation

- Age may be an issue, and age restrictions vary at transplant centers; biologic age, rather than chronologic, is more important.
- Cholangiocarcinoma is sometimes a contraindication; transplant may still be considered, but only in highly selected patients because of the high risk of early recurrence.
- Chronic or refractory infections may preclude transplantation, depending on the nature of the infection and whether it is amenable to cure with available therapy.
- Poor social support may be a contraindication, particularly in biologically older patients with prolonged recovery anticipated after transplantation.

The last decade has shown a changing pattern of indications for transplantation. The total number of patients grafted each year in North America has risen from 1713 in 1988 to 6319 in 2008. Similar observations have been reported in Europe. Over the decades, the practice of transplantation has undergone many changes: the proportion of patients grafted for alcoholic liver disease and viral hepatitis, especially hepatitis C virus (HCV), is rising; whereas the proportion of patients grafted for malignancy and cholestatic diseases is falling.

The use of living donors has not made a significant impact on the number of transplantations. According to United Network for Organ Sharing (UNOS), of the 6319 liver transplantations done in 2008, only 249 (3.9%) were from living donors, and in fact the proportion of living-donor grafts decreased from 10% in 2001 to 3.9% in 2008. In contrast to living donors, use of non–heart-beating donor livers from those who donate after cardiac death has been increasing (0.5% in 1998 vs. 5% in 2007). In addition, new indications for liver transplantation include those with replicative hepatitis B virus (HBV) and for those with human immunodeficiency virus (HIV) infection.

GENERAL ASPECTS

Nutrition

Malnutrition is a common finding in end-stage cirrhosis, with a prevalence of 81% (Caregaro et al, 1996). Malnutrition in these patients has many causes: the disease depletes the patient, and the situation is compounded by poor intake, malabsorption, and dietary restrictions that are often inappropriate. Malnutrition is associated with increased susceptibility to infection and poor healing. Although in liver disease, the degree of malnutrition may be difficult to quantify, malnourished patients fare poorly, with reported mortality of 15% (Campillo et al, 2003). Although no convincing evidence proves that improvement in nutrition alters the outcome, it seems prudent to optimize nutrition (Figueiredo et al, 2000), and it is sensible to correct vitamin and other nutrition deficiencies.

Psychologic Assessment

Transplantation is associated with major psychologic stress, both for the patient and the family. More than half of those in the liver transplant candidate population have a wide range of psychologic health problems (Day et al, 2009). Initially, many centers arranged for full psychologic and psychiatric assessment of all potential transplant candidates, but this is rarely undertaken. Chronic ill health, possible subclinical encephalopathy, and future uncertainties all combine to make it difficult to accurately predict a patient's outcome. In addition, when a history of psychiatric illness is present, expert assessment is required. Some patients with psychiatric illness that is unresponsive to therapy and those with a history of recurrent episodes of self-harm may not be suitable candidates for transplantation.

Age

There is no agreed upper age limit, but advanced age is associated independently with mortality after transplant (Burroughs et al, 2006). The concept of biologic age has superseded that of chronologic age, although the former cannot readily be defined or quantified.

Previous Abdominal Surgery

The presence of adhesions, especially in the presence of portal hypertension, adds considerably to the difficulties of surgery and may affect outcome, especially when this involves surgery to the biliary tree (Neuberger et al, 1999).

Infection

Active bacterial, fungal, or protozoal sepsis is an absolute contraindication to transplantation, but once appropriate therapy has been instituted, the patient may become a suitable candidate for the procedure.

Human Immunodeficiency Virus

Although early studies showed patients with HIV infection fared poorly (Rubin et al, 1987; Tzakis et al, 1990), with the introduction of highly active antiretroviral therapy (HAART), the natural history of HIV infection has been greatly altered (Roland & Stock, 2006), although patients with hepatitis C virus (HCV) coinfection are at high risk for developing end-stage liver disease (Graham et al, 2001). Short-term outcomes in patients with HIV are encouraging (Fung et al, 2004), but the procedure remains limited to a few centers. Indications are becoming better defined (Samuel et al, 2003) and include 1) end-stage liver disease, 2) low or undetectable levels of HIV RNA, 3) no autoimmune deficiency syndrome (AIDS)-defining complication, and 4) a CD4 count greater than 200/mL.

Cardiovascular Disease

As with other diseases, the prognosis of patients with cardiovascular diseases will dictate whether liver replacement is an appropriate therapy. Multivessel, moderate to severe coronary artery disease is present in 15% of patients with end-stage liver disease (Tiukinhoy-Laing et al, 2006). Preoperative assessment of cardiovascular status is, at best, imprecise, as no clear guidelines exist to define limits below which grafting is unsafe. When it is possible to correct coronary artery disease, this should be undertaken prior to transplantation.

Respiratory Function

Arterial hypoxemia, an oxygen saturation less than 92% or arterial oxygen pressure less than 70 mm Hg, may be found in

up to 70% of patients with liver disease. Several possible causes for this hypoxemia include ventilation-perfusion mismatch, diffusion limitation, alveolar hypoventilation, shunt, and diffusion-perfusion abnormality (Krowka & Cortese, 1990). Furthermore, pulmonary dysfunction is present in up to 2% of patients with advanced liver disease. The presence of significant pulmonary disease is usually apparent on history and examination, but significant pulmonary disease may be cryptic. The many possible causes for these abnormalities include 1) diseases unrelated to the liver, such as those caused by smoking; 2) organic liver disease, such as α_1-antitrypsin deficiency; 3) respiratory conditions associated with certain liver disease, such as fibrosing alveolitis associated with primary biliary cirrhosis; 4) the effects of the liver disease on respiratory function, such as ascites that causes a pleural effusion or simple lung compression; 5) hepatopulmonary syndrome, and 6) portopulmonary hypertension.

Hepatopulmonary Syndrome

Hepatopulmonary syndrome is characterized by abnormal intrapulmonary vascular dilation (Hoeper et al, 2004). Clinically, it encompasses a triad of arterial deoxygenation, intrapulmonary vascular dilation, and liver disorder. The diagnosis is suggested by showing orthodeoxia, a fall in arterial blood oxygen when standing, and the presence of intrapulmonary shunting, demonstrated by either bubble echocardiography or nuclear medicine scanning.

Portopulmonary Hypertension

Portopulmonary hypertension results from pulmonary vasoconstriction and leads to vascular remodeling, which results in pulmonary hypertension (Hoeper et al, 2004). Diagnostic criteria include presence of liver disease that results in portal hypertension; mean pulmonary arterial pressure of more than 25 mm Hg at rest or 30 mm Hg during exercise; mean pulmonary artery occlusion pressure of less than 15 mm Hg; and pulmonary vascular resistance more than 240 dyn/sec/cm^{-5} (Krowka, 2003).

Routine screening of patients with chest radiograph, electrocardiogram (ECG), lung function tests, and measurement of peripheral oxygen saturation will usually identify those with pulmonary problems. Additional investigations include assessment of arterial blood gases—both lying and standing, to detect hepatopulmonary syndrome—and on 100% oxygen, to detect shunting; imaging with high-resolution computed tomography (CT) scanning, contrast-enhanced echocardiography, and isotope-labeled macroaggregated albumin lung scan are also helpful. Pulmonary angiography and right-heart catheterization may also be indicated as suggested by the clinical and simple investigations.

No clear guidelines are available that establish when liver transplantation is contraindicated because of pulmonary disease (Krowka et al, 2004). A preoperative partial pressure of oxygen of less than 50 mm Hg and a lung scan with brain uptake of more than 20% (Arguedas et al, 2003) strongly predict mortality, although these patients may be candidates for a triple transplant of heart, lung, and liver. Similar considerations apply to those with cystic fibrosis, cystic lung disease, and liver disease. Long-term oxygen therapy is the most frequently recommended therapy for symptomatic hypoxemic patients, but the use of drugs and transjugular intrahepatic shunt (TIPS) requires validation in this setting.

COEXISTING DISEASE

The presence of coexisting disease may affect the decision to offer the patient a liver graft, either because the prospects of recovery are adversely affected, or because long-term survival may be reduced (Volk et al, 2007). Diabetes mellitus (DM) is commonly found in patients with chronic liver disease, especially in those with HCV infection. DM may occur as a consequence of the insulin intolerance associated with advanced liver disease; if so, it will resolve after successful transplantation. Concerns for those with diabetes center upon the possible microvascular complications. Evidence of a proliferative retinopathy, diabetic nephropathy, or autonomic neuropathy—evidenced by simple tests, such as abnormal beat-to-beat variation on Valsalva maneuver or postural hypotension—may be relative contraindications for transplantation. The presence of advanced microvascular disease puts the patient at risk of major autonomic disruption during the procedure, and the survival of such patients is relatively poor (Haydon & Neuberger, 2001).

Hyponatremia is a common finding in patients with advanced chronic liver disease, and it usually occurs either as a consequence of injudicious diuretic therapy or because of the reduced free-water clearance. Grafting patients with severe hyponatremia (serum sodium <120 mmol/L) has shown an increased risk of central pontine myelinolysis (Yun et al, 2009). Significant hyponatremia should be corrected prior to transplantation, either by simple water restriction and, if appropriate, cessation of diuretic therapy or, if more rapid correction is required, by use of renal support (Elias & McMaster, 1987). The role of aquaretics may also be helpful in this situation (O'Leary & Davis, 2009).

Vascular thromboses are not uncommon in patients with chronic liver disease. These may occur as a consequence of the cirrhosis itself or as part of an associated underlying thrombotic tendency; for example, the myeloproliferative disease associated with Budd-Chiari syndrome, the presence of lupus anticoagulant, deficiency of proteins C or S, or impaired fibrinolysis. In early series, portal vein thrombosis was considered to be a contraindication to transplantation, but it is now appreciated that this is no longer the case, and portal venous inflow to the graft can be provided by the superior mesenteric vein or even by a splenic vein. It is only in those rare patients in whom venous thrombosis is extensive, and where it is impossible to provide a suitable portal supply to the graft, that transplantation is actually contraindicated.

Renal disease may occur either as a consequence of the hepatorenal syndrome or as a result of intrinsic kidney damage. In the hepatorenal syndrome, the kidney is not structurally damaged, and once good liver function is reestablished, the kidney will function normally; so although the prognosis may be poorer in the presence of advanced renal insufficiency (Rimola et al, 1987), the hepatorenal syndrome is not an absolute contraindication to transplantation. When coexisting advanced renal disease is evident, it may be advisable to consider combined liver and kidney transplantation, as renal function remains a major predictive factor for the outcome after transplantation (Nair et al, 2002). It is uncertain whether pretransplant correction of renal parameters—for example, by dialysis—is associated with an improvement in survival.

Past history of malignancy is a relative contraindication to transplantation, because the effect of surgery and the consequent immunosuppression may predispose the patient to early recurrence of tumor (Penn, 1993; Saigal et al, 2001). In 1993,

Box 97A.1

Effect of Immunosuppression on Tumor Recurrence

Low Recurrence Rates (0%-10%)

Incidentally discovered renal tumors
Lymphoma
Testicular carcinoma
Uterine carcinoma
Cervical carcinoma
Thyroid carcinoma

Intermediate Recurrence Rates (11%-25%)

Uterine body carcinoma
Wilms tumor
Colon carcinoma
Breast carcinoma
Prostate carcinoma

High Recurrence Rate (>26%)

Bladder carcinoma
Sarcomas
Melanoma
Symptomatic renal carcinomas
Myelomas
Nonmelanoma skin cancers

This list is derived from patients undergoing renal transplantation and should be used only as a guide when applied to those patients.

From Penn I, 1993: The effect of immunosuppression on pre-existing cancers. Transplantation 55:742-747.

Penn identified those tumors that have a high risk of recurrence after transplantation (Box 97A.1). Most centers will offer transplantation when the risk of recurrence is below 10% at 5 years; however, recurrence rates with other kinds of malignancies—colorectal cancer (18.8%), nonmelanoma skin cancers (23.5%), thyroid carcinoma (25%), oral squamous carcionoma (33%), vulvovaginal cancers (33%), and breast carcinoma (33%)—are associated with a higher risk following liver transplantion (Benten et al, 2008). In only exceptional cases should patients with any of the above extrahepatic malignancies be considered suitable candidates for transplantation.

Bone Disease

Many patients with chronic liver disease will have bone disease. The occurrence of osteomalacia as a consequence of vitamin D malabsorption is low and can readily be corrected by parenteral administration of vitamin D; however, osteoporosis is a far greater problem and is particularly seen in female patients with chronic cholestatic disease. In many cases, successful transplantation will halt or retard the progression and may even improve bone mineralization (Guichelaar et al, 2007). The presence of severe osteoporosis may result in additional complications in the presence of significant thoracic or lumbar vertebral collapse or fractures. The development of severe osteoporosis may well be an indication for transplantation in itself.

SPECIFIC DISEASES

Fulminant Hepatic Failure (See Chapter 97C)

In recent years it has been realized that liver transplantation is an effective form of therapy for patients with fulminant hepatic failure (FHF), that is, the presence of encephalopathy occurring within 8 weeks of the onset of symptoms in a patient with previously normal liver (Peleman et al, 1987; Chapter 97C). FHF requiring transplantation accounts for less than 5% of liver transplantations. In those with severe FHF and grade 4 hepatic encephalopathy, the mortality approaches 80%. Common causes of FHF include paracetamol (acetaminophen) overdose; viral infections, such as hepatitis A, B, E, and rarely C; drug and xenobiotic toxicity, including those caused by herbal remedies; Wilson disease; and liver diseases of pregnancy.

Patients with FHF develop early multiorgan failure and require intensive supportive therapy. The common causes of death are cerebral edema, multiorgan failure, sepsis (bacterial or fungal), cardiac arrhythmia or arrest, and respiratory failure (Ostapowicz et al, 2002). Indeed, FHF poses a difficult problem, because the window is very narrow between the time when it is apparent that the patient's survival is likely to be poor in the absence of transplantation and the onset of irreversible complications that preclude a successful outcome.

Several groups have now published prognostic factors, and based on those, criteria for super-urgent transplantation in the United Kingdom have been published; these are listed in Table 97A.1 (Bismuth et al, 1987; Neuberger et al, 2008; O'Grady et al, 1989). The King's College model has been validated in other centers and was found to be robust, although it is likely that with advances in the medical management of patients with FHF, these prognostic factors will require modification. The inclusion of serum lactate in the King's College prognostic criteria provides greater accuracy (Riordan & Williams, 2002).

Contraindications to transplantation in FHF include the onset of irreversible complications; thus the development of irreversible cerebral edema—characterized either by prolonged, documented elevations of intracranial pressure (ICP) or the presence of fixed dilated pupils for more than 6 hours—precludes transplantation. Active sepsis is also a contraindication.

One of the best guides to progression is given by serial estimation of the prothrombin time (Harrison et al, 1990) or factor V levels (Bernuau et al, 1986), because in the absence of extraneous blood products, these best represent the synthetic function of the liver. Initial improvement in the prothrombin time followed by deterioration suggests the presence of sepsis; therefore such patients should no longer be considered potential candidates. In addition, the patient remains at risk of developing complications related to raised ICP for up to 48 hours after successful transplantation (Dabos et al, 2004; Keays et al, 1991).

Because of the prognostic importance of clotting parameters, patients with FHF should not be given clotting factors until the decision for transplantation has been made; unless, of course, pressing clinical reasons are apparent. Once the decision for transplantation has been made, clotting should be normalized as much as possible within the constraints of volume replacement and avoidance of the complications of intracerebral edema. The ability to give large volumes of fluid may be limited by impaired renal function, but the presence of renal support will allow fluids to be taken off more rapidly.

Because many of the extrahepatic manifestations of FHF may be a consequence of the presence of large amounts of necrotic tissue, some centers have advocated the use of a two-stage procedure, whereby the failed liver is removed, and the patient remains anhepatic until a suitable graft can become available (Ringe et al, 1993). Although there is little doubt that

Table 97A.1

Current Transplant Criteria in the United Kingdom for Registration as a Super-Urgent Transplantation for Fulminant Hepatic Failure

Category	Etiology
1	Acetaminophen poisoning with pH <7.25 >24 h after overdose and after fluid resuscitation
2	Acetaminophen poisoning with PT >100 sec, or INR >6.5 and serum creatinine >300 mmol/L, or anuria and grade 3 to 4 encephalopathy
3	Acetaminophen poisoning with serum lactate level >24 h after overdose >3.5 mmol/L on admission or >3.0 mmol/L after fluid resuscitation
4	Acetaminophen poisoning with 2 of the 3 criteria from category 2 with clinical evidence of deterioration (e.g., increased ICP, FiO_2 >50%, increasing inotrope requirements) in the absence of clinical sepsis
5	Seronegative hepatitis, hepatitis A, hepatitis B, or an idiosyncratic drug reaction with PT >100 sec or INR >6.5 and any grade of encephalopathy
6	Seronegative hepatitis, hepatitis A, hepatitis B, or an idiosyncratic drug reaction; any grade of encephalopathy; and any three from the following: unfavorable etiology (idiosyncratic drug reaction, seronegative hepatitis), age >40 years, jaundice to encephalopathy time >7 days, serum bilirubin >300 mmol/L, PT >50 sec or INR >3.5
7	Acute presentation of Wilson disease or Budd-Chiari syndrome, a combination of coagulopathy, and any grade of encephalopathy
8	Hepatic artery thrombosis on days 0 to 21 after liver transplantation
9	Early graft dysfunction on days 0 to 7 after liver transplantation with at least two of the following: AST >10,000 IU/L, INR >3.0, serum lactate >3 mmol/L, absence of bile production
10	Severe liver failure in any liver donor within 4 weeks of a donor operation

AST, aspartate aminotransferase; FiO_2, inspired oxygen concentration; ICP, intracranial pressure; INR, international normalized ratio; PT, prothrombin time

Modified from Neuberger et al, 2008: Selection of patients for liver transplantation and allocation of donated livers in the UK. Gut 57(2):252-257.

following hepatectomy, the patient's condition may well improve, few convincing data are available at present to suggest that this approach improves outcome; however, such a procedure may be indicated in a patient who is rapidly deteriorating for whom a graft has been found, but logistic conditions may enforce some delay before the graft can be successfully performed.

One of the dilemmas in considering liver transplantation in patients with acute liver failure is that if the liver does recover, a complete return to normal structure and function is likely. The use of auxiliary transplantations, such as auxiliary partial orthotopic liver transplantation, or partial transplantations may allow the earlier use of liver grafting as a safety net; because if the patient's liver does recover, the donor liver can be removed or allowed to atrophy, and the patient can return to a life of good liver function free of immunosuppression. The use of artificial liver support devices (Chapter 72) remains uncertain, but systems such as the molecular absorbent recirculation system (MARS; Gambro AB, Sweden) may offer a bridge to transplantation (Mitzner et al, 2002).

Table 97A.2

Inborn Errors of Metabolism that Have Been Treated by Liver Transplantation

Liver Affected	Other Organs Also Affected
α_1-Antitrypsin deficiency	Primary hyperoxaluria
Wilson disease	Crigler-Najjar syndrome
Protoporphyria	Primary hypercholesterolemia
Tyrosinosis	Niemann-Pick disease
Tyrosinemia	Sea-blue histiocyte disease*
Galactosemia	Hemophilia A and B
Glycogen storage disease types I and IV	Protein C deficiency
Byler disease	Protein S deficiency
Hemochromatosis*	
Cystic fibrosis	
Gaucher disease*	
Urea cycle enzyme deficiencies	

*May recur after transplantation

Patients who develop FHF as a consequence of paracetamol overdose pose a special problem. Those with a long history of psychiatric disease that has been unresponsive to full intervention and support and those with a history of recurrent overdose are not usually appropriate candidates. Many patients who are seen for acetaminophen overdose have taken the drug often on an impulse because of a relatively trivial problem. In such cases, it is appropriate to offer these patients transplantation. In contrast, if the overdose is taken as a consequence of long-term social or domestic problems, it is possible that even after successful grafting, the patient will return to identical problems with the additional burden of a liver transplantation and its consequences; in this setting, grafting may not be appropriate.

Metabolic Diseases

A number of metabolic diseases account for less than 5% of liver transplantations in adults, and these may be corrected by liver transplantation (Table 97A.2). In some cases, where the metabolic defect arises in the liver, transplantation will correct that defect. This is seen, for example, with Wilson disease or hemophilia. In other conditions, such as some types of hypercholesterolemia, the metabolic defect occurs within the liver, but the heart is the organ affected. Some centers have advocated the use of liver transplantation to prevent the onset of severe coronary artery disease, although when cardiac disease is already present, combined heart and liver transplantations may also be performed. Similar considerations apply to hyperoxaluria that requires liver and kidney replacement. In other conditions, such as hemophilia, with alternative therapies such as replacement with factor VIII, transplantation should only be considered if liver disease is extensive, such as may occur with HCV infection transmitted via blood products.

The possibility of recurrence of the metabolic disease should not necessarily be considered a contraindication to transplantation; although the consequences of genetic hemochromatosis are likely to recur following transplantation, organ damage can be prevented by early recognition and treatment. Equally, in

erythropoietic protoporphyria, the disease is likely to recur following transplantation, but the morbidity of disease may be delayed by appropriate treatment with cholestyramine. In these instances, the decision to offer transplantation must be made with a view to the benefits obtained, and the indications remain similar to those in patients with other liver diseases.

Budd-Chiari Syndrome

The role of liver transplantation in patients with Budd-Chiari syndrome remains uncertain (Chapter 77). There may be underlying thrombotic disorders, such as deficiencies in proteins C or S, Factor V Leiden mutation, lupus anticoagulant, polycythemia, or myeloproliferative disorders; some of these will be corrected by transplantation, whereas others will carry the risk of complications, such as malignant transformation (Menon et al, 2004). The early use of anticoagulants and interventional radiology has changed the management of these patients (Darwish Murad et al, 2009). In general, transplantation should be considered when portal decompression has failed, when it is not feasible, or in the presence of established cirrhosis.

Chronic Liver Disease

In many ways, patients with chronic liver disease pose the most difficult problems with respect to transplantation. The main concern lies not with whether the patient is a suitable candidate for transplantation but in deciding on the *appropriate time* to offer the patient the procedure. On the one hand, the fitter the patient, the greater the probability of surviving the procedure; on the other, the patient's life will have been shortened if the procedure is unsuccessful. In addition, if transplantation is offered too late, the chances of success are reduced.

Broadly speaking, two major indications exist for transplantation in patients with chronic liver disease: poor quality of life and poor estimated length of life. Assessment of quality of life is often difficult, because the quality of life that is unacceptable to one person may be acceptable to another. Furthermore, it is often very difficult to disentangle the effects of borderline encephalopathy and depression associated with the knowledge of chronic liver disease from the effects of the tiredness and lethargy that result from the liver disease itself. Some patients do adopt the "sick role," and even after successful transplantation, either the patient or the family is reluctant for that role to be abandoned.

Although intractable pruritus is a valid indication for transplantation, if all other measures for treatment are unsuccessful, lethargy often fails to improve and so is not, in itself, an indication; it is important to exclude extrahepatic disorders, such as coexistent myxedema or therapy that may cause lethargy. Recent evidence (Piche et al, 2005) suggests that ondansetron may be effective in improving the fatigue associated with chronic liver disease.

Most centers consider transplantation appropriate when the estimated length of life in the absence of transplantation is limited to 1 year; however, in practice, this is very difficult to assess for most patients (Box 97A.2). Mostly, chronic liver disease runs a fairly predictable course, although the patient's life may be threatened by unpredictable events, such as sepsis or variceal hemorrhage. It is for this reason that timing of transplantation remains an inexact science. A further feature to be considered is that many of the factors predicting a poor survival in patients with cirrhosis are different from those that predict outcome after transplantation.

The use of prognostic models have helped define those variables that predict outcome, but such models do have disadvantages. First, most prognostic models are defined from retrospective studies that use patient data either at referral or at a certain point in the course of the illness, and it may be inappropriate to reapply these models sequentially, unless time-dependent models are used. Second, models provide data for populations, and their application to an individual is limited by relatively wide confidence intervals. Nonetheless, the Child-Turcotte-Pugh (CTP) classification does provide a useful guide, although it may not be sufficiently detailed for estimation of short-term survival. The MELD score is also a useful marker of short-term prognosis and may be more accurate than the CTP score (Freeman et al, 2004; Olthoff et al, 2004). The onset of hepatic decompensation is often a useful clinical marker of a poor prognosis. Indications for consideration of transplantation are shown in Figure 97A.1 and Box 97A.2.

The development of complications may often precipitate referral for transplantation. Thus the development of severe ascites, spontaneous bacterial peritonitis, recurrent variceal hemorrhage, and intractable encephalopathy are all indications that hepatic reserve is limited (Gines et al, 1988; see Chapters 70, 72, 73, and 74). Both the CTP classification and the MELD score are relatively poor prognostic guides to survival after grafting; however, data suggest that transplantation of a patient with a MELD score less than 12 in those without malignancy is associated with a reduction in survival at 1 year (Neuberger, 2004).

Other centers have concentrated on functional tests of the liver (Chapter 2), and although tests such as the aminopyrine breath test, the monoethyl glycine xylidide (MEGX) test, and the galactosamine elimination clearance have their advocates, none has added greatly to clinical and serologic assessment, and none has been applied widely (Burdelski et al, 1991; Mericel et al, 1992).

Primary Biliary Cirrhosis

The prognostic criteria for transplantation in primary biliary cirrhosis (PBC) are well defined; it accounts for less than 5% of liver transplantations, and a decreasing trend has been observed. Since the early paper by Schaffner and coworkers (Shapiro et al, 1979), it has become clear that the serum bilirubin is the best guide to prognosis. Once the serum bilirubin exceeds 150 μmol/L, median survival in the absence of transplantation is approximately 18 months.

A number of prognostic models have been developed, including both static and time-dependent models (Neuberger, 1989), and these are helpful in defining those variables that predict survival, both in the absence of transplantation and following transplantation (Box 97A.3). From these models, an estimate of survival can be made; however, these models must be used with some care, because the confidence intervals are relatively wide, and any information derived from such models must be made in conjunction with clinical judgment. Ursodeoxycholic acid (UDCA) is now licensed for use in patients with PBC and is associated with a significant delay in transplantation. In most patients, there is a fall in serum bilirubin, but the prognostic models remain valid when applied 6 months after introduction of treatment.

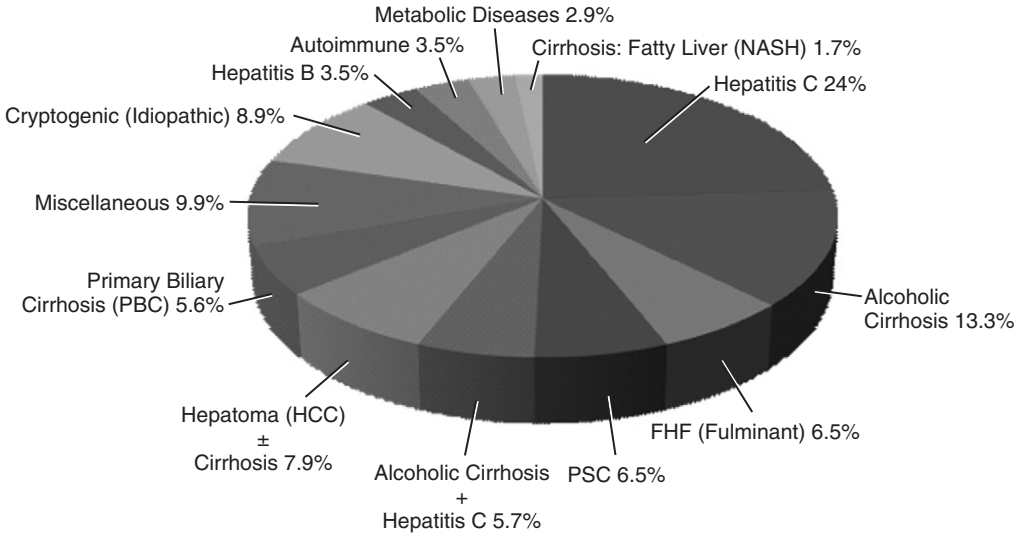


FIGURE 97A.1. Indications for liver transplantation. Based on the Organ Procurement and Transplantation Network cumulative 20-year data, from 1988 through 2008. FHF, fulminant hepatic failure; HCC, hepatocellular carcinoma; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

Box 97A.2

Indications for Transplantation in Patients with Cirrhosis

Symptoms

Hepatic decompensation
Hepatic encephalopathy
Increasing ascites
Recurrent variceal bleeding
Spontaneous bacterial peritonitis

Side Effects of Liver Disease

Increasing osteopenia
Hepatopulmonary syndrome
Intractable symptoms (itching or lethargy)
Development of hepatocellular carcinoma
Muscle wasting

Biochemical Markers

Serum albumin <30 g/dL
Serum bilirubin >50 µmol/L for parenchymal disease
Serum bilirubin >100 µmol/L for cholestatic disease
MELD score >17

MELD, Model for End-Stage Liver Disease

Box 97A.3

Prognostic Models for Estimating Survival in Patients with Primary Biliary Cirrhosis

European Model

2.52 × Log serum bilirubin (µmol/L)
+ 0.069 × (Age [yr] – 20)/10
– 0.05 × Serum albumin (g/L)
+ 0.88 (if cirrhosis present)
+ 0.68 (if central cholestasis present)
+ 0.52 (if not treated with azathioprine)

Mayo Model

0.871 × Log serum bilirubin (mg/dL)
– 2.53 × Log serum albumin (g/dL)
+ 0.039 × Age (yr)
+ 2.38 × Log prothrombin time (sec)
+ 0.859 × Edema score*

*0 for no edema, 0.5 for diuretic-controlled edema, 1 for diuretic-resistant edema

Transplantation in patients with PBC may also be indicated for intolerable and intractable pruritus; however, it is important that all therapies for pruritus be considered before transplantation is decided upon. The therapeutic options are increasing: cholestyramine is the mainstay, but trials of rifampicin, naltrexone, and either plasmaphoresis or MARS should be considered before transplantation is offered to those with good liver function.

The causes for lethargy in patients with PBC are numerous: depression is common and often responds to antidepressant medication. Celiac disease is found in 3% of patients with PBC (Kingham & Parker, 1998) and may cause lethargy if unrecognized and untreated. Low levels of antibodies to gliadin are common in patients with liver disease, so celiac disease should be tested for by measuring antiendomysial antitransglutaminase antibodies; in addition, a small bowel biopsy should be taken when these antibodies are present. Coexisting myxedema should be excluded by measuring serum thyroid-stimulating hormone (TSH), and the patient should be tested for Addison disease if appropriate.

Appropriate treatment of pruritis is important, because sometimes lethargy is caused by inappropriate use of antihistamines to control itching, sometimes it is caused by sleeping tablets. Cholestyramine is effective for the treatment of pruritus, if enough is taken for long enough; for those unable to tolerate the nausea or diarrhea associated with cholestyramine, a formulation without sorbitol, such as Questran Light, or colestid is effective. Other drugs that may be effective include rifampicin and naltrexone, and other remedies that may be beneficial include extraheptic biliary diversion, plasmapheresis, and MARS (extracorporeal albumin perfusion). In the cases of intractable pruritus, after other modalities have been tried and have failed, transplantation offers an extremely effective therapy: pruritus usually disappears within 2 to 3 days after surgery. In contrast, lethargy resolves more slowly and often incompletely.

Box 97A.4

Mayo Prognostic Model for Estimating Survival in Patients with Primary Sclerosing Cholangitis

0.535 × Log serum bilirubin (mg/dL)
+ 0.468 × Histologic stage*
+ 0.041 × Age (yr)
+ 0.705 × Splenomegaly†

*1 for stages 1 and 2; 2 for stages 3 and 4
†0 for absence, 1 for presence

In addition, PBC may recur in the allograft, but this is likely to be at a slow rate, and it should not preclude transplantation. Other extrahepatic manifestations of PBC will not be affected.

Primary Sclerosing Cholangitis (See Chapter 41)

In contrast to PBC, the natural history of primary sclerosing cholangitis (PSC) is far less clear and predictable (Ludwig et al, 1990) and accounts for about 6% of all transplantations. For many patients, the disease runs a fluctuating course with exacerbations and remissions that may be due to episodes of spontaneously occurring bacterial cholangitis. Underlying these fluctuations in liver function is a persistent and relentless progression toward liver failure.

As with other chronic liver diseases, serum bilirubin and serum albumin remain useful markers of progression, and prognostic models will help in timing the procedure (see Box 97A.4). The CTP classification and MELD score are as reliable as the Mayo model (Shetty et al, 1997; see Chapter 70B).

Most cases of PSC are associated with inflammatory bowel disease, usually ulcerative colitis. Patients with PSC and colitis are at increased risk of colonic cancer, compared with those with colitis alone; because the cancers tend to be in the ascending colon, a full colonoscopy is recommended in all potential transplant candidates to exclude colonic neoplasia and to assess the degree of colitis. Quiescent colitis is not a contraindication to transplantation, but active colitis should be treated before transplantation. When surgical treatment is required to control the colitis, this can safely be done at the time of the transplant procedure. Colectomy either before or during transplantation confers a protective effect against recurrent PSC in subsequent grafts (Alabraba et al, 2009).

PSC is a premalignant condition with the patient at increased risk of developing cholangiocarcinoma in any part of the biliary tree (Rosen & Nagorney 1991), and up to 20% of patients with PSC may develop a cancer, especially smokers (see Chapter 50A). Bile duct dysplasia may identify a group of patients at special risk, but this is still controversial. It is often difficult to be certain whether a sudden deterioration in the patient is due to the development of cholangitis, the natural history of the disease, or the development of cholangiocarcinoma (Bergquist et al, 1998).

Methods of detection of cholangiocarcinoma are often unrewarding: serum markers such as carcinoembryonic antigen (CEA) are relatively nonspecific and insensitive; elevated levels of carbohydrate antigen (CA) 19-9 may be more helpful but are not specific (Qin et al, 2004). Imaging techniques including CT, magnetic resonance imaging (MRI), ultrasound, and angiography are often unreliable and miss even quite large tumors. Although the presence of dilated intrahepatic bile ducts is often a useful sign of cholangiocarcinoma, it also is too insensitive and nonspecific for routine use.

The biliary tree can usually be well visualized by magnetic resonance cholangiopancreatography (MRCP), which gives images almost as good as those obtained at endoscopic retrograde cholangiopancreatography (ERCP); however, MRCP does not allow tissue to be taken for histology or cytology (see Chapters 17 and 18). ERCP may be helpful if brushing for bile cytology is combined with biopsy of structures. Although the specificity is high, the sensitivity is relatively low, and the procedure is not without risk of precipitating severe cholangitis. Directed percutaneous biopsy or aspiration cytology again may give a positive diagnosis, but negative findings do not exclude the possibility of cholangiocarcinoma.

It must be emphasized that ERCP in the presence of advanced PSC may lead to sudden deterioration, presumably as a result of the introduction of biliary sepsis. If cholangiocarcinoma is known to be present prior to transplantation, survival is poor; thus clinicians at most centers believe the patient who is known to have cholangiocarcinoma should not be considered for transplantation, although a very small proportion of patients with cholangiocarcinoma may benefit from an aggressive approach with brachytherapy and chemotherapy (Heimbach et al, 2004).

No effective medical treatment is currently available for PSC, although encouraging claims have been made for the use of UCDA at high doses (>20 mg/kg body weight/day), but this has been challenged (Lindor et al, 2009). Surgical intervention may be helpful, although endoscopic dilation or stenting should usually be considered only in the presence of a single, dominant extrahepatic stricture. The use of biliary diversion and reconstruction is associated with a poorer result following transplantation. In our experience in Birmingham, United Kingdom, the 1-year survival of patients with PSC without prior biliary surgery was significantly better (Ismail et al, 1991). Analysis of the Mayo Clinic database suggests that the prognostic markers for patients with PSC after transplantation include disease severity, previous biliary or shunt surgery, concurrent bile duct cancer, and the presence of inflammatory disease (Wiesner et al, 1996; Chapter 42A). Our own analysis confirms these observations, but we did find that although ulcerative colitis was associated with a better outcome, Crohn disease was associated with an adverse outcome (Neuberger et al, 1999).

It is clear, therefore, that as PSC is a premalignant disease, and because cholangiocarcinoma is usually very difficult to detect, patients with PSC should be considered earlier for transplantation and, during the course of their illness, biliary surgery should be avoided if possible.

Alcoholic Liver Disease

Selected patients with alcoholic liver disease are excellent candidates for transplantation, accounting for 13% as a single indication and 19% with HCV. Initial concerns were that these patients would continue to drink alcohol to excess, comply poorly with follow-up, and be unreliable about taking immunosuppression medications. Furthermore, the ravages of alcohol include not only damage to the liver, other organs—including heart, brain, pancreas, and bone marrow—may be affected. Finally, patients with alcoholic liver disease are often more likely to have associated psychiatric problems; however, in 1988, Starzl and colleagues reported an estimated survival of more than 70% in 41 patients transplanted for alcoholic liver disease.

Of these patients, only 2 returned to alcohol abuse and subsequently died. The survival rates of these patients were similar to other patients with cirrhosis. Following these encouraging results, other centers started to consider patients with alcoholic liver disease for transplantation, and most centers now do consider such patients as candidates for the procedure (Kumar et al, 1990). Nonetheless, there remains a decreasing body of opinion that takes the view that, because alcoholic liver disease is a self-induced injury, and in view of the expense of the procedure and the limited supply of donor organs, such candidates should not be considered. In the view of most transplant units, however, this is not considered appropriate, because patients with alcoholic liver disease are not necessarily alcohol dependent; there exists a large number of self-induced diseases, and it would be no more appropriate to deny a patient with alcohol-induced liver disease transplantation for the reason it is self-induced than to deny treatment for a broken limb in a rugby player or mountain climber.

In addition to the usual criteria for transplantation and contraindications to the procedure, other specific factors need to be considered for patients with alcoholic liver disease: the first is the effect of alcohol abstinence, which undoubtedly improves survival in patients who are seen initially without compensated or decompensated cirrhosis. Although those who come to medical attention with variceal hemorrhage or severe ascites often only have limited benefit after abstinence from alcohol, those with mild ascites or other complications may have a significant improvement in both quality and quantity of life once they abstain from drinking (Suterakis et al, 1973). Furthermore, because it is now becoming apparent that those who do not abstain from alcohol are more likely to return to drinking excessively following transplantation and are less likely to comply with follow-up (Beresford et al, 1990), some centers insist on an abstinent period of 6 months. No robust justification exists for this period of abstinence, and the duration of abstinence correlates poorly with posttransplant abstinence. Furthermore, the disease may progress before the stipulated period of abstinence is over. In particular, patients with liver failure are unlikely to survive if they do not recover within the first 3 months of abstinence (Veldt et al, 2002). A period of abstinence is helpful in part to ensure that the native liver will not recover to such an extent that transplantation is no longer required, but also to identify why the person has drunk excessively and to put in place appropriate measures so that there will be a lower risk of recurrence after transplantation. So the period of abstinence must be considered in the light of the patient's condition, and transplantation is offered to the patient who has remained abstinent after being so advised (Neuberger et al, 2002).

It is recommended that the candidate with alcoholic liver disease be carefully evaluated by clinicians expert in substance abuse. Factors that suggest a poor compliance after transplantation include abuse of multiple substances, failure to recognize the nature of the addiction, lack of social support, and failure to find an alternative activity.

The role of transplantation is more difficult to define in patients with alcoholic hepatitis, severe hepatitis characterized by high serum bilirubin and prolonged clotting. Encephalopathy and renal failure have a dismal prognosis: time is usually insufficient to evaluate the patient's background, and the outcome after transplantation is usually poor. Few centers undertake to graft these patients, yet outcomes can be good in those carefully selected; thus in these patients, a multidisciplinary approach to evaluation assumes an even greater importance.

On the physical side, in addition to the routine workup, the extrahepatic effects of alcohol must be assessed, and those with advanced alcoholic cardiomyopathy or pancreatitis may not be suitable on such grounds. Psychiatric assessment is used extensively in some centers (Beresford et al, 1990), and these centers have suggested that patients who are not alcohol dependent, who have found alternative substitutes for alcohol, who have a job, who have taken part in rehabilitation programs, and who have an understanding of their problems often do very well following transplantation. Thus, patients with alcoholic liver disease are certainly potential candidates, and as such they do require appropriate referral for consideration.

Hepatitis A Viral Infection

Rarely, acute hepatitis A virus (HAV) infection is an indication for liver transplantation, and the indications are listed in the section above on FHF. In a few cases, recurrent infection in the graft occurs, but this is of little clinical significance.

Hepatitis B Viral Infection

Patients with hepatitis B virus (HBV) infection can be considered for transplantation either because of FHF or because of chronic liver disease, accounting for less than 5% of transplantations (see Chapter 64). Of those with FHF, the conventional criteria apply as indicated above. Because it is thought that the liver failure in these patients is due to the rapid clearance of virus-infected hepatocytes, most patients at the time of transplantation are HBV DNA negative and, as such, the disease recurs less commonly than in those with chronic HBV infection.

However, different considerations apply to those with chronic liver disease. Those who are HBV DNA positive at the time of transplantation are much more likely, if untreated, to have recurrence of disease following transplantation, and this is associated with a significantly poorer outcome (Freeman et al, 1991; O'Grady et al, 1992; Rizetto et al, 1991); thus patients with high HBV DNA positivity prior to transplantation are not suitable candidates. The management of these patients has been revolutionized by the introduction of effective antiviral therapy (Kim et al, 2004) that has significantly reduced the need for liver transplantation; patients with active viral disease should be treated with antivirals. At present, there are seven approved treatments for chronic HBV, and choice of treatment is based on the e-antigen status, resistance pattern, adverse events, and cost (Lok & McMahon, 2009). Treatment with HBV immunoglobulin (HBIg) and lamivudine or other antiviral agent must be continued after transplantation.

Hepatitis C Viral Infection

The indications for transplantation of patients with HCV infection are increasing, similar to those with cryptogenic cirrhosis (see Chapter 64). After 20 years of infection, up to 20% of HCV-infected patients progress to cirrhosis (Freeman et al, 2001). The optimal time to treat is before onset of advanced fibrosis or liver failure, because 5-year survival is only 50% after the onset of hepatic failure (Fattovich et al, 1997). Patients with detectable HCV at the time of transplant will almost invariably develop recurrent disease, although the extent of

graft damage is variable. Many factors—host, donor, and immunosuppressive—are associated with the extent and rate of graft damage.

Because of the effect of recurrence in the graft, some have tried antiviral therapy with pegylated interferon and ribavirin prior to transplant (Everson, 2004). When this can be done safely, a sustained viral response (SVR) is associated with a much lower risk of graft infection and damage, and 5-year survival after transplantation is similar to patients grafted for other causes of cirrhosis, although concerns remain whether survival in the longer term will be adversely affected by recurrent disease. Treatment with interferon and ribavirin may be effective in selected groups, but SVR is often hard to achieve, and treatment is poorly tolerated.

Patients with hemophilia and HCV infection pose a special problem. Although liver transplantation will correct the defect in hemophilia, this itself is not an indication for liver transplantation. Many patients will have contracted HCV through contaminated blood products. Provided the patient is supported with adequate amounts of the appropriate blood products, liver transplantation poses no major problem, and many patients will not need support beyond 72 hours (McCarthy et al, 1996).

Hepatocellular Carcinoma (Chapters 80 and 97D)

Hepatocellular carcinoma (HCC) may occur in a noncirrhotic liver, but in the Western population, it more commonly arises in the context of cirrhosis and accounts for 8% of transplants, 5.6% in those with cirrhosis. A number of approaches to the treatment of HCC have been adopted and include chemotherapy, resection, embolization, transarterial chemoembolization (TACE), injection with ethanol, cryotherapy, radiofrequency ablation (RFA), and transplantation (see Chapters 83 through 86 and 88). In those with HCC, some have argued that resection should be considered first with salvage liver transplantation used where there is tumor recurrence (Belghiti et al, 2003; Sala et al, 2004). Indications include a normal serum bilirubin and absence of portal hypertension. Such an approach remains controversial. Very few well-conducted prospective randomized trials of treatment have been conducted, and most reports are based on selected patients and compared with historic controls. It must also be remembered that in those with HCC arising in a cirrhotic liver, the optimal treatment will depend not only on the natural history of the HCC but also on the severity and extent of the liver disease.

It has been suggested that patients with the fibrolamellar variant of HCC have a better prognosis, but this is by no means universally agreed. For all those with HCC, transplantation offers the only prospect of long-term survival; given the current shortage of donor organs, guidelines must be agreed upon to determine the indications and contraindications for liver replacement.

Transplantation for patients with HCC raises a number of questions, and at the present time, few hard data are available upon which to base a logical strategy. Most centers currently adopt the Milan criteria for accepting a patient for transplantation (Mazzaferro et al, 1996). These criteria are a single tumor of less than 5 cm in diameter or, in those with multiple tumors, no more than three tumors, all less than 3 cm in diameter. The analysis was based on a small number of patients, but the results have been confirmed in larger series. Extrapolation for these observations to current practice must be done with caution, as imaging techniques have improved, so more lesions are being detected. Thus, it may be inappropriate to extrapolate conclusions based on studies done in the late 1990s.

It is clearly not the size of the tumor per se that is important, but that the size reflects the likelihood of tumor microinvasion and spread and thereby reflects the chance of recurrence after transplant; of course, this is not strictly recurrence but *persistence*. Indeed, other groups have suggested that these criteria are too strict and should be expanded. Thus, the University of California—San Francisco group (Yao et al, 2002) has suggested that the indications should be expanded to include either a solitary tumor at or less than 6.5 cm diameter or three or fewer nodules, with the largest lesion at or less than 4.5 cm and a total tumor diameter at or less than 8 cm; vascular invasion would preclude transplantation. Whether indications for transplant with cadaveric donor livers should be the same as for living donated livers is controversial.

Klintmalm (1998) published the outcome of the findings of the International Registry of Hepatic Tumors in Liver Transplantation that included the outcome of 410 patients with HCC and 12 with the fibrolamellar variant. Of these patients, 40% had incidental tumors—that is, tumors detected on explantation—and 60% had a transplant for known HCC. Overall, after transplantation, 190 patients had died during follow-up, 99 (23.5%) were free of tumor, and in 91 (21.6%), tumor was the cause of death, although many who died early were presumed to be tumor free after transplantation. The 1-year survival was 72%, and 5-year survival was 44%. Univariate analysis identified four factors that predicted patient survival and poor outcome: 1) tumor size greater than 5 cm, 2) vascular invasion, 3) positive lymph nodes, and 4) histologic grade with poor differentiation.

Incidental tumors, fibrolamellar variants, and bilobar tumors were not found to correlate with outcome. When multivariate analysis was used, only histologic grade and known tumors were significantly related to survival. For incidental tumors, survival was negatively influenced by multifocality and age greater than 60 years; tumor histologic grade and size greater than 5 cm were negatively linked to tumor-free survival. Although this report gives invaluable data in selecting patients for transplantation, these findings must be interpreted with some caution, because the data come from 53 units in 21 countries, where there are differences in the etiology of the cirrhosis, in detection, and in management of patients. Many of these factors are interrelated, so a poorly differentiated HCC may be more likely to grow rapidly and metastasize early. Not all single-center experience will confirm the registry report (Rose et al, 1998), however: for example, Achkar et al (1998) found that routine screening of cirrhotic patients will detect small, early stage tumors and that such patients do well after transplantation.

Transplantation is indicated for unresectable HCCs in noncirrhotic livers with no evidence of extrahepatic spread. Although most HCC arises in cirrhotic livers, occasionally HCC may occur in the absence of underlying hepatic parenchymal cirrhosis. In such cases, transplantation is one option usually reserved for those patients in whom other forms of treatment—such as resection, chemotherapy, chemoembolization, RFA, or TACE—are not indicated, and where the characteristics of the HCC fulfill the current indications for transplantation. In those patients with cirrhosis, the decision to resect (if possible) or transplant is more uncertain, because most HCCs in this situation are usually multifocal.

Transplantation may offer a survival benefit (Sarasin et al, 1998) that is also cost-effective, provided the delay from diagnosis to transplantation is less than 6 to 10 months.

The role of pretransplant therapy remains uncertain (see Chapter 83). Some centers are undertaking interventions with either RFA or TACE, but no controlled trials show that such interventions offer a survival benefit; indeed, it is not clear whether any reported benefit is derived from the intervention itself, or whether the delay will help identify those with rapidly growing tumors, those likely to be already outside the liver at the time of transplantation. As RFA and TACE will induce necrosis of the tumor, these and similar interventions may be of help when the waiting time is greater than 6 months in patients with stable liver functions (Bruix & Sherman, 2005). Evaluation involves ultrasound to look for evidence of extrahepatic spread together with CT and/or MRI scan of both the chest and the abdomen along with bone scans to exclude extrahepatic metastasis. Laparoscopy may reveal the presence of nodules ulcerating through the capsule, but it is not usually done. Tumor infiltrating the portal vein, in our view, contraindicates transplantation.

The role of liver biopsy to establish the diagnosis of HCC or assess the biologic characteristics must be considered. Because the risk of tumor seeding may be 2% to 4% along the needle biopsy tract (Navarro et al, 1998), biopsy should be considered only when there is uncertainty as to the diagnosis. This might occur, for example, in the presence of a hepatoma arising in the noncirrhotic liver. It is not usually possible to be sure whether the tumor is malignant or if it is indeed a liver primary. The clear-cell variant of HCC is often difficult to distinguish from pancreatic and renal neoplasm. In contrast, in a patient with known cirrhosis, a primary space-occupying lesion, and rapidly elevating serum α-fetoprotein (AFP) level, there can be little doubt as to the diagnosis; because percutaneous biopsy would only increase the risk of metastasis, it should be avoided.

Cholangiocarcinoma

As indicated above, cholangiocarcinoma (see Chapters 50A, 50B, and 97E) is not usually considered to be an indication for transplantation, because the recurrence rates are high; thus in a literature review, Jeyarajah and Klintmalm (1998) reported a 1-year patient survival of 53% but a 3-year disease-free survival of only 13%. Only in the incidental tumor found at laparotomy is transplantation to be considered, although cures are sometimes possible (Iwatsuki et al, 1998). Some centers have achieved excellent survival after transplantation in highly selected patients treated with an aggressive protocol of radiotherapy and chemotherapy (Hassoun et al, 2002).

Secondary Liver Cancers

With few exceptions, we feel transplantation is not indicated for metastatic liver because of the high rate of recurrence (see Chapter 97E). The major exception is carcinoid and other neuroendocrine tumors, as long-term results are good, and symptomatic relief is rapid (Makowka et al, 1989; see Chapters 81B and 97E). Of 103 patients with unresectable neuroendocrine tumors, the 5-year survival rate was 47%, although the disease-free recurrence rate was only 24% (Lehnert, 1998). In this analysis, multivariate factors that identified a better prognosis included age less than 50 years, primary location in lung or bowel, and pretransplant somatostatin therapy. Multivariate analysis showed that age greater than 50 years, upper abdominal exenteration, and Whipple procedure at the time of transplantation were all associated with a poor outcome.

PEDIATRIC TRANSPLANTATION

The medical indications for liver transplantation in children are similar to those in adults (see Chapters 40, 71, 82, and 98C), although additional indications include growth retardation and the development of metabolic bone disease. The commonest indication for transplantation in children remains disorders of the biliary system, of which biliary atresia (Chapters 40 and 98C) is the commonest. The procedure of portoenterostomy may be effective in some children if performed early, but if performed after 2 months, the chance of a successful outcome is limited; thus if bile drainage is not established soon after surgery, the child should be considered for transplantation rather than have the surgeon make further attempts to reconstruct the bile duct system in an attempt to establish bile flow. Other disorders of the biliary tree that may require transplantation include Alagille syndrome, Byler disease, and nonsyndromatic intrahepatic biliary hypoplasia. Disorders of metabolism are the next commonest indication for transplantation, and these include Wilson disease, tyrosinemia, glycogen storage disease, galactosemia, and Gaucher syndrome.

ASSESSMENT OF PATIENTS FOR LIVER TRANSPLANTATION

When the patient is referred for liver transplantation, it is important to confirm the diagnosis of the liver disease, to assess the indications for liver transplantation and any conditions that may either preclude transplantation or add to the risk of the procedure, and to counsel the patient and family about the benefits and risks of surgery. Although the decision for transplantation rests with the patient, it is important to include the family in discussions, because their cooperation and understanding is essential for successful rehabilitation following transplantation.

Apart from a thorough history, examination, and review of histology, it is clear that investigations required will be dependent on the patient's medical condition. Some chronic liver diseases are associated with extrahepatic diseases, thus primary biliary and autoimmune chronic active hepatitis are associated with thyroid disease, celiac disease, and Addison disease. These should be excluded, because untreated myxedema, for example, may lead to lethargy, and if corrected, this may obviate the need for transplantation.

In patients with chronic liver disease—apart from full blood count, assessment of clotting, renal function tests, and liver function tests—it is important to check viral status for HAV, HBV, HCV, HIV, and cytomegalovirus (CMV). In those who are not immune to HAV and HBV, it is worthwhile to offer immunization prior to transplantation, as there have been occasional reports of HBV being acquired during the transplant procedure, from either infected organ or blood.

In patients with established cirrhosis, HCC should be sought by imaging of the liver and measurements of serum AFP; in addition, bacterial, viral, and fungal cultures should be obtained for a baseline. In patients with a possible history of tuberculosis, tests should be directed to determine the presence of previous infection; in such cases, it is our practice to give isoniazid and

pyridoxine for the first 6 months following transplantation. Additional blood tests will be determined by the nature of the disease and may include autoantibodies, immunoglobulins, copper studies, α_1-antitrypsin phenotypes as appropriate, and crossmatching.

Cardiopulmonary function is difficult to assess. ECG, echocardiography, and simple lung function tests may be adequate to recognize pathology that requires further investigation. For example, in a patient with possible ischemic heart disease, if appropriate, we will proceed with an echocardiogram, an exercise ECG test prior to thallium scanning, and coronary angiography or other imaging as indicated. Measurement of arterial blood gases is important; if the arterial oxygen is low, these tests must be repeated after exercise and after giving 100% oxygen to gain guidance as to the extent of intrapulmonary shunting (Krowka & Cortese 1990).

Radiologic investigations consist primarily of a chest radiograph and an ultrasound of the liver, biliary tree, pancreas, spleen, and vessels. If there is any uncertainty as to the patency of the portal vein, angiography—direct, CT, or MR—can help assess patency of the portal and splenic superior mesenteric veins. Many centers do not routinely perform CT or MRI scans unless malignancy is suggested, but many believe they should be routinely performed prior to initial listing and at least annually thereafter until the time of transplant.

In patients with PSC, as discussed above, investigation of the biliary tree may be indicated. Although this may pick up undiagnosed cholangiocarcinoma, this procedure could result in an episode of cholangitis. Many patients with PSC have colitis, and although it is usually mild and often clinically inapparent, it is important to screen such patients prior to surgery to exclude a coexisting colon cancer. In particular, those with a long history of pancolitis require full investigation by colonoscopy; however, this procedure is not without risk, especially in those with ascites. In the presence of dysplasia, it may be sensible to consider early colectomy, because the additional effect of immunosuppression may further increase the risk of colonic cancer.

Routine psychiatric evaluation is not indicated, unless the history suggests the possibility of psychiatric disease that may preclude successful rehabilitation. A dental examination is required prior to transplantation, and any carious teeth are usually removed. Patients are also routinely assessed by the anesthetist prior to receiving a transplant.

MANAGEMENT OF PATIENTS AWAITING TRANSPLANTATION

In general, patients should be maintained as fit as possible while awaiting transplantation. Any vitamin deficiency should be corrected, and the patient should be asked to consume a high-protein, high-calorie diet. The presence of encephalopathy should not bar a high-protein diet, although other methods should be used to control hepatic encephalopathy, such as use of lactulose and, if necessary, metronidazole or neomycin. It is reasonable to offer nonimmune patients immunization with HAV and HBV vaccines, and any infection should be rigorously sought and actively treated.

The presence of ascites may be an indication for treatment; not only do ascitic patients remain catabolic, but the risk of spontaneous bacterial peritonitis is also present. In the presence of ascites, patients should be treated with prophylactic antibiotics, such as ciprofloxacin or co-amoxiclav, which have been shown to be not only efficacious and cost-effective but also without major risk of developing bacterial resistance. In patients with severe ascites that is resistant to therapy with diet and diuretics, requiring repeated episodes of paracentesis, a TIPS may be considered (see Chapter 76E). The role of such shunts prior to transplantation remains uncertain; they have been shown to reduce portal hypertension and thereby improve ascites and the risk of variceal hemorrhage, but insertion is not without risk, not only of sepsis but also of perforation and portal vein thrombosis.

Patients with recurrent variceal hemorrhage pose a particular problem (see Chapter 75). Injection sclerotherapy in the 2 weeks prior to transplantation is associated with a risk of paraesophageal abscesses following transplantation. Variceal banding is preferable for the treatment of bleeding esophageal varices, and again, the role of TIPS is valuable in selected patients. If successful, TIPS procedure will reduce portal hypertension, but it is not free of risks, which include perforation and portal vein thrombosis; however, current evidence suggests that the benefits outweigh the risks. Patients with portal hypertension and varices should be considered for β-blocker therapy with propranolol or carvedilol, because this will reduce the risk of both primary and secondary hemorrhage and does not impair response to anesthesia.

Finally, it is important to avoid therapy that will exacerbate the liver disease. In particular, nonsteroidal antiinflammatory drugs (NSAIDs) should be avoided because of the risks of gastric hemorrhage, renal failure, and fluid retention. Drugs that result in constipation, such as opiates, and sedative drugs should also be avoided because of the risk of precipitating encephalopathy. Diuretics must be used with care, and renal function must be carefully monitored; renal failure is associated with poor outcome after transplantation, and hyponatremia is associated with the development of central pontine myelinolysis.

Transplant clinicians need to remain in close contact with the patient so that problems can be detected and treated early. As the waiting time for transplantation increases, patients will deteriorate, and it may be that the patient will either develop complications precluding a successful outcome or that the probability of survival will become too small for transplantation to proceed. With the increasing shortage of donor organs, transplant clinicians must consider those criteria that suggest a patient should be removed from the transplant list.

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PART 8: Liver and Pancreas Transplantation

SECTION III Techniques

CHAPTER 98A

Orthotopic liver transplantation

Kendra D. Conzen, M.B. Majella Doyle, and William C. Chapman

OVERVIEW

Since the initial descriptions of orthotopic liver transplantation (OLT) in the 1960s, both the number of patients receiving transplants and the indications for the procedure have increased significantly. OLT represents the only treatment modality for many patients with a diverse spectrum of disease, with the predominant common factor being end-stage liver failure. It also has become an excellent option as curative therapy for early stage hepatocellular carcinoma (HCC). Advances in perioperative care of both donor and recipient, organ preservation methods, and surgical techniques have resulted in a 1-year overall survival of 88% for all recipients (Wolfe et al, 2010).

Although gains over the last 40 years in the field of hepatic transplantation are notable, many limitations remain, not the least of which is the relatively fixed pool of cadaveric organ donors. Techniques such as living donor liver transplantation (LDLT), use of non–heart-beating donors, and splitting cadaveric grafts may extend the benefit of OLT to more patients awaiting transplantation.

This chapter presents a broad overview of liver transplantation, including common criteria for recipient and donor selection (see Chapter 97A), standard operative approaches for donors and recipients (see Chapter 99), common postsurgical complications (see Chapter 100), and outcomes related to the underlying etiology of end-stage liver disease (ESLD). Specialized transplant techniques, such as split-liver and living-related donor liver transplantation, are described in Chapters 98B and 98C.

PATIENT SELECTION

OLT represents the only curative treatment option for most patients with irreversible acute and chronic liver disease and cirrhosis, regardless of cause. Over the past 4 decades, 5-year patient survival after liver transplantation has increased from less than 50% to greater than 70% or more (Busuttil et al, 2005; Jain et al, 2000). The improvement in patient outcome has led to an expansion in the indications for transplantation and a concomitant increase in the number of patients referred to transplant centers (see Chapter 97A). The downside to this success is the persistent disparity between the number of recipients vying for a transplant and the number of donor organs available, a relatively constant supply (Fig. 98A.1).

The number of patients listed for OLT has increased sixfold since 1993, whereas the number of transplantations performed increased by only 45% during the same time. In 2008 in the United States, 15,807 patients were on the waiting list for a liver transplant, a decline from a peak of nearly 17,000 in 2002 (Wolfe et al, 2010); however, only 5817 of the patients on the waiting list received a liver allograft, and 90% of these recipients had a Model for End-Stage Liver Disease (MELD) score above 15 at transplantation (U.S. Scientific Registry of Transplant Recipients [USRTR], 2008).

Historically, the donor-to-recipient disparity leads to longer waiting times and worsening medical status with a peak waiting-list attrition rate of 187 per 1000 patient-years at risk in 1999. This rate declined by 15% and has remained steady over the last few years at 160 per 1000 patient-years at risk (Thuluvath et al, 2010). Because of the limited supply of donor organs, appropriate recipient and donor selection is paramount to improve resource use and long-term outcome.

Recipient Selection

Common indications for OLT (see Chapter 97A) include portal hypertension as manifested by variceal bleeding, ascites, encephalopathy, hyperbilirubinemia, hepatic synthetic dysfunction, and lifestyle limitations. More than 70% of liver transplantations are for noncholestatic liver disease, of which the most common etiologies are viral hepatitis (30%) and alcoholic cirrhosis (16%) (USRTR, 2008). Biliary atresia is the most common indication for liver transplantation in patients younger than 18 years of age (Busuttil et al, 2005; Goss et al, 1998). Nonalcholic steatohepatitis (NASH) is becoming an increasingly common cause of liver cirrhosis, as the prevalence of

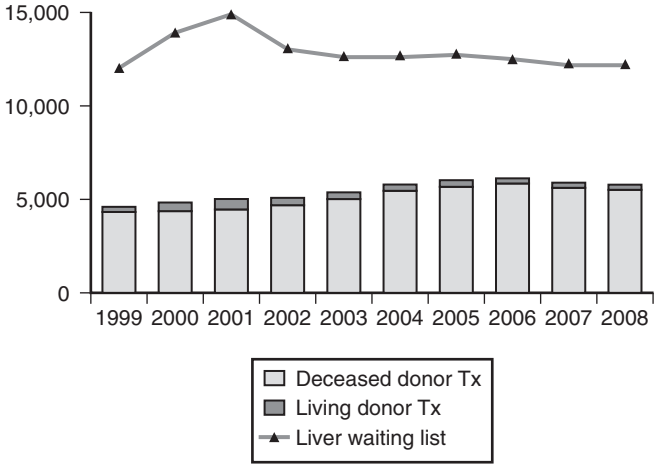


FIGURE 98A.1. Data from the Scientific Registry of Transplant Recipients (SRTR), 2009 *OPTN/SRTR Annual Report*, demonstrates the persistent disparity between patients on the waiting list and recipients of deceased-donor and living-donor allografts. The number of patients awaiting a liver transplant at year's end decreased after the introduction of the Model for End-Stage Liver Disease (MELD) and the pediatric MELD allocation system. Tx, treatment.

nonalcoholic fatty liver disease (NAFLD) increases; NAFLD now affects an estimated 10% of children (Schwimmer et al, 2006).

Few true, absolute contraindications to OLT exist that uniformly portend a poor patient outcome (Box 98A.1). Advanced cardiopulmonary disease, known extrahepatic malignancy, uncontrolled systemic sepsis from a source originating outside the liver, acquired immunodeficiency syndrome (AIDS), and ongoing or recent substance abuse are absolute contraindications. Many of the relative contraindications are conditions that are expected to improve after successful OLT. Examples include severe hemodynamic instability (e.g., shock) requiring multiple pharmacologic agents to maintain perfusion and severe hypoxia uncorrected by conventional intensive care measures in the context of hepatopulmonary syndrome. Other relative contraindications to OLT are extensive mesenteric venous thrombosis, morbid obesity, psychiatric disorders uncontrolled by conventional means, absence of a suitable social support network, and extremes of age (Jain et al, 2000; Loinaz et al, 2002; Rustgi et al, 2004).

Box 98A.1

Contraindications to Orthotopic Liver Transplantation

Absolute

Advanced cardiopulmonary disease
Extrahepatic malignancy
Uncontrolled sepsis
Active substance abuse
ABO incompatibility

Relative

Hemodynamic instability
Severe hypoxia (except with hepatopulmonary syndrome)
Human immunodeficiency virus infection
Refractory psychiatric disorders
Absence of adequate social support

Increasingly, advances in surgical technique and medical supportive care are overcoming obstacles and comorbid conditions formerly considered absolute contraindications to transplantation, including portal vein thrombosis (PVT), human immunodeficiency virus (HIV) infection, and advanced age. Patients who receive liver transplants now have higher rates of diabetes mellitus (DM), renal insufficiency, and morbid obesity (Thuluvath et al, 2010). Although pretransplantation insulin-dependent DM is not a contraindication to transplantation, evidence suggests that better risk stratification of these patients is warranted (Thuluvath, 2005). Likewise, patients with extreme body mass indexes (<18.5 or >40) might be at higher risk for posttransplantation complications (Dick et al, 2009). Morbid obesity is also associated with an increased risk of infectious complications and posttransplantation malignancy.

Although HIV infection has historically been considered a contraindication to OLT, the advent of highly active antiretroviral therapy (HAART) has turned HIV into a chronic condition, and patients are now living long enough to suffer the morbidity and mortality of other diseases, including ESLD. Therefore some patients with HIV may be considered for liver transplantation, if their CD4 T-cell count is greater than 200 and their HIV RNA viral load is less than 50 copies/μL within 12 months prior to transplantation (Di Benedetto et al, 2008). It should be noted that hepatitis C virus (HCV) coinfection with HIV predicts worse outcomes after OLT, with faster and higher rates of HCV recurrence (Di Benedetto et al, 2008).

The etiology of liver failure may be predictive of outcome after OLT, although the correlation between preoperative risk and graft survival sometimes varies. Jain and colleagues (2000) examined outcomes after OLT in 4000 consecutive patients treated at the University of Pittsburgh. Patients with metabolic or autoimmune liver disease experienced 10-year survival rates greater than 60%, whereas the survival rates for viral hepatitis or alcohol-induced cirrhosis were 40% to 50%, and patients transplanted for advanced hepatic malignancy had only a 22% survival at 10 years. Results for all patients were better in the most recent era. Earlier contradictory reports notwithstanding, recipient age probably does not influence transplantation results significantly (Gayowski et al, 1998; Ploeg et al, 1993; Totsuka et al, 2004). Thorough screening for medical comorbidities commonly found in older populations—such as lifestyle-limiting cardiopulmonary disease, systemic vascular disease, and chronic renal insufficiency—is crucial to successful OLT in patients older than 60 years.

The recipient selection process has undergone extensive revisions to ensure equitable allocation of a scarce resource (cadaveric donor livers) while attempting to avoid futile transplantation. Before February 2002, recipients awaiting OLT were prioritized based on the Child-Turcotte-Pugh (CTP) scoring system (Table 98A.1), time on the waiting list, and patient location (e.g., intensive care unit). Waiting lists grew under this system, and it became increasingly clear that these parameters were not good measures of disease severity.

In 2000, the Department of Health and Human Services issued a guideline stating that the allocation of livers for transplantation should be based primarily on medical urgency (Freeman et al, 2002). The United Network of Organ Sharing (UNOS), which administers the Organ Procurement and Transplantation Network, commissioned several subcommittees to examine new methods for allocation. The result was the universal adoption of the MELD criteria (Table 98A.2) as a

Table 98A.1

Child-Turcotte-Pugh Classification

	POINTS		
	1	2	3
Encephalopathy	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	1 to 2	2 to 3	>3
Albumin	>3.5	2.8 to 3.5	<2.8
Prothrombin time (seconds prolonged)	1 to 4	4 to 6	>6

measure of the potential recipient's necessity for OLT. Concurrent revision of the pediatric liver allocation process produced the Pediatric End-Stage Liver Disease (PELD) model, which is discussed further in Chapter 98C. Per a policy change in 2005, PELD is applied to potential transplant recipients younger than 12 years. Adolescents aged 12 to 17 years are stratified using the MELD system.

In contrast to its predecessor, the CTP score, MELD has been validated extensively as a predictor for 3-month mortality from chronic liver disease (Malinchoc et al, 2000; Wiesner et al, 2003a). It incorporates serum creatinine, bilirubin, and international normalized ratio (INR) as markers for risk of death; relies on objective and readily available blood tests; and practically eliminates time on the waiting list from consideration. Using MELD criteria, rates of death while awaiting OLT and removal from the waiting list for being too sick have decreased (Thuluvath et al, 2010). Median time to transplant in 2007 was 361 days.

As shown in Figure 98A.2, the use of MELD criteria for predicting mortality from ESLD results in an appropriate correlation between severity score and actuarial survival at 3 months. Survival benefit analysis of liver transplant recipients stratified by MELD score demonstrates that the risks involved in transplantation are equivalent or less than the risks associated with remaining a transplant candidate on the waiting list with a MELD score over 15 (Merion et al, 2005). The MELD-based allocation process is dynamic and amenable to subtle changes to reflect an evolving understanding of the diverse pathology and physiology seen in patients treated with OLT.

Table 98A.2

Predicted Mortality According to the Model for End-Stage Liver Disease Score*

Score	No. Patients	Mortality Rate (%)	Death or Removal from List Because of Illness (%)
<9	124	1.9	2.9
10-19	1800	6	7,7
20-29	1098	19.6	23.5
30-39	295	52.6	60.2
≥40	120	71.3	79.3

*$R = (0.957 \times \text{Log}_e[\text{creatinine } \{\text{mg/dL}\}] + 0.378 \times \text{Log}_e[\text{total bilirubin mg/dL}] + 1.120 \times \text{Log}_e[\text{INR}] + 0.643) \times 10$

D, donor status; R, recipient status; INR, international normalized ratio

Modified from Wiesner R, et al, 2003: Model for End-stage Liver Disease (MELD) and allocation of donor livers. Gastroenterology 124:91-96.

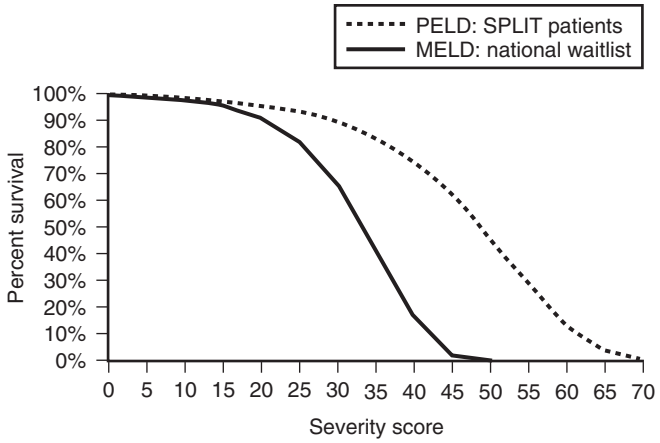


FIGURE 98A.2. Correlation between Model for End-Stage Liver Disease (*MELD*) and the pediatric MELD (*PELD*) score and patient mortality. SPLIT, Studies of Pediatric Liver Transplantation. *(Adapted from Freeman RB Jr, et al, 2002: The new liver allocation system: moving toward evidence-based transplantation policy. Liver Transpl 8:851-858.)*

Special considerations for certain subsets of patients with liver disease are ongoing. Early in the initial evaluation of the MELD criteria, it was recognized that patients with HCC and early cirrhosis should be prioritized lower on the waiting list, when they could potentially benefit most from transplantation (e.g., HCC at an early tumor stage; see Chapter 97D). Conceivably, patients with HCC but low MELD scores could develop progressive disease, which would eliminate OLT as a treatment option. Since the most recent revisions to MELD, patients with stage II HCC currently are allocated 22 MELD priority points. Criteria for selecting HCC patients for transplantation are discussed further in this chapter, including those with more advanced stage disease. Guidelines also exist for awarding priority points for other conditions, such as hepatopulmonary syndrome, portopulmonary hypertension, hepatic artery thrombosis after liver transplant, pediatric hepatoblastoma, inborn errors of metabolism, familial amyloidosis, and primary oxaluria; however, the process is highly variable by region (USRTR, 2008).

Since 2002, the number of patients on the waiting list with exception points for any condition has more than doubled, with close to 900 on the list in 2008 (Thuluvath et al, 2010). Increasingly, stage I and II hilar cholangiocarcinoma is becoming an acceptable indication for OLT, and uniform criteria for obtaining MELD exception points have been proposed (Gores et al, 2006; see Chapter 97E). Eligible patients must be treated according to a specific protocol that requires neoadjuvant chemoradiation, followed by a staging laparotomy to confirm absence of N1 disease (Rea et al, 2005).

Donor Selection

Increased demand for donor organs, as depicted in Figure 98A.1, has resulted in the concomitant increase in the use of less than ideal donors. The theoretic ideal donor is an otherwise healthy, hemodynamically stable young person who suffers an irreversible cerebral insult that results in brain death; this situation is rarely realized. Although marginal donors are being used more frequently, absolute contraindications remain, including

known extracranial malignancy (except for basal or squamous cell cancer of the skin), overwhelming sepsis, hepatic cirrhosis, hepatic macrosteatosis greater than 60%, and HIV infection. Generally, hepatitis B virus (HBV) surface antigen and core antibody positivity in the donor also constitute absolute contraindications (Wachs et al, 1995), although many centers consider transplantation of core antibody-positive livers for HBV-positive recipients, if the graft seems otherwise suitable, and even into non-HBV recipients in selected circumstances. Advanced donor age may adversely affect graft survival, and in practice, donors older than 80 years usually are excluded from consideration.

Data that demonstrate differential effects on specific recipient groups, such as HCV-positive recipients, remain inconclusive (Doyle et al, 2008; Lake et al, 2005; Russo et al, 2004). Although liver allografts with 30% to 60% steatosis are utilized in select groups of recipients, it should be recognized that greater than 60% steatosis significantly increases the risk of primary nonfunction (Urena et al, 1999). A donor risk index (DRI) has been developed to help quantify and stratify allografts by predicted failure risk (Feng et al, 2006).

As a result of the shortage of cadaveric donors, the use of living donors has increased in the United States, from 1996 with a peak in 2001; it has since declined steadily, and LDLTs now represent only 4% of liver transplantations performed (see Chapter 98B). A shift in demographics has also been seen in recipients of LDLT: patients age 50 to 64 years represent the largest group (USRTR, 2008). LDLT is appealing, because it allows elective transplantation after optimizing the health of the recipient, reduces cold ischemic times, and potentially shortens waiting times. The disadvantages include morbidity and rare mortality in the donor population (Brown et al, 2003). The most common practice in adults is transplantation of the right hepatic lobe. Despite initial data indicating worse outcomes in LDLT, a trend has been seen toward improved graft survival and overall survival in the United States in the last 10 years (Thuluvath et al, 2010). Although LDLT from an adult to a child has become well accepted and standardized, adult-adult LDLT continues to evolve, and the place of this approach as part of the overall picture of liver transplant options is not fully defined.

Early reports regarding the successful use of kidneys from non–heart-beating donors and donation-after-cardiac-death (DCD) donors encouraged a similar practice in OLT. Most commonly, DCD donors are patients with severe neurologic injury, such as anoxia and intracranial hemorrhage, and no chance for meaningful recovery, yet they do not meet brain-death criteria; family members and treating physicians must elect to withdraw support. Donor criteria are similar to cadaveric (brain dead) donors.

DCD livers are increasingly being used and now represent 5% of all liver-only transplants (USRTR, 2008). Compared with historic results with brain-dead donors, outcomes using DCD allografts are less optimal, with 1- and 3-year graft survivals of 70% and 60%, 10-year graft survival of 44% for all patients, and a primary nonfunction rate of almost 12% (Abt et al, 2004; Bernat et al, 2006; D'Alessandro et al, 2000; de Vera et al, 2009; Mateo et al, 2006; Thuluvath et al, 2010). The graft survival rate improves when donor warm ischemia time is less than 30 minutes and cold ischemia time is less than 10 hours (Mateo et al, 2006); however, DCD grafts are associated with an increased risk of nonanastomotic intrahepatic biliary strictures (ischemic cholangiopathy) and posttransplantation hepatic artery stenosis (Chan et al, 2008; Pine et al, 2009). Given the risks inherent in DCD allografts, they should be used cautiously in select groups of recipients.

OPERATIVE TECHNIQUES

The first published description of human liver transplantation was by Starzl and colleagues in 1963 at the University of Colorado. In this seminal paper, the dismal outcomes of three OLT recipients were described, including one intraoperative death from uncorrectable coagulopathy and two survivors of 7 and 22 days. In addition to the pioneering conceptual framework and implementation of liver transplantation, several advanced techniques are presented in this reference, including the use of grafts from non–heart-beating donors, venovenous bypass in the recipients, choledochocholedochostomy, and coagulation monitoring using thromboelastography (TEG). Many of these concepts remain or have reentered the realm of liver transplantation more than 40 years after their initial description. Based largely on the initial body of work by Starzl and colleagues, this section describes the surgical procedures commonly used at Washington University in St. Louis during OLT (see Chapter 99).

Donor Hepatectomy

Management of a cadaveric organ donor begins preoperatively, immediately after identification of a candidate and after evaluation by trained transplant coordinators. After brain death, severe physiologic derangements can occur, and physiologic instability increases in proportion to the length of time between declaration of death and organ procurement (Nygaard et al, 1990). The progression from brain death to somatic death results in the loss of 10% to 20% of potential donors (Wood et al, 2004).

Complications that commonly occur in a brain-dead donor include hypotension, the requirement for multiple transfusions, disseminated intravascular coagulopathy (DIC), diabetes insipidus (DI), pulmonary edema and hypoxia, acidosis, and arrhythmias and cardiac arrest. Intravascular volume repletion to normovolemia is the cornerstone of management; however, vasopressors or inotropic agents often are necessary to achieve an adequate perfusion pressure. The use of low-dose arginine vasopressin allows a reduction in the dosing of α-adrenergic agents, which may impair end-organ perfusion (Pennefather et al, 1995). Directed therapy using a pulmonary artery catheter can improve outcome in patients with brain death–induced or traumatic cardiac dysfunction (Wheeldon et al, 1995). A thorough review of the medical management of potential organ donors can be found elsewhere (Wood et al, 2004).

Surgical techniques for procuring abdominal organs from brain-dead, heart-beating donors have been described previously (Farmer et al, 2000; Merkel et al, 1972; Starzl et al, 1984, 1987). A midline incision from the suprasternal notch to the pubis is performed, followed by sternotomy and entry into the peritoneum. The abdomen is inspected for any evidence of malignancy or gross gastrointestinal ischemia, which would preclude transplantation. Procurement proceeds in several phases: warm dissection and cannulation, exsanguination with cold perfusion and organ removal, and back-table dissection and organ preparation.

In the warm dissection phase, the liver is mobilized by dividing the umbilical, falciform, and left triangular ligaments.

Hepatic arterial anatomy is delineated by inspection of the gastrohepatic ligament and porta hepatis to identify aberrant arterial anatomy. A right medial visceral rotation, or Cattel-Brasch maneuver, is performed, by which the right colon and mesentery of the small intestine are mobilized and reflected toward the donor left upper quadrant. The infrarenal aorta is exposed at the bifurcation, and proximal and distal control is obtained. The inferior mesenteric vein is identified, controlled, and cannulated for subsequent portal perfusion.

Next, the intestinal contents are returned to the lower abdomen with attention turned again to the porta hepatis. The distal common bile duct is circumferentially dissected, distally ligated, and transected. The gallbladder is flushed out through a choledochotomy to clear bile from the gallbladder and biliary tree to potentially limit injury to the bile duct epithelium. The common hepatic artery is identified, and the gastroduodenal artery (GDA) is encircled. After reflection of the left lobe of the liver medially, control of the supraceliac aorta is obtained, facilitated by dividing the diaphragmatic crura.

The entire warm dissection phase usually takes 30 minutes or less. At this stage, the donor is ready for heparinization (400 U/kg IV) and for cannulation of the distal aorta, which occurs in coordination with the other procurement teams. When the thoracic and abdominal teams are ready, the donor is exsanguinated via the suprahepatic vena cava. Suction catheters are placed in the chest to remove warm blood, the aorta is cross-clamped in the supraceliac location, and the arterial and portal circulations are flushed—usually with University of Wisconsin (UW) solution or histidine-tryptophan-ketoglutarate—via the previously placed cannulae. Infusion continues until the caval drainage is clear, which typically requires 4 to 5 L via the aorta and another 1 to 2 L via the portal vein. The donor abdomen is packed with ice slush for topical cooling during the flushing phase.

After satisfactory cooling and flushing with preservation solution, the portal dissection is initiated. The general goals of this dissection are to delineate the arterial anatomy and dissect the arterial inflow back to the aorta. This is accomplished by dividing the GDA, dissecting the common hepatic artery down to the celiac trunk, dividing the splenic and left gastric arteries, and dissecting the celiac trunk down to the aorta. This technique is modified in the presence of a replaced or accessory left hepatic artery, in which case preservation of the left gastric artery is mandatory. A search for a replaced or accessory right hepatic artery also is undertaken through identification of the superior mesenteric artery and its proximal branches. Preservation of this artery, if present, is essential.

Next, the portal vein is dissected and divided near the pancreas, although a modification is necessary if pancreas procurement is being performed simultaneously. Excision of the celiac trunk with a Carrel patch of aorta is performed; this common patch, including the superior mesenteric artery origin, is used if an accessory or replaced right hepatic artery is present. Attention is then turned to the infrahepatic inferior vena cava (IVC), which is divided above the level of the renal veins. As a final step, the diaphragm is dissected around the suprahepatic IVC. The diaphragm and all tissues between the right kidney and liver are divided, and the hepatic graft is removed from the donor and packed in ice.

The final preparation of the donor graft usually occurs at the recipient hospital and is a cold, back-table preparation of the arterial and venous cuffs. This work consists of removal of the diaphragm and preparation of the suprahepatic IVC. The adrenal gland is removed, the adrenal vein is ligated, and the infrarenal IVC is prepared. The portal vein is dissected free from surrounding tissue up to the bifurcation and is cannulated for purposes of flushing preservation solution just prior to graft reperfusion. The celiac trunk is dissected up to the GDA with all unnecessary branches ligated. During this phase, arterial reconstruction—that is, donor accessory right hepatic artery to donor GDA—or conduit creation is performed as indicated. At this point, the graft is ready for recipient implantation.

Procurement in a DCD donor requires a slight modification (Bernat et al, 2006; D'Alessandro et al, 2000). In the controlled setting, the donor is brought to the operating room, and support is withdrawn. Heparin is administered to reduce risk of thrombus formation in the graft (Bernat et al, 2006). Apnea and cessation of circulation ensue after a variable amount of time, at which point of death is declared. It is important to note that 10% of potential donors do not die within 2 hours of withdrawal of support; these patients are not candidates for subsequent organ donation and are transferred back to the intensive care unit (ICU) and are allowed to die (Cooper et al, 2004). Circulation is unlikely to resume after 2 minutes of complete cessation; a minimum waiting period of 2 minutes is required, and a 5-minute interval between asystole; pronunciation of death prior to further intervention is strongly encouraged (Bernat et al, 2006).

The goal now becomes rapid reperfusion of the organs for procurement with cold preservation solution; this usually is accomplished via a quick midline laparotomy and cannulation of the aorta. Alternatively, some centers use cannulae placed before death in the femoral artery and vein. Less than 30 minutes of donor warm ischemia time is generally considered acceptable (Bernat et al, 2006). Hepatectomy is performed as in a standard brain-dead donor, commonly followed by a back-table flush. Cadaveric split-liver and living-related liver transplantation techniques are addressed in Chapters 98B and 98C.

Recipient Hepatectomy

Removal of the diseased liver from the recipient can be a challenging technical aspect of liver transplantation. Hepatectomy often is complicated by marked portal hypertension, coagulopathy, extensive collateralization of venous drainage, a friable liver that is prone to hemorrhage, portal venous thrombosis, and possible prior abdominal surgical interventions that may have included portal venous shunting or biliary tract surgery. Preoperative preparation of the recipient includes establishment of central venous monitoring and intravascular access, ensuring availability of at least 10 U crossmatched blood, and timely administration of a second-generation cephalosporin.

Optimal recipient operative exposure is accomplished using a bilateral subcostal incision with an upper midline extension. The umbilical, falciform, and left triangular ligaments are taken down for maximum exposure. The left and right hepatic arteries are ligated in the hilum as the first step in the portal dissection. The cystic duct is divided, if needed for exposure, and circumferential dissection of the common hepatic duct is performed, which is divided in the mid-extrahepatic portion. Sufficient distal bile duct length in the recipient is preserved for the implantation phase, which usually includes choledochocholedochostomy.

Next, the portal vein is skeletonized proximally to just above the confluence of the splenic and superior mesenteric vein. At this point, further dissection is influenced by the use of temporary portocaval shunting or venovenous bypass; both techniques allow decompression of the splanchnic circulation, which reduces bowel edema during the anhepatic phase. When venovenous bypass is used, the portal vein is cannulated, and bypass is instituted as previously described (Shaw et al, 1984). A potential disadvantage of venovenous bypass is the added complexity and potential complications associated with the bypass process (e.g., thrombosis of the bypass circuit). We prefer portocaval shunting with an end-to-side anastomosis between the divided portal vein and infrahepatic IVC. The shunt is kept in place until the suprahepatic caval anastomosis is completed.

Temporary portocaval shunting in conjunction with the piggyback technique may improve intraoperative hemodynamic stability and renal function and may reduce the transfusion requirement (Arzu et al, 2008; Davila et al, 2008; Figueras et al, 2001). If neither venovenous bypass nor temporary portocaval shunting is used, the portal vein simply can be clamped proximally, ligated in the hilum, and divided; however, this method may be associated with a severe reduction in venous return, up to a 50% decrease in arterial blood pressure, mesenteric venous hypertension and associated organ failure, and potential increased hemodynamic instability resulting in intraoperative mortality (Hoffmann et al, 2009).

With the portal vein bypassed or clamped, exposure for the infrahepatic dissection and vascular control of the IVC is easily obtained. The piggyback technique leaves the recipient retrohepatic IVC intact and requires ligation and division of all retrohepatic caval branches (Tzakis et al, 1989). The advantage of this approach is that native caval flow is maintained, and venovenous bypass is not required; the disadvantage is that division of retrohepatic caval branches can be tedious and time consuming. The donor suprahepatic IVC is anastomosed to the confluence of the right, middle, and left hepatic veins, which are joined in a common cuff. Vascular control is achieved by clamping the hepatic veins at their point of entry into the vena cava.

Alternatively, if a bicaval technique is used, the recipient's native retrohepatic IVC is removed with the native liver. The retrohepatic IVC is mobilized out of the retroperitoneum from the left side. The right triangular ligament is taken down, and the retrohepatic IVC is dissected from the right side. The adrenal vein is ligated in the traditional bicaval approach; this dissection frees up the retrohepatic IVC above the hepatic veins to allow application of infrahepatic and suprahepatic IVC clamps. The recipient liver is sharply excised with care taken to leave cuffs of IVC above and below the liver. This technique allows for true orthotopic placement of the donor graft. Retrospective analysis of the bicaval and piggyback techniques suggest that safety and outcomes are comparable (Nishida et al, 2006).

Recipient Implantation

OLT requires three or four vascular anastomoses in the following order: 1) suprahepatic IVC; 2) infrahepatic IVC, if a bicaval technique is used; 3) portal vein; and 4) hepatic artery. Alternatively, the use of the piggyback technique allows just a single caval (end-to-side) anastomosis, with simple ligation of the donor infrahepatic IVC; this results in a reduction in the duration of the anhepatic phase (Hosein Shokouh-Amiri et al, 2000). When the liver is fully reperfused, reconstruction of the biliary tract begins.

Adequate cuffs of suprahepatic and infrahepatic IVC are essential for reconstruction (Starzl et al, 1979). Anastomoses of these cuffs require reconstruction of the posterior walls from within the lumen using a running 3-0 polypropylene suture. The anterior layer is sutured externally using either an interrupted or a continuous technique. Another advantage of the piggyback technique is the use of a side-biting vascular clamp on the IVC at the level of ostia of the hepatic veins. Although this clamp may impair venous return to the heart to some degree during a clamp time of 15 to 30 minutes, it generally produces greater hemodynamic stability during the anhepatic phase than does complete caval occlusion, which requires a bicaval procedure (Moreno-Gonzalez et al, 2003). After the hepatic donor vena cava has been anastomosed to the recipient IVC, the side-biting clamp can be moved to the graft side of the anastomosis, restoring complete venous return, while the remaining vascular connections are performed.

After restoration of caval flow, the portal anastomosis is undertaken. If venovenous bypass is used, interruption of the portal circuit is followed by removal of the portal cannula. In this manner, the donor and recipient main portal veins are exposed for an end-to-end anastomosis using an everting-cuff technique. The use of a fine monofilament suture (6-0 or 7-0) is mandatory. We typically tie this suture with an "air knot" or "growth factor" of approximately half the diameter of the portal vein to reduce the likelihood of portal stricture.

The final vascular anastomosis is arterial. The key principle of hepatic arterialization is to ensure pulsatile inflow through a large caliber vessel over a short length (Farmer et al, 2000). The technique involves the use of a fine (7-0) monofilament suture in a running or interrupted fashion. The vessel ends are frequently spatulated and are sewn from the outside and rotated to achieve the most precise anastomosis. The presence of aberrant hepatic arterial anatomy is encountered in 10% to 30% of grafts, and preservation of these vessels is essential for successful engraftment. Reconstruction of the aberrant vessels to obtain a single inflow vessel is imperative and takes place during the back table preparation of the graft as described earlier.

Recipient inflow is obtained from a branch off the celiac trunk, usually the proper or common hepatic artery. When adequate arterial inflow cannot be obtained by this artery, the use of an arterial conduit is recommended. Inflow originating from the infrarenal and supraceliac aorta has been described; both methods provide excellent inflow, and the choice is based on technical considerations and surgeon preference. The best choice of conduit is usually the donor iliac vessels. When donor vessels are unavailable or inadequate, prosthetic conduits can be used, typically polytetrafluoroethylene (PTFE). In the perioperative period, aortic conduits are associated with increased operating time, greater transfusion requirements, and respiratory and renal failure (Nikitin et al, 2008). In addition, several cases of internal hernias with small bowel volvulus around the intraperitoneal conduit have been reported (Nishida et al, 2002).

Completion of the vascular anastomoses is followed by establishment of biliary continuity. The most common methods used are the choledochocholedochostomy or choledochojejunostomy. The technical goals in biliary reconstruction are to achieve a tension-free anastomosis between viable ducts or intestine. The method used depends on many factors, including

the size match of the donor and recipient common bile duct and the presence of preexisting biliary pathology. Choledochocholedochostomy is preferable, because after OLT, access to the biliary tree is easier and safer with ERCP than with percutaneous transhepatic cholangiography. Choledochojejunostomy is used when the above-mentioned technical goals cannot be realized. Most pediatric recipients require choledochojejunostomy because of small duct size and a history of biliary atresia.

Prior to anastomosis, both the donor and recipient bile ducts should be trimmed sharply to remove devitalized tissues, and brisk bleeding should be evident from the cut ends. The recipient bile duct should be cleared of sludge and stones. Accommodation for size mismatch with ductoplasty of the larger duct or spatulation of both ducts has been described (Buczkowski et al, 2007; Nissen & Klein, 2009). The choledochocholedochostomy and choledochojejunostomy anastomoses are accomplished with the use of fine absorbable monofilament suture in a single-layer closure.

Whether to stent the biliary anastomosis during OLT is subject to debate (Barkun et al, 2003; Bawa et al, 1998; Johnson et al, 2000). Proponents believe that decompression of the biliary tree reduces the rate of clinically significant leaks, whereas others point to data that suggest a higher rate of biliary stricture from internal stents. At our institution, biliary stenting is performed selectively based on individual case circumstances and surgeon preferences.

COMPLICATIONS

Complications resulting from OLT can be divided broadly into technical complications, those arising as a consequence of immunosuppressive medications, and recurrence or recrudescence of the patient's original disease. The risk of surgeon-dependent technical complications increases when more complex surgical techniques, such as split-liver donation, are used. Examples of factors generally attributed to technical error include early thrombosis of the hepatic artery or portal vein, biliary complications such as leak or stricture, and, to a lesser extent, primary graft nonfunction. Invasive infection and certain metabolic complications are side effects of the immunosuppressive regimens currently in use. Finally, subacute and chronic graft rejection and recurrence of certain causes of initial liver failure eventually result in graft loss. Each of these complications is discussed.

Primary Nonfunction

Primary nonfunction is defined as early graft failure after OLT in the absence of identified technical complications. Clinical presentation varies, but patients typically are seen with alterations in mental status, diminished bile production, coagulopathy, markedly elevated transaminases, and metabolic acidosis. Multiorgan failure ensues, with oliguria and hypoxia occurring frequently. The reported rate of primary nonfunction varies between 1% to 7% of all OLTs (Jain et al, 2000; Johnson et al, 2007; Kamath et al, 1991; Kemmer et al, 2007; Taner et al, 2008; Totsuka et al, 2004). Retransplantation is the treatment of choice and typically is required within 72 hours. Some authors also report the distinctly separate category of initial poor function, in which allografts might have a chance for functional recovery; however, no consensus for a clear definition exists.

The etiology of primary nonfunction is unclear but is likely multifactorial. Factors commonly reported to be associated with nonfunction include prolonged cold and warm ischemic times, donation after cardiac death, intraoperative systemic hypotension (mean arterial pressure <40 mm Hg), severity of donor steatosis, advanced donor age, and recipient factors such as portal vein thrombosis (PVT), renal failure, dependence on life support, and status 1 listing (de Vera et al, 2009; Fernandez-Merino et al, 2003; Johnson et al, 2007; Marsman et al, 1996; Nair et al, 2002; Ploeg et al, 1993; Reich et al, 2003; Sharma et al, 2010; Strasberg et al, 1994). Although it has been proven that severe macrosteatosis (>60%) increases risk of graft failure, the influence of moderate steatosis (30% to 60%) remains unclear (Yoo et al, 2003a), and such allografts can be used with careful selection (Doyle et al, 2010).

Donor liver biopsy to quantify graft steatosis should be performed before implantation of any graft that appears marginal (D'Alessandro et al, 1991). As would be expected, the likelihood of primary nonfunction is increased in the presence of multiple risk factors (e.g., steatotic graft with extended total ischemic time) and in allografts with several marginal donor criteria (Pokorny et al, 2005; Salizzoni et al, 2003).

Hepatic Artery Thrombosis

Hepatic artery thrombosis (HAT) can be broadly divided into *early* (acute) and *late* (delayed) clinical presentation, with different etiologies, patient manifestations, and treatments. Although there is no formal consensus, *early HAT* is typically defined as occurring within the first 1 to 2 months after OLT and has a mean incidence of 2.9% in adult OLT patients, with a significantly higher incidence of 8% to 10% in the pediatric population (Bekker et al, 2009; Farmer et al, 2007). Early HAT carries a high risk of graft loss and death—53% and 33%, respectively (Bekker et al, 2009).

Technical, donor, and recipient factors contribute to an increased risk of HAT (Bekker et al, 2009; Del Gaudio et al, 2005; Duffy et al, 2009; Jurim et al, 1995; Soin et al, 1996; Vivarelli et al, 2004). Donor factors may include small-caliber vessels, aberrant anatomy that requires complex arterial reconstruction, use of aortic conduits, or cytomegalovirus (CMV) seropositivity donor-recipient mismatch. Variable recipient anatomy (e.g., replaced hepatic artery from superior mesenteric artery [SMA]) also influences risk of HAT.

Although early HAT may be asymptomatic, it frequently results in massive hepatocellular injury evidenced by increased transaminase levels and impaired hepatic synthetic function. The hepatic artery is the sole blood supply to the donor bile duct; therefore early HAT often presents with bile leak, cholangitis, or sepsis. Duplex ultrasound (US) is diagnostic in virtually all cases of HAT in adults, although visceral angiography remains the gold standard. If diagnosis is prompt, emergency exploration with attempted thrombectomy and revascularization may salvage the graft, although this is usually not possible.

Some reports suggest that endovascular procedures—intraarterial thrombolysis, percutaneous transluminal angioplasty, and endoluminal stenting—can be successful in hepatic arterial revascularization (Singhal et al, 2010); however, a majority of patients eventually require retransplantation (Bekker et al, 2009; Duffy et al, 2009). Because of the severity of this complication, some authors advocate the routine use of postoperative duplex US.

Late HAT is typically more indolent, frequently because a previously undiagnosed stricture allows collateral circulation to develop. Clinical presentation may include fever secondary to perihepatic abscess or biliary leak, biliary strictures, or cholangitis, although in some cases patients may be asymptomatic with no clinical consequences (Gunsar et al, 2003). Contributing factors are active tobacco abuse; coagulation abnormalities, such as factor V Leiden; cerebrovascular accident as donor cause of death; donor death at an age greater than 50 years; recipient CMV positivity; and use of donor iliac interposition graft (Del Gaudio et al, 2005; Gunsar et al, 2003; Pascual et al, 1997; Pungpapong et al, 2002; Stewart et al, 2009; Vivarelli et al, 2004).

Treatment may be attempted with endoscopic or percutaneous biliary decompression, stenting, or even systemic anticoagulation. Retransplantation is required less for late HAT than for early HAT. Because postoperative antiplatelet therapy may reduce the rate of late HAT in high-risk patients (Vivarelli et al, 2007), it is our practice to prescribe daily aspirin (81 mg) for all patients.

Hepatic Artery Stenosis

Hepatic artery stenosis (HAS) without thrombosis is also a recognized complication of liver transplantation, with an incidence of 4% to 11% (da Silva et al, 2008). DCD allografts have been implicated as a risk factor (Pine et al, 2009). Initial presentation typically includes a mild increase in aminotransferase levels with or without associated graft dysfunction or biliary complications. Doppler US demonstrates increased resistance in hepatic arterial flow and is often diagnostic, but confirmation by arteriography is the gold standard. Therapeutic options include angioplasty with or without stenting. Restenosis can occur in up to one third of patients within 1 year after stenting (Ueno et al, 2006).

Portal Vein Thrombosis

PVT occurs less frequently than HAT after OLT, with an incidence less than 2% in adult recipients and 10% in pediatric recipients (Duffy et al, 2009; Lerut et al, 1987; Millis et al, 1996), although PVT adversely affects overall survival after OLT (Duffy et al, 2009). Low portal flow, small-diameter veins (<5 mm), preexisting PVT in the recipient, donor-recipient vessel size mismatch, and the use of vascular grafts for reconstruction are known risk factors for developing PVT (Cheng et al, 2004).

PVT is typically symptomatic, and patients can present with acute hepatic failure, as with HAT, or with the sequelae of portal hypertension, such as increasing ascites, splenomegaly, and variceal hemorrhage (Duffy et al, 2009). Diagnosis is made using duplex US or contrast-enhanced CT portal venography.

Depending on the timeliness of diagnosis and the acuity of the patient, several treatment options exist. In patients with fulminant hepatic failure from PVT, reexploration and attempted portal revascularization are performed. These patients sometimes require retransplantation, particularly in the rare setting of combined PVT and HAT (total absence of hepatic inflow). The use of a portocaval shunt to augment flow through the reconstructed portal vein has been described (Bakthavatsalam et al, 2001), as has the use of transjugular intrahepatic portocaval shunt (TIPS) in conjunction with thrombolytics (Ciccarelli et al, 2001). Systemic anticoagulation may be sufficient in patients with preserved graft function (Duffy et al, 2009). Symptoms of portal hypertension but preserved graft function often can be managed medically with standard therapies for ascites in combination with variceal banding or sclerotherapy; however, the graft salvage rate with these alternative strategies is typically much less than 50% (Duffy et al, 2009).

Portal Vein Stenosis

Portal vein stenosis, in contrast to PVT, is frequently diagnosed on routine screening US in asymptomatic patients. The most common area of stenosis is the extrahepatic portal venous anastomotic site. Narrowing of the main portal vein diameter by more than 50%, presence of a poststenotic jet, or lack of visualized flow on Doppler imaging are diagnostic. Many stenoses can now be managed with percutaneous transhepatic balloon angioplasty and stenting (Woo et al, 2007).

Biliary Complications

Biliary complications are the most common type of posttransplantation complication, and they arise in 7% to 29% of liver recipients. Patients with HAT, living-donor allografts, and DCD livers are at higher risk for biliary complications (Maluf et al, 2005; Pine et al, 2009; Zajko et al, 1988). Historically, Roux-en-Y choledochojejunostomy was associated with higher complication rates than choledochocholedochostomy (O'Connor et al, 1995); however, this remains a controversial topic in transplantation techniques. All patients found to have a biliary complication should undergo US to evaluate HAT as a contributing factor.

Biliary strictures occur twice as frequently as anastomotic biliary leaks and can be classified as *anastomotic* or *nonanastomotic* (ischemic cholangiopathy) (Balsells et al, 1995; Qian et al, 2004). Most anastomotic strictures are managed endoscopically with balloon dilation and stenting. Ischemic cholangiopathy more commonly results from bile duct ischemia or an immune response, appears later and affects multiple sites, tends to be more difficult to manage, and is rarely amenable to endoscopic treatment. Nonanastomotic strictures are associated with a higher rate of graft failure requiring retransplantation (Chan et al, 2008; de Vera et al, 2009; Pine et al, 2009). A multidisciplinary approach to diagnosis and management of biliary complications is necessary and can result in higher patient and graft survival rates (Verran et al, 1997).

In an asymptomatic patient with stable liver function, biliary complications can often be managed nonoperatively. Bile collections should be drained percutaneously under US or CT guidance, and most leaks are controlled with endoscopic stent placement across the anastomosis (Shah et al, 2004). Major leaks or total disruption usually requires operative conversion to a choledochojejunostomy or hepaticojejunostomy, an option that can result in long-term biliary patency (Langer et al, 2009).

Numerous studies have evaluated the use of T-tubes and internal stents for prophylactic biliary decompression. Several have identified T-tube use as an independent risk factor for increased postoperative biliary complications (e.g., biliary-cutaneous fistulae and cholangitis), and their use has not been shown to reduce the need for posttransplantation interventional procedures (Qian et al, 2004; Scatton et al, 2001; Sotiropoulos et al, 2009). Consequently, T-tubes are much less commonly

used in standard adult OLT in the United States; however, a recent prospective European trial did not find evidence of increased biliary complications with T-tubes (Weiss et al, 2009). The effectiveness of internal stenting in reducing biliary complications also remains inconclusive (Welling et al, 2008).

Infection

Infection is the most common cause of death after OLT at all time points (Jain et al, 2000), directly causing 28% of all deaths in liver transplant patients. An autopsy series of OLT patients showed an even higher infection-related mortality rate of 64% (Torbenson et al, 1998). Two thirds of OLT recipients experience at least one serious infectious episode (Winston et al, 1995), despite ever-improving prophylactic regimens. Intraabdominal infections occur in 40% of recipients with a higher incidence in patients with other noninfectious surgical complications (Reid et al, 2009).

Liver transplant patients are immunocompromised as a result of antirejection medications, they are also malnourished, chronically ill, have received multiple blood-product transfusions, and have undergone lengthy and complex surgical procedures—all of which are risk factors for infectious complications. Additionally, the risk of posttransplantation infection is further increased by the prevalence of morbid obesity in the recipient population (Dick et al, 2009).

Diagnosis of infection can be complicated by a relative absence of symptoms, as infection frequently manifests only as a leukocytosis (Reid et al, 2009). As part of the pretransplantation evaluation, recipients should undergo an infectious disease workup and should receive appropriate vaccines. Appropriate antimicrobial prophylaxis can reduce the postoperative infection rate by more than half, depending on the pathogen. The current prophylactic regimen used at Washington University in St. Louis is shown in Box 98A.2.

Box 98A.2

Antimicrobial Prophylaxis for Liver Transplantation Patients at Washington University in St. Louis

Bacterial

Routine use of broad-spectrum antibiotics on-call to operating room, continued for 24 h postoperatively

Fungal

Fluconazole (Diflucan, once weekly) for 3 mo postoperatively in high-risk patients

Pneumocystis Carinii

Trimethoprim-sulfamethoxasole (Bactrim/Septra SS) for 1 yr postoperatively
Pentamidine (Pentam) or dapsone for patients with sulfa sensitivity

Viral

High Risk

Donor CMV+/recipient CMV−: valganciclovir 900 mg daily for 3 mo, then 450 mg daily for 9 mo

Intermediate Risk

(D+/R+ or D−/R+): Valganciclovir 450 mg daily for 6 mo
Low risk (D−/R−): acyclovir 200 mg bid for 3 mo

CMV, cytomegalovirus

Bacterial pathogens are the most common infectious agent in the early postoperative period, and the proportion of posttransplantation infection as a result of bacteremia has increased significantly (Singh et al, 2004). DM and serum albumin less than 3 mg/dL are independent risk factors for bacteremia. Although gram-negative bacilli remain frequent causes of postoperative infection after OLT, gram-positive cocci, such as methicillin-resistant *Staphylcoccus aureus* (MRSA) and vancomycin-resistant enterococci (VRE), have become increasingly prevalent at many transplant centers (Papanicolaou et al, 1996; Reid et al, 2009; Singh et al, 2004). Colonization with MRSA and VRE before transplantation increases the risk of developing infection after OLT with the same organism and, in the case of VRE colonization, is associated with an increased mortality risk (Russell et al, 2008).

Typically presenting in the first 2 to 3 weeks after transplantation, 25% of OLT patients are reported to develop MRSA bacteremia, with colonization of indwelling vascular catheters accounting for about half of the cases (Singh et al, 2000a). Vascular catheters account for one quarter of bacteremia for all pathogens combined. Other sources of post-OLT bacteremia include—in decreasing order of frequency—pneumonia, biliary infections, abdominal sources, and surgical wound infections (Singh et al, 2000b, 2004). The emergence of drug-resistant organisms resulting from overuse of common antibiotics has made the treatment of infected liver transplant recipients increasingly difficult.

CMV is the most common viral pathogen encountered by OLT recipients, although incidence of CMV infection has declined as a result of improved prophylaxis (Singh et al, 2004). Intraoperative hypothermia is a known risk factor for developing CMV infection regardless of prophylaxis (Paterson et al, 1999). Without appropriate prophylaxis, the overall incidence in this population is commonly 50% to 60%, with clinically apparent infections usually occurring 3 to 12 weeks after transplant (Farmer et al, 2000).

The routine use of ganciclovir (Cytovene) has been shown to dramatically reduce CMV infection after OLT in several randomized, controlled trials (Gane et al, 1997; Winston, 1995; Winston & Busuttil, 2003, 2004). The standard regimen includes an induction with intravenous ganciclovir followed by prophylaxis with oral ganciclovir for 3 to 6 months. Some studies suggest that valganciclovir, which can be administered with once-daily dosing because of improved bioavailability, might be as efficacious and safe as ganciclovir in the prevention of CMV infection in low-risk, but not high-risk, liver recipients (Jain et al, 2005; Park et al, 2006; Shiley et al, 2009); prolonged treatment (≥100 days) can be costly and might be unnecessary in low-risk patients (e.g., seronegative donor and recipient). Ganciclovir-resistant CMV has been observed in 20% of solid-organ transplant recipients treated with ganciclovir, with presentation typically observed late in the first year (Limaye et al, 2000). Our current strategy is to reserve prolonged treatment with ganciclovir for seronegative patients receiving a seropositive graft or in patients with evidence of active CMV infection.

Invasive fungal infections usually are caused by *Candida* or *Aspergillus* species, *Cryptococcus,* and non-*Aspergillus* mycelial fungi, with an incidence of 5% to 9% in OLT patients (Pappas et al, 2010; Singh, 2000). Invasive candidiasis and aspergillosis tend to occur relatively early in the postoperative period, whereas *Cryptococcus* infection becomes apparent several

months to years after OLT (Pappas et al, 2010). Traditionally, *Candida albicans* has been the most common fungal pathogen.

Risk factors for developing fungemia include use of broad-spectrum antibiotics or immunosuppressant medications, retransplantation or other reoperative intervention, CMV infection, renal failure, and overall severity of medical illness (Cruciani et al, 2006). Routine prophylaxis with antifungal agents—such as fluconazole, itraconazole, and amphotericin B—significantly reduces fungal infection and infection-related mortality after liver transplantation; however, it does not improve overall mortality (Cruciani et al, 2006). Historically, fluconazole was almost universally included in antimicrobial prophylaxis, but this subsequently led to an increase in reported *Aspergillus* infections, because *Aspergillus* is not susceptible to fluconazole.

Currently, a majority of transplant centers provide antifungal prophylaxis only to high-risk patients, including those requiring retransplantation or reexploration, dialysis, mechanical ventilation, or a prolonged ICU stay and those subject to and graft failure or colonization with *Candida* (Singh et al, 2008). Although prophylaxis against *Aspergillus* is not supported by the literature (Braun et al, 1998; Singh 2000), voriconazole, amphotericin B, and caspofungin may be used alone or in combination for treatment of invasive aspergillosis (Singh et al, 2008), which is associated with a 40% 1 year mortality rate after infection (Pappas et al, 2010).

Infection with the protozoan *Pneumocystis carinii* occurs in 3% to 11% of liver transplant patients in the absence of prophylaxis (Singh, 2000). Because T-cell immunity is the primary defense against this organism, prolonged use of corticosteroids or muromonab-CD3 monoclonal antibodies and active CMV infection increase the risk of infection. Trimethoprim-sulfamethoxazole (single strength, once daily) offers highly effective prophylaxis at a low cost and with minimal side effects. Because the risk of *P. carinii* infection is eightfold higher in the first year after OLT than in subsequent years, prophylaxis generally is continued only during these initial 12 months (Gordon et al, 1999).

Rejection

Rejection can sometimes be a major hurdle to long-term survival after OLT. Previously reported to occur in 40% to 70% of OLT patients (Klintmalm, 1991), the development of novel immunosuppressive regimens has reduced the lifetime rejection rate to less than 20% (McAlister et al, 2001). It is becoming increasingly clear that certain subpopulations of patients receiving OLT can be weaned completely from all immunosuppressive agents without experiencing rejection (Devlin et al, 1998; Mazariegos et al, 1997). The University of Pittsburgh experience shows that immunosuppression can be withdrawn successfully in almost one third of patients, although it is unknown exactly what traits allow such weaning.

Hyperacute rejection is rarely seen today. It typically occurs in the setting of ABO incompatibility, with a reported graft failure rate of 46% observed in 51 patients transplanted across ABO type (Demetris et al, 1988). Hyperacute rejection is mediated by preformed antibodies in the recipient and is directed against the graft endothelium. These antibodies produce activation of the innate immune system via the complement cascade, ultimately leading to rapid graft destruction. Retransplantation is the only treatment option.

Although acute liver rejection usually occurs within the first 4 weeks after transplantation, it can occur later. Patients with acute liver rejection are seen with signs of fever, malaise, right upper quadrant abdominal pain, and elevated liver transaminases. Elevation in liver enzymes is often detected before physical symptoms or signs occur. Percutaneous liver biopsy reveals portal inflammation with predominantly mononuclear cells, bile duct inflammation and injury, centrilobular necrosis, and lobular inflammation. Differentiation from other pathologic processes can be difficult. In contrast to other solid-organ transplants, such as kidney and heart, the occurrence of an acute rejection episode does not seem to reduce the overall graft survival, if treatment is initiated promptly (Wiesner et al, 1998).

The treatment for acute rejection is usually bolus corticosteroids: 1000 mg methylprednisolone (Solu-Medrol), followed by a 5-day taper. Patients who do not respond to bolus steroids may require additional strategies, including the use of monoclonal anti–T-cell antibody therapy (e.g., OKT3); however, this is rarely needed in the current era because fewer than 5% of patients experience rejection. When patients fail to respond to bolus steroid therapy, it is important to be certain of the diagnosis and to consider other potential causes of abnormal liver tests, including biliary or vascular causes. Repeat biopsies can be helpful to confirm the diagnosis and assess the response to therapy.

Today, only about 2% of patients experience chronic rejection after liver transplantation, although the incidence is higher in patients with autoimmune disease (Wiesner et al, 2003). The etiology of chronic rejection is multifactorial, characterized by progressive loss of bile ducts, obliteration of medium-sized and large hepatic arterioles, and cellular portal infiltration (Farmer et al, 2000). Standardized histopathologic evaluation of acute and chronic rejection using the Banff schema (Tables 98A.3 and 98A.4) allows objective decision making and facilitates comparisons of natural histories among patients (Banff Consensus, 1997; Demetris et al, 2000; Racusen et al, 2003).

Metabolic and Systemic Complications

With the increase in overall survival after OLT, a growing recognition has emerged of associated long-term medical sequelae and their impact on patient health. Prolonged use of corticosteroids can produce hyperlipidemia, obesity, DM, arterial hypertension, and mineral-deficient bone disease; commonly used antirejection drugs induce similar derangements. Cardiovascular disease then becomes a leading cause of death in patients who survive more than 3 years after liver transplantation, accounting for more than half of the reported mortality in some series (Asfar et al, 1996; Pruthi et al, 2001). Predictors of perioperative cardiac events include pre-OLT history of stroke, and perioperative mortality was increased with a history of coronary artery disease (CAD) and postoperative sepsis (Safadi et al, 2009).

Renal Dysfunction

Liver transplant recipients have a high risk of developing post-transplant chronic renal failure, with an incidence of 18% at 5 years (Ojo et al, 2003). The average functional decline in renal function is a 38% decrease in glomerular filtration rate, and it is correlated with time elapsed since transplantation (decline by 36 mL/min/1.73m^2) (Bucuvalas et al, 2006; Karie-Guigues

Table 98A.3

Rejection Activity Index from the Banff Schema for Acute Hepatic Rejection

Category	Criteria	Score
Portal inflammation	Mostly lymphatic inflammation involving a minority of the triads	1
	Expansion of most triads by a mixed infiltrate containing lymphocytes, neutrophils, and eosinophils	2
	Marked expansion of most or all triads by a mixed infiltrate containing numerous blasts, with spillover into periportal parenchyma	3
Bile duct damage	Minority of ducts infiltrated by inflammatory cells, with only mild reactive changes in epithelial cells	1
	Most or all ducts infiltrated by inflammatory cells, with occasional degenerative duct changes, such as nuclear pleomorphism, disorder polarity, and vacuolization	2
	As above, with most or all ducts showing degenerative changes	3
Venous endothelial inflammation	Subendothelial lymphocytic infiltration of some portal or hepatic venules	1
	Subendothelial infiltration involving most or all portal or hepatic venules	2
	As above, with perivenular inflammation extending into surrounding parenchyma and associated hepatocyte necrosis	3

This index has a range from 0 to 9, classified as follows: 0 to 3, minimal acute rejection; 4 to 6, mild acute rejection; 7 to 9, moderate to severe acute rejection.

Modified from the Banff Consensus, 1997: schema for grading liver allograft rejection: an international consensus document. Hepatology 25:658-663.

et al, 2009). The use of calcineurin inhibitors (CNIs) is associated with increased risk of renal failure in patients after OLT, although this decline may be partially attenuated with concomitant administration of mycophenolate mofetil and calcineurin dose reduction (Karie-Guigues et al, 2009). Other risk factors for the onset of post-OLT renal dysfunction include age and gender of the recipient, history of HCV infection, DM, and pretransplantation renal insufficiency, CAD, and primary nonfunction (Ojo et al, 2003; Pawarode et al, 2003). Mortality following OLT is four times greater in recipients who develop posttransplantation renal failure (Ojo et al, 2003).

Posttransplantation Metabolic Syndrome

Posttransplantation metabolic syndrome (PTMS) is becoming recognized as an important entity in liver transplant recipients. Prevalence in the post-OLT population is twice that of the estimated 24% prevalence in the general population (Bianchi et al, 2008; Hanouneh et al, 2008; Laryea et al, 2007; Pagadala et al, 2009). Posttransplantation obesity develops in 60% of patients, with most excess weight gain occurring in the first year (Muñoz et al, 1991). The cause of weight gain is multifactorial: corticosteroids and cyclosporine, and to a lesser extent tacrolimus, are known to correlate significantly with the incidence of obesity (Canzanello et al, 1997). Development of PTMS does not seem to be influenced by the etiology of the recipient's ESLD (Bianchi et al, 2008); however, liver transplant recipients who develop PTMS appear to be at higher risk for vascular events (Laryea et al, 2007) and are at higher risk for development of allograft steatosis (Dumortier et al, 2010).

Diabetes Mellitus

De novo DM occurs in up to one third of previously nondiabetic liver transplant recipients (Navasa et al, 1996; Sheiner et al, 2000). Corticosteroids are known to induce insulin resistance, and the occurrence of graft rejection necessitating increased steroid dosing is a risk factor for developing diabetes.

Table 98A.4

Banff Schema for Chronic Hepatic Rejection

Structure	Early Chronic Rejection	Late Chronic Rejection
Small bile ducts (<60 μm)	Degenerative changes involving most ducts: increased nuclear-to-cytoplasmic ratio, nuclear hyperchromasia, uneven nuclear spacing, ducts partially lined with epithelium	Degenerative changes in remaining bile ducts
	Bile duct loss in <50% of portal tracts	Bile duct loss in >50% of portal tracts
Terminal hepatic venules	Intimal/luminal inflammation	Focal obliteration
	Lytic zone 3 necrosis and inflammation	Variable inflammation
	Mild perivenular fibrosis	Severe (bridging) fibrosis
Portal tract hepatic arterioles	Occasional loss involving <25% of portal tracts	Loss involving >25% of portal tracts
Large perihilar hepatic artery branches	Intimal inflammation, focal foam-cell deposition	Luminal narrowing by subintimal foam cells and fibrointimal proliferation
Large perihilar bile ducts	Inflammation damage, focal foam-cell deposition	Mural fibrosis
Other	"Transition" hepatitis with spotty necrosis of hepatocytes	Sinusoidal foam cell accumulation, marked cholestasis

Modified from Demetris A, et al, 2000: Update of the International Banff Schema for Liver Allograft Rejection: working recommendations for the histopathologic staging and reporting of chronic rejection: an international panel. Hepatology 31:792-799.

Tacrolimus and other immunosuppressants also increase insulin resistance. Diabetes in most patients is transient and generally resolves within the first year, as immunosuppressive medications are tapered.

Infection with HCV is another known risk factor for the development of posttransplantation diabetes, and this risk is correlated with increased HCV viral load (Delgado-Borrego et al, 2008). Although the mechanisms underlying the relationship between HCV and diabetes are not fully understood, altered insulin sensitivity is likely to play a role. Pretransplantation glucose intolerance, as determined by formal glucose challenge testing, is present in 53% of candidates awaiting liver transplantation (Blanco et al, 2001). Although some degree of glucose intolerance may improve with OLT, insulin-dependent diabetes almost never resolves after transplantation (Shields et al, 1999; Stegall et al, 1995). Additionally, insulin-dependent DM is a known risk factor for lower survival following transplantation, and CAD is an independent predictor of worse outcomes (Yoo & Thuluvath, 2002).

Neurologic Complications

Neurologic complications occur with greater frequency in recipients of liver allografts than in other solid-organ recipients (Senzolo et al, 2009). The aggregate prevalence of neurologic sequelae is 25%, although such have occurred in more than 60% of patients in some series (Amodio et al, 2007; Bronster et al, 2000; Emiroglu et al, 2006; Ghaus et al, 2001; Lewis & Howdle, 2003; Saner et al, 2006).

Posttransplantation encephalopathy is the most common neurologic complication, followed by seizures (Bronster et al, 2000; Lewis & Howdle, 2003; Saner et al, 2006; Senzolo et al, 2009). Encephalopathy can be caused by anoxia, sepsis, medications (especially CNIs), primary graft nonfunction, renal failure, rejection, and central pontine myelinolysis (CPM) (Erol et al, 2007). Infection, stroke, and CPM are also common causes of seizures (Senzolo et al, 2009). Other neurologic complications include posterior leukoencephalopathy, cerebellar syndrome, focal deficits, headache, tremor, sleep disorders, and peripheral neuropathy. Risk factors for neurologic complications include an operative time longer than 10 hours, high CTP score, and a history of hepatic encephalopathy (Dhar et al, 2008). Older age and higher MELD scores pretransplantation are associated with increased risk of tacrolimus-related neurotoxicity (DiMartini et al, 2008). In cases of CNI-related neurotoxicity, patients can frequently be switched to a different drug within the same class with successful resolution of symptoms (Emiroglu et al, 2006; Erol et al, 2007). Most central nervous system (CNS) complications (80%) occur within 1 month after OLT but may be seen up to several years after transplantation (Bronster et al, 2000). The incidence of neurologic complications in LDLT recipients (17%) approximates that of cadaveric allograft recipients, and outcomes from these complications appear to be similar (Saner et al, 2010).

Immunosuppressant Toxicity

CNIs can cause significant renal and neurotoxicity. Use of sirolimus as an alternative immunosuppressant in patients with these adverse effects may allow patients to recover from CNI toxicity without significant risk of rejection (Di Benedetto et al, 2008; Morard et al, 2007).

OUTCOMES

Survival after OLT has improved markedly as a result of continuing refinements in organ procurement and preservation, recipient selection, surgical and anesthetic techniques, perioperative care, and long-term immunosuppression. Overall patient survival at 10 years is 60% in the United States, with an unadjusted 10-year graft survival of 54% (Thuluvath et al, 2010). In select patient populations, some institutions have achieved near zero short-term mortality (Broering et al, 2004; Sugawara et al, 2002).

Recipient factors associated with reduced survival include recipient age over 65 years, preexisting CAD, insulin-dependent DM, renal insufficiency, and extreme body mass index (BMI) (Busuttil et al, 2005; Dick et al, 2009; Nair et al, 2002; Thuluvath et al, 2010; Yoo & Thuluvath, 2002). Other factors that adversely affect survival include conditions that require urgent transplantation, such as hepatic malignancy as the indication for transplantation, donor hospitalization longer than 6 days, cerebrovascular accident as donor cause of death, prolonged warm (>45 minutes) and cold (>10 hours) ischemic time, and retransplantation (Busuttil et al, 2005).

Deceased-donor split allografts have not been shown to adversely affect outcomes in large series (Busuttil et al, 2005), and LDLT over the last decade has had better long-term outcomes than deceased-donor transplantation (Thuluvath et al, 2010). The overall rate of retransplantation for recipients of DDLT was 7.8% in 2007, representing the lowest level in the last decade (USRTR, 2008). Outcomes after liver transplantation for certain disease processes are discussed below.

Biliary Atresia

The long-term primary hepatic salvage rate after portoenterostomy in infants with biliary atresia ranges from 20% to 45% (Davenport et al, 2004; Otte et al, 1994; Schreiber et al, 2007; see Chapter 40). The remaining infants develop progressive biliary cirrhosis and ultimately require liver transplantation. Biliary atresia is the most common indication for OLT in children younger than 18 years, and the best results are obtained in patients referred for transplantation early, after only a single attempted portoenterostomy. Approximately 80% of children transplanted for biliary atresia have had a prior biliary drainage procedure (Utterson et al, 2005; Visser et al, 2004). Despite this high rate of transplantation, portoenterostomy remains a viable bridge to definitive therapy, allowing infants to grow.

Transplantation is a durable solution for biliary atresia, and this recipient population obtains the best survival rates, with 10-year patient survival greater than 80% and graft survival greater than 67% (Barshes et al, 2005; D'Alessandro et al, 2007; Diem et al, 2003; Farmer et al, 2007; Schreiber et al, 2007; Visser et al, 2004). The use of split-liver cadaveric grafts and living related transplantation has expanded the potential donor pool, extending OLT to an increased number of children with biliary atresia, without a significant increase in post-OLT mortality (Barshes et al, 2005; Chen et al, 2006; Yersiz et al, 2003).

Additionally, use of living-donor liver allografts significantly shortens time on the waiting list (Visser et al, 2004); however, technical variant grafts may increase the risk of graft failure (Utterson et al, 2005). Graft failure and vascular complications

account for the majority of early post-OLT deaths, whereas rejection remains the leading cause of late death in these patients (Barshes et al, 2005).

Primary Sclerosing Cholangitis and Primary Biliary Cirrhosis

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of unknown origin that is frequently associated (70% to 80%) with inflammatory bowel disease, usually ulcerative colitis (UC; see Chapter 41). Patients with PSC also are at risk for the development of cholangiocarcinoma. Although medical palliation exists, the only cure for PSC is liver transplantation. Outcomes after OLT for PSC are excellent, with 5-year patient survival rates ranging from 80% to 85% (Goss et al, 1997; Ricci et al, 1997; Solano et al, 2003) and 10-year survival at 70% (Busuttil et al, 2005). Whether the incidental discovery of cholangiocarcinoma in the explanted liver affects patient survival is controversial (Goss et al, 1997; Solano et al, 2003). Approximately 9% to 11% of patients develop recurrent PSC after transplantation.

Primary biliary cirrhosis (PBC) is an autoimmune disease typically characterized by the development of circulating antimitochondrial antibodies (AMAs). Patients with PBC generally have better long-term survival (>7 years) than patients transplanted for PSC (Maheshwari et al, 2004). They are more prone to chronic rejection, however, and are less likely to be weaned from immunosuppression (MacQuillan et al, 2003). PBC likely recurs in a few patients after OLT, although long-term follow-up data are lacking, and this rate appears to be much less common than for PSC recurrence. Posttransplantation AMA titers are not predictive of disease recurrence; a liver biopsy specimen showing granulomatous destructive cholangitis remains the gold standard (Faust, 2001).

Alcoholic Cirrhosis

Although often producing ESLD in conjunction with viral hepatitis, alcoholic cirrhosis is one of the leading indications for OLT in the United States (Amersi et al, 1998; Thuluvath et al, 2010). Early reports showing equivalent outcomes in patients with alcoholic cirrhosis compared with patients with nonalcoholic cirrhosis resulted in widespread application of OLT for this indication (Bird et al, 1990; Starzl et al, 1988). Medical outcomes in this group continue to be good (Busuttil et al, 2005; DiMartini et al, 1998; Lim & Keeffe, 2004).

Recidivism occurs in roughly 20% to 30% of patients transplanted for alcoholic cirrhosis (Biselli et al, 2010; Pageaux et al, 2003; Rowley et al, 2010). Although there is little convincing evidence that resumption of drinking adversely affects graft or patient survival after OLT, there are ethical concerns over possibly misallocating donor organs to active substance abusers (Lim & Keeffe, 2004). Relapse might also serve as a proxy marker for patients who are likely to have poor nutrition and overall health as well as poor compliance with their immunosuppressive regimen and, therefore, increased risk of rejection (Pageaux et al, 2003). Most transplant centers require potential transplant candidates to participate in a support program, undergo psychologic evaluation, and remain abstinent from substance abuse, with documented random drug and alcohol testing for at least 6 months before placement on the waiting list. Multivariate analysis of alcoholic patients with cirrhosis who have undergone OLT showed that abstinence for 6 months or more before OLT is the strongest predictor for nonrelapse after transplantation (Miguet et al, 2004).

Hepatitis B Virus

Since the standardization of HBV treatment with hepatitis B immunoglobulin (HBIG) and antiviral agents, the rate of recurrent HBV infection in liver transplant recipients has declined from 80% in untreated patients to less than 10% of treated patients at 2 years (Roche & Samuel, 2004; Saab et al, 2009; Todo et al, 1991; see Chapter 64). Current treatment strategies include reducing or eliminating active viral replication before transplantation through the administration of lamivudine or adefovir, in combination with other agents, then combining one of these with HBIG after OLT indefinitely. This approach has resulted in similar outcomes for patients without recurrence compared with patients undergoing OLT for other reasons (Kim et al, 2004; Roche et al, 2003; Steinmuller et al, 2002); however, HBIG administration can be costly and cumbersome, and resistance to lamivudine is reported in 20% of patients after treatment for 1 year.

Although combination prophylaxis with lamivudine and HBIG is highly effective, other methods to combat HBV recurrence are being investigated. Alternative regimens include combination antiviral agents (e.g., lamivudine and adefovir) without routine use of HBIG (Nath et al, 2006). HBV recurrence portends a poor outcome, with a 5-year survival rate of 47% (Saab et al, 2009). For patients with HCC at transplantation, recurrent HBV infection is also significantly associated with a recurrence of HCC after transplantation (Saab et al, 2009).

Hepatitis C Virus

Since its definitive identification in 1989, HCV has been determined to be a major cause of chronic liver disease and cirrhosis, accounting for 37% to 41% of OLT performed in the United States (Thuluvath et al, 2010). Approximately 2% of the general population carries the virus, and 50% to 60% of these individuals develop chronic liver disease (Farmer et al, 2000; see Chapter 64).

Short-term and intermediate-term patient survival after OLT for HCV is not significantly different from HCV-negative patients who receive transplants for other nonmalignant reasons, although graft survival is significantly reduced compared with allografts for alcoholic liver disease (Biselli et al, 2010; Boker et al, 1997; Ghobrial et al, 2001). Unadjusted 10-year survival rates are lower for HCV-positive recipients in the United States (Thuluvath et al, 2010). Recurrent infection is nearly universal, and chronic hepatitis develops in most patients after OLT (Gordon et al, 2009). The clinical course is similar to nontransplanted HCV-positive patients, with only 13% developing hepatic fibrosis (Saab et al, 2009). In these patients with recurrent hepatitis C cirrhosis, 5-year survival decreases to 30% (Saab et al, 2005). Recipients coinfected with HIV tend to experience faster and more aggressive recurrence of HCV (Di Benedetto et al, 2008).

In contrast to HBV, no approved therapies are currently available for prevention of recurrent HCV infection after liver transplantation. Outcomes for transplantation of HCV recipients with extended-criteria livers are significantly worse, and donor age has been reported to affect graft survival adversely

(Lake et al, 2005; Machicao et al, 2004; Russo et al, 2004; Thuluvath et al, 2010); however, older donors can be safely used, with similar results in HCV-positive recipients with short cold and warm ischemia times and careful donor selection (Doyle et al, 2008).

Hepatocellular Carcinoma (See Chapters 80 and 97D)

HCC was one of the first documented indications for OLT (Starzl et al, 1968). The decision to utilize transplantation for this disease is based on the oncologic premise of performing a complete resection (total hepatectomy) with wide surgical margins to effect a cure and to remove potential future sites of tumor formation in the diseased remnant liver. Improved selection of appropriate candidates with HCC for OLT has led to improved outcomes and consequently has more than doubled the number of patients with HCC on the waiting list (Thuluvath et al, 2010).

Liver transplantation in the setting of extrahepatic malignancy is contraindicated. Conversely, the finding of incidental HCC in the explanted specimen after transplantation for a nonmalignant indication does not alter patient or graft outcome significantly (Cillo et al, 2004). The difficulty has been the selection of patients for OLT with malignant disease confined to the liver but at an advanced stage.

In their series examining liver transplantation for HCC, Mazzaferro and colleagues (1996) obtained a 75% 4-year actuarial survival using specific guidelines in highly selected patients. Subsequently termed the *Milan criteria* for OLT, patients under this protocol were offered transplantation if they had a solitary tumor less than 5 cm in diameter or no more than three nodules, each less than 3 cm in diameter (stage II). Largely as a result of this report, UNOS adopted these criteria for placing potential recipients on the waiting list, limiting transplantation to patients with stage I (single tumor up to 2 cm in diameter) or stage II disease.

Currently, MELD exception points (22 points) are awarded only on a routine basis to patients with stage II HCC, who account for 8% to 9% of all deceased-donor liver recipients today (USRTR, 2008). Patients with more advanced HCC can only receive additional MELD priority points through special appeal to regional review boards of transplant surgeons and physicians. Although not equaling the excellent results of Mazzaferro and colleagues (1996), reported 5-year survival after OLT for HCC generally ranges from 60% to 75% in several large, more recent series (Goodman et al, 2005; Yao et al, 2001; Yoo et al, 2003).

Several centers have attempted to expand liver transplantation to patients with tumors exceeding the Milan criteria and have met with varying degrees of success. The University of California–San Francisco (UCSF) criteria permit transplantation for patients with solitary tumors smaller than 6.5 cm diameter, fewer than three tumors, and a maximum diameter less than 4.5 cm or total cumulative diameter less than 8 cm (Yao et al, 2001).

Prospective trials currently are examining multimodal treatment for HCC, whereby patients undergo chemoembolization or other ablative techniques to downstage the tumor clinically, followed by transplantation. We require patients with stage III or IV HCC to undergo tumor downstaging, usually with TACE, to meet Milan criteria and with a minimum period of 3 months of observation without evidence of extrahepatic tumor on restaging. Our results using this strategy in highly selected patients are equivalent to patients initially meeting Milan criteria without the need for downstaging (Chapman et al, 2008). Currently, 58% of patients receiving MELD exception points for HCC have undergone TACE or radiofrequency ablation while on the waiting list, with the majority receiving TACE (Thuluvath et al, 2010). Although no prospective trials demonstrate a long-term oncologic benefit to pretransplantation TACE, retrospective data strongly suggest that this may be beneficial, and we consider this a routine practice in our HCC transplant candidates (Bharat et al, 2006).

Cholangiocarcinoma (See Chapters 50C and 97E)

No effective medical treatment has been found for cholangiocarcinoma. Surgical extirpation is feasible in less than 30% of all patients and produces 5-year survival rates less than 30%, even with complete resection (Jarnagin et al, 2001; Rea et al, 2004). Additionally, patients with PSC, a known risk factor for cholangiocarcinoma, are often poor candidates for resection because of concurrent cirrhosis. Historically, the use of OLT for treatment of cholangiocarcinoma has been associated with 5-year survival rates of 30% and even lower rates in patients with incidentally discovered cholangiocarcinoma at transplantation (Becker et al, 2008). Surgeons at the Mayo Clinic reported successful results using strict treatment protocols for performing OLT in patients with localized, node-negative hilar cholangiocarcinoma, which included the use of neoadjuvant chemoradiation, staging laparotomy, resection to negative margins, and OLT (see Chapter 97E). Using these or similar protocols, 5-year survival rates of 72% have been achieved in a highly selected group of patients, many of whom had PSC (Heimbach et al, 2004; Rea et al, 2009; Sudan et al, 2002). Retrospective analysis revealed improved outcomes for patients enrolled in the Mayo protocol compared with those of patients undergoing major hepatic resection (Rea et al, 2005); however, these outcomes have been difficult to achieve at other institutions, and neoadjuvant therapy is associated with higher rates of arterial and venous complications after transplantation (Mantel et al, 2007).

Fulminant Hepatic Failure (See Chapters 72 and 97C)

The cohort that undergoes OLT for fulminant hepatic failure comprises a diverse group of patients and disease etiologies. By definition, these patients have no previous demonstrable liver disease, yet they present acutely with encephalopathy; synthetic dysfunction, such as coagulopathy; and jaundice. Most commonly, the etiology is never determined, but fulminant hepatic failure (FHF) can be caused by drugs, viruses, toxins, or other liver injuries (Hoofnagle et al, 1995). Although artificial liver support systems are under development, the only widely available cure for acute liver failure is OLT. Limited donor organ availability leads to the relatively high waiting-list mortality rate of 377 deaths per 1000 patient-years at risk. MELD scores tend not to predict outcome accurately in patients with FHF (Kremers et al, 2004); in this setting, outcome after OLT is below average, with approximately 67% of patients surviving to 5 years (Farmer et al, 2003).

Nonalcoholic Steatohepatitis (See Chapter 65)

Cirrhosis secondary to nonalcoholic steatohepatitis (NASH) is a rapidly increasing indication for liver transplantation, accounting for approximately 5% of transplantations performed in 2007 (USRTR, 2008). NASH, a stepwise progression in the natural history of nonalcoholic fatty liver disease (NAFLD), is associated with obesity. Data gathered to study the effects of BMI on outcomes of OLT are inconclusive. Although it has been shown that morbidly obese recipients are at higher risk for PTMS and infectious complications, it has not been definitively shown to affect long-term outcomes (Leonard et al, 2008; Malik et al, 2009). Independent risk factors for development of graft steatosis after OTL include pretransplantation graft steatosis, post-OLT obesity, hypertension, DM, hyperlipidemia, use of tacrolimus, and alcoholic cirrhosis as the primary indication for liver transplantation (Dumortier et al, 2010).

RETRANSPLANTATION

The rate of retransplantation has been gradually declining, reaching a low of 7.8% in 2007 (USRTR, 2008). In particular, the rate of retransplantation for HCV dropped to 5% in 2008 (Thuluvath et al, 2010). The most common indications for retransplantation include primary nonfunction (46% of retransplants), HAT (29%), acute and chronic rejection (7%), and recurrent disease (Busuttil et al, 2005; Jain et al, 2000; Lang et al, 2008; Marti et al, 2008; Thuluvath et al, 2010). Use of DCD allografts is associated with a 13% retransplantation rate, which has remained stable over the last decade (Thuluvath et al, 2010).

Outcome after retransplantation is generally worse than after initial OLT but is slowly improving, with a 10-year graft survival up to 69% in some centers (Marti et al, 2008); however, this varies significantly by primary indication (Adam & Hoti, 2009; Thuluvath et al, 2010). Patients requiring retransplantation are at increased risk for infection, HAT, and acute renal failure (Uemura et al, 2007). Retransplantation for primary nonfunction yields 54% to 60% patient survival at 5 years (Kemmer et al, 2007; Uemura et al, 2007). Recurrent HCV is associated with worse outcomes following retransplantation overall, and most centers avoid retransplantation for this indication; however, a recent multicenter analysis demonstrated similar 3-year survival rates in a highly select group of patients with recurrent HCV compared with non-HCV retransplant recipients (McCashland et al, 2007). Factors portending a poor prognosis include preoperative mechanical ventilation, HCV infection, elevated creatinine and bilirubin, and prolonged donor cold ischemia (Markmann et al, 1999; Yoo et al, 2003).

CONCLUSION

Results after OLT have improved over the past 3 decades, although outcomes may be expected to plateau as further improvements add only a marginal survival benefit to an already refined surgical procedure. The reasons for the successful development of hepatic transplantation are as follows:

1. Organized regional and national networks designed for the early identification of potential organ donors and rapid procurement in select candidates
2. Improved surgical and anesthetic techniques, allowing previous obstacles to OLT to be overcome (e.g., PVT, severe coagulopathy)
3. Novel antirejection and antimicrobial agents, with increasing emphasis on achieving minimal immunosuppression in the shortest time possible
4. Increased vigilance for the occurrence of acute complications after OLT, with the development of rapid screening tests for HAT, PVT, and primary nonfunction

As the only treatment option for thousands of patients, and with the added benefit of being curative for most candidate recipients, OLT will continue to be offered for the foreseeable future. Methods for expanding the donor pool and the more recent revisions to the allocation process may help to ease the shortage of suitable hepatic grafts. Newer immunosuppressive agents and further understanding of the role, or even the necessity, of immunosuppression in some patients may decrease the morbidity for patients after OLT.

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CHAPTER 99

Techniques of liver replacement

J. Wallis Marsh and Thomas E. Starzl

HISTORICAL OVERVIEW

The steps by which liver replacement became the treatment of choice for numerous end-stage liver diseases (Starzl et al, 1989) were summarized in 2002 (Starzl). The basic operation was developed in dogs during the years 1958 through 1960 and was attempted clinically in 1963 under azathioprine-prednisone immunosuppression. The first humans to have liver replacement with prolonged survivals were reported by Starzl in 1969; however, not until the availability of cyclosporine in the 1980s did orthotopic liver transplantation became accepted worldwide as effective therapy. The results improved again with the advent of tacrolimus in the 1990s (see Chapter 96).

Elements other than immunosuppression have contributed to the success of liver replacement, including improved patient selection and pretransplantation management, noninvasive diagnostic techniques, new antibiotics, and advances in anesthetic and perioperative critical care (see Chapters 97A and 97B); however, perfection of the donor and recipient operations was the crucial factor on which all else ultimately depended. Surgical techniques used at the University of Colorado—and since January 1981, at the University of Pittsburgh—are presented in this chapter, with an emphasis on principles rather than details.

DONOR OPERATION

The use of multiple organs from a single cadaveric donor became practical with the development of standard procurement methods in the early 1980s (see Chapter 98A). Subsequently, the University of Wisconsin (UW) and histidine-tryptophan-ketoglutarate (HTK) preservation solutions made storage of hepatic grafts relatively safe for 12 to 18 hours. The availability of this much time has allowed widespread sharing of livers while permitting an accurate assessment of the grafts by histologic and metabolic criteria.

Standard Liver Procurement

In the standard procurement technique, a midline incision is made from the suprasternal notch to the pubis to expose the abdominal and thoracic organs of potential interest (Fig. 99.1). After verification that the liver has a normal consistency and color, the left suspensory ligament is incised, allowing the left lobe to be retracted anteriorly and to the right. This retraction exposes the upper part of the gastrohepatic ligament, which contains the left gastric artery, the smallest branch of the celiac axis, and the arterial supply of the liver (Fig. 99.2). If an anomalous left hepatic arterial branch originates from the left gastric artery (Fig. 99.3), it must be preserved in continuity with the main left gastric artery (see Fig. 99.3, inset). When present, this anomalous left hepatic arterial branch is nearly always present just posterior to the vagus nerve branch, as it courses from the lesser curvature of the stomach through the gastrohepatic ligament to the liver.

The largest branch of the celiac axis usually is the common hepatic artery. The right gastric and gastroduodenal arteries are ligated and divided (Fig. 99.4; see also 99.2). If the left gastric, right gastric, and gastroduodenal arteries are ligated in that order, the subsequent dissection of the common duct and the portal vein is rendered relatively bloodless. The common bile duct is transected near the duodenum, and the gallbladder is incised, permitting the bile to be irrigated out with saline (see Fig. 99.3); this avoids autolysis of the extrahepatic and intrahepatic bile duct epithelium during storage. The portal vein now is dissected inferiorly to the confluence of the splenic and superior mesenteric veins (see Fig. 99.4).

After completing the hilar dissection, the aorta is encircled superiorly, where it passes through the diaphragm, and inferiorly, just proximal to its distal bifurcation. Cannulae for infusion are placed into the inferior mesenteric vein (or splenic vein) and, after total body heparinization, into the distal aorta (see Fig. 99.4). When all procurement teams are ready, the aorta is cross-clamped at the diaphragm or in the chest by the abdominal surgeon (see Fig. 99.4), while the thoracic surgical team clamps the ascending aorta. Moderately rapid infusion of cold preservation solution is started into the portal circulation and aortic cannula. At the same time, a cardioplegia solution is infused into the midportion of the ascending aorta. Congestion of the various organs is prevented by an incision in the suprahepatic inferior vena cava at the level of the right atrium, which allows the blood and infusate to drain into the pericardium (see Fig. 99.4).

In adults, the liver is usually perfused with 2 L of HTK infused through the splenic vein or inferior mesenteric vein and 10 L infused through the aorta, although smaller volumes are used for children. When the liver becomes cold and blanched, and the heart has been removed, the total hepatectomy is completed. The remaining dissection must be performed expeditiously but methodically. If the celiac axis is retained with the graft, a proximal segment of its splenic arterial branch also should be conserved for potential reconstruction of an anomalous hepatic artery (see later). The most common hepatic artery anomaly is an aberrant right hepatic artery that originates from the superior mesenteric artery, commonly found posterior to the portal vein (Fig. 99.5; see Chapter 1B). If the pancreas is to be discarded, the anomalous retroportal artery can be kept in continuity with the superior mesenteric artery (see Fig. 99.5, inset), where its origin can be incorporated into a Carrel patch that is shared with the origin of the celiac axis.

The liver now remains attached primarily by the vena cava above and below the liver. The vena cava below the liver is transected above the entry of the left and right renal veins

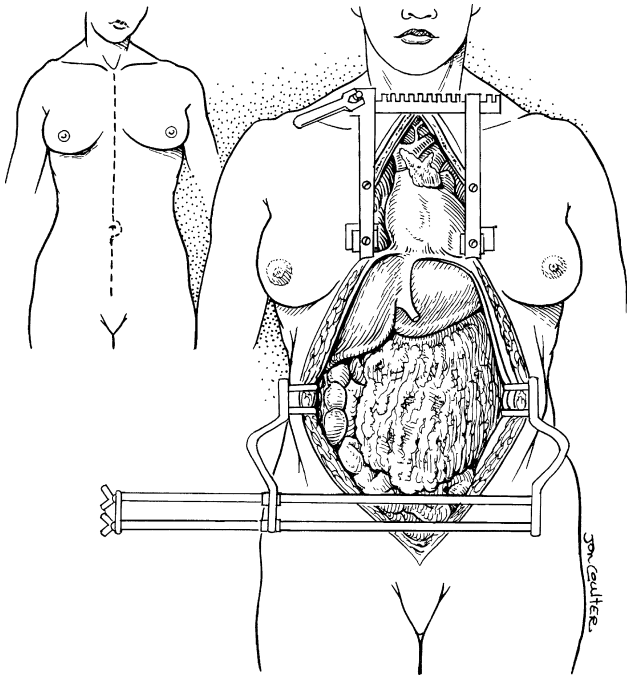


FIGURE 99.1. Initial steps for liver retrieval, including complete dissection of the hepatic hilum with the standard multiple-organ procurement technique.

(Fig. 99.6). The vena cava above the liver is transected with a surrounding rim of diaphragm that is carefully excised on the back table. The retrohepatic vena cava is dissected free, including ligation of the right adrenal vein and posterior lumbar tributaries. The liberated liver is immediately placed in a solution-filled preservation bag packed in ice (Fig. 99.7); some surgeons flush the common bile duct with HTK before packaging the liver.

Modified Donor Procedures

Rapid Procurement

Use of the standard technique in stable donors has allowed the training of relatively inexperienced surgeons in the performance of a donor hepatectomy. When the technique is mastered, faster methods can be applied electively or, if required, by urgent clinical circumstances. With the rapid techniques, little or no preliminary dissection is done except for encirclement of the supraceliac aorta and cannulation of the inferior mesenteric vein and terminal aorta (Fig. 99.8). If the heart is to be removed, the cardiac surgeon proceeds as if other organs are not to be harvested but gives warning before the circulation is stopped.

At the moment heart function ceases, the abdominal aorta is cross-clamped above or just below the diaphragm, and an infusion of cold HTK solution is started in the inferior mesenteric vein and distal aorta (see Fig. 99.8). The amount of preservation fluid with the rapid technique is approximately the same

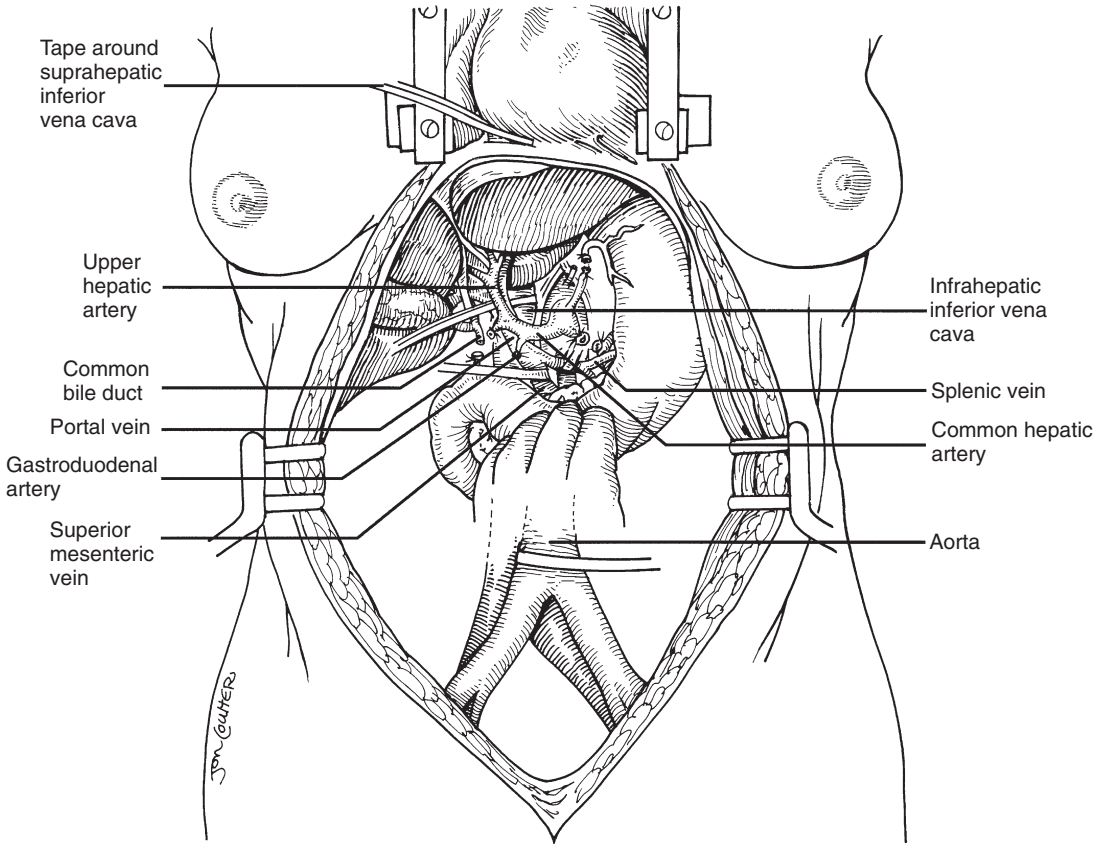


FIGURE 99.2. Exposure for multiple organ retrieval in the cadaveric donor.

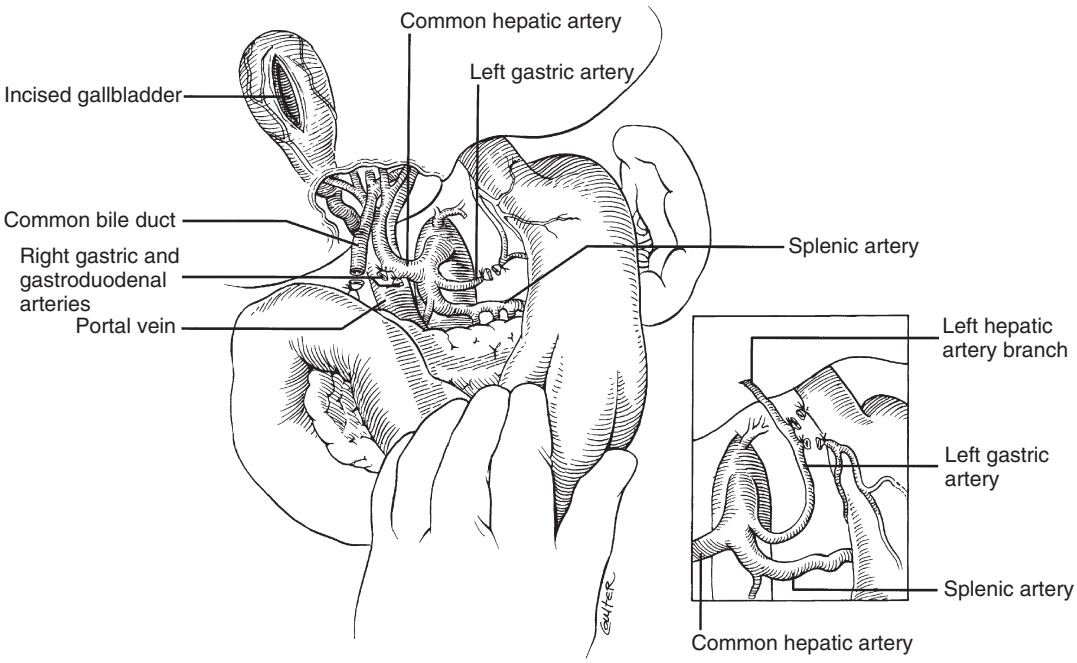


FIGURE 99.3. Normal arterial anatomy. The liver arterial supply is entirely from the common hepatic artery. The inset depicts a common anomaly in which all or part of the left lobar supply is from the left gastric branch of the celiac axis. The anomalous branch must be preserved. During the hilar dissection, the common duct is divided distally, and the gallbladder is incised to flush the biliary tree.

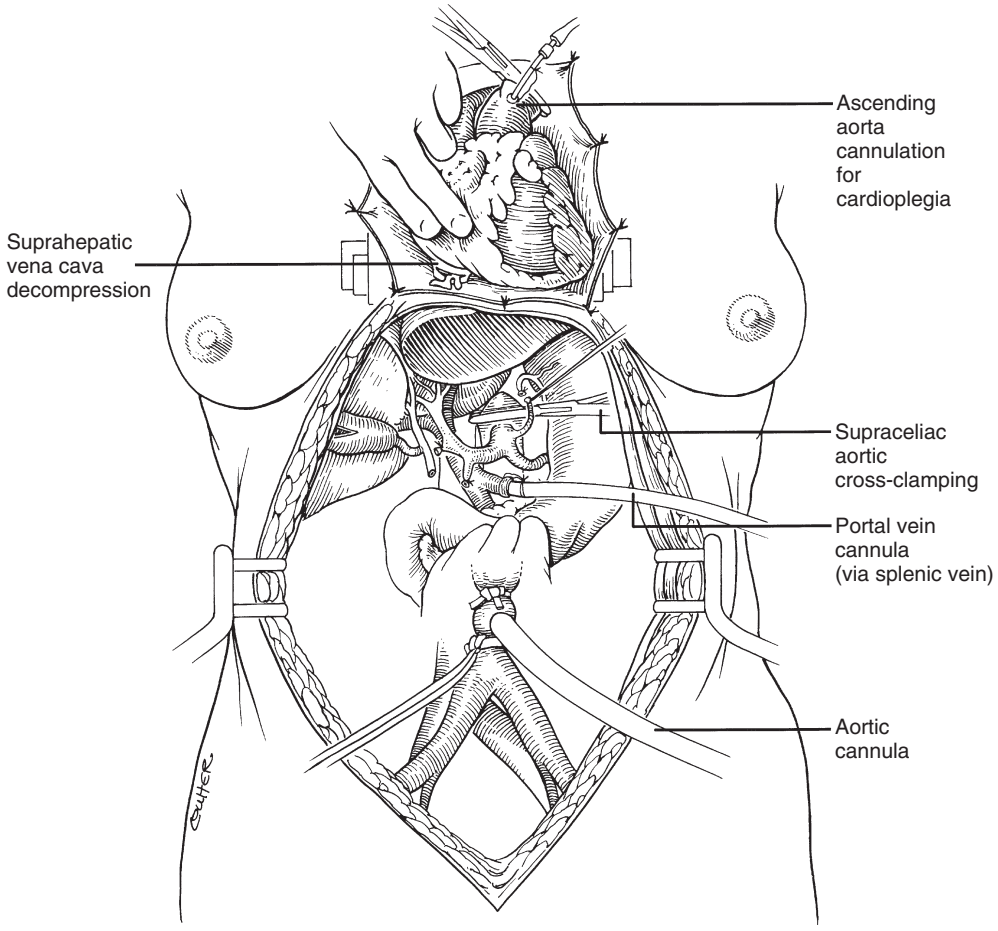


FIGURE 99.4. In situ perfusion technique used when the heart, kidneys, liver, and other viscera are removed from the same donor. University of Wisconsin or histidine-tryptophan-ketoglutarate (HTK) preservation solution are infused into the inferior mesenteric vein or splenic vein and distal aorta with simultaneous venting of the suprahepatic inferior vena cava into the pericardium. Note the aortic cross-clamp above the celiac axis. The cannulation and cross-clamping of the thoracic aorta for infusion of a cardioplegia solution also are shown.

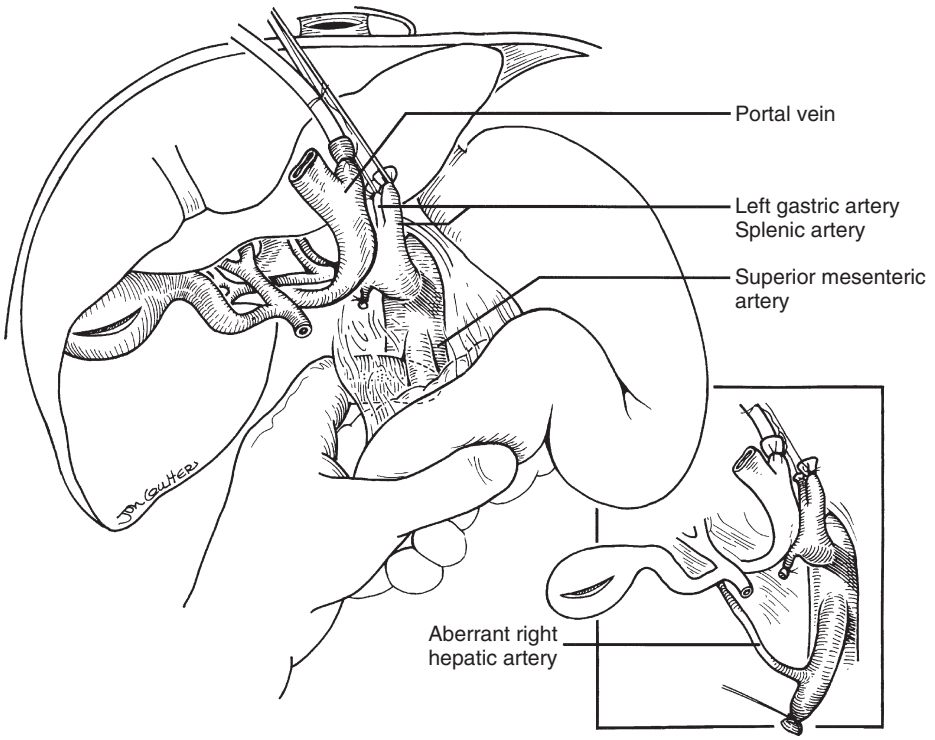


FIGURE 99.5. Retraction of the liver and its portal structures to the right and performance of a Kocher maneuver to free up the duodenum and head of the pancreas. An anomalous right hepatic artery, originating from the superior mesenteric artery (*inset*) just posterior to the portal vein, is sought out.

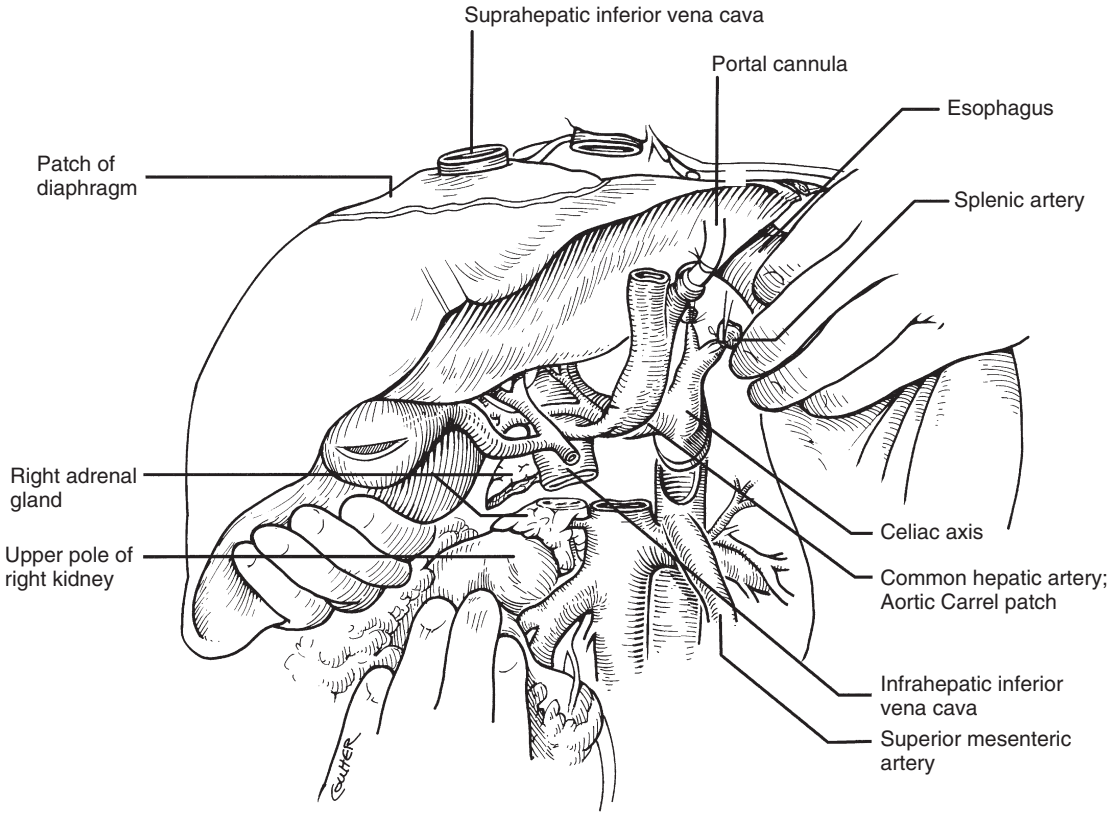


FIGURE 99.6. The suprahepatic vena cava has been transected with inclusion of a generous patch of diaphragm on the liver side. The infrahepatic vena cava is divided just above the origin of the renal veins, and the celiac axis is removed with a Carrel patch of anterior aorta. If an anomalous right hepatic artery originates from the superior mesenteric artery (SMA), the origin of the SMA may be included in the Carrel patch (see Fig. 99.10A).

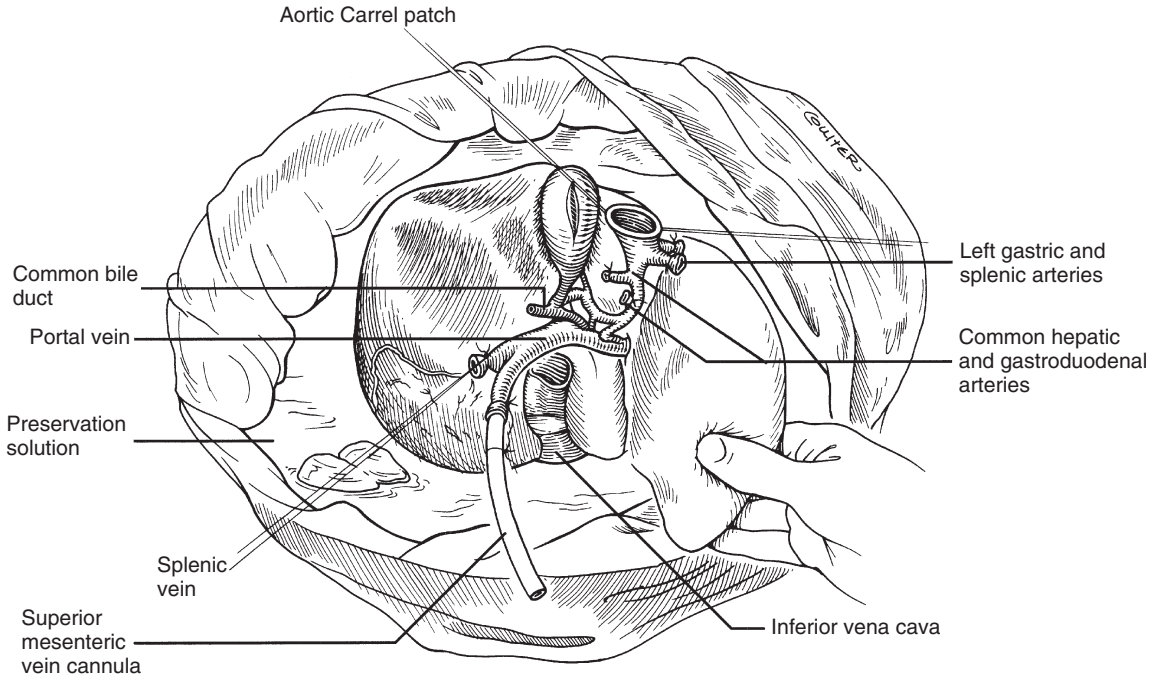


FIGURE 99.7. The liver graft is placed in a basin containing iced preservation solution for back-table preparation. The vascular cuffs are debrided of excess tissue, and any needed arterial reconstruction is performed (see Fig. 99.10).

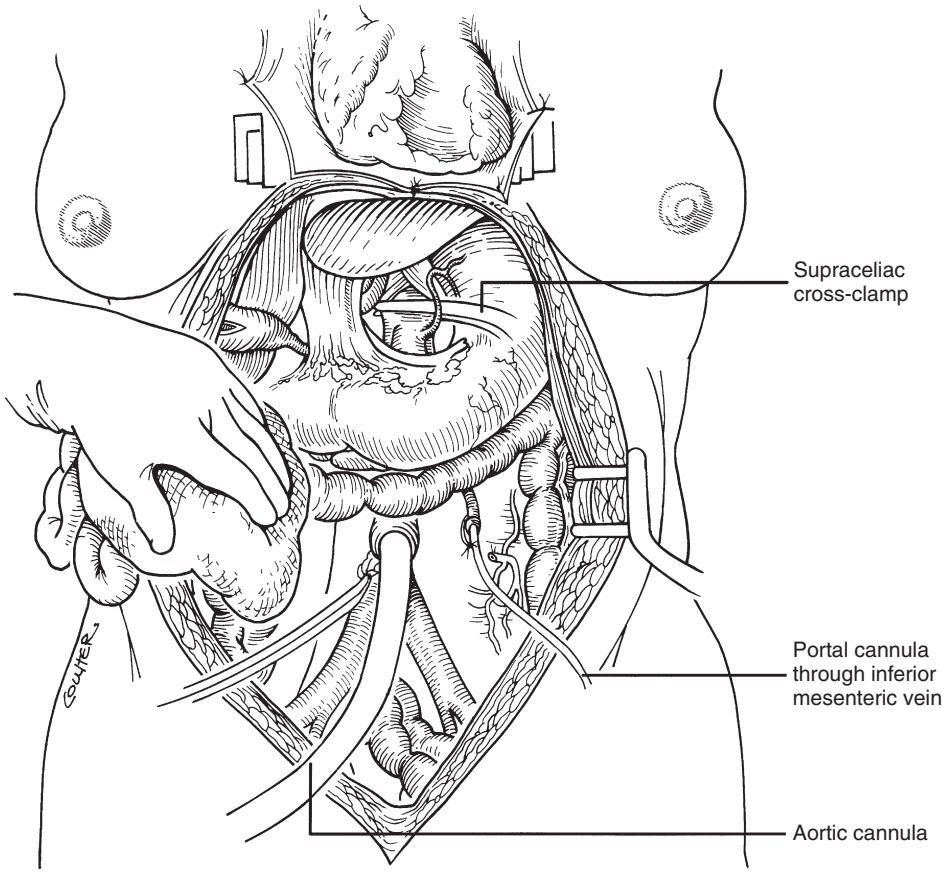


FIGURE 99.8. Rapid technique of organ retrieval in which the initial dissection is limited to the exposure needed for the insertion of perfusion cannulae in the inferior mesenteric vein and distal aorta. If only the abdominal organs are to be used, the aorta is cross-clamped above or below the diaphragm.

as that used for the standard method (i.e., 2 L into the inferior mesenteric vein (IMV)/splenic vein and 10 L through the aorta). When the liver becomes cold, the infusions are slowed. In the now bloodless field, the main vessels of the celiac axis can be quickly dissected, and the hilar dissection can be completed in a matter of minutes.

The portal vein is cleaned inferiorly to the junction of the splenic and superior mesenteric veins, and these two tributaries are divided. As in the standard method, the surgeon must promptly exclude the possibility of a retroportal right hepatic artery originating from the superior mesenteric artery as well as other arterial vascular anomalies. The hepatectomy is then completed. The kidneys, which are excised only after the liver has been removed from the field, are kept cold throughout by continued, slow, intraaortic infusion of the preservation solution. By performing all dissections in the bloodless field, it is possible to remove multiple organs in about half an hour, including the heart, liver, and both kidneys. Procurement of the intestine adds only a few additional minutes.

Super-Rapid Procurement

In arrested or non–heart-beating donors, an even quicker procedure can be used to procure satisfactory organs. This method also can be applied in countries that do not have "brain death" laws or under special legal or religious circumstances. Here, cooling requires urgent cannulation and cold fluid infusion into the distal aorta (Fig. 99.9A). Sternum splitting, thoracic aortic cross-clamping, and severance of the suprahepatic inferior vena cava for venous decompression are performed (Fig. 99.9B), deferring cannulation and perfusion of the portal venous system until after the various organs are at least partly cooled intraarterially (Fig. 99.9C). The various dissections are done in the same way as with the standard and rapid techniques. Effective application of this method requires an extremely high level of skill.

Back-Table Surgery

No matter which procurement method has been used, further preparation of the liver is performed on a separate back table before delivering the graft to the recipient surgeon. The liver should be kept cold by submerging it in a basin containing ice-cold preservation solution surrounded by a bag containing sterile ice slush (see Fig. 99.7). Back-table preparation includes the following:

1. Dissection and removal of extraneous tissue, such as diaphragm, adrenal gland, lymph node, pancreatic, peripancreatic, and ganglionic tissue
2. Preparation of cuffs of the suprahepatic and infrahepatic vena cava, cleaning of the portal vein and hepatic artery, and inspection of the bile duct
3. Verification of secure ligatures on small retrohepatic caval, portal vein, and hepatic arterial branches
4. Ensuring the continuity and integrity of all major structures that must be anastomosed to the companion recipient structures

Failure to have the graft completely ready for implantation when it is brought to the recipient operative field can result in irreversible damage to the graft or may make it impossible to complete the recipient operation. Several methods of back-table vascular reconstruction have been designed to repair technical accidents or to accommodate aberrant vessels or congenital anomalies. A common reason for back-table reconstruction is the presence of an anomalous right hepatic artery originating from the superior mesenteric artery (Fig. 99.10).

Liver, Pancreas, and Intestine Procurement from the Same Donor

The pancreas and intestine can be retrieved independently or together with the liver. Before starting the procurement, the operation should be discussed among the surgeons involved. Considerations include organ priority, type and amount of preservation solution to be used, presence of aberrant hepatic arteries, length of portal vein, and a decision about which organ retains the celiac axis or superior mesenteric artery.

An important step in any cadaveric donor operation is the removal and storage of long segments of the donor iliac arteries and veins as well as other arteries and veins. These vessels can be used as vascular grafts to reconstruct the blood supply of the individual organs. With increased experience, it is rare to see any of the abdominal visceral organs discarded for purely technical reasons.

RECIPIENT OPERATION

The recipient procedure tends to be long and physically demanding. Its different parts are so remarkably dissimilar that a single surgeon operating from "skin to skin" may find it difficult to change emotional and intellectual gears to keep pace with the evolving events. Removal of the diseased liver may be one of the most difficult challenges a surgeon faces. Yet, the vascular anastomoses can be among the most delicate and sophisticated procedures one performs, especially in very small children.

Achieving perfect hemostasis after the donor liver has been revascularized is crucial, because failure of this step can ruin all that has been accomplished; however, this is often an exhausting exercise, particularly at the end of many hours of demanding surgery. Finally, the delicate biliary tract reconstruction becomes the final thread on which the whole enterprise is suspended.

Abdominal Incision and Exposure

The exact location of the incision may be influenced by previous right upper quadrant surgery, the presence of an ileostomy, the size and configuration of the liver, or other factors. A bilateral subcostal incision is the most commonly used, extending on the right to just beyond the midaxillary line and on the left to the lateral edge of the rectus, with an upper midline extension and excision of the xiphoid process (Fig. 99.11A). In unusual circumstances, a lower midline extension may also be needed, especially if exposure of the distal aorta is required for reconstruction of the hepatic arterial supply. Thoracic extensions are rarely needed.

A bilateral subcostal incision (Fig. 99.11B) or a right subcostal incision with or without an upper midline extension (Fig. 99.11C) may also be used. The upper midline extension, shown in Figure 99.11C, is usually unnecessary in pediatric patients. Massive hepatomegaly, extensive prior abdominal surgery, or other factors may mandate the selection of a more extensive incision (see Fig. 99.11). In patients who require concomitant splenectomy or interruption of a prior splenorenal shunt, the incision may need to be extended to the left subcostal region.

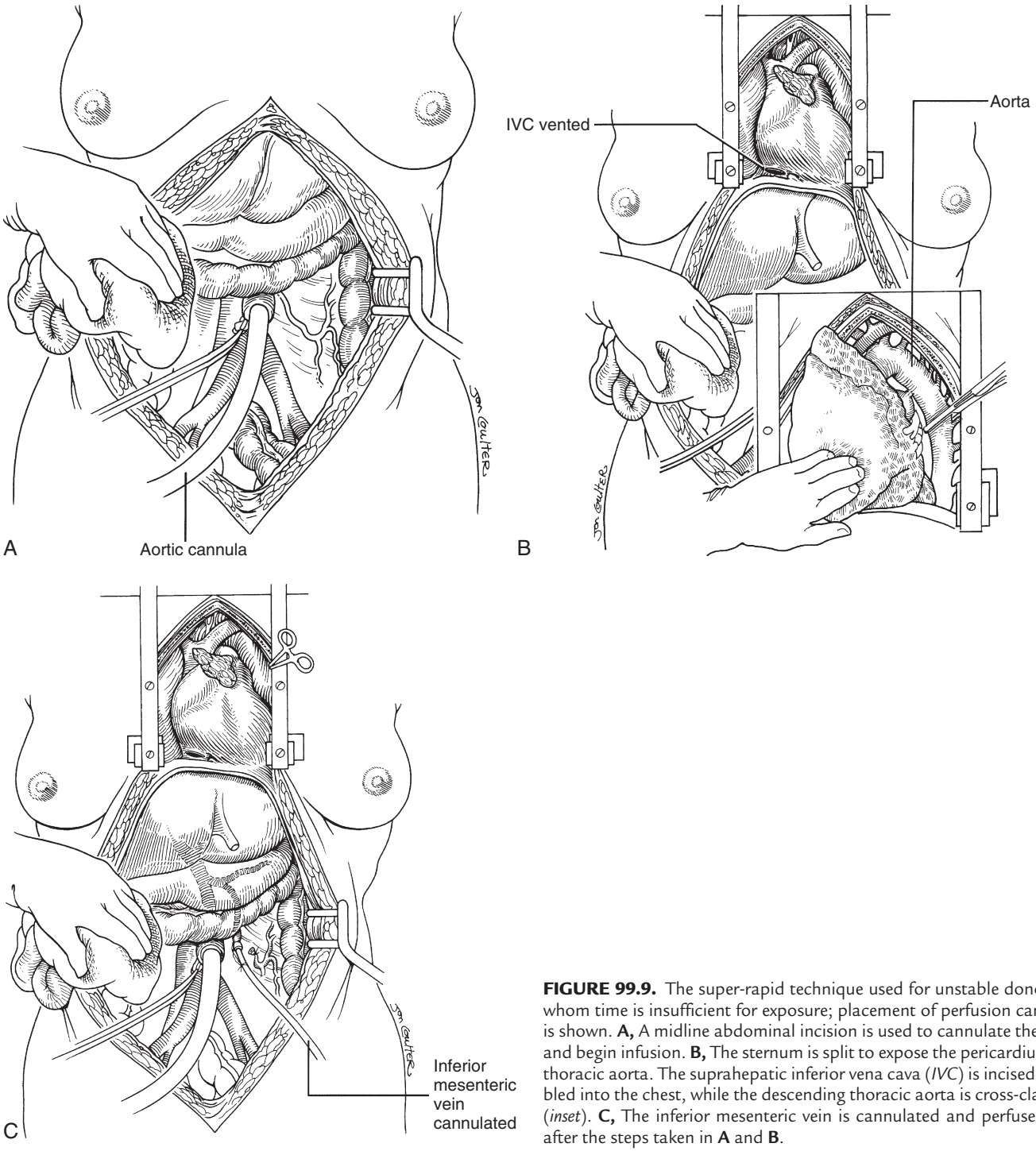


FIGURE 99.9. The super-rapid technique used for unstable donors for whom time is insufficient for exposure; placement of perfusion cannulae is shown. **A,** A midline abdominal incision is used to cannulate the aorta and begin infusion. **B,** The sternum is split to expose the pericardium and thoracic aorta. The suprahepatic inferior vena cava (*IVC*) is incised and is bled into the chest, while the descending thoracic aorta is cross-clamped (*inset*). **C,** The inferior mesenteric vein is cannulated and perfused only after the steps taken in **A** and **B**.

Improved exposure with any of these incisions can be obtained with use of the Bookwalter, Thompson, or another retractor that permits access to the hepatic veins and suprahepatic vena cava (Fig. 99.12). In making the incision, it may be necessary to abandon delicate celiotomy techniques of meticulous hemostasis and resort to continuous hemostatic suturing along the cut edges of the fascia and preperitoneum or to the use of hemostatic devices such as the Salient Surgical Technologies (Portsmouth, NH) Monopolar sealer. When the abdomen is entered, an effort must be made to find a plane of dissection just outside the liver capsule. Movement away from this plane risks an encounter with major venous collaterals, which can result in disastrous hemorrhage early in the operation.

Intraoperative Determination of Surgical Strategy

There is no single best way to carry out orthotopic liver transplantation. When exposure has been obtained, it is important to assess the pathology and decide on the technical approach that best fits the pathologic circumstances. A surgeon who insists on following the same steps in unvarying order for all liver

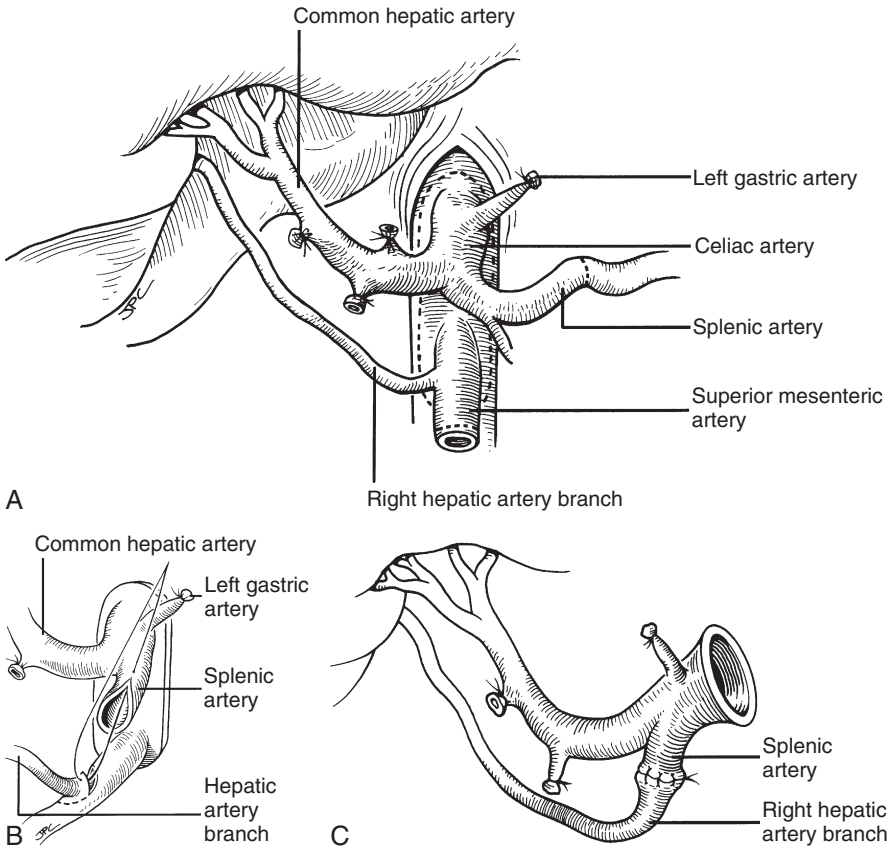


FIGURE 99.10. Examples of reconstruction of an anomalous arterial supply to the liver. **A,** The origins of the celiac axis and superior mesenteric artery are removed from the anterior aorta in a common Carrel patch. **B** and **C,** An anomalous right hepatic artery is anastomosed to the graft splenic artery, leaving only the origin of the celiac axis for anastomosis in the recipient.

recipients experiences unnecessary hardship. The following is a description of the basic ingredients of the recipient operation, with particular emphasis on variations of host hepatectomy.

Venovenous Bypass

The most critical stage of the recipient operation is the anhepatic phase, during which the diseased liver is removed and replaced with the allograft. Obstruction of the portal vein and vena cava during this period results in splanchnic and lower body systemic venous hypertension. This situation can have devastating consequences in some patients. During the early 1980s, a pump-driven venovenous bypass, used without recipient heparinization, was developed in Pittsburgh to allow splanchnic and systemic blood to return to the heart by way of an inflow cannula placed in the axillary vein (Fig. 99.13). This technique permitted the hepatectomy and implantation to be done with significant reductions in blood loss, intestinal edema, and postoperative renal failure.

Infants and small children weighing less than 15 kg tolerate venous occlusion reasonably well. Currently in adults, experienced surgeons use bypass selectively, avoiding it until it becomes apparent that its use cannot be avoided. When required, the cannulae are often now placed percutaneously in the groin and neck, thereby obviating the need for cut-downs as previously required. If bypass is not routine, the decision for or against its use should be made as early as possible in the course of the operation. The decision can be aided by testing the cardiocirculatory effects of test occlusion of the inferior vena cava and portal triad. If the test is conducted after preliminary dissection of the portal triad, and after the triangular and coronary ligaments are cut with entry into the right and left bare areas, it also is possible to evaluate the extent to which bleeding from raw surfaces can be anticipated without bypass. Alternatively, a temporary end-to-side portocaval shunt can also be constructed to prevent mesenteric congestion during the anhepatic phase. This is often created using a small segment of donor iliac vein in order to retain the full length of the recipient portal vein and for ease of creating the shunt. The portocaval shunt should be placed on the vena cava as inferiorly as possible, so its location does not interfere with placement of the vena caval clamp.

Hilar Dissection

In "easy" cases, the individual hilar structures can be readily skeletonized. The hepatic artery and common duct are ligated as close to the liver as possible, and the hepatic artery is dissected proximal to the origin of its gastroduodenal branch, facilitating exposure of the proximal portal vein (Fig. 99.14). If needed, venovenous bypass can be initiated with cannulation of the transected portal vein at this time or later.

Host Hepatectomy with or Without Vena Cava Removal

If the hilar dissection has been accomplished uneventfully, the liver is devascularized and now can be excluded from the circulation by cross-clamping the vena cava above and below the liver (Fig. 99.15A). The diseased organ with or without a

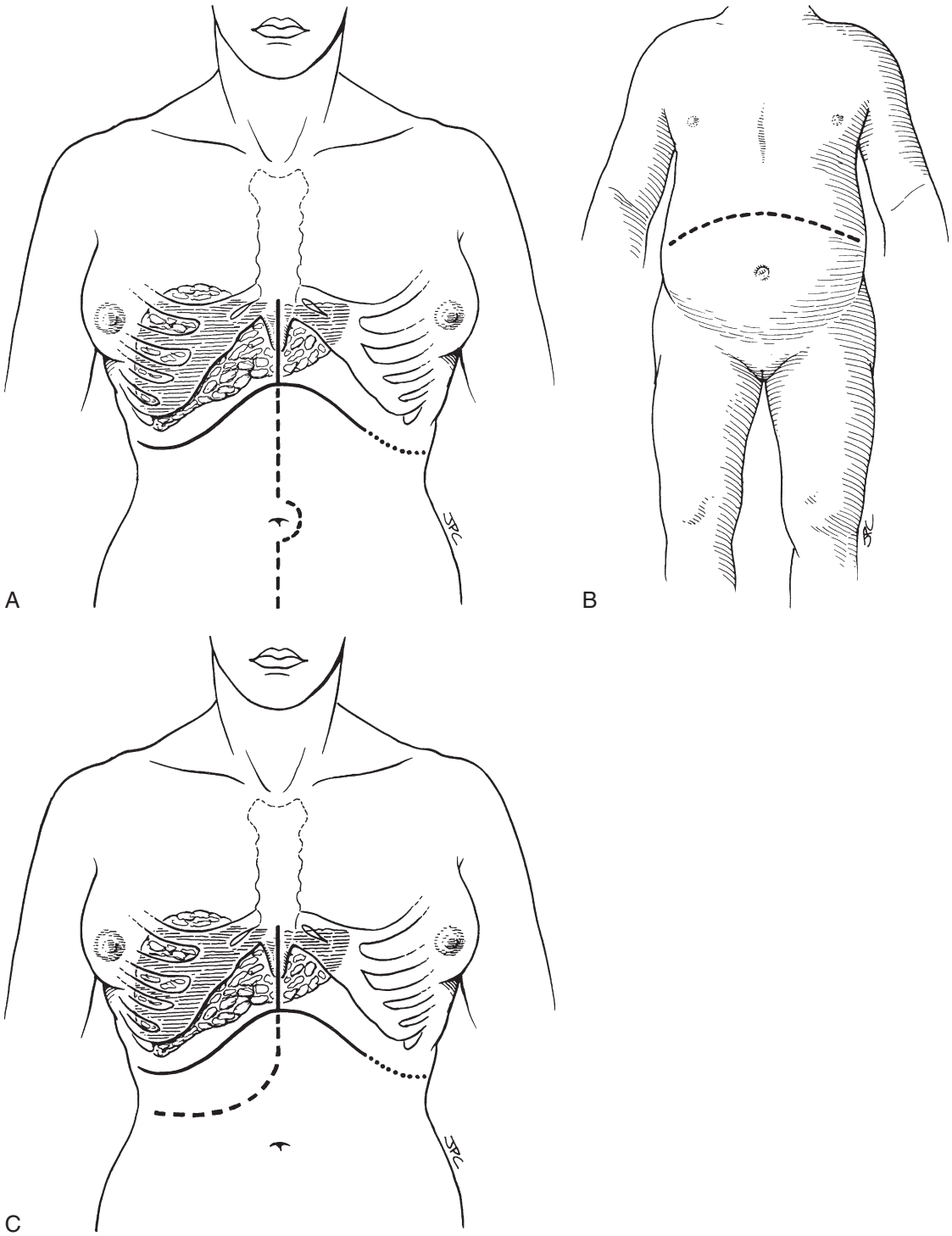


FIGURE 99.11. Potential incisions for orthotopic liver transplantation. **A,** Bilateral subcostal incision with potential superior or inferior extensions. **B,** Inverted half-moon incision sometimes used in infants and small children. **C,** Simple subcostal incision that may be converted to a hockey-stick incision by an upper midline extension, which may include xyphoid resection.

segment of retrohepatic vena cava can be "peeled" out, working from the hilum up or from the diaphragm down. If the vena cava is part of the specimen, the obligatory ligation of the right adrenal vein (Fig. 99.15C) imposes a risk of adrenal infarction. If this occurs with venous hypertension and bleeding, the right adrenal gland should be removed immediately. Other systemic venous tributaries to the vena cava segment from the lumbar regions also must be scrupulously ligated. Because of regional venous hypertension in the right-sided bare area, it may be necessary then or later to obtain hemostasis by closing or oversewing the edges of the exposed bare areas with a continuous suture or by the use of such devices as the LigaSure (Covidien, Mansfield, MA) or the Monopolar or Bipolar sealer (Fig. 99.15D).

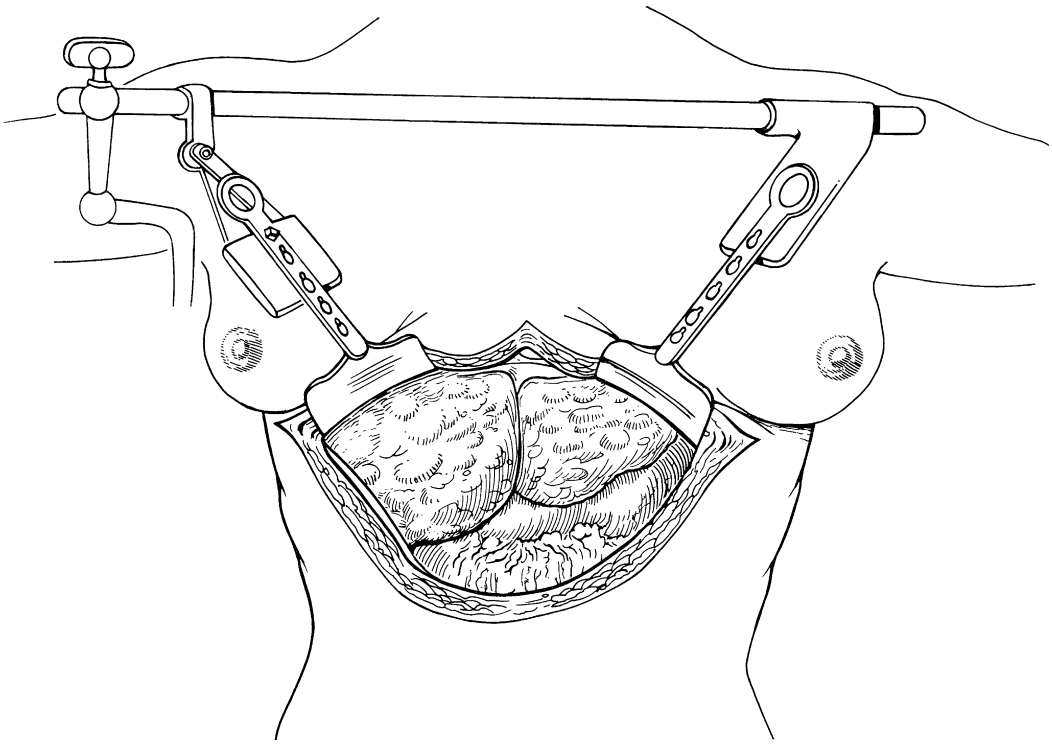


FIGURE 99.12. Exposure, especially of the suprahepatic vena cava, can be facilitated by the use of self-retaining retractors.

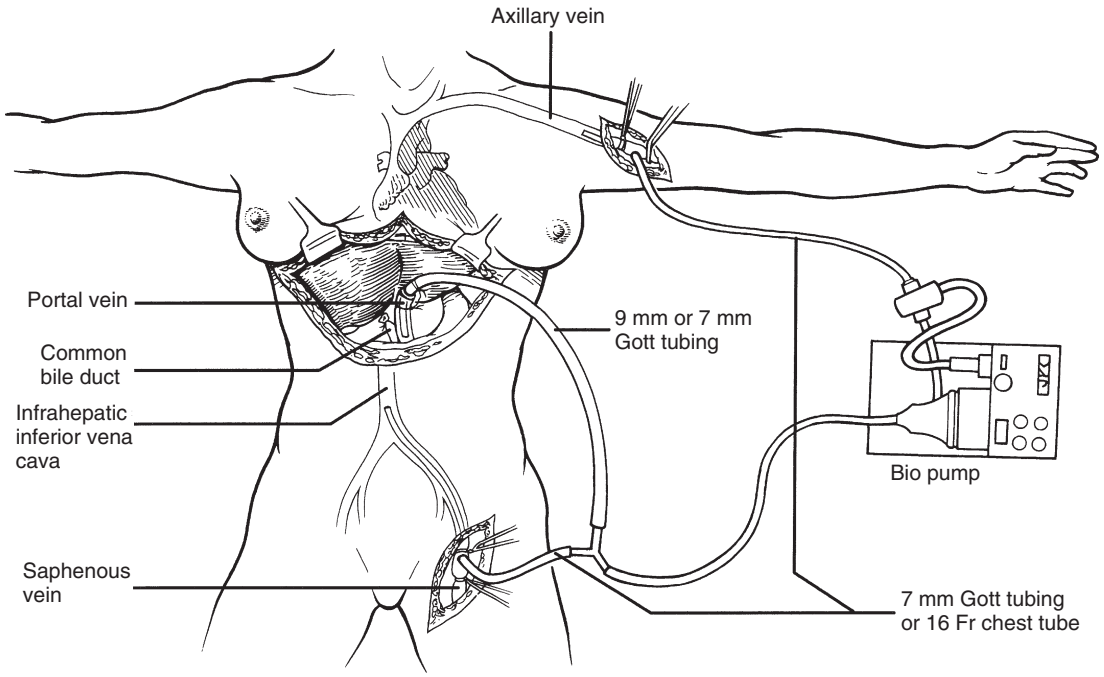


FIGURE 99.13. Pump-driven venovenous bypass used to decompress the systemic and splanchnic venous beds during the anhepatic phase of liver transplantation. The groin and venous return cannulae, when used, are usually placed percutaneously in the left groin and right neck.

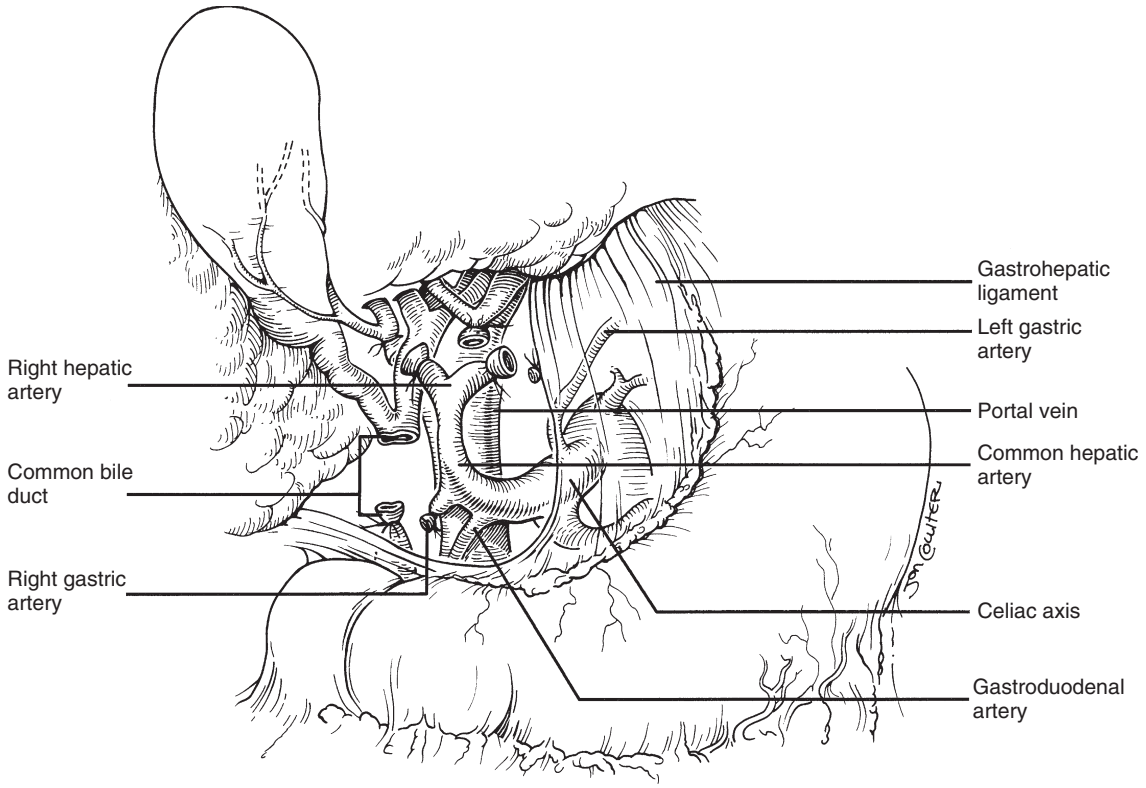


FIGURE 99.14. Hilar dissection in the liver recipient.

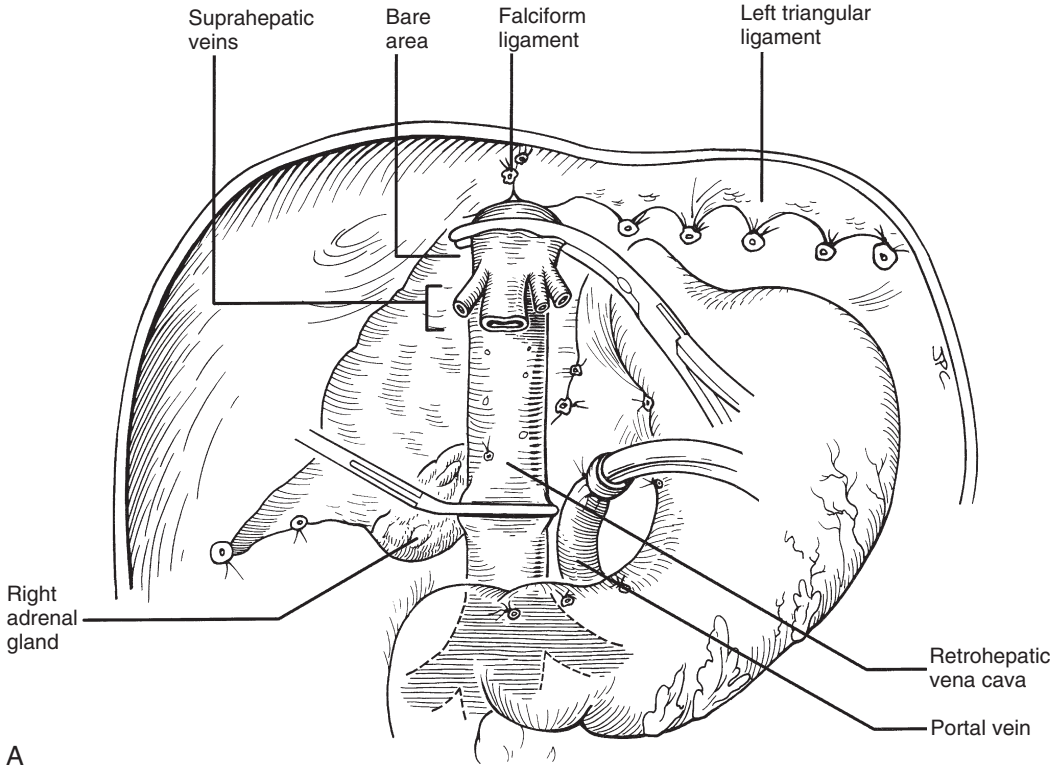


FIGURE 99.15. Completed recipient hepatectomy on venovenous bypass. **A,** With preservation of host retrohepatic vena cava. Note the hepatic vein cuffs.

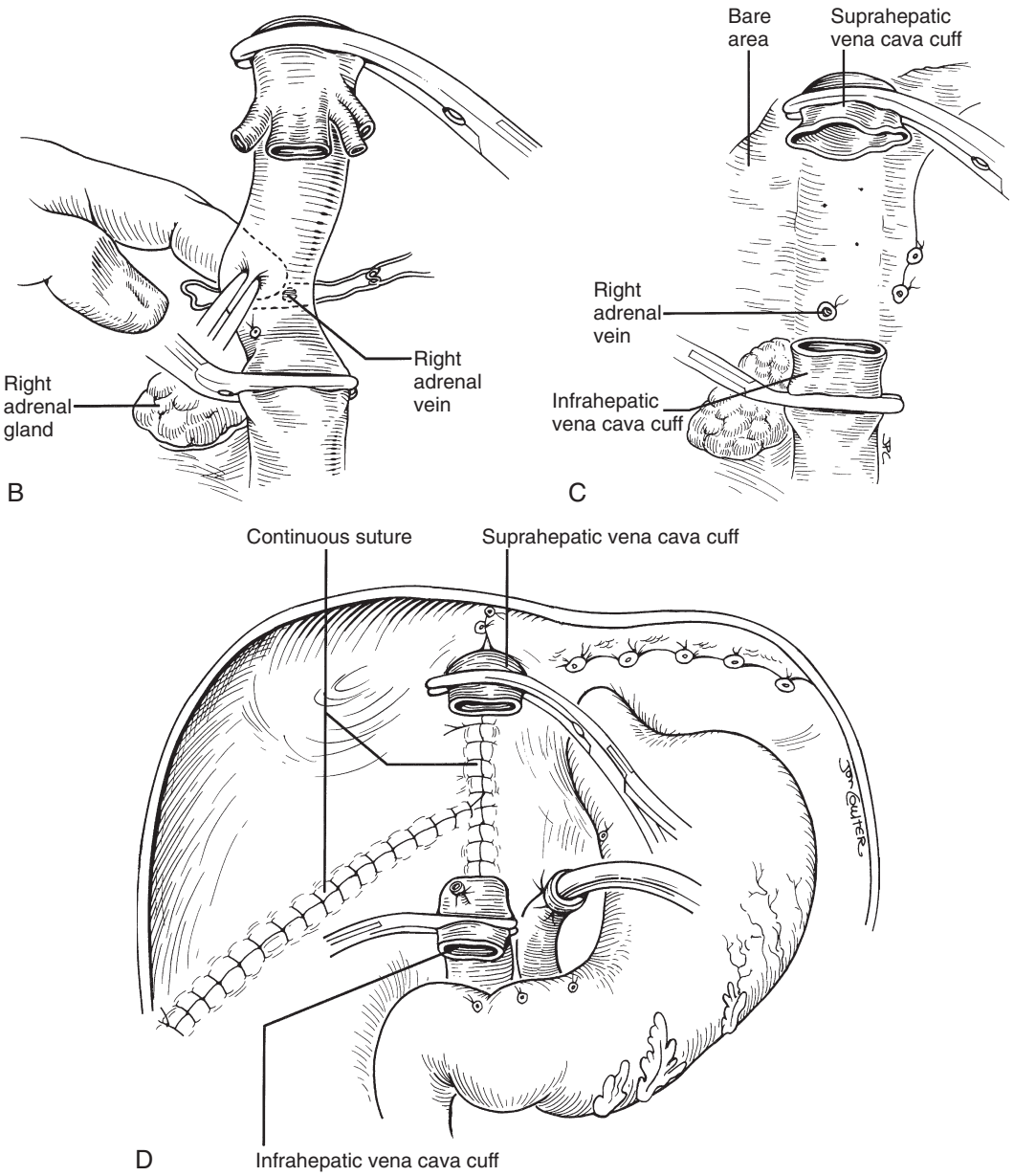


FIGURE 99.15, cont'd **B,** As in **A,** but with an injury to the right adrenal vein, which is being ligated. **C,** The retrohepatic vena cava has been included in the hepatectomy, necessitating ligation of its tributary lumbar veins and the right adrenal vein. **D,** Closure of the bare area to provide hemostasis. Bleeding from the bare area is more severe if the retrohepatic cava is removed or thrombosed because of the loss of venous drainage.

Many of these problems can be circumvented if the host retrohepatic vena cava can be conserved (see Fig. 99.15A). Separation of the diseased liver from the vena cava is done in the same way as in the classic experimental procedure of total canine hepatectomy. With this kind of hepatectomy, stumps of one or more of the main host hepatic veins are retained (Fig. 99.16A) for eventual receipt of the allograft's venous outflow (Fig. 99.16B and C); this is known as the *piggyback method* of liver transplantation. To the extent vena cava flow can be maintained during the sometimes tedious and difficult denudation of the retrohepatic vena cava, the need for venovenous bypass is potentially eliminated, and the extent of retroperitoneal dissection is considerably reduced. Finally, the risk of right adrenal infarction is eliminated, unless the right adrenal vein is injured (see Fig. 99.15B).

Alternative Approaches to Hepatectomy

In many if not most cases, hepatectomy with or without inclusion of the retrohepatic vena cava is uncomplicated; however, dissection of the liver hilum sometimes is difficult or impossible because of scarring or the presence of varices. In these situations, the suprahepatic vena cava can be approached first. After transecting the suprahepatic vena cava, removal of the liver can be done from the top down, approaching the hilar structures from behind the liver (Fig. 99.17). If it is not possible to occlude the hepatic veins on the liver side, bleeding can be minimized by

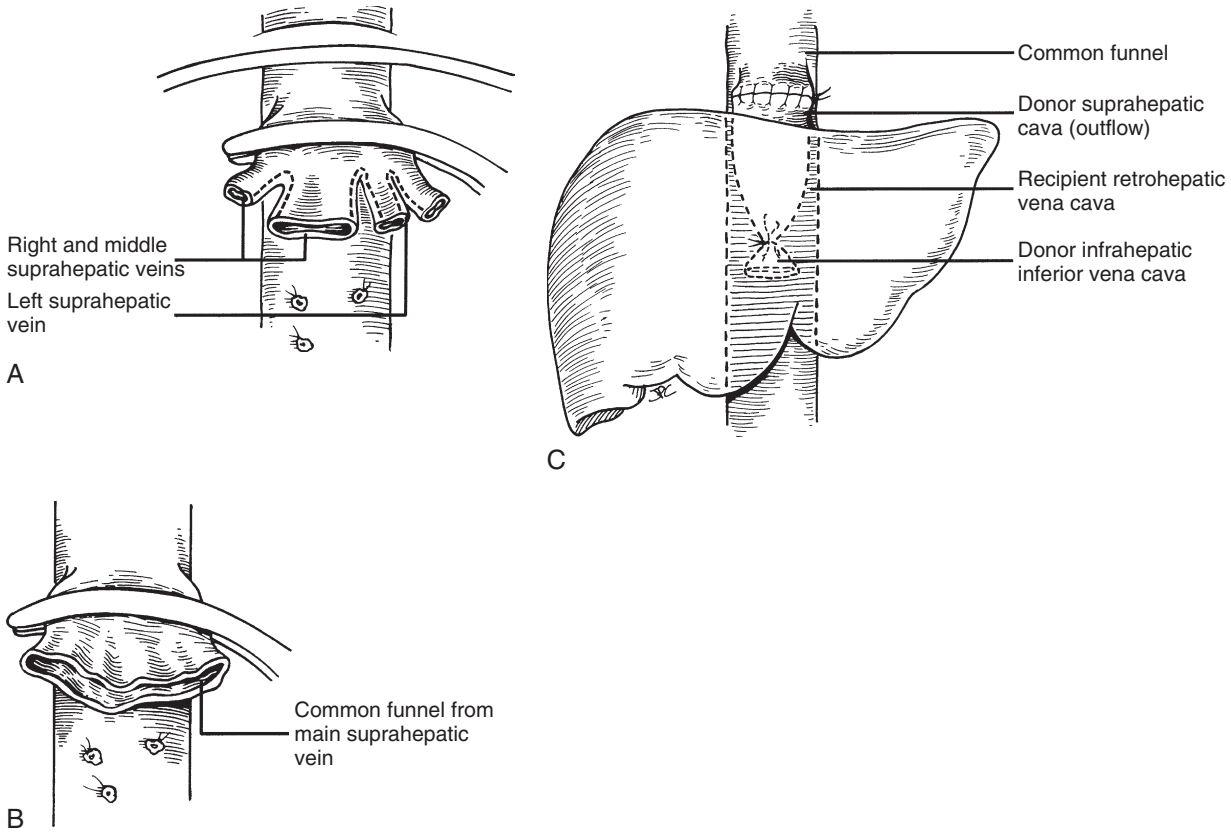


FIGURE 99.16. The piggyback method of graft implantation with a conserved retrohepatic vena cava. **A** and **B,** Creation of an outflow cloaca from two or more hepatic veins. **C,** Completed anastomosis between the host hepatic veins and the suprahepatic vena cava of the graft. The inferior end of the graft vena cava is ligated.

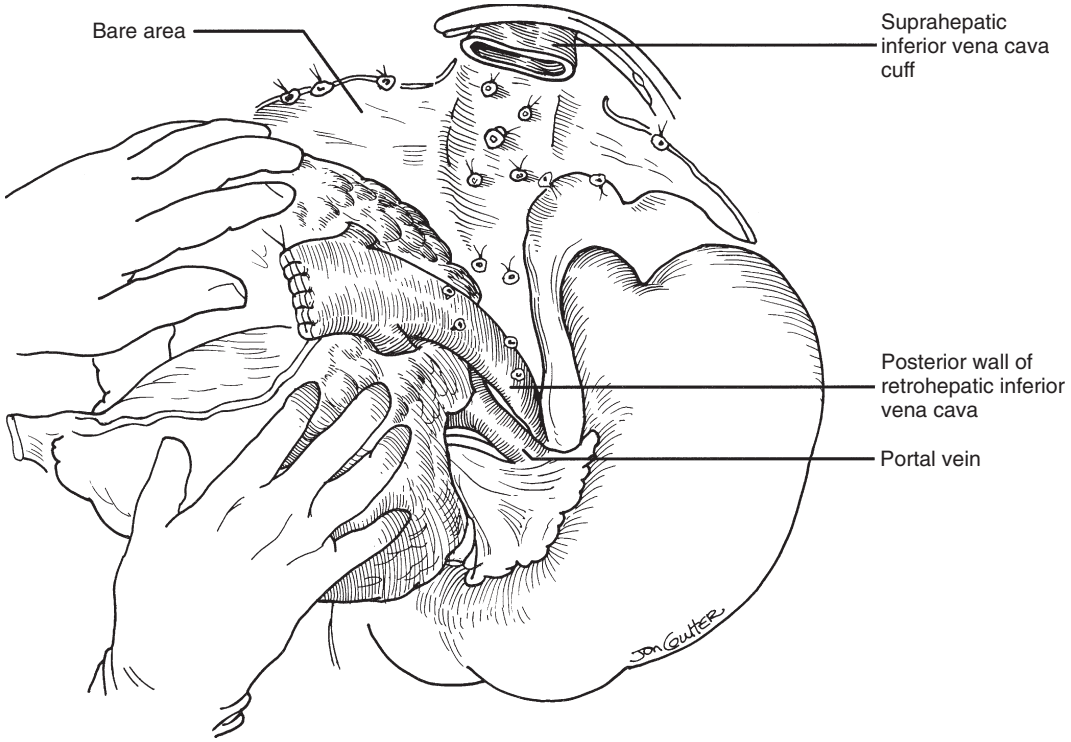


FIGURE 99.17. Removal of the recipient liver from the top down.

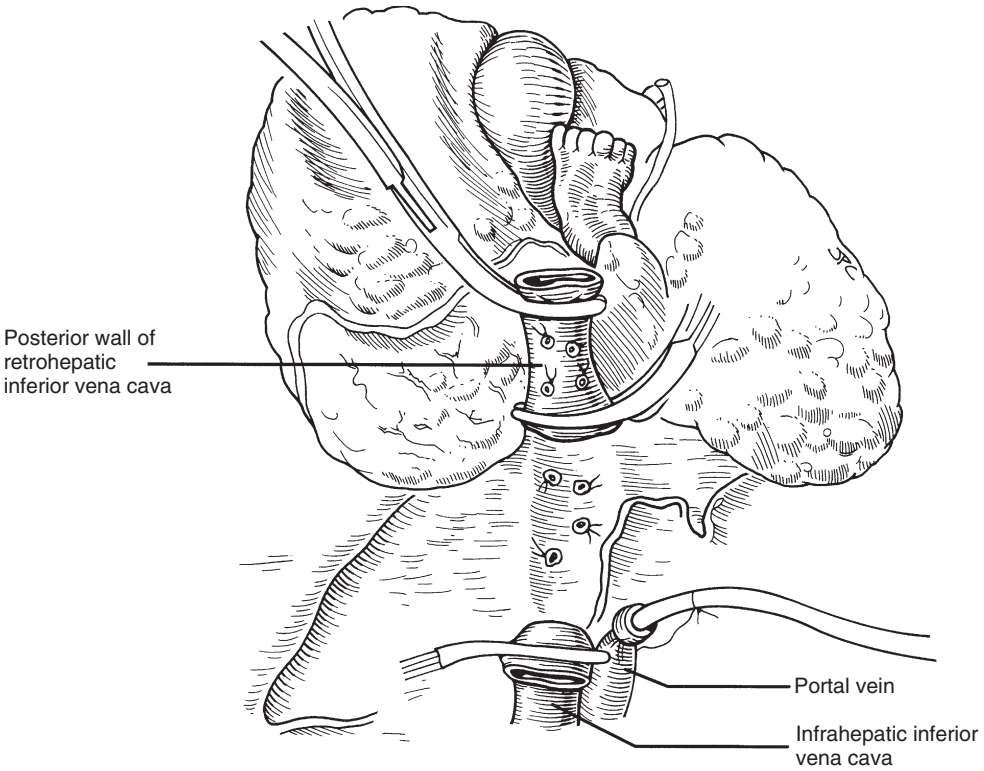


FIGURE 99.18. Removal of the recipient liver from the bottom up.

placing the fingers into the hepatic veins and retrohepatic vena cava or by squeezing shut the venous outflow of the liver. Alternatively, the inferior vena cava below the liver can be used as a "handle" to extract the liver from bottom to top, with cross-clamping or transection of the hilar structures at the earliest possible opportunity (Fig. 99.18). Finally, if adhesions are present that block access to the upper and lower vena cava and to the portal triad, the liver can be split in a superior-inferior direction, exposing the anterior surface of the retrohepatic vena cava from inside the liver (Fig. 99.19). Once bleeding from the raw surfaces is controlled, the two hepatic halves are stripped away from the surrounding structures. All these hepatectomy variations are made easier by venovenous bypass.

Vascular Anastomoses

It is important to have the surgical field completely prepared for implantation before the new liver is brought from the back table. The first graft vessel to be anastomosed is always the

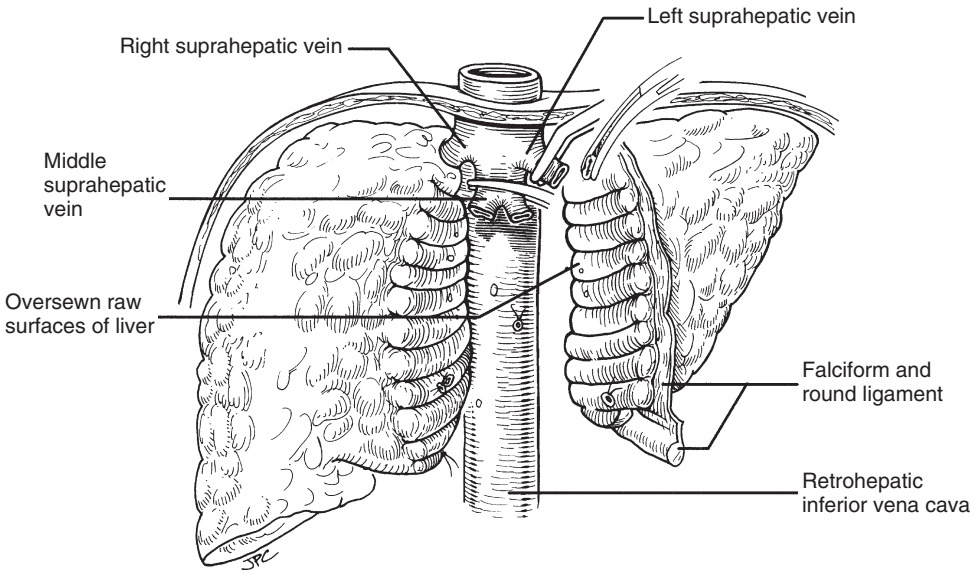


FIGURE 99.19. Splitting technique of hepatectomy. The split is facilitated by inserting a finger along the relatively vein-free anterior midsurface of the vena cava. The correct plane must be determined carefully by finger probing before any pressure is applied.

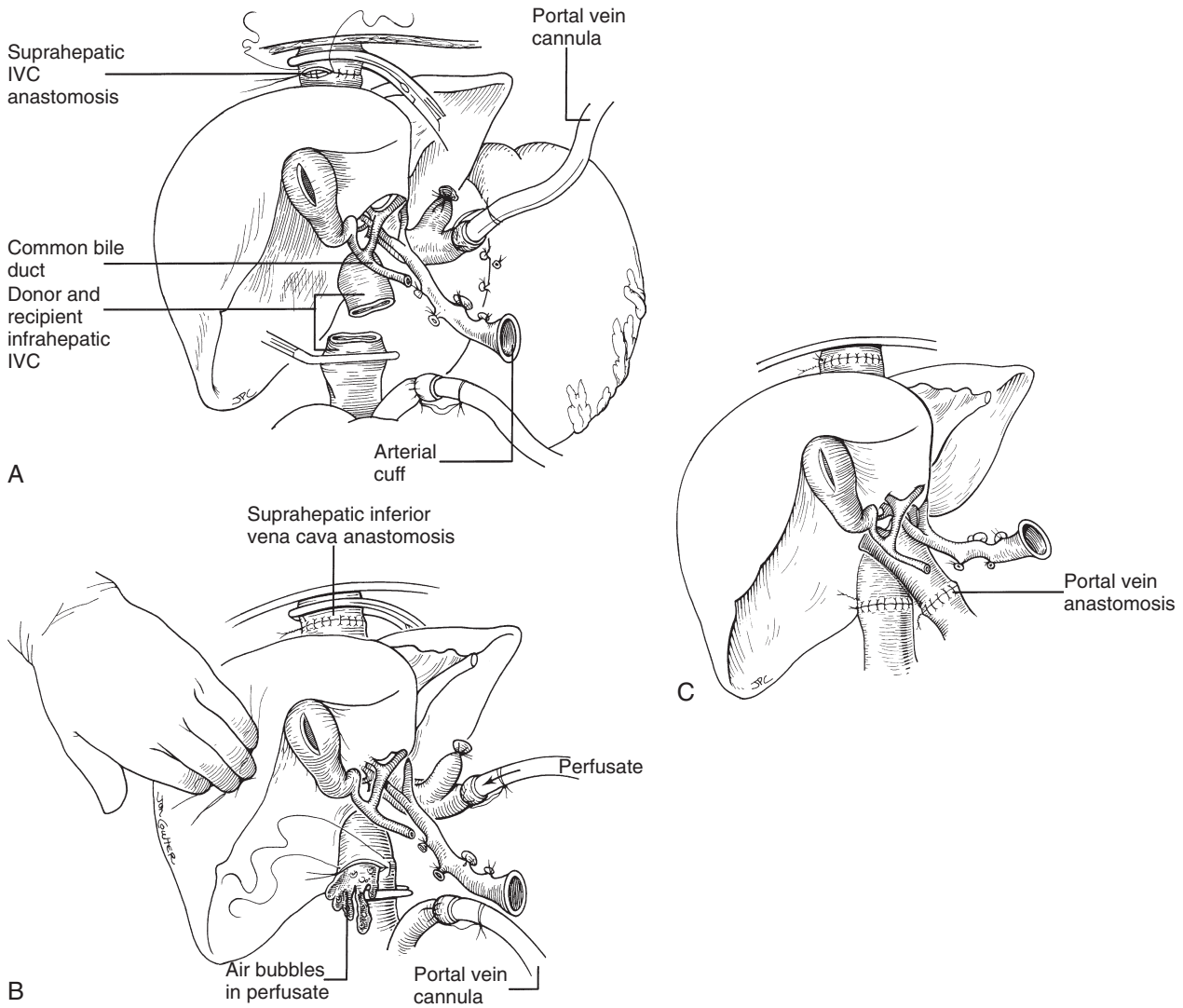


FIGURE 99.20. Implantation steps. **A,** Suprahepatic vena cava anastomosis. **B,** Infrahepatic vena cava anastomosis. Before completing the anastomosis, the portal vein is infused with cold albumin or electrolyte solution when University of Wisconsin solution is used as the preservation solution. This allows air and the potassium-rich preservation fluid to be removed. (Alternatively, the liver can be flushed on the back table, and heparized saline can be used to remove air before completion of the portal vein anastomosis.) **C,** The portal vein anastomosis after removal of the bypass cannula. IVC, inferior vena cava.

segment of donor vena cava into which all the hepatic veins of the transplanted liver drain. If host hepatectomy has included removal of the retrohepatic vena cava, the anastomosis is an end-to-end, suprahepatic to suprahepatic vena cava connection at the diaphragm (Fig. 99.20A). With the piggyback operation, in which the host vena cava is conserved, the suprahepatic vena cava is emptied into a cuff of host hepatic veins (see Fig. 99.16) or by a side-to-side anastomosis between the two vena cava segments (not shown).

The order of the other vascular anastomoses may vary. With the caval-sparing piggyback operation, the infrahepatic vena cava of the graft is ligated or stapled (see Fig. 99.16). When the host caval segment is excised (standard technique), a common practice is to anastomose the infrahepatic vena cava (Fig. 99.20B), followed by removal of the recipient from the portal (but not systemic) bypass and subsequent portal vein anastomosis (Fig. 99.20C). These anastomoses may be done in reverse order (i.e., portal vein first). An experienced surgeon may prefer to perform the arterial anastomosis before the portal vein reconstruction or may complete all four anastomoses before unclamping. These decisions are influenced by the anatomic and physiologic circumstances in the individual case, including the efficiency with which the bypass system has functioned or the degree of venous hypertension when bypass is not used.

In all cases if the preservation solution used is UW solution, it is important before liver reperfusion to flush the allograft with Ringer's lactate solution, although some surgeons prefer albumin or blood. Flushing is done through the cannula placed in the graft portal circulation at the time of procurement (see Fig. 99.20A), either on the back table before beginning implantation or in situ before beginning the portal vein anastomosis. After its passage through the microvasculature of the allograft, the infusate is vented from the vena cava (see Fig. 99.20B). The objectives are to remove air and to rid the graft of any high-potassium solutions (UW solution) used for organ preservation

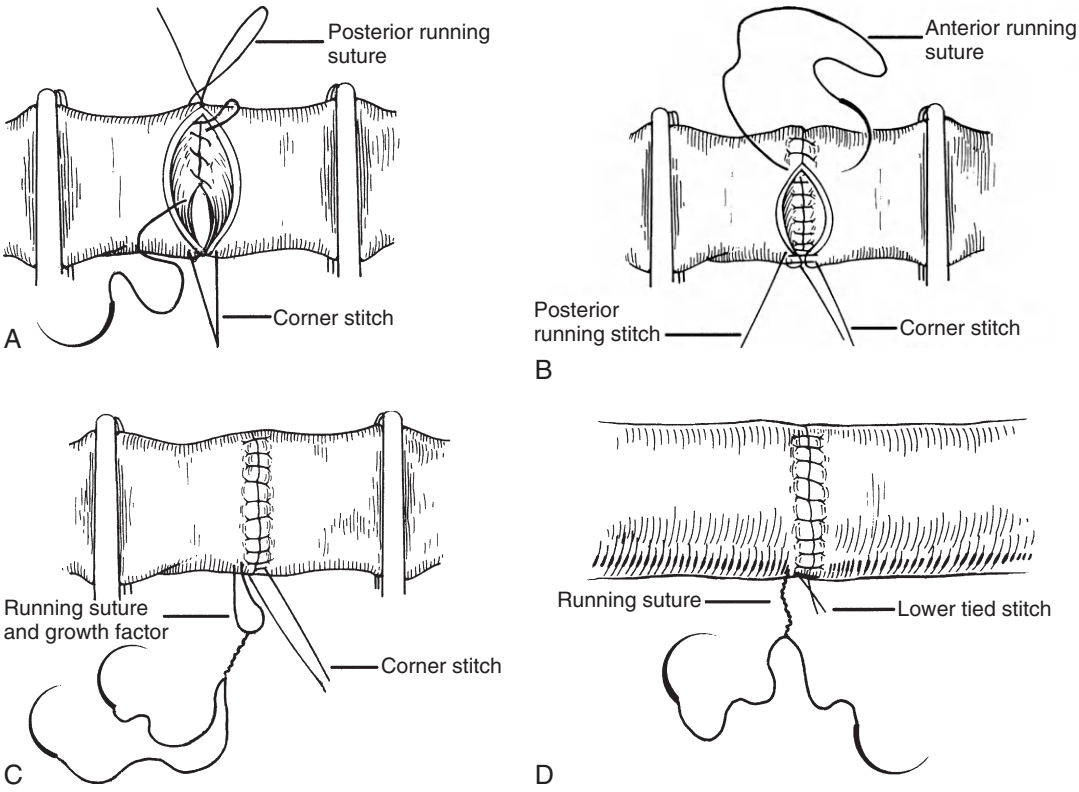


FIGURE 99.21. Technique of venous anastomosis. **A,** Traction sutures are placed at each corner. One end of the far suture is brought to the inside and run in continuous fashion to approximate the back wall. **B,** The other end of the far suture is used from the outside to approximate the anterior wall. **C,** The continuous suture is tied away from the vein wall to allow for a "growth factor." The near corner suture is tied next to the running suture to prevent separation of the vessel. **D,** The excess suture is drawn into the vessel, allowing the circumference to expand when blood flow is restored.

(see Fig. 99.20B). Failure to perform this flush can result in air embolism or hyperkalemic cardiac arrest or dysrhythmias, although this step is not necessary if HTK is used.

All of the venous vascular anastomoses are routinely performed with continuous suture. To avoid anastomotic strictures, particularly of the portal anastomosis, special techniques are developed that are made feasible by the ability of polypropylene (Prolene) suture to glide freely through tissue. A growth factor is left by tying the sutures at a considerable distance above the vessel wall. After flow is restored through the anastomosis, the excess polypropylene recedes back into the vessel and redistributes itself throughout the circumference of the suture line (Fig. 99.21). If leaks develop, these are readily controlled with additional single sutures.

Rather than being whimsical, variations of the order and details of revascularization frequently are mandated by anatomic anomalies or by pathologic factors, including thrombosis of the portal vein that once contraindicated liver transplantation, until techniques were developed to deal with them. Declotting a thrombosed portal vein may be possible (Fig. 99.22A); if not, iliac or other veins from the donor may be used as interposition grafts (Fig. 99.22B) or as mesoportal jump grafts (Fig. 99.22C). A mesoportal graft may be anastomosed end-to-side to the superior mesenteric vein and tunneled through the transverse mesocolon in a relatively avascular plane anterior to the pancreas to reach the hepatic hilum for end-to-end anastomosis to the donor portal vein (see Fig. 99.22C).

Numerous techniques also have been used to restore the hepatic arterial supply. The ideal reconstruction, when the allograft and recipient have normal arterial anatomy, is shown in Figure 99.23A. If anomalies, vascular injuries, or pathologic changes are present in the donor or recipient blood vessels, such as from radiation for cholangiocarcinoma, that preclude effective rearterialization, grafts obtained from the donor can be used (Fig. 99.24; see also Fig. 99.23B and C).

Biliary Tract Reconstruction

Good hemostasis must be achieved before the biliary reconstruction is performed. If the recipient duct is disease-free, and if there is a reasonable size match between the donor and recipient ducts, an end-to-end anastomosis is performed with or without a T-tube stent (Fig. 99.25). The anastomosis usually is performed with 8 to 10 interrupted absorbable sutures, such as 5-0 or 6-0 polyglycolic acid, or with a continuous suture, if the ducts are large enough. Because the integrity of the anastomosis depends primarily on an adequate blood supply of donor and recipient ducts, minimal dissection is performed in the periductal tissues. A small purse-string suture is usually placed around the T-tube exit site to prevent leakage, and the T-limb is brought out through a stab incision on the lateral side of the recipient duct.

If the recipient duct is diseased or otherwise inadequate for anastomosis, a choledochojejunostomy is performed. A 45-cm Roux-en-Y limb of proximal jejunum is brought, usually

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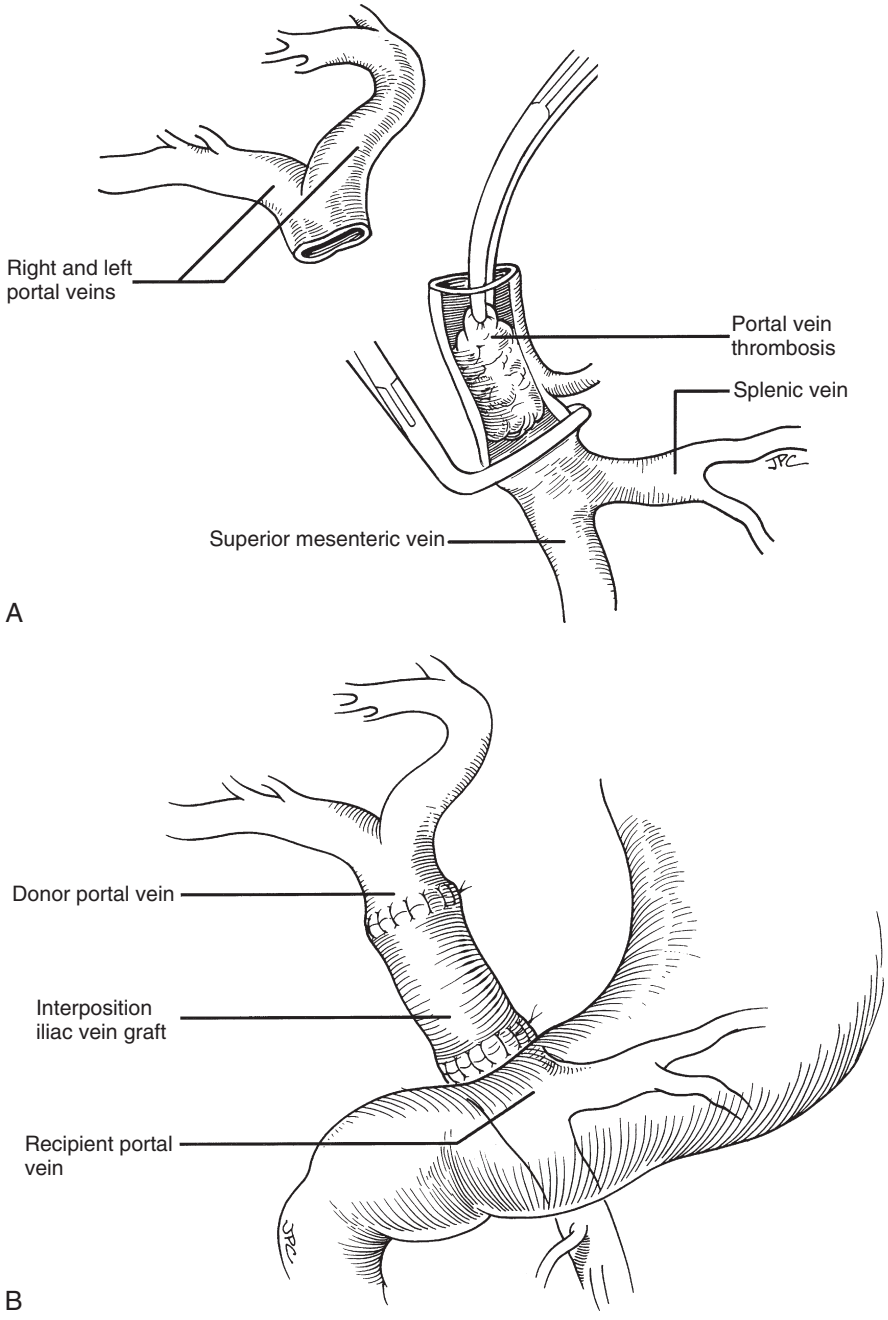


FIGURE 99.22. Management of recipient portal vein abnormalities. **A,** Removal of thrombus. **B,** Use of an interposition graft of donor vein to bridge the gap between donor portal vein and the confluence of the mesenteric and splenic veins.

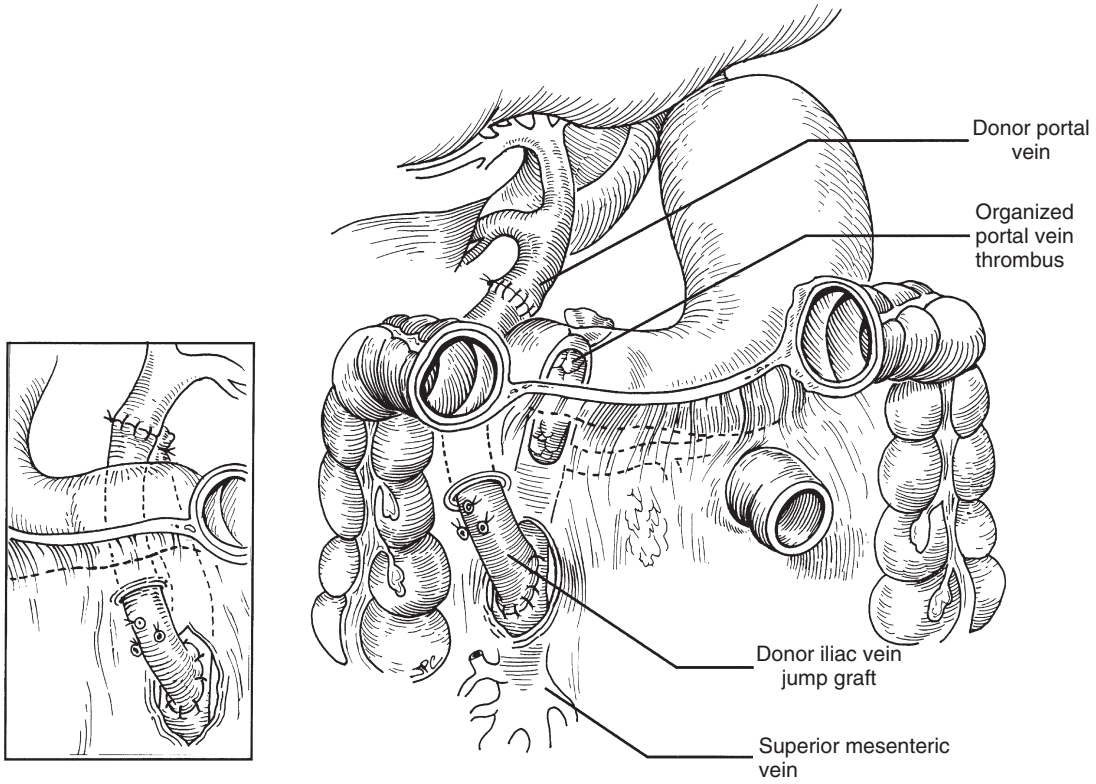


FIGURE 99.22, cont'd C, Donor vein jump graft from the host superior mesenteric vein to the graft portal vein. The jump graft is tunneled through the transverse mesocolon in front of the pancreas to the hepatic hilum. The graft can be anterior or posterior (*inset*) to the stomach.

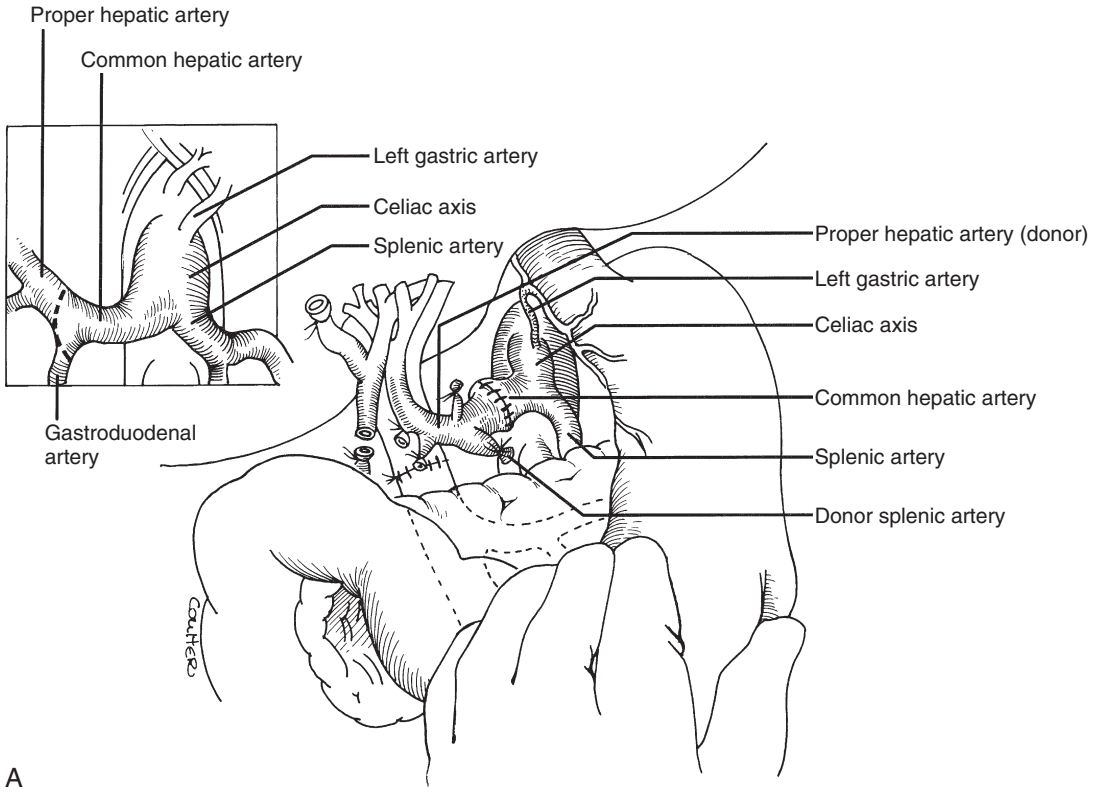
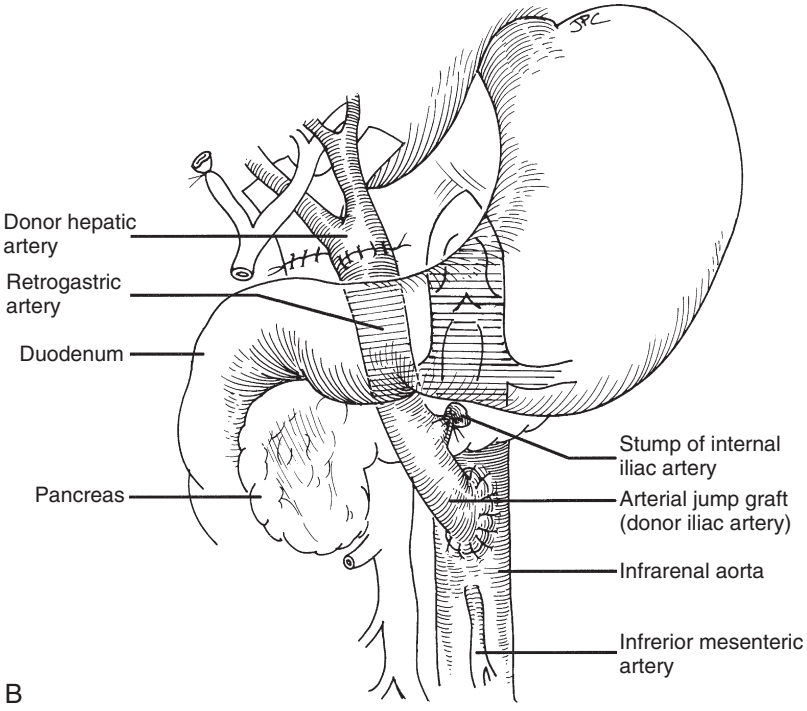
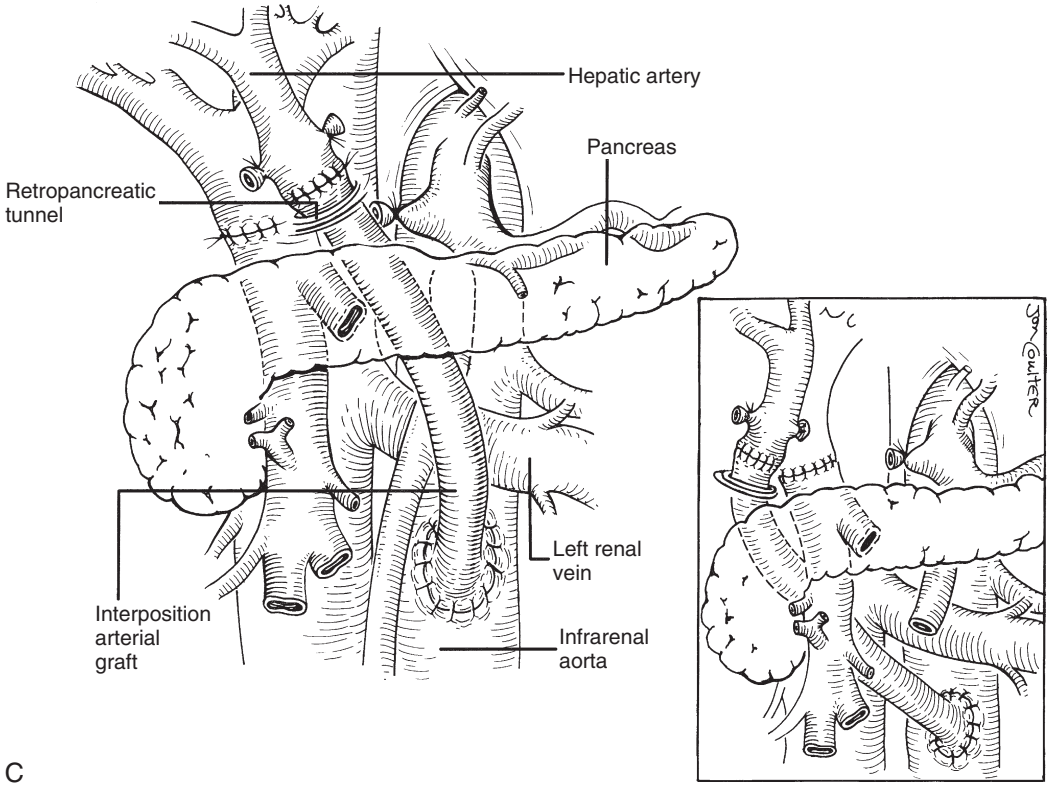


FIGURE 99.23. Hepatic artery reconstruction. **A,** The most common reconstruction, in which the graft celiac trunk is anastomosed to the recipient common hepatic artery. With discrepant sizes, the circumference of the recipient vessel can be increased as shown in the inset.

Continued



B



C

FIGURE 99.23, cont'd B, Jump graft of donor iliac artery based on the infrarenal aorta and tunneled anterior to the pancreas. **C,** Rarely used alternative retroperitoneal tunnel posterior to the pancreas and superior mesenteric artery.

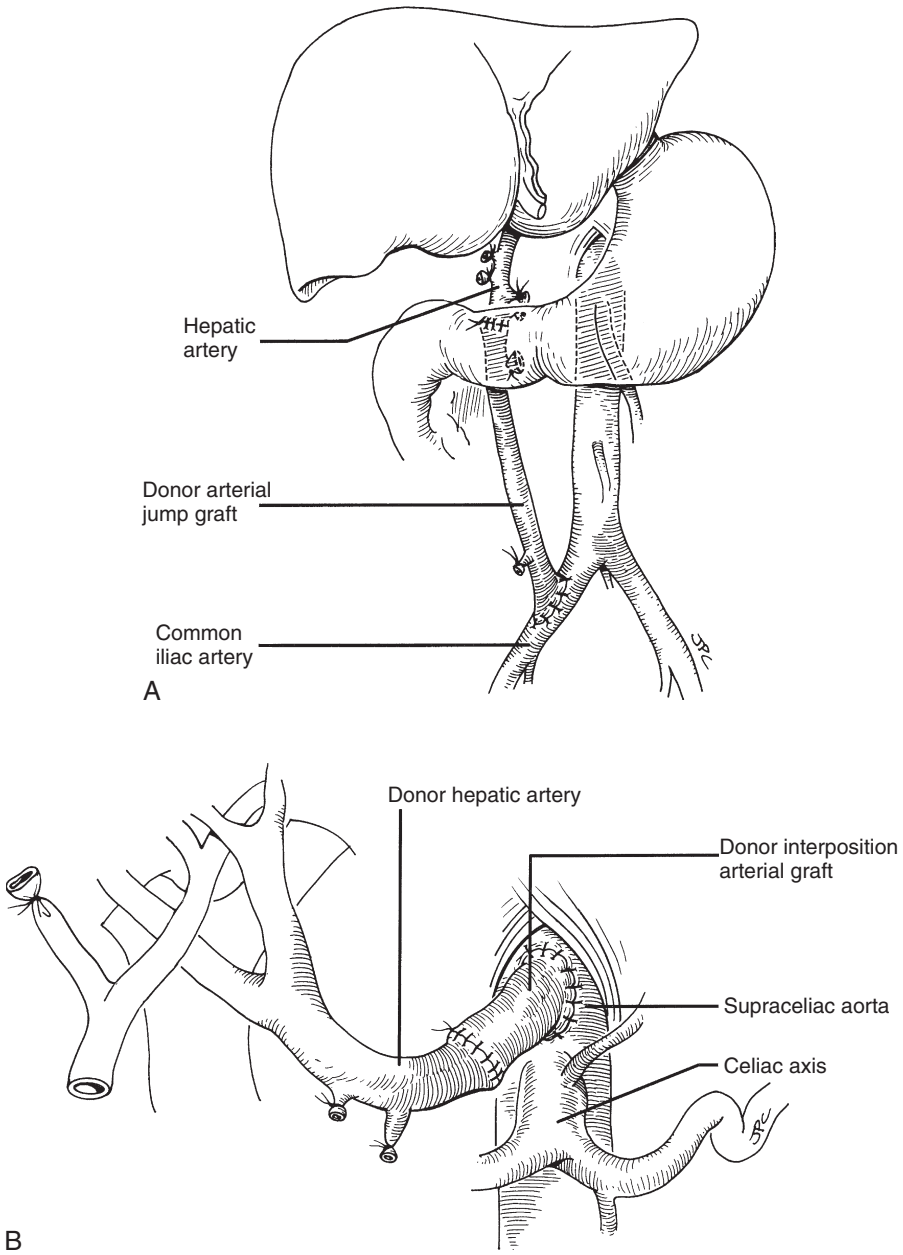


FIGURE 99.24. Other originating sites for an arterial jump graft. **A,** Host iliac artery. **B,** Supraceliac aorta.

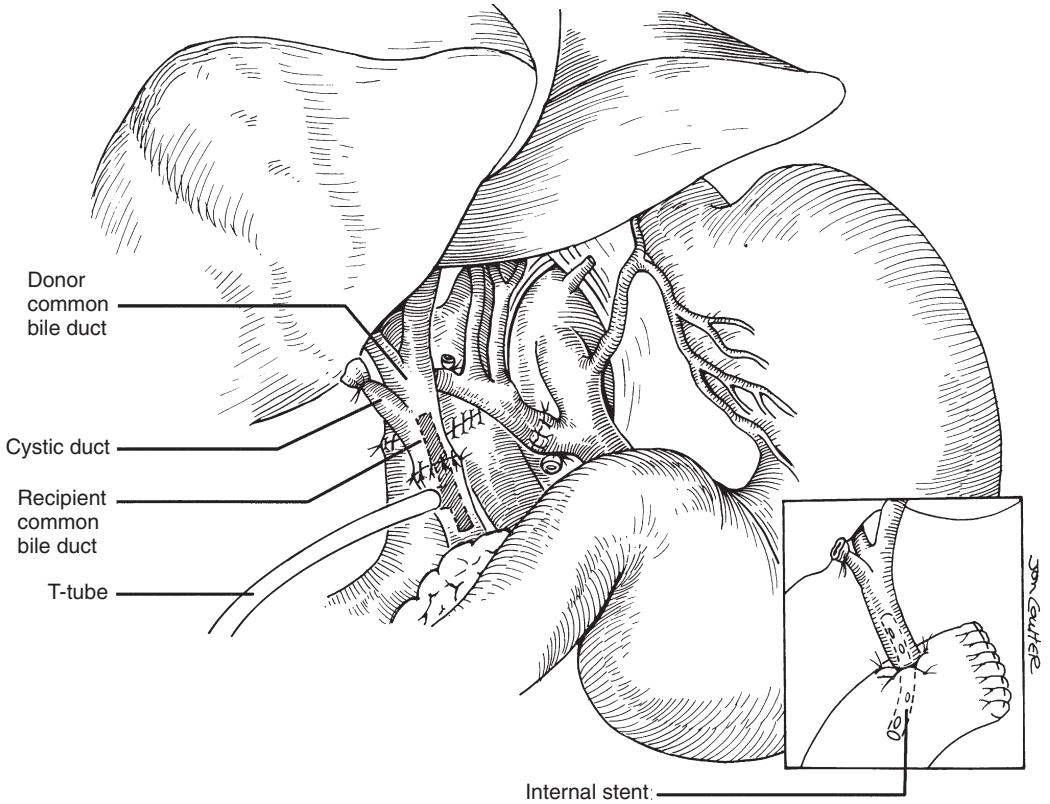


FIGURE 99.25. Biliary tract reconstruction with end-to-end anastomosis over a T-tube. If duct reconstruction is not feasible or is contraindicated, the graft duct is anastomosed to a Roux-en-Y limb of host jejunum (*inset*).

antecolic, to the hepatic hilum; the donor duct is then anastomosed end-to-side to the jejunal limb with a running or interrupted 5-0 or 6-0 absorbable polyglycolic acid suture with or without a stent (see Fig. 99.25, inset). When used, the stent is secured in place with a rapidly absorbed suture with the assumption that the stent will later pass spontaneously through the intestinal tract; however, occasionally the stent is retained and must be pushed into the bowel by an interventional radiologist, or it can be removed by push enteroscopy. Rarely does the stent require removal at laparotomy.

REDUCED-SIZE LIVER TRANSPLANTATION

The scarcity of pediatric donors and the constraints of size matching often prohibit transplantation of a whole donor liver into a child or small adult (see Chapter 98C). Since 1980, the option of using a partial liver has been exercised at most large transplant centers with results equal to or approaching those achievable with whole liver transplantation. Partial liver transplantation, its application in live donors; and the use of divided cadaveric livers, which allow one organ to be used for two recipients, are described elsewhere in this text (see Chapters 98B and 98C).

References are available at expertconsult.com.

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CHAPTER 100

Early and late complications of liver transplantation

James J. Pomposelli and Roger L. Jenkins

OVERVIEW

Liver transplantation has evolved from a risky procedure with high morbidity and mortality to a standard treatment for patients with liver failure. Patients who undergo successful liver replacement have 5-year survival rates that exceed 70% (Muraji et al, 1997; see Chapter 97). Despite this dramatic improvement in outcome, a significant percentage of patients experience life-threatening complications that can result in the need for reoperation. As expertise in the procedure grows, surgeons are willing to attempt liver transplantation in patients who previously were considered poor candidates for surgery. Recipient portal vein thrombosis (PVT) was considered an absolute contraindication to surgery, but now transplantation is commonly performed in the presence of PVT (Shaked & Busuttil, 1991; Stieber et al, 1991).

As surgeons continue to develop new surgical procedures, such as transplantation of reduced-size and split-liver grafts and living-donor liver transplantation (LDLT), a new series of complications unique to these procedures is emerging (Broelsch et al, 2000; Emond et al, 1993). The incidence of hepatic artery thrombosis, bile leaks, and stricture is at least two times higher in patients who receive living-donor grafts compared with those who receive cadaveric grafts (Malago et al, 2003). Despite a higher morbidity rate in recipients of living-donor grafts, patient and graft survival are similar or superior to those observed with deceased donors (Fan et al, 2002; Lo et al, 2002; Pomposelli et al, 2006). This chapter reviews common early and late complications encountered during and after liver transplantation. Because complications after liver transplantation represent a continuum, most can occur at any time after surgery.

PROCUREMENT INJURY TO THE GRAFT

The process of organ transplantation begins with identification of a suitable organ for a particular recipient. When an organ is identified, procurement teams are dispatched for recovery of various organs. In general, the liver procurement team dictates the conduct of dissection below the diaphragm, while the cardiac team works in concert with the thoracic team, if lungs and heart also are to be recovered. Because the infradiaphragmatic dissection takes considerably longer than the thoracic dissection, careful planning is required to minimize cold ischemia time for the heart and lungs, which are more time sensitive. The heart procurement team stays in contact with the recipient heart team to minimize total ischemic time.

Under ideal conditions, the conduct of the operation is orderly and well controlled; however, a patient who progresses to brain death rapidly can show cardiac instability and be difficult to manage. This situation can result in an expedited operation in which perfusion cannulae are hastily placed, and organ procurement rapidly follows. During such events, identification of appropriate anatomy is difficult, and technical errors are more likely to occur.

To increase the number of organs available, donation after cardiac death (DCD) is a new form of donation that is increasing in incidence (Chin et al, 2002). In this form of donation, a patient who is deemed hopeless but has not met criteria of brain death is allowed to die naturally after removal of supportive measures. After a period of usually 5 minutes of asystole, organs can be procured for transplantation. Despite the various periods of hypotension and warm ischemia that develop, outcomes with donation after cardiac death have been acceptable (Chin et al, 2002; Cooper et al, 2004). In liver grafts procured from DCD donors, increased biliary strictures and worse long-term graft survival have been suggested (D'Alessandro et al, 2004).

The most common injury during liver procurement is aberrant hepatic artery ligation and division. This injury occurs by failure to recognize a replaced or accessory right or left hepatic artery during hilar dissection or by unintentional division during organ removal. Such injuries are serious, because segments of the liver are not perfused during recovery and usually require reconstruction on the back table before reimplantation. An additional anastomosis on the back table prolongs ischemic time, increases the chances of thrombosis, and increases the need for retransplantation. Prolonged ischemic time, especially longer than 12 hours, increases the risk for graft loss and bile duct necrosis (Mor et al, 1993; Quiroga et al, 1991). To minimize dissection-related injuries, some authors prefer to use the en bloc method of removing abdominal organs, with back-table dissection (Imagawa et al, 1996). Regardless of the technique used, attention to detail and identification of the appropriate anatomy help avoid graft procurement injury.

INTRAOPERATIVE HEMORRHAGE AND COAGULOPATHY (SEE CHAPTER 70B)

All patients with end-stage liver disease come to the operating room with derangements in coagulation, and many present with severe portal hypertension. The combination of these two conditions results in a significant challenge for the surgeon and anesthesiologist. Patients who have undergone previous operations are at particular risk, because prolonged lysis of adhesions may greatly increase the duration of the operation, create additional raw surface areas for bleeding, and lead to derangements in temperature and fluid homeostasis. The net result is worsening coagulopathy, which creates a vicious cycle during the procedure.

Improvements in surgical techniques and better patient selection have led to the performance of liver transplantation without the need for blood transfusion in selected patients. The advent of the transjugular intrahepatic portosystemic shunt (TIPS) can significantly lower portal hypertension preoperatively and may help to reduce blood loss during transplantation (Forster et al, 1994); however, a misplaced TIPS in the vena cava or portal vein can be a life-threatening complication during liver transplantation. In these situations, TIPS removal is difficult and may lead to massive hemorrhage, if vascular control of the native vessels cannot be achieved.

In the presence of severe portal hypertension and underlying coagulopathy, the infusion of fresh frozen plasma and antifibrinolytic agents is the mainstay of therapy during liver transplantation (Palareti et al, 1991). These modalities cannot supplant the need for sound surgical technique with adequate control of all surgical bleeding sites. Bleeding observed after reperfusion may be related to poor initial graft function but also has been related to the release of heparin and heparin-like substances from the graft. Kettner and colleagues (1998) used heparinase-modified thromboelastography (TEG) to identify patients who developed bleeding secondary to the release of heparin-like substances. Such screening methods may help stratify patients at particular risk for the development of reperfusion fibrinolysis and may offer future therapeutic strategies to control coagulopathy encountered immediately after reperfusion (Kettner et al, 1998).

When medical strategies fail to halt reperfusion fibrinolysis, intraabdominal tamponade with laparotomy packs provides the most conservative management. If the graft functions well, and the patient responds to core temperature warming and continued resuscitation, packs usually can be removed within 24 to 48 hours. Prophylaxis against intraabdominal sepsis with parenteral antibiotics is of unproven benefit but may be prudent in the setting of immunosuppression.

PRIMARY GRAFT DYSFUNCTION OR NONFUNCTION

Numerous conditions can interfere with the initial function of the allograft after transplantation, including donor-related, procurement-related, and recipient-related factors. Donor-related factors that can affect graft function adversely include hemodynamic instability, poor nutritional status, extremes of age, drug toxicity, and steatosis (D'Alessandro et al, 2004; Marsman et al, 1996; Washburn et al, 1996).

Although no uniform definition exists, the severity and prognosis for graft dysfunction vary considerably. The most ominous syndrome is primary graft nonfunction, which usually requires immediate retransplantation. In such instances, a progressive increase is typically seen in serum transaminase levels (>8000 IU/L) within the first 24 to 48 hours in association with diminished bile and urine output. In our practice, postoperative trends in the prothrombin time (PT) have been the most reliable predictor of graft function and outcome. Laboratory studies drawn immediately after surgery serve as the baseline: the PT should plateau and then trend toward normalization in a matter of days with good graft function; any increase in the PT portends a worse prognosis and may represent primary graft nonfunction, especially if this occurs rapidly. An elevated PT that neither increases nor decreases may suggest primary graft dysfunction; recovery usually occurs with time, if no additional insults occur, such as infection or rejection. In these situations, infusion of prostaglandin E_1 may be beneficial in resolving or preventing renal or graft dysfunction (Chavin et al, 1996; Klein et al, 1996).

In addition to trends in the PT, clinical assessment can be helpful in identifying patients with graft dysfunction or nonfunction. Resolution of hepatic encephalopathy, adequate urine production, and absence of metabolic acidosis are reassuring in the early postoperative period. In patients who have received significant quantities of blood products, the development of metabolic alkalosis may be a sensitive indicator of early graft function (Driscoll et al, 1987). Such indicators are based on the ability of the liver graft to process citrate in the administered blood products to bicarbonate; failure to metabolize citrate to bicarbonate may reflect early allograft dysfunction.

In patients with progressive graft dysfunction or nonfunction, early consideration for relisting with a higher urgency (status 1) may be the only way to salvage the patient and prevent mortality. In this situation, aggressive metabolic supportive measures are needed to prevent bleeding complications, maintain acid-base status, and prevent permanent brain injury.

VASCULAR COMPLICATIONS

Hepatic Artery Thrombosis

Vascular complications are a major source of morbidity and graft loss in liver transplant patients. Arterial complications, of which hepatic arterial thrombosis (HAT) is the most common, account for 64% to 82% of the vascular complications encountered (Bell et al, 1990; Leonardi et al, 2004). The overall incidence of HAT is 1.6% to 8% in various adult series, but it can be 15% to 26% in pediatric patients (Busuttil et al, 1991; Mazzaferro et al, 1989; Tan et al, 1988). The incidence of HAT in LDLT varies widely and is influenced by the type of graft, surgeon experience, and donor anatomy.

Doppler ultrasound (US) is the best screening method and should be used liberally in the first 2 weeks after transplantation with any change in graft function or significant elevation in bilirubin or transaminases. Because collateral blood flow through the gastroduodenal artery can result in a false-negative result, care must be taken to establish arterial flow within the hepatic parenchyma. In cases of suspected HAT revealed by US, confirmation should be made by celiac arteriography (Fig. 100.1) or multiphase computed tomography (CT). Failure to make a rapid diagnosis can result in hepatic necrosis and graft loss.

Intimal dissection of the recipient hepatic artery down to the origin of the celiac axis is a common cause of intraoperative HAT. In these cases, immediate reconstruction with a donor iliac allograft is indicated (Fig. 100.2). Under no circumstances should the patient leave the operating room without a completely revascularized graft. When a donor iliac allograft is unusable or unavailable, an autogenous saphenous vein graft should be used. Rarely, an artificial conduit made from Dacron or expanded polytetrafluoroethylene can be used.

The clinical presentation of HAT observed postoperatively ranges from a completely asymptomatic patient with minimal alterations in liver function to a critically ill patient with fulminant hepatic necrosis. A more common presentation of HAT is with postoperative biliary complications, including leaks and stricture formation (Margarit et al, 1998; Orons et al, 1995). Treatment for HAT in the early postoperative period is the

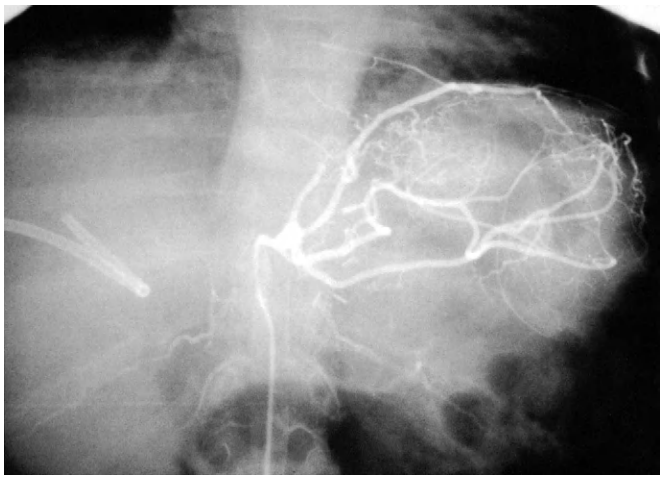


FIGURE 100.1. Hepatic artery thrombosis. The patient developed a rapid increase in serum transaminases in the early postoperative period. Ultrasound could not locate an intrahepatic arterial signal. Celiac arteriography shows left gastric and splenic arterial flow and fails to show any contrast in the liver. This is consistent with intimal dissection of the entire common hepatic artery. The T-tube within the common bile duct is visible.

same, whether symptoms are present or not: rapid reestablishment of arterial inflow should be attempted, which generally requires urgent operation with arterial reconstruction using a donor iliac artery allograft or autogenous graft material. Some authors have attempted thrombolysis using tissue plasminogen activator and urokinase, but this can be expected to be successful only when no technical factors are contributing to the thrombosis (Hidalgo et al, 1989). Hepatic artery intimal dissection is not amenable to thrombolytic therapy, and attempts at systemic thrombolysis waste valuable time and resources and worsen outcome. In most cases, 50% to 70% of patients ultimately require retransplantation (Langnas et al, 1991).

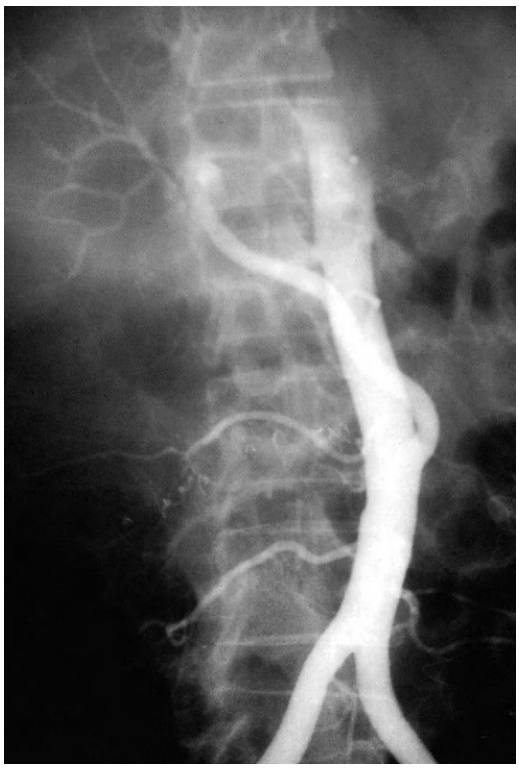


FIGURE 100.2. Hepatic artery reconstruction. With early diagnosis of hepatic artery thrombosis, immediate reconstruction with a donor iliac artery allograft can be performed. In this case, the iliac artery graft is anastomosed between the infrarenal aorta and liver allograft common hepatic artery.

Portal Vein Thrombosis

PVT observed prior to surgery was previously considered an absolute contraindication to orthotopic liver transplantation (OLT). Although this problem no longer precludes successful liver transplantation, its presence may substantially increase the surgical complexity and perioperative morbidity.

Reconstitution of portal flow usually can be obtained through portal vein thrombectomy in most cases or by using a donor iliac vein allograft anastomosed between the superior mesenteric vein and liver allograft portal vein (Davidson et al, 1994; Shaked & Busuttil, 1991). Living-donor grafts that have relatively short portal vein segments can be difficult to reconstruct, and approximately 10% of institutions consider PVT an absolute contraindication to LDLT (Kadry et al, 2002).

PVT observed after transplantation is a rare complication that can occur in the immediate postoperative period, usually for technical reasons, such as incomplete thrombectomy or twisting of the anastomosis. PVT observed several months to years after transplantation usually results from intimal hyperplasia with gradual cavernous transformation with collaterals. A high index of suspicion is needed to make the diagnosis. Accumulation of ascites, splenomegaly, or the presence of varices after transplantation should prompt investigation. Early thrombosis is best treated with reoperation, thrombectomy, and systemic coagulation. The treatment of late thrombosis is more controversial, because direct repair is difficult. Transhepatic angioplasty with the placement of metal stents has been successful in some patients, whereas other patients have responded to selective shunting procedures to control variceal hemorrhage in the setting of adequate liver function (Jenkins et al, 1999; Raby et al, 1991).

Inferior Vena Cava Obstruction

Inferior vena cava (IVC) obstruction is a rare complication that occurs in 1% to 2% of patients after liver transplantation (Wozney et al, 1986). Most surgeons prefer to anastomose the donor IVC to the suprahepatic and infrahepatic IVC. A growing trend is to perform a so-called piggyback transplantation, with the anastomosis of the donor suprahepatic IVC to the confluence of the recipient middle and left hepatic veins, leaving the recipient IVC in situ (Neuhaus & Platz, 1994; Tzakis et al, 1989).

In our experience in 90 consecutive liver transplantations using the piggyback technique, two patients developed thrombus in their native IVC. The first IVC thrombosis developed in a patient with Budd-Chiari syndrome, who had occluded middle and left hepatic veins and a misplaced TIPS in the right hepatic vein that extended into the IVC at the time of transplantation. Postoperatively, the patient developed profound pedal edema and ascites. US confirmed the diagnosis, and the condition was treated successfully with anticoagulation and balloon dilation without further surgery. The second patient was a

young man who was urgently transplanted for fulminant liver failure secondary to hepatitis A. Complicating this operation was the presence of a high-grade bacteremia with *Staphylococcus aureus* at the time of transplantation. Postoperatively, the patient did well but developed persistent fevers of an unknown source. Gallium scanning ultimately disclosed a nearly occluding infected thrombus in the infrarenal IVC. This thrombus was treated with long-term antibiotics and systemic anticoagulation with complete resolution after 6 weeks of therapy.

Treatment of an IVC thrombosis usually depends on the cause. Direct surgical removal is difficult in a critically ill patient and requires extensive mobilization of the right colon and small bowel mesentery to facilitate exposure. Medical management of IVC thrombosis was successful in our experience and that reported by others (Kraus et al, 1992). Our experience suggests that a more conservative management algorithm that employs invasive radiologic procedures and systemic anticoagulation can treat this complication satisfactorily (Kraus et al, 1992). Thrombolytic therapy can also be adjunctive in resolving "fresh" thrombus formation.

BILIARY COMPLICATIONS

Biliary tract complications related to bile duct reconstruction previously were considered the Achilles heel of liver transplantation, but improvements in operative technique have reduced these complications markedly. Nevertheless, bile duct obstruction and leaks are the cause of approximately half of all technical failures after transplantation and require reoperation in 10% to 20% of patients (Lerut et al, 1987). In general, recipients of living-donor grafts have an incidence of biliary complications approximately two times higher than recipients of cadaveric grafts (Pomfret et al, 2001). HAT is associated with biliary complications and may explain the increased incidence among living-donor graft recipients.

Biliary Leaks

The reported incidence of biliary leaks after liver transplantation varies widely from 10% to 50% (Rabkin et al, 1998; Reichert et al, 1998). Leaks are observed most commonly at the site of choledochal anastomosis or the choledochal T-tube insertion site. Leaks at the choledochal tube insertion site are observed most commonly at the time of tube removal and occur in 25% to 40% of patients (O'Connor et al, 1995). Most of these patients can be managed conservatively with a short course of analgesics and antibiotics. To minimize this risk, some surgeons prefer not to place stents.

In our practice, rather than using a conventional T-tube, we stent our choledochal anastomosis with a 5-Fr pediatric feeding tube placed through the cystic duct stump, which is secured with a hemorrhoidal band and polydioxanone suture (PDS). In theory, the hemorrhoidal band obliterates the lumen of the preformed tract at the time of stent removal, usually 6 to 8 weeks postoperatively. Anastomotic leaks encountered in the early postoperative period are related to technical errors, tension at the anastomotic site, or ischemic necrosis after hepatic artery thrombosis.

The bile ducts of living-donor or split-liver grafts can be reconstructed with a duct-to-duct (choledochocholedochostomy) or Roux-en-Y hepaticojejunostomy. The leak rate is similar with both types of reconstructions (Gondolesi et al, 2004). Signs and symptoms related to biliary leaks include bilious fluid in drains (biliary fistula), abdominal or shoulder pain or both, increased serum bilirubin, nausea, vomiting, and fever. Diagnosis can be confirmed by cholangiography if a choledochal tube is in place; otherwise, endoscopic retrograde cholangiography (ERC) or percutaneous transhepatic cholangiography (PTC) can be performed. We favor ERC, because treatment with endoscopic stent placement can be readily achieved without the risk associated with the indwelling transhepatic catheters used during PTC. Large biliary leaks resulting in bile collections adjacent to the liver require percutaneous drainage.

Leaks associated with ischemic necrosis require surgical revision with Roux-en-Y hepaticojejunostomy. The development of early postoperative leaks is associated with late stricture formation, and lifelong surveillance by the surgeon is warranted.

Biliary Stricture or Obstruction

Biliary obstruction occurs in approximately 7% to 15% of patients after liver transplantation (Klein et al, 1991; Lerut et al, 1987). As with leaks, the site of obstruction aids in determining the cause. Anastomotic stricture accounts for 50% of obstruction cases and can occur early in the postoperative period, secondary to edema, or later, as a result of compromised blood supply (Fig. 100.3). Biliary strictures usually present within weeks but may occur years after transplantation. Two types of biliary obstruction usually are found: *anastomotic* and *nonanastomotic*. Nonanastomotic obstruction or stricture can be caused by or associated with bile duct ischemia or sludge and debris that can accumulate in the biliary system after transplanting (Fig. 100.4).

The diagnosis of biliary stricture or obstruction is implied by an obstructive pattern on routine liver function tests. Commonly, patients are seen with constitutional symptoms of rigor, fever, headache, and fatigue. Occasionally, patients present with

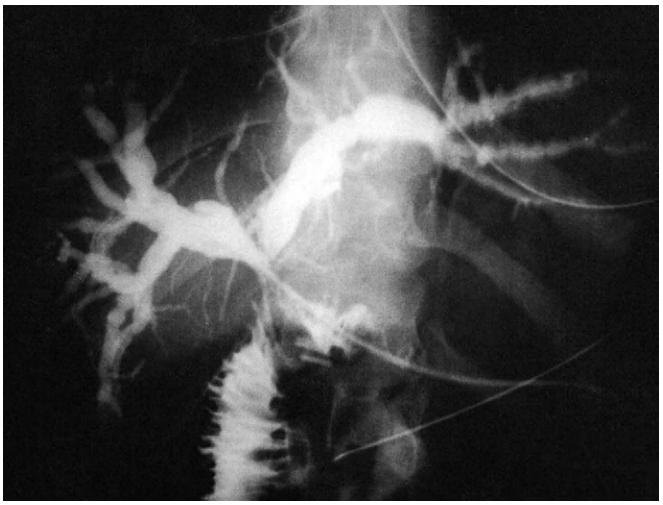


FIGURE 100.3. Biliary stricture. This patient had a previously created Roux-en-Y hepaticojejunostomy and now has an anastomotic stricture. Note the dilated intrahepatic ducts. Percutaneous access of the Roux-en-Y limb affords the ability to make the diagnosis and treat with balloon dilation. Using this technique, placement of transhepatic catheters is avoided.



FIGURE 100.4. Nonanastomotic biliary stricture observed from ischemic injury to a liver graft in a patient who received a liver from a donor who died from cardiac death rather than brain death. Donation after cardiac death (*DCD*), rather than after brain death, is an attempt to expand the organ donor pool; but such grafts are more prone to ischemic injury problems such as bile duct stricture.

severe symptoms of cholangitis and sepsis. Because patients with "mild" signs and symptoms also may reflect the presence of any number of serious conditions—acute rejection, HAT, cytomegalovirus (CMV) infection, or recurrent disease—diagnosis can be difficult. To ascertain the correct diagnosis rapidly, a series of diagnostic studies that include abdominal US, cholangiography, and liver biopsy is obtained immediately after the onset of abnormal clinical signs and symptoms (Kuo et al, 1994).

Regardless of the method used to reestablish the biliary continuity, the most common site of a biliary stricture in the posttransplantation setting is at the biliary anastomosis. Technical error during reconstruction is an important causative factor, but the patency of the hepatic artery also should be assessed, particularly in pediatric recipients. Other factors that have been implicated in the development of biliary stricture include ABO incompatibility, prolonged preservation times, chronic rejection, CMV infections, and recurrence of primary ductal disease, such as sclerosing cholangitis (Feller et al, 1996; Greif et al, 1994; Sebagh et al, 1995).

Biliary reconstruction after LDLT is by Roux-en-Y hepaticojejunostomy or duct-to-duct anastomosis (Kawachi et al, 2002). Anastomotic leak or stricture is generally two times more common after living-donor versus cadaveric liver transplantation (Miller et al, 2001). Nonanastomotic strictures can occur in the hilar region or intrahepatically. As with anastomotic strictures, thrombosis of the hepatic artery or one of its branches should be suspected. Nonanastomotic strictures also have been reported in association with chronic ductopenic rejection, ABO blood group incompatibility, and as a result of ischemia-reperfusion injury associated with allograft preservation (Sanchez-Urdazpal et al, 1992).

After appropriate fluid resuscitation and antibiotic coverage, we recommend ERC to confirm the diagnosis and to implement treatment with immediate stenting if possible. Failure to cross the stricture through endoscopic means requires PTC or surgical revision with Roux-en-Y hepaticojejunostomy. Intrahepatic strictures are best treated with percutaneous balloon dilation. Rarely, stents are needed to achieve a satisfactory outcome (Colonna et al, 1992).

RENAL DYSFUNCTION

Renal dysfunction is observed to some degree in almost every patient who undergoes liver transplantation (Baliga et al, 1992; Lam et al, 2004). Early renal dysfunction usually is characterized by a period of oliguria with a transient increase in serum creatinine but can also be manifested as anuria with acute renal failure. Risk factors include preexisting renal dysfunction and primary graft nonfunction. In patients with normal preoperative serum creatinine and good initial graft function, the usual mechanism is prerenal azotemia secondary to periods of hypotension and hypovolemia during the operative procedure. An additional insult to renal function can be incurred by the administration of nephrotoxic agents, especially the calcineurin inhibitors (CNIs) cyclosporine and tacrolimus; renal failure induced by CNIs occurs in approximately 5% of transplanted patients (Myers et al, 1986).

Although the etiology of renal failure in transplant patients can be multifactorial, long-term exposure (dose/time) to CNIs is a clear risk factor. As a result, there has been increasing interest in automatic dose reduction in patients many years out from transplantation and in those showing signs of progressive renal dysfunction. Another strategy to reduce calcineurin renal toxicity has been substitution of the immunosuppressive regimen by drugs that do not cause renal dysfunction, such as the mammalian target of rapamycin (mTOR) inhibitors.

Sirolimus (rapamycin) is a macrocyclic antibiotic originally developed as an anticandidal and antitumor agent (Vezina et al, 1975). It is often used for renal sparing but has the disadvantage of increasing the risk for dyslipidemia and impaired wound healing. The impairment of wound healing may be related to alterations in vascular endothelial growth factor (VEGF) and may explain the apparent benefit of sirolimus in reducing cancer formation in patients (Fuereder et al, 2010). Because sirolimus has been associated with early hepatic artery thrombosis (HAT) after liver transplantation, the manufacturer recommends waiting at least 4 weeks after transplantation before initiating therapy.

Posttransplantation renal failure so acute as to require dialysis is uncommon, unless the patient is diagnosed with preexisting hepatorenal syndrome or severe hypotension, and hemorrhage is encountered during surgery that results in acute tubular necrosis. In our experience, dialysis for these patients is best performed with continuous venovenous hemodialysis using a dedicated, large-bore, double-lumen venous access device. Recovery of normal renal function usually is achieved within 2 weeks, if no other metabolic stress is incurred.

FLUID AND ELECTROLYTE DISTURBANCES

Fluid and electrolyte disturbances and alterations in acid-base status are universal after liver transplantation. Preoperative protein calorie malnutrition and end-stage liver disease lead to derangements in total body water and electrolyte balance that are worsened initially by the metabolic stress of surgery and massive fluid and blood product resuscitation. The rapidity of recovery depends in large part on the patient's renal and liver

allograft function postoperatively. For a patient with stable postoperative renal and liver graft function, little metabolic manipulation is required to correct such derangements.

The early development of metabolic alkalosis secondary to metabolism of citrate in blood products is a favorable sign of graft function but can be serious if alkalemia develops (Driscoll et al, 1987). In this situation, judicious replacement of chloride in the form of hydrogen chloride is warranted.

Excess total body water and excess sodium are best treated with gentle diuresis with furosemide. Careful repletion of potassium should be instituted, but it must be monitored closely in the setting of medications such as tacrolimus, which tends to increase serum potassium levels (Oishi et al, 2000). Derangements in serum calcium, magnesium, and phosphorus are common in patients with cirrhosis and should be repleted to avoid neurologic, skeletal, and cardiac muscle dysfunction.

ACUTE CELLULAR REJECTION

In the early days of liver transplantation, the importance of rejection was overshadowed by technical complications. As surgical technique has evolved, with concomitant improvement in graft preservation, rejection has taken on greater clinical importance. *Acute cellular rejection* is defined as an acute deterioration in allograft function associated with specific histologic changes in the liver allograft. These changes include a mixed inflammatory cell infiltrate, predominantly lymphocytes, that involves the portal triads and disrupts the biliary, hepatic artery, and portal venous endothelia (*endotheliitis*) (Sedivy et al, 1998).

The incidence of acute rejection is approximately 45% (range, 24% to 80%), depending on the series reported. Although acute rejection has little to no impact on mortality, significant morbidity results in increased hospitalization and higher overall costs (Bucuvalas et al, 2001; Khettry et al, 2002). In the early stage, most patients are asymptomatic, but a variety of clinical signs and symptoms may develop that include fever, abdominal pain, malaise, fatigue, and poor appetite.

The earliest laboratory indicator of acute rejection is elevated bilirubin level, which may be associated with a modest increase in alkaline phosphatase and aminotransferase levels. PT and serum albumin levels are usually unaffected. Because laboratory measurements are neither sensitive nor specific for acute cellular rejection, liver histology obtained from a percutaneous biopsy specimen remains the standard for the diagnosis of cellular rejection (Khettry et al, 2002).

The initial treatment for acute cellular rejection includes high-dose pulse steroids, which is successful in approximately 80% to 90% of cases (Klintmalm et al, 1989). OKT3, a murine monoclonal antibody to the CD3 antigen–receptor complex, is reserved for the approximately 10% to 20% of patients whose acute cellular rejection cannot be not reversed with high-dose corticosteroid therapy. The major risks posed by using this treatment for acute cellular rejection include increased susceptibility to infection and the association between OKT3 use and posttransplantation lymphoproliferative disease (PTLD; Deschler et al, 1995). In addition, a severe systemic inflammatory response can be initiated from OKT3 infusion that can lead to pulmonary edema, hypotension, and shock.

Chronic ductopenic rejection affects approximately 10% of liver transplant patients. *Ductopenic rejection* rarely occurs during the first 2 months after liver transplantation; it is defined as loss of bile ducts in more than 50% of portal tracts, when 20 or more portal tracts are available for evaluation, and is diagnosed on the basis of histologic criteria (van Hoek et al, 1992). In addition, arteriopathy has been described that affects large and medium-sized arteries, characterized by foam-cell infiltration of the intima. The most important manifestation of chronic rejection, the term *ductopenic rejection* is used synonymously with the histologic description *vanishing bile duct syndrome*. No treatment exists with the exception of retransplantation (Koukoulis et al, 2001).

INFECTION

With few exceptions, all patients who undergo transplantation are committed to lifelong immunosuppression therapy to prevent graft rejection. Inadequate immunosuppression can result in graft loss, whereas injudicious use of immunosuppression can result in life-threatening infection or the development of PTLD. A tenuous balance exists between the proper amount of immunosuppression to prevent rejection and minimization of the risk for nosocomial and opportunistic infection. Despite better understanding of the immune response and proliferation of more selective immunosuppressive agents, approximately two thirds of transplant patients experience at least one episode of serious infection, which accounts for more than half of the observed mortality associated with liver transplantation (Kibbler, 1995).

Risk factors for postoperative infection after liver transplantation include those incurred from the donor, recipient, and intraoperative course: donor and recipient viral status, underlying medical comorbidities, and nutritional status all can contribute. Prolonged surgery with massive blood loss, prolonged ischemia time, and violation of the gastrointestinal tract also are risk factors for nosocomial infection (George et al, 1992).

Bacterial infections tend to occur within the first month after liver transplantation and vary from center to center (range, 35% to 68%) (Kibbler, 1995; Kusne et al, 1992). Early risk factors include prolonged operating time, indwelling catheters, biliary obstruction, PVT, and poor graft function. In addition, vascular ischemia, recurrent hepatitis C virus (HCV) infection, patient exposure to resistant organisms, and chronic rejection can contribute to nosocomial infection (Singh et al, 1997). Common bacterial pathogens include gram-negative organisms found in the bile (*Escherichia coli, Enterobacter* spp., *Pseudomonas* spp.) and gram-positive organisms (*S. aureus,* coagulase-negative staphylococci, and group D streptococci). Rarely, *S. aureus* can result in the development of toxic shock syndrome in the early postoperative period. *Listeria, Nocardia,* and *Legionella* are uncommon but significant pathogens (George et al, 1992).

Viral infections are common in immunocompromised patients after transplantation. In addition to the more common viral infections described here, other equally important but less common viral infections can be devastating to immunocompromised transplant patients; these include human immunodeficiency virus (HIV), adenovirus, influenza, and respiratory syncytial virus (RSV). In addition, transplant patients are at risk for acquiring viral hepatitis from infected organs, blood transfusions, and illicit drug use.

Cytomegalovirus (CMV) infection is the single most important infection observed in organ transplant patients. An asymptomatic infection in the general population, CMV attains significant potential severity in immunosuppressed transplant recipients and is the most important pathogen in clinical transplantation (Kusne & Shapiro, 1997). CMV disease usually

occurs 30 to 50 days after transplantation, with clinical manifestations that include fever, malaise, arthralgia, leukopenia and thrombocytopenia, hepatitis, interstitial pneumonitis, enterocolitis, and disseminated disease. Differentiation between *CMV disease* and *CMV infection* is clinically important: *CMV disease* is defined as a histologically evident invasive CMV infection or a positive CMV culture from deep tissue specimens—liver biopsy, endoscopic mucosal biopsy or brushing, bronchoscopic mucosal biopsy or brushing—in the setting of clinical manifestation. The presence of positive blood, body fluid, or serologic tests is insufficient to establish the diagnosis of CMV disease. Liver biopsy with immunostaining using a monoclonal antibody against CMV antigen enables early diagnosis. Common histologic findings include hepatocyte necrosis, parenchymal microabscesses, and a magenta-colored intranuclear inclusion surrounded by a clear halo, the so-called owl's eye nucleus (Everson & Kam, 1997).

Risk factors for the development of CMV disease include a seronegative recipient who received an organ from a seropositive donor, the use of antilymphocyte antibody therapy (particularly OKT3), and retransplantation. In general, the level of immunosuppressive therapy influences manifestation of CMV infection (Furukawa et al, 1996). Chronic CMV infection with persistent CMV replication within hepatocytes is associated with cholestatic hepatitis and vanishing bile duct syndrome.

Patients who manifest CMV disease are treated with a reduction, if possible, of the immunosuppressive regimen, particularly tapering of the steroid dose. For years, intravenous ganciclovir had become the mainstay of therapy and is safe and effective for prophylaxis and treatment. Occasionally, foscarnet is required as an alternative in cases of ganciclovir resistance, but it is less well tolerated and can be nephrotoxic.

Prophylaxis against CMV disease using oral and intravenous ganciclovir after transplantation has been effective. Other prophylaxis regimens using intravenous gancyclovir plus oral acyclovir for 3 months after transplantation or oral acyclovir used alone have been less successful (Nakazato et al, 1993; Oldakowska-Jedynak et al, 2003). More recently, prevention and treatment of mild CMV infection using oral valganciclovir has been demonstrated to be as effective as intravenous ganciclovir (Eid et al, 2010). Because of the effectiveness of oral valganciclovir, most transplant centers have switched to prophylactic regimens that range from 3 to 6 months of daily oral treatment (450 or 900 mg, depending on renal function). Side effects are minimal, but leukopenia can occur. Late-onset CMV disease remains a potential problem, especially in patients on higher doses of immunosuppression and in high-risk groups, whose donor was CMV positive when the recipient was CMV negative (CMV D+/R–).

Herpes simplex seropositivity is present in most patients undergoing liver transplantation. Herpes simplex infection observed postoperatively usually is related to immunosuppression-induced reactivation. Herpesvirus infection usually manifests as a mild mucocutaneous oral or genital disease that responds to acyclovir treatment; however, prompt recognition is important to prevent progression to lethal disseminated disease or fulminant hepatitis with coagulopathy, disseminated intravascular coagulation, and death. Graft involvement is diagnosed by a characteristic histologic picture on liver biopsy.

Epstein-Barr virus (EBV) belongs to the herpes family, and infection in a transplant patient is characterized by a mononucleosis-like syndrome that differs from that observed in the normal host by the absence of a heterophil antibody response and the infrequency of pharyngitis or splenomegaly (Alshak et al, 1993). The clinical significance of EBV infection in a liver transplant patient has to do with its role in the pathogenesis of PTLD (Manez et al, 1997), the development of which is thought to reflect the unrestricted proliferation of B cells stimulated by EBV infection. The incidence and treatment for established PTLD are discussed later.

Opportunistic infections also are commonly encountered. The incidence of clinically significant fungal infection is 20% to 25% in liver transplant recipients. Risk factors for fungal infection include poor nutrition status, retransplantation, bacterial infection with prolonged antibiotic use, high doses of immunosuppression, and biliary reconstruction using Roux-en-Y hepaticojejunostomy (Castaldo et al, 1991).

Disseminated fungal infection with *Candida* or *Aspergillus* can be difficult to diagnose and is associated with a high mortality rate in these patients. If the suspicion of invasive fungal infection is high, every effort should be made to obtain histologic or culture evidence to establish early diagnosis. *Aspergillus*, the second most frequent fungal infection in transplant patients after *Candida*, is acquired by inhalation and colonizes the airways before causing invasive disease. *Aspergillus* is angioinvasive and tends to disseminate to the central nervous system (CNS) and can cause infarcts and cavitation in the lungs. The incidence of invasive aspergillosis is approximately 1% in liver transplant recipients, with a mortality rate close to 100% despite adequate treatment (Kusne et al, 1992).

Infection by *Cryptococcus neoformans* usually occurs months to years after transplantation and affects approximately 0.25% of liver transplant patients (Patel et al, 1996). Because signs and symptoms may be subtle, delayed diagnosis is common. Symptoms that bring the patient to medical attention include changes in mental status, headache, and fever. In our experience, one patient was seen initially with lesions in the CNS and large cavitating masses in the thorax that required operative removal.

Pneumocystis carinii pneumonia was previously a common pathogen in the immunocompromised host. With the introduction of routine use of prophylaxis with daily low-dose oral trimethoprim/sulfamethoxazole for 6 to 12 months, or aerosolized pentamidine in patients intolerant to trimethoprim/sulfamethoxazole, the incidence of *P. carinii* pneumonia has decreased dramatically. Because prophylaxis has been so effective, *P. carinii* pneumonia has occurred almost exclusively in patients who do not receive prophylaxis. Given the low morbidity associated with the prophylactic regimens, no patient should be excluded.

Legionella pneumophila is an uncommon cause of pneumonia in patients after liver transplantation. As in the normal host, the source of legionellosis is usually the water supply. Traditionally, treatment of *Legionella* pneumonia has been with erythromycin, but quinolones also have been proven effective and have the advantage of not interacting with immunosuppressive agents such as cyclosporine and tacrolimus.

POSTTRANSPLANTATION LYMPHOPROLIFERATIVE DISORDER

PTLD is a life-threatening complication of chronic immunosuppression. Lymphoproliferative disorders have been strongly associated with the replication of EBV in B cells induced by

enhanced immunosuppression (Manez et al, 1997; Newell et al, 1996); this has been observed primarily in patients who have received more than one course of polyclonal antilymphocyte globulin or monoclonal OKT3 (Davis et al, 1995). An association with CMV infection also has been noted. The incidence of PTLD varies from 1% to 3% among liver transplant recipients, and prognosis depends on the histologic characteristics of the tumor. Polyclonal PTLD is treatable with discontinuation of immunosuppression with relatively low risk of rejection (Hurwitz et al, 2004). Monoclonal PTLD is more difficult to treat and can result in death. Antibody against CD20 represents a novel approach in treating monoclonal PTLD, with favorable outcome (Yedibela et al, 2003; Zompi et al, 2000). The clinical presentation of PTLD varies and includes fever, malaise, and lymphadenopathy with or without tonsillitis. In addition, gastrointestinal bleeding, perforation, or obstruction; hepatocellular dysfunction; and CNS manifestations, such as seizures, mental status changes, and focal neurologic symptoms also have been described.

Lymphoproliferative disorders occurring after transplantation have characteristics distinct from the lymphoproliferative disorders that occur in the general population. Non-Hodgkin lymphoma accounts for 65% of lymphomas in the general population, compared with 93% in transplant recipients. These tumors are mostly large-cell lymphomas, and most are of the B cell type. Extranodal involvement is common and occurs in approximately 70% of cases (Zompi et al, 2000).

Treatment of polyclonal PTLD consists of reduction of immunosuppressive medications and antiviral therapy (Starzl et al, 1984). Patients with monoclonal PTLD and patients with polyclonal disease that does not respond to reduced immunosuppression have been treated with radiation, chemotherapy, and occasionally surgical resection. Therapy using monoclonal antibody against CD20 shows promising results for patients with monoclonal PTLD (Dotti et al, 2001; Zompi et al, 2000).

ACUTE IMMUNOSUPPRESSIVE DRUG TOXICITY

Immunosuppression after transplantation must achieve a balance between the beneficial effects of the drugs in preventing or reversing rejection and the dangers of excess immunosuppression with the development of acute toxicity symptoms, nosocomial infection, and lymphoproliferative disorders. The most common agents used for immunosuppression in liver transplant patients are the CNIs cyclosporine and tacrolimus (FK506) in combination with steroids. Azathioprine is used less frequently in liver transplant than in kidney transplant recipients, who usually receive triple-drug therapy. Mycophenolate mofetil has essentially replaced azathioprine in the immunosuppression regimen after liver and kidney transplantation. After the initiation of immunosuppression therapy, development of infection and acute toxicity are usually seen early during treatment, whereas lymphoproliferative disorders and other malignancies are long-term sequelae as previously mentioned.

In addition to PTLD, chronic immunosuppression has been associated with an increased frequency of many other neoplasms, including basal skin cancer, non-Hodgkin lymphoma, Kaposi sarcoma, uterine cervical carcinoma, and carcinomas of the external genitalia (Busuttil et al, 1991). As with PTLD, patients who received repeated doses of antilymphocyte antibody have a particularly high incidence of neoplasms (Millis et al, 1995). Long-term use of steroids, particularly at high doses, is associated with obesity, hypertension, bone disease, glucose intolerance, pancreatitis, muscle weakness, hirsutism, and fluid and sodium retention; in children, growth retardation is a major problem (Busuttil et al, 1991).

The side-effect profiles of cyclosporine and tacrolimus are similar and include gastrointestinal disturbances, headache, and tremor. Gingival hyperplasia and hirsutism are encountered frequently during cyclosporine and steroid treatment, whereas glucose intolerance is reported more often with tacrolimus treatment than with cyclosporine therapy. Hyperkalemia, hyperuricemia, hypophosphatemia, and hypomagnesemia are manifestations of renal tubular dysfunction and usually can be controlled by adjusting the dose according to drug levels. Nephrotoxicity is the most clinically significant adverse effect of both drugs and is manifested as acute azotemia. This effect is largely reversible after reducing the dose of the drug and providing adequate hydration. Occasionally, progressive chronic renal disease can develop, which is usually irreversible. In such a situation, dialysis or kidney transplantation is required. Other renal effects of cyclosporine include chronic tubular dysfunction and, rarely, hemolytic uremic syndrome (Cohen et al, 2002).

RECURRENT HEPATITIS (SEE CHAPTER 64)

In patients who develop cirrhosis secondary to chronic hepatitis B virus (HBV) infection, the recurrence rate as evidenced by signs of viral replication (HBV e-antigen–positive or positive titers of HBV DNA) is approximately 80% to 90% in the first year. Given the almost universal recurrence of HBV antigenemia in the early postoperative period, some authors have questioned the utility of liver replacement in these patients. With the advent of hepatitis B immunoglobulin (HBIg) and other adjuvant therapies, such as interferon and lamivudine, to prevent recurrent disease, transplantation now is routinely offered to patients with chronic HBV infection, with excellent results (Dodson et al, 2000; Grellier et al, 1996).

Recurrent HCV infection is universal after liver transplantation (Gordon et al, 1997). In 90% of patients, hepatitis can be confirmed on routine biopsy. Of these, 60% have mild hepatitis, whereas 30% develop a more severe pattern seen on histologic examination. In patients with severe recurrent HCV, 20% go on develop to cirrhosis within 5 years (Gordon et al, 1997). Of 100 patients with HCV infection who are transplanted, approximately 6 will require retransplantation (Gordon et al, 1997). Prophylaxis with ribavirin and interferon has been shown to be beneficial in reducing viral loads to zero, with significant prolongation of graft survival (Ahmad et al, 2001). Given the epidemic growth in HCV infection, it is likely to dominate the indications for liver replacement for years to come.

BONE DISEASE

Almost all patients who undergo liver transplantation have some degree of hepatic osteodystrophy. The mechanism seems to vary according to the underlying disease. The causes are multifactorial and include corticosteroid therapy, bed rest, and cholestasis. Osteoporosis is particularly common 3 to 6 months after transplantation; however, by the end of the first year after transplantation, patients start gaining bone density. This late improvement is probably because of a reduction in corticosteroid therapy and the resolution of the pretransplantation

condition that was deleterious to skeletal health. Atraumatic bone fractures are more frequent within the first 6 months after transplantation as a result of the extensive bone loss that occurs during this period (Navasa et al, 1996). Avascular necrosis and vertebral body collapse may also occur.

NEUROPSYCHIATRIC COMPLICATIONS

Severe neuropsychiatric changes can occur after liver transplantation. In addition to the acute neurophysiologic changes associated with fluid and electrolyte shifts during the perioperative period, anxiety and depression are common psychiatric conditions observed in many transplant patients. Seizures, alterations of the levels of consciousness, and infections of the CNS are infrequent but are significant causes of morbidity and mortality. Encephalopathy observed after transplantation can be related to poor initial graft function, but it is more commonly multifactorial in etiology. Metabolic derangements, hypoxia, sedation, and drug interactions all can contribute.

Neurologic signs and symptoms associated with immunosuppression toxicity related to cyclosporine and tacrolimus include tremors, headaches, and seizures. These can be avoided by close monitoring of drug levels. High-dose steroids can result in emotional lability or mania. Any patients presenting with new neuropsychiatric symptoms should have a cranial CT scan and lumbar puncture to rule out other causes of mental status changes, such as intracerebral bleeding or an infectious etiology.

HYPERTENSION AND HYPERLIPIDEMIA

Common sequelae of immunosuppression are the development of hypertension and hyperlipidemia in the posttransplantation period (Fernandez-Miranda et al, 1998). As patient survival improves, the consequences of these conditions have greater importance on long-term prognosis. Hypertension is observed in approximately 70% of liver transplant recipients at 1 year, and nearly 40% of patients develop sustained hypercholesterolemia and hypertriglyceridemia during the same time period. The pathophysiology of posttransplantation hyperlipidemia is complex. Rapamycin immunosuppression does not cause glucose intolerance, but it can lead to hyperlipidemia (Trotter, 2003). Omega-3 fatty acids found in fish oil can reduce hypertriglyceridemia significantly. In our experience, oral supplementation with over-the-counter fish oil capsules (4 to 6 g/day) has shown a dose-response reduction in serum triglycerides. Given the additional risk of development of coronary artery and peripheral vascular disease, aggressive therapy—with dietary changes, exercise, and medication—is indicated.

SUMMARY

Liver transplantation is a lifesaving treatment modality for patients with end-stage liver disease. The wide range of comorbidities that develop preoperatively contributes significantly to the development of postoperative complications. Aggressive use of immunosuppression is successful in preventing rejection in many cases, but therapy can be complicated by the development of life-threatening neoplasms. Recent trends favor significant reduction of immunosuppression over time and early withdrawal of steroids, once the mainstay of immunosupressive regimens. The reduction of immunosuppression in selected patients and early withdrawal of steroids have significantly reduced morbidity and life-threatening complications.

Positive outcomes after liver transplantation require a multidisciplinary team approach that comprises surgeons, transplant coordinators, hepatologists, and internists to maintain constant surveillance for the inevitable complications that arise. Early diagnosis with rapid treatment provides the best opportunity for disease-free survival.

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CHAPTER 101

Whole-organ pancreas and pancreatic islet transplantation

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OVERVIEW

Type 1 diabetes mellitus, formerly known as *juvenile diabetes,* is characterized by hyperglycemia as a result of the nearly complete destruction of the insulin-producing β-cells of the pancreatic islets of Langerhans. The loss of β-cells is the result of a T-cell–mediated autoimmune attack that typically occurs during childhood or early adolescence. Insulin replacement can lead to acceptable control of blood glucose levels; however, affected individuals are subject to the development of various secondary complications that include cardiac disease, stroke, retinopathy and blindness, nephropathy and renal failure, peripheral and autonomic neuropathy, and amputation (Atkinson & Eisenroth, 2001). Although tight glycemic control has been shown to decrease the number of diabetes-related secondary complications, it also has been shown to lead to an increased number of dangerous hypoglycemic episodes (Diabetes Control and Complications Trial [DCCT] Research Group, 1993).

Transplantation therapy for type 1 diabetes was developed as an alternative to insulin administration with the additional theoretic benefit of reducing or eliminating the development of secondary complications of the disease. Both whole-organ pancreas and isolated pancreatic islets are being transplanted into select individuals with type 1 diabetes. Whole-organ transplantation is already an established and widely available therapy, whereas clinical islet transplantation remains under investigation in diabetic individuals.

WHOLE-ORGAN PANCREAS TRANSPLANTATION

History and Early Results

On December 20, 1893, P. Watson Williams grafted three pieces of a sheep pancreas into the subcutaneous tissues of a diabetic child, who died 3 days later of unrelenting diabetic ketoacidosis (Williams, 1894). This first attempt to treat diabetes with transplantation, although unsuccessful, preceded decades of animal experimentation, in which investigators developed the methods necessary to perform a vascularized pancreas transplant; pancreas transplantation was subsequently used as a model to study diabetes and glucose homeostasis.

The first clinical vascularized pancreas transplantation was performed on December 17, 1966, by William Kelly and Richard Lillehei at the University of Minnesota. The patient had temporary insulin independence but eventually required graft removal and ultimately died of postoperative complications (Kelly et al, 1967). The subsequent early experience with pancreas transplantation at Minnesota and at a few other centers was characterized by some technical success, but no graft functioned beyond 1 year, and the enthusiasm for this procedure dwindled.

During 1975, only six pancreas transplantations were performed worldwide. However, the introduction of cyclosporine as an immunosuppressive medication and further technical refinements allowed for better outcomes following pancreas transplantation such that throughout the 1980s and early 1990s, the number of pancreas transplants performed increased dramatically: almost 1500 pancreas transplantations were performed in the United States during 2004. This number has declined slightly for the past several years, with fewer than 1200 pancreas transplantations performed in the United States during 2010.

Indications and Patient Selection

The majority of patients who undergo pancreatic transplantation have type 1 diabetes mellitus and renal failure. In these individuals, pancreas transplantation is performed with a simultaneous kidney transplantation (SPK; 72% of cases) or after a successful kidney transplantation (PAK; 20% of cases). The normal glucose control achieved by the pancreas transplant may protect the transplanted kidney from recurrent diabetic nephropathy and is beneficial from an overall quality of life perspective. In a small proportion of patients with diabetes that is very brittle and difficult to manage, but with preserved renal function, pancreas transplantation alone (PTA; 8% of cases) is performed. It should be noted that SPK and PAK recipients require immunosuppressive therapy to protect both the kidney and pancreas from rejection, whereas in the case of PTA recipients, the need for immunosuppression is solely for the pancreas itself. This difference becomes important when weighing the risk/benefit ratio for each type of recipient.

Potential pancreas recipients are carefully screened for contraindications to transplantation, such as an ongoing infectious process or malignancy. These candidates almost always have medical comorbidities as a result of secondary complications from diabetes; therefore a thorough assessment of a candidate's cardiovascular status is essential. Cardiac contraindications to pancreas transplantation include the presence of noncorrectable coronary artery disease, significantly decreased ejection fraction, or myocardial infarction within the preceding 6 months. Recipient age is also important, and in some programs, recipients older than 50 years are not considered candidates because of an increased risk of perioperative complications.

Donor Operation

Selection of an appropriate deceased pancreas donor includes standard donor selection criteria. In addition, a bias exists toward using organs from younger, leaner, and more hemodynamically stable deceased donors. Donors with hemodynamic instability or those that require high doses of vasopressors are considered higher risk. In addition, pancreata with significant steatosis are usually avoided, because they are associated with a greater likelihood of postoperative complications, such as pancreatitis, peripancreatic fat necrosis, and infection. Based on these selection criteria, which are relatively stringent compared with those applied to the liver or kidney, only a fraction of deceased donors are deemed suitable for whole-organ pancreas donation. In the United States, there were 8022 deceased donors during 2009. Of these, only 1233 pancreata were transplanted (15%), compared with 6101 livers (76%) and 10,442 kidneys.

The procurement of the pancreas must be performed in conjunction with the liver procurement, carefully delineating the blood supply to the liver to ensure that both organs can be removed and transplanted. In the vast majority of cases, blood supply should not preclude the transplantation of both organs. Initial dissection involves division of the gastrocolic ligament to expose the anterior surface of the pancreas. Visual inspection is considered to be an important element to the pancreas procurement process, because this is an opportunity to assess the organ for the presence of infiltrating fat or hematoma that might preclude transplantation. The portal triad is carefully dissected, with division of the common bile duct and the gastroduodenal artery. In addition, the common hepatic, left gastric, and splenic arteries are all dissected free of surrounding lymphatic tissues. Further dissection of the pancreas includes a Kocher maneuver, to mobilize the head, and division of the lienophrenic and lienocolic ligaments, to mobilize the body and tail. Of note, the spleen is left in continuity with the pancreas to serve as a handle to minimize manipulation of the gland itself. The duodenum is decontaminated by flushing povidone-iodine antifungal/antibiotic solution through a nasoduodenal tube.

After the patient has been systemically heparinized, the abdominal aorta is ligated at its bifurcation and is cannulated in a retrograde direction for perfusion. The liver team may also elect to place a cannula for portal perfusion through the inferior mesenteric vein. The supraceliac aorta is cross-clamped, the vena cava is vented, and the abdominal organs are flushed in situ with preservation solution, typically University of Wisconsin (UW) solution, at 4° C. In addition, topical cooling is also used.

Once the organs have been adequately flushed, the liver and pancreas are either separated in situ and removed individually from the donor, or both organs are removed en bloc and divided at the back bench. In the in situ separation situation, the liver is removed first by dividing the portal vein 1 cm cephalad to the superior margin of the pancreatic head, approximately the level of the coronary vein, and dividing the splenic artery about 3 mm beyond its origin, thus preserving the entire celiac axis with the liver.

Next, removal of the pancreas proceeds. The proximal duodenum just beyond the pylorus and the distal duodenum are divided with gastrointestinal anastomosis stapler. The small bowel mesentery that lies inferior to the pancreas is divided, and the superior mesenteric artery is divided at its origin from the aorta. Long segments of donor iliac vessels are removed to use for vascular reconstruction during back-bench preparation of the pancreas.

Back-Table Preparation of the Pancreas

Relative to other solid organs, the pancreas requires extensive preparation prior to implantation into the recipient. This back-bench preparation is performed in ice-cold preservation solution to minimize any further ischemic injury to the organ. The duodenum is often shortened with a gastrointestinal anastomosis stapler, being careful to exclude any gastric tissue and also being careful not to compromise the opening of the ampulla of Vater. The division of the small bowel mesentery in the donor is shortened by firing a stapler across this mesentery and then reinforcing the staple line with a running vascular suture. The spleen is removed by dividing the vessels in the splenic hilum, being careful not to injure the tail of the gland. Finally, the arterial inflow to the graft must be reconstructed, because the organ has two major sources of blood supply that are not in continuity: the splenic artery supplies the body and tail, and branches of the superior mesenteric artery supply the head.

In most instances, arterial reconstruction can be performed using the donor iliac artery as a bifurcated Y graft. The internal iliac artery is joined to the splenic artery, and the external iliac artery is joined to the superior mesenteric artery. The common iliac artery of the donor Y graft can then be anastomosed to the recipient iliac artery, serving as the arterial inflow to the pancreas. In some instances, it is necessary to create a portal vein extension graft on the back bench using donor iliac vein; however, this technique is avoided if possible, because it may increase the risk of venous thrombosis of the graft.

Recipient Operation

The techniques used for transplanting the pancreas have changed dramatically over the past few decades. Partial segmental grafts that contained only the body and tail were once common; however, this technique is rarely used today. Exocrine secretions were previously managed by pancreatic duct ligation or by injection of a polymer that would cause duct obliteration, however, now exocrine secretions are handled by internal drainage.

In two areas of pancreas transplantation, current-day techniques differ: in the drainage of exocrine secretions and the venous drainage of the graft. Exocrine drainage is performed either via the intestinal tract or via the urinary tract. Throughout most of the 1980s and 1990s, drainage of the pancreatic secretions into the recipient bladder was the most common form of exocrine drainage. This technique is convenient for monitoring organ function by measurement of amylase levels in the urine; however, problems with hematuria, cystitis, bicarbonate loss, and dehydration are all associated with bladder drainage. These complications necessitate surgical revision to enteric drainage in up to 20% of bladder-drained pancreas recipients (Stratta, 2005). Based on these issues, and on the lower rejection rates observed with newer immunosuppressive medications, the majority of transplant centers now perform enteric drainage of the exocrine secretions. This enteric drainage is either directly into a loop of jejunum in a side-to-side fashion or into a Roux-en-Y limb of jejunum.

The venous drainage of the graft is either to the systemic circulation, via an iliac vein or the inferior vena cava, or to the

portal circulation. Portal venous drainage has the theoretic advantage of delivering insulin in a more physiologic manner, because insulin undergoes a "first pass" through the liver, and the hyperinsulinemia that results from systemic drainage is avoided (Gaber et al, 1995). There is also an immunologic advantage of portal drainage that has been observed in several experimental studies, in which the delivery of foreign antigen via the portal system results in diminished immune responses. Despite these potential advantages, no demonstrable difference has been found in outcomes between human transplants drained by the portal vein and those drained by the systemic vein, and systemic venous drainage is how the majority of pancreas transplantations are performed.

There are two common locations in the abdomen where the transplant is placed based on the type of venous drainage planned: either in the pelvis, most commonly the right side, for systemic venous drainage or in the midabdomen for portal venous drainage. When the graft is placed in the pelvis, the donor portal vein is anastomosed to the external iliac vein, the common iliac vein, or the inferior vena cava. In this pelvic position, the graft is oriented with the duodenum in an inferior position, if bladder drainage is planned (Fig. 101.1A), or with the duodenum in either the superior (Fig. 101.1B) or inferior position if enteric drainage is planned. Alternatively, for portal venous drainage, the pancreas is placed in the mid-abdomen below the transverse colon with the duodenum oriented superiorly. The portal vein of the pancreas is anastomosed to a major branch of the superior mesenteric vein, found in the small intestine mesentery, in an end-to-side fashion (Fig. 101.2). Enteric drainage for exocrine secretions must be used with the portal venous drainage technique. With either venous drainage technique, the donor arterial conduit to the pancreas graft is anastomosed in an end-to-side manner to the recipient common or external iliac artery.

Complications

The major complications following pancreas transplantation are often technical in nature. Pancreas graft thrombosis, arterial or venous, is more frequent after pancreas transplantation than after other solid-organ transplants, and the reported incidence is approximately 10%. Thrombosis usually occurs within the first week following transplantation and likely reflects the relatively low blood flow through the organ. In most instances of thrombosis, graft removal is necessary (Humar et al, 2000). Early pancreatitis occurs in 10% to 20% of cases and is largely a reflection of ischemic damage to the gland during preservation and reperfusion injury. Hyperamylasemia and graft edema are characteristic, and graft pancreatitis is usually treated nonsurgically with octreotide. Leakage at the site of pancreatic exocrine drainage is another early complication, with management often dictated by the method of drainage. Bladder-drained transplants with a small leak at the duodenocystostomy can often be managed by Foley catheter drainage of the bladder, allowing the site of leakage to heal over time. Enteric-drained transplants with a leak at the duodenojejunostomy will often result in peritonitis and usually require operative intervention to control the leak.

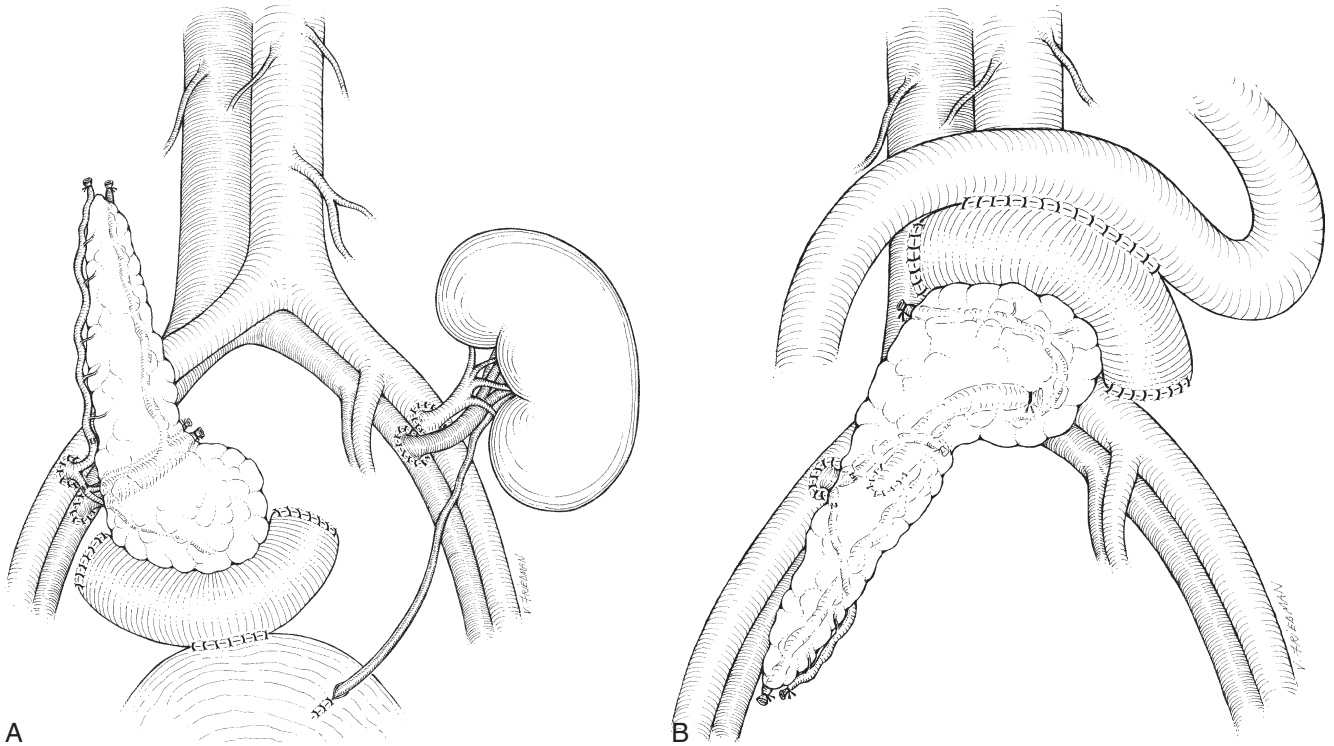


FIGURE 101.1. Whole-organ pancreas transplantation with systemic venous drainage. The pancreas is placed in the right pelvis with anastomosis of the donor iliac artery Y graft to the recipient iliac artery to provide arterial inflow to the graft and anastomosis of the donor portal vein to the recipient iliac vein for venous drainage. Simultaneous kidney transplantation can be performed using the left-sided iliac vessels. **A,** The duodenum is oriented in the inferior direction to allow anastomosis to the bladder (shown) or to the small intestine (not shown). **B,** Alternatively, the duodenum is oriented superiorly for anastomosis to the intestine.

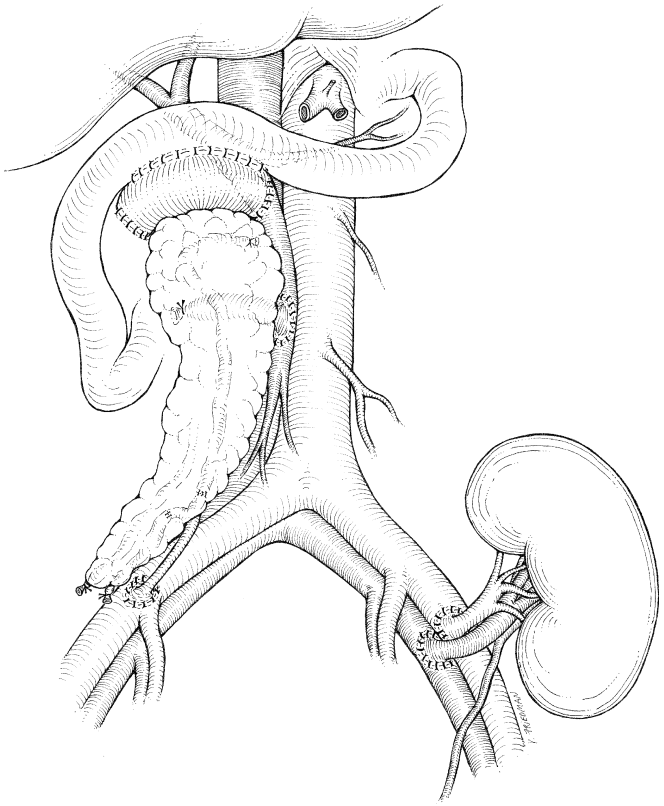
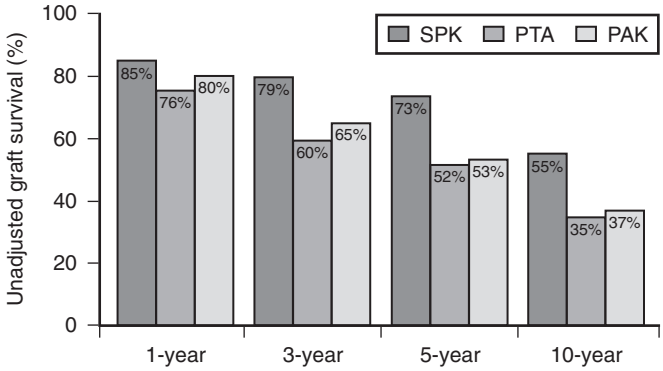


FIGURE 101.2. Whole-organ pancreas transplantation with portal venous drainage. The pancreas is placed in the mid-abdomen with anastomosis of the donor portal vein to a major branch of the superior mesenteric vein and anastomosis of the donor iliac artery Y graft to the recipient iliac artery. The duodenum is oriented in the superior direction for anastomosis to the intestine. A simultaneous kidney transplant can be performed using either the left (shown) or right iliac vessels.

Rejection following pancreas transplantation was once a very common occurrence. Pancreas rejection is often difficult to diagnose, and a variety of indicators are used to help make the diagnosis. These include tenderness over the area of the pancreas allograft, increased serum amylase and lipase, decreased urinary amylase excretion (if bladder drainage is used), biopsy of the pancreas, and hyperglycemia. It is noteworthy that hyperglycemia is a late indicator of rejection, and the pancreas is often difficult to salvage once hyperglycemia has occurred. If SPK transplantation is performed, renal allograft dysfunction can often assist with the diagnosis of pancreatic rejection, because the rejection process is often occurring in both organs. As a result of the high incidence of rejection and the difficulty in making the diagnosis, pancreas transplant recipients usually receive potent induction immunosuppression with a T–cell depleting agent and maintenance therapy with tacrolimus, mycophenolate mofetil, and corticosteroids.

The total amount of immunosuppression pancreas recipients receive is among the highest of any solid-organ transplantation. As a result, they are more susceptible to the complications of immunosuppressive therapy. These complications include infection with opportunistic bacteria, viruses, and fungi; malignancy; gastrointestinal complications; and others. The high incidence of these complications makes effective prophylaxis strategies important.



Death is included as an event.

FIGURE 101.3. Pancreas graft survival rates (unadjusted) at 1 year, 3 years, 5 years, and 10 years following whole-organ transplantation by transplant category. *(Modified from Axelrod DA, et al, 2010: Kidney and pancreas transplantation in the United States, 1999-2008: the changing face of living donation. Am J Transplant 10:987-1002, Copyright 2010 Blackwell Publishing, with permission.)*

Results

Patient and graft survival following pancreas transplantation have improved significantly in recent years. Depending upon the type of transplantation—SPK, PAK, or PTA—patient survival is approximately 96% to 98% at 1 year and 85% to 89% at 5 years after transplantation. Graft survival varies according to the type of transplantation performed (Fig. 101.3). For SPK recipients, 1-, 5-, and 10-year pancreas graft survival rates are 85%, 73%, and 55%, respectively. For PAK recipients, the respective rates are 80%, 53%, and 37%. Finally, for PTA recipients, rates of pancreas graft survival are 76%, 52%, and 35%, respectively (Axelrod et al, 2010).

The impact of a successful pancreas transplantation on the complications associated with diabetes mellitus is debated. Because the successful transplantation restores euglycemia and normal hemoglobin A1c levels, most proponents argue that diabetic complications should cease and perhaps reverse. Neuropathy appears to stabilize and even slowly improve following pancreas transplantation, whereas retinopathy progression is slowed after several years of graft function. The development of diabetic nephropathy in the transplanted kidney of SPK and early PAK recipients appears to be prevented by successful pancreas transplantation. In PTA recipients, diabetic nephropathy appears to stabilize following transplantation (Fioretto et al, 1998); however, the renal benefit is likely outweighed by the detriment to renal function caused by the immunosuppressive agents, specifically tacrolimus and cyclosporine.

Risk/Benefit Considerations

As outlined above, considerable evidence suggests that successful pancreas transplantation can retard, and in some cases reverse, the secondary complications of diabetes. Despite this evidence, the procedure is considered appropriate for only a subset of patients with type 1 diabetes because of its highly invasive nature, compared with insulin therapy, and the potential for significant surgical complications; thus considerations of risk to benefit are of utmost importance in pancreas transplantation and play an essential role in both the donor and recipient selection processes.

One analysis evaluated the survival benefit of pancreas transplantation by examining a large transplant database to compare the survival of pancreas recipients versus those patients listed for transplantation but who did not receive a transplant. Using this study design, the two patient groups were ensured to be as similar as possible. Because the indications, risks, and benefits differ, depending on whether the patient had underlying renal failure, the analysis was stratified based on whether the patient was listed for or transplanted with an SPK, PAK, or PTA (Venstrom et al, 2003). This analysis revealed a marked survival benefit for those patients who received a combined pancreas and kidney transplant; a 57% *reduction* in mortality rate was observed over 4 years compared with similar patients who remained on the waiting list.

In contrast to the clear survival benefit of SPK transplantation, the PAK and PTA recipients experienced an increased mortality following transplantation. During the 4-year follow-up period, PAK recipients experienced a 42% *increase* in mortality rate, and PTA recipients experienced a 57% *increase* in mortality rate compared with the comparable group of patients who remained on the waiting list. A similar analysis was reported that challenged the survival disadvantage of PAK and PTA (Gruessner et al, 2004a). Their analysis found again, as expected, that the SPK procedure conferred a marked survival advantage; however, unlike the Venstrom study, no survival disadvantage was evident in PAK or PTA transplant recipients.

There are two important caveats to these risk/benefit studies by Venstrom and Gruessner: The first is that the impact of pancreas transplantation on quality of life was not evaluated in these nonrandomized retrospective analyses and would likely heavily favor the group with successful PAK and PTA recipients, but whether this factor would outweigh any survival disadvantage in the short-term, and the significant cost of these complex procedures, has not been evaluated. A second critical outcome measure that is lacking from these studies is the long-term impact of successful pancreas transplantation on the secondary complications of diabetes. As noted above, evidence suggests that diabetic nephropathy, neuropathy, and retinopathy may be positively impacted by the long-term restoration of normoglycemia conferred by transplantation; however, these studies have not included well-controlled trials with large numbers of patients.

These results substantiate the marked clinical benefit observed when caring for patients who undergo the SPK procedure (Rayhill et al, 2000). Importantly, the relative contribution of the transplanted kidney versus the transplanted pancreas to overall patient survival has not been differentiated in a controlled study. This issue is significant given the marked patient survival benefit that has been attributed to kidney transplantation (Wolfe et al, 1999).

A recent retrospective database analysis lends important insight into the role that pancreas graft function contributes towards overall patient survival (Weiss et al, 2009). This analysis examined outcomes in individuals on the SPK waiting list who underwent either an SPK or transplantation of the kidney alone. Recipients of an SPK transplant who had pancreas allograft function 1 year after transplantation had significantly greater patient survival at 7 years (89%) compared with SPK recipients who lost their pancreas transplant within the first year after transplantation (74%) or to those recipients that underwent a kidney transplant alone from either a living donor (80%) or a deceased donor (65%).

Although the survival benefit for SPK recipients is clear, the survival benefit for PAK and PTA recipients has not been conclusively demonstrated (Sutherland et al, 2009). The same analysis by Weiss demonstrates improved patient survival at 5 years for diabetic recipients who underwent a PAK compared with kidney transplantation alone, although this did not reach statistical significance and was subject to selection bias. A recent single-center report demonstrates excellent outcomes 3 years after PAK, in which both patient and graft survival are similar to SPK recipients at that center (Fridell et al, 2009). In this report, PAK recipients had a 90% pancreas allograft, 92% kidney allograft, and a 92% patient survival 3 years after PAK transplantation, compared with 83% pancreas allograft, 86% kidney allograft, and 88% patient survival in SPK recipients. If these excellent PAK outcomes persist with further follow-up and can be replicated at other centers, it is reasonable to assume that a survival benefit to PAK could be demonstrated in future data analyses.

Currently, the most meaningful conclusion that can be drawn is that PAK transplantations should be performed in carefully selected recipients with well-preserved kidney allograft function, and these procedures should be performed at transplant centers with excellent outcomes. The field remains dynamic due to improvements in surgical technique and perioperative care and the frequent introduction of new immunosuppressive agents with more favorable safety profiles; however, improving outcomes with pancreatic islet transplantation may ultimately challenge the need to perform whole-organ pancreas transplantation for the treatment of type 1 diabetes.

PANCREATIC ISLET TRANSPLANTATION

History and Early Results

The original descriptions in rodents of successful islet isolation (Lacy & Kostianovsky, 1967) and subsequent transplantation (Ballinger & Lacy, 1972) caused great excitement in the medical community, in the hope that this type of therapy might be applied to patients with type 1 diabetes. Although the ability to obtain normal glucose control in diabetic rodents with an islet transplant was described decades ago (Reckard et al, 1973), translating this success to humans has been more difficult. Various centers worldwide have attempted human islet transplantation, starting in 1974, with 445 recipients receiving islets between 1974 and 2000. The vast majority of these recipients also received a kidney transplant, either prior to or at the same time as the islet transplant. Analysis of the reported cases between 1990 and 2000 demonstrated that only 19% of patients were off insulin for more than 1 week, and at 1-year follow-up, only 11% of recipients were insulin independent (Brendel et al, 2001).

These discouraging results were attributed to a number of factors, including the possibility that recurrent autoimmunity was causing progressive islet damage following transplantation, because the diabetes in these recipients was the autoimmune form. Support for this hypothesis came from a series of patients at the University of Pittsburgh who underwent upper abdominal exenteration, including total pancreatectomy, followed by liver and islet allotransplantation. In this group of 11 patients, who did not have autoimmune diabetes, 6 (55%) exhibited sustained insulin independence, a success rate far greater than what had been achieved in type 1 diabetic recipients (Carroll et al, 1995).

Islet Autotransplantation

Autotransplantation of pancreatic islets was developed for patients with chronic pancreatitis, in whom total pancreatectomy once provided the best option for treatment. Surgically induced diabetes is frequently brittle, characterized by an absence of both insulin and counterregulatory hormones, with a high rate of long-term morbidity. Treatment involves processing of the surgically removed pancreas in the islet isolation laboratory, followed by infusion of either purified islets or crude pancreatic digest into the liver via the portal vein.

Although the overall experience is limited, the success rate in recipients of autotransplantation has been far greater than in those who received allogeneic islets for the treatment of type 1 diabetes. The largest reported series is from the University of Minnesota, where between the years 1977 and 2007, 173 patients with chronic pancreatitis underwent total, near total (95%), or completion pancreatectomy with islet autotransplantation (Sutherland et al, 2008). These investigators achieved a 65% rate of graft function and a 32% rate of insulin independence, rates of success that correlate closely with the average yield of islets from the removed pancreatic tissue following digestion and processing. This group previously reported higher rates of successful islet autotransplantation in patients who had no prior surgery, or only a prior Whipple procedure, whereas those that had a prior Puestow procedure or distal pancreatectomy had lower chances of success (Gruessner et al, 2004b). Similar results have been reported by another group in a series of 22 patients, where 68% of patients showed acceptable graft function, and 41% were insulin independent (Rodriguez Rilo et al, 2003). Interestingly, both of these groups infused unpurified pancreatic digests, where the islets had not undergone the additional purification step performed during deceased-donor pancreas processing for allotransplantation.

The Edmonton Protocol and Beyond

Interest in islet transplantation was piqued by the Edmonton investigators reporting that, for the first time, diabetes in patients could be consistently reversed by transplantation of isolated pancreatic islets (Shapiro et al, 2000). The Edmonton approach relied on a novel immunosuppression regimen that completely avoided steroids and that utilized a unique combination of induction therapy with an anti–interleukin (IL)-2 receptor antibody and maintenance therapy with sirolimus and tacrolimus. The rationale for this combination was based on the desire to avoid agents with known β-cell toxicity. Although this particular drug combination was likely an important factor in the trial's success, perhaps of even greater impact was the large number of islets that patients received; these investigators infused a larger number of islets than were administered in prior islet transplantation trials, using two or three infusions per patient, acquired from multiple deceased donors.

Whereas previous trials in the late 1990s had often achieved partial success with single infusions of islets, as evidenced by a reduced insulin requirement and increased C-peptide levels, in no trial had the further step been taken to retransplant such patients to increase the net islet mass (Hering & Ricordi, 1999). In the Edmonton series, patients who showed evidence of partial success from the first infusion received an additional infusion, sometimes two, until they had accumulated a sufficient islet mass to gain insulin independence; in general, this occurred when a threshold of 8000 to 10,000 islets per kilogram of recipient body weight had been infused.

After the landmark report by the Edmonton investigators, almost 500 recipients received islet transplants at one of approximately 40 centers worldwide (Harlan et al, 2009). In the first concerted effort to replicate the provocative results of the Edmonton Protocol, a multicenter trial sponsored by the Immune Tolerance Network enlisted 10 centers in North America and Europe to each perform four islet transplants using the Edmonton regimen (Shapiro et al, 2006). Despite a diligent attempt to ensure uniformity in technique between centers, the rate of success varied dramatically, depending on the extent of experience at the transplanting site: at the three most experienced centers, reversal of hyperglycemia was routinely achieved; however, less experienced teams gained insulin independence in only a fraction of cases (approximately 20%). Thus, although these results confirmed the efficacy of Edmonton's approach, they also revealed the exacting nature of the technique and demonstrated the inherent difficulty in replicating an identical protocol at all centers.

A number of single-center reports have now validated the Edmonton Protocol (Goss et al, 2002; Markmann et al, 2003), and although this protocol represents a tremendous leap forward for the field, the Edmonton results also delineate the major problem that remains: the need for islets procured from multiple deceased donors to gain insulin independence in a single recipient. This requirement markedly increases costs and represents a distinct disadvantage when compared with whole-organ transplantation; however, it should be remembered that, thus far, the pancreata utilized for isolated islet transplantation have only been organs that were unsuitable for whole-organ transplantation. It seems reasonable to assume that these organs are inferior to those used in whole-organ transplantation, and that improved results may be achieved if islet transplantation candidates had access to the best organs.

The need for such a large number of islets to achieve insulin independence in clinical transplantation was unexpected in light of the finding that as little as 10% of the total islet mass can maintain normoglycemia following partial pancreatectomy. Because the total islet mass in normal individuals is estimated at 1 to 2 million, it would follow that transplanting only 200,000 islets should regain normoglycemia in the majority of diabetic recipients; instead, accumulating evidence from the islet transplant studies by Edmonton and others suggest that for an average individual, 600 to 700,000 islets are required. The nearly two-thirds loss of potency after transplantation has not been fully explained in patients, but experimental data from small animal studies indicates that the majority of transplanted islets fail to engraft (Davalli et al, 1995). Understanding and overcoming the loss of islet mass during the engraftment phase has been an important focus of recent islet transplantation clinical trials.

Some centers have reported improved success at gaining insulin independence with islets from a single donor by refining the Edmonton approach (Hering et al, 2004, 2005; Markmann et al, 2003). The most successful reports are from the University of Minnesota, where investigators have used potent induction immunosuppression and high-quality islets. In their first study, four of six consecutive patients were rendered insulin independent with single-donor islet infusions using induction therapy with the anti-CD3 monoclonal antibody hOKT3γ1 (alanine-alanine) (Hering et al, 2004). This was combined with

the selection of relatively larger donors and somewhat smaller recipients with low daily insulin requirements, thus maximizing the islet mass delivered per recipient body weight.

An even more impressive result was reported by the same group using polyclonal antithymocyte globulin (Thymoglobulin) for induction therapy; in a series of 10 consecutive patients treated with Thymoglobulin induction therapy, 9 were rendered insulin independent with a single infusion of islets (Hering et al, 2005). The 1 patient who did not become insulin independent still had a marked reduction in daily insulin requirement. Collectively, these studies suggest that insulin independence can be achieved consistently with single-donor islet infusions under the correct circumstances. Overcoming the single-donor hurdle will help in the establishment of isolated islet transplantation as a more widely applicable therapy for patients with type 1 diabetes.

A second, more daunting obstacle is the realization that the durability of function after islet transplantation is less than whole-organ pancreas grafts. Whereas it is clear that very experienced islet centers can gain insulin independence in most islet recipients, and that short-term (1-year) insulin-free survival may be close to that seen with whole-organ transplants, the intermediate (2- to 4-year) insulin-free survival is less encouraging. In a report by Edmonton investigators, with follow-up on patients in their ongoing series transplants of islets alone (Ryan et al, 2005), fewer than 25% of patients remained free from exogenous insulin administration at 3 years (Fig. 101.4B). Although a somewhat disappointing result, more encouraging was the observation that more than 85% of these patients had evidence of some islet graft function by C-peptide measurement (Fig. 101.4A). Similar findings of declining islet function over time have been reported by the multicenter Collaborative Islet Transplant Registry: of the recipients who achieved insulin independence, approximately 50% were back on insulin 2 years later (Alejandro et al, 2008).

Despite the eventual need for most recipients to resume doses of insulin, the partial graft function that persists is relevant, because many patients who were transplanted with the indication of hypoglycemia unawareness remain cured of this devastating complication. It is also evident that a partially functioning graft can significantly improve glycemic control as measured by serial hemoglobin A1c determinations. A small group of islet recipients who have resumed insulin therapy have been given supplemental islet infusions several years after the initial islet transplant and have regained durable insulin independence in most cases (Koh et al, 2010).

The mechanisms responsible for the gradual loss of islet function remain unclear. One hypothesis is that inadequate control of the deleterious alloimmune and autoimmune responses compromise islet function over time. The absence of a reliable measure of an antiislet immune reaction and the difficulty in obtaining biopsy tissue for pathologic diagnosis contribute to the complexity in clarifying this issue. One study reported durable insulin independence (>3 years) in islet recipients when more potent induction immunosuppression was used, compared with what was used in the Edmonton Protocol (Bellin et al, 2008). An alternative explanation is that the currently used immunosuppressive agents are toxic to the islets over time. This explanation may fit better with the pace of graft dysfunction and the fact that graft function often stabilizes without antirejection therapy. In addition, studies have documented very high immunosuppressive drug levels in the portal circulation, an expected consequence of the drugs being administered orally (Desai et al, 2003). The role of immune responses

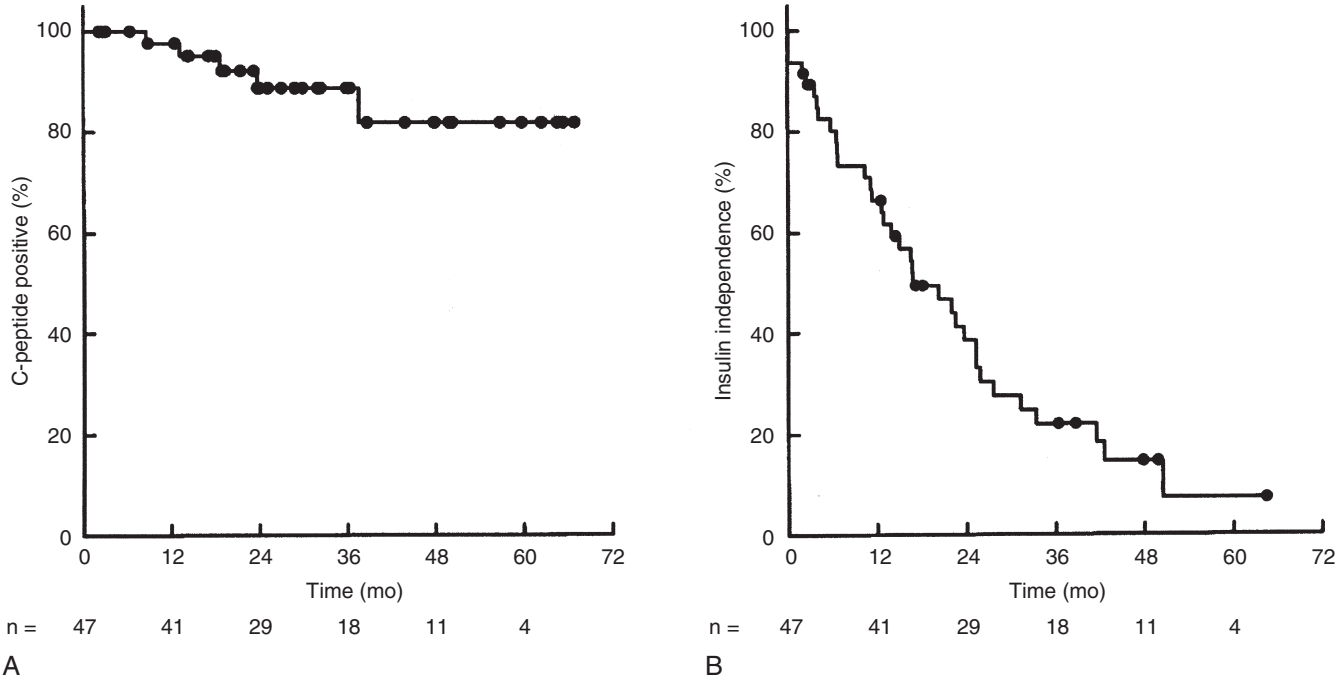


FIGURE 101.4. Islet graft survival rates following isolated islet transplantation at the University of Alberta, Edmonton (Ryan et al, 2005). **A,** Survival analysis for islet function as documented by C-peptide secretion over time, demonstrating 85% graft survival at 3 years. **B,** Survival analysis for insulin independence over time, demonstrating that fewer than 25% of patients are free from exogenous insulin therapy at 3 years. *(From Ryan EA, et al, 2005: Five-year follow-up after clinical islet transplantation. Diabetes 54:2060-2069. Copyright 2005 American Diabetes Association.)*

and medication toxicity to the loss of islet graft function should be clarified by the application of newer immunosuppressive agents in the next generation of islet transplantation studies.

Complications and Risk/Benefit Considerations

The demonstration that the procedure is relatively safe for the recipient has been important in the early trials of isolated islet transplantation. The most feared potential complications include bleeding and portal vein thrombosis. The Edmonton experience in 65 patients demonstrates that bleeding occurred in more than 20% of recipients, most of whom required either transfusion or surgical intervention. Main portal vein thrombosis, the most potentially troublesome complication of portal islet infusion, has fortunately been rare (<1%); however, in the Edmonton experience, 7% of recipients had evidence of segmental portal vein thrombus that resolved without sequelae (Ryan et al, 2005).

The risk of bleeding and thrombosis may be related in part to the technique used to perform the infusion. The procedure can be performed by an interventional radiologist, gaining access to the portal vein via a percutaneously placed transhepatic catheter and releasing the islets into the portal system (Froud et al, 2004). Alternatively, the procedure can be performed via a small laparotomy to gain access to a small mesenteric vein, through which a catheter can be advanced into the main portal vein for islet infusion (Gaber et al, 2004). The small vein is then ligated, eliminating the potential for hemorrhage. Thus the operative approach allows anticoagulation to be administered without the risk of bleeding from a puncture site in the hepatic parenchyma, although it usually requires a general anesthetic.

The relative safety advantage of islet transplantation over whole-organ pancreas transplantation was clearly evident in a comparison of the two approaches (Frank et al, 2004). In this study, major complications that included bleeding that required transfusion and reoperation were more common in the whole-organ group, although a number of minor complications were frequent in the islet transplant group. Some of these minor complications included immunosuppression-related toxicity (mouth ulcerations, edema), periportal hepatic steatosis, and mild liver function test abnormalities. A comparison of the major advantages and disadvantages of whole-organ pancreas and isolated islet transplantation can be seen in Table 101.1.

Islet transplantation also incurs the risk of infusion-related infection. This complication is minimized by screening potential donors for infection, administration of prophylactic antibiotics to the recipient, and by assessment of the islet preparation for bacterial contamination by microscopic examination and endotoxin testing. As with all forms of transplantation, the need for chronic immunosuppression carries with it a risk of opportunistic infection and a small but discernible risk for the development of malignancy, especially lymphoma and skin cancer. Similarly, exposure of the recipient to allogeneic tissue may induce an immune response in the recipient and generate cytotoxic antibodies against the HLA antigens of the donor. This exposure may be especially detrimental in islet recipients who receive transplants from multiple donors, thereby broadening their antigenic exposure. The presence of anti-HLA antibodies could hamper future attempts at islet transplantation or transplantation of lifesaving organs such as the kidney.

Table 101.1

Comparison of Whole Pancreas and Islet Transplantation

	Whole Pancreas Transplantation	Islet Transplantation
Indication	Diabetic patients with renal failure (92% of cases)	Diabetic patients with hypoglycemic unawareness
Availability	Widely available	Research protocols only
Procedure	Major abdominal operation under general anesthesia	Percutaneous or "mini-lap" approach
Metabolic control	Normal	Good on a diabetic diet
Longevity of transplant	79% function at 3 years (SPK)	85% function at 3 years but <25% insulin free
Effect on secondary complications of diabetes	Stabilization and improvement	Unknown

SPK, simultaneous pancreas and kidney transplantation

One of the most common and concerning potential complications of islet transplantation using the Edmonton protocol is calcineurin inhibitor–associated nephrotoxicity. Chronic renal failure in the setting of nonrenal solid-organ transplantation is well described, with an approximate 20% incidence at 10 years (Ojo et al, 2003). Similar results in islet transplant recipients would represent a particularly morbid complication given the well-established detrimental survival impact of renal failure in the diabetic population (Allen & Walker, 2003). A recent report of renal function in islet transplant recipients indicates that renal function remained stable in an appropriately selected and managed cohort of patients despite their being placed on potentially nephrotoxic immunosuppressive medications (Leitao et al, 2009). This study demonstrates that renal function can be adequately preserved in islet recipients under the correct circumstances.

Because of the side effects of chronic immunosuppression, the benefit of isolated islet transplantation, like that of isolated pancreas transplantation, may be for only select individuals. For this reason, most islet trials to date have enrolled type 1 diabetic participants with the most labile and dangerous form of the disease, specifically, diabetics attended by frequent episodes of hypoglycemia unawareness; patients are thought to be at greatest risk of severe morbidity or death from these events. Islet transplantation, even if only partially successful, has been universally found to be highly effective in reducing the frequency of these hypoglycemic episodes (Alejandro et al, 2008).

An alternative strategy has been to select recipients who are already on immunosuppressive therapy to support another organ transplant, such as a kidney (Kaufman et al, 2002). In this situation, the additional risk to the recipient relates mainly to the islet infusion procedure itself, which should be quite safe. In this setting, recipients usually lack severe hypoglycemia unawareness, although glucose control is usually suboptimal, it can be expected to improve following islet transplantation. An additional major concern in patients receiving an islet after kidney (IAK) transplantation is the function of the lifesaving renal allograft that is already in place. The experience to date suggests that IAK transplantation can be performed without

jeopardizing the kidney graft. An important study in this area, although not conducted in a randomized manner, found evidence that IAK transplantation is not only safe, but it likely has a beneficial impact on renal allograft function (Fiorina et al, 2003). They studied 36 IAK recipients and stratified them based on the success of the islet transplant at 1 year, defined by continued C-peptide production. There were 24 successful cases and 12 unsuccessful cases; the successful IAK recipients demonstrated superior renal graft survival up to 7 years after islet transplantation, and the unsuccessful islet recipients developed increased microalbuminuria over time, likely reflecting diabetic damage in the transplanted kidney.

In addition, successful IAK recipients had improved cardiovascular function in terms of ejection fraction and degree of diastolic dysfunction when compared with kidney-only recipients (Fiorina et al, 2005). Finally, an improvement in patient survival was noted in successful IAK recipients compared with recipients with failed IAK transplantation and with diabetic recipients who had undergone kidney transplantation alone. A major caveat to these findings is that they are derived from a small number of IAK patients, therefore they must be substantiated in larger cohorts. In addition, these results are not based on recipients randomized to either treatment arm, thus any benefit in secondary complications attributable to IAK transplantation is subject to selection bias and requires further investigation in properly controlled studies.

Future Directions in Islet Transplantation

There are many areas of active investigation in clinical and experimental islet transplantation, including an important set of collaborative studies being supported by the National Institutes of Health. These trials have the opportunity to secure a place for islet transplantation as a standard therapeutic modality. For isolated islet transplantation to gain equal footing with or to surpass whole-organ pancreas transplantation as the preferred therapy for patients with diabetes, a number of conditions will need to be met. First, improvements must occur so that reversal of diabetes is readily accomplished with the islets from a single donor in the majority of cases. This will require not only advances in isolation techniques that allow greater recovery of healthy islet tissue, it will also require a greater understanding of the events early after transplantation that are responsible for engraftment of only a fraction of the delivered islet mass (Harlan et al, 2009). Second, clarification is needed of the immunologic and physiologic mechanisms that contribute to islet dysfunction over time that lead to the need for reinstitution of low doses of exogenous insulin in a majority of islet transplant subjects.

Finally, should the hurdles mentioned above be overcome, the reliance on deceased donors as the sole source of islets will be insufficient to treat the large number of patients with type 1 diabetes who could benefit from islet transplantation. Living donors are one alternate source of islet tissue as shown in a report of living donor islet transplantation from Japan (Matsumoto et al, 2005); however, the potential for donor morbidity makes this approach highly controversial, until the long-term durability and efficacy of islet transplantation has been firmly established. Ultimately, derivation of β-cells from xenogeneic or stem cell sources promises to provide a limitless supply of transplantable β-cells. The ongoing trials of islet transplantation will provide a critical foundation for these future therapies by defining the optimal site for implantation, the best means to monitor survival, and the most conducive immunosuppression that avoids autoimmune and alloimmune damage without pharmacologic β-cell toxicity.

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CHAPTER 102

Injuries to the liver and biliary tract

William P. Schecter and Asher Hirshberg

OVERVIEW

The surgeon attempting to control torrential bleeding from a high-grade liver injury faces a formidable challenge. The source of bleeding is often difficult to control, and there is only a narrow window of opportunity to save the patient's life prior to the onset of hypothermia, acidosis, and coagulopathy—the markers of an irreversible physiologic insult. Furthermore, the bloodless and meticulous resection techniques of elective hepatobiliary surgery do not apply in this dramatic race against time in a hostile physiologic environment. It is therefore not surprising that the management of major liver injuries has always been one of the most demanding aspects of trauma surgery.

The evolution of the management of liver injury over the past century reflects the rapid progression of trauma surgery as a surgical discipline. The initial therapeutic nihilism evolved as pioneers of a new era attempted formal major hepatic resections, and these were advocated and applauded. Disappointing results with this aggressive approach and better understanding of the injured patient's physiology led to a paradigm shift toward damage control that has dominated modern trauma surgery since the early 1990s. At the same time, better understanding of the natural history of liver injuries in hemodynamically stable patients has led to increased nonoperative management utilizing an array of modern imaging and minimally invasive technologies.

This chapter presents the current approach to hepatobiliary injuries from the perspective of the trauma surgeon, describing the approach to the three major clinical patterns of liver trauma and emphasizing the importance of tailoring the approach to the patient's specific anatomic and physiologic circumstances. Finally, the principles and techniques of operative management for hepatobiliary trauma are reviewed, emphasizing the fundamental differences between emergency and elective hepatobiliary operations.

EVOLUTION OF THE APPROACH TO HEPATIC TRAUMA

More than a century ago, Pringle (1908) described hepatic vascular inflow occlusion in a trauma patient by manual compression of the hepatoduodenal ligament, a maneuver that bears his name. Although less often appreciated, Pringle also described exsanguinating hemorrhage from the liver following hematoma decompression during laparotomy and discussed the use of packing to control bleeding from the liver. Packing is therefore not a new concept. Between the turn of the twentieth century and World War II, surgeons packed deep liver lacerations and sometimes added sutures over the pack to achieve tamponade (Schroeder, 1906).

As techniques for selective hemostasis of liver injuries evolved during World War II and later in Vietnam, packing acquired a bad reputation and was abandoned in favor of alternatives such as deep liver sutures and hepatic artery ligation (Aaron et al, 1975; Lewis et al, 1974; Mays, 1967). The report of anatomic right hepatectomy by Lortat-Jacob and Robert in 1952 and the subsequent dissemination of the technical aspects of the operation (Quattlebaum & Quattlebaum, 1959) was rapidly followed by enthusiastic reports of the successful application of these formal resection techniques to trauma (Ackroyd et al, 1969; McClelland et al, 1964).

In the late 1970s, packing reemerged as a valid hemostatic technique for major liver injuries. In 1976, Lucas reported 3 patients in a series of 637 who survived packing (Lucas & Ledgerwood, 1976), and 3 years later, Calne reported 4 additional patients transferred to their hospital with liver packs in place (Calne et al, 1979). These and other reports (Malhotra et al, 2000) coincided with a growing realization among surgeons that major formal hepatic resection in critically injured patients is ill advised, because the combination of severe trauma and extensive surgery often leads to an irreversible physiologic insult and death (Fang et al, 2000).

The reintroduction of packing in the 1990s was the harbinger of a major paradigm shift in trauma surgery, from long and complex definitive procedures to a staged approach that was aptly referred to as *damage control* (Rotondo et al, 1993). In this new paradigm, the goals of the initial operation are limited to rapid control of bleeding and spillage of intestinal contents. This is followed by resuscitation of the patient in the surgical ICU followed by a planned reoperation for definitive reconstruction of the anatomy several days later. By the beginning of the new millennium, this new approach had become the standard of care for major abdominal trauma (Johnson et al, 2001; Shapiro et al, 2000), thus packing and temporary abdominal closure replaced hepatectomy as the dominant approach for major hepatic wounds (Johnson et al, 2001; Knudson et al, 1990; Malhotra et al, 2000; Pachter et al, 1996).

The application of nonoperative management to liver injuries in the last 15 years represents a similarly dramatic revolution. Computed tomography (CT) permitted precise delineation of the anatomy of injured abdominal solid organs. With better appreciation of the natural history of these injuries came an increasingly conservative approach. Nonoperative management was initially implemented with striking success for pediatric splenic trauma (Aronson et al, 1977) and was then successfully applied to the pediatric liver (Karp et al, 1983) and subsequently to the adult spleen and liver (Meyer et al, 1985).

Since the early 1990s, nonoperative management has evolved into the standard of care for blunt hepatic trauma in hemodynamically stable patients (Stein & Scalea, 2006). However, in

Table 102.1

Liver Injury Scale (1994 Revision)

Grade*	Type of Injury	Description of Injury	ICD-9	AIS-90
I	Hematoma	Subcapsular, <10% surface area	864.01	2
			864.11	
	Laceration	Capsular tear, <1 cm	864.02	2
		parenchymal depth	864.12	
II	Hematoma	Subcapsular, 10%-50% surface area	864.01	2
		Intraparenchymal, <10 cm in diameter	864.11	
	Laceration	Capsular tear 1-3 cm parenchymal depth, <10 cm in length	864.03	2
			864.13	
III	Hematoma	Subcapsular, >50% of the surface area of the ruptured subcapsular or parenchymal hematoma; intraparenchymal hematoma >10 cm or expanding		3
	Laceration	>3 cm parenchymal depth	864.04	3
			864.14	
IV	Laceration	Parenchymal disruption involving 25%-75% hepatic lobe *or*	864.04	4
		Parenchymal disruption involving 1 to 3 Couinaud segments	864.14	
V	Laceration	Parenchymal disruption involving >75% of a hepatic lobe or >3 Couinaud segments within a single lobe		5
	Vascular	Juxtahepatic venous injuries; a retrohepatic vena cava/central major hepatic veins		5
VI	Vascular	Hepatic avulsion		6

*Advance one grade for multiple injuries up to grade III.
AIS-90, Abbreviated Injury Scale; ICD, International Classification of Diseases

From Moore et al, 1995: Organ injury scaling: spleen and liver (1994 revision). J Trauma 38:323-324.

recent years, it has also become apparent that the conservative approach requires more than close monitoring. In fact, these patients often require adjunctive imaging and interventional techniques to manage the sequelae of major liver trauma (see Section II and Chapters 27 and 28; Carrillo et al, 1999). The most important of these adjuncts is selective angiographic embolization of hepatic artery branches, which has largely replaced operative ligation of the right or left hepatic artery at the hilum (see Chapter 28; Wahl et al, 2002).

SURGICAL ANATOMY OF THE LIVER FROM THE TRAUMA SURGEON'S PERSPECTIVE (SEE CHAPTERS 1A AND 1B)

Trauma surgeons view the liver as having two vascular pedicles: the *inflow pedicle*, comprising the portal vein and hepatic artery, is easily accessible in the hepatoduodenal ligament and is controlled by the Pringle maneuver; the *outflow pedicle*, comprising hepatic veins and retrohepatic inferior vena cava, is virtually inaccessible in the massively bleeding trauma patient, and total vascular isolation of the liver is rarely a practical option in this situation.

The American Association for the Surgery of Trauma (AAST) published a liver injury scale that creates a unified framework for describing the severity of hepatic trauma (Table 102.1, Fig. 102.1; Moore et al, 1995). This scale is useful not only as a descriptive tool but also as an outcome predictor that facilitates comparisons across groups of patients.

From the operating surgeon's perspective, the AAST Liver Injury Scale translates into three types of injuries:

1. Superficial parenchymal wounds that require only a simple suture or use of a local hemostatic technique
2. Deep parenchymal injury or extensive parenchymal disruption, which can be packed
3. Deep injury involving major vascular structures, which requires special maneuvers to achieve hemostasis and often carries a poor prognosis

The approach to each type of injury depends on the patient's hemodynamic stability and the cumulative physiologic insult. The segmental anatomy of the liver has little relevance in the trauma patient except as a way to describe the location of injuries.

The Stable Patient with Blunt Hepatic Injury

Blunt hepatic trauma in a hemodynamically stable patient is typically discovered on CT scan. If the patient is stable with no signs of peritoneal irritation, presumably indicating a hollow viscus injury, the current standard of care is nonoperative management, *regardless of the grade or extent of the injury* (McVay et al, 2008). Although the overall success rate of nonoperative management of hepatic trauma ranges between 85% and 98% (Croce et al, 1995; Malhotra et al, 2000; Pachter et al, 1996; Velmahos et al, 2003), high grades of injury carry a greater risk of failure and often require adjunctive measures and a multidisciplinary approach as described below (Carrillo et al, 1999; Sriussadaporn et al, 2002).

Practical Aspects of Nonoperative Management

Stable patients with high-grade liver injuries (grade III and above) are admitted to the intensive care unit for close hemodynamic monitoring and serial abdominal examination. This must include careful palpation of the liver to assess for new tenderness or any increase in liver size; both are indicative of

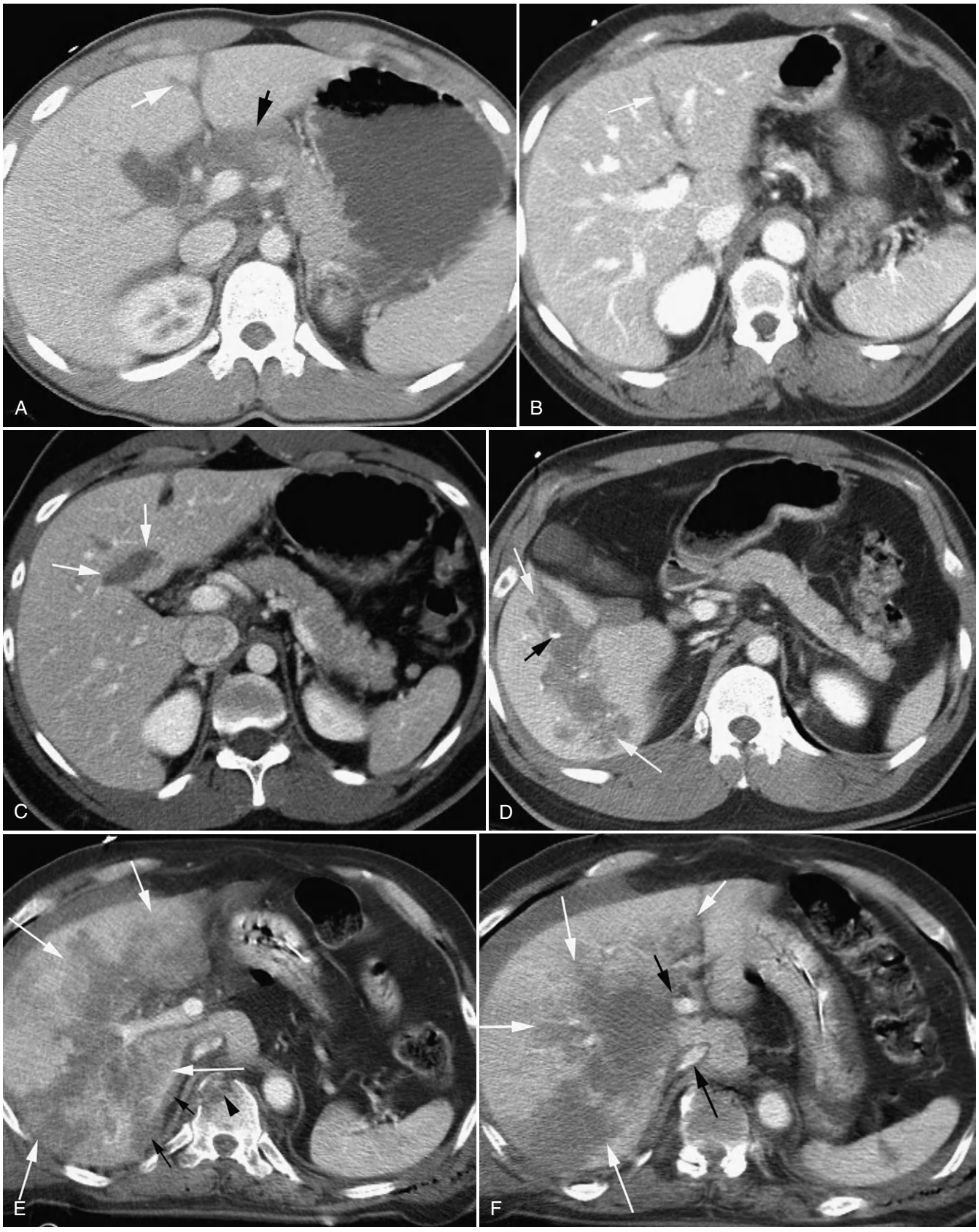


FIGURE 102.1. Liver injury scale. **A,** Grade I injury. **B,** Grade II injury. **C,** Grade III injury. **D,** Grade IV injury. **E,** Grade V injury. **F,** Grade VI injury. *(Courtesy Dr. R. Thoeni.)*

intrahepatic hemorrhage. Many of these patients have associated injuries, such as traumatic brain injury or lung contusions, which also require intensive care. Monitoring bladder pressures for early recognition of intraabdominal hypertension is indicated in patients who have received massive fluid resuscitation and in those who have a firm, distended abdomen (Fusco et al, 2001; Yang et al, 2002).

The duration of ICU monitoring depends on the grade of injury. In general, patients with isolated liver injuries who remain stable are transferred to ward beds after 36 to 48 hours and can be discharged within a week. Routinely obtained laboratory studies include a complete blood count, coagulation profile, and also liver function tests, although these are less important.

The question of routine follow-up imaging is controversial (Alonso et al, 2003). Although routine follow-up imaging is not indicated, most patients with high-grade injuries undergo subsequent CT scans in search of complications such as biloma or hepatic necrosis or because of associated injuries. Fever, leukocytosis, unexplained drops in hematocrit, and a rising bilirubin are obvious indications for repeat imaging (Pachter et al, 1996).

Faliure of Nonoperative Management

Failure of nonoperative management is an uncommon but potentially life-threatening complication that should be recognized early and addressed aggressively (Galvan & Peitzman, 2006). Ongoing bleeding is the major cause of failure. Evidence of ongoing hemorrhage includes hypotension, falling hematocrit, an increase in liver size, or the onset of new or increased pain in the right upper quadrant. If the patient is stable, a repeat CT scan will demonstrate the bleeding, which can then be controlled by angiographic embolization (Misselbeck et al, 2009). The patient in shock is urgently taken to the operating room for laparotomy. The complications of nonoperative management are listed in Box 102.1.

Adjuncts to Nonoperative Management

Adjunctive modalities have a crucial role in the nonoperative management of hepatic trauma. These modalities include angiography, image-guided drainage, endoscopic retrograde cholangiopancreatography (ERCP), and laparoscopy (see Chapters 18, 19, 21, and 28; Carrillo et al, 2010).

Angiography is by far the most important adjunct. A "blush" of intravenous contrast on CT scan (i.e., active extravasation) typically results from injury to a branch of the hepatic artery (Fig. 102.2). This blush is an indication for selective angiographic embolization of the bleeding vessel to prevent pseudoaneurysm formation and delayed hemorrhage (Demetriades et al, 2006; Eubanks et al, 2003).

Box 102.1

Complications of Nonoperative Management of Liver Injuries

Ongoing bleeding
Biloma
Biliary fistula
Intraabdominal abscess
Hepatic abscess
Hemobilia
Liver necrosis
Missed hollow viscus injury
Abdominal compartment syndrome

A blush on CT scan is by no means the only indication for angiography. Evidence suggests that liberal use of angiography for *any* high-grade liver injury is safe and effective, because significant injury to lobar and segmental vessels may occur without a blush, and if left untreated, this may lead to delayed hemorrhage (Mohr et al, 2003).

CT-guided percutaneous drainage plays a key role in nonoperative management, because bile collections are common around the injured liver (Castagnetti et al, 2006). Such drainage obviates the need for laparotomy in the majority of cases. Persistent high-output bile drainage from a percutaneously placed drain indicates injury to a segmental or lobar bile duct. In these patients, ERCP may be used to delineate the site of injury and to decompress the biliary tree by endoscopic papillotomy and stenting (Lubezky et al, 2006); however, in the absence of ductal isolation, adequate external drainage should be sufficient for fistula closure. Image-guided percutaneous drainage is also useful in addressing perihepatic or intrahepatic abscesses.

Delayed laparoscopic lavage is emerging as another useful adjunct to conservative management (Carrillo et al, 2001; Franklin et al, 2007). This minimally invasive procedure is indicated when the patient fails to thrive, with persistent low-grade fever and other signs of ongoing systemic inflammatory response. Port placement is similar to a laparoscopic cholecystectomy with a single subhepatic lateral port. The injured liver is inspected, perihepatic collections are drained and cultured under direct vision, and the infected "rind" of clotted blood and bile on the surface of the liver is gently and bluntly teased off the capsule. The area of injury is typically obvious and is carefully avoided. The liver is irrigated with the suction irrigator, and drains are placed under direct vision in the relevant spaces above or below it.

Other Complications of Nonoperative Management

Rarely, a false aneurysm of a branch of the hepatic artery (Schouten van der Velden et al, 2009) will decompress into an injured biliary radical in a delayed fashion, causing *hemobilia* (Green et al, 2001; see Chapters 104 and 105). The patient presents weeks or months after the injury with upper gastrointestinal bleeding, jaundice, and colicky abdominal pain as a result of blood and clots in the biliary tree that are subsequently passed through the ampulla of Vater. Angiographic embolization (see Chapters 28 and 83) of the source of bleeding is the treatment of choice (Mohr et al, 2003).

Occasionally, a devascularized area of liver will become necrotic. Small areas of *hepatic necrosis* are difficult to diagnose and do not require treatment; however, large areas of necrosis may lead to a systemic inflammatory response or may become infected. On rare occasions, hepatic necrosis may require resectional debridement and wide drainage.

The most devastating complication of nonoperative management is *missed hollow viscus injury*. This complication is very uncommon (Miller et al, 2002), but when it occurs, the mortality rate is high. The diagnosis is particularly difficult, because there is often free fluid in the peritoneal cavity as a result of the liver injury. The abdomen may be firm and difficult to examine, because the patient is intubated and sedated. The signs of a missed hollow viscus injury are therefore subtle, and timely diagnosis requires a high index of suspicion. The decision not to operate should be critically reevaluated with any signs of hyperdynamic physiology. Any adverse change in the abdominal findings or in the expected clinical trajectory should prompt a

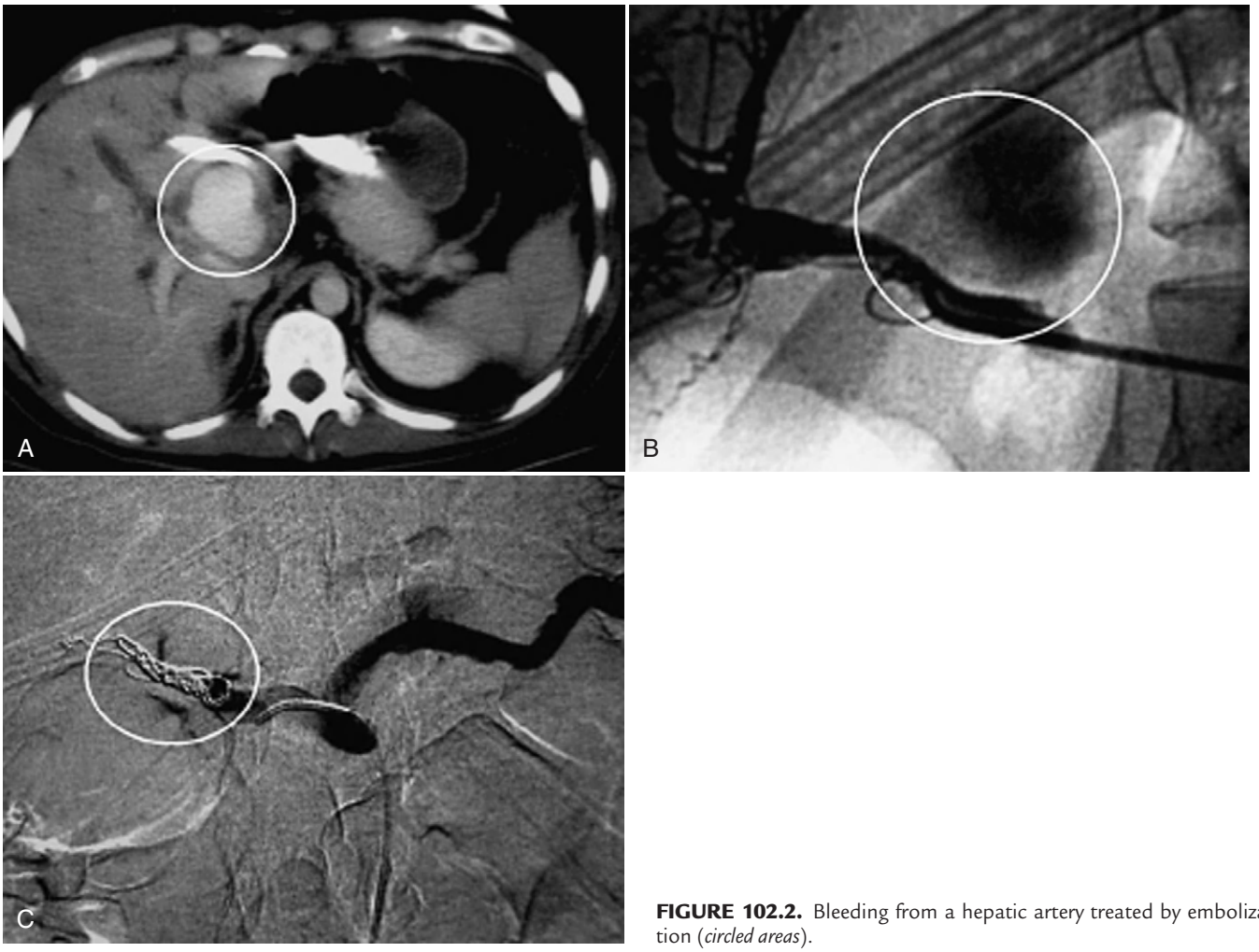


FIGURE 102.2. Bleeding from a hepatic artery treated by embolization (*circled areas*).

repeat CT scan or laparotomy in search of a missed injury. Failure to achieve timely source control results in the patient's death.

Nonoperative Management of Penetrating Hepatic Trauma?

It was only natural that following the dramatic success of nonoperative management for blunt hepatic trauma in the 1990s, attempts would be made to extend the concept to penetrating injuries. Although conservative management of stab wounds to the abdomen, including the liver, has been practiced for years, application of this approach to gunshot wounds is controversial. In 1994, Renz and Feliciano reported 32 patients with right thoracoabdominal gunshot wounds, of whom 7 had CT-documented liver injuries that were successfully treated nonoperatively. Five years later, Demetriades and colleagues (1999) reported 16 patients with penetrating liver injuries, 5 of whom needed a delayed laparotomy; 1 patient died. Clearly, nonoperative management of hepatic gunshot wounds must be applied carefully and selectively and is not currently the standard of care. Success hinges on complete CT delineation of the *entire* bullet trajectory within the liver and the ability to reliably exclude injury to adjacent hollow organs, especially the right colon (Demetriades et al, 2006).

The Unstable Patient with Hepatic Trauma

The patient in shock with hemoperitoneum requires immediate laparotomy to control the bleeding regardless of the injury mechanism. In this stressful situation, the keys to success are careful forethought and orderly conduct of the operation to achieve rapid hemostasis. Immediate availability of type-specific blood is mandatory, and early activation of a transfusion protocol providing for fresh frozen plasma and platelets reduces the risk of coagulopathy in the patient with massive hemorrhage (Dente et al, 2009). A full set of vascular instruments, a rapid infusion device, an autotransfuser, and competent assistance are other essential adjuncts.

Exploratory laparotomy is conducted through a generous midline incision followed by rapid evisceration of the small bowel and packing of all four abdominal quadrants. If hemostasis is achieved, and a liver injury is suspected, the right upper quadrant should be explored *last*.

Superficial, Low-Grade Injuries

Bleeding from a superficial laceration is controlled by local hemostatic techniques, such as temporary packing, while the surgeon is addressing other injuries, or argon beam coagulation. If an argon beam coagulator is not available, cauterization of

the bleeding liver by placing the electrocautery at its highest level and arching the current adjacent to the liver parenchyma without touching it can often achieve the same result. For deeper injuries, local hemostatic agents placed into the laceration followed by manual or pack compression of the edges is a useful adjunct. A portion of healthy omentum stuffed into the laceration and sutured to the liver capsule can serve the same purpose. If manual compression alone controls the bleeding, approximating the laceration with heavy chromic catgut "liver sutures" on a large blunt needle is another useful technique.

Packing of Deep Liver Lacerations

Packing is the workhorse of surgery for hepatic trauma and is especially useful for high-grade lacerations or parenchymal disruptions that are not amenable to the local hemostatic measures described above (Nicol et al, 2007). The technique of packing is often poorly executed, but the goal is to effect hemostasis by compressing the bleeding parenchyma between packs placed *above and below* it. Packing only over the injury without creating an opposing pressure vector often fails.

It is important to note that packing is most effective for venous injuries. For this reason, we advocate immediate postoperative angiography with selective embolization for high-grade liver injuries with arterial hemorrhage that cannot be directly addressed by suture-ligation of the bleeders (Gaarder et al, 2007).

Although assertive packing with laparotomy pads is essential to achieve hemostasis, sometimes overenthusiasm results in overpacking, which can result in hypotension as a result of vena caval compression (Meldrum et al, 1995). The problem should be recognized immediately, and the packs removed gradually, to identify the degree of packing that achieves hemostasis without the adverse effects.

It is important to spend time observing the packs in situ, because ineffective packing takes time to declare itself, as the blood seeps through multiple layers of cloth with very high absorptive capacity. Failure to wait a few minutes before closing the abdomen often results in an urgent reoperation.

Omentum can sometimes be stuffed into a liver defect and serve the same purpose as a laparotomy pad. Although it has the advantage of not requiring removal, rarely is there enough omentum to provide effective tamponade for a large laceration. In desperation, the senior author of this chapter (W.P.S.) once placed several large pieces of Vicryl mesh into a massively bleeding gunshot wound of the right lobe of the liver in a patient with an associated infrahepatic vena caval injury. The Vicryl packs were never removed, and the patient survived. Although this method cannot be routinely recommended, it is nevertheless an example of improvisations that are sometimes called for in a difficult situation.

Other Techniques for Hemostasis of Deep Liver Lacerations

If packing fails to control the bleeding, inflow occlusion is the next step. The index finger is placed through the foramen of Winslow posterior to the hepatoduodenal ligament, and a window is created in the gastrohepatic ligament. An umbilical tape is then passed through the window in the gastrohepatic ligament and out through the foramen of Winslow, thereby surrounding the portal triad, which is then occluded en masse with either a Rummel tourniquet or a vascular clamp. The occlusion time should be kept to a minimum: 15 minutes of hepatic inflow occlusion is safe in elective hepatic resection (Tralhão et al, 2009). Intermittent hepatic inflow occlusion has been used safely with a total inflow occlusion time in excess of 120 minutes (Ishizaki et al, 2006), although no level 1 data are available to define the safe duration of hepatic inflow occlusion in trauma patients.

If the bullet or knife tract is superficial, a tractotomy can expose the injured vessel for direct suture ligation (Badger et al, 2009). Tractotomy can be performed using the Endo GIA (gastrointestinal anastomosis) stapler (Covidien, Boulder, CO) with a vascular stapler load, gradually dividing the roof of the tract in a piecemeal fashion so that the deep bleeders in the tract can be individually suture ligated or doubly clipped with a hemoclip. If the injury involves the left lateral segment, a stapled segmentectomy, using either the Endo GIA or a TA (thoracoabdominal; Covidien) stapler, is an expedient solution (Schemmer et al, 2007).

More often, the problem arises from a deep tract or through-and-through injury to the main mass of the right lobe. Filling the tract with omentum, Flowseal (Baxter Healthcare, Zurich, Switzerland), or Avitene (Davol, Warwick, RI) will often achieve hemostasis. Balloon tamponade is another useful technique (Poggetti et al, 1992), wherein a balloon device is improvised from a red rubber (Robinson) catheter inserted into a 1-inch Penrose drain. The distal end of the drain is tied closed, and the proximal end is secured snugly around the catheter with a pair of heavy silk ties. The balloon device is inserted through an appropriate stab incision in the right upper quadrant abdominal wall and into the tract and is inflated with saline injected through the catheter. A closed suction drain is placed in the subhepatic space. The balloon is deflated and removed either at planned relaparotomy, 48 to 72 hours after the original operation, or percutaneously if the abdomen was closed.

Sometimes a bleeding vessel can be exposed and suture ligated at the base of a deep liver laceration, using the technique of finger-fracture hepatotomy with selective vascular ligation under inflow occlusion (Hirshberg & Mattox, 2006); however, attempts to reach a deep vessel are often ill advised, as they lead to continued blood loss and physiologic deterioration and may even aggravate the bleeding. Packing, when successful, is the best approach, and immediate postoperative angiographic embolization (see Chapters 28 and 83), if available, can be a lifesaving adjunct.

Resectional debridement of the injured tissue is an option for extensive destruction of the periphery of the liver; however, the surgeon must always keep in mind that the one and only major goal of the operation is to achieve hemostasis as rapidly as possible; other considerations are secondary and must wait. Resectional debridement, if necessary, is more frequently used to address devascularized liver tissue during a delayed reoperation rather than bleeding in the initial procedure.

Bleeding from the Hepatic Veins and Juxtahepatic Vena Cava

The large retrohepatic veins are a low-pressure system; when injured, they are often contained by the triangular ligaments of the liver. An injury to the retrohepatic cava or the major hepatic veins can therefore manifest either as bleeding *through* a hole in the liver, if the suspensory ligaments remain intact, or as bleeding *around* the liver, if they are disrupted (Buckman et al, 2000); bleeding through the liver stops with effective packing of the hole in the liver, but bleeding around the liver does not.

Juxtahepatic vena caval hemorrhage should be suspected if a large volume of dark blood gushes around or through a

high-grade liver injury. Posterior and inferior traction on the falciform ligament may compress the liver mass onto the retrohepatic vena cava and reduce the bleeding. The next step is packing, although bleeding around the liver may not stop with packing despite heroic efforts. In these situations, when packing and the Pringle maneuver fail to stop the bleeding, an *early* decision to achieve control of the hepatic outflow tract—that is, the second vascular pedicle—is critical. Delay of the decision ensures failure and patient death as a result of continued massive blood loss.

Vascular isolation of the injured liver is a formidable surgical challenge (see Chapter 91A; Yellin et al, 1971), not only because of the technical complexity involved but also because cross-clamping the suprahepatic and infrahepatic vena cavae (Krige et al, 1990) is poorly tolerated by the hypovolemic patient. Furthermore, although creating a sling to occlude the infrahepatic vena cava can usually be accomplished relatively quickly after a Kocher maneuver, dissection of the infradiaphragmatic suprahepatic cava is difficult, particularly for the emergency surgeon who operates infrequently in this area.

Several options are available for achieving outflow control, and by far the most well-known is the atriocaval shunt (Fig. 102.3; Schrock et al, 1968). After performing a median sternotomy, a No. 32 chest tube is inserted through the purse-stringed right atrial appendage and threaded through the right atrium and juxtahepatic vena cava to a position just above the renal veins. At the same time, a second team isolates the inferior vena cava (IVC) in its suprarenal infrahepatic segment, and a side hole is fashioned at the level of the right atrium. Rummel tourniquets are tightened around the vena cava and the stent within the pericardium and just above the renal veins. Using a 9.5-mm endotracheal tube with a side hole 17 cm from the tip obviates the need to isolate the suprarenal cava, because inflating the balloon of the tube occludes the caval lumen. This maneuver shunts venous return to the heart around the injured segment and controls most of the bleeding, enabling the surgeon to visualize and repair the hole in the vein by completely mobilizing the right lobe of the liver and rotating it medially. This is a difficult and uncommonly used technique, as evidenced by the popular adage that "the number of articles published about atriocaval shunt far exceeds the number of patients who survived it" (Fig. 102.3).

Another option for outflow control is complete hepatic vascular isolation (see Chapter 91A) by clamping the inferior vena cava above and below the liver, in conjunction with simultaneous aortic cross-clamping (Khaneja et al, 1997), or use of a centrifugal pump to return blood to the heart (Baumgartner et al, 1995; Horwitz et al, 1995) to reduce the risk of hypovolemic arrest after caval occlusion. Even hepatic explantation and back-bench repair of hepatic vein avulsion followed by hepatic autotransplantation has been reported (Boggi et al, 2006). Despite all of these elegant technical concepts, which are of very limited utility in the real clinical situation, the mortality rate for

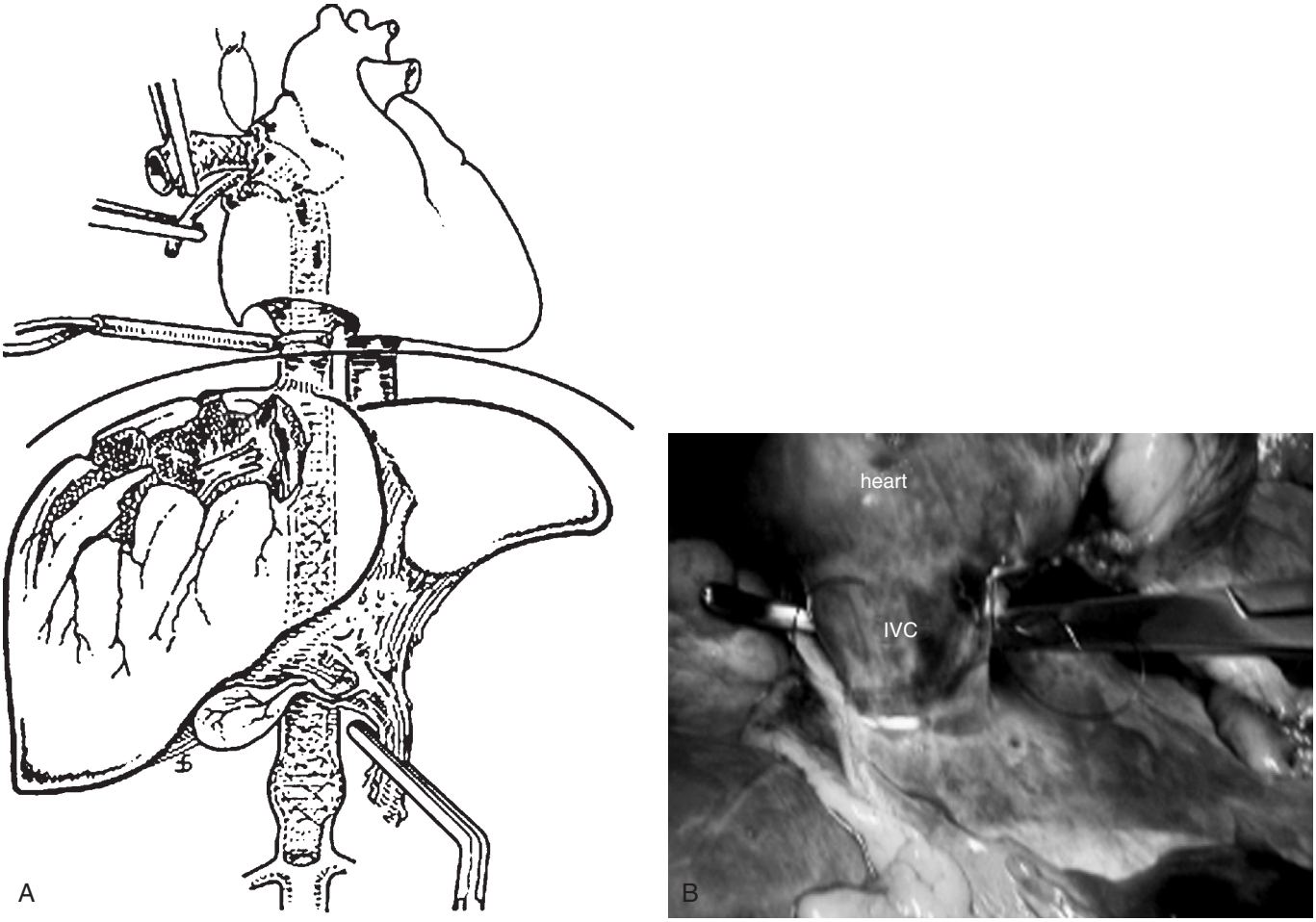


FIGURE 102.3. An atriocaval shunt. *IVC*, inferior vena cava.

unstable patients with juxtahepatic vena caval injury unresponsive to packing remains extremely high (Phelan et al, 2001).

Urgent Reoperation

The three indications for urgent reexploration of a patient with liver injury are 1) continued bleeding, 2) abdominal compartment syndrome, or 3) a missed injury. At laparotomy, the liver packs are removed, and the injury is closely inspected for hemostasis. Thorough exploration of the abdomen in search of other sources of bleeding is then carried out.

The most common causes of bleeding found at urgent relaparotomy for trauma are inadequate hemostasis of the original injury, another source of bleeding in the vicinity, iatrogenic trauma, or diffuse coagulopathy (Hirshberg et al, 1993). In cases of rebleeding, mortality is extremely high, and the prognosis is especially bleak, if no discrete source of hemorrhage is found.

The liver encountered at urgent reoperation is often "hostile" and is very different from the normal organ. It is grossly swollen to twice or more its normal size with a tense capsule that tears easily. The edematous parenchyma does not hold clips or ligatures well, and it is often impossible to properly mobilize such a swollen, friable liver without adding an iatrogenic insult to the original injury. Hemostatic liver sutures tend to tear through the capsule and lose their hemostatic effect. This hostile environment represents a very bad turn of events in an already precarious situation.

Some patients develop intraabdominal hypertension following the initial operation, as previously discussed. In most cases, an urgent decompressive laparotomy with temporary abdominal closure, leaving the abdomen "open," is the only way to save a rapidly deteriorating patient. Occasionally, this problem can be managed by catheter drainage of the peritoneum, if the patient is relatively stable.

Planned Reoperation

Planned reoperation is an integral part of the damage-control sequence for treatment of severe liver trauma. In general, the patient is reexplored 36 to 48 hours after the initial operation, once hemodynamic stability has been achieved. Although such a practice is not supported by data, trauma surgeons are reluctant to remove liver packs sooner than 36 hours after the initial operation, because earlier removal often results in rebleeding and a need to repack the liver. Packs should rarely, if ever, be left in any patient for more than 72 hours (Scott et al, 2006), because the risk of infection increases sharply. If the packed liver injury is associated with damage control of a bowel injury, intestinal reconstruction should be performed, and the packs should be removed last.

Extreme care should be taken to remove liver packing, which should be done slowly and only after flooding the right upper quadrant with saline. A Toomey syringe is used for continuous pulse irrigation and blunt atraumatic separation of the packs off the liver capsule, assisted by the jet of saline. Bleeding should prompt the surgeon to stop and address the bleeding point with the argon beam coagulator or another local hemostatic technique. Special care should be taken to avoid stripping the liver capsule. The area should be widely drained, and resectional (nonanatomic) debridement of areas of obvious necrosis should be considered, if hemostasis has been achieved and the patient is otherwise stable. Ongoing oozing from the unpacked areas should prompt consideration of repacking; it is important to admit defeat early and repack rather than continue with attempts at futile hemostasis in a hostile liver.

Extrahepatic Biliary Injury

Most extrahepatic biliary injuries result from penetrating trauma (Posner & Moore, 1985) and are discovered at exploratory laparotomy. The gallbladder is the most common structure injured, and cholecystectomy definitively solves the problem (Posner & Moore, 1985); however, it may be unwise in an unstable coagulopathic patient with an associated liver injury, because it creates another source of hemorrhage from the liver bed. A tube cholecystostomy or closure with an absorbable stitch and drainage of a small hole in the gallbladder are therefore better options in a damage-control situation.

Small stab wounds to the extrahepatic biliary ducts can be managed by primary closure with absorbable suture and external drainage (Bade et al, 1989). The use of a T-tube for a common bile duct (CBD) injury is rarely a practical option in a healthy young adult with a normal CBD. Major injuries to the extrahepatic bile ducts require Roux-en-Y choledochojejunostomy or hepaticojejunostomy for definitive repair (Degiannis et al, 2001).

Penetrating trauma to the biliary tree is often associated with injuries to vascular structures such as the portal vein, hepatic artery, and vena cava (Jurkovich et al, 1995). Injuries to adjacent structures—such as the duodenum, pancreas, stomach, and liver—are also common. The hemodynamic stability of the patient and the complexity of the other injuries will govern management of the bile duct injury.

Roux-en-Y choledochojejunostomy and hepaticojejunostomy are the definitive treatments of choice, as they are for bile duct injuries complicating cholecystectomy; however, more often than not, the patient is unstable because of associated injuries that preclude a complex biliary reconstruction. Damage-control drainage of the bile duct injury by temporary T-tube drainage of a complex laceration—or via an infant feeding tube tied into the proximal duct, if the duct has been completely transected—and continued resuscitation in the ICU with subsequent elective biliary reconstruction under controlled conditions is a much better option. Although temporary ligation of the proximal transected duct is another option in a damage-control situation, drainage is generally preferred.

Blunt injury to the gallbladder as a result of a "blowout" (Zellweger et al, 2005) or adhesive tear is uncommon, but the treatment principles are similar to those for penetrating injury. Rarely, the surgeon may encounter avulsion of the common bile duct from the duodenum. If this is an isolated injury, the duodenum can be oversewn, and a Roux-en-Y choledochojejunostomy can be constructed (Melton et al, 2003). Regardless of the type of biliary management, wide drainage is essential.

SUMMARY

Nonoperative management of hemodynamically stable patients with blunt hepatic injury has become the standard method of care; however, this conservative approach often requires the use of adjunctive measures to manage sequelae and complications. A missed hollow viscus injury is an unusual but potentially lethal complication of this conservative management strategy.

Hemodynamically unstable patients with a bleeding liver require emergency laparotomy, although most patients with

significant hemorrhage can and should be managed by packing. Rarely, a patient with a juxtahepatic hepatic vein or vena caval injury will not respond to packing. In this situation, an early decision to achieve proximal and distal vascular control of the liver is essential, if there is to be any chance of salvage. Even in the most experienced hands, the mortality rate for juxtahepatic vena caval injuries is high.

Penetrating injuries to the extrahepatic biliary tract are relatively uncommon. Hemodynamically unstable patients should be managed with damage-control techniques, and prolonged procedures to reconstruct the biliary tract should only be undertaken when the patient is stable.

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CHAPTER 103

Pancreatic and duodenal injuries

William P. Schecter and Asher Hirshberg

OVERVIEW

Torrential bleeding from the region of the pancreatoduodenal complex (PDC), surging like a crimson tide, is one of the most intimidating sights in trauma surgery. This particularly lethal pancreatic injury is but one of the challenges posed by this unforgiving organ. Hidden deep in the upper recesses of the retroperitoneum, the injured pancreas exhibits a spectrum of clinical presentations, from that of occult injury to dramatic exsanguination. This chapter reviews the modern approach to the management of pancreatoduodenal trauma with emphasis on the need for a high index of suspicion, modern imaging technology, and safe operative principles.

EVOLUTION OF THE APPROACH TO PANCREATIC TRAUMA

The modern approach to pancreatic trauma reflects advances in elective foregut surgery. Better confidence in surgery of the PDC, advanced imaging, and better physiologic insight have combined to shape the current management of the injured pancreas.

A patient with blunt pancreatic injury was first reported in the Lancet as early as 1827, by Tavers. Although several survivors were subsequently reported after ligation and excision of exteriorized penetrating pancreatic wounds (Otis, 1876), the major advance in the operative treatment came in 1923, when Walton described distal pancreatectomy (see Chapter 62) as the treatment of choice for pancreatic transection. The dramatic reduction in mortality among patients with pancreatic injuries—from 56% in World War II, mostly due to associated injuries, to 22% in the Korean War—was more a result of improvements in general perioperative care than of specific technical innovations (Sako et al, 1955).

In the final decades of the last century, advances in medical imaging and in surgical technique converged to improve the care of patients with pancreatic trauma. The most important of these was computerized tomography (CT) of the abdomen (see Chapter 16), which for the first time allowed detailed visualization of the pancreas (Udekwu et al, 1996). This enabled surgeons to diagnose hitherto unrecognized pancreatic injuries and to drain peripancreatic fluid collections without the need for a laparotomy.

At approximately the same time, the introduction of endoscopic retrograde cholangiopancreatography (ERCP; see Chapter 18) provided a minimally invasive approach to diagnose leakage from the pancreatic duct after trauma (Buccimazza et al, 2006; Gupta et al, 2004; Lin et al, 2004; Wind et al, 1999; Wong et al, 2002). By contrast, the role of magnetic resonance cholangiopancreatography (MRCP; see Chapter 17) in the evaluation of the injured pancreatic duct remains to be defined (Bhasin et al, 2009; Fulcher et al, 2000).

The presumed adverse effect of pancreatic enzymes on the suture lines of duodenal repairs in patients with injuries to both organs led to the development of the Berne duodenal diverticulization, essentially a Bilroth II gastrectomy combined with biliary diversion (Berne et al, 1968, 1974), to preemptively divert gastric secretions around the repaired duodenum. Later, Jordan introduced the pyloric exclusion procedure (Vaughan et al, 1977), which achieves the same result but with a much simpler operation. Because of its conceptual elegance and technical simplicity, pyloric exclusion rapidly became the buzzword of PDC trauma in the 1990s. This led to very liberal use of the procedure in reported series (Feliciano et al, 1987); however, pyloric exclusion has never been subjected to a prospective randomized trial, and most attempts to compare it retrospectively to simple duodenal repair have demonstrated increased morbidity without benefit (DuBose et al, 2008; Seamon et al, 2007).

Resection of the entire PDC (see Chapter 62), which is routinely done in elective pancreatic surgery, is very rarely needed in the trauma situation. When complete disruption of the head of the pancreas and surrounding duodenal loop leaves the surgeon with no other choice, a so-called trauma Whipple (TW) may be necessary, but only as a last resort to save an exsanguinating patient. When necessary, the procedure is performed in a staged fashion with resection during the original operation and reconstruction 24 to 48 hours later (Subramanian et al, 2007). This is a reflection of the move toward damage control surgery, the most important paradigm shift in trauma surgery in the last two decades of the last century (Hoey & Schwab, 2002).

Distal pancreatectomy remains the mainstay of treatment of patients with major ductal disruption (Balasegaram & Lumpur, 1976; Heitsch et al, 1976); however, reports of successful stenting of the injured pancreatic duct via ERCP (Lin et al, 2006, 2007) suggest that this minimally invasive intervention may evolve into a safe management option in selected patients. Pancreatic trauma continues to tax the judgment and operative skills of experienced surgeons, even as sophisticated, minimally invasive diagnostic and therapeutic adjuncts continue to evolve.

SURGICAL ANATOMY OF THE PANCREAS AND DUODENUM: A TRAUMA SURGEON'S PERSPECTIVE (SEE CHAPTERS 1A AND 1B)

The injured pancreas is not immediately accessible during laparotomy for trauma and requires special maneuvers for exposure and access. In addition, the complex pancreatic anatomy

Table 103.1

Pancreas Injury Scale

Grade*	Type of Injury	Description of Injury	ICD-9	AIS-90
I	Hematoma	Minor contusion without duct injury	863.81–863.84	2
	Laceration	Superficial laceration without duct injury		2
II	Hematoma	Major contusion without duct injury or tissue loss	863.81–863.84	2
	Laceration	Major laceration without duct injury or tissue loss		3
III	Laceration	Distal transection or parenchymal injury with duct injury	863.92/863.94	3
IV	Laceration	Proximal† transection or parenchymal injury involving ampulla	863.91	4
V	Laceration	Massive disruption of pancreatic head	863.91	5

*Advance one grade for multiple injuries up to grade III. *863.51, 863.91: head; 863.99, 862.92: body; 863.83, 863.93: tail.
†Proximal pancreas is to the patient's right of the superior mesenteric vein.
AIS, Abbreviated Injury Score; ICD, International Classification of Diseases

From Moore EE, et al, 1998: Staged physiologic restoration and damage control surgery. World J Surg 22:1184-1190. Reprinted with permission.

dictates that the head and the body of the pancreas be managed operatively as two separate organs.

The closest anatomic relationship of the injured *body and tail* of the pancreas is with the spleen. The pancreatic body is typically approached by first mobilizing the spleen medially to enter the anatomic plane behind the spleen and pancreas. The splenic artery and vein are then easily exposed and controlled on the posterior surface of the gland; however, if necessary, control of the splenic vessels can be achieved by mobilizing the body of the gland along its superior and inferior aspects, with no need for splenic mobilization. Based on this anatomic arrangement, trauma surgeons view the body and tail of the pancreas as an organ with a single accessible vascular pedicle, similar to the kidney or spleen. When necessary, the injured pancreatic body can be easily resected by performing an en bloc distal pancreatectomy and splenectomy. The major concern in trauma is whether the main pancreatic duct is damaged, because this can cause a persistent fistula with its associated complications. In contrast, bleeding is usually not a major concern.

The head of the pancreas is densely adherent to the duodenal loop, and it is convenient to group them together as the PDC, which is approached from the right side. The PDC is supplied by multiple vascular arcades with ample collaterals that are not easily controlled. When injured, the PDC is difficult to resect and requires a high-risk reconstruction. The major concern after complex injuries to the PDC is a leaking duodenal suture line.

From the trauma surgeon's perspective, most of the major vascular structures of the upper abdomen converge on a small area, not much larger than a silver dollar, around the PDC. The superior mesenteric vessels, portal vein, inferior vena cava, and hilum of the right kidney are all in close proximity to the pancreatic head. The vascular structures around the PDC are arranged in three overlapping layers. The deepest one consists of the inferior vena cava and right renal pedicle. Above it, just behind and below the gland, are the portal vein and superior mesenteric vessels. The uppermost layer consists of the gastroduodenal artery and pancreaticoduodenal arcades.

As a result of this unique multilayered anatomic arrangement, penetrating trauma to the PDC often involves associated injuries to more than one major vascular structure, some of which—for example, the retropancreatic portal vein—are not immediately accessible from the front. It is therefore not surprising that penetrating trauma to this area presents what is widely held by trauma surgeons to be the most formidable challenge in abdominal trauma.

The organ injury scales for the pancreas and duodenum, developed by the American Association for the Surgery of Trauma (AAST) (Tables 103.1 and 103.2; Moore et al, 1990) are used for grading injuries of these two organs. Unfortunately, these scales do not acknowledge the fundamental anatomic differences between the pancreatic body and tail and the PDC, and therefore their clinical usefulness is limited.

For practical purposes, trauma to the pancreas ranges from superficial injuries that require only drainage (Feliciano, 1989) to ductal disruption that mandates a distal pancreatectomy. Low-grade injuries to the duodenum can be repaired the same as any other penetrating injury to the gut; however, high-grade duodenal injuries, and especially those that combine duodenal and pancreatic trauma, require a different approach because of the high risk and unforgiving nature of a duodenal leak. Injuries that destroy the PDC or disrupt the ampulla are rare and carry very high mortality rates because of associated trauma to adjacent major vascular structures. This perspective on pancreatic anatomy forms the basis for a detailed discussion of the management of pancreatic injuries in the forthcoming sections.

Diagnosis of Pancreatic and Duodenal Trauma

Hemodynamically stable patients with injuries to the pancreas and/or duodenum may exhibit only subtle signs because of the retroperitoneal location of these organs. Patients with a history of acceleration/deceleration injury; forceful anterior compression of the abdomen, such as from kicks or handlebar injuries; and lower thoracic and upper lumbar vertebra fractures are at increased risk. A seatbelt sign across the upper and middle abdomen should suggest the possibility of serious intraabdominal injury (Velmahos et al, 1999); however, the physical examination can be remarkably benign: abdominal pain and peritoneal signs sometimes take days to develop. For all of these reasons, a high index of suspicion is essential to avoid missing an injury (Wright & Stanski, 2000).

Routine laboratory tests are not particularly helpful. Obviously, patients with elevations in white blood cell count, amylase, or lipase require further investigation. Unfortunately, many patients are seen with normal values. In fact, as many as 35% of patients with a pancreatic transection have normal amylase

Table 103.2

Duodenum Injury Scale

Grade*	Type of Injury	Description of Injury	ICD-9	AIS-90
I	Hematoma	Involving single portion of duodenum	863.21	2
	Laceration	Partial thickness, no perforation	863.21	3
II	Hematoma	Involving more than one portion	863.21	2
	Laceration	Disruption <50% of circumference	863.31	4
III	Laceration	Disruption 50%-75% of circumference of D2	863.31	4
		Disruption 50%-100% of circumference of D1, D3, D4	863.31	4
IV	Laceration	Disruption >75% of circumference of D2	863.31	5
		Involving ampulla or distal common bile duct		5
V	Laceration	Massive disruption of duodenopancreatic complex	863.31	5
	Vascular	Devascularization of duodenum	863.31	5

*Advance one grade for multiple injuries up to grade III.

AIS, Abbreviated Injury Score; ICD, International Classification of Diseases; D1, first position of duodenum; D2, second portion of duodenum; D3, third portion of duodenum; D4, fourth portion of duodenum

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levels (Adamson et al, 2003; Jones, 1985; Sriussadaporn, 1994; Takishima et al, 1997).

On abdominal CT scan, injury to the duodenum is usually obvious; however, the initial CT findings of pancreatic injury may be quite subtle (Akhrass et al, 1997; Bradley et al, 1998; Canty & Weinman, 2001; Ilahi et al, 2002) even with a study using thin slices of the pancreatic area. If a definitive diagnosis is not possible, a repeat CT scan 8 to 12 hours later allows time for retroperitoneal edema as a result of leakage of pancreatic secretions, which better delineates the injury. Fluid in the lesser sac, pancreatic hematomas, and pancreatic lacerations all suggest the diagnosis (Subramanian et al, 2007).

Unfortunately, the abdominal CT scan cannot reliably diagnose a laceration of the main pancreatic duct, unless a complete pancreatic transection is visible (Bradley et al, 1998). ERCP (see Chapter 18) is an excellent test for that purpose and can also be used to stent lacerated ducts in selected patients (Bhasin et al, 2009; Silviera et al, 2009); however, the procedure itself has the potential to cause pancreatitis (Cotton et al, 2009; Silviera et al, 2009) and is generally indicated only when diagnosis of a lacerated duct will change the management of the injury. The role of MRCP in the management of pancreatic trauma remains to be determined (Gillams et al, 2006).

OPERATIVE MANAGEMENT OF INJURIES TO THE BODY AND TAIL OF THE PANCREAS (SEE CHAPTER 62)

The operative approach to injuries to the body and tail of the pancreas is similar for both blunt and penetrating injuries. Full exposure is achieved by either dividing the gastrocolic ligament or by freeing the greater omentum from the transverse colon, reflecting the stomach up and taking down any adhesions between the posterior wall of the stomach and the retroperitoneum. The organ is then thoroughly inspected to assess the damage. Any area of injury, contusion, or hematoma is explored by opening the posterior peritoneum over the anterior aspect of the pancreas, because a superficial and seemingly innocent hematoma may hide a deep laceration. Severe bleeding almost never originates from the pancreas itself but rather from adjacent structures.

In assessing the body and tail of the pancreas, the key question that the surgeon must address is whether a pancreatic duct injury is present (Bach & Frey, 1971; Bradley et al, 1998; Tyburski et al, 2001; Voeller et al, 1991). Unless there is an obvious complete transection, it is difficult to diagnose a duct injury by simple inspection. The integrity of the duct can be interrogated by intraoperative imaging, either by amputating the tail and cannulating the distal duct or by cannulating the gallbladder and injecting contrast into the common bile duct. Both these options are cumbersome and do not have high success rates (Berni et al, 1982).

A transduodenal pancreatogram is mentioned here only to be condemned, because it converts a pancreatic injury into a pancreaticoduodenal (PD) injury. Intraoperative ERCP, first reported in 1986, is another option, if it can be organized expeditiously (Laraja et al, 1986). The more practic option in the middle of the night is to simply proceed with empiric distal pancreatectomy, whenever a deep laceration is in the vicinity of the main pancreatic duct, or a large hematoma is found in the center of the gland. An alternative option for nonbleeding pancreatic injuries, particularly in the face of multiple associated injuries, is closed suction drainage of the lesser sac. Patton and colleagues (1997) demonstrated excellent results by simple drainage, regardless of the location of the injury. A disruption of the capsule should be drained without attempting to repair it. Drainage of an injured main pancreatic duct is an effective solution, but it often results in a high output pancreatic fistula, so distal pancreatectomy may be a better option.

The trauma literature of the 1970s and 1980s is replete with descriptions of pancreas-preserving techniques for complete pancreatic transections (Frey, 1982). The most popular of these was anastomosis of the distal pancreatic stump to a Roux-en-Y loop of jejunum to create a pancreatojejunostomy. The proximal stump, which drains into the duodenum, was then oversewn. The rationale for pancreas-preserving approaches is to maintain pancreatic function and to prevent potential long-term complications of exocrine insufficiency and/or diabetes mellitus; however, this elegant technical solution involves a high-risk

jejunal anastomosis to a traumatized edematous pancreatic stump in an unstable patient who will not tolerate a leak. So in spite of the fact that it is sometimes technically feasible, preservation of the distal pancreatic stump is not in the best interests of the trauma patient; distal pancreatectomy is a much safer solution (Krige et al, 2005; Steele et al, 1973).

Distal Pancreatectomy

Distal pancreatography (see Chapter 62) is often performed in unstable patients with associated injuries, which is not the time for splenic preservation (Subramanian et al, 2007). The spleen should be rapidly mobilized to the midline and used as a handle to lift up the body and tail of the pancreas as it is dissected bluntly from the surrounding retroperitoneal fat. The most expedient technique is to use a stapler to divide the gland, followed by selective suture ligation of the splenic artery and vein. If the pancreas is found to be transected already, an effort is made to deploy the stapler immediately to the right of the injury, in healthy tissue. If the pancreatic duct is visible, it should be suture ligated. As an alternative, the free edge of the proximal stump can be oversewn with a 2-0 polypropylene running suture. Closed suction drainage of the pancreatic bed and left upper quadrant is mandatory (Farrell et al, 1996).

POSTOPERATIVE PANCREATIC FISTULA

Approximately 25% of patients develop a fistula after distal pancreatectomy for trauma (Fahy et al, 2002). In most cases, the fistula is controlled by the drains placed at the time of surgery. Neither the technique of pancreatic closure (Ferrone et al, 2008; Sheehan et al, 2002) nor the use of sealants (Fisher et al, 2008; Suc et al, 2003; Yamamoto et al, 2009) significantly affects the risk of fistula. Nutritional support, preferably via jejunal feeding, is a crucial element of fistula management; however, the presence of a pancreatic fistula does not necessarily require abstinence from oral intake; indeed, depending on the nature and extent of associated injuries, most patients will be able to eat normally during the time it takes for the fistula to close. Endoscopically placed pancreatic stents can reduce the volume and duration of fistula drainage in problem cases (Goasguen et al, 2009; Grobmyer et al, 2009). Failure to identify and drain a contained leak can result in a pancreatic pseudocyst, which may on rare occasion require surgery.

INJURIES IN THE STABLE PATIENT

The first step in the operative management of the injured PDC is wide exposure of the area with a Kocher maneuver. Full mobilization of the PDC from the common bile duct to the superior mesenteric vein (SMV) exposes the head of the pancreas, the second and some of the third portions of the duodenum, and the underlying vena cava. Additional exposure of adjacent structures and an improved workspace can be developed by extending the incision in the posterior peritoneum caudad along the white line of Toldt and mobilizing the right colon (Buscaglia et al, 1969), the so-called extended Kocher maneuver. Complete visualization of the entire third and fourth portions of the duodenum is achieved by carrying the peritoneal incision around the cecum and along the line of fusion of the small bowel mesentery to the posterior peritoneum, all the way up to the ligament of Treitz. This *Cattell-Braasch maneuver* is a technique for the exposure of the third and fourth portions of the duodenum (Cattell & Braasch, 1960), which allows complete reflection of the midgut onto the chest wall and provides access to the entire duodenum; however, after performing the maneuver, the entire midgut remains suspended on the superior mesenteric vascular pedicle and should be handled with care.

After complete mobilization, the entire PDC must be thoroughly explored. The trajectory of the wounding missile must be reconstructed to avoid missing an injury, and the number of holes in the gut should be even; an uneven number should prompt a renewed search for another injury. It is especially easy to miss a hole on the medial side of the duodenal loop adjacent to the pancreas. In these cases, the safest option is to enlarge the hole on the free border of the duodenum in a transverse fashion to inspect and repair the medial wall from inside.

Low-grade duodenal injuries are repaired transversely when possible, to avoid narrowing the lumen. A well-vascularized tension-free repair is essential, but the specific technique and suture material are a matter of individual preference. Decompressive tube duodenostomy is unnecessary, but any injury to the PDC, no matter how simple, should be drained. If the duodenum cannot be closed without tension, it is not a low-grade injury.

High-grade duodenal injuries require sound judgment and safe technical solutions. An extensive laceration or loss of a segment of duodenal wall should never be closed under tension. Instead, the simple and versatile solution is a Roux-en-Y jejunal loop anastomosed to the injured portion of the duodenum.

All cases of complex duodenal repair benefit from establishing a route for enteral feeding distal to the duodenal suture line. Despite being recognized as a key principle, it is often forgotten in the excitement of the moment. Either a nasojejunal tube or a feeding jejunostomy will enable early postoperative feeding and greatly facilitates postoperative management if the duodenal repair leaks.

High-grade PDC injuries are an indication for *pyloric exclusion* (Degiannis & Boffard, 2000), the goal of which is to preemptively divert the gastric effluent around the injured duodenum by temporarily occluding the pylorus. If the duodenal repair leaks, a low-output end-duodenal fistula is much easier to manage than a high-output side fistula.

Pyloric exclusion begins with a generous longitudinal gastrotomy in the anterior wall of the antrum, close to the pylorus. The pylorus is grasped with two Babcock clamps, delivered through the gastrotomy and oversewn with size 0 PDS sutures. A side-to-side gastrojejunostomy with a short afferent limb is then constructed at the gastotomy site (Fig. 103.1). Some surgeons prefer to staple across the duodenum just distal to the pylorus, instead of suturing it from the inside. In most cases, the duodenum spontaneously opens several weeks later regardless of the method of closure; we prefer to use an absorbable synthetic suture.

The gastrojejunostomy is the source of most postoperative morbidity after a pyloric exclusion. This led Ginzburg and colleagues (1997) to attempt pyloric exclusion without gastrojejunostomy, relying on the spontaneous reopening of the sutured pylorus. Pyloric exclusion is, in theory, an ulcerogenic operation, but the incidence of marginal ulcers is unknown (Buck et al, 1992; Feliciano et al, 1987; Martin et al, 1983). Routine vagotomy or delayed takedown of the gastrojejunostomy is not indicated. Routine pyloric exclusion has recently been criticized

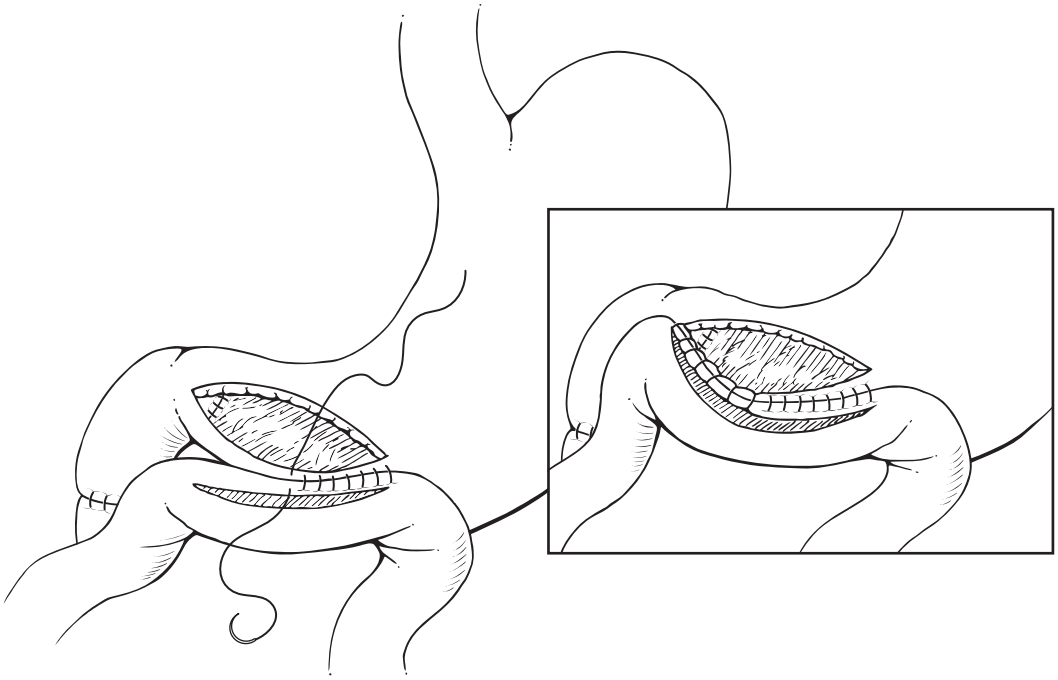


FIGURE 103.1. Pyloric exclusion showing occlusion of the duodenum just distal to the pylorus followed by a gastrojejunostomy.

because of reported increased complications and no effect on outcome (Seamon et al, 2007); however, in our practice, we continue to perform pyloric exclusion in patients with tenuous duodenal closures and in those with high-grade pancreatic injuries associated with a duodenal injury of any grade.

Occasionally, a high-grade injury to the PDC is encountered during a trauma laparotomy with massive blood loss unrelated to the PDC. In this situation, a rapid damage control solution is the only feasible alternative (see Chapter 102). The damage-control option for the injured nonbleeding pancreas is external drainage, regardless of the grade of injury. Similarly, the "bail-out" solution for duodenal injuries is either rapid closure with external drainage or placement of a large Malecot catheter through the hole affixed in place with a purse-string suture to create a controlled fistula.

MANAGEMENT OF A LEAKING DUODENAL REPAIR

A leak from the duodenal suture line after a PDC injury is unusual but can be devastating (Seamon et al, 2007). Leakage of bile from the drain in a Morison pouch, or any deviation from the patient's expected clinical trajectory, especially signs of unexplained sepsis, mean a duodenal leak until proven otherwise. A CT scan with contrast in the gastrointestinal tract will demonstrate the leak and establish whether it is controlled. If the leak is uncontrolled—that is, if free fluid is present in the peritoneal cavity—an urgent laparotomy is indicated to achieve source control and effective drainage. Such leaks can be difficult to manage, especially if the pylorus is open; the duodenum cannot be resected or exteriorized. Proximal diversion, if not done during the original procedure, is rarely an option; in addition, the inflamed duodenal wall does not hold sutures well. Inserting an appropriately sized Malecot tube into the hole, combined with wide regional drainage, is often the only feasible option. A creative variation of tube drainage is insertion of a spiral three-channel tube for continuous intraluminal irrigation (Parc et al, 1999). Although we have no personal experience with this method, it nevertheless underscores the technical difficulty of controlling a duodenal leak.

Late discovery of a duodenal leak in a septic patient is an indication for open-abdomen management with planned reoperations for peritoneal toilet to optimize drainage; this is not the time for complex duodenal reconstructions. If the leak is discovered early, pyloric exclusion may perhaps still be feasible, but in most cases, it is a hazardous undertaking in the inflamed peritoneal cavity of a septic patient.

If the CT scan demonstrates a leak but not collection or free fluid in the peritoneum, the leak is controlled. The appropriate conservative approach in this situation hinges on early and aggressive nutritional support while awaiting spontaneous closure. If a pyloric exclusion was done, fluid management of the low-output fistula is usually straightforward. Most duodenal leaks close spontaneously; if the leak does not close, it is important to rule out distal obstruction. If the leak persists, but no distal obstruction is found, the approach is to wait at least 6 weeks or more and then perform a Roux-en-Y duodenojejunostomy to the fibrotic edges of the hole in the duodenum.

A complex PDC injury in the second portion of the duodenum resulting in destruction of the ampulla of Vater and/or the ductal systems draining both the biliary tree and the pancreas requires a pancreatoduodenectomy (PD). This situation is very rare—neither of us has encountered it in a hemodynamically stable patient. The technical details of a TW are discussed in the next section.

PANCREATODUODENAL INJURIES IN THE UNSTABLE PATIENT

Severe bleeding from the area around the PDC is seen either immediately upon entering the peritoneal cavity, or it begins suddenly, when a periduodenal hematoma is explored. In either

case, the surgeon must be prepared technically and mentally to deal with a major vascular injury, often more than one.

The first step is temporary packing of the bleeding area, until the rest of the peritoneal cavity is explored; however, each time the packs are removed, the operative field is immediately immersed in blood, which precludes accurate visualization of the injuries. The complex multilayered vascular anatomy around the PDC does not allow simple proximal and distal control of the injured vessels. The solution is to encircle the injured area with a ring of tightly rolled laparotomy pads held on sponge-holding forceps and firmly pressed downward by assistants. This "compressive ring" of pads occludes the major veins around the PDC, giving the surgeon an opportunity to identify and repair the injured vessels.

Injuries to the retroduodenal inferior vena cava (IVC) are typically associated with trauma to the PDC and sometimes also to the right renal pedicle. The key to rapid exposure is a complete Kocher maneuver. Once the IVC is exposed, bleeding is controlled by compressing it above and below the bleeding site. The pararenal segment of the IVC is especially difficult to access and control. Two helpful maneuvers to improve access are application of assertive retraction to the liver in a cranial direction, using a deep Deaver retractor, and rapid mobilization of the right kidney. Simple lacerations of the IVC are repaired using a running monofilament suture. A hole in the posterior wall must occasionally be repaired from within the vessel by enlarging the hole on the anterior wall of a through-and-through injury.

It is important to remember that complex IVC injuries can be treated with ligation. Lacerations of the pararenal segment are especially difficult to repair, even if both renal veins are first isolated and controlled, because bleeding continues from lumbar veins, and ligation of the pararenal IVC means loss of at least the right kidney. Unfortunately, in the massively bleeding patient with several sources of hemorrhage, this may be the only realistic option to save the patient's life. Injuries to the renal hilum in the context of penetrating trauma to the PDC are best addressed by a rapid right nephrectomy. Rapid mobilization of the right kidney out of the Gerota fascia and medially also allows the surgeon to gain access to the lateral and posterior aspect of the pararenal IVC.

Exsanguinating hemorrhage into the lesser sac is most often due to an injury to the peripancreatic portal vein and is almost always associated with a penetrating injury to the neck of the pancreas. Effective circular compression as described above will dramatically reduce the bleeding, allowing the surgeon to perform a Kocher maneuver and widely open the lesser sac (Fig. 103.2).

One of the authors (A.H.) always performs a Cattell-Braasch maneuver in these situations to gain maximal exposure of the infrarenal retroperitoneum. Careful dissection along the inferior border of the mobilized duodenal loop is carried all the way to the point at which the SMV dives behind the pancreatic neck. The portal vein is then identified in the hepatoduodenal ligament along the upper border of the first portion of the duodenum. Bluntly developing the plane between the common bile duct and the portal vein from above allows the surgeon to pass a finger behind the pancreatic neck, divide it, and repair the portal vein directly from the front (Fig. 103.3). An early decision to transect the pancreas limits blood loss. A distal pancreatectomy is performed after the vascular repair, and the proximal stump is oversewn. In a damage-control situation, the SMV and the portal vein may be ligated (Sheldon, 1985); however, repair is preferable whenever possible, because massive bowel edema inevitably ensues that complicates fluid and wound management. The early fluid requirements during the first 24 hours after ligation of the SMV or portal vein can exceed 20 L. A second-look laparotomy is mandatory approximately 24 hours after the original operation to assess bowel viability.

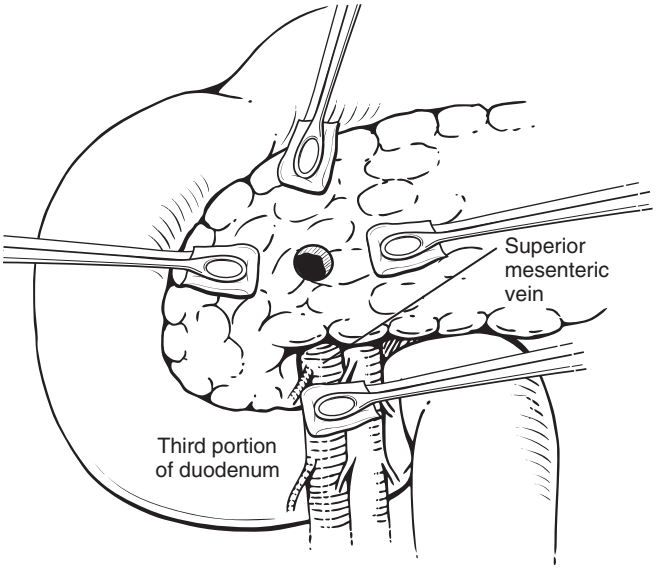


FIGURE 103.2. Sponge-stick control of bleeding from the portal vein. The white circles indicate areas of compression.

These vascular injuries usually occur in the context of multiple injuries to the PDC and adjacent structures. Damage-control solutions, rather than definitive repairs, are the rule in these situations, because the exsanguinating patient is racing toward a lethal physiologic insult. It is far better to stop the bleeding, close the holes in the bowel, and drain the entire area than to attempt a complex visceral reconstruction in an unstable, coagulopathic patient. Reconstruction of the anatomy can safely be done 36 to 48 hours after completion of resuscitation in the ICU.

Trauma Whipple

Complete disruption of the PDC, usually in association with major hemorrhage from the vena cava and/or portal vein, is the only indication for PD in trauma—the TW. A popular saying among trauma surgeons is that a PD is indicated only when the gunshot has done the dissection for you. The paradox of the TW is that the patients who need it are too unstable to tolerate it, and those who are stable enough to tolerate it probably do not need it (Hirshberg & Mattox, 2006). In the 1970s and 1980s, these operations were reported with enthusiasm and applauded as heroic achievements. Unfortunately, patients rarely survived the combined insults of the external injury and the operative trauma. In the era of damage-control surgery, the TW is viewed as a weapon of last resort that is very rarely indicated. In fact, one of the authors (W.S.), during a career in trauma surgery spanning some 30 years, has never found himself in a situation in which a TW was necessary.

On the very rare occasions when a TW seems like the only possible solution, it is important to keep in mind several key

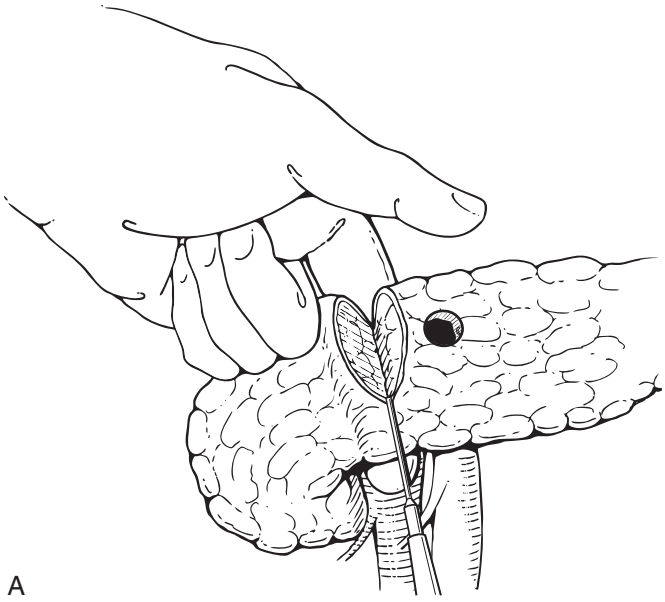


FIGURE 103.3. A, Division of pancreas to expose portal vein. **B,** Portal vein injury with distal pancreatectomy and splenic preservation.

technical differences from the elective oncologic operation. Most importantly, a TW should always be done as a staged procedure. Only resection and hemostasis are done during the original operation; reconstruction is performed 24 to 48 hours later on a stable, resuscitated patient.

During resection, early division of the stomach opens up the injured area behind it and facilitates access and exposure of the injuries. Preserving the gallbladder is important, because it is much safer to suture the bowel to the fundus of the gallbladder than to suture it to an edematous, friable, common bile duct of normal caliber; however, it is imperative to ensure that a low-entry cystic duct is not present and transected, thereby precluding decompression of the biliary tree with a cholecystoenterostomy. Time should not be wasted on meticulous dissection of the uncinate process off the SMV, because this is not an oncologic procedure. Instead, the uncinate process should be divided longitudinally parallel to the superior mesenteric vessels; its medial segment remains attached to the SMV and can be oversewn if necessary.

The staged reconstruction generally takes place in the inflamed and edematous peritoneal cavity of a patient who, albeit hemodynamically stable, is still critically ill with extensive third spacing and a massive systemic inflammatory response. If the bowel is edematous, and the peritoneal cavity is grossly inflamed, the distal pancreatic stump should be oversewn instead of creating a pancreatoenteric anastomosis. The soft, friable, edematous pancreas does not hold sutures well, and such a patient will not tolerate a leak.

CONCLUSION

Injuries to the pancreas and duodenum are uncommon. Most pancreatic injuries do not involve the pancreatic duct and can be managed by simple drainage. Ductal injuries to the body and tail of the pancreas should be treated by distal pancreatectomy. The emerging role of endoscopically placed stents in the treatment of pancreatic ductal injuries remains to be defined; however, isolated ductal injuries in the head of the pancreas are not an indication for a trauma Whipple, and these should be drained with or without ductal stenting.

Most injuries to the duodenum can be treated with simple closure. A preemptive pyloric exclusion should be considered in patients with PDC injuries at high-risk for a duodenal leak. Penetrating injuries to the medial wall of the second duodenum are best repaired from within the duodenum through an incision on the lateral duodenal wall. Complex injuries to the duodenum are best repaired with a Roux-en-Y duodenojejunostomy.

Major disruption of the PDC is very rare. Even a busy trauma surgeon can expect to see only a handful of these injuries in his or her career. In the overwhelming majority of cases, simple damage-control solutions are a much better option than heroic operations that involve long and elaborate resections; therefore, a TW should be considered only as a last, desperate resort.

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CHAPTER 104

Aneurysm and arteriovenous fistula of the liver and pancreatic vasculature

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OVERVIEW

Traumatic injuries to the hepatic pedicle generally occur in conjunction with injuries to the liver or pancreas. Hemorrhage or hematoma at the porta hepatis can be indicative of injury to the hepatic artery, portal vein, or both. In blunt trauma, injury is often secondary to compression or shearing forces and disruption at the points of maximal fixation, where the porta hepatis is relatively fixed to the retroperitoneum. An isolated pedicle injury may occur with penetrating trauma, which may involve intrahepatic or extrahepatic vessels with disruption of any structure in the trajectory; see Chapters 102 and 103 for further discussion on traumatic injuries.

Vascular control can be attempted using the Pringle maneuver (1908) or by clamping the porta hepatis; this controls arterial and portal vein hemorrhage from the liver. Continuing hemorrhage is due to retrograde bleeding from the vena cava or hepatic veins. Kocherization of the duodenum and head of the pancreas by dividing the peritoneum along the lateral border of the duodenum allows for better exposure (see Chapter 63A). This maneuver is especially useful for distal pedicle injuries or those to the retropancreatic portion of the portal vein.

In cases of severe injury, hepatic arterial ligation can be used in the operating room or with the aid of angiography; this should be considered if the patient has a noticeable decrease in bleeding after the Pringle maneuver is performed. Complete selective hepatic arterial ligation is used in approximately 1% of patients (David et al, 2000). Disruption of the right or left hepatic artery may be treated by ligation, providing the ipsilateral portal vein is intact. Simple lacerations of the common hepatic artery may be repaired primarily, but blind placement of sutures should be avoided because of the proximity of the common bile duct and potential for iatrogenic injury. With vascular injuries to the pedicle, common bile duct injury should be suspected, and a cholangiogram should be performed. If right or common hepatic artery ligation is performed, or if injury to the common bile duct is evident, a cholecystectomy should be performed.

Injuries to the portal vein are difficult to manage because of profuse bleeding and the relative inaccessibility of the portal vein owing to its posterior position in the porta hepatis. These injuries are associated with a 50% to 70% mortality rate and carry a high risk of other vascular injuries (Asensio et al, 2007; Buckman et al, 2001; Coimbra et al, 2004; Fraga et al, 2009; Pearl et al, 2004). Shock or systolic blood pressure below 90 mm Hg is a significant predictor of survival, and 90% of injuries to the portal vein are caused by penetrating trauma; the most common location of injury is within the hepatoduodenal ligament. The three classifications of portal vein injuries are *type A*, less than 50% of vein circumference is disrupted; *type B*, disruption is greater than 50%; *type C*, complete transection is evident (Coimbra et al, 2004).

Patients with portal vein injuries are often hemodynamically unstable at presentation and require emergent exploration. Immediate control of portal vein bleeding is by the Pringle maneuver, and visualization is obtained by kocherization of the duodenum, followed by mobilization of the hepatic flexure and medial reflection of the right colon. Division of the gastroduodenal artery provides further exposure. In certain cases, the pancreatic neck may be divided, and the lower common bile duct and pancreas are reflected to the right to facilitate exposure of the retropancreatic portal vein. In most cases of retropancreatic portal vein injury, it is typical to find associated pancreatic injury that requires repair or resection.

Primary venorrhaphy is the preferred approach for repair of portal vein injuries in the stable patient (Fraga et al, 2009; Pearl et al, 2004). The hemodynamic status of the patient generally determines the complexity of the repair. Other alternatives are end-to-end anastomosis, portocaval shunt, graft interpostition, vein patch graft, and portal vein ligation (Coimbra et al, 2004; Fraga et al, 2009; Pearl et al, 2004; Stone et al, 1982). Portal vein ligation can be performed only if the hepatic artery is intact, and it is an appropriate damage control option in an unstable and coagulopathic patient. Portal vein ligation has been reported with a 50% to 80% survival rate and low incidences of subsequent portal hypertension (Coimbra et al, 2004; Stone et al, 1982). Following ligation of the portal vein or superior mesenteric vein (SMV), bowel will become edematous with areas of ischemia. Most surgeons would recommend temporary abdominal closure followed by a second-look laparotomy in 48 to 72 hours. Injury to both the hepatic artery and portal vein are rare and technically difficult to manage, and at least one of these structures must be repaired to avoid hepatic necrosis.

SMV injuries are uncommon but devastating; this is due to the difficulty in obtaining exposure and getting control of hemorrhage quickly. Primary venorrhaphy is the preferred repair, when such is possible; although ligation of the SMV has been performed with variable success, it should be reserved for use in the hemodynamically unstable patient (Asensio et al, 2000, 2007). It should also be noted that superior mesenteric venous injuries are often associated with portal vein and other vascular injuries (Asensio et al, 2007).

HEPATIC ARTERY ANEURYSMS AND PSEUDOANERYSMS

Visceral artery aneurysms are rare, with an average incidence of approximately 0.1% to 2% (Hossain et al, 2001; Panayiotopoulos et al, 1996). Splenic artery aneurysms account for approximately 60% of all visceral aneurysms, followed by hepatic artery aneurysms, which constitute 20% (Abbas et al, 2003). Hepatic artery aneurysms were initially described by Wilson in 1809 (O'Connor et al, 1995). The first successful surgical repair was performed by Kehr in 1903, in which he ligated the feeding vessel proximal to the hepatic artery (Carr et al, 1996; Guida & Moore, 1966). Within the past 2 decades, endovascular therapy has been utilized with increasing frequency, and O'Connor and colleagues reported successful endovascular stent exclusion of a hepatic artery aneurysm in 1995.

Hepatic artery aneurysms are more common in men, with a 2:1 prevalence (Abbas et al, 2003; Panayiotopoulos et al, 1996). The mean age of presentation is generally around 60 years of age, but hepatic artery aneurysms have been reported in all age groups (Abbas et al, 2003). The etiology of nontraumatic hepatic artery aneurysms remains unclear. True aneurysms undergo dilation and thinning of the vessel wall, although the blood is still contained within the vessel wall (Ikeda et al, 2008). A common histopathologic feature is medial degeneration of the arterial wall, which may be congenital but is further stressed by various factors (Abbas et al, 2003; Panayiotopoulos et al, 1996). Atherosclerosis is present in approximately 30% of aneurysms, but it is debatable whether it is a causative event or a secondary phenomenon (Messina & Shanley, 1997).

Several other conditions have been associated with hepatic artery aneurysms; these include arterial fibrodysplasia, vasculitis, polyarteritis nodosa, systemic lupus erythematous, tuberculosis, Marfan syndrome, Ehler-Danlos syndrome, arteritis, and hyperflow conditions (Abbas et al, 2003; Ikeda et al, 2008; Panayiotopoulos et al, 1996; Messina & Shanley, 1997). In the early twentieth century, most true hepatic artery aneurysms were mycotic, with bacterial endocarditis being the most common cause. With the advent of antibiotics, this form is generally only found in intravenous drug users (Shanley et al, 1996a).

Approximately 50% of all hepatic artery aneurysms are false aneurysms, or *pseudoaneurysms,* caused by a ruptured arterial wall with subsequent periarterial hematoma formation. These are generally the result of trauma, iatrogenic injury, inflammation, or infection (Carr et al, 1996; Guida & Moore, 1966). Pseudoaneurysms that result from iatrogenic injury to the hepatic arterial system are usually secondary to biliary, hepatic, or pancreatic interventions and to the laparoscopic or open treatment of abdominal and retroperitoneal pathologies (Bulut et al, 2002; Duce et al, 2002; Grego et al, 2003; Ikeda et al, 2008; Larson et al, 2002; Tessier et al, 2003; Tulsyan et al, 2007; see Chapters 28, 33, 34, and 54). Aneurysms resulting from laparoscopic cholecystectomy frequently affect the right hepatic artery but may be confined to the cystic artery remnant (Tessier et al, 2003). Pancreatitis and other inflammatory diseases can damage the arterial wall and lead to pseudoaneurysm formation (Mallick & Winslet, 2004). Additionally, hepatic artery pseudoaneurysm after resection of a hilar cholangiocarcinoma has been reported (Briceno et al, 2008).

Most hepatic artery aneurysms are solitary (80%), either saccular or fusiform, with a maximum diameter ranging from 1 to 14.5 cm (Abbas et al, 2003; Shanley et al, 1996). Other concomitant visceral artery aneurysms are present 31% of the time, and nonvisceral artery aneurysms are evident in 42% (Abbas et al, 2003). The majority, 66% to 80%, occur extrahepatically; however, the incidence of intrahepatic aneurysms may be increasing, compared with extrahepatic aneurysms (Abbas et al, 2003; Messina & Shanley, 1997). This change in presentation is likely the result of increasing use of percutaneous and laparoscopic interventions and also of improved imaging modalities utilized in the trauma setting (Kasirajan et al, 2001).

In one review of reported cases from 1985 to 1995, the right hepatic artery was found to be most commonly affected (47%), followed by the common hepatic artery (22%), the proper hepatic artery (16%), the left hepatic artery (13%), and rarely the cystic artery (1%) (Shanley et al, 1996). The natural history of these lesions is that of progressive growth, and it is probable that increasing size is accompanied by an increasing rate of rupture, in spite of a paucity of supporting evidence (Abbas et al, 2003). Nonatherosclerotic aneurysms carry a higher risk of rupture than atherosclerotic aneurysms (Abbas et al, 2003).

The lifetime risk of rupture for hepatic artery aneurysm ranges from 14% to 80% (Abbas et al, 2003; Carr et al, 2001; Dolapci et al, 2003; Ikeda et al, 2008; Lagana et al, 2006; Panayiotopoulos et al, 1996), and the mortality rate for ruptured hepatic artery aneurysms is 3% to 40% (Abbas et al, 2003; Ikeda et al, 2008; Panayiotopoulos et al, 1996; Shanley et al, 1996; Tessier et al, 2003). Rupture can occur into the peritoneal cavity (43%), biliary tree (41%), gastrointestinal (GI) tract (11%), or portal vein (5%) (Carr et al, 2001). Abdominal pain is often present, usually in the epigastrium with radiation to the back or right shoulder. Approximately 60% of patients with rupture come to medical attention in hypovolemic shock.

In 1871, Quincke described jaundice, hemobilia (see Chapter 105), and biliary colic in a patient with a hepatic artery aneurysm. These symptoms have become known as the *classic triad,* but in actuality, they are present in fewer than 40% of cases (Messina & Shanley, 1997). These symptoms are caused by erosion into the biliary tree, which causes intraductal clot or external compression of the bile duct (Messina & Shanley, 1997); rupture into the bile duct causes hemobilia. Occasionally, with a large hepatic artery aneurysm, a mass may be palpated in the upper abdomen, often with an associated bruit or thrill; however, pulsatile masses and bruits are uncommon in intact aneurysms. Expanding aneurysms can cause upper abdominal discomfort with pain radiating into the back, and pseudoaneurysms that result from placement of transhepatic biliary drainage catheters often manifest with a sentinel hemorrhage and blood in the collection bag.

With recent advances in cross-sectional imaging and arteriography, true hepatic artery aneurysms are being detected earlier in their course. Asymptomatic aneurysms (30% to 60%) may be discovered incidentally during radiologic investigation performed for other indications (O'Connor et al, 1995; Panayiotopoulos et al, 1996; Tulsyan et al, 2007). On plain radiographs, a hepatic artery aneurysm may appear as an eggshell-like calcification in the right upper quadrant (O'Driscoll et al, 1999). If this diagnosis is suspected, further investigation with contrast-enhanced computed tomography (CT) scan or magnetic resonance angiography is warranted to delineate the extent of the lesion and define its relationship to surrounding structures. Angiography (see Chapter 19) can be used to characterize hepatic artery blood flow

prior to operative treatment (Messina & Shanley, 1997), but ultrasound is rarely used to diagnose hepatic artery aneurysms. A hepatic artery aneurysm may be discovered during abdominal surgery for another indication and will appear as a calcified nodule on the hepatoduodenal ligament.

Improvements in the quality and availability of cross-sectional imaging (see Chapters 16 and 17) have led to an increasing number of aneurysms being detected prior to rupture. Although it is unclear whether the actual incidence of true hepatic artery aneurysms is increasing, incidental discovery during imaging performed for unrelated reasons has increased. For example, the routine use of CT scan in trauma patients has led to increased detection of false aneurysms of the intrahepatic arterial branches (Messina & Shanley, 1997). Also, the increased use of diagnostic and therapeutic biliary interventions have contributed to the increasing incidence of false aneurysms (Messina & Shanley, 1997).

Recent studies demonstrate that a selective approach can be used to manage asymptomatic hepatic artery aneurysms. Currently, no consensus exists regarding size criteria for intervention, but many advocate that small (<2 cm) lesions can be safely observed (Abbas et al, 2003; Ikeda et al, 2008); however, surgical repair, ligation, or embolization should be considered for aneurysms larger than 2 cm in a patient who is a reasonable operative risk with a life expectancy greater than 2 years. In patients with marginal or poor health and aneurysms that measure 2 to 5 cm, careful observation may be warranted (Abbas et al, 2003). The presence of multiple aneurysms is a risk factor for rupture and warrants intervention. Likewise, it is generally recommended that all pseudoaneurysms should be treated, given the high risk of rupture that they pose.

Although some centers allow for a degree of permissive hypotension, the management of ruptured hepatic artery aneurysms consists of volume resuscitation and correction of coagulopathy followed by definitive treatment involving surgical repair, embolization, occlusion, or endovascular stenting (Carr et al, 2001). Occasionally, angiographic intervention may be used as an adjunct prior to repair. In the elective setting, the choice of open surgical repair versus endovascular treatment depends on many factors, including the size and anatomy of the aneurysm, the shape of the sac and its accessibility to endovascular device placement or embolization, the need to restore arterial continuity, and the general health of the patient. A past failure of endovascular intervention does not necessarily preclude further attempts.

Open repair of hepatic artery aneurysms depends on the anatomy and location of the aneurysm, collateral blood flow, operative risk, and clinical status. In the elective setting, the anatomy of the aneurysm, delineation of arterial circulation, and identification of collateral vessels in the port hepatic are ideally determined preoperatively by angiography. In general, aneurysms of the common hepatic artery may be ligated, with or without resection of the aneurysm sac, as long as the portal vein is patent. Reconstruction is usually unnecessary secondary to collateral circulation via the gastroduodenal and right gastric arteries. Failure to confirm adequate collateral vessel circulation can lead to hepatic necrosis (Rokke et al, 1997).

If the patient has underlying hepatic parenchymal disease or is in a state of hemorrhagic shock, reconstruction is recommended, because the liver will be more sensitive to ischemia (Messina & Shanley, 1997; Shanley et al, 1996). Arterial reconstruction is recommended for aneurysms of the proper hepatic artery and its extrahepatic branches, because ligation may interfere with collateral circulation and may induce ischemic necrosis. Autogenous vein grafts, synthetic grafts, aneurysmorraphy with vein patch closure, and aortohepatic bypass have been utilized to restore blood flow. Aortohepatic bypass with saphenous vein or polytetrafluoroethylene (PTFE) graft that originates at the supraceliac aorta is generally preferred when bypass is required.

Intrahepatic aneurysms usually require ligation of the branch hepatic arteries and may require liver resection. Simple ligation of proximal vessels can help control bleeding intrahepatic aneurysms and may be a safer alternative to resection in critically ill patients, despite the risk of necrosis. In all hepatic aneurysms, vascular control can be gained from within the aneurysm, if surrounding inflammation prevents adequate exposure and dissection of adjacent arteries (Messina & Shanley, 1997). Complications after surgical repair are generally related to ischemic necrosis of the liver, abscess formation, and sepsis (Abbas et al, 2003).

Endovascular management of hepatic artery aneurysms has become increasingly popular over the past decade and is particularly useful for treating pseudoaneurysms that arise from iatrogenic injuries (Figs. 104.1 and 104.2). These procedures offer an alternative to conventional open surgical intervention with the benefit of lower morbidity and mortality (Ikeda et al, 2008; Larson et al, 2002; Saltzberg et al, 2005; Tulsyan et al, 2007). Recent studies found rates of technical success from 75% to 98% (Kasirajan et al, 2001; Mallick & Winslet, 2004; Sachdev et al, 2006).

Various minimally invasive techniques are available to treat aneurysms and pseudoaneurysms. Selective catheterization of the involved vessel and embolization with coils or polymerizing agents has been used for ablation of hepatic artery aneurysms, and percutaneous embolization is being used with increasing frequency in cases of emergent aneurysm rupture (Tulsyan et al, 2007). Endovascular stent grafts allow for preservation of end-organ flow and exclusion of the aneurysm. The arterial anatomy and the location of the aneurysm have a significant impact on the technical ability to place a stent graft (Larson et al, 2002); sufficient normal caliber artery must be available on either side of the aneurysm to allow for a proper stent graft seal and aneurysm exclusion, although further studies are needed to elucidate the long-term durability of stents.

The tortuosity and redundancy of the visceral vessels can increase the difficulty of endovascular interventions. Migration of embolic material and stent graft occlusion are recognized complications of transcatheter treatment. Additional complications include endoleak, failure to completely occlude the aneurysm, hepatic ischemia, and recanalization (Abbas et al, 2003; Kasirajan et al, 2001).

HEPATIC ARTERIOVENOUS FISTULAE AND SHUNTS

Congenital Hepatic Vascular Shunts

The vascular system begins to form during the third week of gestation as a network of interlacing blood spaces in primitive mesenchyme. The system gradually develops by processes of vascular coalescence and cellular differentiation that culminates in separate arterial and venous conduits. Congenital intrahepatic shunts are very rare anomalies characterized by abnormal

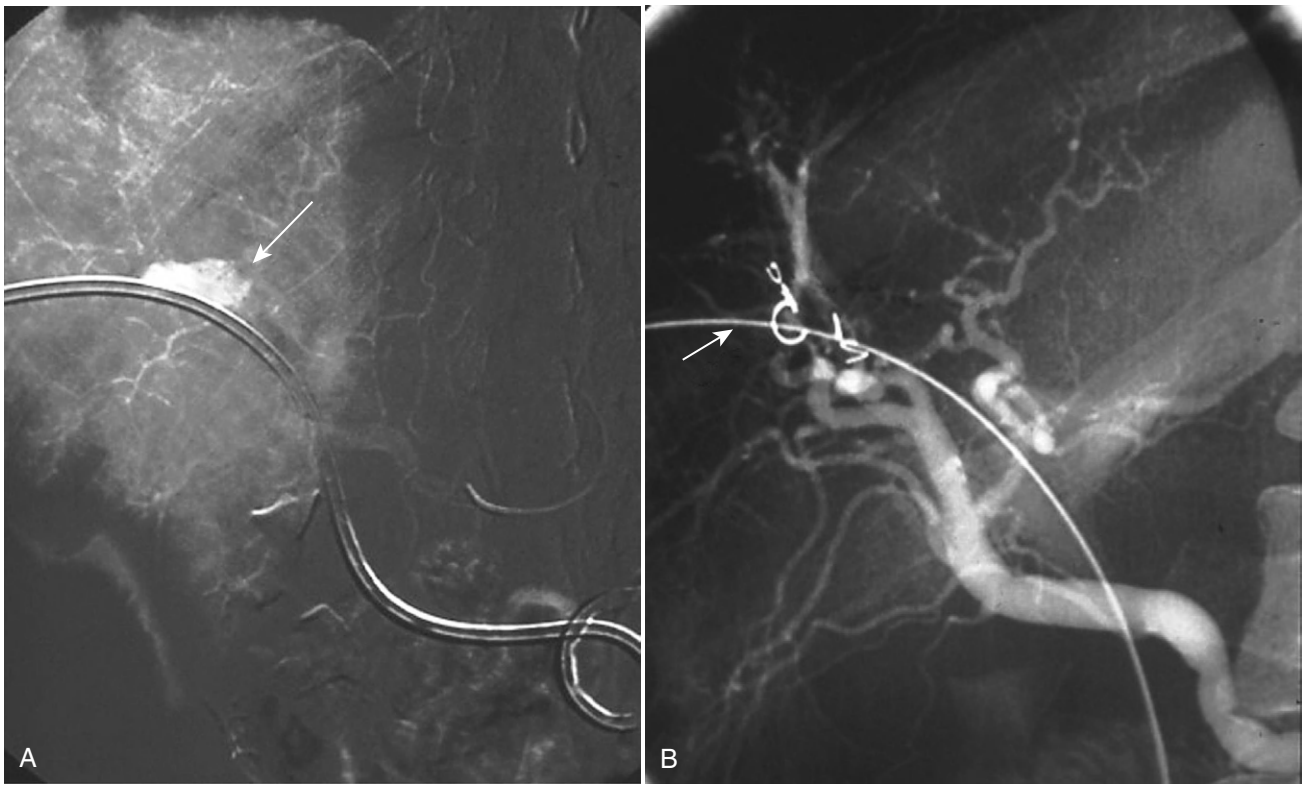


FIGURE 104.1. Hepatic pseudoaneurysm. **A,** After percutaneous biliary stent insertion (*arrow*). **B,** Managed by embolization (*arrow*).

communication between the hepatic arterial system, portal veins, hepatic veins, or systemic veins as a result of disordered embryologic development around the fifth gestational week. Normal development of the hepatic vascular system commences with anastomosis of the paired vitelline veins, as they enter the *septum transversum* and intersperse with rapidly proliferating hepatocytes. The left vitelline vein involutes, and the blood is redistributed to the right vitelline vein, which enlarges and forms the terminal inferior vena cava, hepatic veins, and portal vein.

The paired umbilical veins bring oxygenated blood to the embryo and course on either side of the liver. When they contact the hepatic sinusoids, the right umbilical vein and portions of the left umbilical vein become obliterated; the persistent left umbilical vein carries blood from the placenta to the fetus. A large channel, the *ductus venosus,* connects the left umbilical

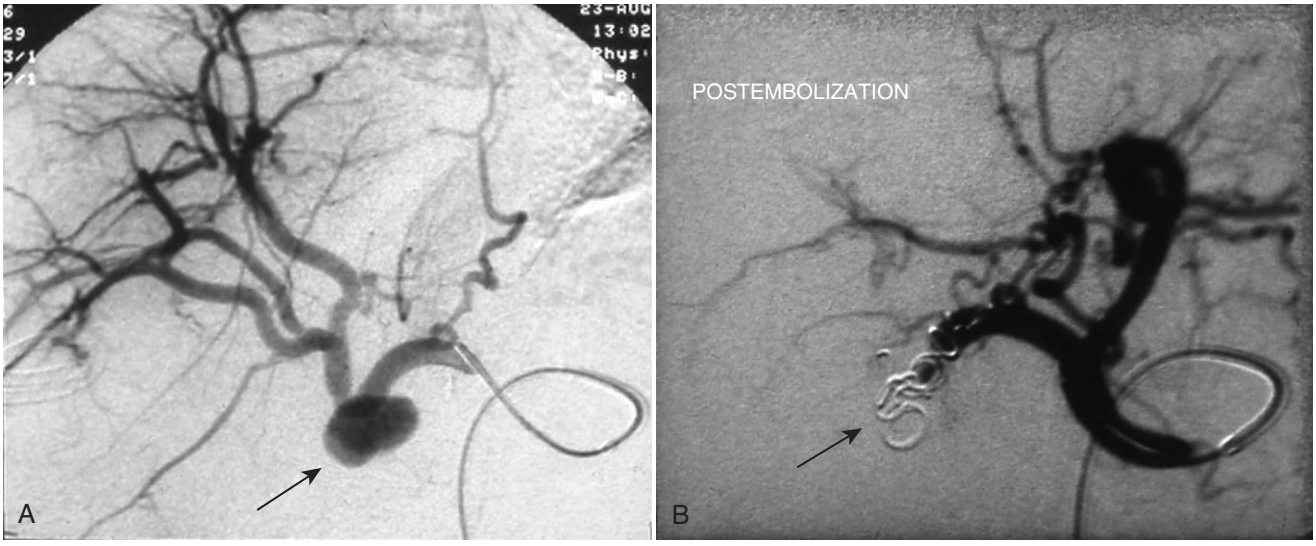


FIGURE 104.2. Pseudoaneurysm of hepatic pseudoaneurysm. **A,** Artery after laproscopic cholecystectomy (*arrow*). **B,** Managed by embolization (*arrow*).

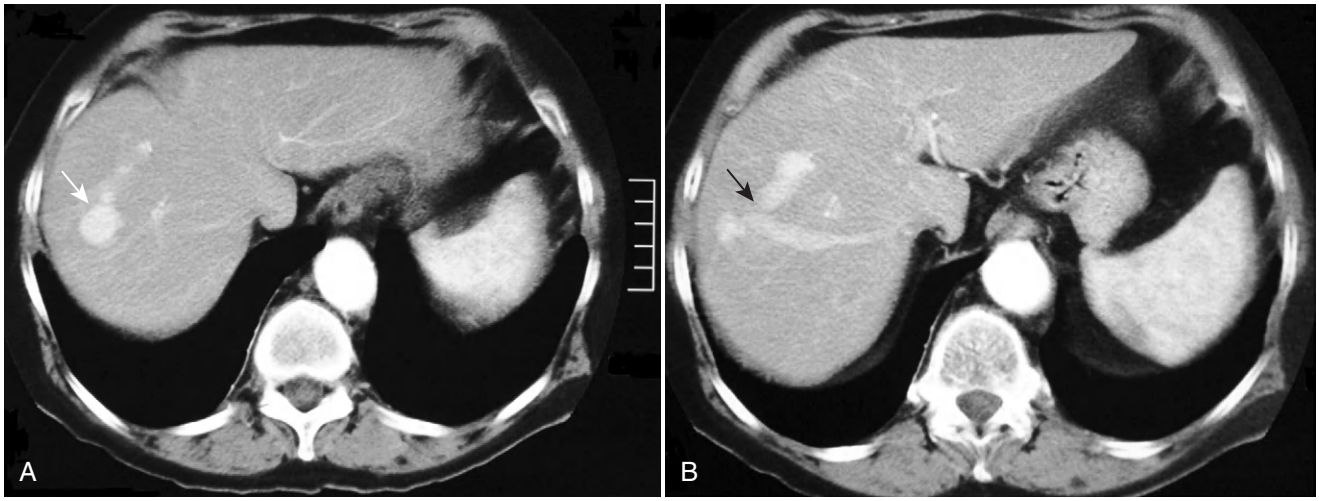


FIGURE 104.3. **A,** Contrast-enhanced computed tomography scan shows an aneurysmal fistula (*arrow*). **B,** Fistula between the right portal vein and right hepatic vein (*arrow*).

vein to the inferior vena cava to allow oxygenated blood to bypass sinusoid circulation (Gallego et al, 2004). Any deviation from the normal vascular system's embryologic development can lead to abnormal fistulae and shunting (Fig. 104.3).

HEMANGIOMAS

Some congenital hepatic neoplasms can cause vascular shunting; these include hemangiomas, hepatoblastomas, angiosarcomas, hamartomas, and metastatic neuroblastomas (Burrows et al, 2001; Gallego et al, 2004; Ingram et al, 2000). Infantile hemangiomas are a group of benign vascular tumors with a high rate of endothelial cell proliferation that results in a large mass and dilation of vascular channels, which are often accompanied by arteriovenous (AV) shunting. Following rapid growth, these tumors typically undergo a period of involution and increasing fibrosis (Boon et al, 1996). They are more common in females and may be solitary or multiple. Many small, asymptomatic hemangiomas remain undetected or are discovered on imaging indicated for another reason. Symptomatic presentation may include high-output congestive heart failure, hepatomegaly, anemia, thrombocytopenia, respiratory distress, hemorrhage, jaundice, and hypothyroidism secondary to overproduction of type III iodothyronine deiodinase (Boon et al, 1996; Burrows et al, 2001; Christison-Lagay et al, 2007; Ho et al, 2005; Huang et al, 2000; Konrad et al, 2003; Prokurat et al, 2002; see also Kasabach-Merritt syndromein Chapter 80A). Association with cutaneous hemangiomas and hemangiomatosis of the central nervous system, GI tract, and respiratory tract have been observed (Christison-Lagay et al, 2007). All patients with significant multifocal or diffuse disease should be screened with thyroid function tests and echocardiogram (Dickie et al, 2009).

Magnetic resonance imaging (MRI) is the diagnostic modality of choice for hemangiomas; lesions appear as hypointense relative to liver on T1-weighted images and hyperintense on T2-weighted images (Christison-Lagay et al, 2007; Gallego et al, 2004; see Chapters 17 and 79A). A gadolinium sequence typically demonstrates centripetal enhancement, and multiple flow voids can be present adjacent to or within the lesions (Gallego et al, 2004; Fig. 104.4). Selective arteriography can be used to determine the extent of the lesion and to evaluate the large vessels feeding the tumor, but this is rarely necessary (Stocker, 2001).

Hepatic hemangiomas should be individually assessed based on initial presentation, size, and disease progression (Dickie et al, 2009). Asymptomatic patients without evidence of cardiac failure or significant shunting can be monitored with ultrasonography to assess for change (Christison-Lagay et al, 2007; Isaacs, 2007), and solitary tumors can often be successfully treated by resection (von Schweinitz, 2003). Large, multiple, and diffuse lesions are associated with significant morbidity and mortality; for these, treatment options include medical management, surgery, embolization, radiation, or transplantation (Dickie et al, 2009).

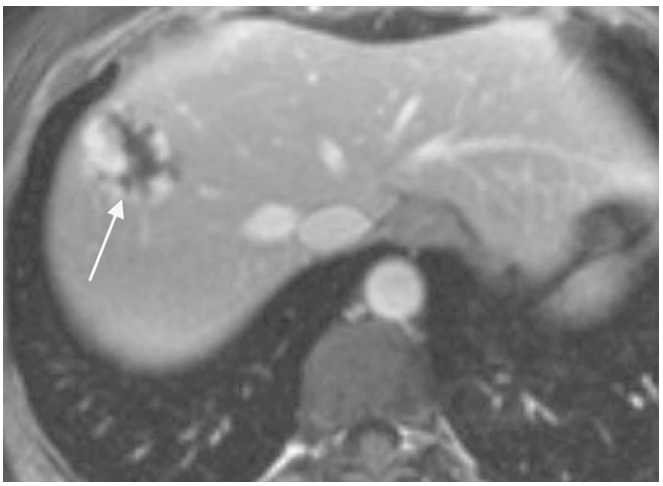


FIGURE 104.4. Axial portal venous phase of contrast-enhanced T1-weighted magnetic resonance imaging shows a hepatic hemangioma with the typical findings of early peripheral nodular enhancement and progressive centripetal filling. *(From Elsayes KM, et al, 2005: Focal hepatic lesions: diagnostic value of enhancement pattern approach with contrast-enhanced 3D gradient-echo MR imaging. Radiographics 25:1299-1320.)*

The mortality of large multiple hemangiomas treated with supportive observation has been reported to range from 30% to 80% (Boon et al, 1996; Gallego et al, 2004;). Patients with significant shunting are initially treated with corticosteroids or interferon (IFN)-α with close observation by ultrasonography for spontaneous regression (Deb et al, 2002; von Schweinitz, 2003). Pharmacotherapy failure is an indication for angiographic embolization, but the presence of multiple collaterals can make embolization difficult. When embolizing tumors with a large portal venous component, the portal vein should be done prior to the hepatic arterial component to prevent hepatic necrosis (Burrows et al, 2001). In patients with large hemodynamically significant shunts and cardiac failure, consider early angiographic intervention or ligation. Embolization can be used for interim control of congestive heart failure during pharmacotherapy or prior to operative intervention. Patients with diffuse intrahepatic hemangiomas often respond poorly to pharmacotherapy or other interventions and may require transplantation (see Chapter 97A; Christison-Lagay et al, 2007).

HEPATIC ARTERIOVENOUS MALFORMATIONS

True congenital arteriovenous malformations (AVMs) are malformations of the vascular channels and are classified by the predominant endothelium lining the channel and also by flow characteristics (Lima et al, 2005). Blood is shunted through direct arteriovenous connections that have no growth potential and that do not regress spontaneously. They are generally localized to one lobe of the liver (Boon et al, 1996; Gallego et al, 2004; Prokurat et al, 2002) and are usually present in neonates with congestive heart failure, portal hypertension, hepatomegaly, and anemia (Boon et al, 1996). Cardiac failure is noted in 50% to 60% of affected newborns with an associated 50% to 90% mortality rate (Boon et al, 1996; Luks et al, 1991). AVMs can also come to medical attention in late childhood in the clinical setting of hereditary telangiectasia with heart failure, portal hypertension, and hepatic ischemia (Boon et al, 1996; Burrows et al, 2001).

Duplex ultrasound (see Chapter 13) may show a nest of tortuous, dilated vessels with increased venous pulsatility and high peak Doppler shifts in both arteries and veins (Gallego et al, 2004). Contrast-enhanced CT scan shows homogeneous enhancement in the arterial or early portal venous phase with rapid washout of contrast material. MRI shows intrahepatic AVMs as large flow voids and localized masses that are hyperintense on T1-weighted images (Boon et al, 1996). MRI is a useful tool for differentiating AVMs from infantile hemangiomas, because AVMs will show an absence of delayed uptake of contrast material around the hypertrophic vessels (Gallego et al, 2004). Arteriography shows anomalous blood supply and arteriovenous shunting within the vasculature and can help delineate anatomy and resectability criteria.

Many different therapies have been used in the treatment of hemangiomas, including corticosteroids, radiotherapy, embolization, hepatic artery ligation, and hepatic lobectomy (Boon et al, 1996; Gallego et al, 2004; Lima et al, 2005). Superselective catheterization and embolization (see Chapter 28) with total occlusion of the feeding arteries close to the AVM must be achieved for effective treatment (Lima et al, 2005). Some studies advocate embolization with subsequent hepatic resection (Boon et al, 1996), but complications include incomplete occlusion, rapid development of collateral vessels, and necrosis. Liver transplantation is indicated for very large or diffuse lesions.

CONGENITAL ARTERIOPORTAL FISTULAE

Arterioportal fistulae are characterized by anomalous communication between the arteries and the portal venous system. Congenital arterioportal fistulae are discovered during infancy by portal hypertension, as compared with congestive heart failure with AVMs. Rarely, these fistulae are associated with hereditary telangiectasia, Ehler-Danlos syndrome, and biliary atresia (Burrows et al, 2001; Gallego et al, 2004). Age of presentation varies, but infants with congenital arterioportal fistulae generally come to medical attention within the first year of life. Hepatofugal flow in the portal vein causes arterialization of the portal vein and resultant portal hypertension, which can cause subsequent splenomegaly, gastroesophageal varices, ascites, diarrhea, and intestinal malabsorption (Gallego et al, 2004).

Doppler ultrasound shows arterialization of the portal vein, turbulent flow at the site of the fistula, increased peak velocities, and heterogeneous hepatic parenchyma secondary to vibration artifact (Gallego et al, 2004; Marrone et al, 2006). An enlarged hepatic artery and dilated portal vein segment at the fistula site may also be visible (Gallego et al, 2004). Contrast enhancement of the portal vein on arterial phase images and perfusion anomalies of adjacent hepatic parenchyma are demonstrated by CT scan and MRI (Fig. 104.5; Gallego et al, 2002).

Arteriography with embolization is the preferred therapeutic option, and it should be performed soon after diagnosis to minimize hepatoportal sclerosis and portal radicle fibrosis secondary to progressive portal hypertension (Altuntas et al, 1998). If angiography is unsuccessful, surgical ligation of the arterial feeding vessels may be performed with or without liver resection. Resection of the fistula proper is not necessarily required, although fistulae may recur through arterial collateralization, and patients must be followed closely after intervention. In infants with biliary atresia, liver viability usually depends on arterial inflow, and embolization may precipitate liver ischemia. Liver transplantation is preferred in this subset of patients (Choi et al, 2002).

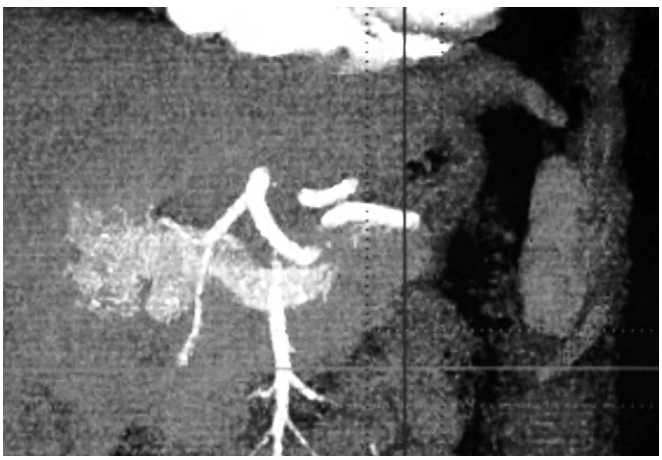


FIGURE 104.5. Multislice computed tomographic scan with intravenous contrast administration shows arterioportal fistula with retrograde filling of the portal vein.

ACQUIRED ARTERIOPORTAL FISTULAE

The most common causes of acquired arterioportal fistulae are cirrhosis, trauma, iatrogenic trauma stemming from hepatic or biliary intervention, hepatic neoplasms, inflammation, and gastrectomy (Gallego et al, 2004; Marrone et al, 2006; Tomczak et al, 1997). Acquired arterioportal fistulae often present with bleeding from an upper GI source secondary to mucosal congestion, and upper endoscopy shows friable and edematous mucosa. The diagnosis is often missed because patients generally enter a quiescent phase, as collateral circulation forms over the next 6 months to 5 years. As with congenital fistulae, portal hypertension develops and causes GI bleeding and varix formation, splenomegaly, ascites, and intestinal dysfunction (see Chapters 70A and 71; Blumgart & Fong, 2000).

When blood flow through the portal vein is decreased, the hepatic arterial flow increases, causing an arterioportal shunt through multiple anatomic routes (Choi et al, 2002; Park et al, 1990). In localized portal vein obstruction—such as from tumor thrombus or external compression—blood flows from the hepatic artery through the communicating *vaso vasorum* into distal unobstructed portal vein. In hypervascular tumors, arterial blood may flow directly through the tumor into the portal vein. In patients with increased hepatic vein resistance secondary to Budd-Chiari syndrome or cirrhosis, arterial blood fills the portal vein by retrograde flow through the sinusoids (see Fig. 104.5). In cases of complete obstruction of the portal vein, a peribiliary vascular plexus develops along the intrahepatic and extrahepatic biliary tree.

Contrast enhancement of the portal vein on arterial phase images and perfusion anomalies of adjacent hepatic parenchyma are demonstrated by CT scan and MRI (Gallego et al, 2002). As with congenital arterioportal shunts, treatment options include embolization, surgical correction, and transplantation. Fistulae may recur through arterial collateralization, and patients need to be followed closely after intervention.

PORTOSYSTEMIC VENOUS SHUNTS

Portosystemic shunts can be intrahepatic or extrahepatic; congenital shunts are the apparent result of disruption of the complex embryologic process of vitelline, umbilical, and hepatoportal venous involution. In 1793, Abernethy first reported an extrahepatic portosystemic shunt. Two types of extrahepatic portosystemic shunts are found: in *type I,* the portal vein is congenitally absent, and portal blood flow is completely diverted into the vena cava; in *type II,* a side-to-side extrahepatic communication exists between the vena cava and portal vein, through which some of the portal flow is diverted to the vena cava (Gallego et al, 2004). These shunts have been observed alone or in combination with other congenital malformations, including biliary atresia (see Chapter 40), genitourinary malformations, mental retardation, and as a part of Goldenhar syndrome (Gallego et al, 2004). Hepatic tumors may also be associated with systemic diversion of portal blood flow.

Congenital intrahepatic portosystemic shunts are abnormal connections between branches of the portal vein and hepatic veins thought to be due to persistent communication between the vitelline veins of the omphalomesenteric system and the *sinus venosus* (Lane et al, 2000). Infantile hepatic hemangiomas and cutaneous hemangiomas have been associated with these shunts (Gitzelmann et al, 1997). Intrahepatic shunts are classified into four types: 1) a single, large tube that connects the right portal vein to the inferior vena cava, 2) one or more communications present in a single hepatic segment, 3) portosystemic shunt through an aneurysm, and 4) multiple communications between portal and hepatic veins (Park et al, 1990).

Doppler ultrasound may demonstrate abnormal communicating structures between the portal venous branches and hepatic veins and may also reveal an absence of portal vein at the liver hilum. A pulsatile triphasic or biphasic spectral pattern in the portal or splenic veins suggests the presence of a portosystemic shunt (Gallego et al, 2004), the ratio of which can be determined by portal scintigraphy using iodine 123 iodoamphetamine. The isotope is administered rectally, is absorbed into the inferior mesenteric vein, and travels to the liver. When a shunt is present, the isotope can be detected in the liver and lungs simultaneously, and the ratio is determined by dividing the lung counts by the liver counts (Gallego et al, 2004).

Portosystemic venous shunting causes elevated levels of galactose, bile acid, glucose, and ammonia (Gallego et al, 2004). The clinical manifestations may include cataract formation (hypergalactosemia), encephalopathy, liver dysfunction secondary to lack of hepatocyte nutrition, and GI dysfunction. Adults are more susceptible to hepatic encephalopathy than young children. Reduced portal inflow causes liver dysfunction, fatty degeneration, and atrophy as a result of lack of nutrition, but liver function can be improved with restoration of portal blood flow.

Intrahepatic shunts generally close within the first 2 years of life, thus observation is sufficient in asymptomatic infants. With mild metabolic abnormalities, a protein-free diet supplemented with branched-chain amino acids, and lactulose is recommended. In all patients, shunt ratios greater than 60% require correction by embolization or surgical interruption (Gallego et al, 2004). If these interventions fail, hepatic transplantation is often necessary.

AQUIRED HEPATIC VASCULAR FISTULAE

Hepatic neoplasms, cirrhosis, and trauma are the most common causes of acquired fistulae of the hepatic vasculature. Additionally, iatrogenic injury from procedures such as endoscopic retrograde cholangiopancreatography (ERCP), liver biopsy, and chemoembolization and hepatic, biliary, or gastric surgery can precipitate fistula formation.

GASTRODUODENAL AND PANCREATODUODENAL ARTERY ANEURYSMS

Since 1895, when Ferguson first described a superior pancreatoduodenal artery (PDA) aneurysm, few studies have addressed the management and natural history of these lesions (Moore et al, 2004). True aneurysms of the PDA and the gastroduodenal artery (GDA) are rare and account for 2% and 1.5% of all splanchnic artery aneurysms, respectively (Shanley et al, 1996). Pseudoaneurysms are more common and are generally seen in the setting of inflammation, specifically pancreatitis (see Chapter 54). It is important to distinguish between true and false aneurysms, because the implications for diagnosis and management will be different.

A review of all reported PDA and GDA aneurysms between the years 1946 and 2001 identified approximately 146 cases

(Moore et al, 2004). The mean age at presentation was 58 years (range, 20 to 72 years), with an equal distribution across ethnic groups and an equal male/female gender distribution; however, past studies have demonstrated a male predominance, which might be explained by a lack of distinction between true and false aneurysms (Moore et al, 2004; Shanley et al, 1996).

Approximately 50% of true PDA aneurysms are associated with celiac stenosis or occlusion (Moore et al, 2004), and aneurysms have also been described with common hepatic artery stenosis or occlusion (Bracale et al, 1996). Sutton first described the association of PDA aneurysms with celiac artery occlusion or stenosis in 1973 (Sutton & Lawton, 1973). Celiac artery entrapment by the median arcuate ligament can cause increased blood flow through collateral vessels and may be an etiologic factor (de Perrot et al, 1999b). Hyperdynamic flow and retrograde flow through the pancreatic collateral vessels leads to arterial hypertension and subsequent weakening of the arterial wall (Kalva et al, 2007). Other possible etiologies include degenerative disease of the arterial wall, fibromuscular dysplasia, Takayasu disease, and polyarteritis nodosa. In addition, the presence of a second aneurysm in a remote location—such as in the cerebral vasculature, found in 18% of GDA aneurysms and 24% of PDA aneurysms—suggests a systemic factor contributes to aneurysm formation (Moore et al, 2004). Medial arterial wall degeneration and atherosclerosis are present on pathologic examination.

The majority of patients with GDA or PDA aneurysms are symptomatic at the time of presentation. Epigastric pain with radiation to the back is common in the majority of symptomatic patients, and about 6% are seen initially for a palpable abdominal mass (Moore et al, 2004). Nonruptured aneurysms may also manifest with GI bleeding, occasional jaundice, and nonspecific GI symptoms (Shanley et al, 1996). Approximately 38% to 62% of PDA aneurysms and 35% to 56% of GDA aneurysms are brought to medical attention by rupture, which is associated with a mortality rate that ranges from 21% to 50% (Chiesa et al, 2005; Ikeda et al, 2008; Moore et al, 2004; Saltzberg et al, 2005; Sessa et al, 2004). About 20% of PDA aneurysms have the potential to rupture into the bowel and cause hematemesis, melena, and other signs of GI hemorrhage. Approximately 50% of GDA aneurysms will erode into the duodenum and cause GI bleeding. Aneurysms may also erode into adjacent vessels, organs, the bile duct (*hemobilia;* see Chapter 105), and the pancreatic duct (Ikeda et al, 2008). Aneurysms rupture into the intestinal tract and peritoneal cavity with equal frequency.

Ruptured aneurysms are treated with volume resuscitation, CT scan and angiography, and endovascular treatment or laparotomy, depending on the hemodynamic status of the patient. Nonruptured aneurysms should be treated aggressively, because they pose a high risk of subsequent rupture, and the risk is not necessarily related to the size of the aneurysm (Bageacu et al, 2006; Carr et al, 2001; Messina & Shanley, 1997; Moore et al, 2004; Takao et al, 2010).

In general, PDA aneurysms are more difficult to manage operatively than GDA aneurysms, because they are located deep within the parenchyma of the pancreas, and exposure may be difficult. Intraoperative duplex scanning or arteriography may aid in diagnosis and delineation of these aneurysms (Moore et al, 2004). Hemostasis may be difficult to obtain secondary to the extensive collateralization of the peripancreatic vessels and anatomic distortion from a retroperitoneal hematoma, and pancreatoduodenectomy has occasionally been required (de Perrot et al, 1999). Suture ligation of afferent and efferent vessels from within the aneurysm sac may be useful for aneurysms embedded in the pancreas. GDA aneurysms are slightly more accessible after duodenal mobilization, although adherence to bowel and surrounding structures can increase the difficulty of the operation.

Endovascular treatment has been increasingly utilized in the management of visceral aneurysms over the past decade. Peripancreatic aneurysms are often difficult to identify and isolate operatively, and catheter-based techniques are emerging as the treatment of choice. Various methods have been employed for embolization: coils, gelatin, foam, cyanoacrylate glue, ethanol sclerosant, and balloons (Coll et al, 1998). Recently, more selective embolization has become possible with the advent of smaller catheters and wire-based techniques that decrease risk of visceral ischemia (Moore et al, 2004). Selective embolization uses selective catheterization of the superior mesenteric artery followed by subselective catheterization of the branches feeding the aneurysm sac. Ideally, both the inflow and outflow of the aneurysm should be embolized to prevent reperfusion. If the aneurysm sac cannot be occluded for technical reasons, the parent artery can be occluded with coils (Kalva et al, 2007). Percutaneous embolization under CT guidance has recently been described (Williams et al, 2006).

Most studies advocate celiac revascularization, in addition to aneurysm ligation or embolization, when the celiac axis is stenotic or occluded (Bageacu et al, 2006; Moore et al, 2004). Celiac revascularization can be accomplished with either an open bypass or transluminal endovascular intervention. Revascularization may be performed through angioplasty and stenting in cases of atherosclerotic narrowing or by surgically dividing the median arcuate ligament in patients with median arcuate ligament syndrome (Tien et al, 2004). In addition, a bypass graft between the celiac axis or hepatic artery and superior



FIGURE 104.6. Contrast-enhanced computed tomographic arteriogram demonstrates gastroduodenal artery aneurysm in a patient with chronic pancreatitis. *(From Nosher JL, et al, 2006: Visceral and renal artery aneurysms: a pictorial essay on endovascular therapy. Radiographics 26:1687-1704.)*

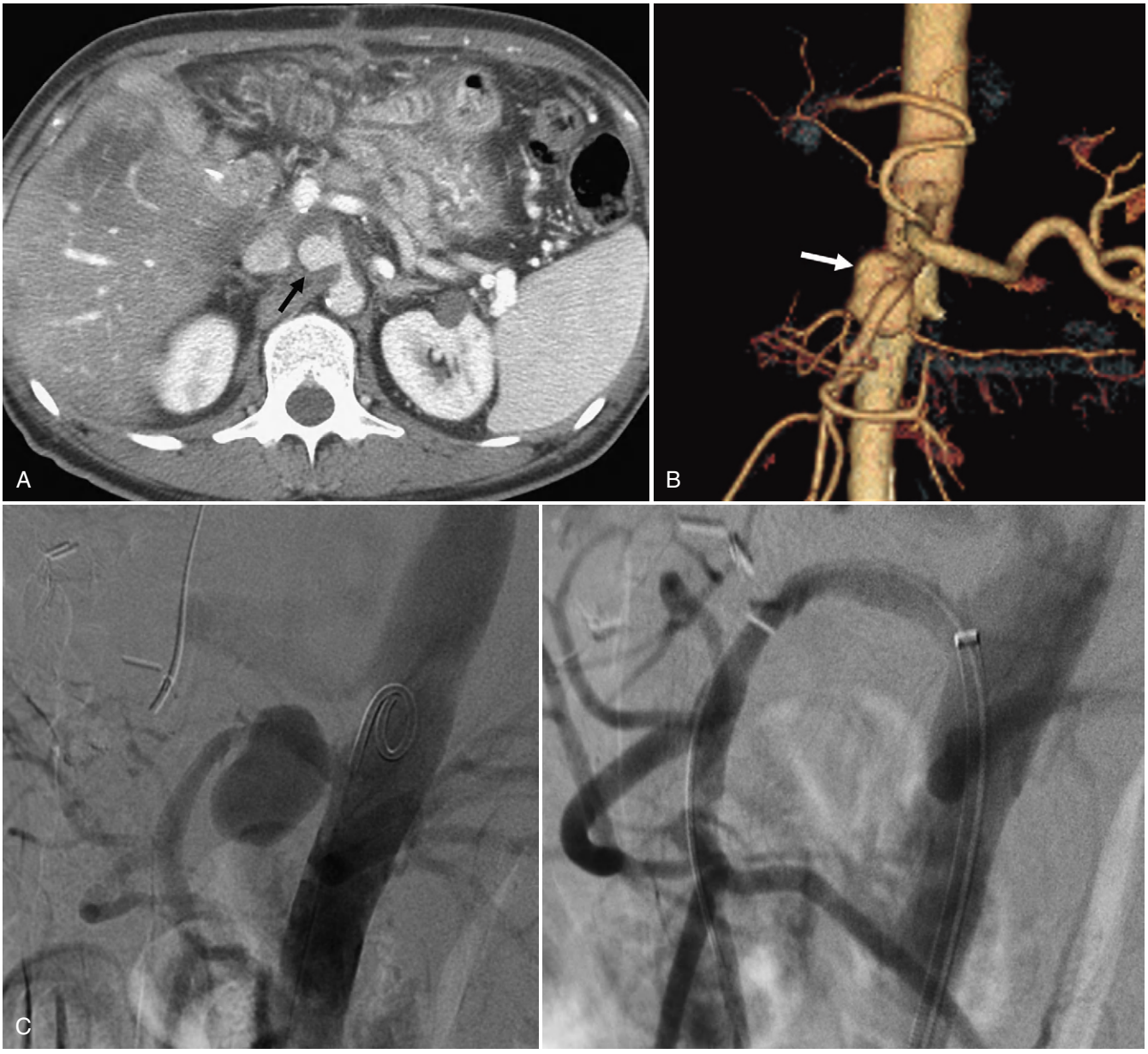


FIGURE 104.7. Pseudoaneurysm of the superior mesenteric artery in a patient with pancreatic cancer treated with chemoradiation therapy. **A,** Axial, contrast-enhanced computed tomographic angiogram. **B,** Three-dimensional reconstruction. **C,** Transfemoral visceral angiogram shows the pseudoaneurysm before (*left*) and after (*right*) placement of an endovascular stent. *(Courtesy Dr. Karen Brown, Department of Radiology, Memorial Sloan-Kettering Cancer Center.)*

mesenteric artery can be performed (Kalva et al, 2007). In nonruptured true aneurysms, it may be safer to restore celiac axis patency prior to aneurysm occlusion (de Perrot et al, 1999; Moore et al, 2004). Mesenteric ischemia and death following aneurysm occlusion in the absence of a patent celiac axis has been reported.

PSEUDOANEURYSMS

Most pseudoaneurysms that affect the peripancreatic and pancreatic vasculature are complications of pancreatitis (Fig. 104.6; see Chapter 54), but these may also result from treatment of pancreatic tumors (see Chapters 62 and 63). Pseudoaneurysms complicate 3% to 10% of acute pancreatitis cases and affect 10% to 17% of patients with chronic pancreatitis (de Perrot et al, 1999; Mallick & Winslet, 2004; Woods et al, 1995). The temporal relationship of pseudoaneurysm formation to pancreatitis is highly variable, and it is complicated by the fact that the presenting features of abdominal pain—tachycardia and hypotension—are also features of pancreatitis. A pseudoaneursym associated with chronic pancreatitis is often identified at the time of an acute exacerbation, and it remains unclear whether the pseudoaneurysm caused the exacerbation or was the result of a new episode of inflammation.

The likelihood of pancreatic pseudocyst appears to increase with the severity of the inflammation in acute pancreatitis (Flati et al, 2003). An expanding pseudocyst may erode into an adjacent vessel and form a pseudoaneurysmal pseudocyst as a result

of constant compression, ischemia, and elastolytic action (Flati et al, 2003; Shanley et al, 1996). Additionally, severe inflammation, infection, release of pancreatic enzymes, and necrosis may cause pseudoaneurysm formation and vessel erosion, which can precipitate subsequent rupture with resultant massive bleeding into the GI tract, retroperitoneum, and peritoneal cavity (Flati et al, 2003; Mallick & Winslet, 2004; Woods et al, 1995). Manipulation of friable tissue during necrosectomy may precipitate vascular damage as well. Periarterial inflammation, vascular necrosis, trauma, infection, vascular intervention, biliary intervention, and autoimmune disorders have also been identified as causative agents of pseudoaneurysms.

The splenic artery is the most frequently involved (40%), followed by the GDA (30%) (Mallick & Winslet, 2004). The size of the pseudoaneurysm is not predictive of rupture, which may occur into the abdomen, retroperitoneum, adjacent hollow organ, or blood vessel. The mortality associated with a ruptured pseudoaneurysm ranges from 7.5% to 80% (Burli et al, 2008; Flati et al, 2003), and symptoms include exacerbation of abdominal pain, hypotension, tachycardia, hematemesis, melena, or bleeding from surgical drains in patients who have recently undergone a pancreatic procedure.

The management of ruptured pseudoaneurysms of the peripancreatic vasculature and GDA is similar to that described for true aneurysms with resuscitation, CT scan, angiography, endovascular therapy, or open surgical therapy (Fig. 104.7). Immediate surgery is indicated if the patient is hemodynamically unstable. Conservative management is associated with a higher overall mortality rate (21% to 54%) than intervention (18% to 34%), therefore definitive treatment is recommended (Flati et al, 2003; Moore et al, 2004). Patients with angiographic evidence of bleeding can be treated with endovascular embolization or percutaneous thrombin injection into the aneurysm sac. Because of the extensive collateral circulation, it is imperative to occlude the artery proximal and distal to the lesion and to interrupt any collateral supply (Burli et al, 2008).

Timing of surgical intervention is critical, because open surgery during an acute episode of pancreatitis is potentially dangerous. Delaying surgery until after resolution of acute pancreatitis has fewer bleeding complications but increases the chance of rupture of a pseudoaneurysm. The optimal time for intervention is determined on a case-by-case basis.

PANCREATIC ARTERIOVENOUS MALFORMATIONS

AVM of the pancreas is a rare anomaly, first reported by Halpern in 1968 and described as a vascular mass lesion that arises via an aberrant bypass anastomosis of the arterial and venous systems in the pancreas (Halpern et al, 1968a, 1968b). Congenital pancreatic AVMs are more common (approximately 90%) and are likely a remnant of the fetal vascular network. One third of these cases are associated with Osler-Weber-Rendu syndrome (Chang et al, 2004), and acquired malformations are generally the result of trauma, tumor, infection, or inflammation, especially pancreatitis. Pancreatic AVMs have been reported in pancreatic allografts following transplantation (Barth et al, 2008).

AVMs typically come to medical attention in the fifth decade of life, but ages at presentation range from infancy to the seventh decade. Some studies note a male predominance (Takemoto et al, 2007). The most commonly involved vessels are the splenic artery (42%), GDA (22%), and small pancreatic arteries (22%; Rezende et al, 2003). Most patients are diagnosed based on presentation with complicating symptoms such as GI bleeding, portal hypertension, or pancreatitis. GI bleeding is present in 50% of patients and may be caused by rupture into the pancreatic duct, rupture of superficial vessels into the duodenum, duodenal erosion, hemobilia as a result of erosion into the bile duct (see Chapter 105), or bleeding AVMs at other sites within the GI tract (Aida et al, 2002). Pancreatic AVMs can cause portal hypertension, leading to esophageal varices, GI bleeding, and other related sequelae. Early diagnosis and intervention is warranted to prevent complications.

Angiography demonstrates an abnormal communication between the arterial and venous system with dilated feeding vessels, transient pancreatic staining, and early filling of the portal vein. Doppler ultrasound shows a mosaic pattern and abnormal blood flow and a pulsatile waveform in the portal vein (Koito et al, 2001). CT scan features include conglomeration of strong nodular stains and early enhancement of portal venous system in the arterial phase (Ogawa et al, 2009). MRI shows a circular lesion with signal void in T1- and T2-weighted images, consistent with rapid blood flow (Ogawa et al, 2009).

Angiographic embolization is the first-line treatment for pancreatic AVMs. The recurrence rate is 30% to 40% secondary to the development of multiple collateral vessels (Rezende et al, 2003). For large lesions confined to the head of the pancreas, surgical resection by pancreatoduodenectomy and total pancreatectomy has been performed. Some studies advocate embolization prior to operative intervention to potentially decrease intraoperative bleeding and postoperative morbidity and mortality (Iwashita et al, 2002; Rezende et al, 2003). Lesions localized to the tail of the pancreas can be treated by distal pancreatectomy.

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CHAPTER 105

Hemobilia and bilhemia

Adam Yopp

OVERVIEW

Hemorrhage into the biliary tract occurs when disease or trauma produces an abnormal communication between blood vessels and bile ducts, termed *hemobilia* (Sandblom, 1948), from the Greek *haima* ("blood") and the Latin *bilis* ("bile"); the term *bilhemia* describes the rare condition of bile in the bloodstream. Causes of hemobilia include iatrogenic and accidental trauma, gallstones, inflammation, vascular disorders, and neoplasms. With the increasing use of invasive diagnostic and therapeutic procedures that involve the biliary tract, iatrogenic trauma has become the predominant etiology of hemobilia (see Chapters 28, 50D, 102, and 104).

Major, profuse hemobilia is a rare and sometimes life-threatening complication of liver or biliary tract disease or trauma. Minor hemobilia occurs more frequently but is rarely of long-lasting clinical significance. Although often difficult to recognize, hemobilia should be in the differential diagnosis of upper gastrointestinal (UGI) bleeding, especially in patients with a recent or remote history of liver trauma or biliary tree instrumentation (see Chapters 19, 28, 50D, and 102).

With the advent of interventional radiologic approaches, treatment of symptomatic hemobilia has shifted from surgical therapy to selective transcatheter hepatic arterial embolization (see Chapter 104). Surgical therapy via partial hepatectomy, hepatic artery ligation, or a combination of both procedures is rarely necessary and is reserved for hepatic arterial branches that cannot be safely or adequately embolized, for anatomic or technical reasons, or in patients who have large intrahepatic hematomas or sepsis.

HISTORY

Because of its obscure appearance and apparent rarity, hemorrhage into the biliary tract, although first described in the seventeenth century, was not called *hemobilia* until more recently. In the first detailed description of hepatic anatomy from 1654, Francis Glisson (Fig. 105.1) discussed the possibility of hemorrhage into the biliary tract when describing the case of a man who died from presumed GI hemorrhage following a stab wound to the liver suffered in a duel: "I believe that if the liver is injured by a contusion, it may lead to blood leaving the body by way of vomit or the stool for there is no doubt that the biliary tract takes unto itself (to the great good of the patient) some of the blood issuing into the liver and leads it down to the intestines. From there it is either impelled upwards through reverse peristalsis or downwards the normal way" (Glisson, 1654).

Over a century elapsed before the subject of hemorrhage into the biliary tract was brought up again. In Morgagni's Epistles (1765), the founder of clinical pathology noted, in the section on the causes of dilation of the biliary tract, that abscesses in the liver and the voiding of sharp gallstones could lead to bleeding through the biliary ducts (Morgagni, 1765). In 1777, Antoine Portal presented a case in which he made the diagnosis before the death of the patient and confirmed it at autopsy. In this early treatise, Portal drew attention to the difficulty of finding the source of hemorrhage in the biliary tract, "when they are slight in quantity and occur but seldom," and to the risk of mistakenly tracing them to a healthy organ, a mistake that has been made repeatedly in the history of hemobilia (Portal, 1813).

The first published case in North America was by a Boston surgeon who reported on the clinical and pathologic consequences of an "aneurysm of the hepatic artery bursting into the hepatic duct," the first direct observation of an abnormal communication between the blood vessels and biliary ducts (Jackson, 1834; see Chapter 104). In 1871, the German surgeon Quincke further characterized biliary tract hemorrhage by establishing three cardinal symptoms—GI hemorrhage, biliary colic, and jaundice—commonly referred to as *Quincke's triad* (Quincke, 1871). Hemobilia formerly was regarded as a medical curiosity, but it is now being diagnosed with increasing frequency, owing to more widespread knowledge of the syndrome and to improved diagnostic means (Sandblom, 1972).

ETIOLOGY

Common causes of abnormal vascular and biliary communication giving rise to hemobilia include trauma (accidental and iatrogenic), gallstones, neoplasms, inflammatory processes, and vascular disorders. Other less common causes include nematodes, blood coagulation defects, choledochal cysts, pancreatitis, and portal hypertension. Figure 105.2 illustrates the three largest reported case series of hemobilia and demonstrates a shift in etiology over the course of time from accidental to iatrogenic trauma. In one of the first publications devoted solely to hemobilia, Sandblom reported on 355 cases reported prior to 1972, with the largest number secondary to accidental trauma (Sandblom, 1972). Over the ensuing 30 years, iatrogenic trauma surpassed all other causes of hemobilia, and today it is responsible for the majority of cases (Green et al, 2001; Yoshida et al, 1987). The increase in hemobilia caused by iatrogenic trauma parallels the advent and increasing use of both diagnostic and therapeutic instrumentation of the biliary tract.

Iatrogenic Trauma

To an increasing extent, biliary hemorrhage is reported as a complication of diagnostic and therapeutic procedures on the liver or the bile ducts and is now responsible for the majority of reported cases of hemobilia (Fig. 105.3). The incidence of clinically significant hemobilia following percutaneous liver



FIGURE 105.1. Francis Glisson (1957–1677) gave the first account (1654) of hemorrhage into the biliary tract in his treatise *Anatomica Hepatis.*

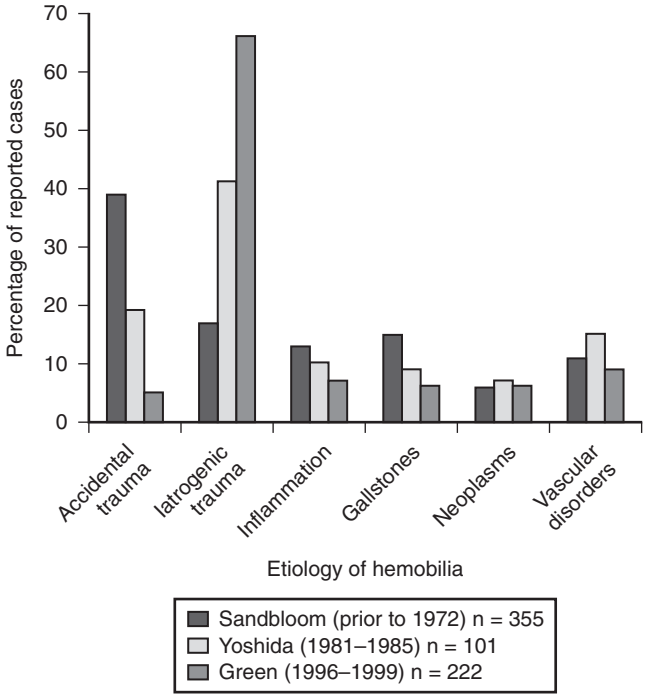


FIGURE 105.2. The distribution of 678 reported cases of hemobilia in the three largest case series. Over the course of 30 years, the predominant etiology of hemobilia changed from accidental trauma to iatrogenic trauma, presumably in parallel to the advent and increasing use of diagnostic and therapeutic manipulation of the biliary tree.

biopsy is between 0.01% and 0.2% (Piccinino et al, 1986; Seeff et al, 2010; see Chapter 20). Hemobilia arises secondary to unintentional laceration of a hepatic artery during the procedure and results in subsequent communication with the biliary tree (Fig. 105.4). Previous studies demonstrated that the risk of hemobilia following percutaneous liver biopsy may be greater in patients with chronic liver disease because of the presence of ascites, coagulopathy, and platelet dysfunction; the risk may also be higher following liver transplantation (Jabbour et al, 1995; Piccinino et al, 1986). In a recent study 2740 percutaneous liver biopsies were performed on patients with advanced chronic liver disease (cirrhosis), and it was determined that only an elevated international normalized ratio (INR) above 1.3 and a platelet count below 60,000 was associated with an increased risk of periprocedural hemobilia (Seeff et al, 2010).

Percutaneous transhepatic biliary drainage (PTBD) and percutaneous transhepatic cholangiography (PTC) are associated with a significantly higher rate of hemobilia than percutaneous liver biopsy because of the proximity of the hepatic vasculature to the biliary tree (Fig. 105.5; see Chapters 28 and 50D). In a series of 1397 patients undergoing PTBD or PTC, the incidence of clinically significant hemobilia was 1.9% (Fidelman et al, 2008). Patients undergoing PTBD had a 3.7-fold higher incidence of hemobilia compared with patients undergoing PTC, and they had a delayed presentation of hemobilia; presumably this was due to multiple catheter exchanges and a tamponade effect in PTBD patients. In this series, only large-bore needles were associated with hemobilia.

Other studies have demonstrated that use of a 21-gauge needle to access the biliary tree during PTC or PTBD, rather than an 18-gauge needle, is associated with a reduced incidence of hemobilia (Burke et al, 2003; Dousset et al, 1997; Harbin



FIGURE 105.3. Iatrogenic trauma. Percutaneous transhepatic stent placement produced a large, subcapsular hepatic hematoma and hemobilia. *(Courtesy William R. Jarnagin.)*

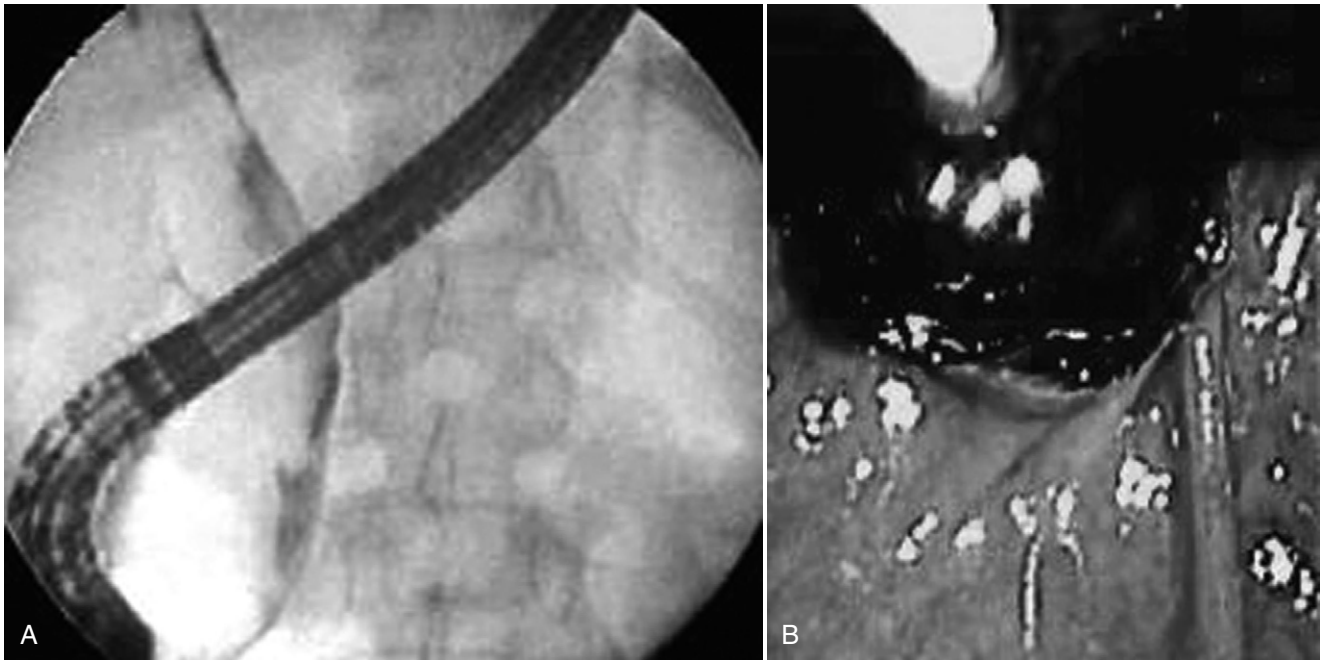


FIGURE 105.4. Iatrogenic trauma causing hemobilia. **A,** Endoscopic retrograde cholangiopancreatography (ERCP) findings of hemobilia that resulted from a percutaneous liver biopsy. Note the filling defect within the common bile duct consisting of blood clots. **B,** Removal of blood clots of the same patient during ERCP. *(From Martins FP, et al, 2008: Obstructive jaundice caused by hemobilia after liver biopsy. Endoscopy 40:E265-E266.)*

et al, 1980). In addition, correction of coagulopathy should reduce the development of clinically significant hemobilia (Hines et al, 1972). Another study concluded that neither a left-sided or right-sided hepatic approach to either PTBD or PTC is specifically associated with a higher incidence of hemobilia (Rivera-Sanfeliz et al, 2004). Other potential risk factors include cirrhosis, ascites, and absence of biliary dilation; extensive hepatic metastases do not appear to be predictive of hemobilia.

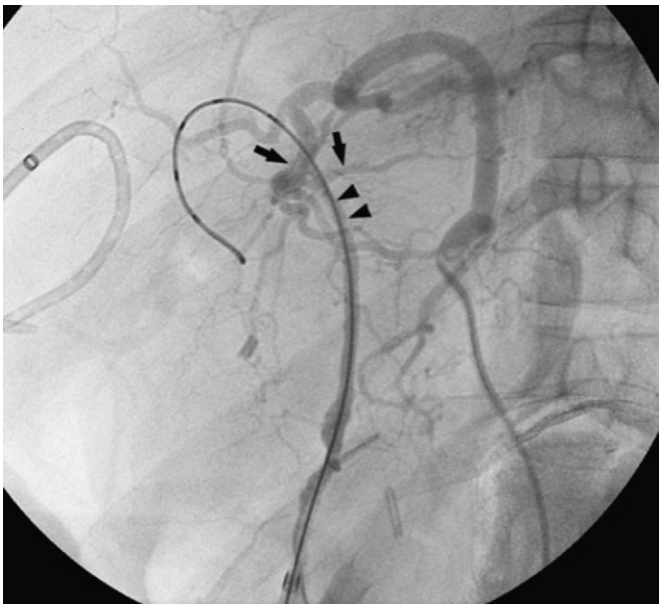


FIGURE 105.5. Hemobilia secondary to percutaneous transhepatic biliary drainage (PTBD). Angiogram obtained following placement of PTBD demonstrates a connection between the left hepatic artery (*arrows*) and biliary tree (*arrowheads*). *(From Fidelman N, et al, 2008: Hepatic arterial injuries after percutaneous biliary interventions in the era of laparoscopic surgery and liver transplantation: experience with 930 patients. Radiology 247: 880-886.)*

Surgery of the biliary tree may also lead to hemobilia as a result of injury of the hepatic artery by suture, dissection, diathermy, clip migration, erosion and subsequent arteriobiliary fistula, or pseudoaneurysm eroding into the extrahepatic bile duct (Fig. 105.6). The development of a hepatic artery pseudoaneurysm may precede the clinical manifestations of hemobilia by several weeks because of a delayed presentation; therefore, a high clinical suspicion and accurate history taking is often needed to accurately diagnose hemobilia (see Chapter 19). The advent of laparoscopic cholecystectomy for treatment of cholelithiasis and cholecystitis was originally feared to have produced an increased incidence of hemobilia secondary to vascular injury within the porta hepatis, specifically to the right hepatic artery (see Chapter 34). Stewart and colleagues (1995) reported five cases of hemobilia following laparoscopic cholecystectomy, and four of these were the result of traumatic aneurysm of the right hepatic artery; however, a large registry of 77,604 cases of patients undergoing laparoscopic cholecystectomy demonstrated that significant vascular injury was seen in only 0.16% (Deziel et al, 1993). It appears that fears of increased incidence of hemobilia following laparoscopic cholecystectomy were unfounded, overstated, and most likely secondary to the learning curve of laparoscopic surgery; however, the presentation of UGI bleeding from an unknown source weeks after laparoscopic cholecystectomy should heighten the suspicion of a potential injury to the right hepatic artery and resultant hemobilia.

Surgical procedures and exploratory instrumentation of the intrahepatic ducts may damage their walls, and the risk of hemorrhage is great. Minor bleeding constantly accompanies such procedures, but the bleeding generally ceases spontaneously, and the resulting clots promptly dissolve. Forceful

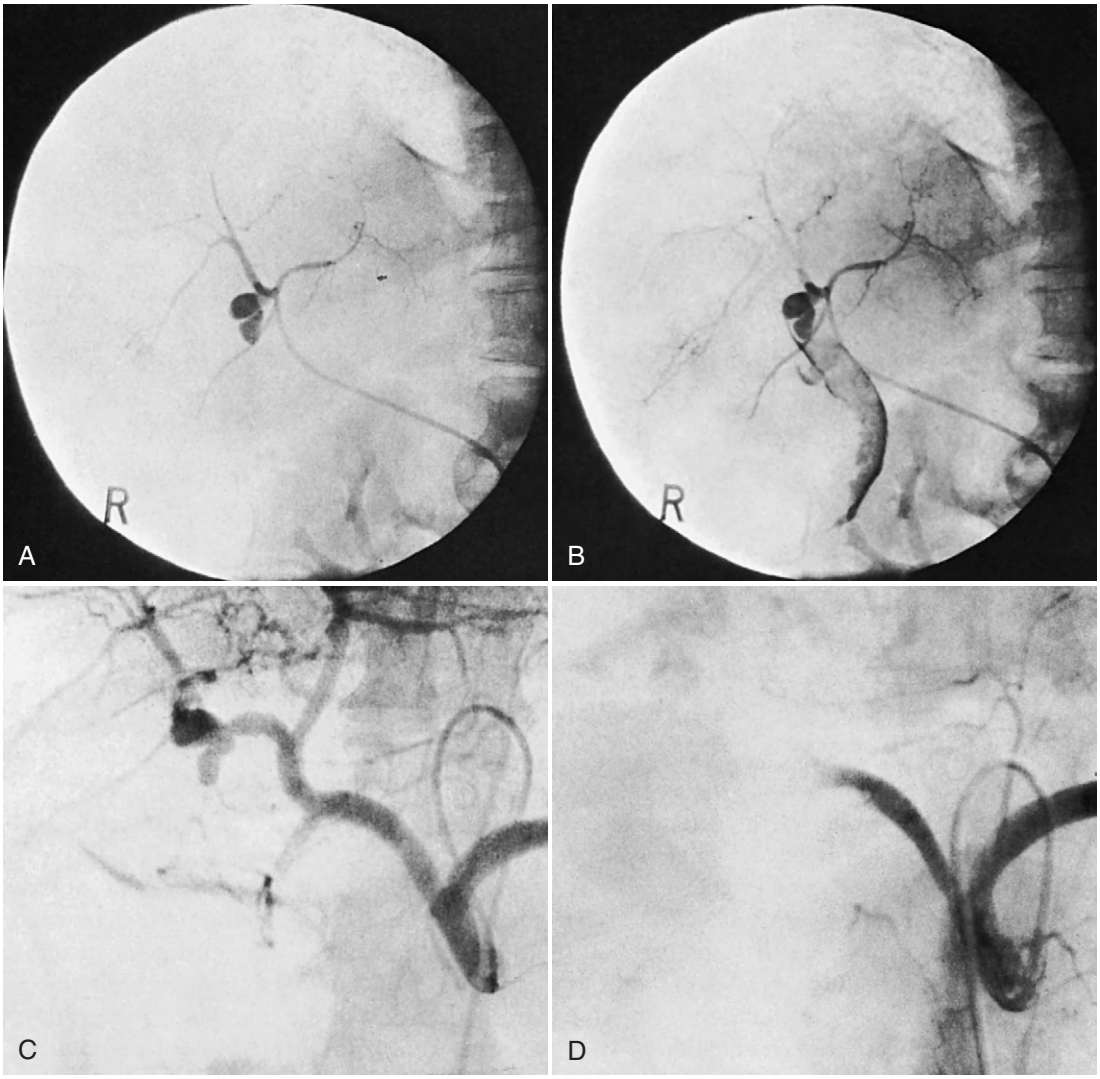


FIGURE 105.6. After complicated cholecystectomy, an iatrogenic pseudoaneurysm developed. It ruptured into the biliary tract and caused exsanguinating hemobilia, diagnosed through duodenal endoscopy and treated successfully with embolization. **A,** Selective arteriogram shows a pseudoaneurysm of the hepatic artery located at the liver hilum. **B,** A few seconds later, the contrast material is seen flowing down the hepatic duct, displaying the arteriobiliary fistula. **C** and **D,** The same aneurysm before and after obliteration of the feeding artery with artificial embolus. *(From Kelley CJ, et al, 1983: Non-surgical management of post-cholecystectomy hemobilia. Br J Surg 70:502.)*

instrumentation during exploration of the biliary tree and extraction of stones can result significant hemorrhage (Fig. 105.7). Bleeding from a T-tube occasionally can be caused by local erosion of the mucosa from tube, but if an arteriogram is done, it frequently exposes another source: a pseudoaneurysm that originates from an intraductal lesion, caused by instrumentation (see Fig. 105.7). As in other kinds of traumatic hemobilia, sometimes a considerable interval passes between the trauma and the bleeding episode.

Profuse biliary bleeding rarely complicates elective hepatic resections, although minor intraductal bleeding can result in confusing temporary postoperative jaundice. Although uncommon, hemobilia following liver transplantation may be a clinically challenging management issue; it typically occurs secondary to a percutaneous liver biopsy, and only selective embolization, which will be described later, should be used out of concern for periprocedural hepatic necrosis, ischemic biliary stricture, and sepsis.

Accidental Trauma

The liver is one of the organs most commonly injured by blunt trauma, with injuries detected in almost 25% of patients on routine computed tomography (CT) scan (Matthes et al, 2003; see Chapter 102). Nonsurgical management of blunt liver trauma in hemodynamically stable patients has become the standard treatment and is successful in 50% to 80% of patients (Carrillo et al, 1998; Forlee et al, 2004). The incidence of hemobilia following major liver injury has been reported to be as high as 3% in one series (Merrell & Schneider, 1991), but in other reports, the overall incidence is less than 0.2% (Parks et al, 1999). Other accidental traumas that result in hemobilia include injuries to the gallbladder, which is the organ injured in up to 2% of blunt abdominal trauma cases (Erb et al, 1994).

The clinical manifestations of blunt trauma to the liver are dependent on the anatomic site of damage. Tearing or injury to the liver capsule without deep parenchymal injury typically

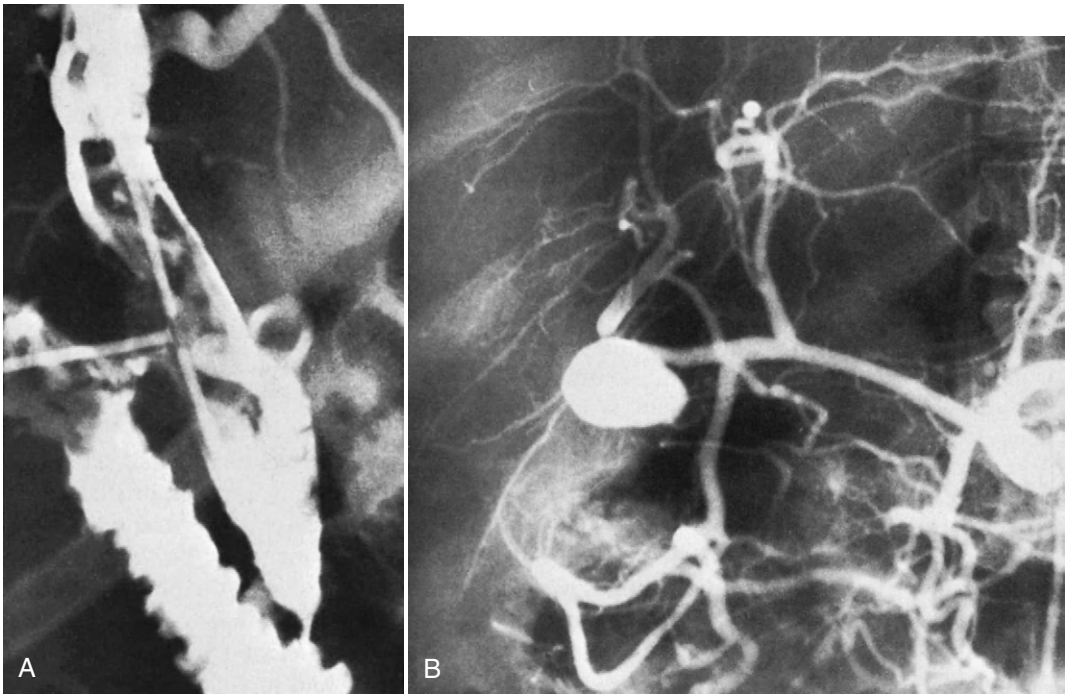


FIGURE 105.7. Iatrogenic hemobilia. Operative lesion from instrumentation during common bile duct exploration. **A,** Postoperative cholangiogram after occurrence of profuse hemobilia through the T-tube; the large filling defects represent blood clots. **B,** Hepatic arteriogram reveals the source of bleeding: a false aneurysm in the right hepatic artery.

results in intraperitoneal hemorrhage that is most often managed with emergent operative exploration. Deep parenchymal injury or a central rupture may leave a large cavity, into which damaged bile ducts and blood vessels drain; the resulting biloma or hematoma may continue to expand, liver healing is impaired, and subsequent necrosis of the cavity wall may cause erosion of adjacent structures or formation of an intrahepatic artery pseudoaneurysm (Fig. 105.8).

If operation for blunt liver trauma is necessary, careful exploration of central injuries should be performed to ensure adequate hemostasis and ligation of biliary radicles before using packs to control bleeding. Indiscriminate use of deep parenchymal sutures should be avoided to prevent further injury to biliary radicles and vessels, potentially creating a central cavity that predisposes to the development of postoperative hemobilia. The conservative management of liver injuries has not resulted in an increase in the incidence of hemobilia following accidental trauma (Carrillo et al, 1998). In a series of 135 patients with severe liver injuries managed nonoperatively, only two developed hemobilia (Carrillo et al, 1999).

Vascular Disorders

Vascular disorders account for only about 10% of cases of clinically significant hemobilia (see Chapter 19; Green et al, 2001; Yoshida et al, 1987). Hepatic artery aneurysms are the most common primary vascular disorder to produce hemobilia. Other less common causes include angiodysplasia, arteriovenous malformations, and hemangiomas (Vishnevsky et al, 1991). The frequency of true aneurysms (Ryan et al, 2002) of the hepatic artery or its branches (Maralcan et al, 2003; Morioka et al, 2004) rupturing into the biliary tract is diminishing with the disappearance of mycotic aneurysms, leaving only aneurysms of atherosclerotic origin or those associated with polyarteritis nodosa (Dutta et al, 2004;Yazici et al, 1997), fibromuscular dysplasia (Shussman et al, 2008), or trauma. When an aneurysm only leaks, it might give rise to inconspicuous hemobilia; when it ruptures into the biliary tract, the symptoms are generally clinically significant, with exsanguinating hemorrhage and intense biliary colic. Sometimes, vascular lesions associated with arterial hypertension can result in hemobilia; the structure usually affected is the gallbladder, and the disorder is known as *apoplexy of the gallbladder* (Parekh & Corvera, 2010; Fig. 105.9).

Neoplasms

Neoplasms account for only about 5% of all cases of major hemobilia (Green et al, 2001; Sandblom, 1972; Yoshida et al, 1987). Primary and secondary malignant neoplasms of the liver, bile ducts, gallbladder, and pancreas can all lead to hemobilia when the tumors invade the biliary system. The rate of blood loss is rarely rapid and in most instances produces the slow onset of microcytic anemia. Malignant tumors are three times more likely to cause hemobilia than benign tumors, and liver metastases hardly ever cause hemobilia; similarly, hemobilia is not a frequent sequela of primary cancers in the liver (Kitagawa et al, 1999), although it has been described from metastases in such rare locations as the gallbladder wall (Kubota et al, 2000) or from melanoma in the ductal mucosa. In cases of hemobilia caused by malignant tumors in the gallbladder (Hernandez-Castillo et al, 2002), the bleeding is most marked if the tumor grows in a polypoid fashion (Strauss, 1929). In the bile ducts, benign adenoma (Teter, 1954), polyps, and polyposis have a protracted course of hemobilia. Treatment of hepatic tumors, both primary and metastatic, with either chemotherapy

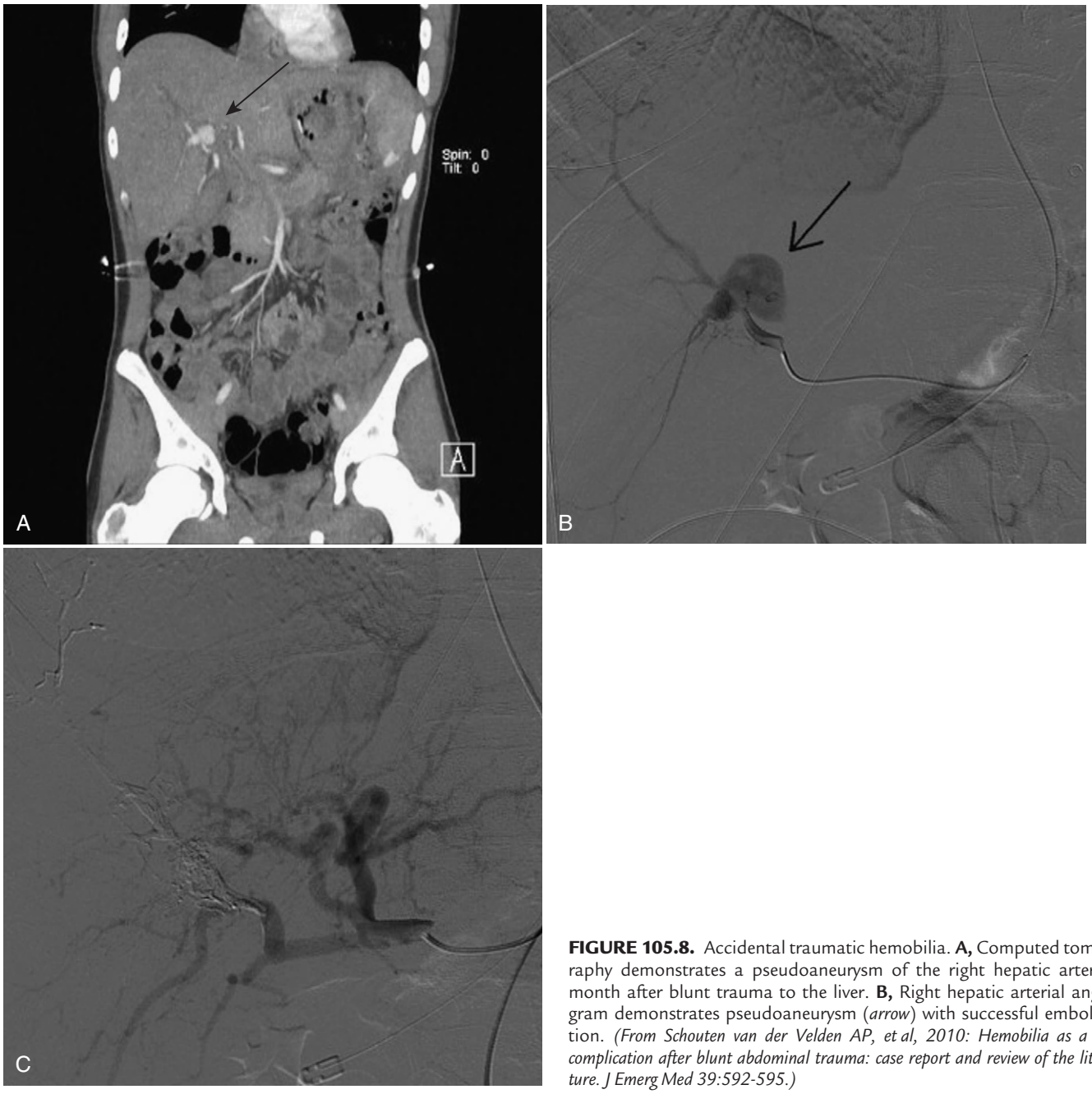


FIGURE 105.8. Accidental traumatic hemobilia. **A,** Computed tomography demonstrates a pseudoaneurysm of the right hepatic artery a month after blunt trauma to the liver. **B,** Right hepatic arterial angiogram demonstrates pseudoaneurysm (*arrow*) with successful embolization. *(From Schouten van der Velden AP, et al, 2010: Hemobilia as a late complication after blunt abdominal trauma: case report and review of the literature. J Emerg Med 39:592-595.)*

(Verset et al, 2010) or locoregional therapy (Goto et al, 2010) has also been reported to result in major hemobilia.

Gallstones

In gallstone disease, microscopic hemorrhage can be demonstrated in one of four cases with stones in the gallbladder and in one of three with stones in the common duct (Gad, 1962). Macroscopic hemobilia is rare, constituting less than 10% of all major hemobilia cases reported (Green et al, 2001; Sandblom, 1972; Yoshida et al, 1987). It generally occurs when large stones erode the cystic artery or penetrate into an adjacent viscus or vessel (Ben-Ishay et al, 2010; Contini et al, 2009; Fig. 105.10). The stones may cause profuse, exsanguinating hemobilia, and 11 out of 20 patients in one report bled to death. Hemobilia should be regarded just as seriously but is a much less frequent complication of neglected gallstones (Joo et al, 2003) compared with obstructive jaundice, cholecystitis, and pancreatitis.

Infections and Inflammation

Parasitic infection by various organisms has been reported in association with hemobilia, and it should be considered in patients with a history of travel to endemic regions, including Africa and the Asian Rim (see Chapter 45). *Ascaris lumbrocoides,* a nematode with a tendency to invade the bile ducts, frequently produces bleeding (Fig. 105.11). In India, 500 cases of biliary ascariasis have been reported (Khurro et al, 1990).

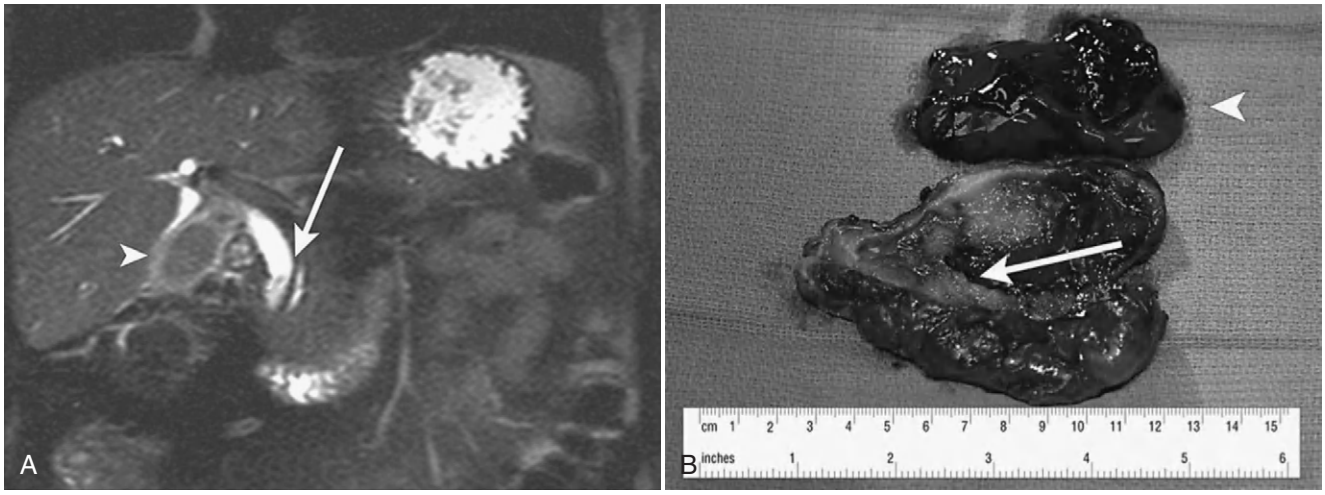


FIGURE 105.9. A case of apoplexy of the gallbladder causing hemobilia. **A,** Magnetic resonance imaging demonstrates clot within the gallbladder (*arrowhead*) and common bile duct (*arrow*). **B,** Operative specimen from the same patient reveals a large clot removed from the gallbladder. *(From Parekh J, Corvera CU, 2010: Hemorrhagic cholecystitis. Arch Surg 145:202-204.)*

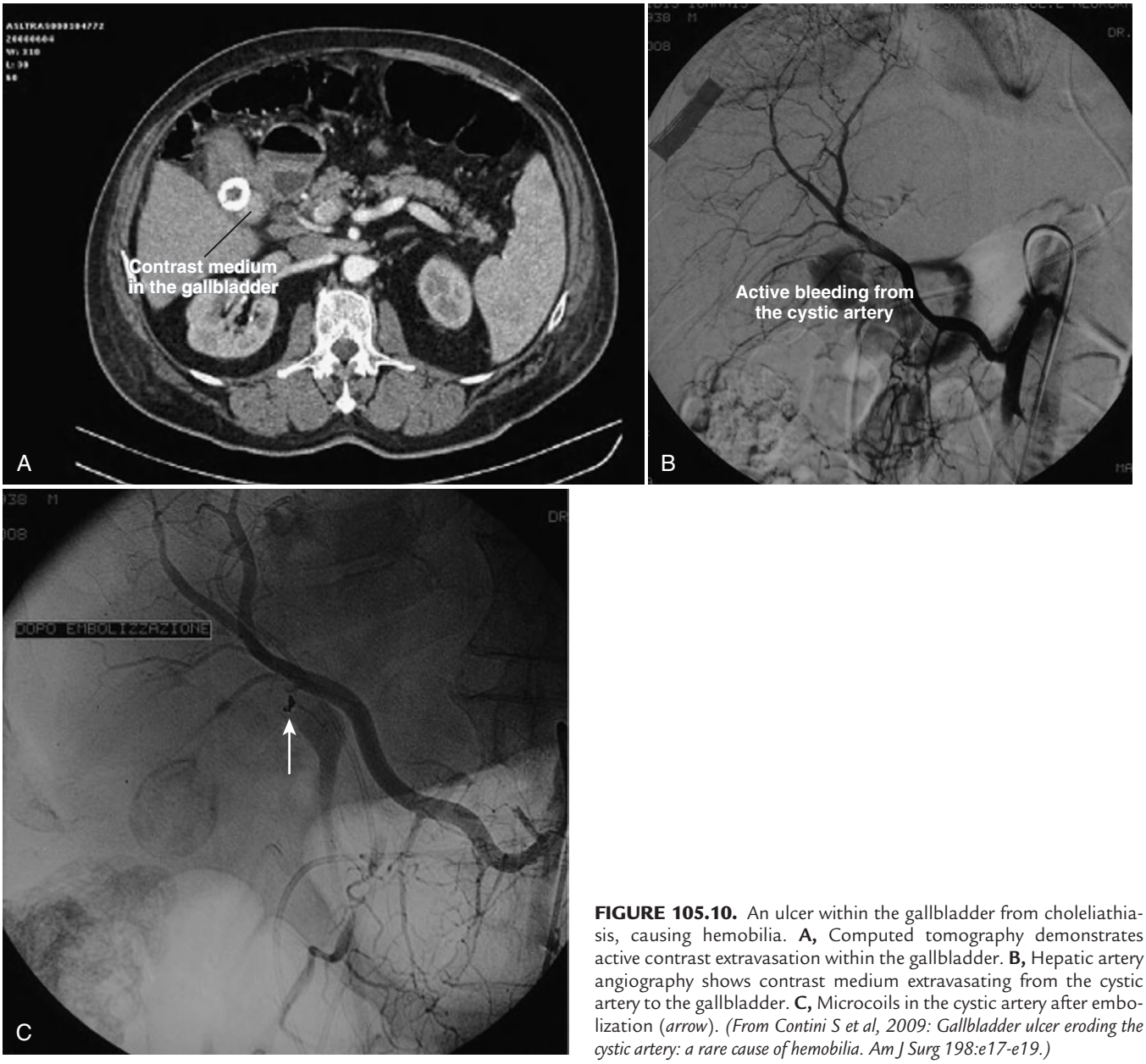


FIGURE 105.10. An ulcer within the gallbladder from choleliathiasis, causing hemobilia. **A,** Computed tomography demonstrates active contrast extravasation within the gallbladder. **B,** Hepatic artery angiography shows contrast medium extravasating from the cystic artery to the gallbladder. **C,** Microcoils in the cystic artery after embolization (*arrow*). *(From Contini S et al, 2009: Gallbladder ulcer eroding the cystic artery: a rare cause of hemobilia. Am J Surg 198:e17-e19.)*

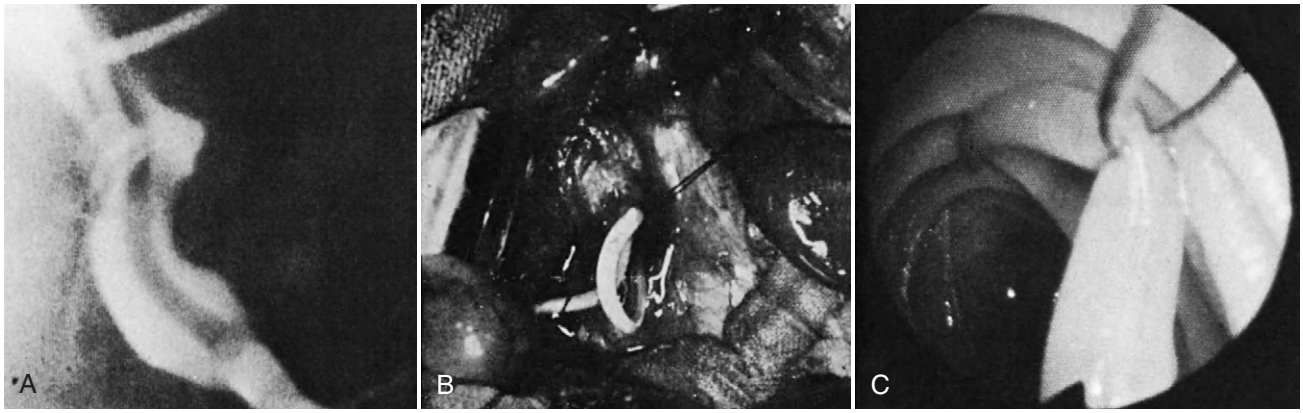


FIGURE 105.11. Hemobilia from *Ascaris* infection. **A,** T-tube cholangiogram visualizes a string like filling defect. **B,** Operative extraction of an *Ascaris* through a choledochotomy. **C,** Endoscopic extraction of an *Ascaris,* protruding through the papilla. *(**A,** Courtesy J. Sawyer, Vanderbilt University; **B,** courtesy G.B. Ong, University of Hong Kong; **C,** Courtesy R. Cavin, Lausanne, Switzerland.)*

Suppuration, but no bleeding, is mentioned. Because blood iron levels were low, and no examination for hematochezia was performed, it may be that many cases were overlooked. In addition, ruptured liver abscess has caused hemobilia in a few cases (Liou et al, 1996).

CLINICAL MANIFESTATIONS

The bleeding in hemobilia may originate in the liver parenchyma, intrahepatic biliary tract, or extrahepatic biliary tract, including the gallbladder. Most episodes of significant hemobilia are the result of an abnormal fistulous communication between a hepatic arterial branch and the biliary tree. The clinical manifestations of hemobilia are due to blood loss and formation of clots within the biliary tree. Major hemobilia causes shock and possible death from exsanguination, unless an emergency intervention is performed. Occult or minor hemobilia, if continued, may result in chronic secondary anemia as can be seen with biliary tract neoplasms (Ahmad et al, 2010).

GI bleeding in connection with biliary symptoms should arouse the suspicion of biliary tract hemorrhage. Quincke described a triad of signs and symptoms associated with hemobilia: upper abdominal pain, UGI hemorrhage, and jaundice (Quincke, 1871). The GI bleeding manifests as melena in 90% of cases and as hematemesis in 60%. Biliary colic symptoms are seen in 70% of cases, and jaundice is identified in up to 60% of patients. All three findings are seen in approximately a quarter of patients with hemobilia (Green et al, 2001). In addition to retained blood clots within the biliary tree, which produce the signs and symptoms of obstructive jaundice, patients may be seen initially with ascending cholangitis and accompanying high fevers and rigors (Kurisu et al, 2005).

The fate of blood in the biliary tree depends on a variety of factors, including the *rate*, the *source* (arterial or venous), the *timing* (continuous or intermittent), and the *frequency* (solitary or recurrent) of the bleeding. A sudden onset of massive bleeding, as in a ruptured hepatic artery aneurysm, may produce such a rapid volume of blood that the initial clinical presentation is hematemesis or melena. The formation of clots depends on the quality and quantity of the bleeding, and their fate depends on whether they are dissolved, expelled into the intestine, or retained in the biliary tract (Sandblom & Mirkovich, 1979). When clots are retained, they act like calculi and cause symptoms of biliary colic when passed (Clancy & Warren, 1997), jaundice when retained (Prata Martins et al, 2008), cholecystitis if lodged in the gallbladder (Parekh & Corvera, 2010), and pancreatitis if they obstruct a common channel above the sphincter (Alis et al, 2010). Only rarely do clots remain in the biliary tree long enough to be encrusted and form stones (Luzuy et al, 1987; Olsen, 1982).

DIAGNOSIS

A high index of suspicion is necessary to accurately diagnose and treat hemobilia. The actual workup of a patient with suspected hemobilia is ultimately dependent on the presentation and suspected etiology. It is important to remember that hemobilia may have a delayed presentation and may recur repeatedly over months, even years (Ahmad et al, 2010). For patients who come to medical attention with UGI bleeding, esophagogastroduodenoscopy (EGD) is the initial diagnostic test of choice. Although blood or clot at the ampulla ofVater is the *sine qua non* of hemobilia (Fig. 105.12), about 10% of upper endoscopies will be nondiagnostic and will necessitate additional diagnostic tests to confirm the diagnosis (Yoshida et al, 1987).

Other imaging modalities employed include endoscopic retrograde cholangiopancreatography (ERCP), which sometimes reveals clots in the bile ducts (Guitron-Cantu et al, 2002; Hendriks et al, 2009; Jornod et al, 1999; see Chapter 18 and Fig. 105.12). A lesion often first appears on ultrasonography (Trakarnsanga, et al, 2010) or CT (Burns & Slakey, 2009); these imaging modalities may show even small traumatic lesions, if a hematoma is produced, but not if there is only an arteriobiliary fistula. The ultrasound appearance of intracholecystic blood produces less distinctive shadows (or defects) than stones, and the shadows often are interpreted as being due to gravel or inspissated bile (Fig. 105.13). Magnetic resonance imaging (MRI) also can show active bleeding to the biliary tract, and

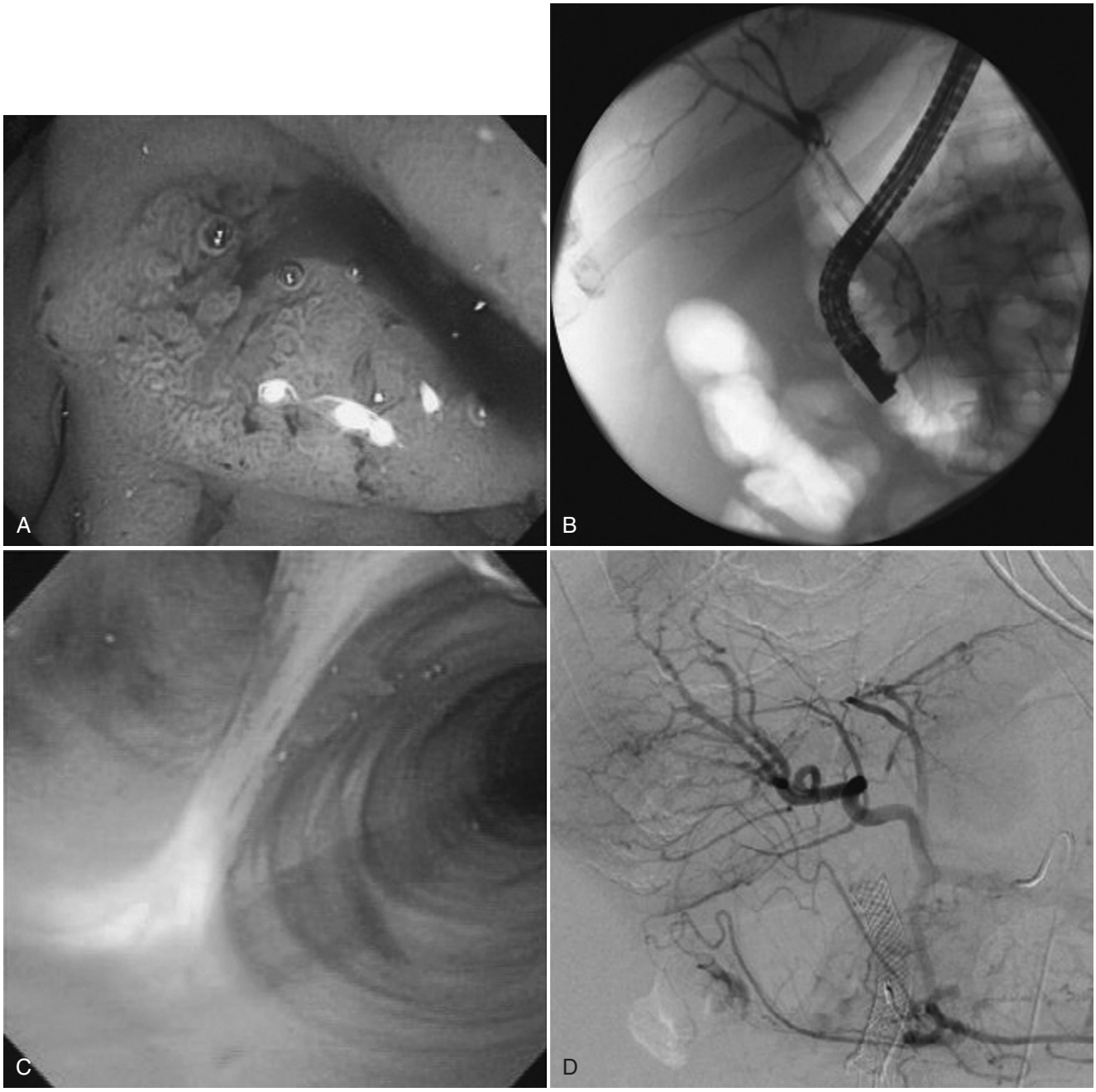


FIGURE 105.12. A case of hemobilia secondary to a transjugular liver biopsy. **A,** Upper endoscopy demonstrates blood emanating from the ampulla of Vater. **B,** Cholangiography from endoscopic retrograde cholangiopancreatography demonstrates an extensive filling defect within the extrahepatic biliary tree. **C,** Endoscopic finding of blood emanates from left hepatic duct. **D,** Subsequent angiography demonstrates no evidence of overt bleeding. *(From Parsi M, 2010: Hemobilia: endoscopic, fluoroscopic, and cholangioscopic diagnosis. Hepatology 52:2237-2238.)*

MR cholangiopancreatography (MRCP) can improve visualization of the biliary tract and gallbladder (Tseng et al, 2001; see Chapter 17).

The best way to verify a suspected diagnosis of hemobilia is by selective arteriography of the hepatic artery (see Chapter 19), which reveals the source of major bleeding in most cases (Xu et al, 2005; Yao & Arnell, 2010); hemobilia may also be demonstrated by extravasation; by displacement of the vessels around a liver mass; or by filling of a true aneurysm (see Fig. 105.7). When caught at the right moment, contrast material may be seen traveling down the hepatic duct, proving the existence of a communication with the biliary tract (see Fig. 105.6; Kelley et al, 1983), and in some cases, the artery also opens into the portal system (Gurakuqi et al, 2008). The arteriographic catheter should not be withdrawn until it has been decided whether embolization of the feeding artery should be considered as treatment. Arteriography is of special value in discovering central liver lesions, which may be difficult or impossible to localize during exploratory laparotomy. Although selective angiography is considered the gold standard for diagnosis in

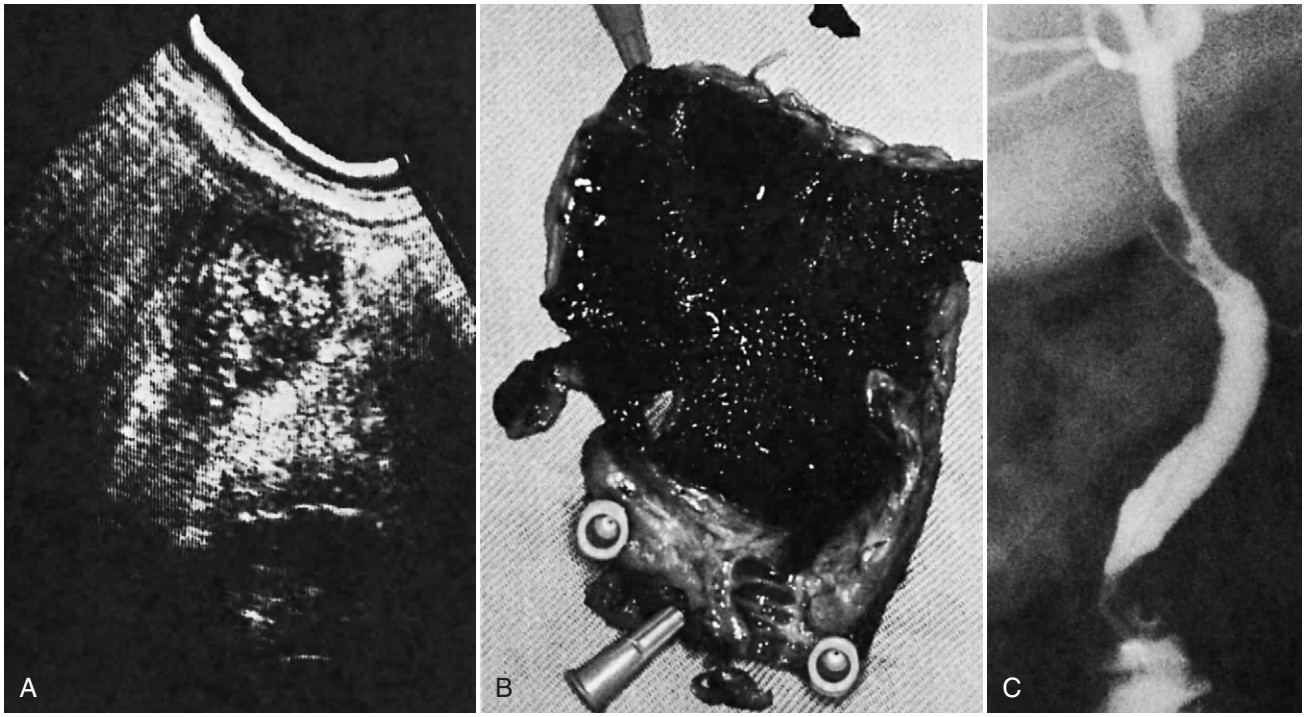


FIGURE 105.13. Hemobilia caused by clotting defect during anticoagulation therapy. **A,** Sonogram indicating dense material in the gallbladder, interpreted as *microcalculi* or *inspissated bile*. **B,** In the gallbladder, clotted blood was firmly attached to the wall. **C,** Defects in the perioperative cholangiogram caused by blood clots, the large proximal one attached to the wall and the distal one bandlike.

hemobilia, care must be taken in interpreting arteriograms; they may appear normal if the study is performed when there is no active bleeding.

Cholangiography done postoperatively through a T-tube by means of ERCP or through diagnostic percutaneous liver puncture (Fig. 105.14) may reveal a lesion by contrast filling of a cavity or by demonstration of clots, which appear as defects in the contrast filling (Millbourn, 1951).

TREATMENT

The treatment of hemobilia is predicated on resuscitation, stopping potentially life-threatening hemorrhage, and relieving biliary tract obstruction. Depending on the underlying etiology of hemobilia and briskness of hemorrhage, treatment modalities include surgical resection, arterial ligation, transcatheter arterial embolization, and conservative management.

Surgical Intervention

In 1903, Kehr first demonstrated that ligation of the proper hepatic artery could be successfully used in hemobilia in a case of communication between a hepatic artery aneurysm and the cystic duct. The predominant initial treatment method for hemobilia, surgical intervention in the form of surgical resection or arterial ligation, has declined in popularity with the advent of nonoperative approaches (see Chapters 19, 28, and 102; Green et al, 2001; Sandblom, 1972; Yoshida et al, 1987); however, surgical intervention still has a role in cases where transarterial embolization (TAE) has failed, or where the etiology demands an operative approach. Cholecystectomy done for gallstones and surgical resection for intrahepatic or extrahepatic neoplasms are suitable approaches in patients who are hemodynamically stable with signs and symptoms of hemobilia. The surgical approach involves ligation of the bleeding vessel and/or excision of the pseudoaneurysm. If the bleeding vessel is not appropriately identified intraoperatively, ligation of the right or left hepatic artery can be done with little concern for perioperative necrosis, provided free flow of the respective portal vein is demonstrated to ensure adequate oxygenation of liver parenchyma.

Arterial Embolization (See Chapters 19 and 28)

Since the description of the first successful TAE of a hemobilia-producing right hepatic pseudoaneurysm in 1976 by Walter and colleagues, nonoperative embolization has become the preferred approach for the management of hemobilia (Fig. 105.15). The goal of TAE is to decrease blood flow to the abnormal communication between the vessel and biliary tree by placement of the catheter at the periphery of the bleeding vessel and embolization with occluding materials, such as absorbable gelatin sponge, coils, polyvinyl alcohol particles, cyanoacrylate, or microballoons. As a result of the selective embolization of the bleeding vessel, oftentimes a segmental branch of the hepatic artery, the risk of hepatic necrosis is minimal, especially if the portal vein is patent. It is important to perform selective embolization, because occlusion of a major hepatic arterial branch not only allows the possibility of rebleeding, owing to revascularization, it also makes impossible repeat embolization, which may be necessary. TAE successfully manages hemobilia in 75% to 100% of cases with little to no periprocedural morbidity (Lygidakis et al, 1991; Srivastava et al, 2006; Vaughan et al, 1984).

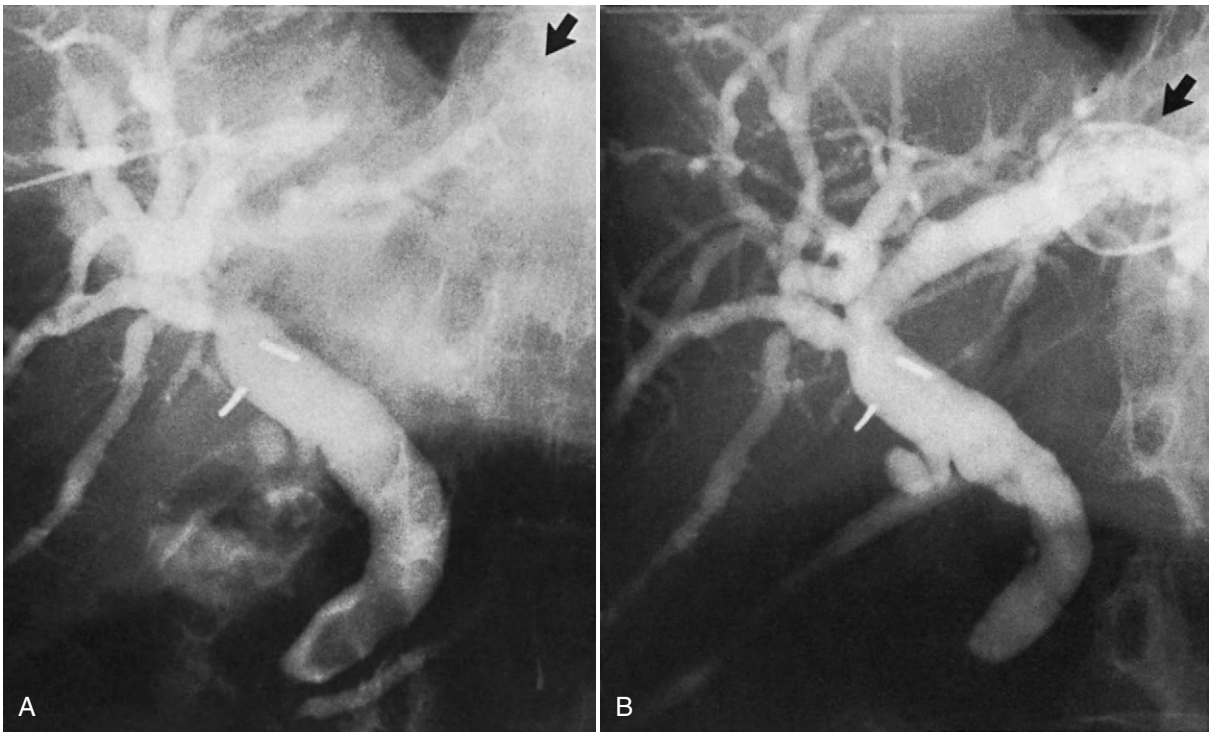


FIGURE 105.14. Lesion from transhepatic cholangiography, producing a blood clot in the common duct. **A,** The *arrow* points toward a lesion in the left hepatic duct. Filling defect in the common duct is caused by a gelatinous bile plug, probably a blood clot that disappeared through the sucker. **B,** Postoperative cholangiogram shows the extravasation from the ductal lesion responsible for the hemobilia.

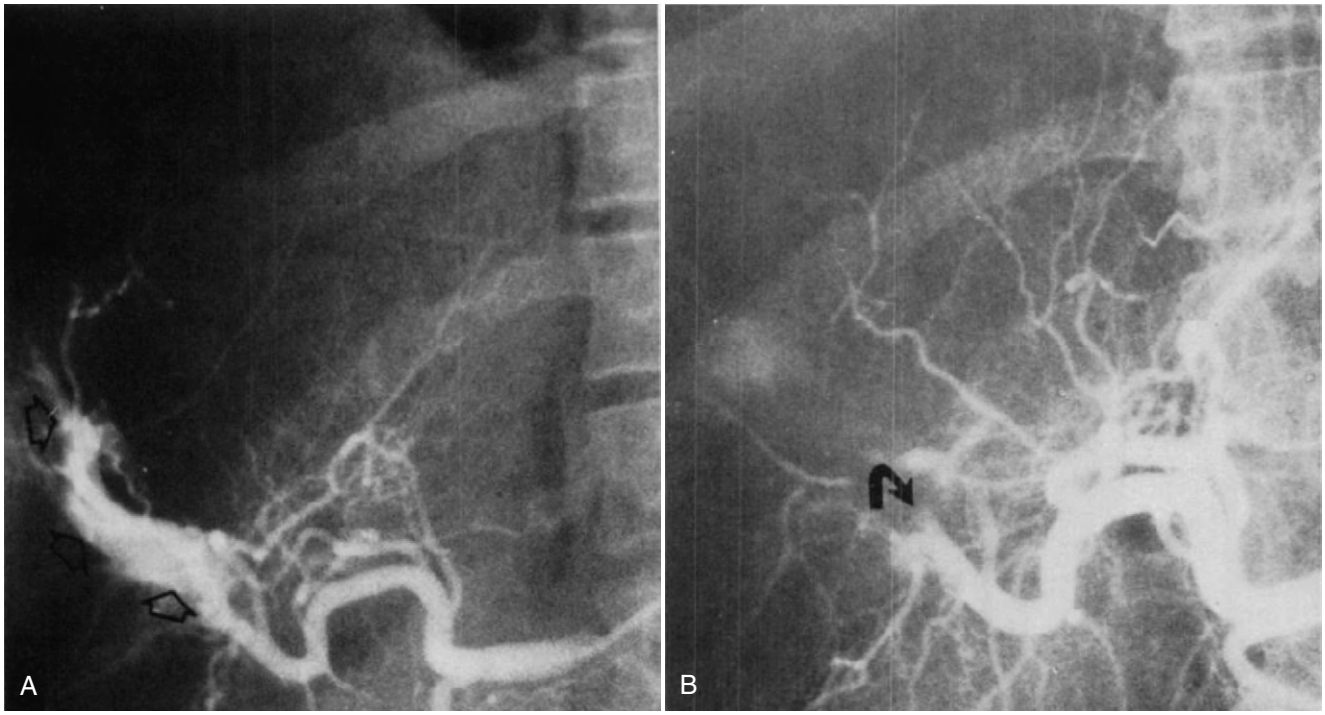


FIGURE 105.15. First successful documented report of embolization for treatment of hemobilia secondary to a pseuduoaneurysm from a liver biopsy. **A,** Selective common hepatic arteriogram demonstrates pseudoaneurysm of the right hepatic artery (*arrows*). **B,** Follow-up arteriogram after Gelfoam embolization demonstrates complete occlusion of the right hepatic artery (*arrow*). *(From Walter JF, 1976: Successful transcatheter embolic control of massive hemobilia secondary to liver biopsy. AJR Am J Roentgenol 127:847-849.)*

Biliary Tract Management

Patients who present with hemobilia after transhepatic biliary drainage often require emergent cholangiography and arteriography to identify the cause and treat the bleeding. These patients will come to medical attention with a sudden output of blood into their biliary drainage bags. After resuscitation, the biliary drainage tube must be examined to ensure its proper position. If the tube has become partially dislodged, a side hole may have migrated into the hepatic parenchyma, in which case simple repositioning of the side holes may stop the bleeding.

To address the issue, the initial procedure should be cholangiography, which may identify a biliary-venous fistula or a biliary-arterial fistula. Portal venous fistulas are easily treated by upsizing the biliary stent; that usually will be sufficient to tamponade the fistula tract (see Chapter 50D). If arterial hemorrhage is suspected, the patient should proceed to diagnostic angiography and TAE. If a bleeding site is not identified with the biliary drainage catheter in place, it may be necessary to remove the catheter prior to performing the arteriogram.

The management of obstructive jaundice that results from clotting within the biliary tree is usually accomplished with ERCP and removal of the clot. If an external biliary drainage tube is in place, simple irrigation of the tube may be all that is required to successfully relieve the obstruction.

BILHEMIA

Bilhemia denotes the reverse of hemobilia, with bile entering the bloodstream through a communication with the hepatic veins (Sandblom, 2000; Turk et al, 2010) or with branches of the portal vein (Lagagne et al, 1988). The reversed flow is due to inversion of the pressure gradient (François et al, 1994) caused by high intraductal biliary pressure, generally resulting from a peripheral obstruction or low venous pressure. In a large series of cases of obstructive jaundice, the pressure in the bile ducts was invariably higher than in the hepatic veins (Wiechel, 1964). In five instances, gallstones eroded into the portal vein. The first case was reported in 1559, preceding the description of hemobilia by more than a century, at the necropsy of Saint Ignatius of Loyola, with three gallstones found in the portal vein.

Portal vein bilhemia was recognized relatively recently. The first recent case to be reported was caused by liver biopsy, described by Brown and Walsh in 1952; a second description was provided 15 years later by Mehta and Rubenstone (1967). The condition, which was named by Clemens and Wittrin in 1975, is rare but dangerous. Of the 50 cases reported in the literature, half were fatal. The cause of the pathologic passage was often accidental: blunt trauma in 25 cases and iatrogenic injury or manipulation during operation in 3 cases (Koehler et al, 1978). The symptoms are a rapidly increasing jaundice with elevated direct bilirubin without increase of liver enzymes. Septicemia has occurred through bilhemia with infected bile (Morettin & Dodd, 1972). Selective arteriography is nondiagnostic in bilhemia, whereas scintigraphy has been useful (François et al, 1994). ERCP, in which the contrast material follows the direction of the biliary flow, is the best means to show the fistula (Singh et al, 2007; Sugiyama et al, 2000; Fig. 105.16).

Treatment aims at release of the ductal obstruction, sometimes through endoscopic sphincterotomy or, with a higher location, through a percutaneous transhepatic drain. This procedure sometimes causes the fistula to close or at least gives temporary relief (Sears et al, 1997); more lasting effect can be obtained with endostenting (Gable et al, 1997; Weintraub et al, 2006). For definitive cure, the affected liver may have to be resected (Clemens & Wittrin, 1975), or the fistula can be occluded via angiography or ERCP (Struyven et al, 1982).

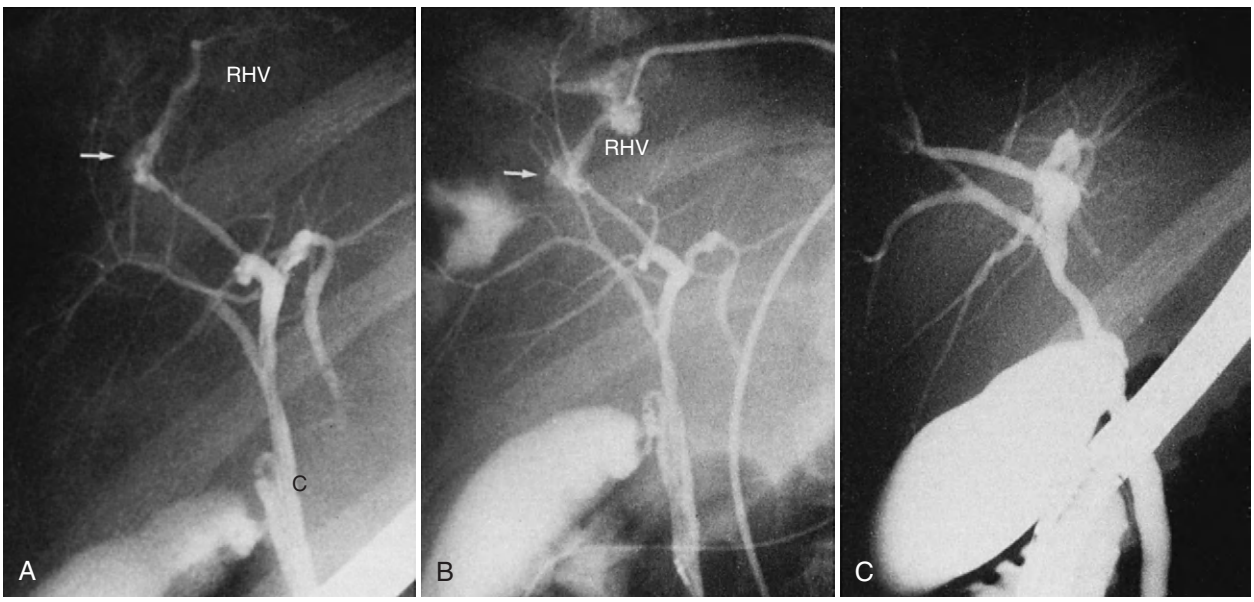


FIGURE 105.16. A, Endoscopic retrograde cholangiopancreatography (ERCP). Bile ducts injected by catheter (*C*) positioned in common bile duct. Opacification of fistula (*arrow*) and segmental branch of right hepatic vein (*RHV*). **B,** Selective opacification of segmental branch of right hepatic vein, fistula (*arrow*), and bile ducts. Balloon catheter is positioned tip to diagnostic catheter. **C,** ERCP 25 days later. Normal biliary pattern. *(From Struyven et al, 1982: Post-traumatic bilhemia: diagnosis and catheter therapy. AJR Am J Roentgenol 138:746.)*

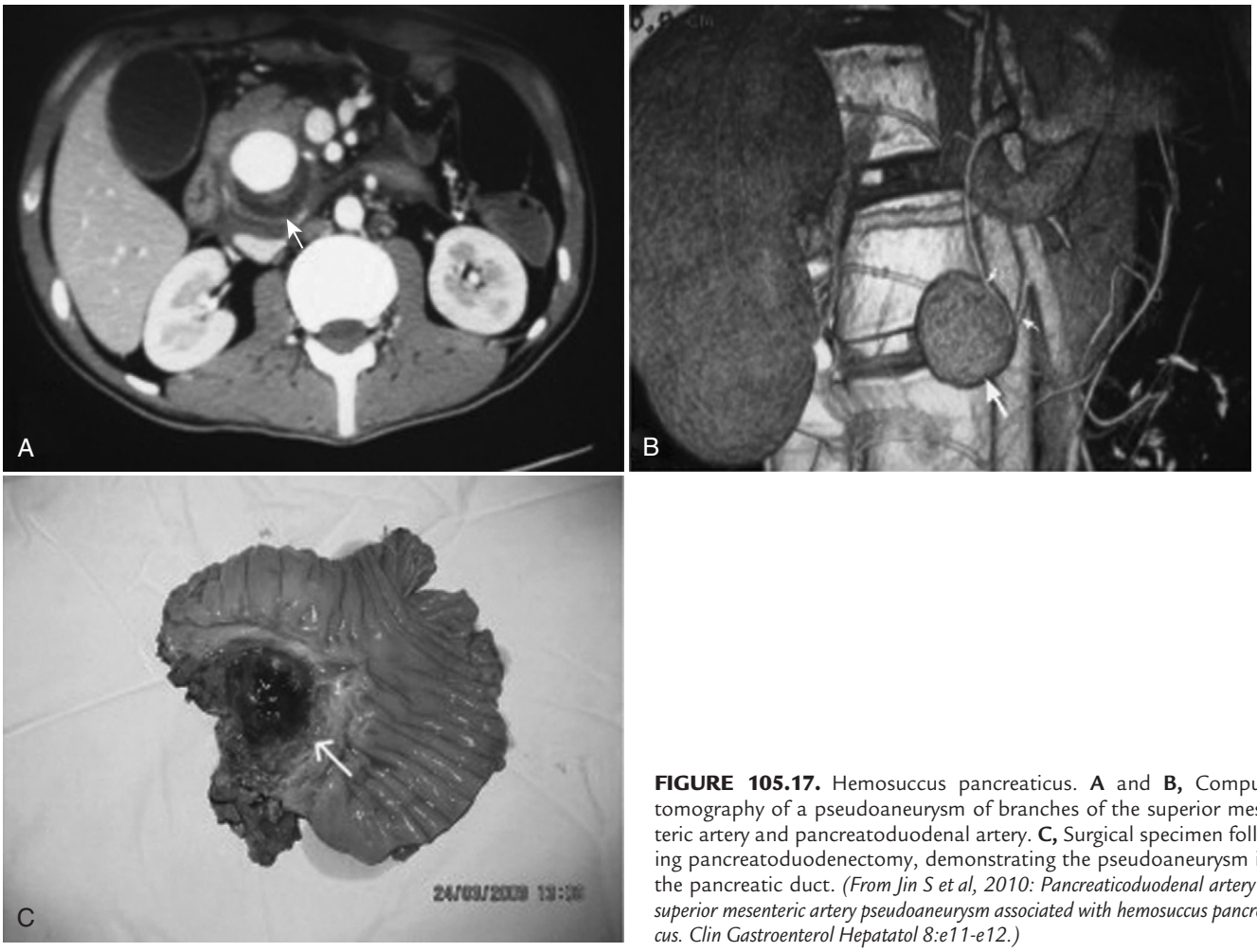


FIGURE 105.17. Hemosuccus pancreaticus. **A** and **B,** Computed tomography of a pseudoaneurysm of branches of the superior mesenteric artery and pancreatoduodenal artery. **C,** Surgical specimen following pancreatoduodenectomy, demonstrating the pseudoaneurysm into the pancreatic duct. *(From Jin S et al, 2010: Pancreaticoduodenal artery and superior mesenteric artery pseudoaneurysm associated with hemosuccus pancreaticus. Clin Gastroenterol Hepatatol 8:e11-e12.)*

HEMOSUCCUS PANCREATICUS

Hemosuccus pancreaticus, defined as hemorrhage into the pancreatic duct and through the ampulla of Vater into the GI tract, is a rare cause of intermittent UGI bleeding. First described by Lower and Farrell in 1931, the term was not popularized until 1970 by Sandblom. It is typically caused by the rupture of a pseudoaneurysm from the celiac trunk vasculature into the pancreatic duct (Fig. 105.17) secondary to acute and/or chronic pancreatitis (Sakorafas et al, 2000), although rupture of primary celiac trunk aneurysms (Massani et al, 2009) and rupture of vessels secondary to cystic neoplasms of the pancreas have also been described (Shinzeki et al, 2010; see Chapter 104).

Similar to the diagnosis of hemobilia, a high degree of clinical suspicion is needed to diagnose hemosuccus pancreaticus. Although there is no named triad, the combination of abdominal pain, hyperamylasemia, acute upper GI bleeding, and a history of acute and/or chronic pancreatitis should raise clinical suspicion of the diagnosis. The clinical sign of abdominal pain is present in most cases secondary to raised intraductal pressure from hemorrhage into the pancreatic duct, and it is accompanied by elevated serum amylase (Sakorafas et al, 2000).

Upper endoscopy is the preferred first diagnostic test, as the diagnosis of hemosuccus pancreaticus is so rare that other sources of UGI bleeding need to be ruled out. If the hemorrhage is active, blood can be seen emanating from the ampullary papilla at the time of upper endoscopy; however, because the bleeding can be intermittent in nature, a negative upper endoscopy does not preclude the diagnosis. Axial imaging with CT can often aid in the diagnosis of a pseudoaneurysm of the celiac trunk artery. ERCP can also be of a diagnostic help in unclear cases, as cholangiography can demonstrate the filling of the pancreatic duct with clots (Toyoki et al, 2008). Similar to hemobilia, selective angiography is the optimal imaging modality for suspected hemosuccus pancreaticus. The angiogram can demonstrate findings of a pseudoaneurysm of the celiac trunk vessels, and in rare instances, it can demonstrate a connection between the vessel and the pancreatic duct (Arnaud et al, 1994).

Two treatment options are available for hemosuccus pancreaticus: surgery and angiographic embolization. Following resuscitation and hemodynamic stabilization, the initial treatment should be angiographic embolization of the aneurysm with particles, as mentioned previously (see Chapters 19 and 104). Definite treatment of the bleeding using this technique is successful in 67% to 100% of cases (Lermite et al, 2007). Surgical treatment is generally reserved for uncontrolled hemorrhage or failure of angiographic embolization.

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Hepatobiliary and pancreatic surgery: historical perspective

Leslie H. Blumgart

A cursory examination of the Table of Contents of this book reveals how some of the extraordinary achievements of modern medical science and clinical practice have been applied to the management of liver, biliary, and pancreatic disease. The near-miraculous developments in our understanding of the molecular nature of disease combined with the wonders of modern imaging technology, advances in anesthesiology, and refinements in surgical technique can be so absorbing as to blind a contemporary physician to the rich history that lies behind today's practice. This introductory essay, with an appended list of references, examines the achievements of the past, on which the modern practice of liver, biliary, and pancreatic surgery depends.

ANCIENT HISTORY UNTIL THE EIGHTEENTH CENTURY

> *"For the King of Babylon stood at the parting of the way, at the head of the two ways, to use divination: he made his arrows bright, he consulted with images, he looked in the liver."*
>
> *Ezekiel 21:21*

In ancient societies, the priest had the simultaneous duties of divination, protection, and treatment of the ill. For individuals with the responsibility of divining the future, the liver was of central importance. As exposed by wounds sustained in combat, at sacrificial offerings, and at incisions after death, the liver is the most obvious organ in the abdomen and was observed to contain the most blood; because life and blood were perceived to be synonymous, the liver was considered the seat of the soul.

A tablet believed to be from the time of Hammurabi (about 2000 BCE), now in the British Museum, names the various parts of the liver and indicates the prognostic significance of each (Jastrow, 1908). The liver was divided into about 50 portions for individual inspection in an effort to overlook as little as possible. Such hepatoscopy was widely in vogue over the following centuries and was practiced by the Etruscans, as evidenced by a bronze tablet in a museum at Piacenza depicting the liver, this being strikingly similar to the Babylonian clay tablet in the British Museum.

The Roman Celsus in his text *De Medicina,* translated by W.G. Spencer in 1935, mentioned the liver and described its anatomic location: "[T]he liver, which starts from the actual partition under the praecordia on the right side, is concave within (that is on the inferior surface) and convex without; its projecting part rests lightly on the stomach and it is divided into four lobes. Outside its lower part, the gallbladder adheres to it." Celsus lived in the first century and described symptoms attributable to liver disease. Gallstones were recognized in the embalming of mummies in ancient Egypt. In 1909, a mummy with a preserved liver and a gallbladder containing 30 gallstones was presented to the Museum of the Royal College of Surgeons in London. This mummy came from Deir-el-Bahn at Thebes and was that of a priestess of the twenty-first dynasty around 1500 BCE. Elliot-Smith, an outstanding English anatomist and Egyptologist, described the gallbladder as being large and containing "many spherical calculi." The specimen was destroyed by German bombs during World War II, but the description of it was accepted as evidence that the gallstones contained therein were the earliest specimen of such calculi to have survived from antiquity (Glenn, 1971). Gordon-Taylor, a noted surgical historian in England, had likewise called attention to the terminal illness of Alexander the Great at the age of 34 (323 BCE) as an example of fatal biliary tract disease. The description of Alexander's illness as recounted by Weigall (1933) suggests that he died of complications culminating in peritonitis.

Rhazes (850-923) and Avicenna (980-1037), two Persians, wrote on general surgical topics and the nature of disease and appreciated the gallbladder but lacked knowledge of the common bile duct. Biliary fistulae were known to have formed after the drainage of an abdominal wall abscess, and it was known that individuals with fistulae had a better prognosis than those who had an external communication with the intestines (Glenn, 1971).

Greek academic achievements surpassed that of all other civilizations until the fifth century BCE. Hippocrates, widely acclaimed in medicine then and since that time, recognized the seriousness of biliary tract disease as evident in the following passage from *The Genuine Works of Hippocrates* (translated by Adams in 1939): "[I]n a bilious fever, jaundice coming on with rigor before the seventh day carries off the fever, but if it occurs without the fever, and not at the proper time, it is a fatal symptom." He also noted that in the case of jaundice, "[I]f the liver hardens it is a bad sign."

A few centuries after Aristotle recognized jaundice as an element of disease, Galen viewed biliary tract disease as a recognized clinical entity to be treated successfully in part by diet. Although Celsus had drawn attention to the gallbladder and liver in the first century CE, in the second century, Galen was the most noted author of the Greco–Roman age. Galen named three main organs that govern the body: the *heart,* the source of heat and the principal organ; the *brain,* the source of sensitivity for all parts; and the *liver,* as a principal part of the nutritive facility (Green, 1951). Galen considered jaundice to be due to yellow bile flowing into the skin and recognized that although jaundice could be the result of hepatic disease, it also could

arise when the liver was not involved at all. Galen's teaching persisted for centuries, and until the middle of the seventeenth century, many disorders were described as alterations in the balance of the main humors of the body brought about by hepatic dysfunction. As recorded by Rosner (1992), ancient Hebrew physicians used pigeons to treat jaundice by placing the pigeon on the patients umbilicus. "The pigeon will draw all yellowness out."

Many subsequent advances came from Italy about the time of the Renaissance. Benivieni (1506) in Florence described a series of autopsies in his patients, which was the first record of special reference to biliary tract disease and its clinical manifestations. Two examples are cited in the translation by Singer and Long (1954) of Benivieni's book, *The Hidden Causes of Disease:*

> *"A case of stones found in the coat of the liver—a woman of noble birth had been for long tormented by pain in the region of the liver. She had consulted many physicians but could not drive out the evil by any remedy … a few days afterward, the disease took stronger hold and she departed this life. … I then had her dead body cut open. There were found in the lower part of the membrane around the liver a collection of small stones varying in shape and color. Some were round, some pointed, some square, according as position and chance had determined, and they were also marked with reddish, blue and white spots. These stones by their weight had caused the membrane to hang down in a bag a palm's length and two-fingers wide. This we judge the cause of her death."*

The second quotation also suggests death from gallstones:

> *"Stone in the middle of the gallbladder–there died recently a noble lady, Diamantes, laid low by the pain due to stones. As she had felt no harm from it before, the physicians decided to cut open her body. A great many stones were found but none in the urinary bladder as they had expected, but save for one, which was in the gallbladder, was black and as big as a dried chestnut. [A]ll were in the covering of the liver and made its coat hang down in a little bag. This we decided was the cause of her death and declared that a wise man would be well advised to make no definite pronouncements on obscure and uncertain diseases."*

Much of the next phase of development of knowledge was centered around northeast Italy, particularly Padua, and many of the eponyms that we now use in surgery evolved from that period. The publication of Vesalius's *De Humani Corporis Fabrica* in 1543 (Fig. 1) and Harvey's *De Mortu Cordis* 100 years later marked the emergence of a new scientific spirit in anatomy and physiology. As was the custom of the times, Vesalius often recorded descriptions of findings of dissections on individuals who had recently died and expressed an opinion on the cause of death. Rains (1964), in his treatise *Gallstones—Causes and Treatment,* stated "Vesalius found [that he had] a hemoperitoneum coming from an abscess, which had eroded the portal vein. The gallbladder was yellow and contained 18 calculi. Very light, of a triangular shape with even edges and surfaces everywhere, green by color somewhat blackish. The spleen was very large." Similarly, Rains recounted that Falloppio described stones in the gallbladder and common bile duct in 1543, and that Fernell in his *De Morbis Universilibus et Particularibus* (1588) proposed that the predisposing cause of gallstone formation was stasis and observed that in jaundice, the feces become white and the urine dark, and that stones may be passed per anum. Falloppio, Vesalius, and Fernell all were active in the first half of the sixteenth century and probably discussed their theories of the cause of gallstones and the changes in the liver with which they were associated.



FIGURE 1. Andreas Vesalius, anatomist. *From* De Humani Corporis Fabrica*, 1543.*

William Harvey (1578-1657), who also worked in Padua, is held by many to be the greatest of the contributors to the study of anatomy and physiology, and he established a clear understanding of the circulation. There is little doubt that Harvey also gave thought to the liver and its relation to the circulation and to the heart in particular. Harvey's student and younger contemporary, Francis Glisson, investigated the structure and function of the liver extensively. His book *Anatomia Hepatis* was published in 1654 and is the first major modern work on hepatology. Glisson gave a clear description of hepatic anatomy, especially of the hepatic capsule and of the investment of the hepatic artery, portal vein, and bile duct. He described the fibrous framework of the liver and illustrated hepatic vascular and biliary anatomy on the basis of cast and injection studies (Fig. 2). Glisson was the first to mention a sphincteric mechanism around the orifice of the common bile duct (Boyden, 1936). He also deduced the flow of blood through the portal veins traversing the capillaries into the vena cava at a time when no microscopic studies of the liver had been done (Walker, 1966). Some of his illustrations are remarkably similar to those of Couinaud (1954, 1957, 1981) and to the images displayed

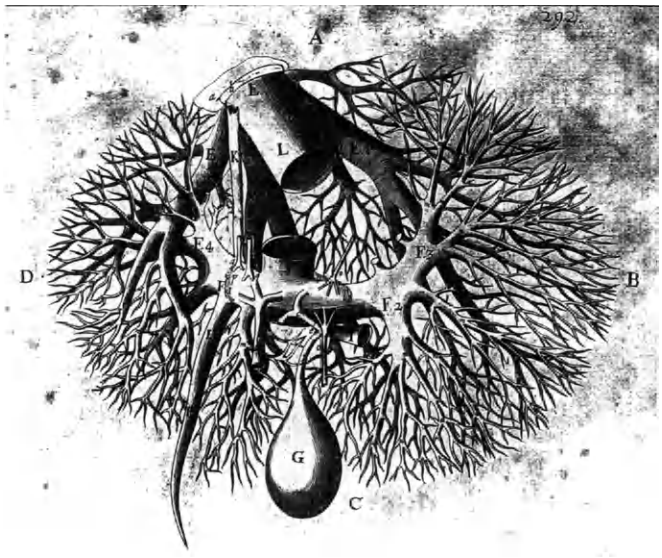


FIGURE 2. Illustration of the vasculature of the liver. *From Glisson F, 1654:* Anatomia Hepatis.

today in three-dimensionally constructed computed tomography (CT) scans. Glisson was one of the great clinical physicians of all time, yet his name is related to an anatomic structure of limited importance.

In the century that followed the time of Harvey, great activity in publication among individuals engaged in medicine occurred. As today, senior professors often held opposing opinions and expressed their feelings based on fact or fancy with equal fervor. In an attempt to select the factual, Morgagni, senior professor of anatomy and president of the University of Padua, published in 1761 an analysis of disease (translated by Benjamin Alexander in 1960) under the title *Seats and Causes of Disease,* among which are those of the liver and biliary tract. In referring to gallstones, this text analyzed the distribution of stones in male and female patients, including the age, incidence, and treatment:

> *"[A]s to the lithotomy, which has also lately been thought of, in the gallbladder, do not be surprised that I made no mention of it above. For in the first place, the pains which were excited by gallstones, that were endeavoring to discharge themselves, are not only brought on by those which come from the cysts but also by those that come from the hepatic duct. In the second place, those cystic stones which are the largest, and on account of which lithotomy seems, to some persons, to be chiefly desirable, neither endeavor to disengage themselves nor create any great uneasiness; or at least for the most part."*

This is a remarkable analysis recognizing the presence of stones in the common bile duct and the relatively innocuous nature of the large stone. A further quotation is as follows:

> *"Last of all, although there were no danger in cutting, can you suppose there would be of no great difficulty in healing the wound? We have, before our eyes, examples of three women, one of Bologna, of Frankfurt, and of Göttingen, in whom a tumor, having arisen in the epigastrium, and being opened, either by art or spontaneously discharged cystic calculi at its aperture… the first was cured; the second had a fistula left, by which a thin and chylous kind of liquor, but of a yellow color, distilled; and the third had an ulcer remain, which with its sanies discharged bilious calculi at times."*

Morgagni, as is evident in his text, presented the matter of biliary tract disease in logical sequence. He considered the incidence and the population affected in the different decades of the life span. His descriptions of the possible mechanisms by which calculi might be formed remind one of much of the writings today. Finally, he considered therapy under conservative medical management and warned about attempting to deal with the condition by operation.

As outlined by Wood (1979), numerous eponyms currently used pertain to the names of these early physicians. Johann Georg Wirsung (1600-1643) also studied in Padua and was the first to dissect the human pancreatic duct and to describe it in a letter to Riola, professor of anatomy and botany at the University of Paris in 1642. Wirsung was subsequently murdered by a Dalmatian physician, the dispute probably related to who had described the duct first (Major, 1954; Morgenstern, 1965). Abraham Vater (1684-1751) was the first to describe the papilla of the duodenum. In 1720, he wrote that "those double ducts (bile and pancreatic ducts) … come together in single combination" (Boyden, 1936). He described not an ampulla but an elevation of the mucosa of the duodenum and described the first case of an ampulla with two orifices. Likewise, the duct of Santorini takes its name from the Venetian Giovanni Domenico Santorini (1681-1737), a brilliant anatomist and one of the most exact and careful dissectors of his day. While Vater was describing the tubercle at the confluence of the pancreatic and bile ducts, Santorini was relating the first detailed observation of the orifice of the two ducts (Boyden, 1936). In observations printed posthumously, Santorini noted a second pancreatic duct of normal occurrence and named the upper one the superior pancreatic duct and the lower one the main pancreatic duct. It was not until Oddi in 1864, working in Bologna, rediscovered "Glisson's sphincter" and did studies in dogs that the holding quality of the sphincter of the outlet of the choledochus was recognized (Boyden, 1936).

The work of Morgagni was seminal in the understanding of liver and biliary disease. It started the movement toward anatomic and pathologic appreciation. Belief in the humoral causation of disease became untenable, and scientific medicine was launched. The end of the seventeenth century and the beginning of the eighteenth could be said to mark the initiation of modern medical science.

EIGHTEENTH CENTURY TO MODERN TIMES

The period from 1700 to the present day can be considered in two phases: the era before the discovery of general anesthesia, antisepsis, and x-rays in the middle of the nineteenth century and the period that followed, bringing important discoveries in blood transfusion, antibiotics, and immunology. These major developments have been followed by the birth of the electronic age, the flowering of radiologic imaging, and the increasing power of genetics and gene manipulation. The passage of surgery through these milestones is fascinating to observe, and the enormous strides in the maturation of hepatobiliary and pancreatic surgery to a recognized specialty is an important part of this story.

IMAGING IN HEPATOBILIARY AND PANCREATIC SURGERY

"Where there is no vision, the people perish. …"
PROVERBS 29:18

Following the discovery of x-rays by Roentgen (Fig. 3) in 1895, there have been continual important and extraordinary developments in radiology. A contemporary surgeon who examines images to determine the cause of disease, sometimes before taking a history or examining the patient, can hardly contemplate a time when precise imaging was not available. A landmark development in hepatobiliary imaging occurred when, after experimenting with various iodine compounds, Graham, a North American surgeon, developed oral cholecystography (Graham & Cole, 1924). Although biliary calculi had been observed by plain x-rays since 1898 (Buxbaum, 1898), the problem of detecting radiotransparent calculi was evident, and the development of oral cholecystography marked an important turning point. Postoperative cholangiography was soon developed by Mirizzi (1932) in Argentina. Intraoperative cholangiography (Mirizzi, 1937) and choledochoscopy (Bakes, 1923; McIver, 1941) also were developed.

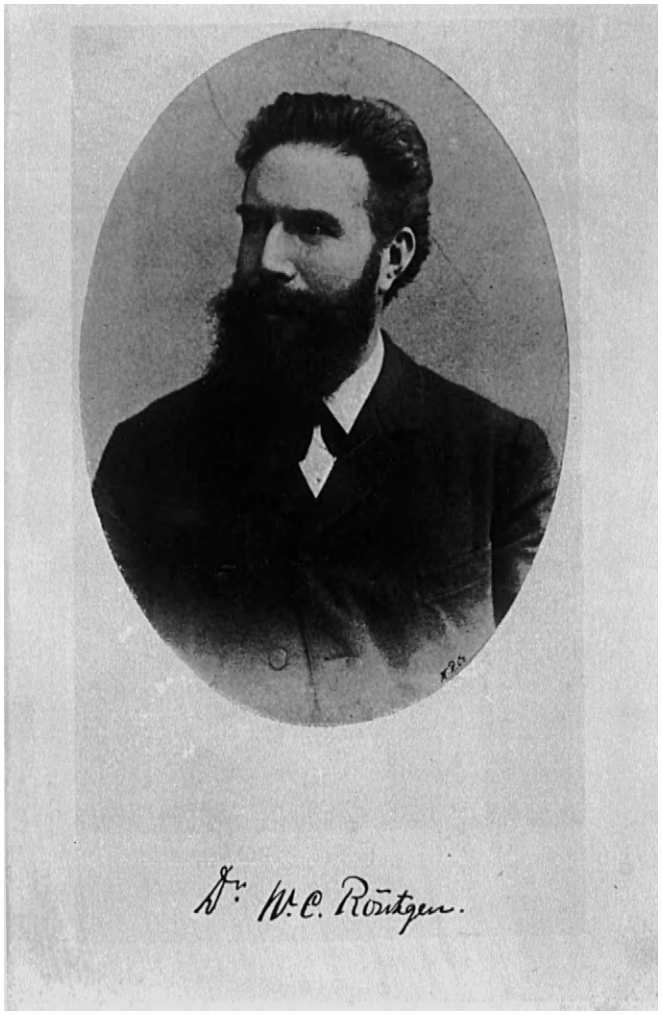


FIGURE 3. W.K. Roentgen (1845–1923). He discovered x-rays on November 8, 1895.

In the 1970s, endoscopic cholangiopancreatography (McCune et al, 1968; Demling & Classen, 1970; Oi et al, 1970; Blumgart et al, 1972; Cotton et al, 1972a, 1972b) and endoscopic papillotomy (Classen & Demling, 1974) revolutionized biliary and pancreatic radiology and approaches to common bile duct stones. The 1970s saw not only the introduction of endoscopic approaches to the biliary tract but also the development of good methods for percutaneous transhepatic cholangiography (Ohto & Tsuchiya, 1969; Okuda et al, 1974), CT of the liver (Grossman et al, 1977), and the use of ultrasound (Bryan et al, 1977) in liver and biliary surgery. Magnetic resonance (MR) axial imaging (Damadian, 1971; Lauterbur, 1973) was conceived and has led to the development of magnetic resonance imaging cholangiopancreatography (MRCP).

Not only were endoscopic and transhepatic approaches to stones now possible, endoscopic and percutaneous transhepatic intubation of the biliary tree for the relief of jaundice and for dilation of strictures became a reality. Arteriography developed to a fine degree, so that good hepatic arteriography and portography were developed (Hemingway & Allison, 1988), which inevitably led to the development of techniques for hepatic artery embolization in the management of liver tumors and of hemobilia (Allison et al, 1977).

Surgeons today have seen their world transformed by imaging; it may be said that the rapid developments in the radiology of the liver, biliary tract, and pancreas have enabled the extraordinary progress in the management of the diseases of these organs. Reference to almost any chapter in this book will attest to this fact. The extraordinary advances in technology using image guidance, rather than open operation, continue to evolve so that CT, ultrasound, and angiography now allow percutaneous image-guided methods for tumor ablation, arterial embolization, alcohol injection, and injection of other substances directly into tumors, along with the continuing development of a host of other techniques.

SURGERY OF THE BILIARY TRACT AND PANCREAS

Biliary Tract

The early part of the eighteenth century saw rapid development in the understanding of biliary disease. The ideas of Morgagni rapidly spread and were a firm basis for the changes to come. Studies regarding the structure, origin, and functions of bile were initiated in the latter half of the eighteenth century and culminated in Wieland's clarification of the structure of the various bile acids and Windaus's demonstration of the relationship of bile acids to steroids, which earned him a Nobel prize in 1927 and 1928. Boerhaave (1668-1738) established a wide surgical reputation at the University of Leiden in Holland and worked extensively on diseases of the liver and biliary tract. In 1743, Jean Louis Petit presented to the Paris Academy of Surgery a paper entitled "Considerations Concerning Tumors Produced by Retained Bile in the Gallbladder of the Liver, Sometimes Taken for Liver Abscesses." He introduced the term "biliary colic" and established the clinical treatment of it and of obstructive cholecystitis. In cases in which the gallbladder adhered firmly to the abdominal wall, Petit advised that it be punctured and opened to remove calculi, and he applied this procedure successfully in the case of one patient; this preceded Morgagni's publication of 1769

referred to earlier. Petit also coined the term "biliary colic" ("colique hepatique").

Biliary surgery began in Indiana on July 15, 1867, when John Bobbs operated on a woman who had a large tumor that he believed to be an ovarian cyst. To his amazement, when the abdomen was opened, he found an enormous gallbladder filled with stones. He opened it and extracted the calculi, sutured it carefully, and replaced it back in the abdomen (Bobbs, 1868). It was nearly a decade before a similar cholecystostomy was performed almost simultaneously by a Swiss, Theodore Kocher (Fig. 4), a North American, Sims, and an Englishman, Lawson Tait. All three surgeons planned operations in which the gallbladder was affixed to the abdominal wall to allow extraction of stones and pus and to leave it open to the exterior, so that peritonitis as a result of maneuvers within the abdomen could be avoided.

Sims worked on both sides of the Atlantic, and in Paris he operated on a patient with long-standing jaundice and a tumor in the right hypochondrium. With antiseptic technique, he opened the gallbladder and extracted 60 calculi then sutured the gallbladder to the abdominal wall; this was perhaps the first elective surgical procedure for obstructive jaundice (Sims, 1878). In the same year, in Bern, Switzerland, Kocher performed a cholecystostomy in two stages (Glenn, 1971). In the first stage, he packed the wound with gauze to the bottom of the gallbladder, and 8 days later, he emptied the residual stones from the gallbladder. Incidentally, Kocher, who won the Nobel prize in medicine in 1909 for his work on the physiology and surgery of the thyroid gland, also described sphincterotomy, or internal choledochoduodenostomy. His name is remembered by every biliary surgeon who performs mobilization of the duodenum as described by the great master (Kocher, 1903). Kocher originally described the maneuver for use in gastric surgery, but similar to so many other firsts in surgery at that time, the maneuver was first described by Jourdan (1895) and was first performed in biliary surgery by Vautrin (1896). Perhaps the maneuver should be referred to as "Vautrin's maneuver" rather than Kocher's. Tait, the great British surgeon, is given credit for performing the first cholecystostomy for gallbladder lithiasis in one stage. The patient, a 40-year-old woman, survived, and by 1884, he had performed the procedure in 14 cases with only 1 death (Tait, 1885).

The first elective cholecystectomy was done by Langenbuch (Fig. 5). While others were pursuing the construction of biliary fistulae and direct removal of gallstones, Langenbuch observed



FIGURE 4. Theodore Kocher (1841–1917), surgeon.



FIGURE 5. Karl Langenbuch (1846–1901), surgeon.

that because stones were known to recur, others had "busied themselves with the product of the disease, not the disease itself" (Langenbuch, 1882). As he was later to recount, two thoughts kept occurring to him: first, that in animal experiments, Zambeccari in 1630 and Teckoff in 1667 had performed cholecystostomy and cholecystectomy in dogs and had shown that the gallbladder was not essential to life (Langenbuch, 1896); second, that his medical colleagues believed that the gallbladder itself gave rise to stones. He developed the technique for cholecystectomy over several years of cadaver dissection and performed the operation at the Lazarus hospital in Berlin on July 15, 1882. The patient had had biliary colic for 16 years and was addicted to morphine. He was afebrile the day after the operation, had little pain, and was smoking a cigar; the patient was walking at 12 days and left the hospital 6 weeks later, pain free and gaining weight (Traverso, 1976). Report of this case (Langenbuch, 1882) led to a controversy over cholecystostomy as championed by Tait. Langenbuch's operation was the new cholecystectomy.

In 1886, Gaston had tabulated 33 cholecystostomy operations with a mortality of 27% compared with 8 cholecystectomies (5 by Langenbuch) with 1 death recorded, a mortality of 12%. By 1890, 47 cholecystectomies had been done by 27 surgeons, and in 1897, the number had increased to nearly 100 operations with a mortality of less than 20% (Gaston, 1897).

The most important recent advance in surgery of the gallbladder came 100 years after Langenbuch's first cholecystectomy. Laparoscopic cholecystectomy was conceived and first performed in Germany by Muhe in 1985. Between 1985 and 1987, he performed 94 laparoscopic cholecystectomies (Muhe, 1986, 1991). Mouret in Lyon, France, performed the first video laparoscopic cholecystectomy. He did not publish his experience, but the news spread rapidly, and Dubois in Paris published the first series of laparoscopic cholecystectomies (Dubois et al, 1989, 1990). Perissat, working in Bordeaux, further developed the laparoscopic approach and introduced it to the United States in 1989 (Perissat et al, 1990). The procedure has since been extended, so that laparoscopic exploration of the common bile duct is now possible and is routinely carried out. Today, most cholecystectomies are done using laparoscopic techniques, such that the modern surgical trainee often has little or no experience in open cholecystectomy. More recently, cholecystectomy has been done via minimally invasive techniques using robotics (Marescaux et al, 1998; Satava, 1999) to manipulate the instruments.

Not long after the performance of the first cholecystectomy, attempts were made to remove stones from the bile ducts. In 1898, Thornton performed the first removal of a stone from the common bile duct. A year later, Courvoisier operated successfully on another case of choledocholithiasis and published his well-known monograph on the pathology and surgery of the biliary ducts. He also enunciated the law that was to bear his name, which established that in cases of jaundice, if the gallbladder is not distended, the case is more likely to be one of stones. The operative procedure for exploration of the common bile duct for choledocholithiasis was not popularized, however, because of the risk of peritoneal infiltration of bile.

In 1897, Kehr (Fig. 6) performed the procedure and placed a rubber tube in the common bile duct through the cystic duct; this was the first systematic use of biliary intubation. Kehr's name is properly associated with the development of biliary intubation; Kehr (1912) and Quenu and Duval (1908) were



FIGURE 6. Hans Kehr (1862–1916), surgeon.

able to extract stones along the tunnels created by the drainage tubes. These were the precursors for techniques later developed by Mondet (1962) and Mazzariello (1966, 1974). Kehr had developed numerous combinations of drainage in patients with biliary stones, and many other surgeons rapidly developed choledochotomy without suture and using tube drainage.

Surgery of the bile ducts rapidly disseminated across Europe, England, and the United States, and in 1912, Kehr developed what came to be known as the *T-tube*. Not only was choledochotomy simplified, but biliary tract repair was done over these tubes. Kehr became justly famous for his introduction of biliary intubation and was probably the most outstanding biliary surgeon of his day. In 1913, he published a treatise entitled *Surgery of the Biliary Tract,* which for more than 40 years was the most respected text on the subject. Kehr (1908a, 1908b) described the resection of cancerous gallbladders, including hepatic resection, and he resected hepatic tumors and aneurysms of the hepatic artery. He also performed the first hepaticoenteric anastomosis.

Before the development of Kehr's tubes, choledochotomies often became biliary fistulae, either because of residual supraampullary stones, or because the surgeon had inadvertently opened the bile duct proximal to a cancer. German and Austrian surgeons were the first to perform supraduodenal choledochoduodenostomy (Riedel, 1892; Sprengel, 1891). Sprengel's operation described a side-to-side choledochoduodenostomy, and it subsequently became popular in Europe

and the United States (Madden et al, 1965). Cholecystenterostomy also was developed initially by von Winiwarter (1882) and was used later by many surgeons, including Oddi (1888).

Transduodenal surgery was not long in developing. In 1895, Kocher wrote an article on internal choledochoduodenostomy to remove supraampullary choledochal calculi; by 1899 he had performed the operation 20 times. MacBurney (1898) published his experience with duodenostomy and papillotomy in patients with impacted periampullary calculi. These early procedures of a choledochotomy and choledochoenteric anastomosis for the treatment of jaundice and of stones in the biliary tract are still used today, with frequent application of the same principles but with the use of the endoscope.

At about the same time, surgeons began to operate on cancer of the papilla. In Baltimore in 1900, Halsted resected a portion of the duodenum that included a tumor and reimplanted the common duct, at the same time performing a cholecystostomy. He then reoperated to remove the gallbladder. Mayo (1901) reported an operation on a 49-year-old man with papillary cancer. Mayo opened the duodenum, removed the tumor, and carried out a choledochoduodenostomy. This was the first transduodenal ampullectomy. Kausch (1912) in Germany and Harmann (1923) in France gave accounts of resections of ampullary tumors. In Lausanne, Switzerland, Roux, a disciple of Kocher, had described preparation of a "jejunal loop" for use in gastric surgery, and it soon became an adjunct in biliary surgery (Roux, 1897). This Roux-en-Y procedure was soon used by Monprofit (1904) in the performance of cholecystojejunostomy, and he proposed it for hepaticojejunostomy at the French Congress of Surgery in 1908. Dahl (1909), in what he called "a new operation on the bile ducts," was the first to advocate the Roux anastomosis in biliary surgery.

With the advent of cholecystectomy and choledochostomy came the inevitable sequelae of residual bile duct stones and iatrogenic lesions. Initially, these were treated by various forms of intubation, similar to the techniques advocated by Kehr, but many leading surgeons, such as Moynihan and Mayo, used hepaticoduodenal anastomoses (Estefan et al, 1977). Dahl (1909) used the Roux-en-Y loop, but more recently, other authors (Madden et al, 1965; Schein & Gliedman, 1981) have preferred choledochoduodenostomy as described previously.

Operative biliary drainage in upper biliary tract cancer and in patients with severe scarring in the porta hepatis is always difficult. Kehr (1913) successfully performed three operations in which he fixed a jejunal loop to a cut section of a hepatostomy wound; similar procedures were done by others, as cited by Praderi (1982). Longmire and Sanford (1948) performed a similar operation, resecting the end of the left lobe of the liver and anastomosing it to a jejunal loop. This technique, although popular for a short time, was complicated by stenosis and has fallen out of favor.

Goetze (1951) developed a procedure of transanastomotic drainage with a catheter that went through the hepatic parenchyma, the anastomosis, and the jejunal loop. Goetze's contribution was apparently forgotten but was reinvented and popularized by others, including Praderi in 1962 (Praderi, 1982). Praderi argued strongly that Goetze's procedure was the answer to difficult procedures in the high biliary tract but conceded that the development of transhepatic percutaneous cholangiography (Okuda et al, 1974) allowed for the development of transhepatic percutaneous methods for intubation and dilation of the biliary tract, which are now common procedures throughout the world.

The greatest advances in techniques for repair of biliary injuries came from two sources. At the Lahey clinic in the United States, three generations of famous surgeons headed by Lahey, Cattell, and Warren perfected the reconstruction of the common bile duct as an immediate or delayed procedure and splinted their anastomoses with a variety of tubes (Estefan et al, 1977). The results of these techniques were unsatisfactory, with numerous recurrent strictures. However, following the detailed study of the anatomy by Couinaud in France (1954), Hepp and Couinaud (1956) and Soupault and Couinaud (1957) developed techniques for direct biliary–enteric anastomosis, either to the left hepatic duct or to the segment III duct of the left liver. These surgical techniques have become widely accepted and are used throughout the world (Bismuth & Corlette, 1956; Bismuth et al, 1978; Voyles & Blumgart, 1982; Warren & Jefferson, 1973).

Pancreas

Like liver surgery, pancreatic surgery developed largely as a result of responding to wounds inflicted in wars. Claessen (1842), Ancelet (1866), Da Costa (1858), and Nimier (1893) documented the early development of pancreatic surgery. In 1923, Harmann wrote an extensive review of the French, German, and English literature. Early efforts at elective pancreatic surgery largely revolved around drainage of cysts (Thiersch, 1881). In 1883, Gussenbauer marsupialized a pancreatic pseudocyst, and the patient survived. Other surgeons, including Senn (1886), soon performed similar procedures.

Direct anastomosis of the pancreas to the gastrointestinal tract followed in the early part of the twentieth century, when Coffey (1909) performed an anastomosis of the tail of the pancreas to the small bowel. Ombredanne (1911) anastomosed a pancreatic cyst to the duodenum, and Jedlicka (1923) anastomosed a cyst to the posterior wall of the stomach. Chesterman (1943) performed a cystojejunostomy, and König (1946) carried out the same operation to a Roux-en-Y loop of jejunum.

Operations for pancreatic tumors were being done at about the same time. Ruggi (1890) reported a resection of a large lesion of the tail of the pancreas, and Briggs (1890) performed a similar operation. Biondi (1897) reported resection of a tumor arising from the inferior part of the head of the pancreas, and the patient was still alive 18 months later.

Whipple (Fig. 7) and associates (1935) published a technique for cephalic duodenopancreatectomy, done in two stages, for cancer of the ampulla of Vater. In the first operation, they performed a cholecystogastrostomy and gastroenterostomy. In the second and subsequent procedure, they resected the head of the pancreas with a portion of the duodenum without anastomosis to the stump of the pancreas, which they sutured. Whipple (1941) subsequently performed this operation in one stage and reported 41 cases with a mortality of 27%. Eventually, the technique of this operation was perfected. Although English-speaking surgeons throughout the world continue to call this operation "Whipple's operation," the procedure had been done many years before.

Sauve (1908) reviewed the literature on pancreatectomy and reported that several surgeons had resected small tumors from the head of the pancreas, and larger ones from the body of the organ, without touching the duodenum. Codivilla of Italy is

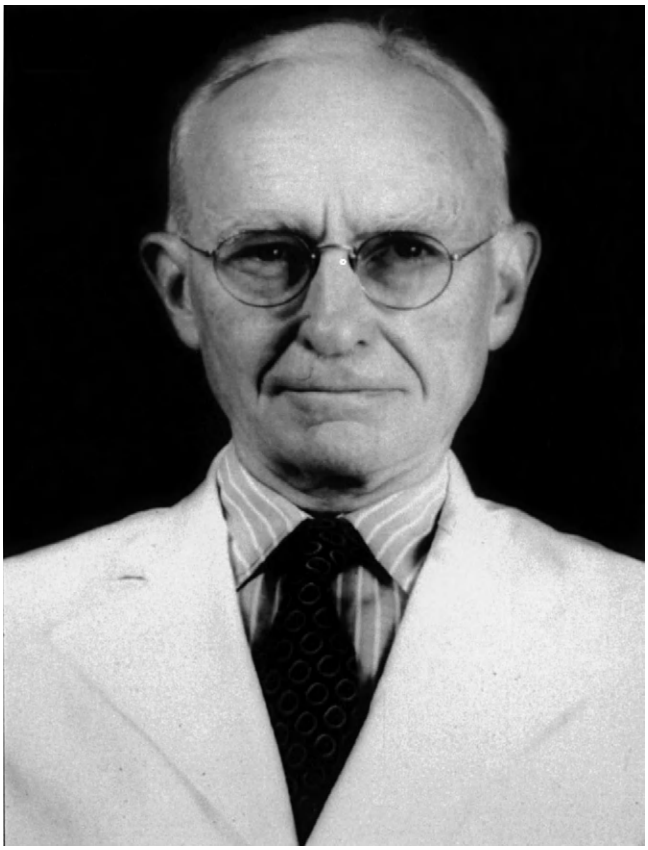


FIGURE 7. Allen O. Whipple (1881–1963), surgeon.

reported to have resected the duodenum and head of the pancreas and performed a cholecystojejunostomy in 1898, but the patient died in the postoperative period. The first surgeon to perform cephalic pancreaticoduodenectomy successfully was Kausch, a professor of surgery in Breslau and later in Berlin. On June 15, 1909, he performed a cholecystojejunostomy on a jaundiced 49-year-old man; on August 21, 1909, Kausch reoperated, performing a posterolateral gastroenterostomy and resection of the head of the pancreas with the tumor, the pylorus, and the first and second part of the duodenum. He anastomosed the third portion of the duodenum to the pancreatic stump. Kausch (1912) published a report entitled "Cancer of the Duodenal Papilla and Its Radical Treatment." He gathered in that publication all reports that included excisions of the papilla. Tenani (1922) reproduced this operation with success, also in two stages but with one difference: Tenani performed a choledochojejunostomy, and the patient survived 3 years. Kausch and Tenani, although cited by Whipple (1941), are generally ignored in the English and American literature.

Resection later was extended to deal with cancers of the common bile duct and of the duodenum (cancers of the proximal bile duct are described subsequently in the section on liver surgery). Recognition of endocrine tumors of the pancreas later led to operations for these conditions. Wilder and colleagues (1927) reported the first case of resection of an insulinoma arising from the islet cells of the pancreas. Mayo operated on a patient in whom he found a tumor of the pancreas with metastases to the liver, and an extract from one of the metastases produced an insulin-type reaction when injected into a rabbit. Graham and Hartman (1934) reported subtotal pancreatectomy for hypoglycemia, and total pancreatectomy was performed by Priestley and colleagues (1944) for a patient in whom there was proven hyperinsulinism, but no tumor of the pancreas was to be found. The patient was cured by the operation, and the small tumor causing the syndrome was discovered during the pathologic examination.

Later, Fallis and Szilagyi (1948) performed total pancreatectomy for cancer, and this procedure was developed further in the hope that total removal of the gland would reduce morbidity and mortality and perhaps lead to better results. ReMine and colleagues (1970) and Brooks and Culebras (1976) adopted this approach, but early suggestions regarding efficacy were not fulfilled, and total pancreatectomy for pancreatic cancer has largely been abandoned. Fortner (1973) described the even more extensive procedure of regional pancreatectomy. The operation included an extensive total pancreatectomy and resection of the pancreatic segment of the portal vein—and sometimes the hepatic and superior mesenteric arteries, if these vessels were invaded by tumor—together with subtotal gastrectomy and regional lymph node dissection. Fortner's results have not been reproduced by others.

Surgery for pancreatitis also developed over the same period, and the severity of acute pancreatitis was recognized. Ockinczyc (1933) revealed the frustration of the times when he advocated "the use of drainage of the pancreas and hope." Because the mortality of emergency surgery reached 78%, the conservative approach to acute pancreatitis was advocated. Nevertheless, some patients with acute pancreatitis still came to operation because of the necessity to treat gallstones and pancreatitis or to deal with complications, such as abscess and pseudocyst (Cattell & Warren, 1953).

The development of intensive care, antibiotics, and better metabolic management of patients with acute pancreatitis led to improvements in outcome, although the death rates remained unacceptably high. Ranson and colleagues (1976) and Imrie (1978) made important contributions in that they defined the evaluation of the severity of an attack. The surgical treatments of abscess and peritonitis were made systematic. The role of gallstones in acute pancreatitis was defined, particularly by Acosta and Ledesma (1974), and endoscopic papillotomy to extract calculi impacted at the papilla of Vater was also described.

Surgical procedures aimed at the treatment of chronic pancreatitis had been developing since the beginning of the twentieth century. As mentioned previously, Coffey (1909) had anastomosed the tail of the pancreas to a loop of jejunum, and in 1953, Link reported external drainage of a pancreatic duct in a patient who lived for a prolonged period but expelled calculi periodically from the fistula tract. Roget (1958) described 50 cases treated this way, but only a few patients were cured by drainage. Doubilet and Mulholland (1948) attempted sphincterotomy in the treatment of pancreatitis. As a result of the success of cystojejunostomy in the treatment of pancreatic pseudocyst mentioned earlier, Cattell in 1947 used a side-to-side anastomosis between a loop of jejunum and the pancreatic duct in an attempt to relieve pain in a patient with cancer of the head of the pancreas. Subsequently, Longmire and associates (1956) carried out end-to-end pancreaticojejunostomy to a Roux-en-Y loop of jejunum; however, this procedure proved unsuccessful. Du Val (1957) performed a similar operation in an attempt to drain the pancreatic duct, but this too was unsuccessful.

Leger and Brehand (1956) and von Puestow and Gillespy (1958) performed pancreatic ductal drainage in chronic pancreatitis patients for the relief of pain. Longitudinal opening of the pancreactic duct allowed better decompression after anastomosis to a jejunal loop. Mercadier (1964) performed a similar operation without the need for splenectomy, and further technical variations were introduced more recently by Prinz and Greenlee in 1981 and by Frey and Smith in 1987. Mallet-Guy (1952) and Mercadier (1964) performed resection of the left pancreas for chronic pancreatitis. This approach subsequently was extended, so that only a small portion of the head of the pancreas remained. A more modern approach aimed at conserving pancreatic parenchyma has since been developed (Beger et al, 1985) and was further promoted by Buchler and collegues (Di Sebastiano et al, 2007).

LIVER SURGERY

Liver surgery has evolved from being almost nonexistent to comprising a repertoire of operations that can safely remove nearly any amount of liver tissue (Chakravorty & Wanebo, 1987; Fortner & Blumgart, 2001). These operations are now performed at numerous hospitals and medical centers throughout the world. Courageous surgeons were enabled by extraordinary developments in anesthesiology, blood transfusion, infectious disease, and radiologic imaging.

Features of the anatomy and physiology of the liver that allow major resection were known in ancient times. The structural arrangement of the liver into lobes was apparent to individuals preparing animals for food or for ceremony or to those preparing humans for mummification. Two other properties of the liver, functional reserve and rapid regeneration, were suggested by the early Greek mythology of Prometheus, in which Prometheus's liver grew back nightly after the eagle's daily and apparently bloodless "resections." This oft-cited myth does not necessarily mean that the ancient Greeks knew about liver regeneration; however, more recent evidence provides dramatic proof of the liver's power to grow back rapidly (Blumgart et al, 1971).

Knowledge of the liver's lobar and segmental structures, functional reserves, and capacity to regenerate and the prevention of hemorrhage are essential for major surgical resection. This knowledge also is relevant to transplantation, particularly of split-liver homograft transplantation and in the use of living, related donors.

Early descriptions of operations on the liver usually concerned complete or partial avulsion of some portion that was protruding externally as a result of abdominal trauma. Berta in 1716 amputated a portion of liver protruding from the abdomen after a wound, and Von Bruns in 1870 (Beck, 1902) removed a lacerated part of the liver of a soldier wounded in battle. Despite these anecdotal descriptions, true hepatobiliary operations were not possible until the advent of anesthesia (Fig. 8) and antisepsis (Lister, 1867a, 1867b; Fig. 9). Although Warvi (1945) recounted that Couzins performed a liver resection in 1874, Langenbuch (1888) recorded the first planned hepatic resection in Germany. In the United States, Tiffany (1890) resected a liver tumor, and Lucke (1891) reported a liver resection for cancer. Keen (1899) in the United States reported 76 liver resections, of which 37 were for benign or malignant tumors.

About the time of these surgical developments, Rex (1888) and later Cantlie (1897a, 1897b) did detailed anatomic studies of the liver and its intrahepatic architecture. These studies established the lobar and segmental structure of the liver and of the Glissonian sheath enclosing structures that enter or leave the organ at the porta hepatis. They delineated the planes within the parenchyma of the organ that were relatively devoid of major blood vessels and bile ducts. These descriptions would make possible controlled hepatic resection.



FIGURE 8. Ether anesthesia. The first public demonstration of surgical anesthesia was given in Boston by Professor J.C. Warren and W.T.G. Morton on October 16, 1846. This photograph depicts a second procedure carried out on October 17th.

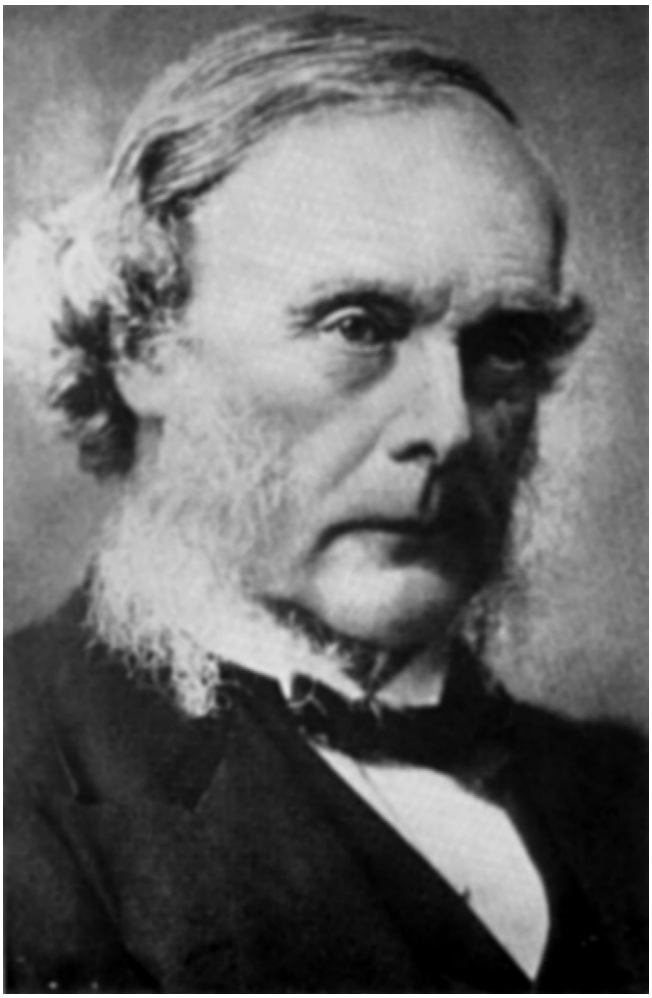


FIGURE 9. Joseph Lister (1827–1927), surgeon.

Surgeons quickly learned to fear the liver's friability and capacity for bleeding and its propensity for biliary leakage after operation. Elliot (1897) wrote that the liver is "so friable, so full of gaping vessels and so evidently incapable of being sutured that it seemed impossible to successfully manage large wounds of its substance." Kousnetzoff and Pensky (1896) reported, however, passing ligatures in the liver substance at a sufficient distance from the margins of the wound to ensure that they would not slip, and reported that, by pulling these up tightly, it was possible to allow them to cut into the liver parenchyma and compress the blood vessels. In writing about surgical approaches for parenchymal transection of the liver and the arrest of bleeding during operations on the liver, Garre (1907) paid respect to Kousnetzoff and Pensky's work, in which they had essentially shown that the vessels in human liver are no less resistant than arteries and veins of similar caliber in other parts of the body, and that they were suitable for ligature. These basic techniques for suture of the liver substance and ligation of vessels as a means of controlling hemorrhage have persisted to modern times and find recent application in the control of the pedicles of the liver within its parenchyma, as described by Ton (1979), and more recently in approaches to the control of the pedicles of the liver described by Couinaud (1954), Patel and Couinaud (1952a, 1952b), Takasaki and others (1986), and as developed and practiced by Launois and Jamieson (1992). Although ligatures and suture ligation remain the basic mainstays for the control of intrahepatic vessels, stapling techniques are now used for the same purpose (Fong & Blumgart, 1997).

Garre (1907) described the use of Doyen's elastic stomach clamp to provide compression of the liver before it is transected, and he referred to the work of Masnata and Lollini in Bologna, who used a similar clamp. This method also has been used more recently by Storm and Longmire (1971) and Balasegaram (1972a, 1972b). Although almost totally abandoned in recent times, such clamps still are occasionally employed. Garre (1907) mentioned attempts to provide perforated plates to be used on either side of a wound of the liver, through which sutures could be passed to allow compression of liver tissue and bleeding vessels. This technique also was conceived more recently for the management of bleeding after elective liver resection (Wood et al, 1976) and for the control of bleeding from liver injury (Berne & Donovan, 2000).

Garre (1907) also emphasized the use of packing bleeding hepatic wounds, and he advocated that packing ought to be considered more frequently in cases of injury; this, too, was prophetic. Having passed through the phases of vascular ligation and hepatic resection for wounds of the liver, modern surgeons now rely much more frequently on packing to control oozing and hemorrhage for ragged and exposed liver lacerations (Berne & Donovan, 2000). The use of such packing recognizes, but does not specifically state, that major hemorrhage in the liver does not usually occur from the cut surface of the parenchyma but rather occurs from the main hepatic veins or lacerations to the vena cava.

In a seminal contribution in 1908, Pringle described a method of temporarily compressing the portal inflow vessels so as to reduce liver bleeding, but all eight patients he described died during surgery or shortly thereafter. Later, Pringle described the method as being uniformly successful in animals and used the technique successfully on a patient. This technique has been used ever since to control hepatic inflow, and although initially used to occlude the inflow for periods of 1 hour or more, it is now employed in an intermittent fashion.

The early understanding of liver structure and function and of the first operations on the liver in the latter half of the nineteenth century set the scene for the rapid advances of the twentieth century. Not only did anatomic description reach a high level of accuracy relevant to the operating surgeon, advances in operative technique and extraordinary developments in diagnostic imaging as outlined previously allowed the flowering of hepatobiliary surgery as a specialty.

Major Hepatic Resection

Wendell (1911) was the first to perform a successful right hepatic lobar resection using hilar ligation. Nevertheless, his achievement was lost to his colleagues for many years, and it was not until the detailed anatomic studies of Hjortsjo in 1951, Healey and Schroy in 1953, and Couinaud in 1954 that the concept of segmental anatomy as originally described by Rex and Cantlie was finally accepted. Couinaud's (Fig. 10) seminal work in 1954 simplified the understanding of segmental liver anatomy and made it easily applicable by numbering the liver segments I through VIII. Goldsmith and Woodburne (1957) used a different nomenclature but subdivided the liver similarly. Subsequent refinements in the description of the liver were



FIGURE 10. Claude Couinaud (1922–2008), surgical anatomist.

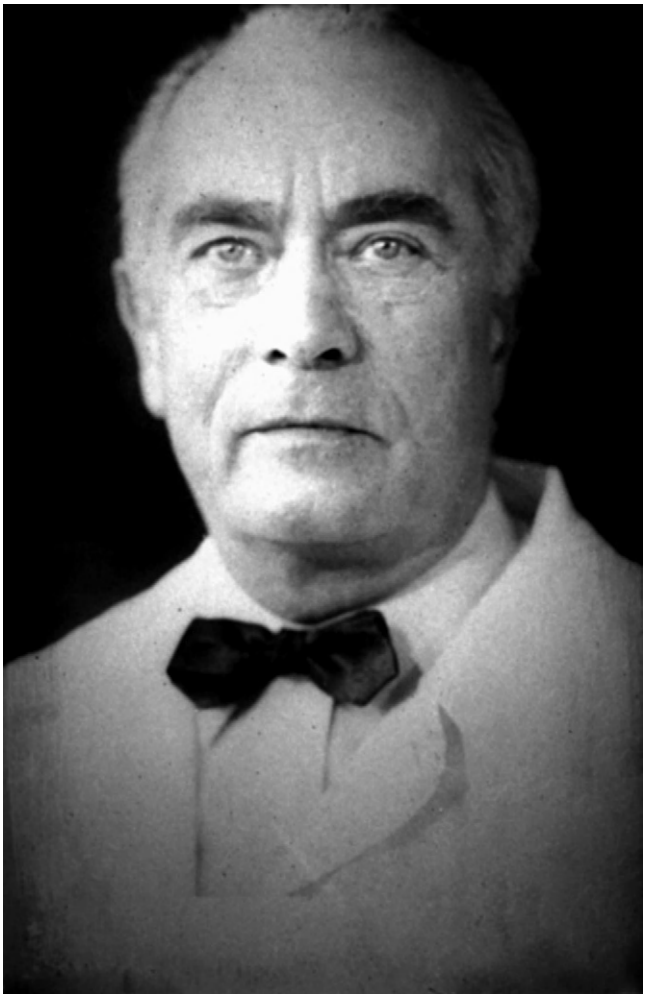


FIGURE 11. Jean Louis Lortat-Jacob (1908–1992), surgeon.

offered by Couinaud (1981) in a monograph, which contributed greatly to the understanding of practical surgical anatomy.

In 1950, Honjo published a case of anatomic right hepatectomy; the operation was performed in Kyoto, Japan, on March 7, 1949, and was later reported by Honjo and Araki (1955) in English. In 1952, Lortat-Jacob (Fig. 11) and Robert performed a true anatomic liver resection with preliminary vascular control. These reports opened the way for the development of liver surgery. Lortat-Jacob's operation captured much attention, and many further case reports followed. As recounted by Fortner and Blumgart (2001), at the Southern Surgical Association's meeting in the United States on December 10, 1952, Quattlebaum (1953) described a right hepatic lobectomy for hepatoma. The operation had been done about 4 months after that of Lortat-Jacob and Robert. Apparently unaware of Quattlebaum's achievement, and thinking he would be the first to do a so-called right hepatic lobectomy in the United States, Pack at Memorial Sloan–Kettering Cancer Center in New York performed the operation on a 40-year-old woman on December 14, 1952 (Pack et al, 1955).

Pack and colleagues (1962) recognized quickly the opportunity to study liver regeneration. Their studies were the first to describe and document regeneration of the human liver after major resection and suggested that complete regeneration occurs over 3 to 6 months. Later, Lin and Chen (1965) studied metabolic function and regeneration of the cirrhotic liver and found no discernible regeneration after resection. Blumgart and colleagues (1971) described the speed of liver regeneration as recovery of liver size within 10 to 11 days after major hepatic resection for trauma.

Contrary to the trends toward anatomic precision, Lin (1958) advocated a finger-fracture technique for liver resection, removing a hepatic lobe in 10 minutes with an average of 2000 mL of blood replacement. The surgical bluntness of this approach and the absence of the customary surgical principles and techniques precluded widespread acceptance of the technique. Similarly, a prominent figure in the early development of liver surgery, Brunschwig (1953; Serrea & Brunschwig, 1955) advocated nonanatomic resection, but his results—with a very high operative mortality for so-called simple right lobectomy, mostly from uncontrolled hemorrhage—led him to accept the approach of Lortat-Jacob. Brunschwig's report of long-term survivors after hepatic resection for advanced cancer challenged the prevailing skepticism about resecting liver tumors.

The laparothoracotomy approach of Lortat-Jacob and Robert in 1952 quickly became the standard for major hepatic resection. Opening the chest added operating time and increased morbidity but gave needed exposure to the liver. Later, the introduction of costal arch retractors made thoracotomy

extension obsolete for most hepatic resections. Steps generally considered unnecessary, such as T-tube drainage of the common bile duct, were eliminated in the 1970s. Opinions were divided in the 1970s and 1980s about the superiority of either intrahepatic or extrahepatic management of the major hepatic veins. Closed drainage was substituted for multiple Penrose drains and packing, although these were still advocated by some in the 1980s. Many hepatic resections have been done without drainage, as described by Franco and associates (1989) and subsequently at Memorial Sloan–Kettering Cancer Center (Fong et al, 1996).

Methods for anatomically based segmental liver resection that conserves parenchyma were developed and have proved valuable in hepatic resection for tumor. Numerous methods to transect the liver parenchyma had been advocated, including the knife handle (Quattlebaum, 1953), nitrogen knife (Serrea & Brunschwig, 1955), electrocautery (Fortner et al, 1978), microwave tissue coagulator (Tabuse, 1979), waterjet (Papachristou & Barters, 1982), ultrasonic aspiration dissector (Hodgson & DelGuercio, 1984), and harmonic scalpel; other techniques are described on an almost daily basis, and simple crushing of the liver tissue remains in use by many.

Bleeding has remained a problem in many cases, and preliminary vascular control is difficult or impossible in some clinical settings. Inflow occlusion using the Pringle maneuver for longer than 15 to 20 minutes was considered hazardous. Local and general hypothermia was used in an effort to increase the liver's tolerance of the presumed ischemic anoxia associated with the procedure (Longmire & Marable, 1961). More complete vascular control was obtained by Heaney and colleagues (1966), without hypothermia, by employing aortic cross clamping and temporary occlusion of the porta hepatis and vena cava for 24 minutes without ill effect. Fortner and colleagues (1971) described isolation-hypothermic perfusion of the liver, making prolonged vascular isolation for complicated resections possible. Huguet and associates (1978) challenged the long-held belief that the liver could tolerate only 15 to 20 minutes of normothermic perfusion by extending the period to 65 minutes. This observation was subsequently confirmed (Bismuth et al, 1989; Huguet et al, 1992, 1994). As described previously, however, major bleeding during liver resection usually arises from the major hepatic veins or vena cava, and development of techniques of low central venous pressure anesthesia during liver resection, as first described by Blumgart and colleagues (Cunningham et al, 1994, Melendez et al, 1998), have proved simple and efficacious and have rendered vascular isolation techniques rarely necessary (Jarnagin et al, 2002).

Apart from hepatic resection, many other techniques for the enucleation of tumors and of hydatid cysts have been developed. Garre (1907) had first noted that if he kept close to the line of the dense membrane around hydatid cysts—so as not to enter the tissues of the liver too deeply, where large vessels may be encountered—it was possible to resect such lesions with minimal blood loss. Enucleative techniques are now used by contemporary surgeons, not only for the removal of hydatid cysts but also for the enucleation of giant hemangiomata (Baer et al, 1992; Blumgart et al, 2000; Hochwald & Blumgart, 2000). As described in this book, enucleation also may be used for resection of certain neoplasms of the liver, such as fibronodular hyperplasia.

The widespread use of laparoscopic cholecystectomy led to the development of techniques for laparoscopic resection of the liver. First used by Gagner and colleagues (1992), laparoscopic partial hepatectomy has been used by many surgeons. Ferzli and colleagues (1995) and Azagra and colleagues (1996) developed the operation for anatomic resection of the left lateral segment, and most operations have involved this procedure. More recently, major hepatectomy has been performed using laparoscopic techniques. Experience is limited, however, and the indications and place of laparoscopic liver resection are under active investigation.

Liver Tumors

The management of liver tumors has a relatively short history. After the initial reports of hepatic resection for tumors performed by Langenbuch (1888), Tiffany (1890), Lucke (1891), and Keen (1899), no significant reports were published until Foster's review in 1970 of a multiinstitutional survey conducted on 296 adults who had liver resection for primary cancer and were followed for at least 5 years or until death. The operative mortality rate was 24%. Foster also studied the records of 115 patients who had had hepatic resection for metastatic colorectal cancer. Operative mortality was 17.3%, and 21% survived for at least 5 years. Hemorrhage during operation was still a problem, and the operative mortality rate was essentially the same or higher than the cure rate so that skeptics remained unconvinced.

In the 1970s, major hepatic resection for tumors became more frequent, and this coincided with improvements in anesthesia, surgical technique, postoperative support, and significantly with the development of better imaging modalities. In the United States, Wilson and Adson (1976), Fortner and colleagues (1974), and Thompson and colleagues (1983) were major figures in this area of endeavor. In Asia, Ong (1977) and others were early explorers in the field, and other major centers made significant technical improvements with encouraging results (Attiyeh et al, 1978; Cady et al, 1979; Starzl et al, 1975).

Morbidity and mortality rates decreased dramatically, and major centers began to provide encouraging preliminary long-term survival figures. As described by Fortner and Blumgart (2001), by the 1980s, the early reluctance by many surgeons to accept the therapeutic benefit of hepatic resection for tumors faded before the onslaught of encouraging reports from a variety of institutions in the United States, Europe, and Southeast Asia.

Methods for limiting the extent of the parenchymal transection developed along with the emergence of surgical resection for tumors in cirrhotic and noncirrhotic livers. Although suggested originally by Pack and Miller (1961) and by McBride and Wallace (1972), Asian and European surgeons soon assumed a leadership role in developing isolated segmental resection and described various operations (Bismuth et al, 1982; Hasegawa et al, 1989; Scheele, 1989; Ton, 1979). The development of reliable intraoperative ultrasound allowed further developments in liver resection (Bismuth et al, 1982; Makuuchi et al, 1985), and subsegmental resection was developed. More recently, the segmental approach was reported and popularized in the United States, particularly by Blumgart and others (Billingsley et al, 1998; DeMatteo et al, 2000). The difficulty of the approach to the caudate lobe was addressed, and the surgical anatomy and technique for caudate resection, either as an isolated segment (Lerut et al, 1990) or in combination with major resections, was described by Blumgart and colleagues (Bartlett et al, 1996).

Probes to perform cryosurgical ablation were developed (Ravikumar & Kaleya, 2000), and cryosurgery-assisted segmental resection has been described (Polk et al, 1995). Radiofrequency ablation for liver tumors also has been evaluated (Curley et al, 1999; Wood et al, 2000). In the future, surgeons may perform controlled tumor ablation or hepatic resection for tumors using robotic techniques and refinements in the development of virtual reality techniques (Marescaux et al, 1998; Satava, 1999). Image-guided surgery opens great possibilities for developments in hepatic surgery in the future.

The evolution of liver surgery for cancer was influenced profoundly by the geographic distribution of the disease. Surgeons in the United States and Europe were confronted much more often with metastatic cancer or hepatocellular carcinoma (HCC) in otherwise normal livers. In the 1980s and early 1990s, surgeons in the United States had no great drive to conserve normal liver tissue. By contrast, surgeons in Asia were confronted frequently with HCC in patients with hepatitis B and cirrhosis of the liver. Estimating the functional reserve of the cirrhotic liver became a major concern, and methods for limiting the resection of nontumorous liver were developed. Screening programs for the detection of HCC at an early stage were a natural corollary.

Primary liver cancer (HCC) occurs mainly in areas where viral hepatitis is endemic. Because of the prevalence of hepatitis B infection in Southeast Asia, most of the initial, significant, published experiences examining the treatment of primary HCC are from Southeast Asia. Improved diagnostic and surgical approaches in Japan permitted the Liver Cancer Study Group of Japan (1990) to report a 5-year survival rate of 57.5% for HCC; a high proportion of the cases were small, encapsulated tumors. From China, Tang (1993) reported a 5-year survival rate of 40.2%.

In the West, experience with HCC differed from that reported in the East in material ways: tumors were generally large at presentation, the incidence of viral hepatitis was much lower, and many patients did not have underlying cirrhosis. There were several reports of surgical mortality rates for hepatic resection in cirrhotic patients, ranging from 15% to 100%. In recent years, spread of hepatitis B and hepatitis C has changed the demographics of the disease in the United States and in Western Europe. This change has allowed a much greater surgical experience, and better techniques and improved patient selection have led to vastly improved results. Blumgart's group (Fong et al, 1999) reported a mortality rate of 5% in 100 resections, 57 being major resections, in patients with HCC and cirrhosis, and a 5-year survival of 37% was reported among patients operated on since 1990.

Today the surgical mortality rate in noncirrhotic patients, even for the most extensive resections, is uniformly less than 5% in major centers. The overall 5-year survival is approximately 35% in patients with HCC reported from Western series, in which small HCC is relatively rare (Bismuth et al, 1986; Ringe et al, 1991). In a study reported by Blumgart and others (Fong et al, 1999), patients who had HCC with a median tumor size of 10 cm but no cirrhosis had hepatic resection with a surgical mortality of 3.7% and a 5-year survival of 42%. Although survival rates have not changed substantially, a great improvement has been seen in morbidity and mortality.

In recent years, a move toward hepatic transplantation has been seen in selected patients with small HCCs within a cirrhotic liver. Patients with small HCCs and compromised liver function seem to be ideal candidates for total hepatectomy and allotransplantation.

The treatment of metastatic liver tumors by hepatic resection was viewed initially as highly dubious. Many regarded the removal of tumor from the liver by hepatic resection as an irrational approach. The natural history of colorectal cancer offered the opportunity for resection of liver metastases more often than any other cancer in Western countries. The multiinstitutional report from Foster (1970) in the United States suggested a 5-year survival rate of 25%, and multiple other reports supported that view. However, the question remained: How long could patients have lived without surgical operations?

A landmark article from Glasgow (Wood et al, 1976) described the natural history of colorectal hepatic metastases. It was shown that survival depended on the extent of the disease, and that multiple bilobar metastases indicated a much more serious prognosis than single or multiple nodules on one side of the liver. In Wood's study, only one patient survived for 5 years (1%). It was clear that if the operative mortality declined, as it had in many reported series, the issue was closed. A major study from Memorial Sloan–Kettering Cancer Center (Fong et al, 1999) described the results in 1,001 consecutive patients with a 5-year overall survival of 37% and an operative mortality rate of 3.4%. Five-year survival reached more than 50% in patients with favorable prognostic factors. Tumor recurrence with the liver being the only site of recurrence is common, and such hepatic recurrences are often amenable to repeated resections, with risks and results similar to those of the initial operation (Elias et al, 1992; Fong et al, 1994; Scheele & Stangl, 2000).

More recently the Memorial Sloan-Kettering Cancer Group reported 1,600 patients with metastatic colorectal cancer treated since 1985 (House et al, 2010) and showed an improvement of results over time with results between 1999 and 2004 showing a 5-year survival of 51% in 563 patients, who had an operative mortality of only 1%.

Pichlmayr and colleagues (1990) did the first ex situ tumor resection on the liver, removing the liver for bench surgery, then autotransplanting it back into the patient. The liver was preserved by hypothermic perfusion, as had been described earlier for the in situ procedure (Fortner et al, 1974). This approach may prove to have merit in highly selected cases, but it has not been accepted generally.

Although initially completely ineffective, systemic chemotherapy improved dramatically with the development of new agents, and its use as a neoadjuvant agent and as adjuvant chemotherapy after resection has been extensively explored. The use of neoadjuvant chemotherapy to convert unresectable tumors to resectable ones was reported by Bismuth and colleagues (1996), and extensive studies were reported regarding the possible benefits of chemotherapy after hepatic resection using hepatic arterial infusion of chemotherapy (Kemeny et al, 1999). Kemeny's study followed the demonstration in 1982 by Ensminger and colleagues of an implantable pump for hepatic arterial infusion therapy. Others have studied regression of advanced refractory cancer in the liver using isolated hepatic perfusion chemotherapy (Alexander et al, 2000).

As described in this book, hepatic resection also has been shown to yield satisfactory results in terms of relief of symptoms and prolonging of life in the management of hepatic metastases from neuroendocrine cancer and sarcoma. Hepatic resection for biliary and gallbladder cancer also has developed in a

remarkable fashion. Launois and associates in France (1979) reported the first major series of patients in whom hepatic resection was performed to ensure clearance of hilar cholangiocarcinoma. Working contemporaneously, Fortner and colleagues (1976) and Blumgart and Beazley and associates (Beazley et al, 1984; Blumgart et al, 1984) reported similar results, and in some patients, hepatic resection was accompanied by resection of the portal vein and portal venous reconstruction (Blumgart et al, 1984). Multiple other reports have confirmed that hepatic resection offers advantages in the management of hilar cholangiocarcinoma and helps achieve negative tumor margins and that this is associated with long-term survival (Hadjis et al, 1990; Jarnagin et al, 2001; Klempnauer et al, 1997; Nimura et al, 1990). Surgeons in Southeast Asia and Japan have contributed considerably in this area and in particular have contributed to the development of caudate lobe resection and vascular reconstruction (Mizumoto & Suzuki, 1988; Nimura et al, 1990).

Pack and colleagues (1955) advocated a similar radical approach for gallbladder cancer. They believed that an extended right hepatic lobectomy had its greatest applicability for gallbladder cancer, and they recommended an en bloc lymph node resection of the porta hepatis to be included with the operation. Brasfield (1956) reported a microscopic focus of metastatic cancer in a patient without gross liver involvement and helped establish the need for hepatic resection for gallbladder cancer. More recent reports indicate that for more invasive lesions and for patients seen after initial cholecystectomy, at which cancer was inadvertently found, an extensive resection seems to be effective (Fong et al, 2000). Fortner and colleagues (1970) performed total hepatectomy and orthotopic liver transplantation in two such patients with short-term survival.

Tumor ablation has been a major feature of the recent history of liver surgery for tumors. Cryosurgery (Adam et al, 1997; Crews et al, 1997; Zhou et al, 1988) has been used for treatment of small tumors and for the management of recurrent disease after resection or for the management of unresectable tumors in combination with chemotherapy. More recently, radiofrequency ablation of tumors has been developed, and its use in primary and metastatic cancer has been reported (Curley et al, 1999; Wood et al, 2000). This technology is still being explored, but it seems to have limitations similar to those of cryosurgery in that tumor cell necrosis is inadequate, particularly when the tumor is located close to large blood vessels. The technique can be used percutaneously, but as with cryosurgery, local recurrence remains a problem.

Ethanol injection has been used in the management of small HCCs (Ebara et al, 1990; Tanikawa, 1991). It is of particular interest because it is inexpensive, widely available, and easily used with a low complication rate even in poor-risk patients, and it can be repeated frequently. Hepatic arterial embolization can also be used to ablate tumors and may be particularly effective in primary HCCs and in metastatic tumors arising from primary neuroendocrine sources (Allison et al, 1977; Allison, 1978).

Liver Transplantation

Starzl (2001) has provided a fascinating overview of the origins of clinical organ transplantation. A historical consensus development conference was convened in March 1999 at the University of California, Los Angeles, to identify the principal milestones leading to the clinical use of various transplantation procedures; the conclusions were published in the July 2000 issue of the *World Journal of Surgery* (Groth & Longmire, 2000). The early history of the evolution of organ transplantation followed the first convincing evidence that organ rejection is a host-versus-graft immune response (Gibson & Medawar, 1943; Medawar, 1944). For further details, the reader is referred to the publications of Starzl (2001) and of Murray and Hills (2005). This portion of the review of the history of liver surgery is concerned with the history of liver transplantation.

In a magnificent leap forward, Starzl (Fig. 12) and associates (1968) in the United States did the first successful total hepatectomy with orthotopic liver transplantation. Calne and Williams (1968) in the United Kingdom reported similar studies. The contributions of both groups to the development of liver transplantation and immunosuppressive therapy have been monumental. Fortner and colleagues (1970) reported the first successful heterotopic (auxillary) liver homograft. This contribution was the forerunner of the further development of heterotopic liver transplantation and of split-liver and living related-donor transplants. Liver transplantation underwent continued evolution despite the only modestly effective immunosuppressive therapy initially available. One-year survival



FIGURE 12. Thomas Starzl (1926–), surgeon.

rates slowly reached 50% by 1979 (Calne & Williams, 1979; Starzl et al, 1979). Chronic infection, rejection, and surgical infections diminished the small group to only a few long-term survivors. The report in 1979 of immunosuppression with cyclosporine by Calne and associates (1979) transformed the field rapidly. A consensus conference held in 1983 declared that liver transplantation was now an acceptable therapy and no longer an experimental procedure. Zeevi and colleagues (1987) reported on another powerful immunosuppressive agent, tacrolimus.

Serious complications of immunosuppressive therapy for liver and other organ transplants have been described, including de novo malignancy (Penn, 1988; Penn & Brunson, 1988; Penn & Starzl, 1972). In 1988, Iwatsuki and associates reported an overall 54% survival of patients at 5 years. Development was rapid, and by 1992, more than 3,000 orthotopic liver transplantations were done annually in the United States (United Network for Organ Sharing).

Total hepatectomy and liver transplantation were initially disappointing for liver cancer. Iwatsuki and colleagues (1988) reported that three of every four patients who lived at least 2 months after transplantation for cancer had recurrence, and adjuvant chemotherapy had no demonstrable benefit. Ringe and associates (1989) reported a 5-year survival of 15.2% for such patients, and Calne and colleagues (1986) had similar results. The best results and apparent cure were obtained when a cancer was an incidental finding in a liver removed for noncancerous disease (e.g., alcoholic cirrhosis). Geevarghese and associates (1998) reported an 1-year survival of 85% and a 5-year survival of 78% for such cases.

Current adjuvant chemotherapy may improve the results. Olthoff and colleagues (1995) reported a 3-year survival of 45% using fluorouracil, doxorubicin, and cisplatin, but only three survivors had cancers larger than 5 cm. Laine and associates (1999) reported five children with advanced hepatoma who were alive at a mean of 4.6 years after transplantation preceded by induction chemotherapy.

Improved immunosuppression has allowed surgical techniques to blossom. Bismuth and Houssin (1984) reported reduced-size orthotopic liver grafts in children, and Pichlmayr and colleagues (1988) reported the use of one donor liver for two recipients (split-liver transplantation). Raia and associates (1989), in a letter to the *Lancet,* and Strong and colleagues (1990) were the first to report living-donor liver transplantation using segments II and III of the liver; Yamaoka and colleagues (1994) reported using the right lobe of the liver. Use of split-liver grafts and living, related donors for grafts of both the right and left lobes has been driven by cultural restrictions and by a shortage of donor organs. This has been a major development, and the potential for mortality and morbidity not only of recipients but also of the live donors has remained a major ethical concern.

Liver transplantation for tumors has evolved considerably in the field of primary HCC. Although liver resection remains the treatment of choice for HCC in patients with good liver function, similar patients with compromised liver function and patients with hepatitis C and a small tumor in a portion of the liver geographically unfavorable for resection are now considered best treated by liver transplantation. Liver transplantation has come to be a recognized therapy for many patients with small HCCs (Bismuth et al, 1999), a wide range of benign disease, and in particular for patients with compromised liver function as a result of cirrhosis of the liver, Budd–Chiari syndrome, polycystic liver and kidney disease, sclerosing cholangitis, and for patients with a wide variety of other parenchymal and metabolic liver diseases. Liver transplantation for patients with hilar cholangiocarcinoma is under investigation and is occasionally indicated for patients with widespread neuroendocrine metastatic disease of the liver. Patients with metastatic disease from adenocarcinoma have had poor results, and transplantation is no longer used for this indication.

In writing this historical account, I have drawn freely on the work of the following excellent publications: Chakravorty and Wanebo (1987), Glenn (1971), Praderi (1982), and Starzl (2001). I have no doubt that there will be some inaccuracies and disputed claims as to "firsts," but I have attempted to relate a fascinating surgical story. I apologize for any disagreement I may ignite.

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CHAPTER 1B

Surgical and radiologic anatomy of the liver, biliary tract, and pancreas

Leslie H. Blumgart and Lucy E. Hann

ANATOMY OVERVIEW

Precise knowledge of the internal architecture of the liver, biliary tract, and pancreas and specific and detailed knowledge of related blood vessels and lymphatic drainage is essential for the successful performance of surgical operations on these organs.

LIVER

The liver lies protected under the lower ribs, closely applied to the undersurface of the diaphragm and astride the vena cava posteriorly. Most of the liver bulk lies to the right of the midline, where the lower border coincides with the right costal margin, but it extends as a wedge to the left of the midline, between the anterior surface of the stomach and the left dome of the diaphragm. The upper surface is boldly convex and molded to the diaphragm, and the surface projection on the anterior body wall extends up to the fourth intercostal space on the right and to the fifth intercostal space on the left. The convexity of the upper surface slopes down to a posterior surface that is triangular in outline. The liver is invested with peritoneum except on the posterior surface, where the peritoneum reflects onto the diaphragm, forming the right and left triangular ligaments. The undersurface of the liver is concave and extends down to a sharp anterior border. The posterior surface of the liver is triangular in outline with its base to the right, and here the liver lying between the upper and lower "leaves" of the triangular ligaments is bare and devoid of peritoneum. The anterior border lies under cover of the right costal margin, lateral to the right rectus abdominis muscle, but it slopes upward to the left across the epigastrium. Anteriorly, the convex surface of the liver lies against the concavity of the diaphragm and is attached to it by the falciform ligament, left triangular ligament, and upper layer of the right triangular ligament.

Retrohepatic Inferior Vena Cava

The inferior vena cava (IVC) runs on the right of the aorta on the bodies of the lumbar vertebrae, diverging from the aorta as it passes upward. Below the liver, the IVC lies behind the duodenum and head of the pancreas as a retroperitoneal structure passing upward behind the foramen of Winslow posterior to the right hilar structures of the liver. The renal veins lie in front of the arteries and join the IVC at almost a right angle on the left and obliquely on the right. Behind the liver, the IVC is embraced in a groove on its posterior surface (Figs. 1B.1 and 1B.2). The IVC comes to lie on the right crus of the diaphragm, behind the bare area of the liver; it extends to the central tendon of the diaphragm, which it pierces on a level with the body of T8, behind and higher than the beginning of the abdominal aorta. As the IVC courses upward, it is separated from the right crus of the diaphragm by the right celiac ganglion and, higher up, by the right phrenic artery. The right adrenal vein is a short vessel that enters the IVC behind the bare area (see Fig. 1B.1). There may be a small accessory right adrenal vein on the right that enters into the confluence of the right renal vein and the IVC. The lumbar veins drain posterolaterally into the IVC below the level of the renal veins, but above this level, there are usually no vena caval tributaries posteriorly.

Hepatic Veins

The hepatic veins (Figs. 1B.3 to 1B.5) drain directly from the upper part of the posterior surface of the liver at an oblique angle directly into the vena cava. The right hepatic vein, which is larger than the left and middle hepatic veins, has a short extrahepatic course of approximately 1 cm. The left and middle hepatic veins may drain separately into the IVC but are usually joined, after a short extrahepatic course, to form a common venous channel approximately 2 cm in length that traverses to the left part of the anterior surface of the IVC below the diaphragm (see Figs. 1B.3 and 1B.5). In addition to the three major hepatic veins, there is the umbilical vein, which is single in most cases and runs beneath the falciform ligament between the middle and left hepatic veins; it empties into the terminal portion of the left hepatic vein, although rarely it drains into the middle hepatic vein or directly into the confluence of the middle and left hepatic veins. Additional posteriorly and inferiorly draining hepatic veins, with a short course into the anterior surface of the IVC, are frequent and may be large (see Fig. 1B.4). Hepatic venous drainage of the caudate lobe is directly into the IVC, as described below.

This classic description of the anatomy of the liver is sufficient for gross appreciation and for mobilization of the liver to allow access for repair of injuries, liver transplantation, or the placement of probes onto or into the liver substance. Hidden within this external gross appearance is a detailed internal anatomy; however, an understanding of which is essential to the performance of precise hepatectomy. This internal anatomy has been called the *functional* anatomy of the liver.

Functional Surgical Anatomy

The internal architecture of the liver is composed of a series of segments that combine to form sectors separated by scissurae

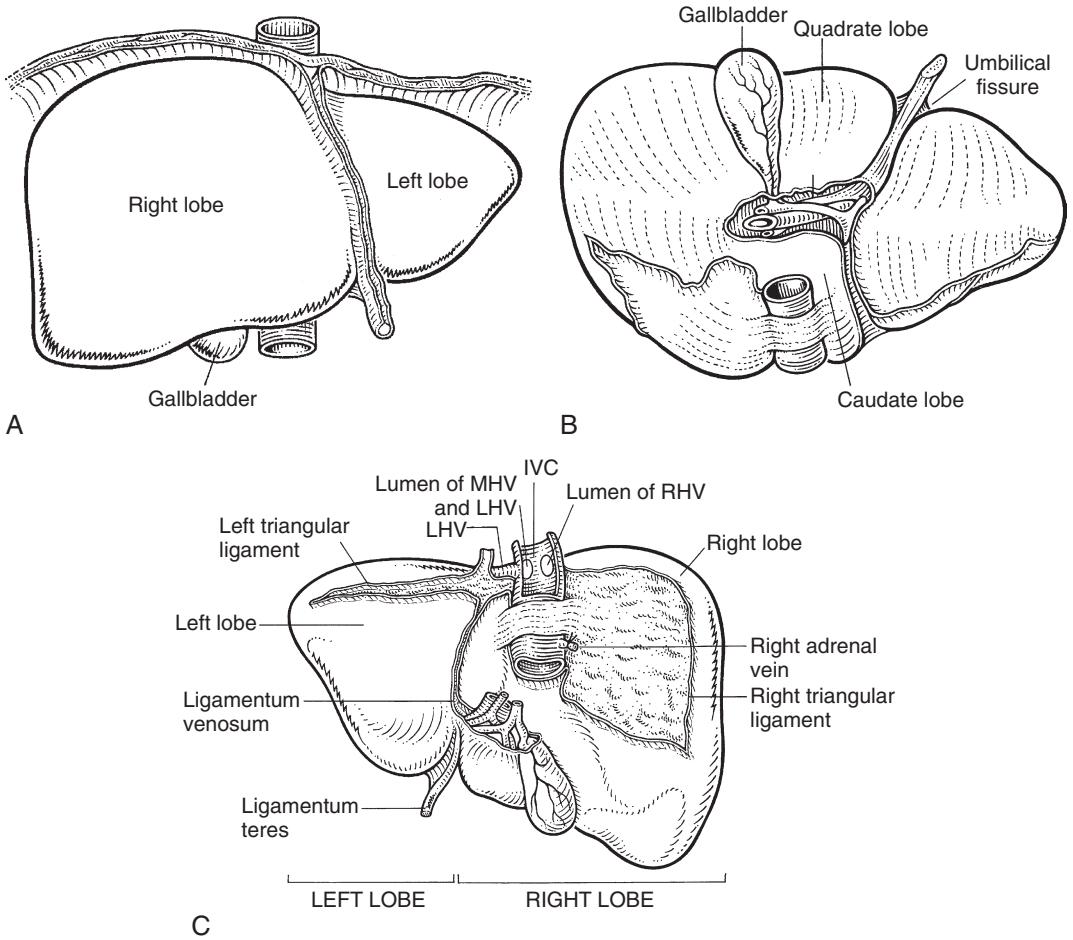


FIGURE 1B.1. **A,** The liver has two main lobes, a large right and a smaller left, and conventional description places their line of fusion on the upper surface of the liver along the attachment of the falciform ligament at the inferior extent of which the ligamentum teres enters the umbilical fissure. **B,** On the inferior surface of the right lobe is the transverse hilar fissure, which constitutes the posterior limit of this lobe. The portion of the right lobe located anterior to the fissure is called the *quadrate lobe*, limited on the left by the *umbilical fissure*, on the right by the gallbladder fossa. Posterior to the hilar transverse fissure is a fourth lobe, the *caudate lobe*, which hugs the inferior vena cava (IVC) and extends upward on its left side. The liver comprises two main lobes and two smaller lobes, separated by visible, well-defined fissures on the liver surface. **C,** The IVC lies snugly in a deep groove within the bare area; the hepatic veins open directly into it. Within this bare area, the right suprarenal gland lies adjacent to the IVC, and the adrenal vein drains into the right of the IVC. The remainder of the bare area of liver is directly in contact with the diaphragm. To the left of the IVC, the caudate lobe slopes upward from the inferior to the posterior surface of the liver and is demarcated on the left by a fissure, within which lies the ligamentum venosum. The gastrohepatic omentum is attached to the ligamentum venosum, placing the caudate lobe within the lesser sac of the peritoneum; but the left lobe of the liver is situated anteriorly in the supracolic compartment of the peritoneal cavity. The posterior surface of the left lobe is narrow; there is a very fine bare area on this side. As the vena cava traverses upward in the groove on the posterior surface of the liver, it is shielded on the right side by a layer of fibrous tissue that passes from the posterior edge of the liver backward toward the lumbar vertebrae and fans out posteriorly, especially in the upper part. Behind the IVC, a prolongation of this fibrous layer joins a less marked fibrous extension from the lateral edge of the caudate lobe. This layer of fibrous tissue, sometimes called the *ligament of the vena cava*, must be divided on the right, to allow surgical exposure of the IVC and the hepatic veins, and on the left, to allow mobilization of the caudate lobe. Occasionally, the liver tissue embraces the vena cava completely, so that it runs within a tunnel of parenchyma. LHV, left hepatic vein; MHV, middle hepatic vein; RHV, right hepatic vein.

that contain the hepatic veins (Fig. 1B.6). Together or separately, these constitute the visible lobes described previously. The internal structure has been clarified by the publications of McIndoe and Counseller (1927), Ton That Tung (1939, 1979), Hjörtsjö (1931), Healey and Schroy (1953), Goldsmith and Woodburne (1957), Couinaud (1957), and Bismuth and colleagues (1982); however, the description by Couinaud is the most complete, exact, and useful for the operating surgeon, so it is generally used here. An alternative terminology suggested by a committee of the International Hepato-Pancreatico-Biliary Association (Strasberg et al, 2000) adds little to the understanding or practicality of Couinaud's description. The main difference is that in the alternative terminology, Couinaud's sectors are referred to as *sections*, particularly in describing the anatomy of the left liver (see Chapters 90A to 90F for differences in the terminology of the various hepatic resections).

Essentially, the three main hepatic veins within the scissurae divide the liver into four sectors, each of which receives a portal

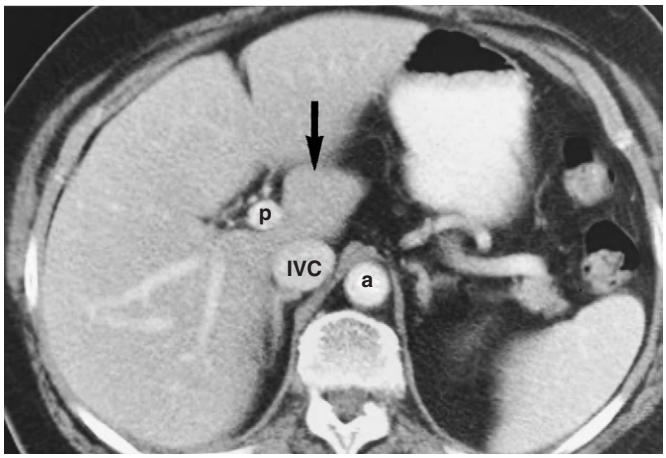


FIGURE 1B.2. Contrast-enhanced computed tomographic scan of the liver shows the intimate relationship of the caudate lobe (*arrow*), inferior vena cava (*IVC*), portal vein (*p*), and aorta (*a*).

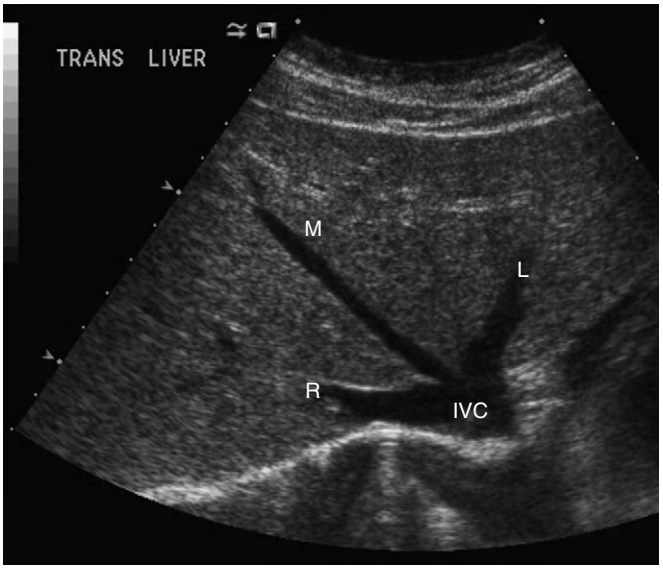


FIGURE 1B.3. Transverse ultrasound image of the hepatic vein confluence shows the left (*L*), middle (*M*), and right (*R*) hepatic veins as they join the inferior vena cava (*IVC*).

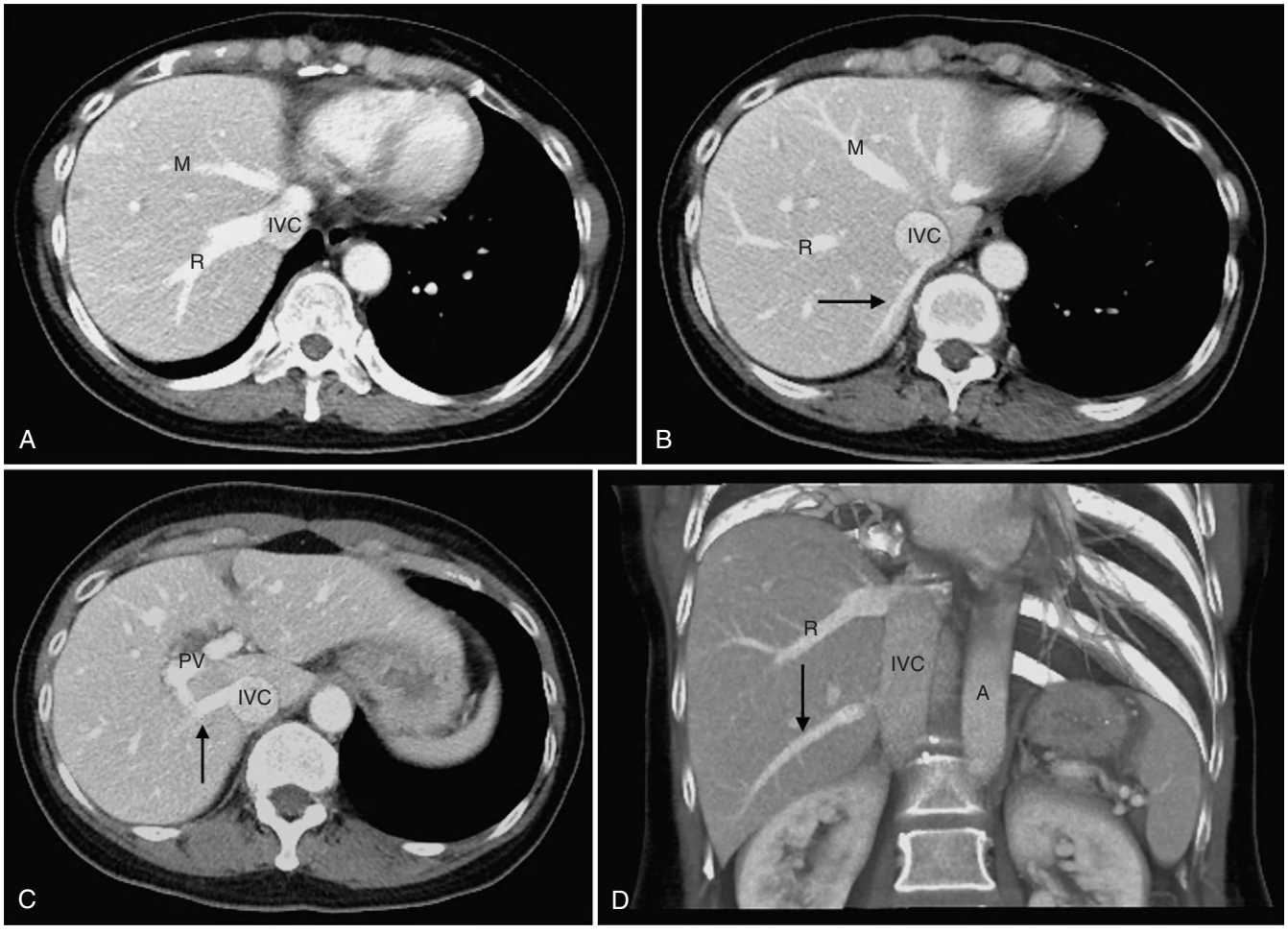


FIGURE 1B.4. Two inferior accessory right hepatic veins. **A,** Contrast-enhanced computed tomographic (CT) image of the hepatic vein confluence. R, right hepatic vein; M, middle hepatic vein; IVC, inferior vena cava. **B,** A small right inferior accessory vein (*arrow*) enters the IVC below the hepatic venous confluence. **C,** The second, larger right inferior accessory right hepatic vein (*arrow*) is seen more inferiorly. PV, portal vein. **D,** CT coronal reconstruction image shows the right hepatic vein (*R*) and one right inferior accessory vein (*arrow*); A, aorta.

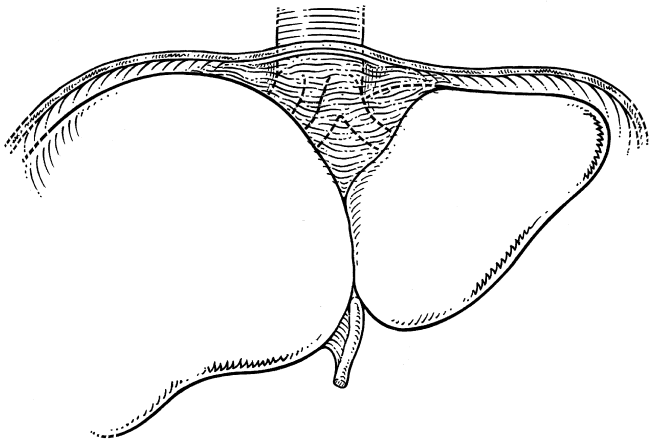


FIGURE 1B.5. The anterior surfaces of the major extrahepatic veins and the inferior vena cava are retroperitoneal and masked behind the layers of the falciform ligament, as it splits and passes to the right and left triangular ligaments.

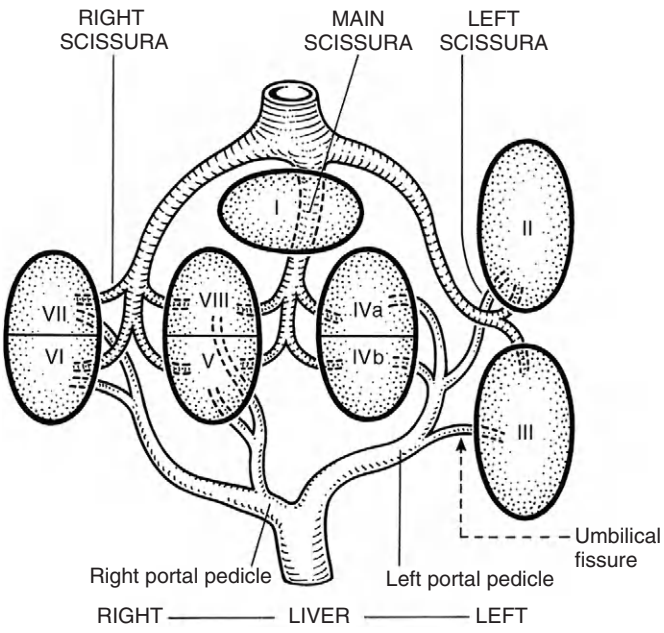


FIGURE 1B.6. The portal vein, hepatic artery, and draining bile ducts are distributed within the liver in a beautifully symmetric pedicular pattern, which belies the asymmetric external appearance. Each segment (I to VIII) is supplied by a portal triad composed of a branch of the portal vein and hepatic artery and drained by a tributary of the right or left main hepatic ducts. The four sectors demarcated by the three main hepatic veins are called the *portal sectors*; these portions of parenchyma are supplied by independent portal pedicles. The hepatic veins run between the sectors in the portal scissurae; the scissurae containing portal pedicles are called the *hepatic scissurae*. The umbilical fissure corresponds to a hepatic scissura. The internal architecture of the liver consists of two hemilivers, the right and the left liver separated by the main portal scissura, also known as *Cantlie's line*. It is preferable to call them the *right* and *left liver*, rather than the *right* and *left lobes*, because the latter nomenclature is erroneous; there is no visible mark that permits identification of a true hemiliver.

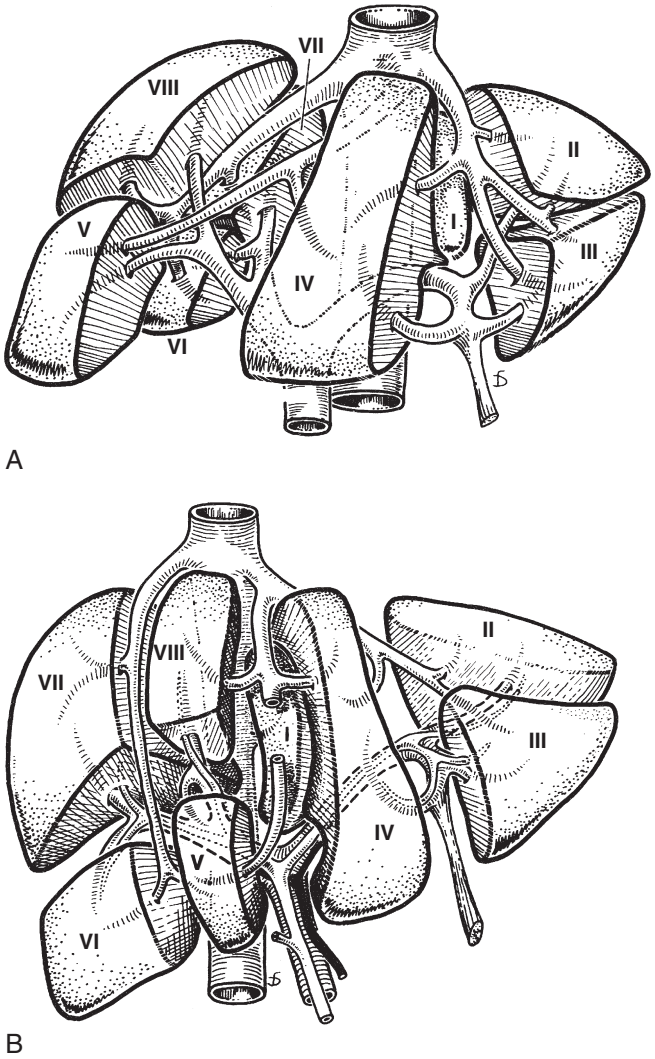


FIGURE 1B.7. The functional division of the liver and its segments according to Couinaud's nomenclature. **A,** As seen in the patient. **B,** In the ex vivo position.

pedicle, with alternation between the hepatic veins and portal pedicles. The main portal scissura contains the middle hepatic vein and progresses from the middle of the gallbladder bed anteriorly to the left of the vena cava posteriorly. The right and left parts of the liver, demarcated by the main portal scissura, are independent in terms of portal and arterial vascularization and biliary drainage (Fig. 1B.7). These right and left livers are themselves divided into two by the remaining portal scissurae. These four subdivisions are referred to as *segments* in the description of Goldsmith and Woodburne (1957), but in Couinaud's nomenclature (1957), they are termed *sectors* (see Figs. 1B.6 and 1B.7).

The right portal scissura separates the right liver into two sectors: *anteromedial* (anterior) and *posterolateral* (posterior). With the body supine, this scissura is almost in the frontal plane. The right hepatic vein runs within the right scissura. The left portal scissura divides the left liver into two sectors, but the left portal scissura is not within the umbilical fissure, because this fissure is not a portal scissura and contains a portal pedicle. The left portal scissura is located posterior to the ligamentum teres

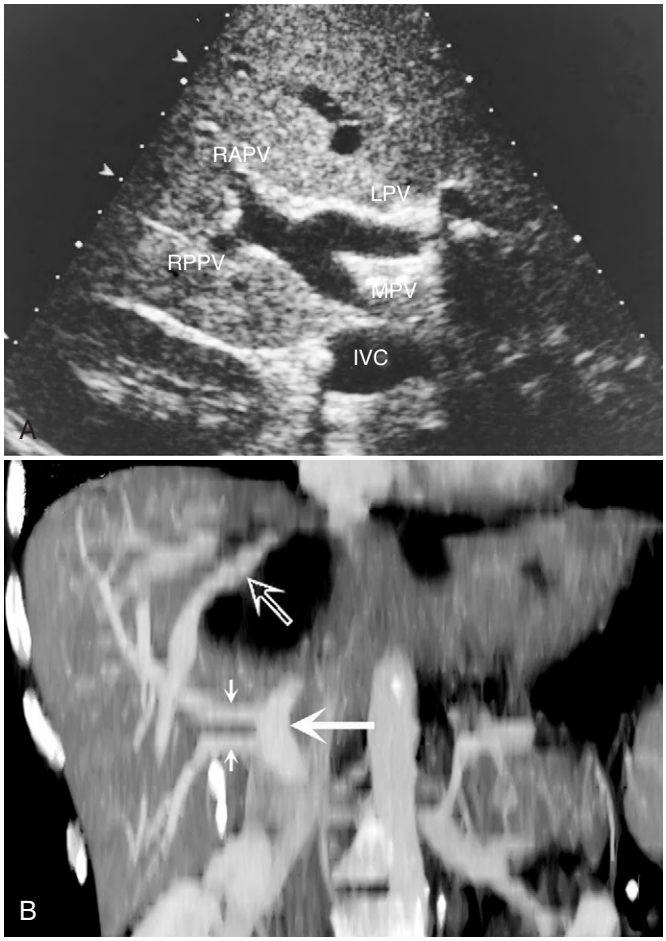


FIGURE 1B.8. A, Transverse sonogram at the level of the portal vein bifurcation. The main portal vein (*MPV*) bifurcates into the left and right portal veins (*LPV* and *RPV*). The RPV bifurcates shortly into the right anterior (*RAPV*) and right posterior (*RPPV*) branches, but the LPV has a longer horizontal course within the hilar plate. The inferior vena cava (*IVC*) is seen posteriorly. **B,** Coronal view of computed tomographic angioportography. Reconstruction shows the right hepatic vein (*open arrow*) and the portal vein (*large arrow*); anterior and posterior sectoral branches of the RPV (*small arrows*) are seen to arise independently from the main portal trunk.

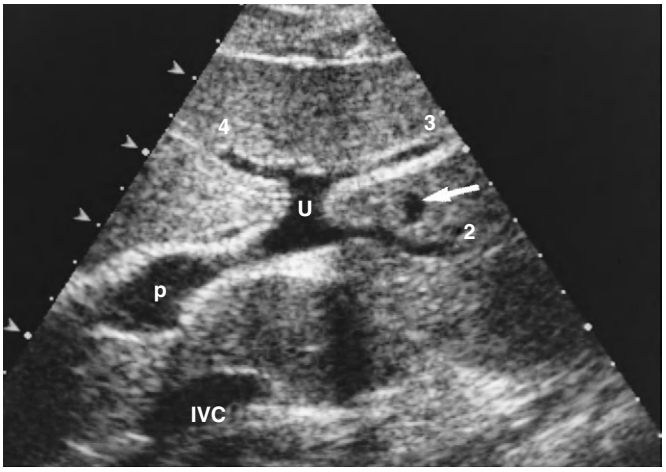


FIGURE 1B.9. Transverse sonogram shows the branching pattern of the left portal vein (*p*), which courses horizontally and into the umbilical fissure. The umbilical portion of the left portal vein (*U*) gives branches to the left hepatic segments (II to IV). The left hepatic vein (*arrow*) and inferior vena cava (*IVC*) also are shown.

and within the left lobe of the liver, along the course of the left hepatic vein. The anterior sector of the left liver—the left medial section, in the terminology of Strasberg and others (2000)—is composed of a part of the right lobe (segment IV), to the left of the main portal scissura, and of the anterior part of the left lobe (segment III; see Figs. 1B.6 and 1B.7). The left posterior sector is the only sector composed of one segment (segment II; the left posterior section in terminology of Strasberg et al).

At the hilus of the liver, the right portal triad pursues a short course of approximately 1 to 1.5 cm before entering the substance of the right liver (Fig. 1B.8A). In some cases, the right anterior and posterior pedicles arise independently, and their origins may be separated by 2 cm (see Fig. 1B.8B). In some cases, it appears as if the left portal vein arises from the right anterior branch (see also Fig. 1B.40). On the left side, however, the portal triad crosses over approximately 3 to 4 cm beneath the quadrate lobe, embraced in a peritoneal sheath at the upper end of the gastrohepatic ligament and separated from the undersurface of the quadrate lobe by connective tissue (hilar plate). This prolongation of the left portal pedicle turns anteriorly and caudally within the umbilical fissure, giving branches of supply to segments II and III and recurrent branches to segment IV (Fig. 1B.9; see also Fig. 1B.6). Beneath the quadrate lobe, the pedicle is composed of the left branch of the portal vein and the left hepatic duct, but it is joined at the base of the umbilical fissure by the left branch of the hepatic artery.

The branching of the portal pedicle at the hilus (Fig. 1B.10; see also Figs. 1B.6, 1B.8, and 1B.9), the distribution of the branches to the caudate lobe (segment I) on the right and left sides, and the distribution to the segments of the right (segments V through VIII) and left (segments II through IV) hemiliver follow a remarkably symmetric pattern and, as described by Scheele (1994), allow separation of segment IV into segment IVa superiorly and segment IVb inferiorly (see Fig. 1B.6). This arrangement of subsegments mimics the distribution to segments V and VIII on the right side. The umbilical vein provides drainage of at least parts of segment IVb after ligation of the middle hepatic vein, and it is important in the performance of segmental resection.

The caudate lobe (segment I) is the dorsal portion of the liver lying posteriorly and embracing the retrohepatic IVC. This lobe lies between major vascular structures: On the left, the caudate lies between the IVC posteriorly and the left portal triad inferiorly and the IVC and the middle and left hepatic veins superiorly (Figs. 1B.11 and 1B.12). This portion of the caudate is sometimes referred to as *segment IX*.

The portion of the caudate on the right varies but is usually quite small. The anterior surface within the parenchyma is covered by the posterior surface of segment IV, the limit being an oblique plane slanting from the left portal vein to the left hepatic vein. Thus, there is a caudate lobe (segment I) with a

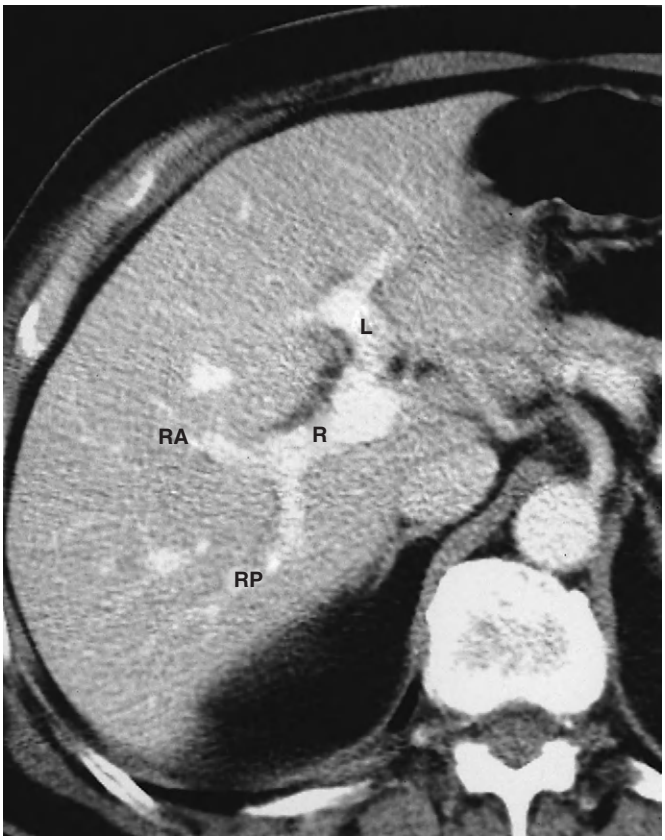


FIGURE 1B.10. Contrast-enhanced computed tomographic image of the portal vein bifurcation. L, left portal vein; R, right portal vein; RA, right anterior portal vein; RP, right posterior portal vein.

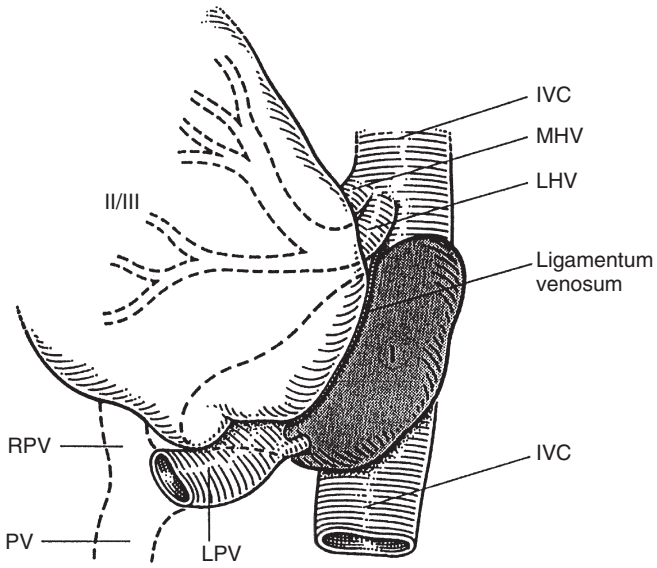


FIGURE 1B.12. The caudate lobe (*shaded*) and segments II and III, rotated to the patient's right. Superiorly, the left portion of the caudate lobe is linked by a deep anterior portion, embedded in the parenchyma immediately under the middle hepatic vein (*MHV*), reaching inferiorly to the posterior margin of the hilus of the liver and fusing anterolaterally to the inferior vena cava (*IVC*) on the right side to segments VI and VII of the right liver. The major blood supply arises from the left branch of the left portal vein (*LPV*) and the left hepatic artery close to the base of the umbilical fissure of the liver. The hepatic veins (MHV, LHV) are short in course and drain from the caudate directly into the anterior and left aspect of the vena cava. LHV, left hepatic vein; RPV, right portal vein; PV, main trunk of portal vein.

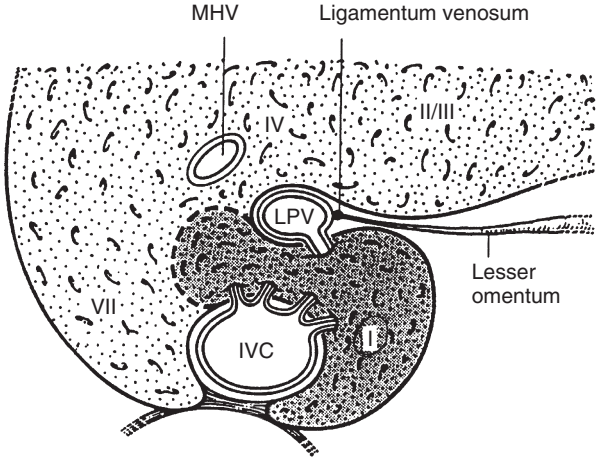


FIGURE 1B.11. The main bulk of the caudate lobe (segment I; *dark area*) lies to the left of the inferior vena cava (*IVC*); the left and inferior margins are free in the lesser omental bursa. The gastrohepatic (lesser) omentum separates the left portion of the caudate from segments II and III of the liver, as it passes between them to be attached to the ligamentum venosum. The left portion of the caudate lobe inferiorly traverses to the right between the left portal vein (*LPV*) and IVC as the caudate process, where it fuses with the right lobe of the liver. Note the position of the middle hepatic vein (*MHV*).

constantly present left portion and a right portion of variable size (see Figs. 1B.11 and 1B.12).

The caudate lobe is supplied by blood vessels and drained by biliary tributaries from the right and left portal triad. Small vessels from the portal vein and tributaries joining the biliary ducts also are found, usually two on the left side and one on the right. The right portion of the caudate lobe, including the caudate process, predominantly receives portal venous blood from the right portal vein or from the bifurcation of the main portal vein, whereas on the left side, the portal supply arises from the left branch of the portal vein almost exclusively. Similarly, the arterial supply and biliary drainage of the right portion is most commonly associated with the right posterior sectoral vessels and the left portion with the left main vessels. The hepatic venous drainage of the caudate is unique in that it is the only hepatic segment that drains directly into the IVC. These veins can sometimes drain into the posterior aspect of the vena cava, if a significant retrocaval caudate component is present.

In the usual and common circumstance, the posterior edge of the caudate lobe on the left has a fibrous component, which fans out and attaches lightly to the crural area of the diaphragm; but it extends posteriorly, behind the vena cava, to link with a similar component of fibrous tissue that protrudes from the posterior surface of segment VII and embraces the vena cava (see Figs. 1B.1C and 1B.11). In 50% of patients, this ligament is replaced by hepatic tissue, in whole or in part, and the caudate may completely encircle the IVC and may contact segment VII

on the right side; a significant retrocaval component may prevent a left-sided approach to the caudate veins. The caudal margin of the caudate lobe has a papillary process that occasionally may attach to the rest of the lobe via a narrow connection. It is bulky in 27% of cases and can be mistaken for an enlarged lymph node on computed tomography (CT) scan (Fig. 1B.13).

To summarize:

1. The liver is divided into two hemilivers by the main hepatic scissura, within which runs the middle hepatic vein.
2. The left liver is divided into two sectors by the left portal scissura, within which the left hepatic vein runs (see Fig. 1B.6). The posterior sector comprises only one segment, segment II, which is the posterior part of the left lobe. This is the only sector that comprises one segment, referred to as the *left posterior section* by Strasberg and others (2000). The anterior sector is divided by the umbilical fissure into two segments: a *medial segment*, the quadrate lobe (segment IV), and a *lateral segment* (segment III), which is the anterior part of the left lobe.
3. The right liver is divided into two sectors by the right portal scissura, containing the right hepatic vein. Each of these *sectors* is further divided into two segments: an anterior segment V inferiorly and segment VIII superiorly, and a posterior segment, segment VI inferiorly and segment VII superiorly (see Figs. 1B.6 and 1B.7).
4. Segment I, the caudate lobe, lies posteriorly and embraces the vena cava, its intraparenchymal anterior surface abutting the posterior surface of segment IV and merging with segments VI and VII on the right (Fig. 1B.14; see Fig. 1B.11).

Further details of segmental anatomy important in sectoral or segmental resection are described in Chapters 90A to 90F and 92.

Surgical Implications and Exposure

All methods for precise partial hepatectomy depend on control of the inflow vasculature and draining bile ducts and of the outflow hepatic veins of the portion of liver to be excised, which may be a segment, a subsegment, or an entire lobe. The remnant remaining after partial hepatectomy must be provided with an excellent portal venous and hepatic arterial supply and biliary drainage and an unimpeded hepatic venous outflow. Under such circumstances, hepatic regeneration is usually prompt. The classification of the various partial hepatic resection procedures, incisions and exposure, necessary mobilization of the liver, and the methods of control of the structures within the portal triads and of the hepatic veins are described in detail in Chapters 90A to 90F and 92.

BILIARY TRACT

Biliary exposure and precise dissection are the most important steps in any biliary operative procedure. A thorough anatomic knowledge is essential if optimal results are to be obtained.

Intrahepatic Bile Duct Anatomy

The right and left livers are drained by the right and the left hepatic ducts, whereas the dorsal lobe (caudate lobe) is



FIGURE 1B.13. Computed tomographic image of the caudate lobe with papillary process. **A,** Caudate lobe (*asterisk*) positioned between the left portal vein (*arrow*) and inferior vena cava (*v*); a, aorta. **B,** Papillary process of the caudate (*p*) represents the lower medial extension of the caudate (*asterisk*) and may mimic a periportal lymph node.

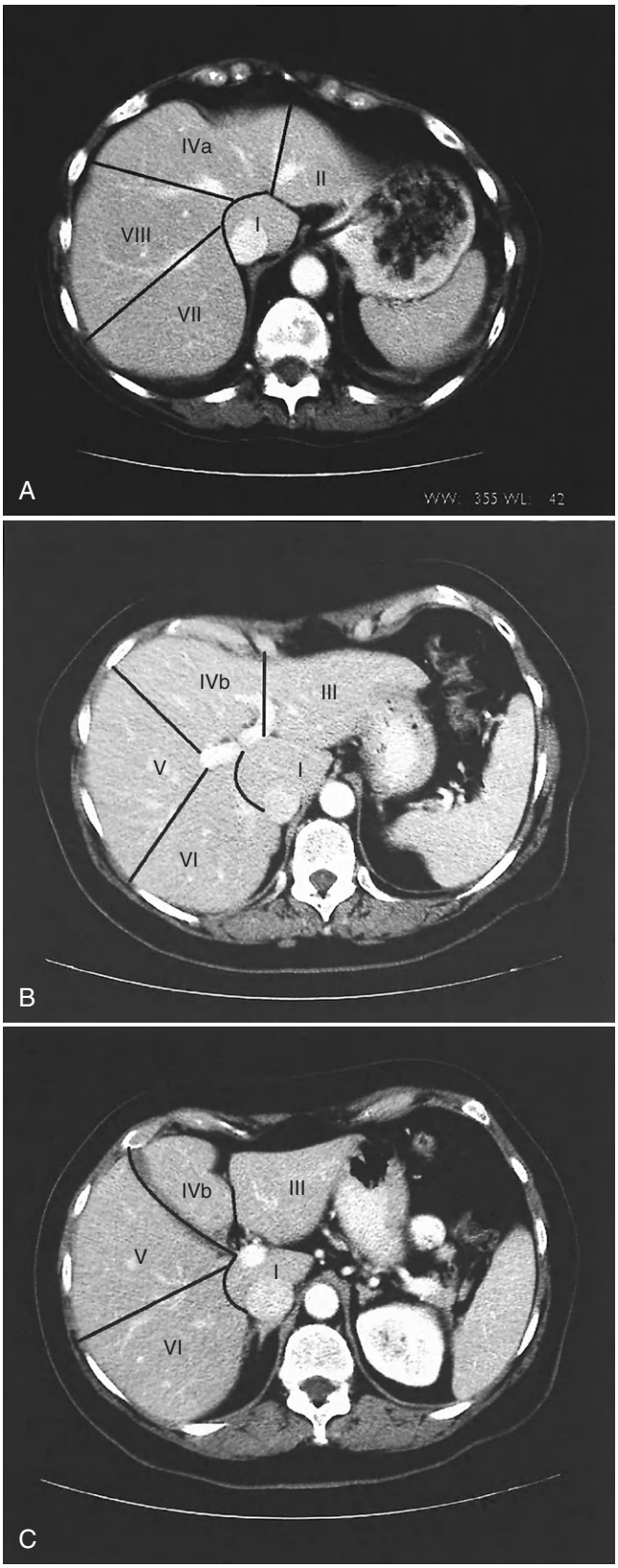


FIGURE 1B.14. Hepatic segmental anatomy as shown by computed tomography. **A,** At the level of the hepatic veins. **B,** At the portal vein bifurcation. **C,** Below the hepatic hilus.

drained by several ducts that join both the right and left hepatic ducts. The intrahepatic ducts are tributaries of the corresponding hepatic ducts, which form part of the major portal triads that penetrate the liver, invaginating the Glisson capsule at the hilus. Bile ducts usually are located above the corresponding portal branches, whereas hepatic arterial branches are situated inferiorly to the veins. Each branch of the intrahepatic portal veins corresponds to one or two bile duct tributaries that join to form the right and left hepatic ductal systems, converging at the liver hilus to constitute the common hepatic duct. The umbilical fissure divides the left liver, passing between segment III and segment IV, where it may be bridged by a tongue of liver tissue. The ligamentum teres passes through the umbilical fissure to join the left branch of the portal vein (see Fig. 1B.1).

The left hepatic duct drains the three segments—II, III, and IV—that constitute the left liver (Fig. 1B.15). The duct that drains segment III is located slightly behind the left horn of the umbilical recess. It is joined by the tributary from segment IVb to form the left duct, which is similarly joined by the duct of segment II and the duct of segment IVa, where the left branch of the portal vein turns forward and caudally. The left hepatic duct traverses beneath the left liver at the base of segment IV, just above and behind the left branch of the portal vein; it crosses the anterior edge of that vein and joins the right hepatic duct to constitute the hepatic ductal confluence. In its transverse portion, it receives one to three small branches from segment IV.

The right hepatic duct drains segments V, VI, VII, and VIII and arises from the junction of two main sectoral duct tributaries (Fig. 1B.16). The posterior or lateral duct and the anterior or medial duct are each accompanied by a corresponding vein. The right posterior sectoral duct has an almost horizontal course and constitutes the confluence of the ducts of segments VI and VII (see Figs. 1B.15 and 1B.16). The duct then runs to join the right anterior sectoral duct, as it descends in a vertical manner. The right anterior sectoral duct is formed by the confluence of the ducts draining segments V and VIII. Its main trunk is located to the left of the right anterior sectoral branch of the portal vein, which pursues an ascending course. The junction of these two main right biliary channels usually occurs above the right branch of the portal vein. The right hepatic duct is short and joins the left hepatic duct to constitute the confluence lying in front of the right portal vein and forming the common hepatic duct.

The caudate lobe (segment I) has its own biliary drainage (Healey & Schroy, 1953). The caudate lobe is divided into right and left portions and a caudate process. In 44% of individuals, three separate ducts drain these three parts of the lobe, whereas in 26% a common duct lies between the right portion of the caudate lobe proper and the caudate process and an independent duct that drains the left part of the caudate lobe. The site of drainage of these ducts varies. In 78% of cases, drainage of the caudate lobe is into the right and left hepatic ducts, but in 15% drainage is by the left hepatic ductal system only. In about 7%, the drainage is into the right hepatic system.

Extrahepatic Biliary Anatomy and Vascular Anatomy of the Liver and Pancreas

The extrahepatic bile ducts are represented by the extrahepatic segments of the right and left hepatic ducts, joining

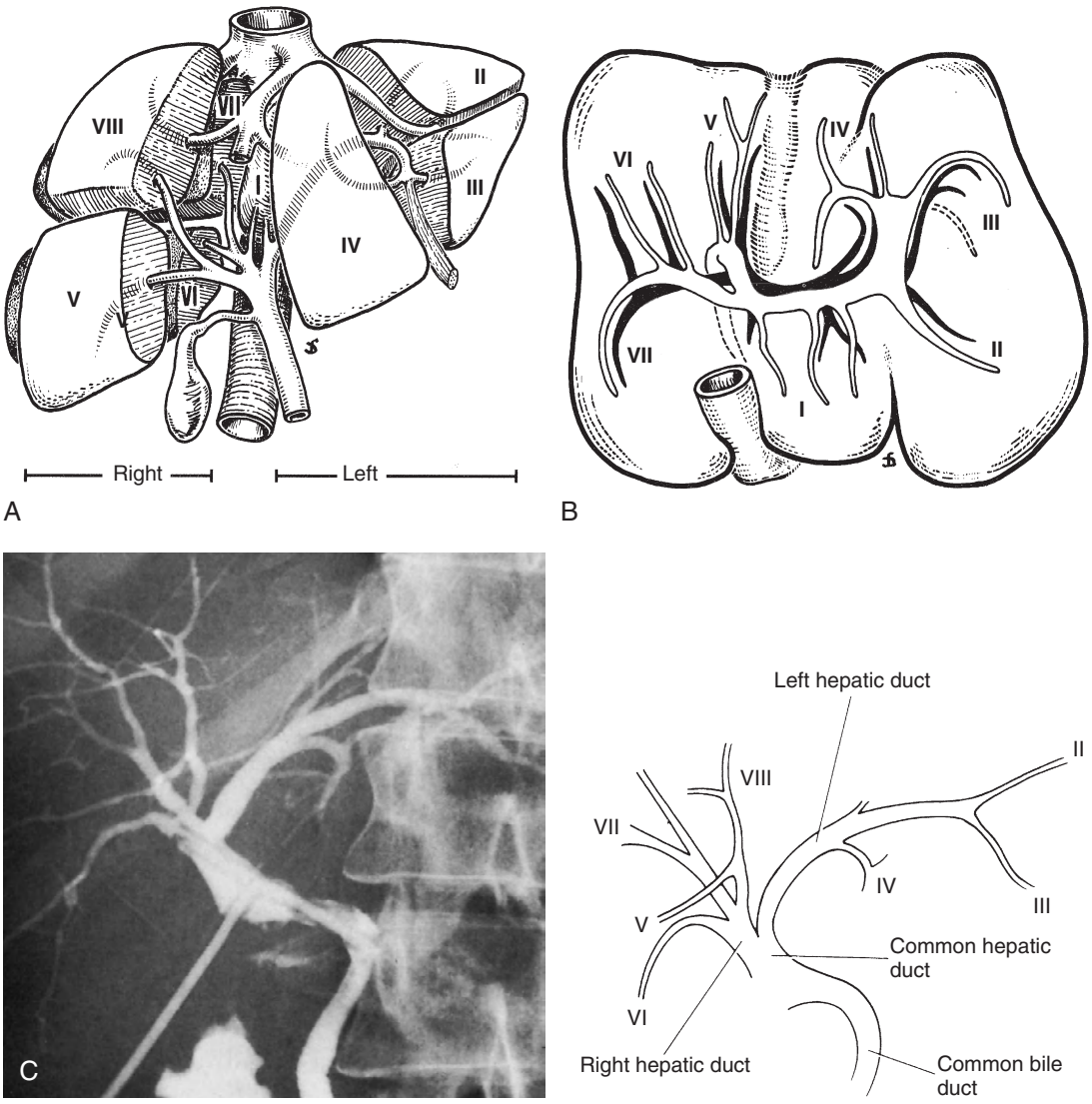


FIGURE 1B.15. **A,** Biliary drainage of the two functional hemilivers. Note the position of the right anterior and right posterior sectors. The caudate lobe drains into the right and left ductal system. **B,** Inferior aspect of the liver. The biliary tract is represented in black, and the portal branches are represented in white. Note the biliary drainage of segment IV (segment VIII is not represented because of its cephalad location). **C,** T-tube cholangiogram shows the most common arrangement of hepatic ducts.

to form the biliary confluence and the main biliary channel draining to the duodenum. The accessory biliary apparatus, which constitutes a reservoir, comprises the gallbladder and cystic duct (Figs. 1B.17 and 1B.18). The confluence of the right and left hepatic ducts occurs at the right of the hilar fissure of the liver, anterior to the portal venous bifurcation and overlying the origin of the right branch of the portal vein (see Fig. 1B.17). The extrahepatic segment of the right duct is short, but the left duct has a much longer extrahepatic course. The biliary confluence is separated from the posterior aspect of the quadrate lobe of the liver by the hilar plate, which is the fusion of connective tissue enclosing the biliary and vascular elements with the Glisson capsule (Fig. 1B.19). Because of the absence of any vascular interposition, it is possible to open the connective tissue constituting the hilar plate at the inferior border of the quadrate lobe and, by elevating it, to display the biliary confluence and left hepatic duct (Fig. 1B.20).

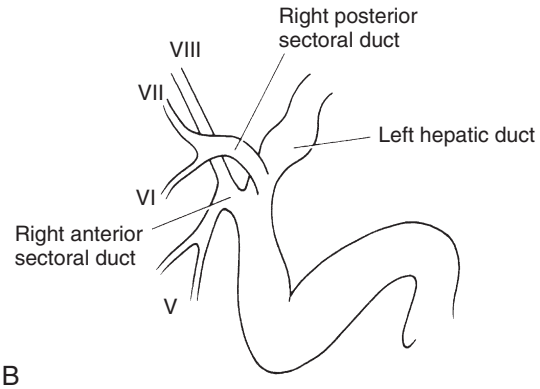
Main Bile Duct and Sphincter of Oddi

The main bile duct (see Fig. 1B.17), the mean diameter of which is about 6 mm, is divided into two portions: the upper is called the *common hepatic duct* and is situated above the cystic duct, which joins it to form the lower portion, the common bile duct (see Fig. 1B.18). The common duct courses downward anterior to the portal vein, in the free edge of the lesser omentum; it is closely applied to the hepatic artery, which runs upward on its left, giving rise to the right branch of the hepatic artery, which crosses the main bile duct usually posteriorly, although in about 20% of cases, it crosses anteriorly. The cystic artery, arising from the right branch of the



A





B

FIGURE 1B.16. A, Biliary and vascular anatomy of the right liver. Note the horizontal course of the posterior sectoral duct and the vertical course of the anterior sectoral duct. **B,** Transtubal cholangiogram shows a common normal variant: the right posterior sectoral duct drains into the left hepatic duct. In this case, the posterior duct is anterior to the posterior sectoral duct. Frequently in this variant, the posterior duct passes posteriorly to the anterior sectoral pedicle.

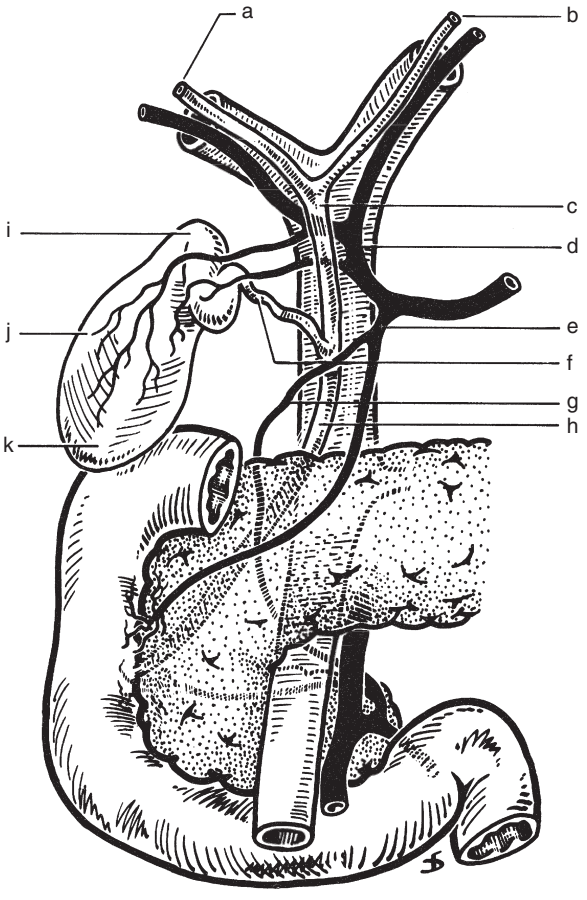


FIGURE 1B.17. Anterior aspect of the biliary anatomy and of the head of the pancreas: right hepatic duct (*a*); left hepatic duct (*b*); common hepatic duct (*c*); hepatic artery (*d*); gastroduodenal artery (*e*); cystic duct (*f*); retroduodenal artery (*g*); common bile duct (*h*); neck of the gallbladder (*i*); body of the gallbladder (*j*); fundus of the gallbladder (*k*). Note particularly the position of the hepatic bile duct confluence anterior to the right branch of the portal vein, the posterior course of the cystic artery behind the common hepatic duct, and the relationship of the neck of the gallbladder to the right branch of the hepatic artery. Note also the relationship of the major vessels (portal vein, superior mesenteric vein, and artery) to the head of the pancreas (see also Figs. 1B.29, 1B.35, and 1B.45).



FIGURE 1B.18. Endoscopic retrograde choledochopancreatogram showing the pancreatic duct (*arrow*), gallbladder, and biliary tree.

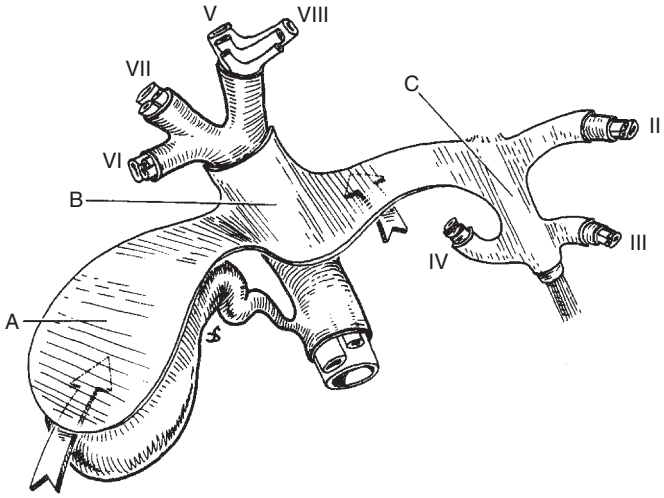


FIGURE 1B.19. Anatomy of the plate system. *A,* Cystic plate, above the gallbladder. *B,* Hilar plate, above the biliary confluence and at the base of the quadrate lobe. *C,* Umbilical plate, above the umbilical portion of the portal vein. Large, curving arrows indicate the plane of dissection of the cystic plate during cholecystectomy and of the hilar plate during approaches to the left hepatic duct.

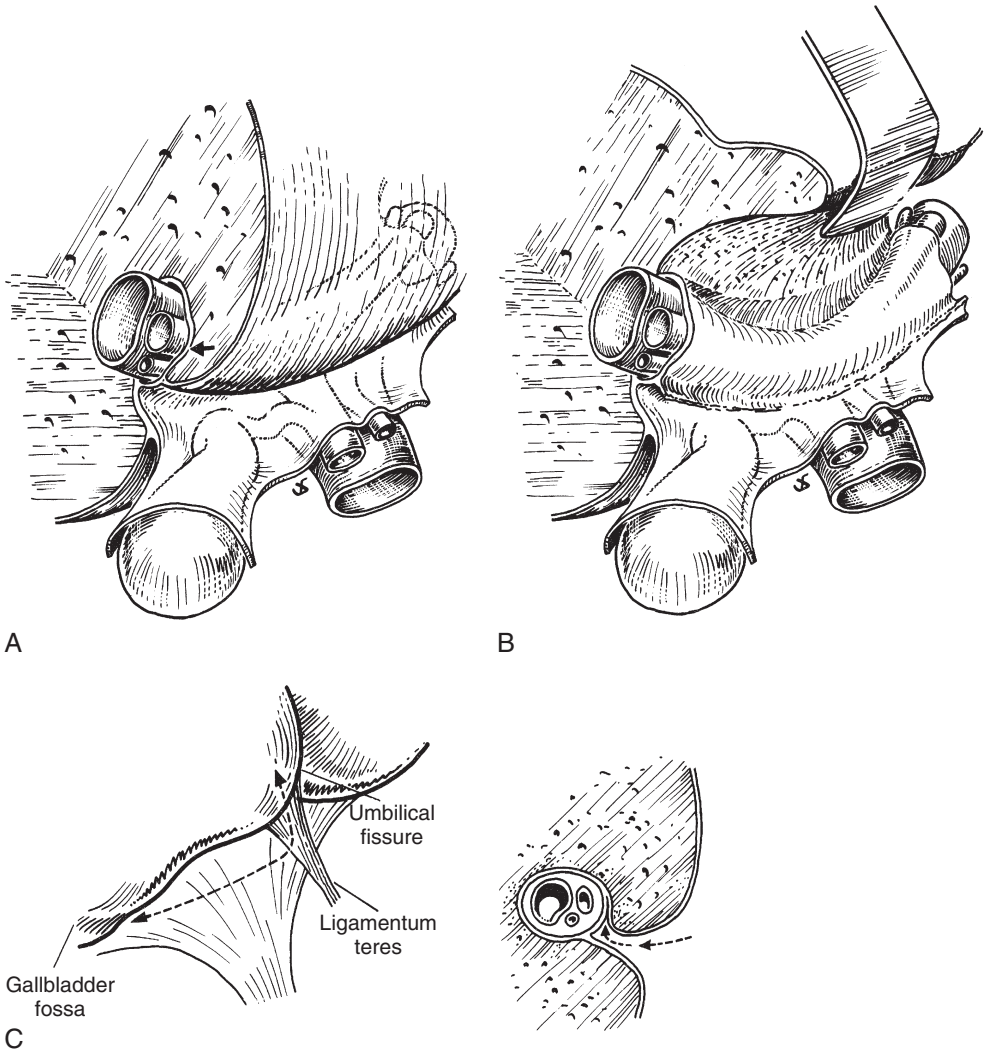


FIGURE 1B.20. A, Relationship between the posterior aspect of the quadrate lobe and the biliary confluence. The hilar plate (*arrow*) is formed by the fusion of the connective tissue enclosing the biliary and vascular elements with the Glisson capsule. **B,** Biliary confluence and left hepatic duct exposed by lifting the quadrate lobe upward after incision of the Glisson capsule at its base. This technique, *lowering of the hilar plate* (Hepp & Couinaud, 1956), generally is used to display a dilated bile duct above an iatrogenic stricture or hilar cholangiocarcinoma. **C,** Line of incision (*left*) to allow extensive mobilization of the quadrate lobe. This maneuver is of particular value for high bile duct stricture and in the presence of liver atrophy or hypertrophy. The procedure consists of lifting the quadrate lobe upward (see **A** and **B**), then not only opening the umbilical fissure but also incising the deepest portion of the gallbladder fossa. *Right*, Incision of the Glisson capsule to gain access to the biliary system (*arrow*).

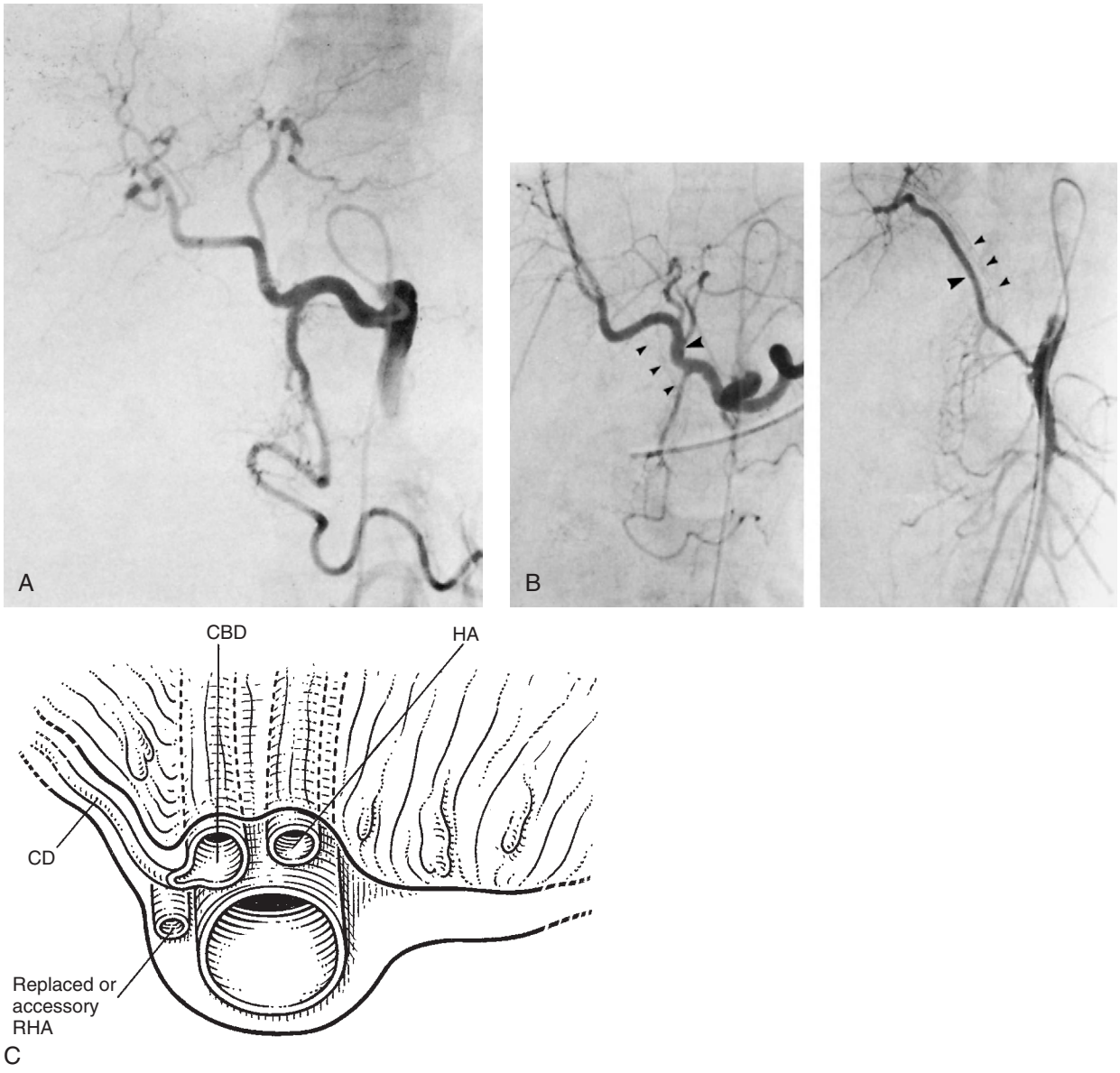


FIGURE 1B.21. Hepatic artery variations shown by angiography. **A,** Replaced common hepatic artery arises from the superior mesenteric trunk. **B,** Angiogram. *Left*, The hepatic artery (*large arrowhead*) arises from the celiac axis. The small *arrowheads* indicate a drainage catheter in the bile duct. *Right*, An accessory right hepatic artery (*large arrowhead*) is arising from the superior mesenteric artery and lies lateral to the catheter (*small arrowheads*) in the common bile duct. **C,** The accessory right hepatic artery usually courses upward in the groove posterolateral to the common bile duct (*CBD*), appearing on the medial side of the triangle of Calot, usually running just behind the cystic duct (*CD*). This common variation occurs in about 25% of individuals. HA, hepatic artery; RHA, right hepatic artery.

hepatic artery, may cross the common hepatic duct posteriorly or anteriorly. The common hepatic duct constitutes the left border of the triangle of Calot, the other corners of which were originally described as the cystic duct below and the cystic artery above (Rocko et al, 1981). The commonly accepted working definition of the triangle of Calot recognizes, however, the inferior surface of the right lobe of the liver as the upper border and the cystic duct as the lower border (Wood, 1979). Dissection of the triangle of Calot is of key significance during cholecystectomy, because in this triangle runs the cystic artery, often the right branch of the hepatic artery, and occasionally a bile duct, which should be displayed before cholecystectomy. If there is a replaced or accessory common or right hepatic artery, it usually runs behind the cystic duct to enter the triangle of Calot (Fig. 1B.21).

The common variations in the relationship of the hepatic artery and origin and course of the cystic artery to the biliary apparatus are shown in Fig. 1B.22. Ignorance of these variations may provoke unexpected hemorrhage or biliary injury (Champetier et al, 1982) during cholecystectomy and may result in bile duct injury during efforts to secure hemostasis. The union between the cystic duct and the common hepatic duct may be located at various levels. At its lower extrahepatic portion, the common bile duct traverses the posterior aspect of

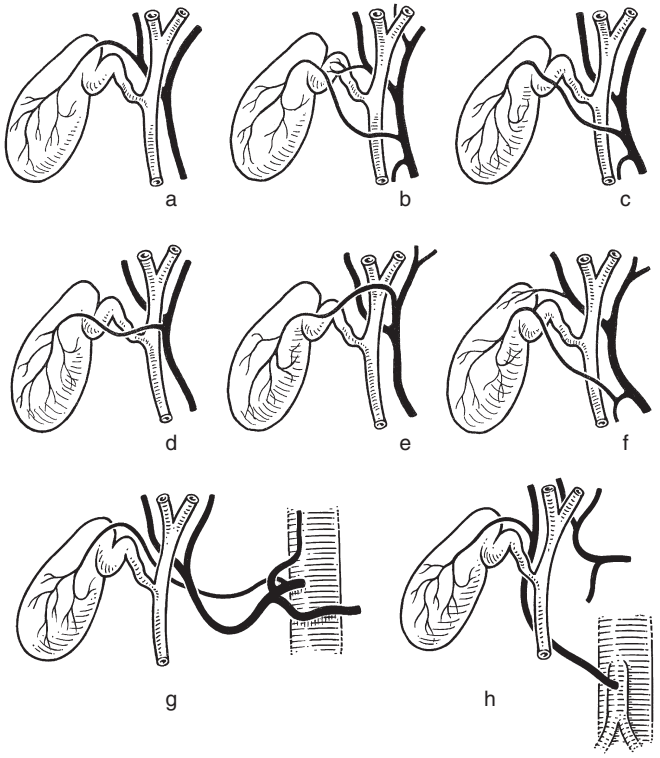


FIGURE 1B.22. The main variations of the cystic artery: typical course (*a*); double cystic artery (*b*); cystic artery crossing anterior to main bile duct (*c*); cystic artery originating from the right branch of the hepatic artery and crossing the common hepatic duct anteriorly (*d*); cystic artery originating from the left branch of the hepatic artery (*e*); cystic artery originating from the gastroduodenal artery (*f*); cystic artery arising from the celiac axis (*g*); cystic artery originating from a replaced right hepatic artery (*h*).

the pancreas, running in a groove or tunnel. The retropancreatic portion of the common bile duct approaches the second portion of the duodenum obliquely, accompanied by the terminal part of the pancreatic duct of Wirsung.

Gallbladder and Cystic Duct

The gallbladder is a reservoir located on the undersurface of the right lobe of the liver, within the cystic fossa; it is separated from the hepatic parenchyma by the cystic plate, which is composed of connective tissue closely applied to the Glisson capsule and elongating the hilar plate (see Fig. 1B.19). Sometimes the gallbladder is deeply embedded in the liver, but occasionally it occurs on a mesenteric attachment and may be susceptible to volvulus. The gallbladder varies in size and consists of a *fundus*, a *body*, and a *neck* (Fig. 1B.23). The tip of the fundus usually, but not always, reaches the free edge of the liver and is closely applied to the cystic plate. The cystic fossa is a precise anterior landmark to the main liver incisura. The neck of the gallbladder makes an angle with the fundus and creates the Hartmann pouch, which may obscure the common hepatic duct and constitute a real danger point during cholecystectomy.

The cystic duct arises from the neck or infundibulum of the gallbladder and extends to join the common hepatic duct. Its lumen usually measures about 1 to 3 mm, and its length varies,

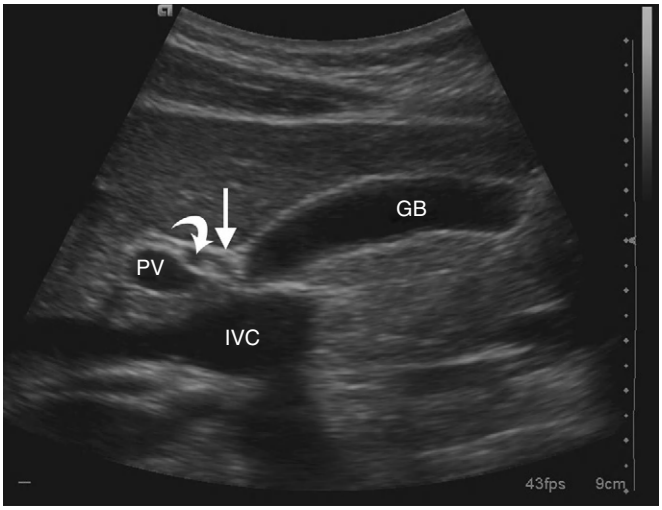


FIGURE 1B.23. Longitudinal sonogram shows the relationship of the liver, gallbladder (*GB*), portal vein (*PV*), inferior vena cava (*IVC*), hepatic artery (*curved arrow*) and common bile duct (*arrow*).

depending on the type of union with the common hepatic duct. The mucosa of the cystic duct is arranged in spiral folds known as the *valves of Heister* (Wood, 1979). Although the cystic duct joins the common hepatic duct in its supraduodenal segment in 80% of cases, it may extend downward to the retroduodenal or retropancreatic area. Occasionally, the cystic duct may join the right hepatic duct or a right hepatic sectoral duct (Fig. 1B.24).

BILIARY DUCTAL ANOMALIES

Full knowledge of the frequent variations from the described normal biliary anatomy is required when performing any hepatobiliary procedure. The constitution of a normal biliary confluence by union of the right and left hepatic ducts as described previously is reported in 72% of patients (Healey & Schroy, 1953). There is a triple confluence of the right anterior and posterior sectoral ducts and the left hepatic duct in 12% of individuals (Couinaud, 1957), and a right sectoral duct joins the main bile duct directly in 20%. In 16% the right anterior sectoral duct, and in 4% the right posterior sectoral duct, may approach the main bile duct in this fashion (Fig. 1B.25A). In 6%, a right sectoral duct may join the left hepatic duct (the posterior duct in 5% and the anterior duct in 1%; see Fig. 1B.16B). In 3%, there is an absence of the hepatic duct confluence, and the right posterior sectoral duct may join the neck of the gallbladder, or it may be entered by the cystic duct in 2% (Couinaud, 1957). In any event, these multiple biliary ductal variations at the hilus are important to recognize in resection and reconstructive surgery of the biliary tree at the hilus and during partial hepatectomy.

Intrahepatic bile duct variations also are common (Fig. 1B.26; Healey & Schroy, 1953). The main right intrahepatic duct variations are represented by an ectopic drainage of segment V in 9%, of segment VI in 14%, and of segment VIII in 20%. In addition, a subvesical duct has been described in 20% to 50% of cases. This duct, sometimes deeply embedded in the cystic plate, joins either the common hepatic duct or the right

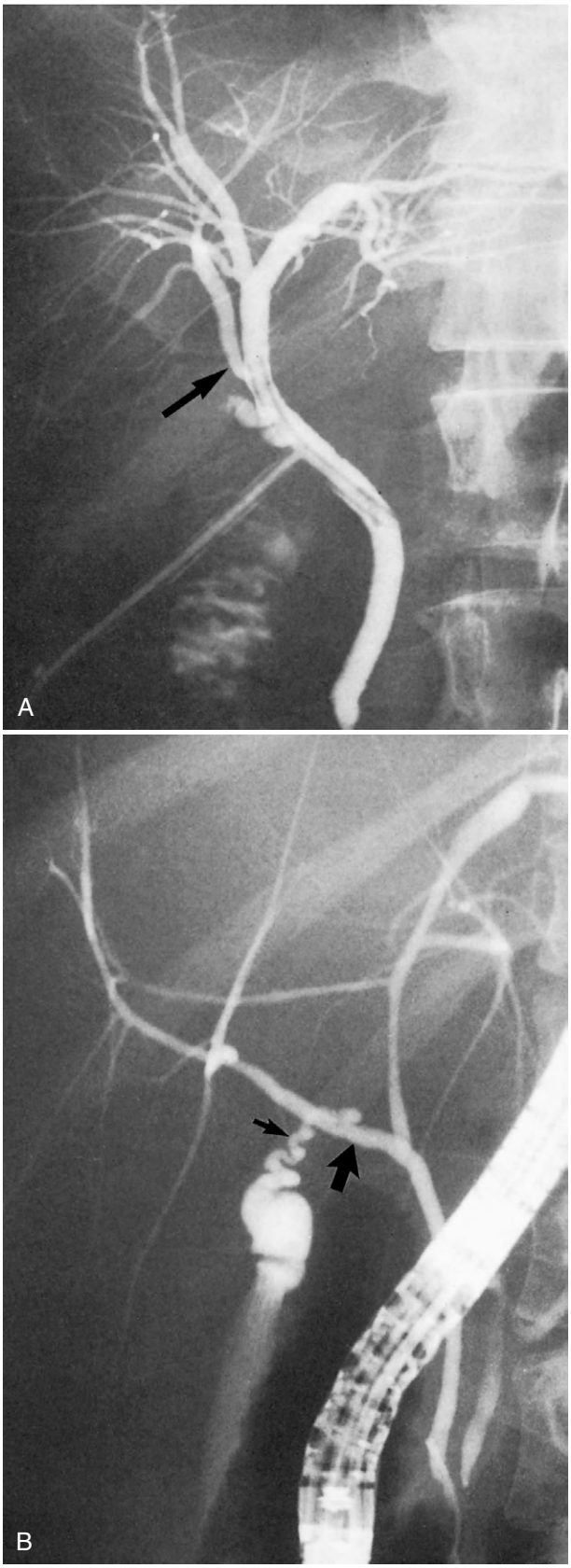


FIGURE 1B.24. **A,** T-tube cholangiogram shows a very low insertion of a right sectoral duct into the common hepatic duct (*arrow*). **B,** Endoscopic retrograde choledochopancreatogram shows a low right sectoral duct (*large arrow*), into which is draining the cystic duct (*small arrow*), an uncommon but important normal variant.

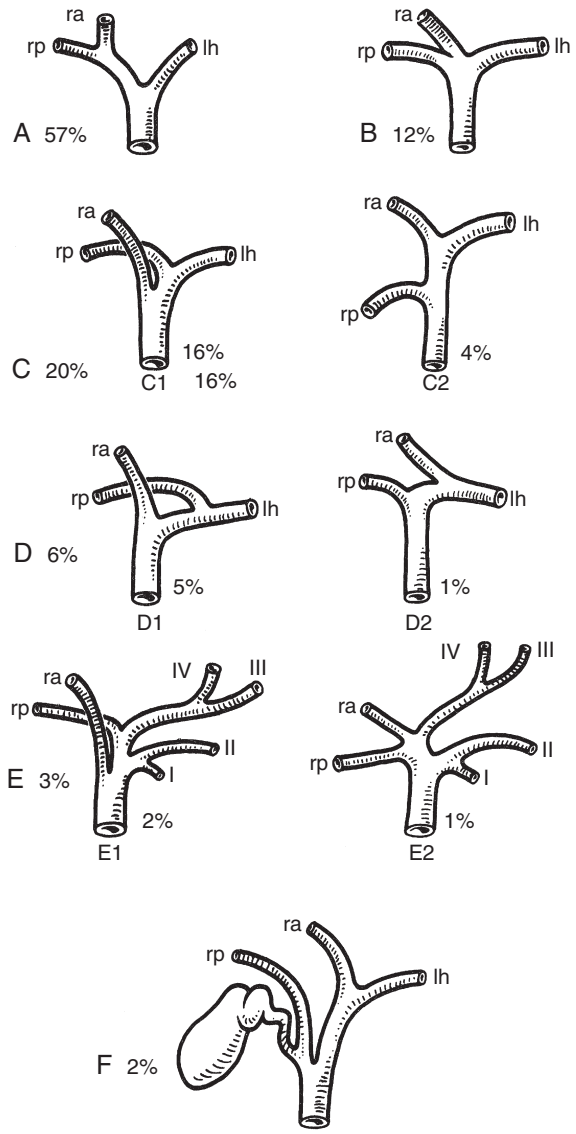


FIGURE 1B.25. Main variations of the hepatic duct confluence (Couinaud, 1957). **A,** Typical anatomy of the confluence. **B,** Triple confluence. **C,** Ectopic drainage of a right sectoral duct into the common hepatic duct (*C1*, Right anterior [*ra*] duct draining into the common hepatic duct; *C2*, Right posterior [*rp*] duct draining into the common hepatic duct). **D,** Ectopic drainage of a right sectoral duct into the left hepatic ductal system (*D1*, Right posterior sectoral duct draining into the left hepatic [*lh*] ductal system; *D2*, Right anterior sectoral duct draining into the left hepatic ductal system). **E,** Absence of the hepatic duct confluence. **F,** Absence of right hepatic duct and ectopic drainage of the right posterior duct into the cystic duct.

hepatic duct. It does not drain any specific liver territory, never communicates with the gallbladder, and is not a satellite of an intrahepatic branch of the portal vein or hepatic artery. Although not of major anatomic significance, injury may occur during cholecystectomy if the cystic plate is not preserved, which may lead to a postoperative biliary leak.

In 67% of patients (Healey & Schroy, 1953) a classic distribution of the main left intrahepatic biliary ductal system exists. The main variation in this region is represented by a common

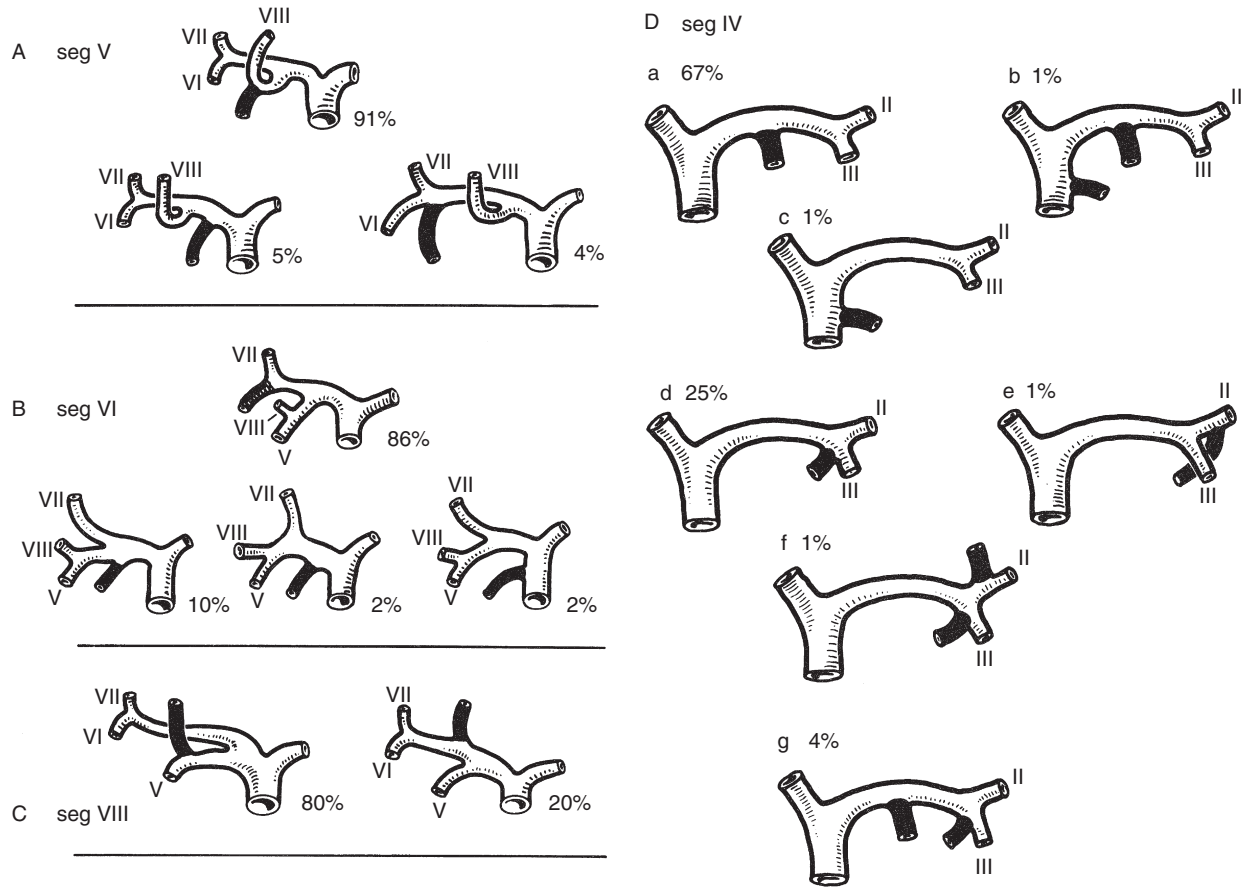


FIGURE 1B.26. Sketch shows the main variations of the intrahepatic ductal system. **A,** Variations of segment V. **B,** Variations of segment VI. **C,** Variations of segment VIII. **D,** Variations of segment IV. There is no variation of drainage of segments II, III, and VII.

union between the ducts of segments III and IV in 25%, and in only 2% does the duct of segment IV join the common hepatic duct independently. Several anomalies of drainage of the intrahepatic ducts into the neck of the gallbladder or cystic duct have been reported (Fig. 1B.27; Albaret et al, 1981; Couinaud, 1957), and these must be kept in mind during cholecystectomy (see Chapter 33).

ANOMALIES OF THE ACCESSORY BILIARY APPARATUS

Many anomalies of the accessory biliary apparatus have been described (Fig. 1B.28A; Gross, 1936). Although rare, agenesis of the gallbladder (Boyden, 1926; Rachad-Mohassel et al, 1973; Rogers et al, 1975), bilobar gallbladders with a single cystic duct but two fundi (Hobby, 1970), and duplication of the gallbladder with two cystic ducts all have been described. A double cystic duct may drain a unilocular gallbladder (Perelman, 1961), and congenital diverticulum of the gallbladder with a muscular wall may also be found (Eelkema et al, 1958). More frequently reported are anomalies of position of the gallbladder, which may be in an intrahepatic position, completely surrounded by normal liver tissue, or it may be found on the left of the liver (Newcombe & Henley, 1964).

The mode of union of the cystic duct with the common hepatic duct may be angular, parallel, or spiral (see Fig. 1B.28B). An angular union is the most frequent and is found in 75% of patients (Kune, 1970). The cystic duct may run a parallel course to the common hepatic duct in 20%, with connective tissue ensheathing both ducts. Finally, the cystic duct may approach the common bile duct in a spiral fashion. The absence of a cystic duct is probably an acquired anomaly, representing a cholecystocholedochal fistula.

BILE DUCT BLOOD SUPPLY

The bile duct may be divided into three segments: *hilar, supraduodenal*, and *retropancreatic* (lower common bile duct). The blood supply of the supraduodenal duct is essentially axial (Fig. 1B.29; Northover & Terblanche, 1979). Most vessels to the supraduodenal duct arise from the superior pancreaticoduodenal artery, the right branch of the hepatic artery, the cystic artery, the gastroduodenal artery, and the retroduodenal artery. On average, eight small arteries, each measuring about 0.3 mm in diameter, supply the supraduodenal duct. The most important of these vessels run along the lateral borders of the duct and have been called the *3 o'clock* and *9 o'clock arteries*. Of the blood vessels vascularizing the supraduodenal duct, 60% run

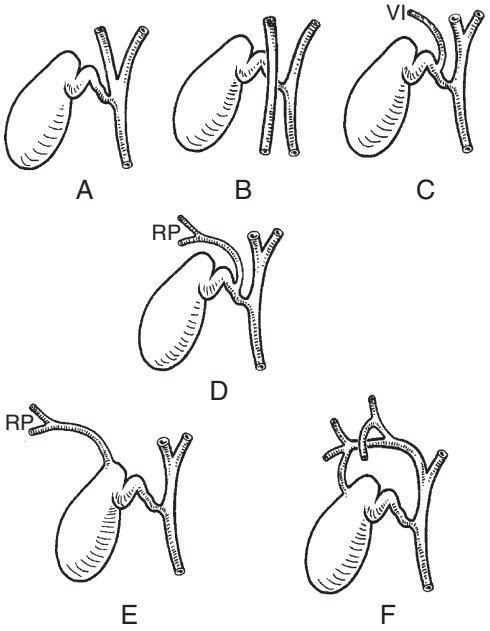


FIGURE 1B.27. The main variations of ectopic drainage of the intrahepatic ducts into the gallbladder and cystic duct. **A,** Drainage of the cystic duct into the biliary confluence. **B,** Drainage of cystic duct into the left hepatic duct, associated with no biliary confluence. **C,** Drainage of segment VI duct into the cystic duct. **D,** Drainage of the right posterior (*RP*) sectoral duct into the cystic duct. **E,** Drainage of the distal part of the right posterior sectoral duct into the neck of the gallbladder. **F,** Drainage of the proximal part of the right posterior sectoral duct into the body of the gallbladder.

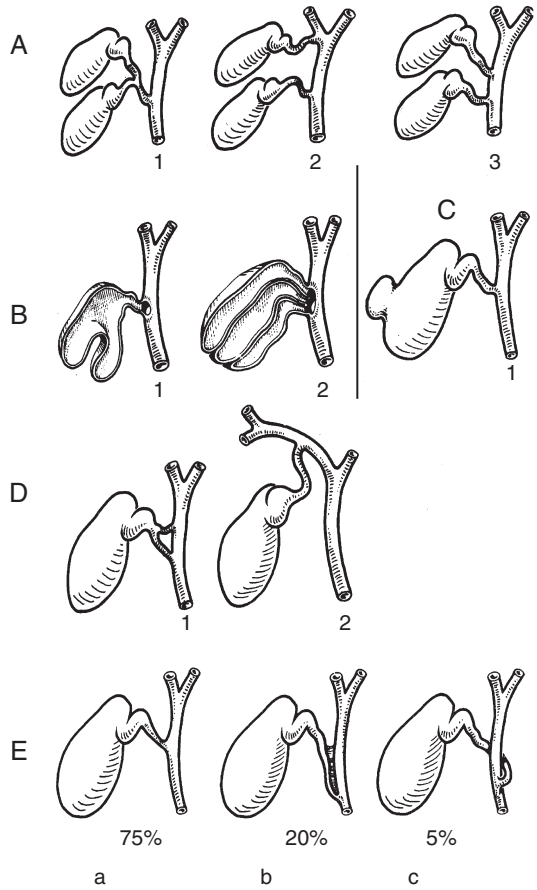


FIGURE 1B.28. Main variations in gallbladder and cystic duct anatomy: **A,** Duplicated gallbladder. **B,** Septum of the gallbladder. **C,** Diverticulum of the gallbladder. **D,** Variations in cystic ductal anatomy. **E,** Different types of union of the cystic duct and common hepatic duct: angular union (*a*), parallel union (*b*), spiral union (*c*).

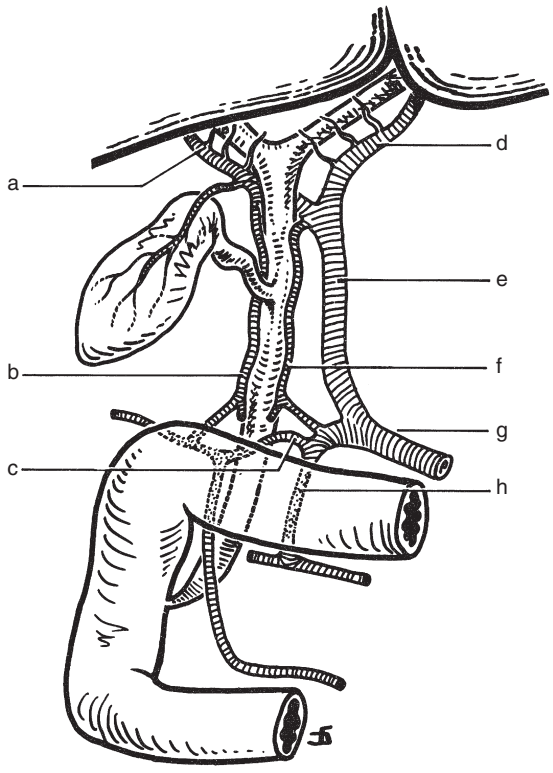


FIGURE 1B.29. The bile duct blood supply. Note the axial arrangement of the vasculature of the supraduodenal portion of the main bile duct and the rich network enclosing the right and left hepatic ducts: right branch of the hepatic artery (*a*); 9 o'clock artery (*b*); retroduodenal artery (*c*); left branch of the hepatic artery (*d*); hepatic artery (*e*); 3 o'clock artery (*f*); common hepatic artery (*g*); gastroduodenal artery (*h*).

upward from the major inferior vessels, and only 38% of arteries run downward, originating from the right branch of the hepatic artery and other vessels. Only 2% of the arterial supply is nonaxial, arising directly from the main trunk of the hepatic artery, as it courses up parallel to the main biliary channel. The hilar ducts receive a copious supply of arterial blood from surrounding vessels, forming a rich network on the surface of the ducts in continuity with the plexus around the supraduodenal duct. The source of blood supply to the retropancreatic common bile duct is from the retroduodenal artery, which provides multiple small vessels running around the duct to form a mural plexus.

The veins draining the bile ducts are satellites to the corresponding described arteries, draining into 3 o'clock and 9 o'clock veins along the borders of the common biliary channel. Veins draining the gallbladder empty into this venous system, not directly into the portal vein, and the biliary tree seems to have its own portal venous pathway to the liver.

ANATOMY OF BILIARY EXPOSURE

Biliary-Vascular Sheaths and Exposure of the Hepatic Bile Duct Confluence

Fusion of the Glisson capsule with the connective tissue sheaths surrounding the biliary and vascular elements at the inferior aspect of the liver constitute the plate system (see Figs. 1B.19 and 1B.20), which includes the hilar plate above the biliary confluence, the cystic plate related to the gallbladder, and the umbilical plate situated above the umbilical portion of the left portal vein (Couinaud, 1957). Hepp and Couinaud (1956) described a technique whereby lifting the quadrate lobe upward and incising the Glisson capsule at its base offers a good exposure of the hepatic hilar structures (see Fig. 1B.20A and B). This technique was referred to as *lowering of the hilar plate*. It can be carried out safely because only exceptionally (in 1% of cases) is there any vascular interposition between the hilar plate and the inferior aspect of the liver. This maneuver is of particular value in exposing the extrahepatic segment of the left hepatic duct, because it has a long course beneath the quadrate lobe. It is not as effective in exposing the extrahepatic right duct or its secondary branches, which are short. The technique is of major importance for the identification of proximal biliary mucosa during bile duct repair after injury. Basically, an incision is required at the posterior edge of the quadrate lobe, where the Glisson capsule is attached to the hilar plate (see Fig. 1B.20B and Chapter 29). The upper surface of the hilar plate can be separated from the hepatic parenchyma and, by lifting the quadrate lobe upward, display of the hepatic duct convergence, which is always extrahepatic, is effected. Bile duct incision allows performance of a mucosa-to-mucosa anastomosis. Rarely, it may be hazardous to approach the biliary confluence in this manner, especially when anatomic deformity has been created by atrophy or hypertrophy of liver lobes and in patients in whom there appears to be a very deep hilus that is displaced upward and rotated laterally. Frequently, by a simultaneous opening of the deepest portion of the gallbladder fossa and the umbilical fissure (see Fig. 1B.20C), good exposure of the biliary duct confluence, and especially the right hepatic duct, can be obtained without the necessity for full hepatotomy.

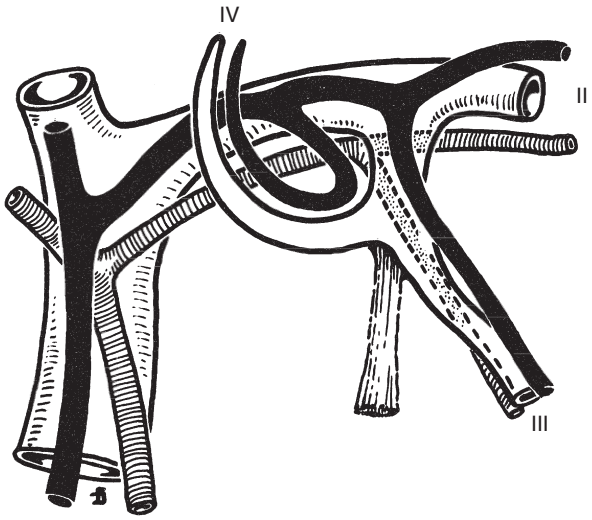


FIGURE 1B.30. Biliary and vascular anatomy of the left liver. Note the location of the segment III duct above the corresponding vein. The anterior branch of the segment IV duct is not represented.

Umbilical Fissure and Segment III (Ligamentum Teres) Approach

The round ligament, which is the remnant of the obliterated umbilical vein, runs through the umbilical fissure to connect with the left branch of the portal vein. The round ligament is sometimes deeply embedded in the umbilical fissure. At the junction of the round ligament and the termination of the left portal vein, elongations containing channels that are elements of the left portal system course into the liver. The bile ducts of the left lobe of the liver (Figs. 1B.30 and 1B.31A) are located above the left branch of the portal vein and lie behind these elongations, whereas the corresponding artery is situated below the vein. Dissection of the round ligament on its left side and division of one or two vascular elongations of segment III allow display of the pedicle or anterior branch of the duct of segment III (see Fig. 1B.31B). In the event of biliary obstruction with intrahepatic biliary ductal dilatation, the segment III duct is generally easily located above the left branch of the portal vein. It is often preferable to split the normal liver tissue just to the left of the umbilical fissure to widen the fissure further, which allows access to the ductal system without having to divide any elements of the portal blood supply to segment III (Fig. 1B.32; see Chapter 29).

Surgical Approaches to the Right Hepatic Biliary Ductal System

Because of the lack of precise anatomic landmarks, exposure of the right intrahepatic ductal system is much more hazardous and imprecise than that of the left. In some cases of hilar cholangiocarcinoma, the planned surgical procedure—partial hepatectomy or segment III duct bypass—seems impossible at operation. In such a critical operative situation, intrahepatic right ductal system drainage is an option. Anatomically, the anterior sectoral duct and its branches run on the left side of the

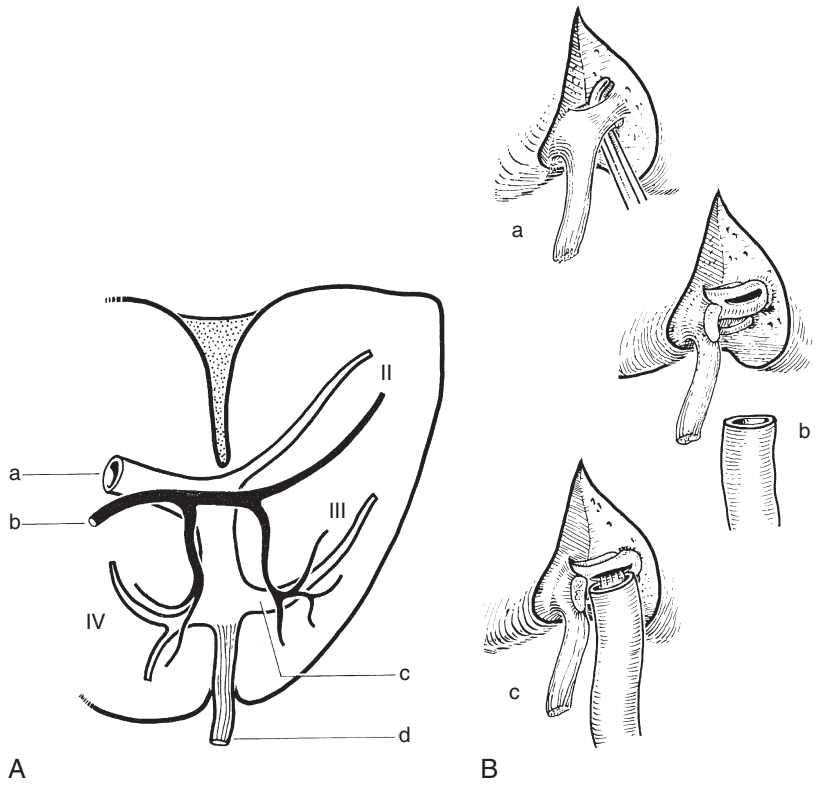


FIGURE 1B.31. A, The biliary and vascular anatomy of the left liver. Note the relationship of the left horn of the umbilical recess with the segment III ductal system: left portal vein (*a*); left hepatic duct (*b*); segment III system—note that the duct (*black*) lies adjacent to the portal venous branch indicated (*c*); ligamentum teres (*d*). **B,** Segment III ductal approach: exposure of the left horn of the umbilical recess (*a*); division of the left horn of the umbilical recess, including segment III portal vein branches (*b*); exposure and opening of segment III duct: hepaticojejunostomy to the segment III ductal system (*c*; see also Chapter 29).

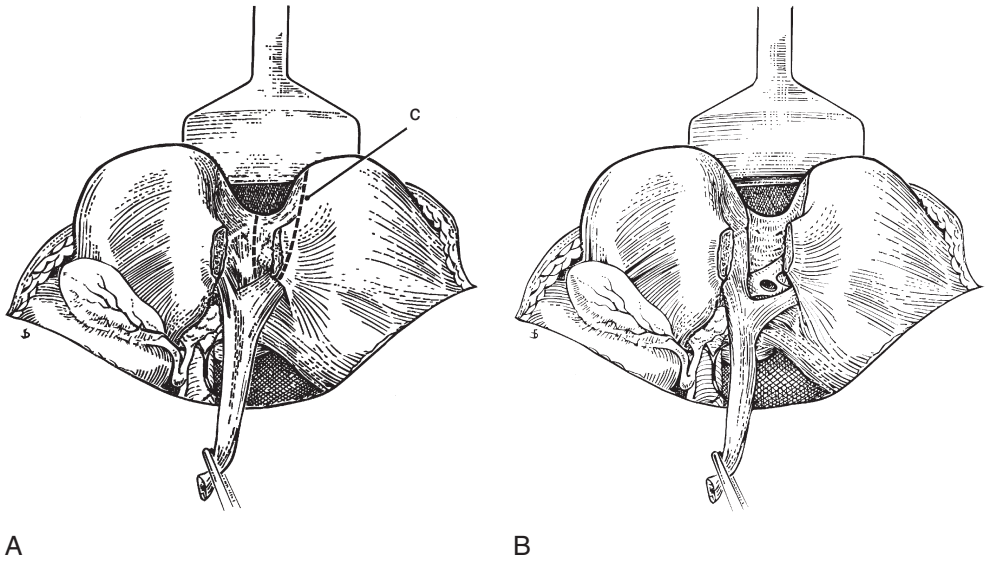


FIGURE 1B.32. A, The liver is split to the left of the ligamentum teres in the umbilical fissure. It may be necessary to remove a small wedge of liver tissue (*c*). **B,** Segment III duct is exposed at the base of the liver split, above and behind its accompanying vein, and is ready for anastomosis (see also Chapters 29 and 42).

corresponding portal vein. In essence, the end of the liver scissura, within which lies the right branch of the portal vein, is opened over a short distance. The anterior sectoral duct is displayed on the left aspect of the vein, and the dilated duct is opened longitudinally and anastomosed to a Roux-en-Y loop of jejunum (Fig. 1B.33). Although this technique is rarely used, it may be valuable in selected cases. An alternative method is to open into the segment V duct through the gallbladder fossa, although we seldom use this approach and prefer the anterior sectoral duct approach.

Exposure of the Bile Ducts by Liver Resection

This chapter does not detail exposure of the bile ducts by resection of liver substance. In essence, a segment of the left lobe may be amputated to expose the segment II or III ducts, or a

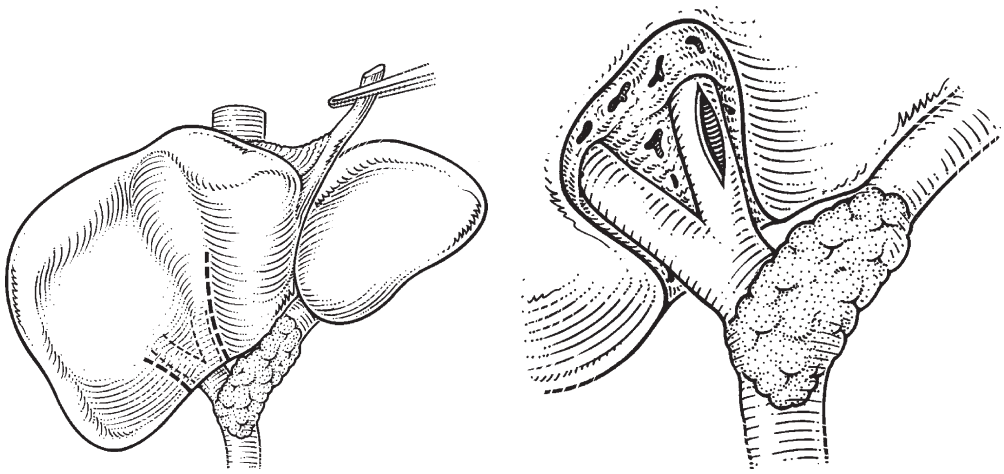


FIGURE 1B.33. **A,** Anterior sectoral approach. If necessary, the liver substance is opened over a short distance in the line of the right anterior sectoral pedicle. **B,** The duct is displayed anterior and to the left side of the corresponding vein. This can be facilitated using a posterior pedicular approach as described by Launois (see Chapters 90A to 90F).

similar procedure may be carried out after removal of the inferior tip of the right lobe. Finally, in some instances, removal of the quadrate lobe may be carried out to effect exposure of the biliary confluence. This procedure really represents a simple extension of the mobilization of the quadrate lobe after opening of the principal scissura and the umbilical fissure as described previously.

EXTRAHEPATIC VASCULATURE

Celiac Axis and Blood Supply of Liver, Biliary Tract, and Pancreas

The usual classic description of the arterial blood supply of the liver, biliary system, and pancreas is found in only about 60% of specimens (Figs. 1B.34 to 1B.36). The right and the left hepatic arteries, the former in the right of the hilus of the liver and the latter in the left at the base of the umbilical fissure, become enclosed in the sheath of peritoneum, forming the right and left portal triads. In this sheath, further branching to the right anterior and posterior sectors of the liver and on the left to segments II, III, and IV occurs within the respective pedicles, which also come to enclose the portal vein branches and the tributary bile ducts from these sectors and segments. The arterial supply of the common bile duct was described earlier; it arises from branches of the hepatic artery, the gastroduodenal artery, and the pancreaticoduodenal arcades.

For practical surgical issues, the most important relationships in the anatomy of the pancreas concern the arterial blood supply and the venous drainage. The dorsal pancreatic artery is a major branch, usually arising from the splenic artery, but it can arise directly from the hepatic artery. When splenectomy is performed, it is important to establish the site of origin of the distal pancreatic artery by proximal arterial ligation to avoid distal pancreatic ischemia. The superior mesenteric artery (SMA) arises from the aorta posteriorly behind the pancreas and runs forward and upward to run first behind and then to the left of the superior mesenteric vein (see Fig. 1B.35).

Variations in the Hepatic Artery

As a result of the complex embryologic development of the celiac axis and SMA, wide variations in the arterial supply of the liver are found (Fig. 1B.37). These variations are important to the angiographer and the surgeon. Failure to show all arteries feeding the liver at angiography may not only result in errors of diagnosis but may also seriously mislead the surgeon or the interventional radiologist. In most cases, the hepatic artery arises from the celiac axis as described earlier, but it may be entirely replaced by a common hepatic artery taking origin from the SMA. In this instance, the hepatic artery passes lateral to the portal vein and lies posterior and lateral to the common bile duct in the hepatoduodenal ligament, where it is susceptible to operative injury if not recognized. This applies to a replaced or an accessory hepatic artery. Other variations in the origin of the common hepatic artery include its origin from the aorta and the persistence of a primitive embryologic link between the celiac and superior mesenteric systems. These variations are of considerable importance in controlling the arterial blood supply to the liver during hepatic resection or enucleative procedures, in the performance of devascularization of the liver, in the placement of intraarterial hepatic infusion devices, and in the resection of the head of the pancreas.

Portal Vein

The portal vein (Fig. 1B.38) is formed behind the neck of the pancreas by confluence of the superior mesenteric and splenic veins (Fig. 1B.39). The venous drainage of the pancreas runs in the main parallel to the arterial supply. There are anterior and posterior and superior and inferior pancreaticoduodenal veins that drain to the portal vein and the superior mesenteric vein (SMV). The left gastric vein and the inferior mesenteric vein (IMV) usually drain into the splenic vein, but they can drain directly into the portal vein, whereas the various small splenic tributaries drain directly to the splenic vein.

The anatomic relationship of the pancreas to the SMV, the splenic vein, and the portal vein (see Fig. 1B.38) is important

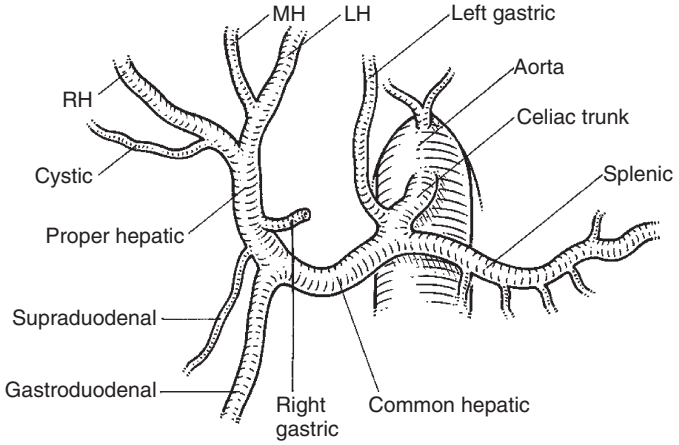


FIGURE 1B.34. The celiac trunk is a short, thick artery originating from the aorta just below the aortic hiatus of the diaphragm and extending horizontally and forward above the pancreas, where it divides into the left gastric, common hepatic, and splenic arteries. An inferior phrenic artery, usually arising from the aorta or the splenic artery, occasionally arises from the celiac trunk. The left gastric artery curves toward the stomach and extends along its lesser curve, forming anastomoses with the right gastric artery. The splenic artery, the largest of the three celiac branches, takes a tortuous course to the left, behind and along the upper border of the pancreas and at the hilus of the spleen, where it splits into numerous terminal branches. The splenic artery usually approaches and runs superiorly to the splenic vein. An uncommon but dangerous abnormality can occur when the splenic artery runs inferiorly and behind the splenic vein, close to the splenic vein–mesenteric vein confluence. The left gastroepiploic artery and the short gastric arteries originate from one of these terminal branches. The common hepatic artery passes forward into the retroperitoneum then curves to the right to enter the right margin of the lesser omentum, just above the pancreas, and ascends; it approaches the common bile duct on its left side and runs usually anterior to the portal vein. As it turns upward just above the pancreas, it gives rise to the gastroduodenal artery, which also may originate from the right hepatic artery. This descends to supply the anterior, superior, and posterior surfaces of the first inch of the duodenum. The gastroduodenal artery can be duplicated and often has a small branch running with it toward the pylorus. The right gastric artery passes to the left along the lesser curve of the stomach, and anastomosis is to the left gastric artery. The continuation of the common hepatic artery, beyond the origin of the gastroduodenal artery and right gastric artery, is known as the *proper hepatic artery* and usually soon divides into a right and a left branch. The left branch extends vertically, directly toward the base of the umbilical fissure, and usually gives off a branch known as the *middle hepatic artery* (*MH*), which is directed toward the right of the umbilical fissure and is destined to supply the quadrate lobe (segment IV) of the liver. A further branch of the left hepatic artery (*LH*) courses to the left to supply the caudate lobe, and further smaller caudate branches arise from the left and right hepatic artery. The right hepatic artery (*RH*) usually passes behind the common hepatic duct and enters the cystic triangle of Calot; in some cases it passes in front of the bile duct, which is important in surgical exposure of the common bile duct. The cystic artery usually arises from the right hepatic artery but has many variations.

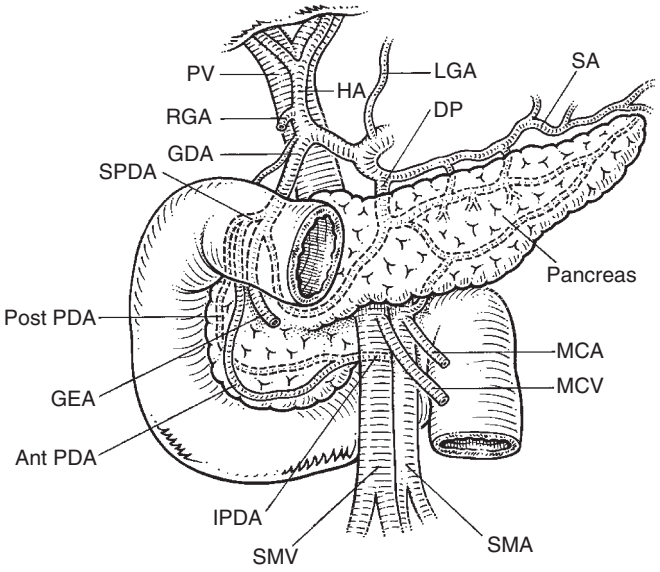


FIGURE 1B.35. The primary arteries supplying the pancreas are the gastroduodenal artery (*GDA*), which arises usually from the common hepatic artery (*HA*) as it crosses the portal vein (*PV*) above the pancreas proper, and the dorsal pancreatic artery (*DP*), arising from the splenic artery (*SA*). The superior pancreaticoduodenal arteries (*SPDAs*) arise from the GDA and join the inferior pancreaticoduodenal arteries (*IPDAs*) from the superior mesenteric artery (*SMA*), forming two arcades along the anterior and posterior aspects of the head of the pancreas. The GDA, after giving rise to the pancreaticoduodenal artery (*PDA*), passes forward and to the left as the right gastroepiploic artery (*GEA*). The GDA is a good landmark for the identification of the portal vein above the pancreas, and surgical division of the GDA just at its origin from the common HA gives much greater access to the anterior surface of the portal vein at this site. The right gastric artery (*RGA*) also usually arises from the common HA just distal to the GDA, but it can arise from various sites. The GDA commonly divides into a larger right GEA and smaller SPDA. The right GEA runs forward between the first part of the duodenum and pancreas; the SPDA divides into anterior and posterior branches. The anterior superior PDA continues downward on the anterior surface of the head of the pancreas to anastomose with the IPDA, which arises from the SMA. The posterior superior PDA behaves similarly. MCA, middle colic artery; MCV, middle colic vein; SMV, superior mesenteric vein; LGA, left gastric artery.

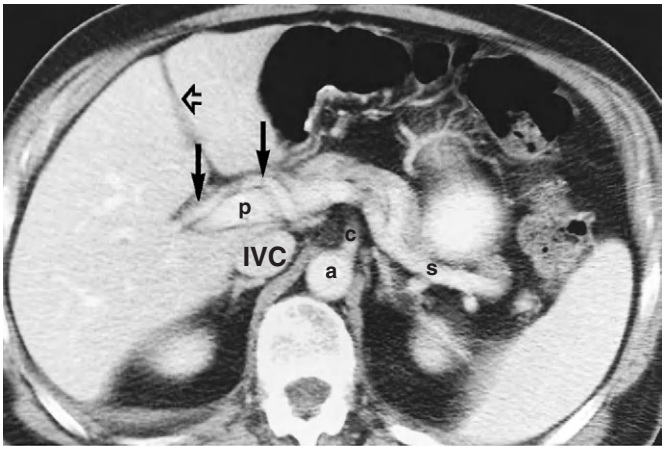
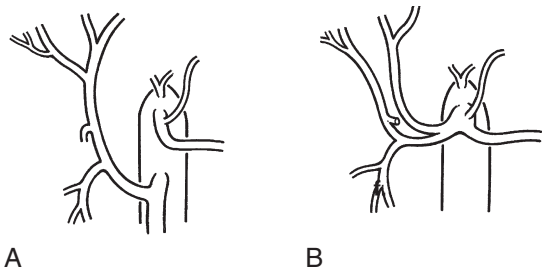
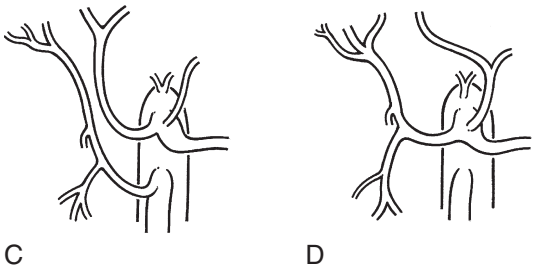


FIGURE 1B.36. Computed tomographic image of the main portal vein shows the hepatic artery (*arrows*) coursing anterior to the portal vein (*p*). The interlobar fissure (*open arrow*), splenic vein (*s*), celiac axis (*c*), aorta (*a*), and inferior vena cava (*IVC*) are also shown.





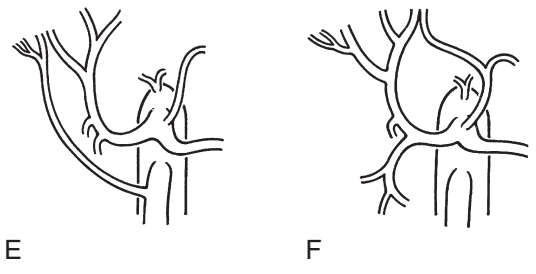


FIGURE 1B.37. In approximately 25% of individuals, the right hepatic artery arises partially or completely from the superior mesenteric artery (**A, C, E**); in a similar proportion of patients, the left hepatic artery may be partially or completely replaced by a branch arising from the left gastric artery, coursing through the gastrohepatic omentum to enter the liver at the base of the umbilical fissure (**D, F**). Rarely, the right or left hepatic arteries originate independently from the celiac trunk or branch after a very short common hepatic artery origin from the celiac, and the gastroduodenal artery may originate from the right hepatic artery (**B, C**).

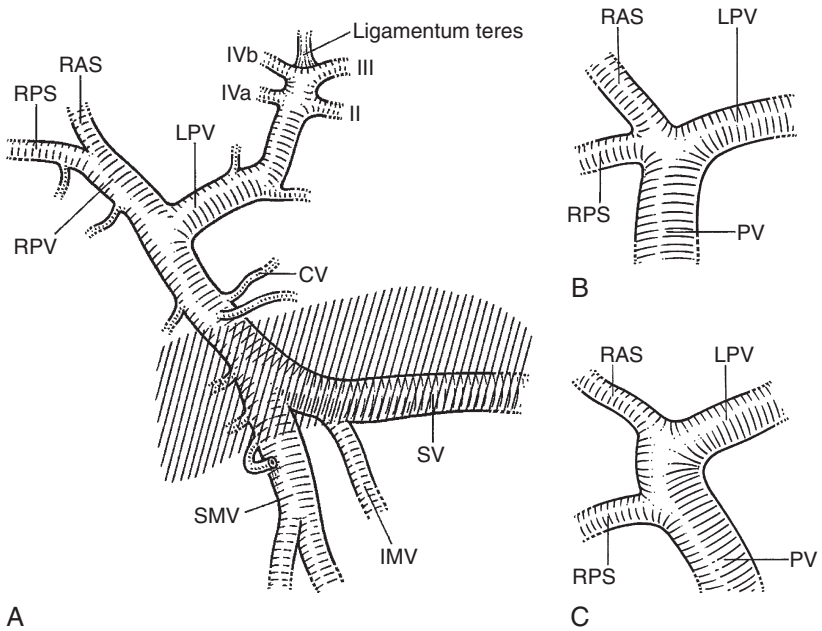


FIGURE 1B.38. **A,** The superior mesenteric vein (*SMV*) at the root of the lesser omentum is usually a single trunk; two or sometimes even three branches may unite as the vessel enters the tunnel beneath the neck of the pancreas (*shaded*) to form a superior mesenteric trunk. This trunk ascends behind the neck of the pancreas and is joined by the splenic vein (*SV*), which enters it from the left to form the portal vein (*PV*), which emerges from the retroperitoneal upper border of the neck of the pancreas and ascends toward the liver within the free edge of the lesser omentum, lying behind the bile duct and the hepatic artery and surrounded by the lymphatics and nodes of the lesser omentum. During this course, it receives blood through the coronary vein (*CV*), which communicates with esophageal venous collaterals, which connect with the gastric vein and the esophageal plexus. Sometimes a separate right gastric vein enters the PV in this area. A superior pancreaticoduodenal vein often enters the PV just above the level of the pancreas, and several smaller veins enter the SMV and PV from the right side beneath the neck of the pancreas. As the PV ascends behind the common bile duct and common hepatic duct, it approaches the hilus of the liver and bifurcates into two branches, a larger right (*RPV*) and a smaller left portal vein (*LPV*). The branch on the left courses below the left hepatic duct to enter the umbilical fissure, in company with the left hepatic artery, and subsequently branches to supply the left liver segments (II-IV). Just before its entry into the umbilical fissure, it gives off a major caudate vein, segment I, which runs posteriorly and laterally to the left. Sometimes this vein consists of two or more branches; the right portal branch, which is much shorter in length before its entry into the liver, divides at the extremity of the hilus into the right anterior (*RAS*) and posterior (*RPS*) sectoral branches and is accompanied by the respective arterial branches and biliary tributaries. **B,** The division of the portal vein may arise more proximally, however, and the right anterior and posterior sectoral portal veins may arise independently from the portal venous trunk. **C,** See also Figs. 1B.8B, 1B.40, and Chapters 90 A through F.

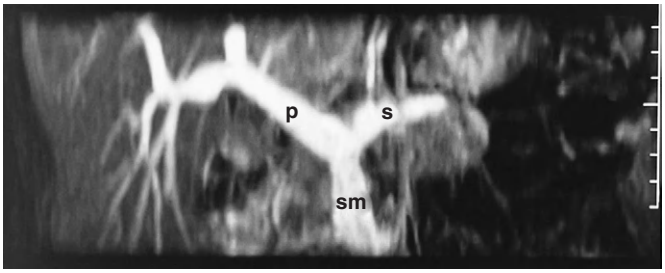


FIGURE 1B.39. Magnetic resonance imaging of the splenoportal confluence: postcontrast, T1-weighted, three-dimensional gradient-echo coronal maximum intensity projection. Shown are the splenic vein (*s*); portal vein (*p*); superior mesenteric vein (*sm*).



FIGURE 1B.40. Contrast-enhanced computed tomographic scan of variant portal vein branching with trifurcation pattern. *M,* main portal vein; *L,* left portal vein; *RA,* right anterior portal vein; *RP,* right posterior portal vein. *(From Covey AM, et al, 2004: Incidence, patterns, and clinical relevance of variant portal vein anatomy. Am J Roentgenol 183:1055-1064.)*

in pancreaticoduodenectomy (see Chapter 62). The uncinate process can extend behind the SMV to well behind the SMA (see Fig. 1B.35). Access to the portal vein behind the pancreas usually is obtained from below by elevating the pancreas from the surface of the SMV just before it joins the splenic vein. With the exception of the inferior pancreaticoduodenal veins, which enter the SMV at the inferior border of the pancreas, it is uncommon to see branches from the pancreas run directly posteriorly into the SMV. Fixation here is usually by some inflammatory or neoplastic process. Superiorly, the portal vein runs behind the pancreas and is identified first in the gap between the curvature of the splenic vein, splenic artery, common hepatic artery, and gastroduodenal artery. Division of the gastroduodenal artery provides much greater access to the superior surface of the portal vein. If difficulty is encountered in this area, division of the common bile duct, usually above the cystic duct, can provide excellent access to the right lateral aspect and anterior surface of the portal vein. The SMA can be approached behind the pancreas above the point at which it is embraced by the uncinate process at the origin from the aorta. This allows dissection of the most proximal part of the SMA from behind.

Occasionally, the middle colic artery and other vessels of supply to the colon can arise from the more proximal SMA, such that they pass through the pancreas; this abnormality should be searched for carefully. Division of the middle colic artery is usually not a problem, however, because the colon is well supplied, and ischemia typically does not occur.

Of special importance to the surgeon is the direct relationship of the head of the pancreas to the duodenum and posteriorly to the right renal vein and the anterior surface of the IVC, and of the neck and body of the pancreas posteriorly to the SMA and the splenic vessels and their branches, the left renal vein, and, more laterally, the left kidney. The right gastroepiploic vein commonly drains into the anterior surface of the SMV just at the inferior border of the pancreas; this can often be involved by tumor, as can the anterior branch of the inferior pancreaticoduodenal vein; the middle colic vein may also join at this point. In mobilizing the SMV, these vessels are ligated so as to avoid bothersome hemorrhage. Abnormalities of the IVC are uncommon, with duplication of the vena cava and a left-sided vena cava seen rarely.

Several variations in anatomy and rare congenital anomalies of the portal vein are of surgical significance (Figs. 1B.40 to 1B.43). For example, performance of right hepatic resection, with division of what appears to be the right portal vein in a patient with absence of the left portal vein (Fig 1B.42), can deprive the entire liver of blood; this surgical error is usually fatal. Agenesis of the right branch of the portal vein is associated with agenesis of the right hemiliver and left liver hypertrophy. This may be associated with biliary and hepatic venous anatomic changes, which can compromise surgical approaches to the liver and to biliary repair (Fields et al, 2008).

Portal venous blood is derived from the venous drainage of the stomach, small bowel, spleen, and pancreas, and this drainage is important when considering surgery of the pancreas and in patients with portal hypertension; it is described in detail along with the description of the anatomy of the pancreas.

PANCREAS

The pancreas is a posteriorly situated retroperitoneal organ draped across the major vessels and the vertebral column (Fig. 1B.44). The organ is composed of a *head*, *neck*, and *body*; the head is encompassed by the duodenum, and the tail rests in the splenic hilum (Figs. 1B.45 and 1B.46). A portion of the head inferiorly is termed the *uncinate process* and is intimately related to the SMV and SMA (see Figs. 1B.45 and 1B.46). Posteriorly, the pancreas is related to the IVC, aorta, left renal vein and kidney, and spleen (see Figs. 1B.44 and 1B.46B). Usually 4 to 6 inches in length, the relative dimensions of the pancreas have been evaluated more recently. The mean weight is 91.8 g (range, 40.9 to 182 g). To the right of

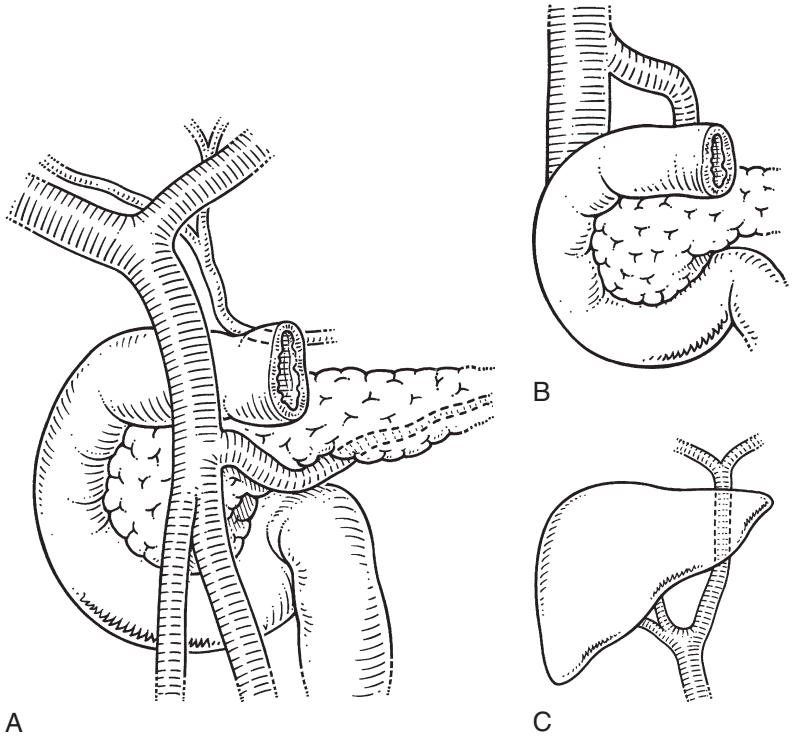


FIGURE 1B.41. **A,** The portal vein anterior to the head of the pancreas and the duodenum may be in an abnormal position. **B,** Another rare but interesting anomaly is the entrance of the portal vein into the inferior vena cava. **C,** Very rare, the entrance of a pulmonary vein into the portal vein.

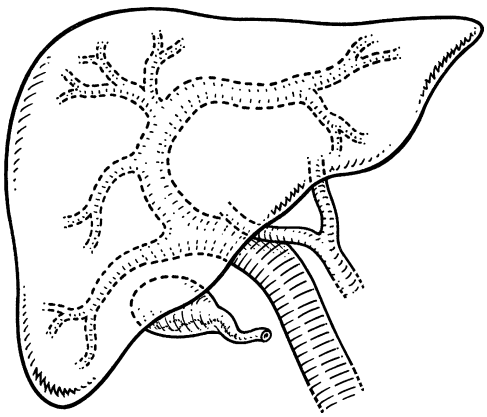


FIGURE 1B.42. In a congenital absence of the left branch of the portal vein as described by Couinaud, the right branch courses through the right lobe of the liver supplying it and curves within the liver substance to supply the left lobe, which in such instances is usually smaller than normal.



FIGURE 1B.43. Computed tomographic scan in a patient with Caroli disease shows a large right portal trunk. The left branch of the portal vein is absent, with findings confirmed at operation for left hepatic lobectomy.

the common bile duct, the average weight of the pancreas is 11.4% of its total weight; the portion lateral to the portal vein averages 56.4% of the total weight. The pancreatic capsule is loosely attached to the surface of the pancreas and is contiguous with the anterior layer of the mesocolon, such that it can be dissected in continuity if necessary. The mesenteric attachments to the pancreas tend to be contiguous (see Fig. 1B.46). The arterial blood supply and venous drainage and the relationships to the common bile duct were described and illustrated earlier (see Figs. 1B.17, 1B.29, 1B.34, 1B.35, and 1B.38).

Pancreatic Duct

The duct of Wirsung, beginning in the distal tail as a confluence of small ductules, runs through the body to the head, where it usually passes downward and backward in close juxtaposition to the common bile duct (see Fig. 1B.45). The sphincter of Oddi (Fig. 1B.47) has been thoroughly studied (Boyden, 1957; Delmont, 1979) and consists of a unique cluster of smooth muscle fibers distinguishable from the adjacent smooth muscle of the duodenal wall. The papilla of Vater at the termination of the common bile duct is a small, nipplelike structure that protrudes into the duodenal lumen and is marked by a longitudinal

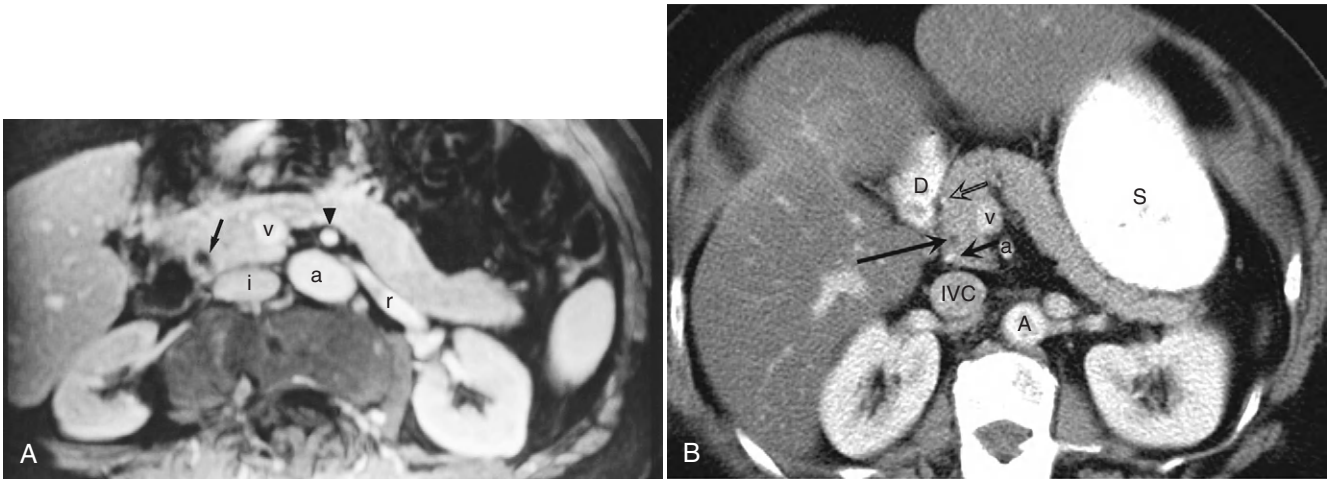


FIGURE 1B.44. A, Magnetic resonance imaging of the pancreas, oblique axial reconstruction, T1-weighted three-dimensional gradient-echo technique. Aorta (*a*), inferior vena cava (*i*), common bile duct (*arrow*), inferior mesenteric vein at the splenoportal confluence (*v*), superior mesenteric artery (*arrowhead*), and left renal vein (*r*) are shown. **B,** Normal pancreatic anatomy. Postcontrast computed tomographic scan at the level of the pancreas. *S,* stomach; *D,* duodenum; *A,* aorta; *v,* superior mesenteric vein; *a,* superior mesenteric artery. *Long arrow*, common bile duct; *short arrow*, inferior pancreaticoduodenal artery; *open arrow*, gastroduodenal artery.

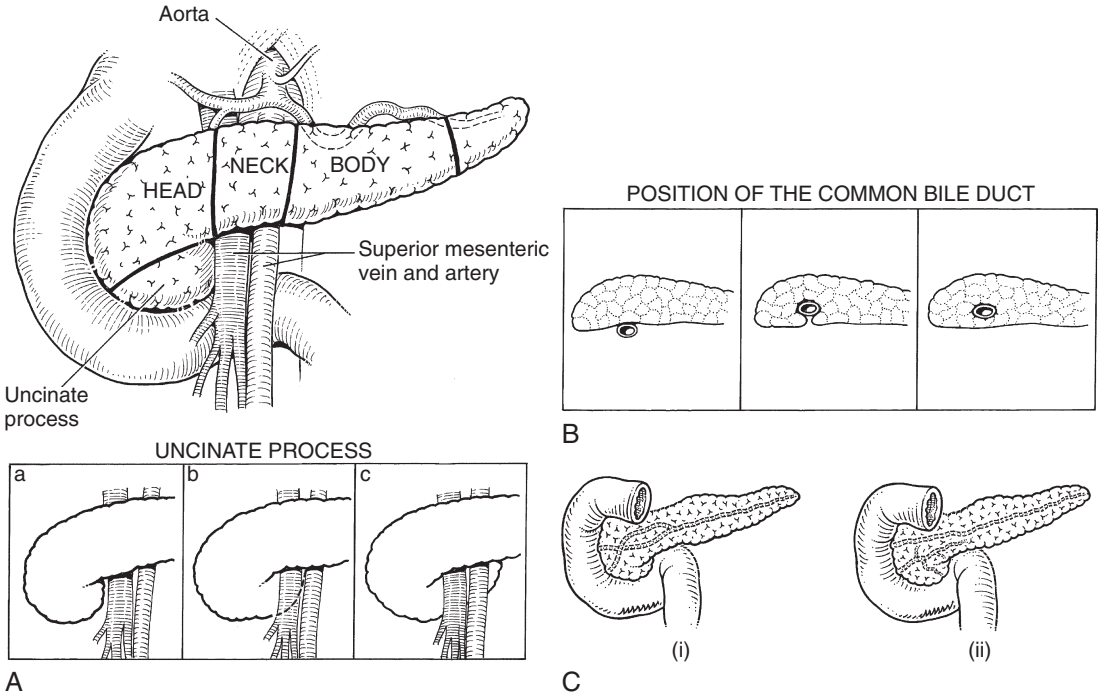
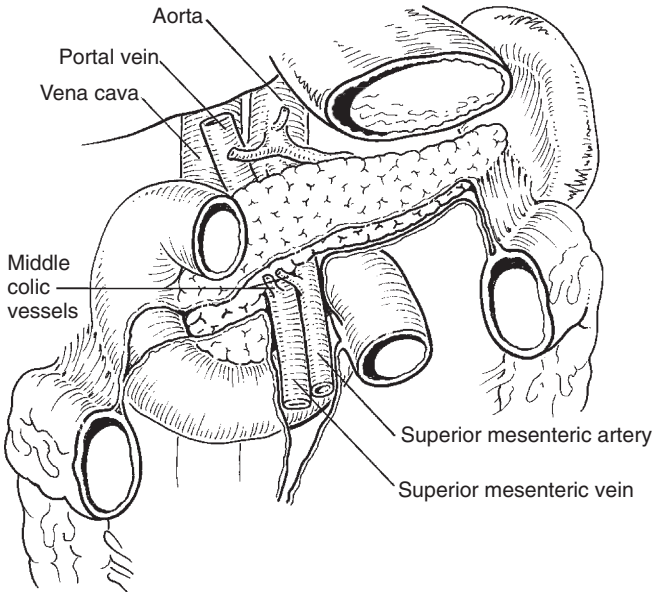
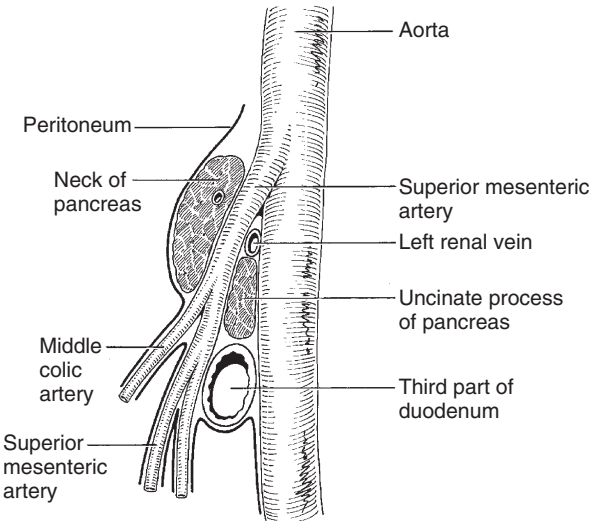


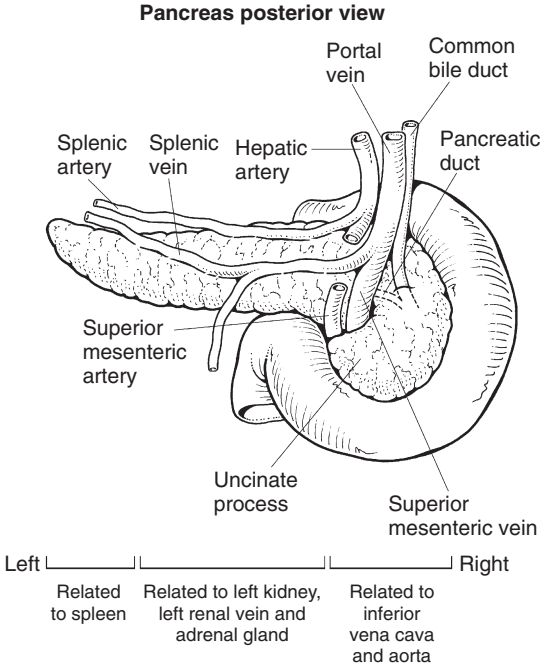
FIGURE 1B.45. A, The head of the pancreas is globular with an extension, the *uncinate process*, which curves behind the superior mesenteric vessels and may end even before it embraces the superior mesenteric vein (*a*), or it may pass completely behind between the aorta and the left of the patient's superior mesenteric artery (*b, c*). All variations are commonly seen. Posteriorly, the head of the pancreas lies in juxtaposition to the inferior vena cava at the level of the entry of the left and right renal veins. The head of the pancreas forms a narrow *neck* in front of the superior mesenteric and splenic vein confluence. The neck joins to the *body* of the gland, which forms a narrow *tail*. **B,** The common bile duct (CBD) passes through the pancreas, either directly in the substance of the gland or initially with a posterior groove. **C,** The *duct of Wirsung* courses from left to right within the pancreas, curves downward approaching the CBD, and runs parallel with but separated from it by the *transampullary septum* to enter the duodenum, 7 to 10 cm distal to the pylorus, at the *papilla of Vater* after traversing the *sphincter of Oddi.* An accessory duct, the *duct of Santorini,* runs more proximally in the head of the pancreas and usually terminates in the duodenum at an accessory papilla. Multiple variations of the ductal system occur, depending on the extent of development of the duct of Santorini, such that rarely the accessory duct can enter the duodenum inferior to the main duct. It can be in communication with the main duct directly (*i*), or it can occur in duplicate version known as *pancreas divisum* (*ii*). The duct of Santorini drains the body and tail of the organ, and the duct of Wirsung drains the head and the uncinate process.



A



B



C

FIGURE 1B.46. **A,** The anterior surface of the pancreas, covered by the posterior layer of the omental bursa or lesser peritoneal sac, can often be obliterated by adhesions. The transverse mesocolon arises from the lower border of the pancreas and envelops the middle colic vessels as they arise from the superior mesenteric vessels just beneath the pancreatic neck. **B,** The relationship of the pancreatic neck and uncinate process to the aorta and superior mesenteric artery. Note the position of the left renal vein and duodenum. **C,** The posterior relationships of the duodenal loop and pancreas. Note the relationship to the inferior vena cava, aorta, and hilum of the spleen.

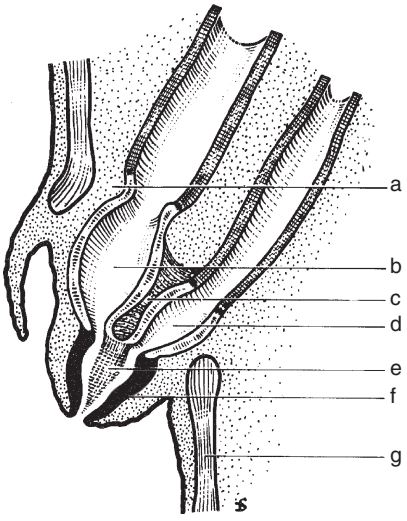
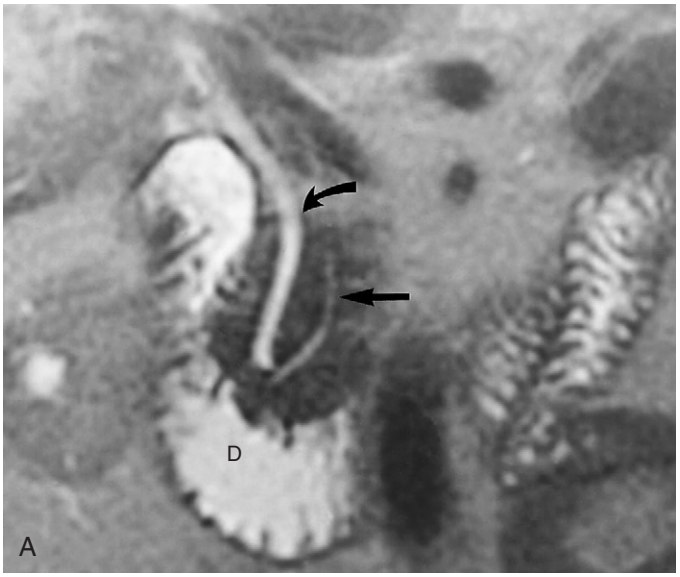


FIGURE 1B.47. Schematic representation of the sphincter of Oddi: notch (*a*); biliary sphincter (*b*); transampullary septum (*c*); pancreatic sphincter (*d*); membranous septum of Boyden (*e*); common sphincter (*f*) ; smooth muscle of duodenal wall (*g*).



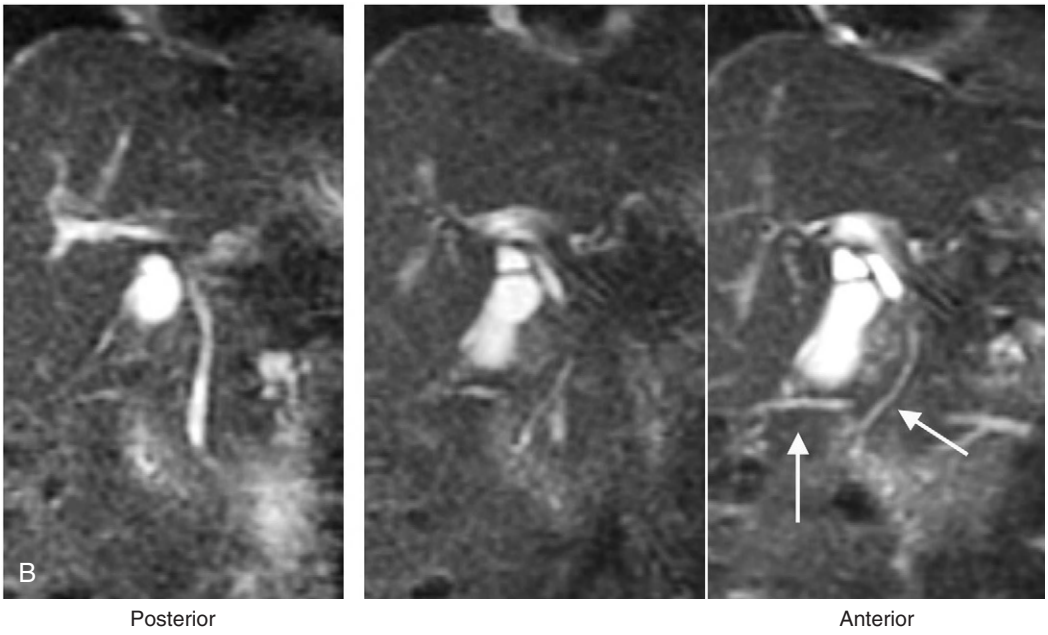


FIGURE 1B.48. **A,** Magnetic resonance imaging (MRI) cholangiography, T2-weighted coronal image at the level of the ampulla, shows the duodenum (*D*) and the pancreatic head with common bile duct (*curved arrow*) and pancreatic duct (*straight arrow*). **B,** MR cholangiopancreatography (*MRCP*) shows pancreas divisum. Anterior projection shows variant anatomy with the duct of Santorini (*vertical arrow*) between the duodenum above the duct of Wirsung (*angled arrow*). The two ducts are separate; the duct of Santorini drains mainly the neck and body of the pancreas, and the duct of Wirsung drains mainly the uncinate process portion of the head of the pancreas.

fold of duodenal mucosa. The duct of Wirsung runs downward and parallel to the common bile duct for approximately 2 cm and joins it within the sphincter segment in 70% to 85% of patients; it enters the duodenum independently in 10% to 13% of patients and is replaced by the duct of Santorini in 2% of patients (Fig. 1B.48; see also Fig. 1B.45). Rarely, the duct of Santorini and the duct of Wirsung are separate, which is known as *pancreas divisum* (see Figs. 1B.45Cii and 1B.48B). The islands or islets of Langerhans, which provide the endocrine component of the gland, are scattered throughout the pancreas.

Annular Pancreas

Annular pancreas is the development of a ring of pancreatic tissue that surrounds and often embraces the duodenum. This ring may contain a large duct and can be firmly affixed to the duodenal musculature. The duodenum beneath this annulus is often stenosed, such that dividing this ring does not always relieve chronic duodenal obstruction. This accounts for the common process of applying duodenojejunostomy to relieve strictures caused by such an annulus.

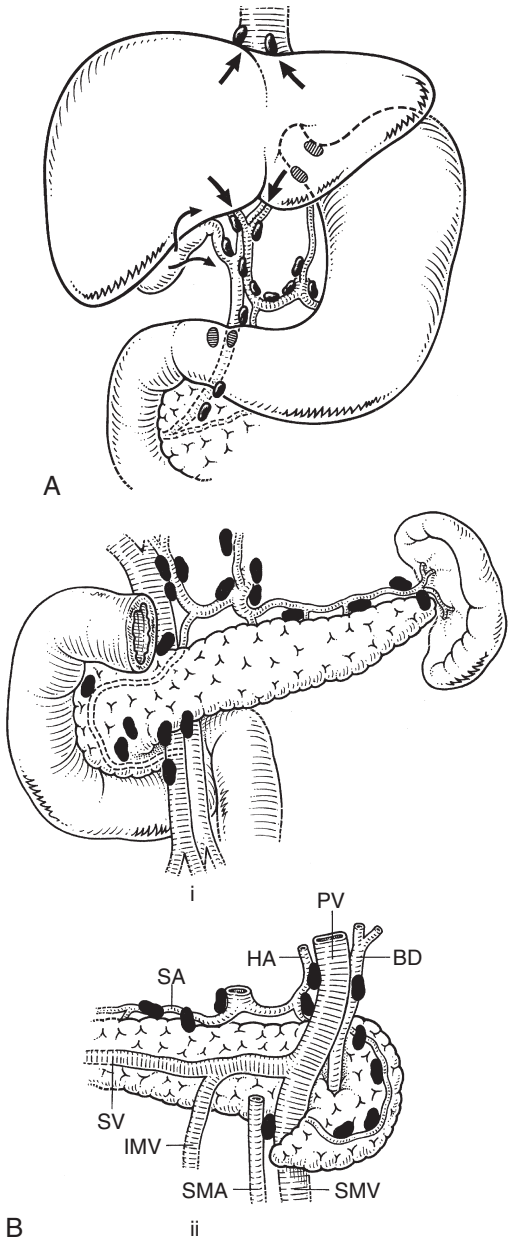


FIGURE 1B.49. A, The liver drains principally to hepatoduodenal nodes at the hilus and along the hepatic artery and portal vein. The gallbladder drains partly to the liver, but it also drains via the cystic node to nodes of the hepatoduodenal ligament and to suprapancreatic nodes. **B,** Numerous nodes (*i*) lie along the superior mesenteric vein along the borders of the pancreas, draining back into the splenic hilar nodes; along the superior border of the pancreas to the superior pancreatic nodes; and to the celiac trunk and nodes at the base of the common hepatic artery. A large node commonly lodges in intimate association with the surface of the superior border of the pancreas and the right side of the common hepatic artery. This node often needs to be dissected and elevated to gain access to the anterior surface of the portal vein. Removal of this node often improves access, as does division of the gastroduodenal artery. Posterior pancreaticoduodenal nodes (*ii*) lie along the posterior pancreatic duodenal arterial arcade. *BD,* bile duct; *HA,* hepatic artery; *IMV,* interior mesenteric vein; *PV,* portal vein; *SA,* splenic artery; *SMA,* superior mesenteric artery; *SMV,* superior mesenteric vein; *SV,* splenic vein.

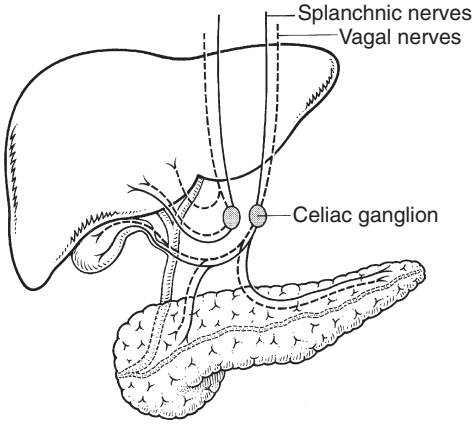


FIGURE 1B.50. Note the distribution of sympathetic and parasympathetic nerves to the liver and pancreas from the celiac ganglion, mainly in association with major arteries.

LYMPHATIC DRAINAGE

Liver and Pancreas

The lymphatic drainage of the liver and gallbladder is mainly to nodes in the hepatoduodenal ligament and along the hepatic artery; this is shown in Fig. 1B.49A. The lymphatic drainage of the pancreas is predominantly to the nodes that lie in juxtaposition to the arteries and veins (see Fig. 1B.50B).

Lymph Node Metastasis and Carcinoma of the Head of the Pancreas

Most patients who have carcinoma of the head of the pancreas have nodal positivity in the infrapyloric and common hepatic nodes, in the nodes along the splenic artery, or in those in the hepatoduodenal ligament. The most common are posterior pancreaticoduodenal lymph nodes, constituting 50% to 60% of all lymph nodes positive for carcinoma of the head of the pancreas. Other common sites are along the SMA and the paraaortic and anterior pancreaticoduodenal areas. In order of frequency, the anterior and posterior duodenal lymph nodes are most commonly involved.

In carcinoma of the distal bile duct or of the ampulla of Vater, the two most common sites for nodal involvement are the suprapyloric and posterior pancreatic lymph nodes. It is important to maximize staging so that at the time of resection, an adequate dissection of the lymph nodes is performed posterior to the pancreas. This is best done by dissection that begins on the anterior surface of the right renal veins and elevates the tissue in front of the vena cava and the left renal vein across to the aorta. The delivery of this soft tissue is not difficult, and it maximizes the likelihood of identifying nodes that can be expected to be positive.

NERVE SUPPLY TO THE LIVER AND PANCREAS

The nerve supply to the liver and pancreas (Fig. 1B.50) is from branches of the celiac ganglion. It is composed of sympathetic and parasympathetic elements.

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CHAPTER 8B

Molecular pathogenesis of biliary tract cancer

George Miller

CHOLANGIOCARCINOMA

Cholangiocarcinoma, or biliary tract adenocarcinoma, was first described by Durand-Fardel in 1840 (Olnes & Erlich, 2004). This malignancy arises from the ductal epithelium of the biliary tree, either within the liver (intrahepatic cholangiocarcinoma) or from the extrahepatic bile ducts (extrahepatic biliary adenocarcinoma) or gallbladder. It is a rare disease, and because of its infrequent occurrence, relatively little is known about the underlying biology of these tumors. In addition, this disease is fatal in most cases because of its late clinical presentation and the lack of effective nonsurgical therapeutic modalities (see Chapters 49 and 50) (Ishak et al, 1994). However, in recent years, important work has been done toward understanding the natural history and biology of these tumors and establishing patterns upon which future treatment regimens can be based.

CLASSIFICATION

More than 90% of cholangiocarcinomas are adenocarcinomas (Nakeeb et al, 1996), and they most commonly arise at or near the hepatic duct confluence. These fall under the general category of *extrahepatic cholangiocarcinomas* (see Chapter 50B) but are further subclassified as *hilar cholangiocarcinoma,* or *Klatskin tumors,* after the Yale University pathologist who was one of the first to report a series of patients with this condition (Nakeeb et al, 1996). Bismuth further subclassified hilar cholangiocarcinomas by precise location with reference to the biliary bifurcation and the lobar hepatic ducts (Bismuth et al, 1992). This classification may be useful for descriptive purposes and for operative planning. The remaining extrahepatic cholangiocarcinomas occur in the lower bile duct (periampullary) and are further subclassified as *distal cholangiocarcinomas.* These account for a relatively small fraction of all bile duct tumors. Mid–bile duct tumors are exceedingly rare but do occur in very small numbers, and even less common is disease that diffusely involves the biliary tree.

Cholangiocarcinoma may also arise from the intrahepatic ducts peripherally in the liver, giving rise to the subgroup known as *intrahepatic* or *peripheral cholangiocarcinoma* (see Chapter 50A) (Liver Cancer Study Group of Japan, 2000). Intrahepatic cholangiocarcinomas were poorly understood until recently. These are usually grouped by International Classification of Disease (ICD) codes with hepatocellular carcinoma as primary liver tumors (Khan et al 2002a, 2002b). Furthermore, many cases previously referred to as *liver adenocarcinoma of unknown primary* were likely unrecognized intrahepatic cholangiocarcinomas. Worldwide, intrahepatic cholangiocarcinoma is increasing in incidence and mortality. Intrahepatic tumors have been subcategorized by their growth characteristics into *mass-forming, periductal-infiltrating,* or *intraductal-growing* types (Liver Cancer Study Group of Japan, 2000).

EPIDEMIOLOGY

Although rare, cholangiocarcinoma has a distinctly higher incidence in certain demographic groups and geographic areas. The peak age for cholangiocarcinoma is the seventh decade, with a slightly higher male preponderance (Olmes & Erlich, 2004). The reported incidence in the United States is 1 to 2 cases per 100,000 (3500 new cases per year) with no clear racial predisposition. Cholangiocarcinoma incidence rates vary markedly worldwide, presumably reflecting differences in either local environmental risk factors or genetics. The highest disease incidence rates are in northeast Thailand (96 per 100,000 men), where it occurs approximately 100 times more often than in the West.

Epidemiologic studies have shown that, globally, the mortality and incidence of intrahepatic biliary tract neoplasms are rising, but those of extrahepatic tumors are static or falling. World Health Organization (WHO) mortality data were examined for the United States, United Kingdom, France, Italy, Japan, and Australia from 1979 to 1998 (Ishak et al, 1994). Mortality rates for intrahepatic cholangiocarcinoma were increased in both sexes in all countries except among Japanese women.

A U.S. study examined trends in intrahepatic cholangiocarcinoma incidence using data from the Surveillance, Epidemiology, and End Results (SEER) program, which represents over 10% of the total U.S. population. Data from 1976 to 2000 were analyzed by age, gender, and ethnicity. The incidence of intrahepatic cholangiocarcinoma increased by 165%, from 0.32 per 100,000 from 1975 through 1979 to 0.85 per 100,000 from 1995 through 1999. This increase was reflected in all groups but was highest in black men (139%), followed by white men (124%) and white women (111%). The increased incidence may be attributable in part to increased detection (Olnes & Erlich, 2004). However, increased detection of a tumor is usually associated with an increase in the proportion of patients with early-stage disease or smaller lesions. The rise in intrahepatic cancer was not associated with a significant change in the proportion of early stage cancers, histologically confirmed tumors, or smaller lesions (Broome et al, 1996). Furthermore, the incidence does not seem to be plateauing, as would be expected if the increase were due to an improvement in diagnostic modalities, such as magnetic resonance imaging (MRI) and computed tomography (CT), which have become

established practice in the past several years (Khan et al, 2002a; Shaib & El-Serag, 2004; Taylor-Robinson et al, 2001). Conversely, the incidence of extrahepatic cholangiocarcinoma has shown no such change and may be declining (Tullo et al, 2000). According to the SEER data, U.S. age-standardized mortality rates for extrahepatic tumors fell from 0.6 per 100,000 in 1979 to 0.3 per 100,000 in 1998; and age-standardized incidence rates decreased from 1.08 per 100,000 to 0.82 per 100,000 in the same period.

Most patients have unresectable disease when they are first seen and typically die within 12 months of diagnosis. Sepsis from cholangitis, frequently related to interventions performed for biliary obstruction and progressive liver failure, contribute to the high mortality (Shaib & El-Serag, 2004). Survival is poor, even in resected patients, with less than 5% of patients diagnosed with cholangiocarcinoma surviving to 5 years, a rate which has not changed significantly over the past 30 years. Although cholangiocarcinoma is a relatively rare tumor with an overall dismal prognosis, interest in the biology of this disease has grown in recent years (Khan et al, 2002a; Patel, 2001, 2002; Taylor-Robinson et al, 2001).

CLINICAL RISK FACTORS FOR CHOLANGIOCARCINOMA

Most cases of cholangiocarcinoma, regardless of location, occur without obvious predisposing risk factors. However, there are well-accepted clinical risk factors associated with a minority of cases, and most of these are related to chronic inflammation of the biliary epithelium.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC; see Chapter 41) is the most common condition predisposing to cancer of the biliary tree. Cholangiocarcinoma rates of 8% to 40% have been reported in patients with primary sclerosing cholangitis in follow-up studies and explant specimens (Khan et al, 2002a). Cholangiocarcinoma in such patients tends to present earlier in life, most commonly in the 30- to 50-year age groups, than in sporadic cases (Pitt et al, 1995; Bergquist et al, 1998). Approximately one third of patients with primary sclerosing cholangitis who develop cholangiocarcinoma do so within 2 years of diagnosis, and the risk of carcinogenesis appears to be unrelated to the duration of the inflammatory disease (Pitt et al, 1995; Watanapa & Watanapa, 2002). Two thirds of patients with primary sclerosing cholangitis have associated inflammatory bowel disease, usually ulcerative colitis (Pitt et al, 1995; Watanapa & Watanapa, 2002); however, no association has been found between the risk of cholangiocarcinoma and the severity of inflammatory bowel disease in this cohort of patients (Pitt et al, 1995; Watanapa & Watanapa, 2002).

To date, no reliable factors have been described that reliably stratify cholangiocarcinoma risk in PSC patients, and the clinical diagnosis of cholangiocarcinoma in this setting is difficult. Therefore, molecular markers of cholangiocarcinogenesis, such as *KRAS* or other mutations, may improve the early diagnosis. In a study by Kubicka and colleagues (2001), *KRAS* mutations were analyzed by enriched polymerase chain reaction/restriction fragment length polymorphism in the bile fluid of 56 PSC patients and 20 patients with other cholestatic diseases. To assess the value of *KRAS* mutations as a risk factor for cholangiocarcinogenesis, patients were prospectively investigated over a mean period of 31.5 months. Seventeen patients (30%) with PSC harbored *KRAS* mutations in bile fluid. In contrast to the group of PSC patients with wild-type *KRAS*, four cholangiocarcinomas and two cases of bile duct dysplasia were diagnosed in the group of patients with the mutation during the follow-up investigation. Their results indicate that *KRAS* mutations in bile fluid of PSC patients may represent an early event in cholangiocarcinogenesis; however, most of the PSC patients with *KRAS* mutations remained tumor free after a long follow-up investigation, consistent with the notion that these mutations are not specific for malignancy but may also occur in normal bile duct mucosa or in dysplasias. Therefore, analysis of *KRAS* mutations in bile specimens is not useful to make a definitive diagnosis of cholangiocarcinoma in PSC patients, but it is considered a marker of increased risk.

Parasitic Infection

A large body of experimental and epidemiologic data suggest a pathogenic association between cholangiocarcinoma and liver fluke infestation, especially *Opisthorcis viverrini* and less definitively *Clonorchis sinensis* (see Chapter 45) (Watanapa, 1996). Most epidemiologic data are from Thailand, which has the highest incidence of cholangiocarcinoma worldwide—87 per 100 000 population—and where an estimated 7 million people are infected with opisthorchiasis (Parkin et al, 1991). Human beings become infected by eating undercooked fish, whereupon adult worms inhabit and lay eggs in the biliary system. In addition to a strongly positive correlation between liver flukes and cholangiocarcinoma in case-control studies (Thamavit et al, 1978), malignant change in the biliary epithelium of Syrian hamsters has been shown after infection with *Opisthorcis viverrini*, especially when fed nitrosamines (Thamavit, 1988), which are produced by bacteria in fish and other foods and are thought to act as cofactors in carcinogenesis.

Fibrotic and Cystic Liver Hepatobiliary Diseases

Congenital abnormalities of the biliary tree associated with Caroli syndrome, congenital hepatic fibrosis, and choledochal cysts (cystic dilatations of the bile ducts) carry a 15% risk of malignant change after the second decade, at an average age of 34 years (see Chapter 46) (Scott et al, 1980). The overall incidence of cholangiocarcinoma in patients with untreated cysts is up to 28% (Lipsett et al, 1994; Obtsuka et al, 2001). The mechanism of carcinogenesis is unclear but appears to be related to biliary stasis; reflux of pancreatic juice, causing chronic inflammation; activation of bile acids (van Mil et al, 2001); and deconjugation of carcinogens. Bile duct adenomas and biliary papillomatosis are also associated with the development of cholangiocarcinoma.

Bile Salt Transporter Protein Polymorphisms

Bile salt transporter protein polymorphisms in *BSEP, ATP8B1,* and *ABCB4* genes can lead to unstable bile content and deconjugation of xenobiotics previously conjugated in the liver (Jacquemin, 2001; Thompson & Strautnieks, 2001; Meier et al, 2004). In the background of congenital bile duct abnormalities, this process can lead to the development of cholangiocarcinoma at an early stage in life (Kubo et al, 1995). Individuals who

are heterozygous for bile salt transporter polymorphisms are thought to have an increased predisposition to cholangiocarcinoma as adults after exposure to cofactors that result in chronic inflammation in the biliary tree (Kubo et al, 1995).

Intrahepatic Biliary Stones

Hepatolithiasis, the presence of interhepatic biliary stones (see Chapters 39 and 44), is rare in the West but relatively common in parts of Asia, and it is associated particularly with peripheral intrahepatic cholangiocarcinoma (Shaib & El-Serag, 2004). Up to 10% of patients with hepatolithiasis develop cholangiocarcinoma (Chen, 1999). In Taiwan, up to 70% of patients with cholangiocarcinoma undergoing resection reportedly have intrahepatic biliary stones; in Japan this figure is 6% to 18% (Okuda et al, 2002; Khan et al, 2003). Biliary stones are thought to cause bile stasis, predisposing to recurrent bacterial infections and subsequent inflammation, a potential cofactor for carcinogenesis (Khan et al, 2003).

Chemical Carcinogen Exposure

Several chemical toxins have been associated with cholangiocarcinoma. Promutagenic DNA adducts have been identified in cholangiocarcinoma tissue, indicating exposure to DNA-damaging agents (Sahani, 2003). Thorotrast, a radiologic contrast agent banned in the 1960s for its carcinogenic properties, has been strongly associated with the development of cholangiocarcinoma many years after exposure and has been reported to increase the risk of cholangiocarcinogenesis to 300 times that of the general population (Shaib & El-Serag, 2004; Hardell et al, 1984). Associations have also been made with exposure to byproducts from the rubber and chemical industries, including dioxins and nitrosamines (Sorensen et al, 1998), and with alcohol and smoking (Chalasani et al, 2000), but results have been conflicting, and no firm conclusions can as yet be drawn.

Viral Hepatitis

Chronic liver disease from any cause has also been associated with cholangiocarcinoma (Shin et al, 1996). A cohort study of over 11,000 patients with cirrhosis, followed up over 6 years, showed a tenfold risk compared with the general population (Shin et al, 1996). More specifically, an association has been shown with chronic hepatitis B and C virus infection. A case-control study from Korea reported that 12.5% of patients with cholangiocarcinoma tested positive for hepatitis C virus (HCV) and 13.8% for hepatitis B virus surface antigen (HBsAg) compared with 3.5% and 2.3% of controls, respectively (Donato et al, 2001). In a second case-control study from Italy, 23% of patients with cholangiocarcinoma were positive for anti-HCV, and 11.5% were HBsAg positive compared with 6% and 5.5% of controls, respectively (Kobayashi et al, 2000). A prospective, controlled study from Japan reported the risk of developing cholangiocarcinoma in patients with cirrhosis related to HCV as 3.5% at 10 years—1000 times greater than the risk in the general population (Yin & Chen, 1998). HCV is an established risk factor for hepatocellular carcinoma, and both hepatocytes and cholangiocytes have the same progenitor cell, supporting a role for the virus in cholangiocarcinogenesis. Furthermore, RNA from HCV has been identified in cholangiocarcinoma tissue (Berthiaume & Wands, 2004). A U.S. case-controlled study of risk factors for intrahepatic cholangiocarcinoma showed adjusted odds ratios (ORs) of 6.1 for HCV carriers and 5.9 for HIV-infected individuals. Diabetes was also prevalent in patients with intrahepatic tumors, with an adjusted OR of 2.0; the pathogenic mechanisms are unclear in diabetics but may be related to an associated increased risk of steatohepatitis (Tulio et al, 2000).

MOLECULAR PATHOGENESIS

Genome-wide Analysis

Investigation into the molecular pathogenesis of biliary tract tumors has not been an area of vigorous investigation, but slow progress is being made in the understanding of the genetic basis of this disease. A recent study investigated genome-wide mutations in carcinomas of the biliary tree, including intrahepatic and extrahepatic cholangiocarcinoma and gallbladder cancer, using frozen specimens from patients who underwent surgical resection (Miller et al, 2009). Unsupervised hierarchical clustering analysis revealed that cancers from these different sites did not cluster separately, implying that there was no difference in the global gene expression patterns between the biliary cancer subgroups. Figure 8B.1 depicts the top 40 upregulated and downregulated genes for all cancers combined versus normal biliary epithelia control specimens. Although the individual cancer subtypes did not cluster separately, unique differential expression of many genes was seen, compared with normal biliary epithelium in each of the tumor types.

The relationship of gene transcriptional changes among the three biliary cancer subtypes is depicted in a Venn diagram (Fig. 8B.2). Overall, 165 probe sets were commonly differentially expressed in all three cancer types. Selected commonly differentially expressed genes are listed in Table 8B.1. This study also investigated alterations in gene copy number in biliary tract cancers using array-based comparative genome hybridization (CGH) analysis. Considerable heterogeneity in the extent of chromosomal instability between patients was found, even within the same subtype. For example, some patients had mutations in nearly every chromosomal arm, and other patients with the same diagnosis had structural genomic changes (Fig. 8B.3A). But despite the heterogeneity, segments of chromosomes 3p, 6q, 8p, 9p, and 14q were commonly deleted across subtypes of biliary cancers. Commonly amplified regions across cancer types include segments of 1q, 3q, 5p, 7p, 7q, 8q, and 20q (Fig. 8B.3B).

Oncogenes and Tumor Suppressor Genes

Several studies have shown abnormal expression of the *KRAS* oncogene in 21% to 100% of cases of cholangiocarcinoma and of the *TP53* tumor suppressor gene in up to 37% of archival specimens (Isa et al, 2002). These genetic alterations are associated with a more aggressive phenotype in biliary tract tumors (Isa et al, 2002). *KRAS* and *TP53* mutations have also been identified in bile and pancreatic juice of affected patients (Isa et al, 2002; Itoi et al, 1999), but neither *KRAS* nor *TP53* mutational analysis have been shown to be superior to conventional cytopathology in the diagnosis of pancreaticobiliary tumors, but combined analysis of both can increase sensitivity in tissue biopsy and bile specimens (Isa et al, 2002; Itoi et al, 1999; Aishima et al, 2002). Increased expression of c-*MET* and

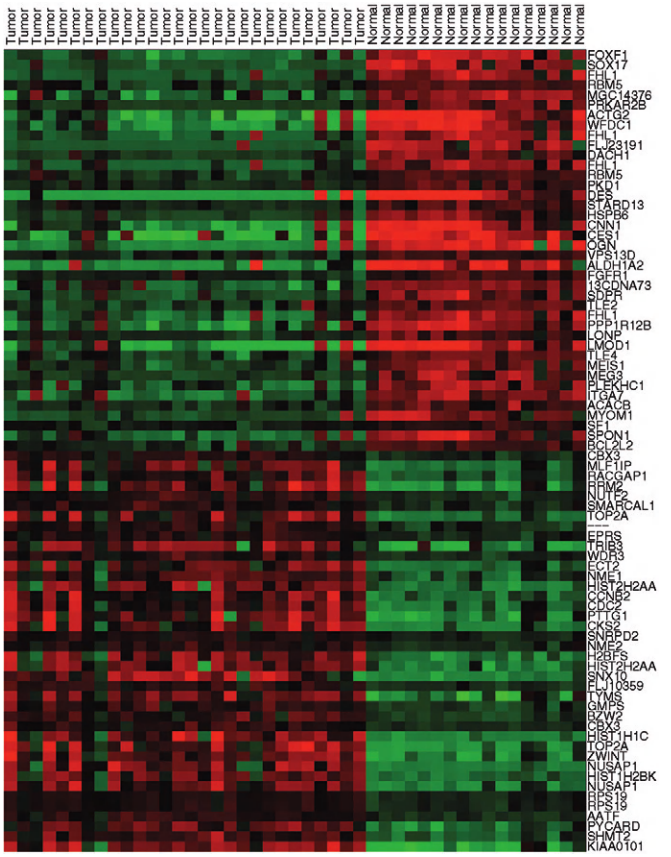


FIGURE 8B.1. Gene expression alterations in biliary tract cancers. The transcript products of more than 22,000 genes were investigated in biliary cancer specimens and compared with control tissue from normal biliary epithelium. Heat maps showing the top 40 overexpressed and underexpressed genes for extrahepatic cholangiocarcinoma, intrahepatic cholangiocarcinoma, and gallbladder cancers combined are compared with benign bile duct and gallbladder controls.

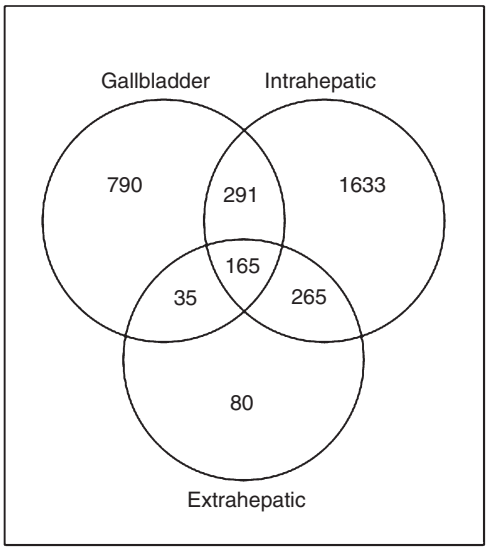


FIGURE 8B.2. Common alterations in gene expression in biliary cancer subtypes. A Venn diagram is used to depict the relationship of transcriptional changes among biliary cancer subtypes. There were 165 common genes with significantly altered expression in intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer.

c-*ERBB2* protooncogenes have been shown in cholangiocarcinoma specimens, and it has been suggested that they participate in the metastatic transformation of intrahepatic tumors (Aishima et al, 2002). Point mutations leading to promoter methylation of cell-cycle regulators $p16^{INK4a}$ and $p14^{ARF}$ have also been identified in cholangiocarcinoma related to PSC. Overexpression of the protooncogene *BCL2* has been reported to reduce apoptosis in cholangiocarcinoma cell lines (Okaro et al, 2001), and although human cholangiocarcinoma does not express Bcl-2, other antiapoptotic proteins, Mcl-1 and Bcl-xl, are expressed (Taniai et al, 2002).

Genetic Polymorphism at P450

Similar to the development of other tumors, cholangiocarcinogenesis is thought to be a multistep process dependent on the interaction between environmental factors and host genetic factors. Most of the putative environmental risk factors for cholangiocarcinoma cause chronic biliary irritation and can contribute to a promotional stage of carcinogenesis. Genetic polymorphisms in the cytochrome P450 enzymes or in the bile salt transporter proteins are thought to lead to alterations in the efficiency with which environmental toxins (xenobiotics) are handled by the liver. The development of cholangiocarcinoma probably needs a "second hit" to deconjugate such xenobiotics and to expose the bile duct epithelium to damage. Putative secondary hits include chronic inflammation, viral hepatitis, parasitic infestation, and recurrent cholangitis (Khan et al, 2005).

MRP2/ABCC2, MUTYH, NEIL1, *and AID*

Hoblinger and colleagues (2009) reported that multidrug resistance–associated protein 2 (MRP2/ABCC2) is one of the ATP-binding cassette (ABC) transporters expressed on the apical membrane of hepatocytes and cholangiocytes. ABCC2 plays an important role in the biliary clearance of endogenous and exogenous toxic compounds. The ABCC2 variant c.3972C>T in exon 28 has been shown to be associated with the risk of carcinogenesis. Forsbring and colleagues (2009) recently found that the human h-*MUTYH* and *NEIL1* genes encode DNA glycosylases involved in repair of oxidative base damage, and mutations in these genes are associated with cholangiocarcinoma.

Other work has also suggested that chronic inflammation can play a critical role leading up to cholangiocarcinogenesis. Komori and colleagues (2008) from Japan found that the proinflammatory cytokine–induced aberrant production of activation-induced cytidine deaminase (AID), a member of the DNA/RNA-editing enzyme family, might link bile duct inflammation to an enhanced genetic susceptibility to mutagenesis, leading to cholangiocarcinoma. Ectopic AID production is induced in response to TNF-α stimulation via an NF-κB–dependent pathway. Aberrant expression of AID in biliary cells results in the generation of somatic mutations in tumor-related genes, including *TP53,* c-*MYC,* and the promoter region of the *CDK2NA* sequences. In human tissue specimens, reverse transcription polymerase chain reaction (RT-PCR) analyses revealed that AID was increased significantly in 28 of 30

Table 8B.1

Selected Genes with Significantly Altered Expression in Gallbladder Cancer (GB), Intrahepatic Cholangiocarcinoma (Intra), and Extrahepatic Cholangiocarcinoma (Extra) Along with the Fold Change (Δ) in Expression in Each Cancer Subtype

Δ GB	Δ Intra	Δ Extra	Gene	Gene Title	Chromosomal Location	Functional Pathway
58	11	11	*RRM2*	Ribonucleotide reductase M2	2p25-p24	Nucleotide metabolism
41	6	10	*PTTG1*	Pituitary tumor–transforming 1	5q35.1	Cell cycle
26	9	7	*TYMS*	Thymidylate synthetase	18p11.32	Nucleotide metabolism
19	4	5	*CDK1*	Cell division cycle 2, G_1 to S, and G_2 to M	10q21.1	Cell cycle
18	4	7	*CCNB2*	Cyclin B2	15q22.2	Cell cycle
12	3	4	*RACGAP1*	Rac GTPase activating protein 1	12q13.12	S1P signaling
6	5	4	*SHMT2*	Serine hydroxy-methyltransferase 2 (mitochondrial)	12q12-q14	Amino acid metabolism
3	3	3	*PPAT*	Phosphoribosyl pyrophosphate amidotransferase	4q12	Purine metabolism
3	3	5	*MCM6*	MCM6 minichro-mosome maintenance component 6	2q21	Cell cycle
3	3	3	*GMPS*	Guanine monphosphate synthetase	3q24	Nucleotide metabolism
2	2	2	*RPS19*	Ribosomal protein S19	19q13.2	Ribosomal protein
2	3	2	*CBX3*	Chromobox homolog 3	7p15.2	Circadian exercise
2	3	2	*EIF2AK1*	Eukaryotic translation initiation factor 2-α kinase 1	7p22	Translation factor
2	2	2	*EPRS*	Glutamyl-prolyl-tRNA synthetase	1q41-q42	Glutamate metabolism
2	2	2	*PARP1*	Poly (ADP-ribose) polymerase 1	1q41-q42	Apoptosis
2	2	2	*SNRPD2*	Small nuclear ribonucleoprotein D2 polypeptide 16.5 kD	19q13.2	mRNA processing
−2	−2	−2	*UBE2G2*	Ubiquitin-conjugating enzyme E2G 2 (UBC7 homolog, yeast)	21q22.3	Proteolysis
−2	−2	−2	*HNRNPH1*	Heterogeneous nuclear ribonucleoprotein H1 (H)	5q35.3	mRNA processing
−2	−3	−3	*EIF1*	Eukaryotic translation initiation factor 1	17q21.2	Translation factor
−3	−4	−3	*RBM5*	RNA binding motif protein 5	3p21.3	mRNA processing
−3	−2	−2	*SFRS5*	Serine/arginine-rich splicing factor 5	14q24	mRNA processing

Continued

Table 8B.1

Selected Genes with Significantly Altered Expression in Gallbladder Cancer (GB), Intrahepatic Cholangiocarcinoma (Intra), and Extrahepatic Cholangiocarcinoma (Extra) Along with the Fold Change (Δ) in Expression in Each Cancer Subtype—cont'd

Δ GB	Δ Intra	Δ Extra	Gene	Gene Title	Chromosomal Location	Functional Pathway
−3	−3	−3	*BCL2L2*	BCL2-like 2	14q11.2-q12	Apoptosis
−4	−10	−7	*CDKN1C*	Cyclin-dependent kinase inhibitor 1C (p57, Kip2)	11p15.5	G_1 to S cell cycle
−4	−8	−5	*ZNF423*	Zinc finger protein 423	16q12	TGF-β signaling
−4	−3	−3	*ACACB*	Acetyl-coenzyme A carboxylase β	12q24.1	Fatty acid synthesis
−5	−7	−5	*PRKAR2B*	Protein kinase, cAMP-dependent, regulatory, type II β	7q22	G protein signaling
−5	−4	−4	*ACACB*	Acetyl-coenzyme A carboxylase β	12q24.1	Fatty acid synthesis
−6	−4	−4	*ITGA7*	Integrin α 7	12q13	Cellular adhesion
−6	−7	−5	*RGS2*	Regulator of G-protein signaling 2, 24 kD	1q31	Calcium regulation
−6	−9	−5	*KLF9*	Kruppel-like factor 9	9q21.11	Circadian exercise
−7	−7	−7	*RPS6KA2*	Ribosomal protein S6 kinase, 90 kD, polypeptide 2	6q27	Ribosomal protein
−7	−15	−10	*ANK2*	Ankyrin 2, neuronal	4q25-q27	Ribosomal protein
−10	−4	−4	*MYOM1*	Myomesin 1 185 kD	18p11.31	Muscle contraction
−13	−27	−14	*CDKN1C*	Cyclin-dependent kinase inhibitor 1C (p57, Kip2)	11p15.5	G_1 to S cell cycle
−61	−27	−26	*ALDH1A2*	Aldehyde dehydrogenase 1 family, member A2	15q21.2	Metabolism/ biosynthesis
−67	−20	−7	*CNN1*	Calponin 1, basic, smooth muscle	19p13.2-p13.1	Muscle contraction
−85	−51	−18	*CES1*	Carboxylesterase 1	16q22.2	Irinotecan pathway
−102	−30	−24	*DES*	Desmin	2q35	Muscle contraction

cholangiocarcinoma tissues (93%), whereas only trace amounts of AID were detected in the normal liver. Immunohistochemistry showed that all of the cholangiocarcinoma tissue samples examined showed overproduction of endogenous AID protein in cancer cells. Moreover, immunostaining for AID was detectable in 16 of 20 bile epithelia in PSC.

Human CYP1A2 and Arylamine N*-Acteyltransferases (NAT1 and NAT2)*

The *CYP1A2, NAT1,* and *NAT2* genes have been shown to be potential modifiers of an individual's susceptibility to certain types of cancers. Prawan and colleagues (2005) evaluated the relationship between *CYP1A2, NAT1,* and *NAT2* polymorphisms and cholangiocarcinoma in Thailand. A total of 216 cholangiocarcinoma patients and 233 control subjects were genotyped using PCR. Two *CYP1A2* alleles (CYP1A2*1A wild type and *1F), six *NAT1* alleles (NAT1*4 wild type, *3, *10, *11, *14A, and *14B), and seven *NAT2* alleles (NAT2*4 wild type, *5, *6A, *6B, *7A, *7B, and *13), were analyzed. The CYP1A2*1A/*1A genotype conferred a decreased risk of the cancer (adjusted OR, 0.28; 95% confidence interval [CI], 0.08 to 0.94), compared with CYP1A2*1F/1*F. Frequency distributions of rapid NAT2*13 and two slow alleles, *6B and *7A, were associated with lower cholangiocarcinoma risk. This study suggested that the *NAT2* polymorphism may be a modifier of individual risk of cholangiocarcinoma.

Trefoil Factor Family (TFF1)

Trefoil factor family 1 (*TFF1*) is critical for mucosal protection and tumor suppression in the stomach. To examine its role

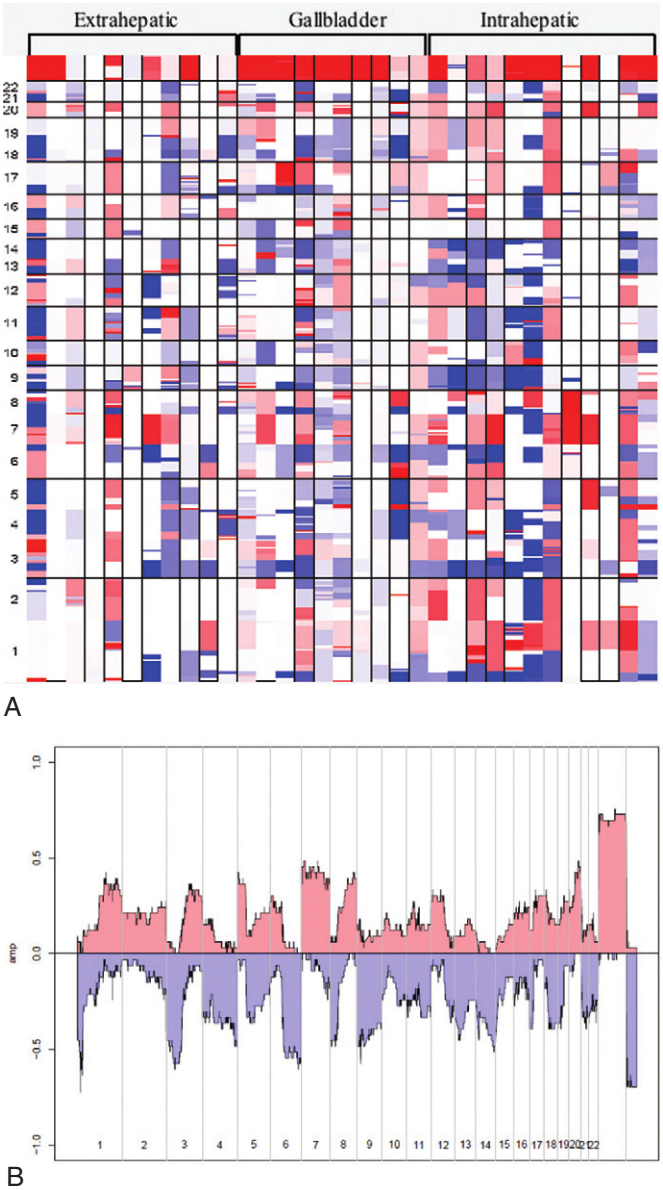


FIGURE 8B.3. Chromosomal structural mutations in biliary tract cancers. Genomic DNA was extracted from biliary tract cancer specimens and subjected to array-based CGH analysis to detect areas of DNA copy number gain or loss. **A,** A cumulative depiction of the copy-number changes across the genome for all biliary cancer specimens is shown. Chromosomal number is listed on the left. White is unchanged from genomic DNA controls. **B,** The percentage of patient specimens that have either amplifications or deletions at each chromosomal locus is shown for extrahepatic cholangiocarcinoma, intrahepatic cholangiocarcinoma, and gallbladder cancer specimens combined.

in cholangiocarcinogenesis, specimens with varying degrees of dysplasia were examined: intrahepatic cholangiocarcinoma (ICC) as a result of hepatolithiasis, biliary epithelial dysplasia with hepatolithiasis, hepatolithiasis without dysplasia or carcinoma, cholangiocarcinoma without hepatolithiasis, and control normal livers (Sasaki et al, 2003). *TFF1* expression in the biliary epithelium was increased in hepatolithiasis compared with control livers ($P < .01$). In biliary epithelial dysplasia and noninvasive intrahepatic cholangiocarcinoma with hepatolithiasis, *TFF1* was extensively expressed, and *MUC5AC* gastric mucin was usually colocalized with *TFF1*. However, *TFF1* expression was significantly decreased in invasive intrahepatic cholangiocarcinoma, despite preserved expression of *MUC5AC*. A total of four missense mutations were detected: three were found in two noninvasive intrahepatic cholangiocarcinomas with hepatolithiasis (29%) and one in invasive ICC (11%). Loss of heterozygosity of the *TFF1* gene was not detectable. The decreased expression of *TFF1* in invasive intrahepatic cholangiocarcinoma may be explained by the methylation of the *TFF1* promoter region. Upregulation of *TFF1* coupled with *MUC5AC* in biliary epithelium in hepatolithiasis, biliary epithelial dysplasia, and noninvasive intrahepatic cholangiocarcinoma may reflect gastric metaplasia and early neoplastic lesion. Under such conditions, decreased *TFF1* expression may lead to increased cell proliferation and then to the invasive character of intrahepatic cholangiocarcinoma.

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CHAPTER 8C

Molecular biology of liver carcinogenesis and hepatitis

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OVERVIEW OF MOLECULAR ETIOLOGY

Recent advances in molecular genetics have emphasized the multistep process of tumorigenesis. It is evident that cancer is a genetic disease involving aberrant chromosome rearrangements, genetic mutations, and epigenetic silencing of tumor suppressor genes (Farazi & DePinho, 2006). Independent of the etiology, hepatocellular carcinoma (HCC; see Chapter 80) generally develops where sustained hepatocyte turnover occurs in the setting of injury-inflammation-regeneration, which leads to the accumulation of chromosomal aberrations. In this context, monoclonal populations of hepatocytes become preneoplastic and, following additional genomic alterations, change into dysplastic cells and eventually HCC (Thorgeirsson & Grisham, 2002). Accumulated genetic alterations in preneoplastic lesions and HCC result in the activation, as well as inactivation, of many growth factor signal transduction pathways involved in hepatic transformation. It is believed that increased hepatocyte turnover associated with chronic liver injury may be a major feature of hepatic oncogenesis. However, another central question is whether hepatitis viruses, the leading cause of HCC worldwide, directly contribute to the development of this disease. Accumulating evidence suggests that chronic hepatitis B (HBV) and hepatitis C virus (HCV) infection play a direct role in the molecular pathogenesis of HCC through specific viral–cellular protein interactions (Branda & Wands, 2006; see Chapter 64).

EPIDEMIOLOGY

Hepatocellular carcinoma is the fifth most common cancer in men and the eighth most common in women worldwide. It is estimated that more than 700,000 new patients with HCC were diagnosed in 2007 (Garcia et al, 2007). The 5-year survival rate is less than 11% in developed countries, and the United States has a survival rate of only 8.9%, making HCC the second most fatal tumor after pancreatic cancer (Hertl & Cosimi, 2005; Garcia et al, 2007). Presumably because of its poor prognosis, HCC is the third leading cause of cancer death in men and the sixth among women in the world. It is estimated that about 680,000 individuals worldwide died from this disease in 2007 (Garcia et al, 2007).

Primary liver cancers consist of numbers of histologically distinct types of tumors that arise from hepatocytes, biliary epithelial cells, and fibroblasts. The most common is HCC, which accounts for 70% to 85% of all hepatic tumors (Perez et al, 2006). Approximately 80% of HCC worldwide is caused by chronic infection with HBV or HCV or both. The HCC burden is unevenly distributed worldwide; areas where tumors are most prevalent include West and Central Africa and East and Southeast Asia, with China alone accounting for more than 50% of the world cases (El-Serag & Rudolph, 2007). It is noteworthy that HBV is highly endemic in these areas, with the exception of Japan, where HCV is more prevalent. Oceania, North and South America, and Northern and Eastern Europe are low-rate areas. Trends in HCC incidence are likely to be different in regions of high and low persistence of HBV and HCV infection (El-Serag & Rudolph, 2007).

Comparative studies performed between 1977 and 1982 and between 1993 and 1997 show that the incidence of HCC in Hong Kong, Shanghai, Singapore, and Japan has begun to decrease (Parkin et al, 2002). The fall in incidence is apparently due to vaccination against HBV, which has been accomplished in over 80% of newborns (Chang et al, 2009), because chronic HBV infection in those countries is usually acquired through mother-to-newborn or sibling-to-sibling transmission at a young age. In contrast, the incidence of HCC has rapidly increased in some countries, such as Australia, the United States, and the United Kingdom, as a result of chronic HCV infection. For example, HCC is the fastest growing cause of cancer-related deaths in the United States, where the annual incidence increased from 1.3 per 100,000 for the years 1978 through 1980 to 3.3 per 100,000 for 1999 through 2001 (El-Serag et al, 2003). Reasons for this increased incidence are not entirely clear but may reflect a greater prevalence and role of persistent HCV infection (McGlynn et al, 2001).

Age-specific rates of HCC peak at 75 years and older in most regions of the world (El-Serag & Rudolph, 2007). With the exception of Africa, the peak incidence in women occurs 5 years later than that found in men. In the United States, recent trends have revealed a peak incidence shifting toward a relatively younger age group (El-Serag & Rudolph, 2007).

Significant gender and ethnic variation in incidence, as well as mortality from HCC, has also been found; male rates are more than double that of females (Perz et al, 2006). The most likely explanation for gender variation is that men have more risk factors, such as exposure to hepatitis virus infection, excessive alcohol intake, smoking, and increased iron stores in the liver (El-Serag & Rudolph, 2007). In addition, androgens may accelerate the progression of HCC (Ma et al, 2008). The incidence of HCC also varies with race and ethnicity in the same area. In the United States, the incidence and subsequent mortality rates from HCC are two times greater in Asians than African Americans, which are two times greater than those

Table 8C.1

Comparison of Epidemiologic Features Between HBV- and HCV-Induced HCC

	HBV	HCV
Virus carriers (% of global population)	350 million (6%)	170 million (3%)
Highly prevalent areas	Southeast Asia, China, sub-Saharan Africa, Alaska, Peru, northwest Brazil	East Asia, Southeast Asia, Africa, Bolivia, Brazil
Relative risk of HCC	5-fold to 15-fold	17-fold
5-Year cumulative incidence rates of HCC from cirrhosis	10% (Europe) 15% (Singapore and Taiwan)	17% (Europe and United States) 30% (Japan)

HBV, Hepatitis B virus; *HCV,* hepatitis C virus; *HCC,* hepatocellular carcinoma.

found in whites (El-Serag & Rudolph, 2007). These variations are explained in part by the accumulation of major risk factors in each ethnic group.

RISK FACTORS

Unlike most malignancies, HCC has well-established extrinsic risk factors that account for at least 80% of tumors, namely chronic infection with HBV or HBC. Key epidemiologic aspects of HBV- and HCV-induced HCC are summarized in Table 8C.1. Chronic HBV infection is the leading cause of HCC, and it has been estimated that there are 350 million HBV carriers, which account for 6% of the global population. About 59% of HCC patients in developing countries and 23% of HCC patients in developed countries are chronically infected with HBV (Garcia et al, 2007). Reported relative risks of HCC among HBV carriers range between 5-fold and 15-fold compared with the general uninfected population (El-Serag & Rudolph, 2007). The 5-year cumulative incidence rates of HCC from HBV-related cirrhosis are 15% in highly endemic areas and 10% in Europe (Fattovich et al, 2004). In addition, approximately 70% to 90% of HBV-related HCC develops in patients with cirrhosis.

Chronic HCV infection is the second leading cause of HCC. The estimated number of HCV carriers worldwide is 170 million, which accounts for 3% of the global population. Approximately 33% of HCC tumors in developing countries and 20% of HCC in developed countries are attributable to persistent HCV infection (Garcia et al, 2007). According to a meta-analysis of case-control studies, HCC risk was increased 17-fold in HCV-infected persons compared with the HCV-negative population (Donato et al, 2002). The 5-year cumulative incidence of HCC with HCV-related cirrhosis in developed countries is 17%, with an exception for Japan, where the 5-year cumulative incidence is 30% (Fattovich et al, 2004). The high incidence of HCV-related HCC in Japan may be due to the prevalence of HCV genotype 1b. Aflatoxin B1 (AFB1) is produced by *Aspergillus flavus* and related fungi that contaminate corn, rice, and peanuts in China and sub-Saharan Africa. High rates of dietary exposure to AFB1 increase the risk of HCC 4-fold. When people with chronic HBV infection are exposed to AFB1, the relative risk for HCC dramatically increases to about 60-fold (Kew, 2003). This synergistic effect between AFB1 exposure and chronic HBV infection is an important observation because in some regions of the world, AFB1 exposure and chronic HBV infection rates are high.

Excessive ethanol consumption (>50 to 70 g/day) is another well-defined risk factor for HCC. In the United States, ethanol-induced HCC accounted for more than 20% of HCC patients between 1996 and 1999 (Davila et al, 2004). The 5-year cumulative HCC incidence in alcoholic cirrhosis without HBV and HCV infection is 8% (Fattovich et al, 2004); however, it is unlikely that ethanol itself has a direct carcinogenic effect. Rather, excessive ethanol ingestion indirectly affects hepatocarcinogenesis through the promotion of cirrhosis. Indeed, more than 80% of HCC tumors found in alcoholics develop in the background of a cirrhotic liver. One case-control study observed a strong synergistic effect between heavy alcohol consumption and chronic HCV infection. The relative risk of HCC attributable to heavy alcohol consumption alone was only 2.4-fold, whereas in combination with chronic HCV infection, it increased to 50-fold (Hassan et al, 2002).

Growing evidence now suggests that metabolic dysfunction—including obesity, diabetes, and nonalcoholic fatty liver disease (NAFLD)—are important risk factors for HCC, especially in developed countries. Several large cohort studies reveal that obese men have 2-fold to 5-fold higher rates of HCC. The association of HCC with obesity in women is controversial. Other investigations suggest that diabetes is a moderately strong risk factor for HCC (El-Serag & Rudolph, 2007). Nonalcoholic steatohepatitis (NASH) is strongly associated with obesity and diabetes; therefore NASH may be a risk factor for HCC (see Chapter 65). Epidemiologic studies have searched for a direct correlation between NASH and HCC, but the results have not been sufficiently convincing to draw a firm conclusion.

Other risk factors for HCC include hemochromatosis and hepatic porphyria. It should be noted that daily coffee intake reduces the incidence of HCC between 25% and 75% in the general population in a dose-dependent manner (Inoue et al, 2005). This effect may be attributable to the inhibition of TGF-β signaling by methylxanthine caffeine, which reduces liver fibrosis (Gressner, 2009).

GENETIC AND EPIGENETIC ALTERATIONS

Chronic inflammation accompanied by sustained cycles of injury and regeneration of hepatocytes over 20 to 40 years promotes the development of liver fibrosis, cirrhosis, and eventually HCC (Fig. 8C.1A; see Chapter 6). Pathologically, HCC occurs early within cirrhotic nodules, which can form in areas of adenomatous hyperplasia or dysplasia. These cells eventually become more atypical, and the malignant transformation process becomes complete (Theise et al, 2002). Hepatocellular carcinoma is like other malignancies and represents a DNA disease with accumulation of many alterations in oncogenes and tumor suppressor genes. The accumulation of genetic aberrations that induces cellular transformation may take 20 to 40 years, suggesting that liver carcinogenesis involves a multistep process. Indeed, the number of genetic alterations in HCC correlates with the histologic differentiation of the tumors. For example, loss of heterozygosity (LOH) of chromosomes 16q, 17p, 13q, and *TP53* tumor suppressor genes was principally found in poorly differentiated HCC, which suggests these chromosomal alterations and mutations tend to occur at a late stage of tumor development (Laurent-Puig & Zucman-Rossi, 2006). In contrast, β-catenin mutations were associated with

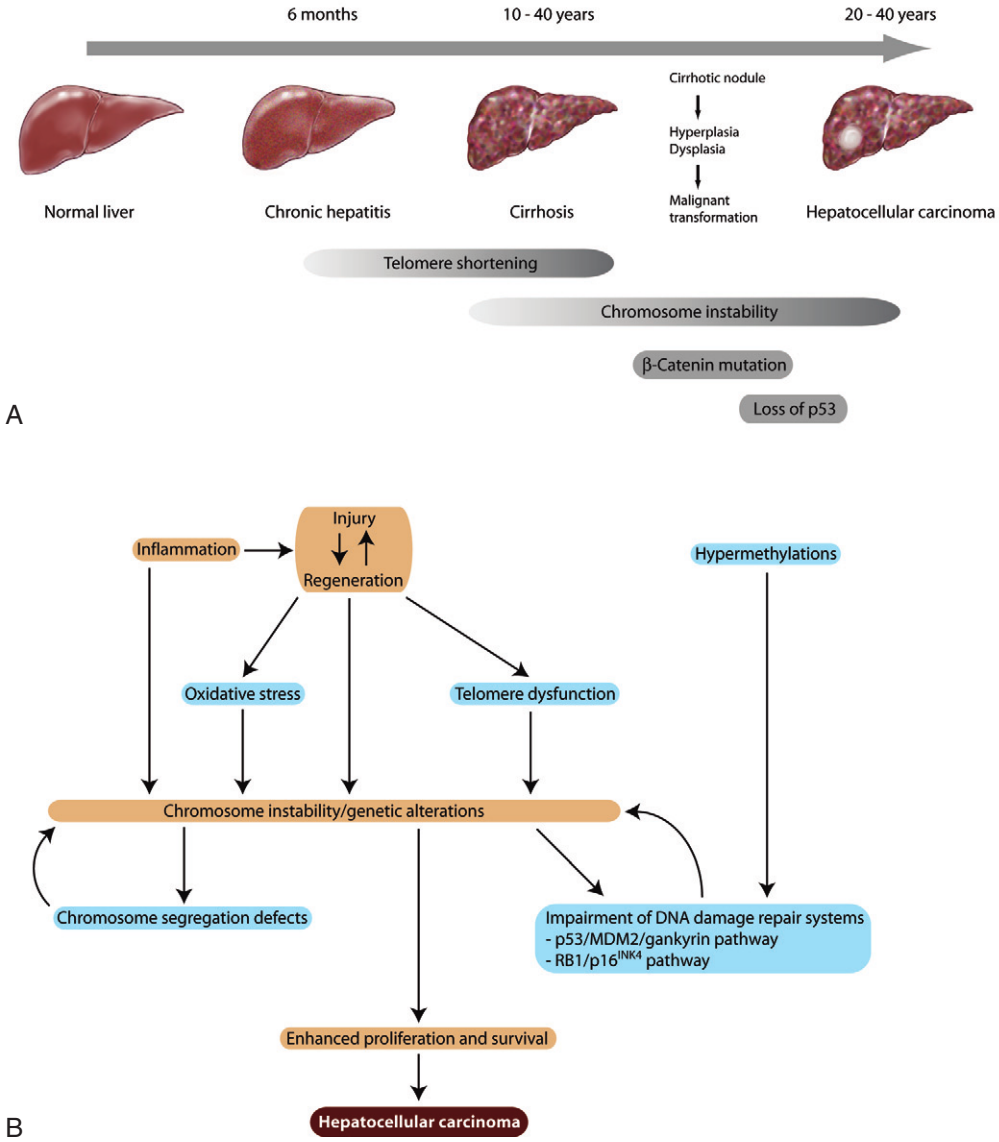


FIGURE 8C.1. A, Diagram showing progression of liver disease and genetic events accompanied by chronic inflammation. **B,** Common mechanisms underlying hepatocarcinogenesis. A number of factors contribute to chromosome instability and other genetic alterations, which lead to the formation of hepatocellular carcinoma.

well-differentiated HCC and a more favorable prognosis, indicating that these mutations may occur at an early developmental stage (Mao et al, 2001).

Cirrhosis may represent end-stage liver disease as a result of persistent HBV or HCV infection. Because 80% to 90% of HCC tumors originate from cirrhotic liver, it is evident that continuous rounds of cellular injury followed by regeneration in the milieu of chronic inflammation fundamentally contributes to the oncogenic processes. The sustained cycles of injury and repair increase the chance of genomic alteration. Furthermore, the host inflammatory response to viral infection, including activation of stellate cells, causes the release of proinflammatory cytokines, which accelerate hepatic carcinogenesis by augmenting oxidative stress and DNA damage (Bataller & Brenner, 2005; Giannelli et al, 2005; Ogata et al, 2006).

Continuous rounds of this process in the presence of inflammation not only increase the chance of genomic alterations but also produce chromosome instability. For example, hyperploidy has been observed in 43% of dysplastic peritumoral regions and in about 50% of HCC tumors (Laurent-Puig & Zucman-Rossi, 2006). Molecular mechanisms underlying such genomic instability include telomerase dysfunction, defective segregation of chromosomes, and an impaired DNA damage response (Fig. 8C.1B).

Telomere shortening is a key feature of chronic liver disease that allows sustained proliferation of hepatocytes (Urabe et al, 1996). In human HCC, telomere shortening has been shown to have a positive correlation with increased chromosome instability—chromosomal gains, losses, and translocations—by promoting chromosomal fusions (Plentz et al, 2004). A study of telomerase-deficient mice reveals that telomere dysfunction initiates tumor formation (Farazi et al, 2003). It is noteworthy that 90% of human HCC shows robust activation of telomerase (Lee et al, 2004; Nagao et al, 1999; Shimojima et al, 2004). In

some HBV-induced HCC tumors, the viral genome was found to be integrated into the *TERT* locus, which results in increased expression of telomerase (Ferber et al, 2003; Murakami et al, 2005). Other findings related to telomerase biology indicate amplification of telomerase RNA component gene (*TERC*) mRNA and allelic loss of chromosome 10p, where a putative telomerase inhibitor resides (Nishimoto et al, 2001; Takeo et al, 2001). Such telomerase reactivation and telomere shortening in HCC cells may be explained in part from investigations performed in *TERC*-knockout mice (Farazi et al, 2003). This study indicates that telomerase reactivation occurred and appeared to be necessary for late-stage tumor progression; thus, the reactivated telomerase enzyme maintains the shortened telomere length in these tumor cells and prevents them from undergoing apoptosis.

Dysregulation of genes involved in chromosome segregation results in altered copy numbers during cell division. Aneuploidy has been frequently found in HCC, suggesting dysfunction of the segregation machinery. Indeed, aurora kinase A, a protein required for proper chromosome segregation, was shown to be abnormal (Smith et al, 2003). Furthermore, the spindle-assembly checkpoint is defective in HCC cell lines (Saeki et al, 2002). These cytogenetic dysfunctions may lead to the aberrant segregation of chromosomes in human HCC.

DNA damage-response pathways are safeguards that regulate cell-cycle checkpoints and prevent DNA-damaged cells from further proliferation. Several studies report that the functions of key regulatory molecules, including p53, Mdm2, Rb1, p16INK4a, and gankyrin, were impaired in human HCC. The p53 protein, encoded by the *TP53* gene, is a master molecule that maintains genome integrity by inducing cell-cycle arrest followed by activation of DNA repair systems. When excessive DNA damage occurs, p53 initiates apoptosis. *TP53* missense mutations in codon 249 (R249S) was the main cause of AFB1-induced liver cancer (Bressac et al, 1991). This specific *TP53* mutation was found in more than 50% of AFB1-related HCC; other mutations of *TP53* are found in 20% to 40% of HCC without molecular evidence of AFB1 exposure (El-Serag & Rudolph, 2007).

The Rb1 pathway also regulates cell cycle checkpoints. The loss of an *RB1* locus, located on chromosome 13q14, has been frequently observed in human HCC; the second allele may then be inactivated by an epigenetic mechanism, such as hypermethylation of promoter sequences to promote cell proliferation (Zhang et al, 1994; Lin et al, 1996). Cellular levels of p53 and Rb1 proteins are low due to rapid degradation. In this regard, Mdm2 an E3 ubiquitin ligase, was shown to be a key regulator of ubiquitin-proteasome degradation of these tumor suppressor proteins. Strikingly, gankyrin, which promotes such protein degradation by Mdm2, was overexpressed in 100% (n = 34) of human HCC (Higashitsuji et al, 2000, 2005). The *CDKN2A* gene encodes for two splice variant products, including p16INK4a and p14ARF, which are components of the p53 and Rb1 signaling pathways. The expression of the *CDKN2A* gene was suppressed in 30% to 70% of human HCC as a result of methylation of the promoter region (Jin et al, 2000; Liew et al, 1999; Matsuda et al, 1999; Weihrauch et al, 2001). LOH of chromosome 9p where *CDKN2A* is located was found in 15% to 20% of tumors (Boige et al, 1997; Laurent-Puig et al, 2001; Nagai et al, 1997). Interestingly, *CDKN2A* deletion rarely occurs in HCC when *TP53* is also mutated (Tannapfel et al, 2001). Taken together, impairment of the p53 and Rb1 pathways is a common genetic feature of HCC. In addition, chromosome instability caused by telomere shortening, as well as defects in chromosomal segregation, contributes to the molecular abnormalities often observed in this disease.

As a result of chromosome instability and impaired DNA repair systems, chromosome gains and losses and gene mutations are frequently found in human tumors, as shown in Table 8C.2. Numerous genetic studies performed during

Table 8C.2

Chromosome Gains and Losses Frequently Found in HCC

		Dysplasia	Early-Stage HCC	Late-Stage HCC	HBV-HCC Without Cirrhosis
Gain	**Oncogene**				
1q	HDGF				
7q					
8q	MYC		✓	✓	✓
17q	ERBB2	✓			
20q				✓	✓
Loss	**Tumor Suppressor Gene**				
1p					
4q	*DRLM*	✓			✓
6q	*IGF2R*		✓		
8p	*LTPS*			✓	
9p	*INK4*				
13q	*RB1, BRCA2*			✓	
16p	*AXIN1*				
16q		✓		✓	
17p	*TP53*	✓		✓	

HBV, Hepatitis B virus; *HCC,* hepatocellular carcinoma.

Data from Laurent-Puig P, Zucman-Rossi J, 2006: Genetics of hepatocellular tumors. Oncogene 25:3778-3786; and Farazi PA, DePinho RA, 2006: Hepatocellular carcinoma pathogenesis: from genes to environment. Nat Rev Cancer 6:674-687.

hepatocarcinogenesis provide an overview of chromosomal aberrations by using karyotypic analysis, LOH mapping, and comparative genomic hybridization (CGH). To summarize, chromosome 17p (*TP53*), 8p (*PINX1*), 16p (*AXIN1*), 16q, 4q (*NAP1L5*), 9p (*CDKN2A*), 13q (*RB1, BRCA2*), 1p, and 6q (*IGF2R*) were often deleted. Chromosomes 1q (*HDGF*), 7q, 8q (*MYC*), and 17q (*ERBB2*) were the most frequent to shown gain of genetic material (Laurent-Puig & Zucman-Rossi, 2006). Some chromosome gains and losses have been reported to be specific to etiologic factors such as chronic HBV and HCV infection. Notably, gains of chromosome 8q and 20q and loss of chromosome 4q have been found in HBV-induced HCC without cirrhosis, indicating that these chromosomal aberrations may enhance hepatocyte transformation (Feitelson et al, 2002; Wong et al, 1999).

It is evident that the expression and function of oncogenes and tumor suppressor genes are affected by copy number because of chromosomal gains and losses and by point mutations in the genes. However, recent studies have revealed that epigenetic mechanisms—such as DNA methylation and short, noncoding RNA (21 to 23 nucleotides) species, or *micro RNA* (miRNA)—also contribute to aberrant expression of oncogenes and tumor suppressor genes. In human HCC, aberrant DNA methylation patterns have been detected (Kanai et al, 1999; Thorgeirsson & Grisham, 2002; Yu et al, 2003). More important, hypermethylation has been observed at the earliest stages of HCC development, and the extent of hypermethylation tends to increase with tumor progression (Lee et al, 2003). Specific gene targets for hypermethylation include *CDKN2A*, *PTGS2, CDH1*, *PYCARD,* and *DLC1*. Among these genetic elements, it has been shown that *CDKN2A* and *PTGS2* expression were directly affected by methylation using human HCC cell lines (Liew et al, 1999; Matsuda et al, 1999; Murata et al, 2004).

In addition, miRNA contributes to messenger (mRNA) instability by hybridizing with its complementary target sequence, followed by mRNA degradation, so that a protein cannot be generated. Several studies reveal aberrant expression of some miRNAs in human HCC compared with the adjacent, nontumorous counterpart. For example, miR-21 was expressed in human HCC; it targets the *PTEN* tumor suppressor gene (Meng et al, 2007). Another example was overexpression of miR-122, which targets the cyclin G_1 cell-cycle regulator (Gramantieri et al, 2007). More recently, evidence was presented that links aberrant expression of miRNA to the multistep process of hepatocarcinogenesis. The expression of miR-26a was diminished in murine and human tumors, resulting in enhanced activity of cyclin D2 and E2 to promote cell proliferation. Moreover, when exogenous miR-26a was overexpressed in mice prone to form multiple HCCs, substantial protection from disease progression was observed, indicating a possible therapeutic approach for this disease (Kota et al, 2009). These findings indicate that epigenetic and posttranscriptional regulation of gene expression plays an important role in hepatic oncogenesis.

SIGNAL TRANSDUCTION PATHWAYS

Genetic alterations of oncogenes and tumor suppressor genes impinge on a wide variety of signal transduction pathways involved in proliferation and tumor cell viability. Although the spectrum of affected signal transduction pathways in HCC cells is more heterogeneous compared with that of affected signals in other tumor types, key pathways are commonly dysregulated in human HCC, such as the Wnt/β-catenin, ErbB/ERK/PI3K, and IGF/IRS/ERK/PI3K cascades (Fig. 8C.2).

The Wnt/β-catenin pathway regulates cell proliferation, motility, and differentiation. Wnt proteins are ligands that bind to Frizzled cell-surface receptors to stabilize β-catenin in the cytoplasm, followed by translocation to the nucleus, where it upregulates Wnt-responsive genes (Thompson & Monga, 2007). In the absence of Wnt signaling, the amount of cytosolic β-catenin is low as a result of proteolytic degradation produced by the action of GSK-3β/APC/Axin kinase destruction complex. However, when Wnt ligands bind to the Frizzled/LRP-5/6/Dishevelled (Dvl) receptor complex, phosphorylation of β-catenin by GSK-3β is inhibited to allow its accumulation in the cytoplasm. The β-catenin molecules are then transported into the nucleus and bind to TCF/LEF transcription factors; this complex acts as transcriptional regulators. Finally, the TCF/LEF/β-catenin complex promotes activation of target genes—including *CCND1, MYC, PTGS2,* and c-*JUN*—which leads to proliferation of HCC cells.

Mutations of β-catenin are found in 13% to 43% of human HCC (Laurent-Puig & Zucman-Rossi, 2006). The frequency of β-catenin nuclear accumulation varies between 17% and 75% as determined by immunohistochemical staining (Fujito et al, 2004; Inagawa et al, 2002; Ishizaki et al, 2004; Mao et al, 2001; Wong et al, 2001). These findings suggest that nuclear accumulation of β-catenin is an excellent biomarker for activation of Wnt signaling in HCC. More important, β-catenin activation occurs at an earlier stage of the oncogenic process in dysplastic cells, suggesting that the Wnt/β-catenin cascade is directly involved in tumor formation (Calvisi et al, 2001, 2004; de la Coste et al, 1998; Merle et al, 2004; Thorgeirsson & Grisham, 2002).

The other cell-surface molecules that play a major role in the activation of Wnt/β-catenin signaling are called *Frizzled receptors.* Indeed, studies reveal that 90% of HBV-related HCC overexpresses the Frizzled-7 receptor. Overexpression of Frizzled-7 correlated with accumulation of wild-type β-catenin in the cytoplasm and nucleus of human tumors and HCC cell lines. The functional consequences of Frizzled-7 overexpression were enhanced cell motility and invasion. In murine HCC models, overexpression of Frizzled-7 occurred in dysplastic nodules and HCC tissue but not in normal liver (Merle et al, 2004, 2005). These findings illustrate that Frizzled-7 overexpression was a common event during hepatic oncogenesis and that it promotes tumor cell motility and invasion. Among other candidate genes involved in stabilization of β-catenin, the scaffold protein AXIN1 of the destruction complex was mutated in 5% to 8% of HCC (Laurent-Puig et al, 2001; Satoh et al, 2000), whereas *APC* mutations were exceptionally rare (Huang et al, 1999).

The ErbB family consists of four receptor tyrosine kinases, including ErbB1/EGFR/Her1, ErbB2/Her2/Neu, ErbB3/Her3, and ErbB4/Her4 (Yarden & Sliwkowski, 2001). When ligands bind to the ErbB1 receptor, autophosphorylation occurs that leads to an association with the Grb2 adaptor molecule and phosphatidyl inositol-3 kinase (PI3K). When phosphorylated ErbB1 binds to Grb2, the complex activates the Ras oncoprotein, resulting in enhancement of Raf serine/threonine kinase activity. Activated Raf kinase triggers MEK/ERK kinases, as well as ERK, which translocates to the nucleus and upregulates the transcription of oncogenes such as c-*FOS,* c-*JUN,* and c-*MYC*. When phosphorylated ErbB1 binds to PI3K, ErbB1 activates PI3K and the downstream Akt kinase. Akt phosphorylates a number of important molecules including mTOR,

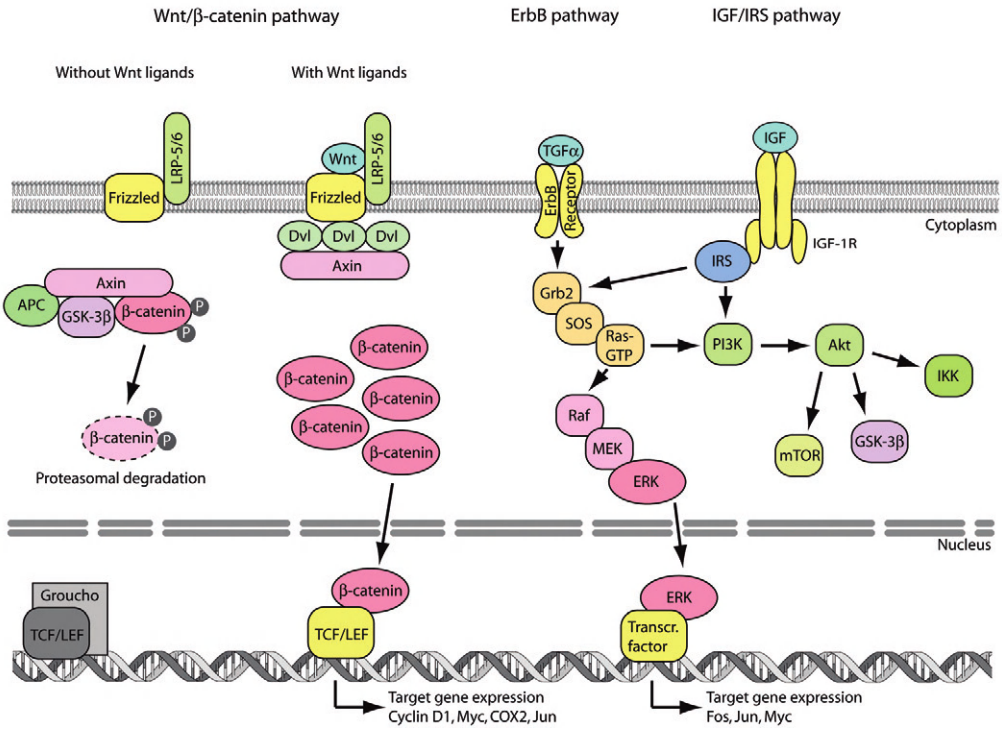


FIGURE 8C.2. Schematic diagram showing the major components of three signal-transduction pathways involved in hepatic oncogenesis. In the Wnt/β-catenin cascade, accumulation of β-catenin is regulated by Wnt ligands. The ErbB and IGF/IRS pathways both use downstream activation of several kinases, including the Ras/Raf/MEK/ERK and PI3K/Akt cascades. APC, antigen-presenting cell; ERK, extracellular signal-regulated protein kinase; GSK, glycogen synthetase kinase; IGF, insulin growth factor; IKK, inhibitor κB kinase; I/R, ischemia/reperfusion; IRS, insulin receptor substrate; LEF, leukocyte enhancer factor; MEK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; TCF, T-cell factor; TGF, transforming growth factor; transcr., transcription.

GSK-3β, and IKK to promote proliferation and viability of tumor cells.

It has been established that ErbB1 and ErbB3 were overexpressed in 68% and 84% of HCC, respectively, which correlated with a more clinically aggressive phenotype (Ito et al, 2001a). Ligands for ErbB include epidermal growth factor (EGF), transforming growth factor-α (TGF-α), heparin-binding EGF (HB-EGF), amphiregulin, β-cellurin, and epiregulin. In this regard, TGF-α and HB-EGF proteins may play a role in the pathogenesis of HCC. TGF-α was frequently upregulated at an earlier stage of tumor formation (Schaff et al, 1994; Yeh et al, 1987; Zhang et al, 2004). In murine models, HCC develops in TGF-α–overexpressing transgenic mice, whereas TGF-α–knockout mice were resistant to chemically induced hepatic neoplasms, indicating that TGF-α upregulation was closely linked to the oncogenic process (Jhappan et al, 1990; Russell et al, 1996). HB-EGF protein was a potent mitogen for hepatocytes, detected in 59% to 100% of HCC (Inui et al, 1994). Moreover, overexpression of HB-EGF was found at an earlier stage of HCC with moderately or well-differentiated features (Ito et al, 2001b), suggesting that HB-EGF is an important ligand in initiation of this disease.

The insulin-like growth factor (IGF)/insulin receptor substrate (IRS) signaling cascade is a well-defined pathway that regulates energy metabolism and cell growth. The IRS proteins are phosphorylated on tyrosine residues after stimulation of the insulin/IGF receptors by insulin, IGF-1, and IGF-2. The IRS-1 protein is the main intracellular substrate for receptor tyrosine kinase activity of the insulin/IGF-1 receptor, emitting downstream signals through interaction with SH2 domain-containing molecules that bind to specific motifs located in the C-terminal region. Such protein–protein interactions activate the Ras/Raf/MEK /ERK cascade involved in cell growth and survival. Phosphorylated IRS proteins also trigger the PI3K/Akt signaling pathway, which results in enhanced proliferation and survival of HCC cells. Thus, evidence has been accumulating to suggest that this pathway plays an important role in tumor development (Pollak, 2008).

In human HCC, the insulin/IGF/IRS pathway was dysregulated because of the overexpression of upstream components. The IGF-2 ligand was also overexpressed in 16% to 40% of tumors, as well as in dysplastic tissue, suggesting that IGF-2 may act by autocrine and/or paracrine mechanisms (Breuhahn et al, 2006). IRS-1 is overexpressed in 80% to 100% of human HCC (Cantarini et al, 2006; Nishiyama & Wands, 1992); overexpression was associated with increased tumor size and progression via activation of the MEK/ERK cascade, which promotes cell proliferation (Tanaka et al, 1997). Constitutive MEK/ERK pathway activation may also occur via downregulation of a Raf kinase inhibitor protein (RKIP); this event promotes HCC cell proliferation and migration (Lee et al, 2006). Indeed, downregulation of RKIP was found in 90% of human HCC and suggests that it plays a role as a tumor suppressor protein in this disease. IRS-2 has also been found to be overexpressed in the majority of human tumors and in HCC cell lines (Boissan et al, 2005).

The importance of the IGF/IRS and signal transduction cascades of ErbB is illustrated by the fact that many antitumor

drugs that target one of the components of these cascades have been or are under development. For example, a randomized, controlled trial revealed that sorafenib (Nexavar)—an inhibitor of Raf kinase and downstream MEK/ERK activity—modestly prolonged survival (3 months) in patients with HCC (Llovet et al, 2008). This is the initial report showing some effectiveness of a systemic treatment for HCC. Other potential anti-HCC drugs under development include inhibitors of ErbB1 tyrosine kinase, Ras farnesyl transferase, MEK, and mTOR.

The finding of insulin/IGF/IRS signaling in HCC have led to the development of several monoclonal antibodies that bind and neutralize the IGF-1 receptor as a potential therapeutic approach; such agents are undergoing preclinical and early-phase clinical trials for solid tumors and HCC (Pollak, 2008).

HEPATITIS B VIRUS

HBV is the prototype member of the *Hepadnaviridae* family. Viral members of this group also infect ducks, ground squirrels, and woodchucks. These small, partially double-stranded DNA viruses contain four overlapping open reading frames (ORFs) including preC/core, preS/S, P, and X, except for the duck, in which it is missing (Fig. 8C.3A and B). PreC/core ORF encodes for the precore protein, a precursor of HBeAg and core protein (HBcAg), a component of the nucleocapsid. PreS/S ORF encodes for three proteins, including large (L), middle (M), and small (S; HBsAg) proteins. The S accounts for approximately 90% of all protein produced from preS/S transcripts. The P gene encodes for a DNA-dependent DNA polymerase, which also has reverse transcriptase and RNase H activities. The partially double-stranded HBV genome (approximately 3.2 kb in length) exists within a nucleocapsid. The X region encodes for a multifunctional protein, HBx. Although HBx is not a component of HBV particles, it is believed to play a crucial role in viral replication. Acute and chronic infection of the liver with HBV appears not to produce cytopathic effects on hepatocytes; however, several components of the viral particles activate the host's immune response, and cytotoxic T cells (CTLs) eliminate HBV-infected hepatocytes (Fattovich, 2003; Bertoletti & Ferrari, 2003). Such immune responses induce sustained cycles of hepatocyte injury and regeneration that contribute to cirrhosis and HCC tumor formation.

HBV enters the hepatocyte by means of one or more yet to be defined cell-surface receptors, and the envelope glycoprotein is subsequently removed (Fig. 8C.3C). The partially double-stranded DNA is repaired to form a covalently closed circular DNA (cccDNA) moiety in the nucleus to serve as a stable template for transcription of the pregenomic mRNA and other species required for productive viral replication. This cccDNA template remains in the nucleus during chronic viral infection and may persist in the liver for the lifetime of the individual (Wands, 2004).

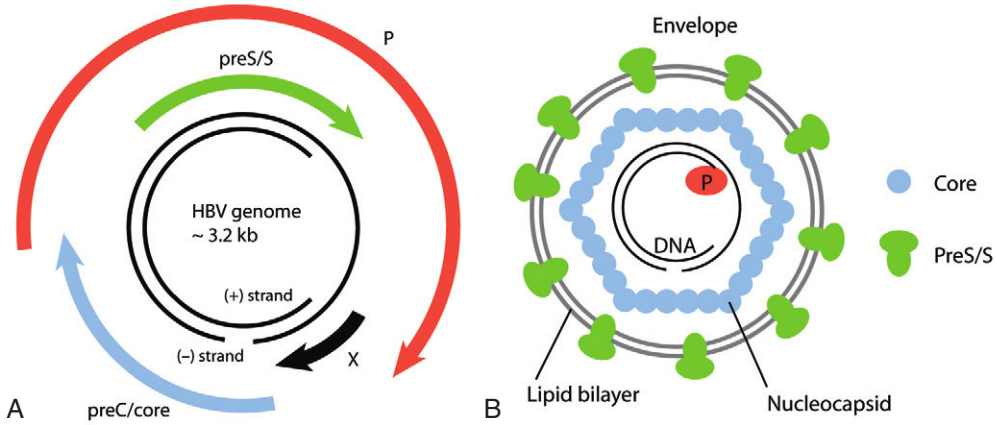
The DNA of the HBV integrates randomly into hepatocyte chromosomes and acts as a nonselective insertional mutagenic agent. Secondary chromosomal rearrangements involving duplications, translocations, and deletions reveal that the major oncogenic effect of HBV integration may be increased genomic instability of the host's cellular DNA. In greater than 90% of patients with HBV-related HCC, fragments of viral DNA have been found integrated into the host genome. Most HCCs contain integrated forms of a high molecular weight, as shown by Southern blot analysis of DNA extracted from tumor tissue. This event occurs randomly, because no common chromosomal site of insertion has been detected (Bréchot, 2000). However, a large-scale analysis of HBV DNA integration sites revealed that in some special instances, the integration event can disrupt the function of specific regulatory genes (Murakami et al, 2005). Of note, out of 50 HBV-related tumors studied, insertion of viral DNA into the *TERT* locus was observed in three with HBV-induced HCC. Telomerase reactivation was found, suggesting that the HBV integration event into the *TERT* locus was an important pathologic event in these tumors.

Another gene family recurrently affected by HBV integration includes those involved in calcium signaling. Studies indicate that HBV DNA had inserted into the gene encoding for SERCA (sarco/endoplasmic reticulum calcium adenosine triphosphatase), which plays a pivotal role in regulating intracellular calcium levels and shows as a second messenger involved in cell proliferation and programmed cell-death pathways (Chami et al, 2000). Collectively, cellular genes involved in chromosomal integrity and in growth factor–mediated signaling pathways are occasionally targeted by HBV integration events, but in the vast majority of tumors, the viral integration is random throughout the host genome (Murakami et al, 2005; Paterlini-Bréchot et al, 2003). Thus integration of HBV into hepatocyte DNA produces specific and nonspecific genetic alterations that contribute to hepatocarcinogenesis.

Studies on murine models expressing HBV-related transgenes such as HBx, as shown in Figure 8C.4, as well as truncated preS/S regions, provide evidence for their role in hepatic tumor development (Kim et al, 1991; Chisari et al, 1989). The most well-established transgene in this regard encodes for the HBx protein. This is a 154–amino acid molecule highly conserved among mammalian hepadnaviruses (Chen et al, 1993), and it has multifunctional and pleiotropic properties that modulate cellular functions that include transcription, signaling cascades, DNA repair, protein degradation, and cell cycle control (Murakami, 1999). During viral replication, HBx is localized in the cytosol with a minor fraction present in the nucleus. Cytosolic HBx activates Ras/Raf/MEK/ERK, PI3K/Akt pathway, Src kinase, and JAK/STAT cascades, leading to the increased cell proliferation (Bouchard & Schneider, 2004). Constitutive expression of HBx also promotes hepatocarcinogenesis, in combination with activation of the insulin/IGF-1/IRS-1/MEK/ERK cascade (Longato et al, 2009). In addition, nuclear HBx has been reported to act as a transcriptional coactivator, although it does not directly bind to DNA. Growth molecules known to be influenced by HBx expression include cAMP response element–binding protein (CREB), activating transcription factor 2 (ATF2), AP-2, and CREB-binding protein/p300 (Bouchard & Schneider, 2004).

Several reports indicate an interaction between HBx and p53 tumor suppressor protein. In this context, HBx binds to p53 and may suppress its functions. For example, HBx binds to p53 in the nucleus and inhibits expression of p53 responsive genes. Nuclear HBx also alters the association of p53 with transcription factors, such as ERCC3 and TFIIH, which are involved in nucleotide excision repair (Jia et al, 1999; Wang et al, 1994, 1995). Moreover, HBx expression has been shown to block p53-mediated apoptosis, and it provides a clonal selective advantage to HBV-infected hepatocytes (Elmore et al, 1997; Huo et al, 2001; Wang et al, 1995).

Interestingly, HBx can trigger the release of calcium ion from mitochondria, leading to the enhanced replication of HBV



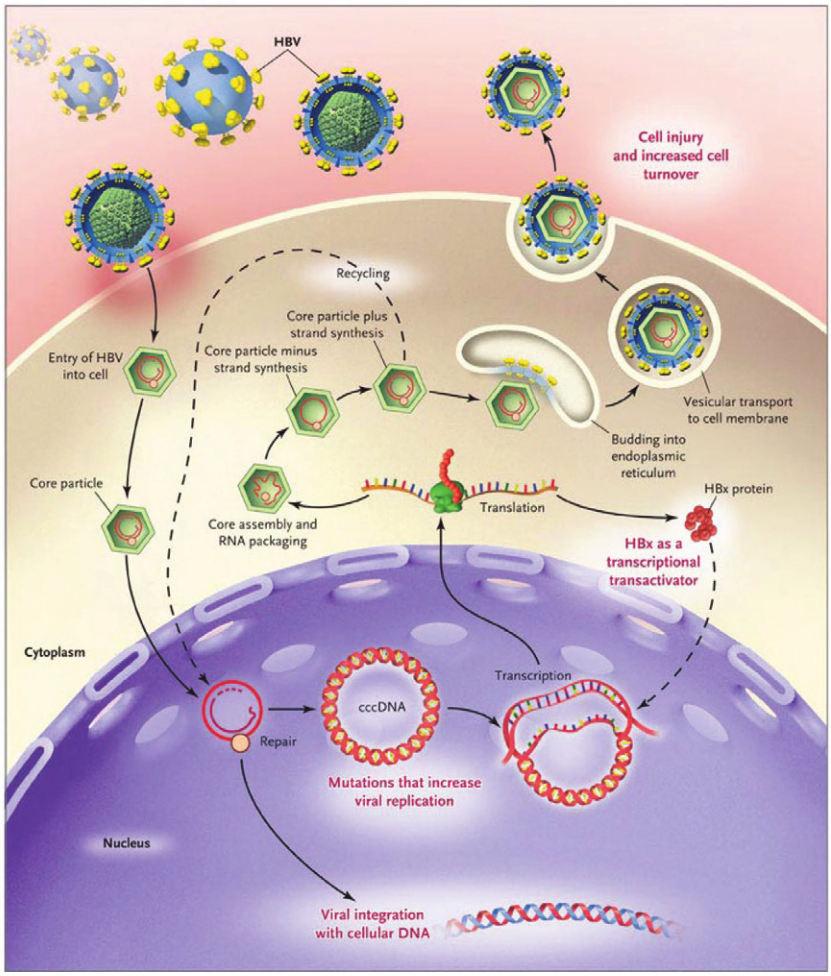


FIGURE 8C.3. **A,** Structure of the hepatitis B virus (*HBV*) DNA genome, showing the four open reading frames involved in generation of preC/core, preS/S, P, and X proteins. **B,** Structure of infectious HBV particle, showing the nucleocapsid containing an HBV genome and polymerase (*P*) and an envelope derived from the lipid bilayer, where preS/S proteins are embedded. **C,** Life cycle of HBV, showing viral entry through receptors, followed by uncoating and translocation of HBV DNA to the nucleus, where it is repaired to generate a cccDNA form that serves as the template for transcription of the pregenomic and other viral mRNA necessary for replication. *(From Wands JR, 2004: Prevention of hepatocellular carcinoma. N Engl J Med 351:1567-1570. Copyright © 2004 with permission from Massachusetts Medical Society. All rights reserved.)*

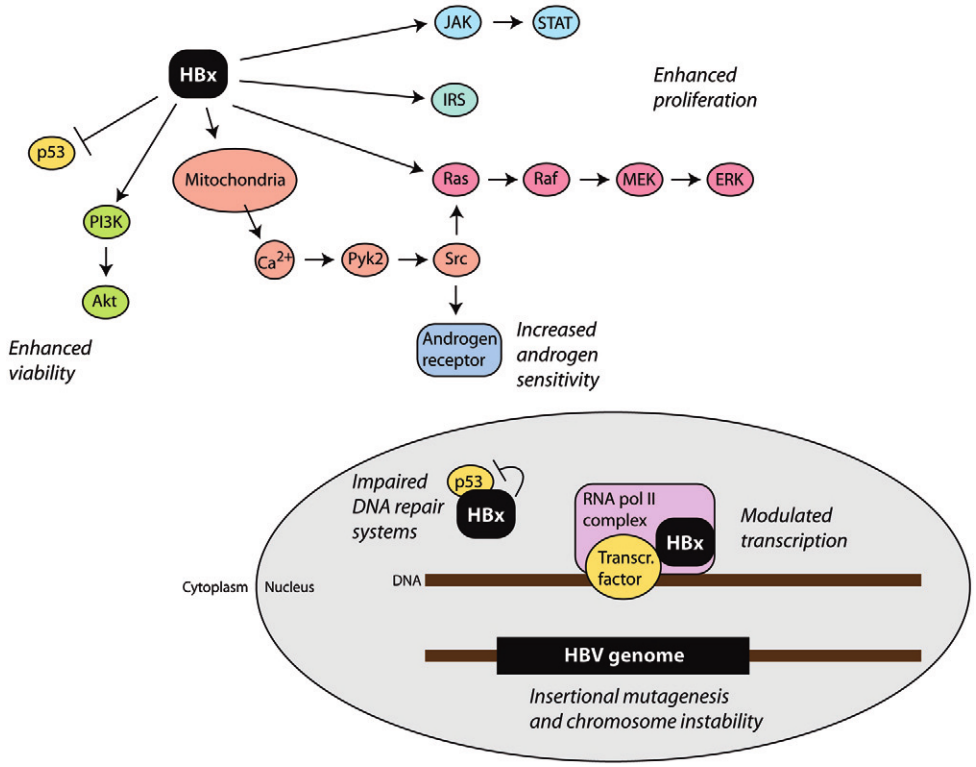


FIGURE 8C.4. Characteristics of the HBx protein and its involvement in tumor formation. HBx plays a crucial role in hepatitis B virus (*HBV*)-induced carcinogenesis. HBx is located in the cytoplasm and activates cellular signaling cascades. This viral nonstructural protein also inhibits p53-mediated apoptosis. Nuclear HBx modulates a set of transcription factors through interaction with a RNA polymerase complex. The HBV genome integrates into the host genome during persistent viral infection and promotes chromosome instability.

DNA through interaction with a proline-rich tyrosine kinase 2 (Pyk2) and Src kinase (Bouchard et al, 2001). HBx also influences the androgen signaling pathway, which may explain in part the known male predominance of HBV-induced HCC (Chiu et al, 2007). Taken together, these findings indicate that HBx plays a complex and pleiotropic role in the multistep process of tumor development.

Evidence has been accumulating that the risk of HCC is substantially increased by viral factors, such as the level of HBV replication produced by naturally occurring mutations in the core and precore promoter regions (Baptista et al, 1999; Kao et al, 2003; Kuang et al, 2004). A high viral replication phenotype places the infected liver at greater risk for transformation, as shown in Figure 8C.3C. Finally, with the development of diagnostic techniques sensitive enough to detect very low levels of serum HBV DNA (<100 copies/mL), it has become increasingly apparent that many patients with chronic HCV infection also are infected with low levels of HBV. In this setting, HBV maintains its oncogenic properties, and evidence has accumulated that occult HBV infection, defined as less than 10,000 virions per mL of serum, may be associated with chronic hepatitis and cirrhosis of heretofore unknown origin (Wands, 2004).

HEPATITIS C VIRUS

HCV is a member of the *Flaviviridae* family and is the only member of the genus *Hepacivirus* (Tellinghuisen & Rice, 2002). The HCV genome consists of a single positive-strand RNA of approximately 9.6 kb in length (Fig. 8C.5A). HCV RNA contains a large (approximately 9.0 kb) ORF in which structural and nonstructural coding regions are located near the 5′ and 3′ ends of the viral genome, respectively. Both 5′ and 3′ untranslated (UTR) domains have been found to be essential for viral RNA replication. Translation of the HCV RNA can be initiated by an internal ribosome entry site (IRES) located in the 5′ UTR. The single ORF encodes for a polyprotein precursor, consisting of about 3000 amino acids; it is cleaved into 10 smaller proteins by the action of several proteases derived from both host and virus. These 10 viral-related molecules include three structural (core [C], E1, and E2) and 7 nonstructural (NS; p7, NS2, NS3, NS4A, NS4B, NS5A, NS5B) proteins. The core forms a nucleocapsid that contains the HCV genome. The nucleocapsid is covered by an envelope composed of a lipid bilayer, in which the two structural proteins E1 and E2 are embedded. The function of p7 is not well understood, but it appears to be a transmembrane protein with ion channel activity. NS2 is a metalloprotease that cleaves between NS2 and NS3. The NS3 is a serine protease that produces NS4A, NS4B, NS5A, and NS5B viral proteins; it also has RNA helicase and NTPase activity. NS4A acts as a cofactor for NS3 activity, and NS4B is an integral membrane protein located on the cytoplasmic side of endoplasmic reticulum (ER); it has been implicated in the assembly of replicase complex. The NS5A protein is believed to act as a component of RNA replicase complex, and it plays a role in evasion of the host's cellular immune response. The NS5B is an RNA-dependent RNA polymerase essential for the replication of the HCV genome.

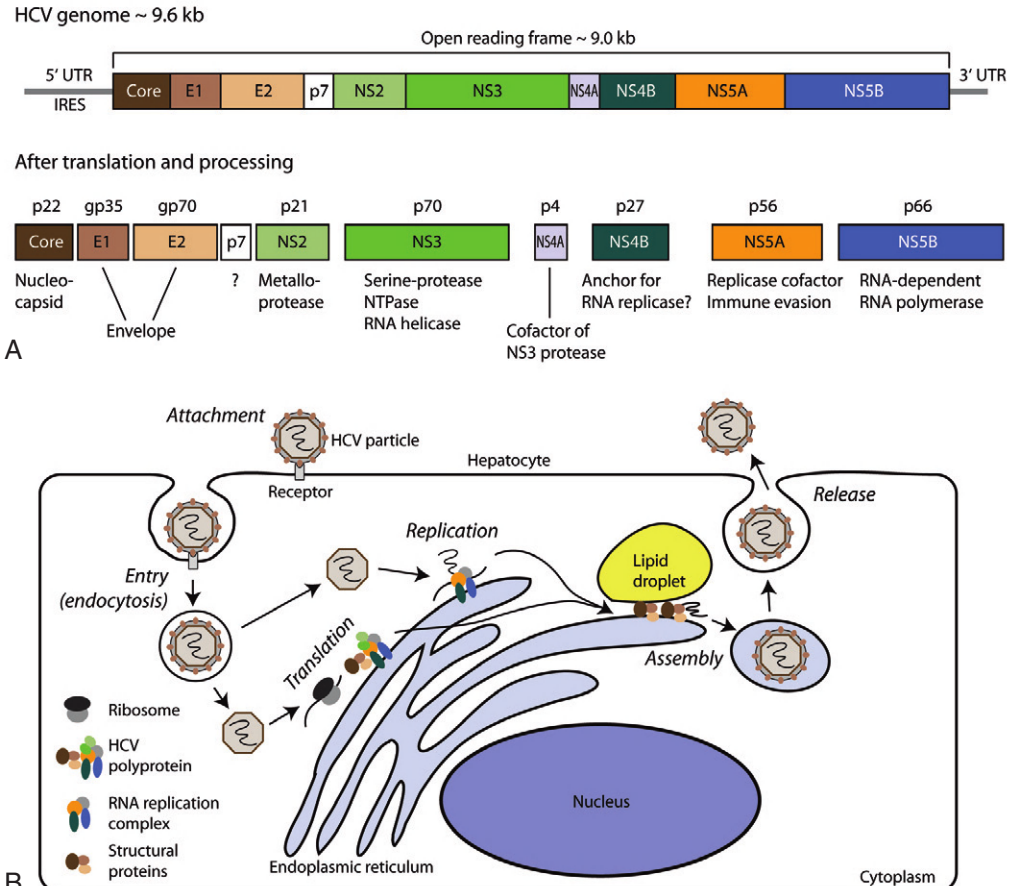


FIGURE 8C.5. Diagram of hepatitis C virus (*HCV*) and the replication process. **A,** Components of the HCV genome, showing the structure of HCV RNA. HCV proteins, including their role in HCV replication, are presented. **B,** Life cycle of HCV, showing the known steps of viral replication, including attachment/entry, translation, replication, processing, assembly, and release of virus into the blood. IRES, internal ribosome entry site; NTPase, nucleoside triphosphatase; UTR, untranslated region.

The life cycle of HCV consists of at least six different stages: *attachment/entry, translation, processing, genome replication, assembly,* and *release* into the circulation (Fig. 8C.5B). HCV particles attach to the hepatocyte cell surface membrane and enter the cell via key proteins such as CD81, SR-BI, claudin-1, and occludin. After entry into the hepatocyte, the nucleocapsid is delivered to the cytoplasm, and the HCV RNA is released and immediately translated. The large polyprotein is processed on the cytoplasmic side of the endoplasmic reticulum (ER), and nonstructural proteins form a complex and initiate replication of the RNA genome in collaboration with some host proteins. Viral particles are assembled from the structural proteins, and the RNA genome becomes encased between membranes derived from lipid droplets and the ER. Assembled particles are delivered to the plasma membrane and released into the blood by exocytosis. Importantly, the entire process related to HCV replication is restricted to the cytoplasm; unlike HBV, the viral RNA does not form a DNA intermediate, thus the HCV genome does not integrate into the host's cellular DNA.

The evolution of chronic hepatitis to cirrhosis during persistent HCV infection may be mediated by the host immune response directed against epitopes that reside on the various viral proteins. Chronic HCV infection may develop as a result of immune evasion as a function of quasispecies formation during active viral replication. The RNA polymerase of HCV lacks proofreading capacity and contributes to rapid diversification of the viral population, therefore mutant HCV can escape from the adaptive immune response because of selection pressure (Rehermann & Nascimbeni, 2005). Moreover, several viral proteins, including NS3 and NS5A, may contribute to viral persistence as a result of attenuation of cellular interferon activity, which appears essential for virus elimination (Foy et al, 2003; Polyak et al, 2001). These immune-evasion mechanisms promote chronicity of HCV infection, which promotes hepatic inflammation, cirrhosis, and HCC (Fig. 8C.6).

At least four HCV proteins—including core, NS3, NS5A, and NS5B—have been proposed to have cellular transforming activity both in vitro and in vivo as depicted in Figure 8C.6. Transgenic mice overexpressing HCV core in the liver have been shown to develop steatosis as well as HCC (Moriya et al, 1998). In addition, the core protein has been shown to have transforming potential in vitro (Ray et al, 1996). HCV core binds numerous cellular proteins and modulates the Raf/MEK/ERK signal transduction pathway (Levrero, 2006). The core protein also augments the TGF-β pathway by upregulating TGF-β expression in hepatic stellate cells to promote fibrosis (Bataller et al, 2004). Enhanced proliferation of HCC cells has been demonstrated by overexpression of the HCV core protein in vitro. This phenomenon was due to upregulation of Wnt-1 expression, suggesting a functional link between HCV core expression during active viral replication and subsequent

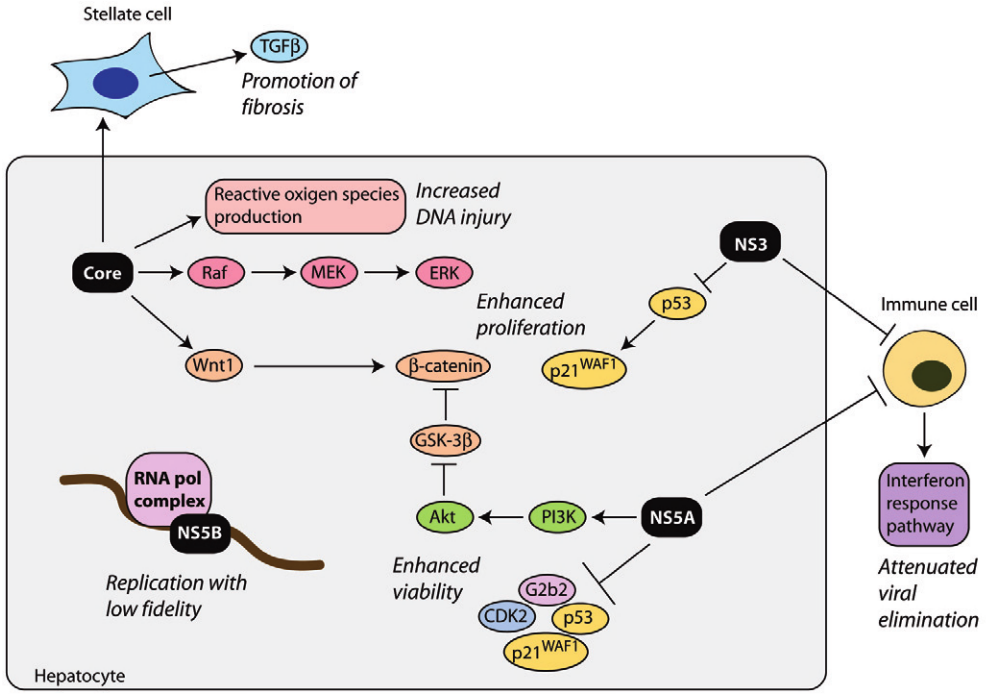


FIGURE 8C.6. Pathogenic role of hepatitis C virus (*HCV*) proteins. This diagram illustrates how HCV proteins—including core, NS3, NS5A, and NS5B—may modulate cellular function. Such proteins promote hepatocarcinogenesis in diverse ways via activation of signaling pathways and stellate cells, and they suppress immune responses to the virus and generate oxidative stress in the liver. ERK, extracellular signal-regulated protein kinase; GSK, glycogen synthetase kinase; MEK, mitogen-activated protein kinase; pol, polymerase; TGF, transforming growth factor.

activation of the Wnt/β-catenin signaling cascade (Fukutomi et al, 2005).

NS3 has been shown to complex with the wild-type p53 protein (Ishido & Hotta, 1998). By modulating the activity of p53, NS3 inhibits transcription of *LCMT2*, a gene encoding for a cell cycle regulator p21WAF1/CIP1. In addition, it has been found to repress *LCMT2* promoter activity in a dose-dependent manner and stimulates cell growth (Kwun et al, 2001).

The NS5A protein may act as a transcriptional modulator through interactions with other cellular proteins, such as Grb2, p53, p21WAF1/CIP1, and CDK2. The functional consequences have been inhibition of hepatocyte apoptosis leading to persistent HCV infection (Reyes, 2002). One potential mechanism by which NS5A may be able to exert an effect on gene expression and cellular growth is through functional associations with p53 and TATA box-binding proteins (TBP). In addition, NS5A can bind directly to the p85 regulatory subunit of PI3K and phosphorylate Akt, resulting in activation of pro-cell survival signals (Street et al, 2004). More recently, it has been observed that NS5A-mediated activation of PI3K resulted in the stabilization and accumulation of β-catenin in the cytoplasm and nucleus through inactivation of GSK-3β (Street et al, 2005).

Another possible pathway activated in HCV-induced HCC involves oxidative stress generated by increased production of reactive oxygen species (ROS) during persistent viral infection. Indeed, ROS production in the liver has been found to be increased in HCV core transgenic mice (Moriya et al, 1998). Moreover, iron loading in transgenic mice expressing the full-length HCV genome promotes HCC formation, again implicating chronic oxidative stress in the pathogenesis of HCV-mediated HCC (Furutani et al, 2006). The mechanisms underlying oxidative stress–induced hepatocarcinogenesis involve increased chromosome instability and mutations in the host cellular DNA produced by the action of ROS (Machida et al, 2006; Naganuma et al, 2004). Collectively, many of the HCV proteins are believed to contribute to hepatocyte transformation during persistent viral infection through stimulation of cell proliferation, increased cell survival, induction of genomic instability, and promotion of immune evasion.

FUTURE DIRECTIONS

In the postgenomic era, comprehensive examination of tumors via microarray gene expression profiles makes it highly likely that molecular genetic changes evolving from normal liver to dysplasia to HCC will be more precisely defined. Moreover, rapid advances in epigenetics analysis, miRNA function, and cancer stem cell biology will greatly enhance our understanding of the molecular pathogenesis of HCC. Traditional anticancer drugs, which target the DNA replication machinery, have marginal therapeutic effect on HCC growth, and new molecular targets will need to be defined. However, understanding altered signaling pathways in tumor cells will provide a stimulus to develop new drugs for treatment of this devastating disease. Such investigations emphasize the importance of unraveling the molecular mechanisms of liver carcinogenesis, which may ultimately result in "personalized" medical approaches for these tumors.

References are available at expertconsult.com.

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CHAPTER 42B

Biliary fistulae

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OVERVIEW

Abnormal communication may develop between distinct parts of the biliary tract itself or between the biliary tract and other parts of the gastrointestinal (GI) system. These abnormal biliary communications, or fistulae, can be grouped into two main types: internal or external. *Internal biliary fistulae* are usually rare and spontaneous, and they occur without a significant collection of bile. *External biliary fistulae* are more common and are often caused by iatrogenic injury after operations, invasive procedures, or trauma involving the biliary tract; they are characterized by persistent discharge of bile or bile-containing fluid and can be further defined as either controlled or uncontrolled. A *controlled fistula* has bile drainage to the exterior, through the abdominal wall, but no significant intraperitoneal collection; an *uncontrolled fistula* denotes a communication with an internal collection of bile.

Regardless of the nature of the biliary fistula, management of patients with this condition is optimized when treatment is directed by a multidisciplinary team composed of experienced interventional radiologists, gastroenterologists, and surgeons.

INTERNAL BILIARY FISTULAE

Incidence and Etiology

Whether occurring as a consequence of calculous biliary tract disease, trauma, neoplasm, or congenital anomalies, internal biliary fistulae are uncommon. Estimates of incidence are crude, gleaned only from many small series, usually with fewer than 50 patients. If all types of internal biliary fistula are included, calculous biliary tract disease accounts for 90%; peptic ulcer disease, 6%; and neoplasm, trauma, parasitic infection, and congenital anomalies make up the remaining 4% (Piedad & Wels, 1972).

Overall, 1% to 3% of patients with cholesterol cholethiasis in Western countries develop biliary-enteric fistula, with a female/male ratio of 3:1. In 11,808 cases of nonmalignant biliary tract disease encountered at New York Hospital/Cornell Medical Center during the years 1932 through 1978, the incidence of biliary-enteric fistula was 0.9% with a male/female ratio of 2.3:1 (Glenn et al, 1981). A large series from Greece (Lygidakis, 1981) showed an incidence of 2%, and in Native Americans, the incidence is 3.2% (Zwemer et al, 1979). In Japan, where bilirubin stones and primary intraductal disease predominate, the incidence of fistula is between 13% and 18% with a slight male predominance (Urakami & Kishi, 1978). The type of fistula noted in this group of patients usually involves the ductal system rather than the gallbladder. The pathogenic sequence of events for calculous biliary tract disease has been well described by Glenn and Mannix (1957). It consists of pressure necrosis and erosion of part of the biliary tract wall into an adjacent structure to which it has become adherent in the course of repeated bouts of inflammation, often with distal biliary tract obstruction. The likelihood of the branches of the hepatobiliary tree to become inflamed and anatomic proximity to adjacent hollow viscera largely determine the relative incidence of the different types of spontaneous biliary-enteric fistulae secondary to calculous disease.

The various types of biliary-enteric fistulae can best be subclassified from an anatomic point of view, by the names of the principal organs involved (Fig. 42B.1). Some names for a particular fistula between two structures vary in the literature (e.g., *bronchobiliary* vs. *biliobronchial*) but do not connote differences in etiology or pathogenesis.

Fistulae Involving the Gallbladder

In Western countries, where cholesterol cholelithiasis abounds, the gallbladder is most often the site of severe inflammation and obstruction. Cholecystenteric fistulae constitute 70% to 85% of all biliary fistulae reported in the world literature up to 1982 (Rau et al, 1980; Safaie-Shirazi et al, 1973). Of these, 55% to 75% are cholecystoduodenal, 15% to 30% are cholecystocolic, and 2% to 5% are cholecystogastric (see Fig. 42B.1). Multiple fistulae (e.g., cholecystoduodenocolic) are very rare (Shocket et al, 1970). Of the 23 cases reported up to 1978, 21 were secondary to gallstone disease, and one case of each was due to duodenal ulcer and a primary carcinoma of the gallbladder (Morris et al, 1978).

Gallstone ileus, a dramatic clinical presentation of a cholecystenteric fistula, is reported in 8% to 20% of large series of patients with biliary-enteric fistulae (Clavien et al, 1990; Heuman et al, 1980; Kasahara et al, 1980; LeBlanc et al, 1983; Rau et al, 1980; Safaie-Shirazi et al, 1973; VanLandingham & Broders, 1982). As a cause of intestinal obstruction alone, gallstone ileus accounts for 1% to 4% of cases, although in patients older than 65 years, gallstone ileus may account for 25% of cases of small bowel obstruction, regardless of a history of prior abdominal surgery (Clavien et al, 1990; Reisner & Cohen, 1994; Rodriguez-Hermosa et al, 2001; Lassandro et al, 2004; Kirchmayr et al, 2005; Chou et al, 2007).

Although most fistulae between the gallbladder and intestinal tract become obvious preoperatively or intraoperatively, cholecystocholedochal fistulae are insidious and may not be appreciated even at surgery. These biliobiliary fistulae develop between the ampulla of the gallbladder or cystic duct and the proximal common hepatic or common bile duct (CBD; see Fig. 42B.1D). In either instance, the mechanism of formation is the

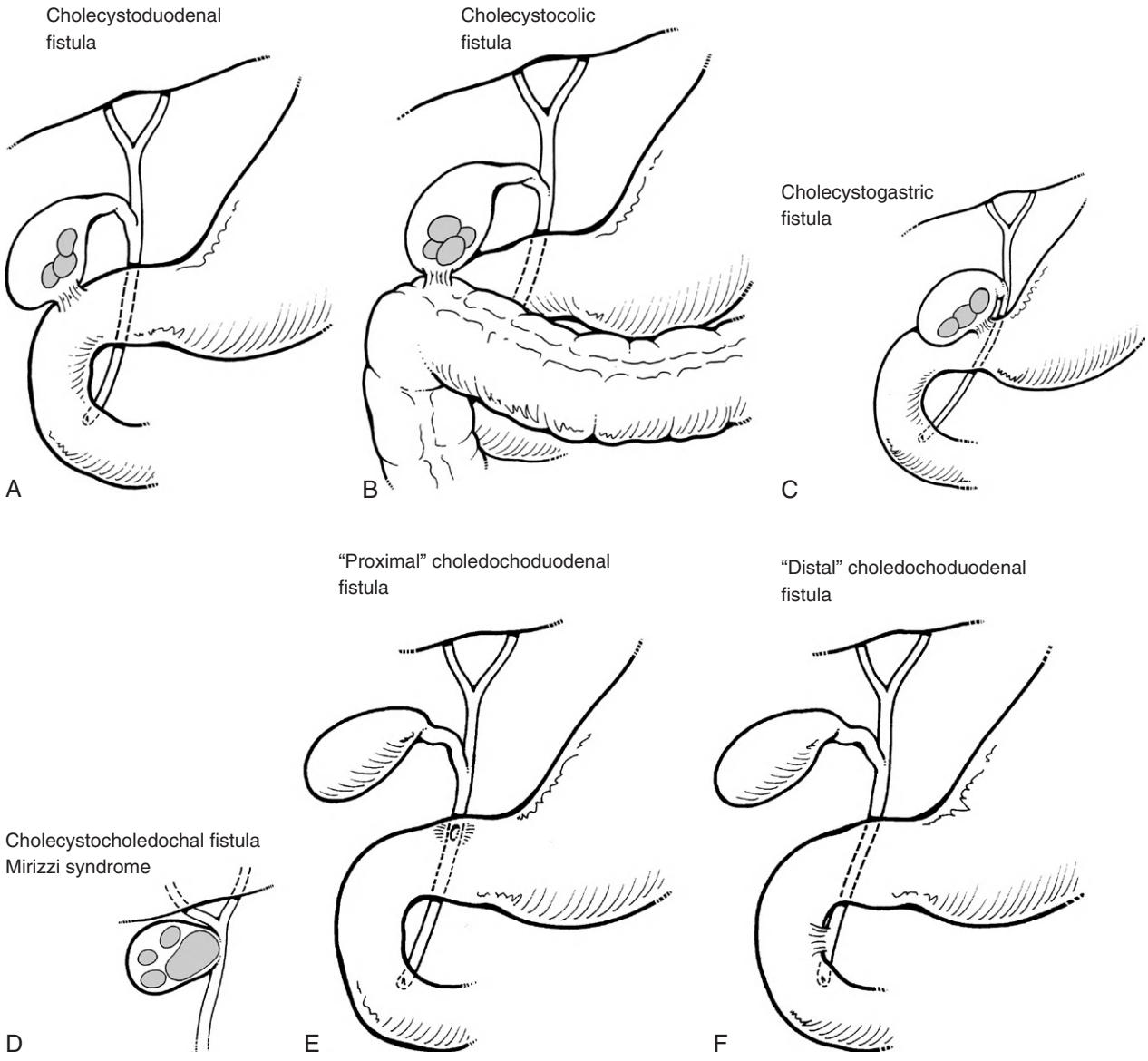


FIGURE 42B.1. **A** through **F,** Various types of biliary-enteric fistulae.

same: pressure necrosis into the common duct by a large solitary calculus impacted in either the ampulla of the gallbladder or the intramural portion of the cystic duct. Cholecystocholedochal fistula has been estimated to occur in 1% to 6% of biliary operations for calculous disease (Corlette & Bismuth, 1975). Although this estimate seems high and is not corroborated by other reports, an awareness of the possibility of cholecystocholedochal fistula is important and may help avoid damage to the common duct at operation.

Fistulae Involving the Common Bile Duct, Cystic Duct Remnant, and Other Extrahepatic Ducts

Choledochoduodenal fistulae are classified as either proximal or distal (see Fig. 42B.1E and 42B.1F). A *proximal choledochoduodenal fistula* is the principal form of abnormal communication between the CBD and adjacent structures and represents 4% to 20% of all biliary-enteric fistulae. At one time, 80% were caused by peptic ulcer erosion from the first portion of the duodenum into the proximal CBD. This cause is now much less common as a result of the development of effective medical therapy with antacid drugs. Other, less common causes of choledochoduodenal fistula include cholelithiasis, operative trauma, duodenal diverticula, echinococcal infection, Crohn disease, and neoplasms of the stomach, distal bile duct, ampullary region, and duodenum (Feller et al, 1980; Sarr et al, 1981; Kuroki et al, 2005). Since the beginning of the acquired immunodeficiency syndrome (AIDS) epidemic, there have only been three known case reports of choledochoduodenal fistula caused by AIDS/human immunodeficiency virus–associated tuberculous infection (Patino et al, 2003).

Distal choledochoduodenal fistulae connect to the duodenum in the distal 2 cm of the CBD, and the fistula opening can be seen during percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiopancreatography (ERCP). The incidence of distal choledochoduodenal fistula secondary to cholelithiasis or operative trauma is variable in different parts of the world. With the development of PTC and ERCP studies of pathologic anatomy (see Chapters 18, 27, and

28), it is becoming apparent that many patients with minor or major biliary-digestive complaints and gallstone disease may have a distal choledochoduodenal or parapapillary choledochoduodenal fistula. Large series from Argentina showed the incidence of parapapillary choledochoduodenal fistula to be 0.7%. Jorge and colleagues (1991) reviewed 2012 ERCP studies from 1976 through 1989, and only 14 cases were found: two cases were from stone disease and the other 12 were from iatrogenic causes.

In Japan, where there is a high incidence of primary intrahepatic calculous biliary tract disease, Tanaka and Ikeda (1983) reported a 5.3% incidence of parapapillary fistula in ERCP studies of 1500 patients. The male/female ratio was roughly equal, in keeping with the Japanese sex distribution of gallstone disease. Ikeda and Okada (1975) classified these as *type I fistula*, characterized by a small fistula opening on the longitudinal fold of the duodenum just proximal to the papilla, probably caused by penetration of a small calculus through the intramural portion of the common duct into the duodenum, and *type II fistula*, a larger opening of the duodenum wall adjacent to the longitudinal fold, probably caused by a relatively large stone eroding from the extramural portion of a greatly dilated common duct into the duodenum.

In Turkey, Karincaoglu and colleagues (2003a) reported an incidence rate of 4.9% on review of 1347 ERCP studies in 841 patients. This study also found an intriguing association between peripapillary fistula with common duct stones and complications of cholangitis. The incidence of parapapillary choledochoduodenal fistula is probably less in Western Europe, the United Kingdom, and the United States, and perhaps a greater proportion of these fistulae are not due to spontaneous gallstone disease itself but rather to iatrogenic surgical injury or other instrumental damage to the distal common duct in operations directed against choledocholithiasis. Hunt and Blumgart (1980) and Tytgat and colleagues (1979) published their experience of these fistulous complications of biliary tract surgery.

Unusual choledochal fistulae are mentioned only briefly in this context. Spontaneous fistula formation between the common duct and the colon has been recorded only four times in the English literature (Bose & Sastry, 1983; Rawas et al, 1987; Guitron-Cantu et al, 2001; Anees et al, 2008). We are also aware of one case of a choledochocolonic fistula that developed after blunt abdominal trauma (Benson et al, 2001) and another that developed as a complication from diverticulitis (Blanco-Benavides & Rodriguez-Jerkov, 1992). Peptic ulcer disease has rarely produced fistulae between the common duct, duodenum, and pancreas (Aitken et al, 1986). We have observed one case and are aware of several other cases of severe pancreatitis or pancreatic cancer producing a fistulous communication between pancreatic pseudocysts or necrotic pancreatic cavities and the CBD (DeVanna et al, 1983; Ellenbogen et al, 1981; Lebovics et al, 1990; Miller et al, 1988). Chandar and Hookman (1980) reported one case of GI hemorrhage resulting from a choledochocolonic fistula that developed from a cystic duct remnant 28 years after cholecystectomy, and it was associated with a benign stricture in the ampullary segment of the CBD. More recently, a bile duct stricture associated with a choledochocolonic fistula was reported following an uncomplicated open cholecystectomy four months prior (Munene et al, 2006). Woods and colleagues (1992) reviewed four cases of cystic duct remnant fistulization to the GI tract.

Fistulae Involving the Intrahepatic Ducts, Liver, and Lung

Thoracobiliary and bronchobiliary fistulae are quite rare (Boyd, 1977; Chan et al, 1984; Cleve & Correa, 1958); the former refers to communications between the biliary tree and the pleural cavity and the latter to communications between the bile ducts and the bronchial tree. The three major categories of bronchobiliary fistula are 1) those resulting from infection, especially parasitic, or those acquired, such as from iatrogenic injury as a result of biliary tract surgery or, less commonly, from gastric and pancreatic operations; 2) traumatic fistula; and 3) congenital fistula. The many diverse causes of acquired bronchobiliary fistulae have been well referenced by Sane and colleagues (1971) and more recently by Gugenheim and colleagues (1988). The two main factors responsible for the development of bronchobiliary fistulas are "mechanical" biliary obstruction and infection. Worldwide, the principal cause of bronchobiliary fistula in adults is parasitic disease of the liver, either echinococcal or amebic abscess (see Chapters 67 and 68). In developed countries, iatrogenic injury to the biliary ductal system is the most frequent cause of these fistulae.

The hallmark symptom of a bronchobiliary fistula is biliptysis in conjunction with other pulmonary complaints, jaundice, cholangitis, and external biliary fistula or subphrenic abscess. Radiologic confirmation of the diagnosis is possible by a variety of methods. In the presence of an external fistula, injection of contrast solution (fistulogram) is the most facile and direct approach. PTC and ERCP are equally effective in their ability to show the fistula and have the advantage of offering an avenue for potential therapeutic intervention. The choice of one or the other of these techniques depends on the presence or absence of dilated ducts and the expertise available. Bronchobiliary fistulae also have been shown by cholescintigraphy (Gunlemez et al, 2009; Santra et al, 2009; Uramoto et al, 2008; Andalkar et al, 2004; Savitch et al, 1983; Velchik et al, 1991). Computed tomography (CT) and magnetic resonance imaging cholangiopancreatography (MRCP) have been used to assess bronchobiliary fistulae (see Chapters 16 and 17). These imaging techniques, although helpful in assessing the upper abdomen, rarely visualize the fistula tract (Oettl et al, 1999; Yeatman et al, 2004; Kuroki et al, 2005; Ragozzino et al, 2005).

The surgical treatment of parasitic disease of the liver is discussed elsewhere in this book (see Chapters 67 and 68). In large series of surgically treated cases of hepatic echinococcal disease in Greece and Turkey, only 2% were complicated by rupture into the lung or bronchi (Alestig et al, 1972). Amebic abscess of the liver has been reported in association with bronchobiliary fistula in 8% of cases (Razemon et al, 1963). These complications of parasitic disease are more likely to be suspected in patients from Mediterranean countries, North Africa, Mexico, and some of the southern border states of the United States. The successful treatment of these fistulae depends on the use of appropriate surgical drainage or resection in conjunction with appropriate drug therapy.

The incidence of bronchobiliary fistula as a consequence of surgically treated calculous or neoplastic disease of the hepatobiliary tract and adjacent structures has been decreasing, as patients are operated on earlier in the course of their disease and by better-trained surgeons (Ramesh et al, 1991; Warren et al, 1983). Then again, modern surgical techniques and equipment have contributed to a new cause of biliary fistulae: reports of bronchobiliary fistula caused by new liver tumor ablative therapies, such as radiofrequency ablation (RFA), are

beginning to emerge (Kim et al, 2005; Tran et al, 2007; Yoon et al, 2009; see Chapter 85). In all these case reports, the fistula responded to conservative treatments focused on biliary drainage.

The incidence of bile duct injury in the course of cholecystectomy has increased with the advent of laparoscopic removal of the calculous gallbladder (Davidoff et al, 1992). Most of the injuries are repaired at or shortly after their occurrence. Bronchobiliary fistulae secondary to bile duct injury are a late consequence of the event in patients with neglected or recurrent strictures after unsuccessful operations. Less frequently, gastric or pancreatic procedures may result in injury to the extrahepatic bile ducts.

Untreated choledocholithiasis complicated by repeated episodes of bile duct obstruction and cholangitis is another, albeit infrequent, cause of bronchobiliary fistula. Brem and colleagues (1990) reported the successful treatment of an 87-year-old patient with this clinical situation by endoscopic papillotomy alone. Indeed, bronchobiliary fistulae should be treated first by biliary decompression, either by endoscopic papillotomy or by transampullary drainage to reduce the fistula tract pressure. Some patients with a persistent fistula or infection will require debridement by thoracotomy.

Posttraumatic thoracobiliary fistulae are extremely rare. Although penetrating or blunt trauma to the abdomen and chest is a common enough civilian and wartime occurrence, the number of fistulae resulting has remained small, often because their initial surgical treatment has been excellent, and because no obstruction to proper bile flow existed (Oparah & Mandal, 1978). Ivatury and colleagues (1984) reported on three cases and reviewed 32 previously reported patients. This series included 20 thoracobiliary and 15 bronchobiliary fistulae. Twenty-six patients sustained penetrating injuries, including 16 with gunshot wounds, 6 with stab wounds, and 4 in which the weapon was not specified. Seven patients were admitted because of blunt trauma, and in an additional four patients, the mechanism of injury was not documented. All of the patients in this report had thoracoabdominal injuries, and the causes of the fistulae were nonoperative therapy, missed or overlooked injury to the diaphragm, inadequate drainage, and subphrenic abscess. All patients had pleural effusion, and bile was aspirated by thoracentesis. Successful treatment frequently required pulmonary decortication, repair of the diaphragm, and adequate drainage above and below the diaphragm. More recent publications support the notion that inadequate drainage caused posttraumatic bronchobiliary fistulae (Navsaria et al, 2002; Eryigit et al, 2007; Ball et al, 2009).

Neuhauser and colleagues (1952) first described congenital bronchobiliary fistula in an infant with a tract communicating between the right main stem bronchus and the hepatic duct that passed through the posterior mediastinum. The diagnosis was made antemortem, but the infant died before surgical therapy. Tommasoni and colleagues (2000) described two newborn infants who were promptly diagnosed and successfully treated surgically. These authors emphasized the importance of a high index of suspicion for early diagnosis and recognition of the very high incidence (approximately 36%) of coexisting hypoplasia or biliary atresia. Therefore, all of these patients need laparotomy and thoracotomy for successful treatment (Tommasoni et al, 2000). The fistulous tract in the posterior mediastinum adjacent to the esophagus should also be excised to avoid repeat thoractomy (Gunlemez et al, 2009). Yamaguchi and colleagues (1990) reported one adult patient with a congenital bronchobiliary fistula and summarized the data of 16 previously reported cases, four of them adults. Interestingly, all adults were younger than 32 years (range, 22 to 32 years). The only congentital bronchobiliary fistula in an elderly person was reported recently by Uramoto (2008).

On microscopic examination, the proximal portion of the fistula in most patients resembles the bronchus, and the distal segment resembles the esophagus; the embryologic explanations for this anomaly are conjectural (Dyon et al, 1978; Sane et al, 1971). Transthoracic excision of the fistula and surgical correction of associated biliary anomolies is usually curative.

Diagnostic Tests

Sputum analysis for bilirubin and viable scolices or membranes can be used as laboratory evidence to establish the diagnosis of bronchobiliary fistulae secondary to echinococcosis (Gerazounis et al, 2002). Although no specific serologic tests for biliary-enteric fistula are available, in the evaluation and management of an elderly, high-risk, or critically ill patient with a symptomatic biliary fistula, tests of liver function, electrolytes, and blood count are useful.

Plain and Contrast Radiographs

Pneumobilia, the presence of air in the biliary tree, may be noted on plain films of 30% to 50% of patients with gallstone ileus (Fig. 42B.2A). Other, less common causes of pneumobilia include an incompetent sphincter of Oddi, emphysematous cholecystitis, suppurative cholangitis, and prior biliary-enteric bypass surgery. Hricak and Vander Molen (1978) suggested that the low incidence of pneumobilia in gallstone ileus is due to the cystic duct obstruction that led to the acute cholecystitis and perforation into an adjacent viscus; the obstruction also prevents retrograde passage of air into the extrahepatic and intrahepatic bile ducts.

Other classic radiographic signs of gallstone ileus are visualization of a calcified gallstone in the peritoneal cavity a distance away from the gallbladder (Fig. 42B.2B), change on repeat films in the position of a previously observed calcification, and a change in the level of mechanical intestinal obstruction—the so-called *tumbling obstruction* (Day & Marks, 1975; VanLandingham & Broders, 1982). However, only 30% of gallstones are sufficiently calcified to be radiopaque.

A barium meal or upper GI series shows reflux of contrast material into the fistula in 40% of cholecystoduodenal communications and 75% of choledochoduodenal fistulae of peptic ulcer origin (Balthazar & Gurkin, 1976; Kourias & Chouliaras, 1964). If the plain film and barium swallow are used in concert, more than 60% of biliary enteric fistulae are correctly diagnosed preoperatively (see Fig. 42B.2A; Balthazar & Schechter, 1975). A negative upper GI series in the presence of pneumobilia is an indication for a barium enema, which discloses more than 95% of cholecystocolic fistulae. CT scans with contrast material, endoscopy, radionuclide imaging, and sonography are also useful in the diagnosis of biliary fistulae (Becker et al, 1984); and more recently, MRCP has yielded valuable information.

Endoscopy and Iodinated Dye Studies

Direct injection of contrast material is the best way to outline the normal and pathologic anatomy of the biliary tract.

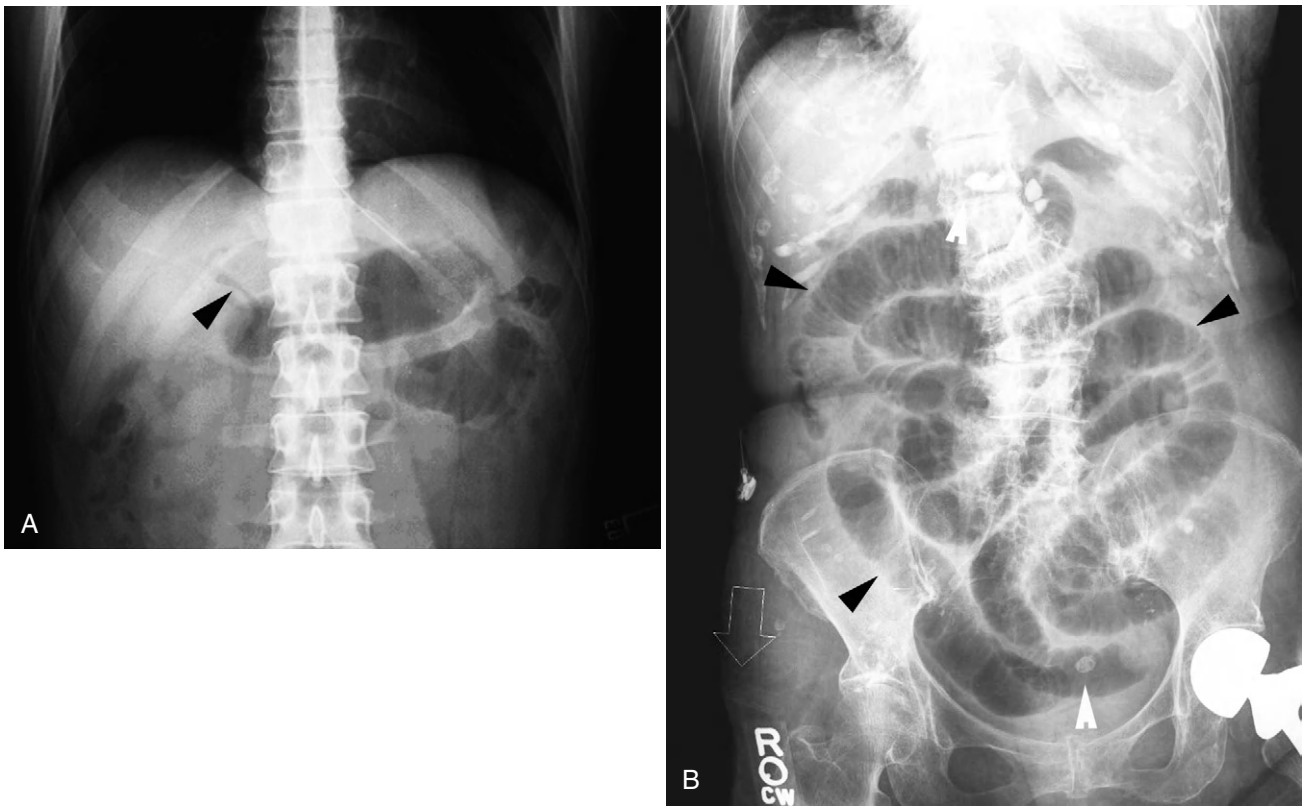


FIGURE 42B.2. A, Plain radiograph shows pneumobilia (*arrowhead*). **B,** Plain radiograph shows multiple dilated loops of small bowel (*black arrowheads*), several calcified gallstones (*white arrowhead*), three gallstones located in small bowel in the upper abdomen, and one obstructing gallstone in the pelvis. *(**A,** Courtesy Dr. Rizwan Aslam. **B,** Courtesy Dr. Fergus V. Coakley.)*

Preoperatively, this imaging is accomplished by ERCP or PTC; when an external bile fistula exists, a fistulogram should be performed. Intraoperative or postoperative cholangiograms are often invaluable.

Since 1970, numerous reports have appeared in the literature supporting the efficacy of ERCP in documenting surgical or spontaneous biliary fistulae (Al Nakib et al, 1982; Tanaka & Ikeda, 1983; Tytgat et al, 1979; Van Linda & Rosson, 1984). Endoscopically, the alimentary side of a fistula can be visualized directly, be it gastric (Stempfle & Diamantopoulos, 1976), duodenal, or colic; the fistula itself or the ampulla of Vater can be cannulated to obtain a high-quality radiograph of the communicating biliary anatomy (Moreira et al, 1984; Watkins et al, 1975; Chatzoulis et al, 2007). Similarly, the largely unappreciated and frequently asymptomatic parapapillary choledochoduodenal fistula has been found to be quite common (Hunt & Blumgart, 1980; Karincaoglu et al, 2003b; Tanaka & Ikeda, 1983; Kuroki et al, 2005). There have been far fewer reports of the role of PTC in showing biliary fistulae, but PTC has been helpful in the diagnosis and treatment of bronchobiliary fistula in association with echinococcal disease of the liver and dilated intrahepatic ducts (e.g., cholecystocholedochal fistula; Cornud et al, 1981; Mannella et al, 1999).

Radionuclide Imaging (See Chapter 15)

With the introduction of the imidoacetic acid agents bound to technetium (p-isopropylacetanilido iminodiacetic acid [PIPIDA] and hepatobiliary iminodiacetic acid [HIDA]), radionuclide scans have rapidly become the preferred method of outlining the normal and pathologic anatomy of the extrahepatic bile passages. These relatively noninvasive procedures do not rely on hepatocellular concentration of bile or on short critical time-flow periods for satisfactory visualization of the biliary tree. Prolonged (24 hours) accumulation of radioactivity, measured by patient scanning or quantitative isotopic counts of body secretions (e.g., sputum), has been used to show very small or intermittent fistulae from the biliary tract to the respiratory passages (Fig. 42B.3) and the colon (Benson et al, 2001; Santra et al, 2009; Uramoto et al, 2008; Andalkar et al, 2004; Bretland, 1983; Edell et al, 1981; Henderson et al, 1981; Savitch et al, 1983; Taillefer et al, 1983).

Sonography

Sonography is a useful noninvasive diagnostic aid in the preoperative evaluation of a patient with a suspected biliary fistula (Porta et al, 1981; Renner et al, 1982) and even gallstone ileus (Davies et al, 1991; Pedersen et al, 1988; see Chapter 13). Although the radionuclide scan may readily show a fistula, the sonogram indicates the presence of calculi in the gallbladder; common duct stones; and inflammatory, cystic, or infiltrative disease of the liver and pancreas (Griffin et al, 1983). Sonography can readily detect pneumobilia, indicating a high likelihood of a biliary-enteric fistula. In gallstone ileus, sonography can detect an ileal stone not seen on plain films and is increasingly being used by emergency room physicians (Zironi et al, 2007). Ripolles and colleagues (2001) reported that 22 of 23 patients who had undergone surgery for gallstone ileus were found on sonogram to have pneumobilia. This information is valuable in



FIGURE 42B.3. A 49-year-old woman with symptoms of pneumonia and clinical evidence of biliptysis. Anterior image from hepatobiliary iminodiacetic acid scan at 40 minutes after injection shows communication of the liver with the right lung and central airways. Radiopharmaceutical is present in the right and left main bronchi (*small curved arrows*) and in the trachea (*large curved arrow*), confirming the presence of bronchobiliary fistula. *(Courtesy Dr. Douglas S. Katz.)*

the decision-making process, such as to evaluate the need for or advisability of cholecystectomy and dismantling of a fistula at the time of operation for gallstone ileus in an elderly or high-risk patient. This information may be obtained more rapidly and safely, and probably with equivalent accuracy, by a preoperative sonogram rather than by intraoperative manipulations about the mass of inflamed tissue in the right upper quadrant. Ultrasound (US) has been used to document the persistence or closure of biliary enteric fistulae after initial emergent surgical or combined endoscopic lithotripter treatment of gallstone ileus, and it has aided the decision for or against further surgery (Clavien et al, 1990).

Computed Tomography and Magnetic Resonance Imaging Cholangiopancreatography (See Chapters 16 and 17)

CT and MRCP are better able to show a moderately calcified ectopic gallstone, air in the biliary tree, the presence of additional stones, and a cholecystoduodenal fistula (Swift & Spencer, 1998). CT is useful also for estimating the size of the impacted stone and determining the site of obstruction for planning the operative approach (Fig. 42B.4). Indeed, new multidector CT scanners that use multiplanar or three-dimensional volume-rendering reconstruction will further improve the diagnostic role of CT in detecting fistulae. Already, modern MRI and MRCP scans with improved image resolution and reduced motion artifact have been shown to accuarately detect a small fistulous tract (Chatzoulis et al, 2007). Although such scanning may disclose fusion of the biliary tract to an adjacent viscus, it may not always precisely show a fistula; but MR scanning should be used to show other important pathologic changes, such as distal common duct stones or other obstructive processes, the presence of a subphrenic abscess, pleural effusion, or parasitic disease of the liver (Porta et al, 1981). Scanning also can be used to verify and localize contrast extravasation after interventional procedures, such as PTC or ERCP, or after contrast injection of an existing controlled external fistula (Fig. 42B.5).

Specific Clinical Presentations and Treatment

Gallstone Ileus

Gallstone ileus is the blockage of the intestinal tract by a gallstone large enough to occlude its lumen partially or completely. This dramatic presentation of intestinal obstruction is too indelibly fixed in the medical imagination to permit amendment of the inappropriate term *ileus*; perhaps this derives from the frequent initial clinical impression of an unexplained ileus, in that many patients with gallstone obstruction are initially seen without any clinical history or physical signs to suggest mechanical intestinal obstruction. Similar to other patients in Western Europe and English-speaking countries, where

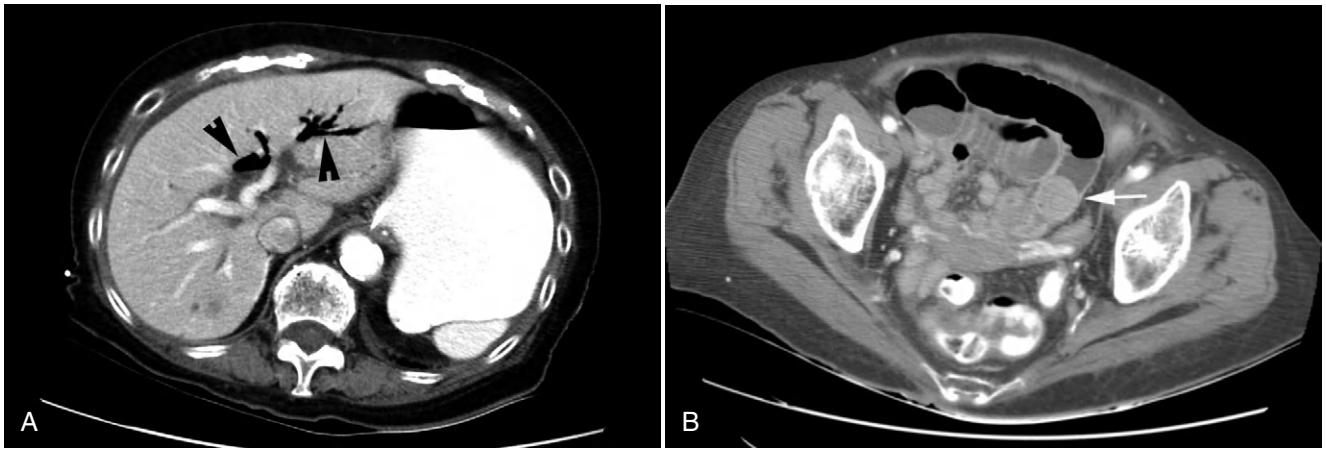


FIGURE 42B.4. A 92-year-old woman with recurrent pyogenic cholangitis and increasing abdominal pain, anorexia, constipation, nausea, and vomiting over a 36-hour period. **A,** Computed tomography through the liver showing extensive pneumobilia (*arrowheads*). **B,** In the pelvis, a soft tissue–attenuated, round, 2.5-cm gallstone (*arrow*) is seen at the transition point between dilated and decompressed bowel. *(Courtesy Dr. Fergus V. Coakley.)*

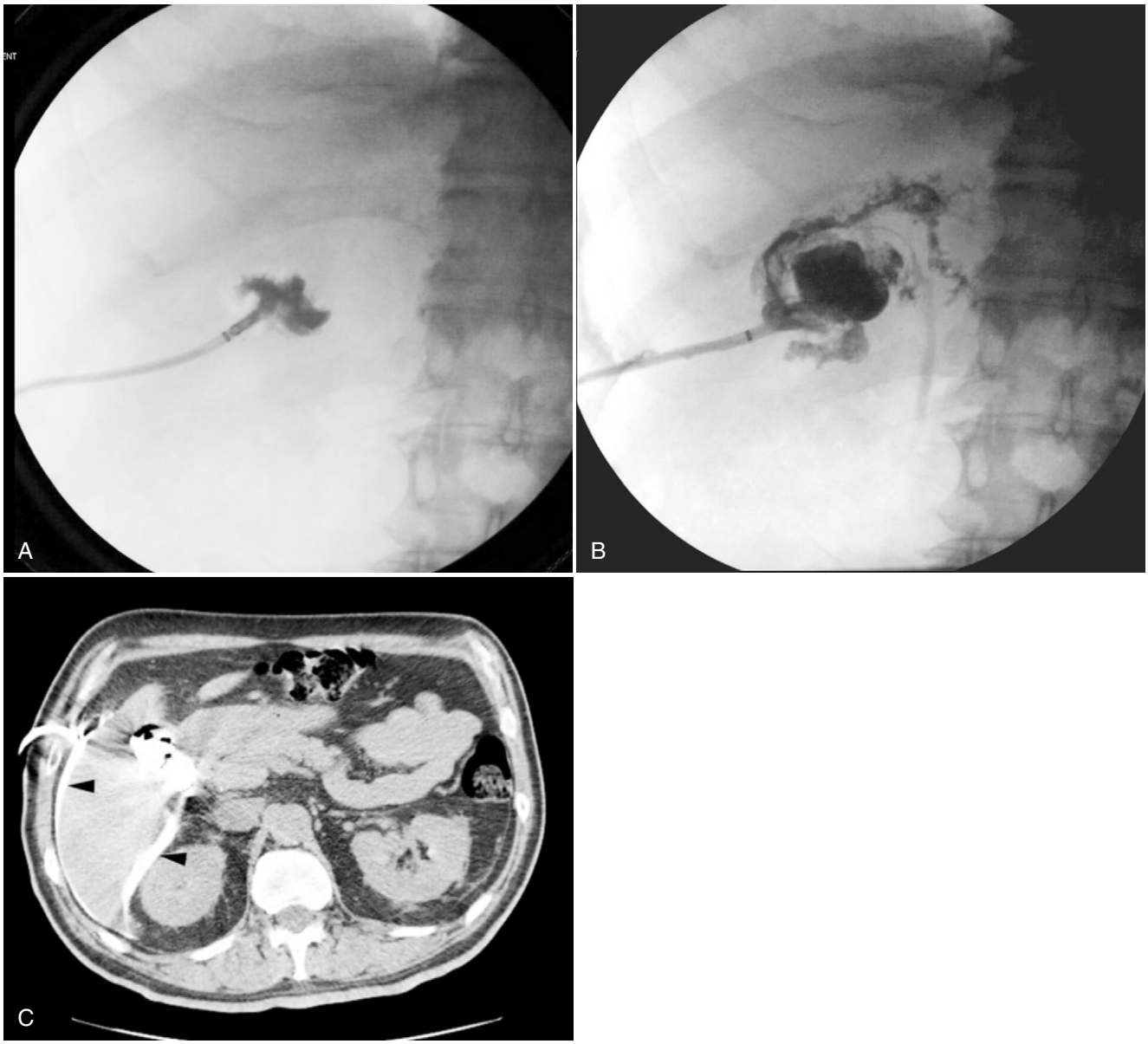


FIGURE 42B.5. **A** and **B,** Cholecystograms showing extravasation: percutaneous cholecystostomy tube. **C,** Axial computed tomographic scan shows contrast extravasation into right upper abdomen (*arrowheads*).

cholesterol cholelithiasis predominates, patients seen with this manifestation of advanced biliary tract disease are usually elderly, female, and beset by multiple other medical conditions that may delay or complicate prompt diagnosis and appropriate treatment.

When an elderly person presents with typical signs and symptoms of intestinal obstruction or, perhaps less dramatically, an unexplained ileus without obvious incarcerated abdominal wall hernia, scar of a previous laparotomy, and little suspicion of an occult malignancy, calculous obstruction by a gallstone must be considered. Approximately half of such patients presenting with gallstone ileus give a history suggesting prior calculous biliary tract disease. At the time of clinical presentation with gallstone obstruction, however, signs of active gallstone disease—pain, tenderness in the upper abdomen, cholangitis, and jaundice—may be absent. Laboratory data are consistent with fluid and electrolyte disturbances appropriate to the degree and duration of intestinal obstruction, and some abnormalities of liver function tests (LFTs) may suggest chronic disease of the liver and biliary tract in one quarter of patients.

The classic plain abdominal film triad of small bowel obstruction, pneumobilia, and ectopic gallstone is considered pathognomonic of gallstone ileus (Rigler et al, 1941); however, the triad is encountered in only 30% to 35% of cases (Balthazar & Schechter, 1978). Pneumobilia is often not appreciated even in retrospect. If biliary-enteric fistula is suspected, and a barium meal is administered, reflux of barium into the biliary tree yields a correct preoperative diagnosis in 60% of patients (Fig. 42B.6). Calculi large enough to obstruct the intestine usually do so in the last 50 cm of ileum, although sometimes also in the jejunum or duodenum and rarely in the sigmoid colon. Such calculi are usually larger than 2.5 cm; if partially calcified, they are readily apparent on a plain radiographs (see Fig. 42B.2B).



FIGURE 42B.6. Upper gastrointestinal series shows a choledochoduodenal fistula with reflux of contrast medium into the biliary tree. *(Courtesy Dr. Benjamin M. Yeh.)*

Abdominal ultrasound, as mentioned earlier, often establishes the diagnosis of gallstone ileus or provides other information relevant to the diagnosis (Clavien et al, 1990; Davies et al, 1991; Pedersen et al, 1988; Ripolles et al, 2001; Zironi et al, 2007), revealing pneumobilia; the site of the fistula; additional stones still in the gallbladder, or more importantly, in the common duct; and occasionally the location of an ectopic calculus. The diagnositic superiority of CT over abdominal plain films and sonography for gallstone ileus is now well established (Ayantunde & Agarwal, 2007; Lassandro et al, 2005; Loren et al, 1994; Reimann et al, 2004; Swift & Spencer, 1998). In fact, the clinical significance of Rigler's triad has been revitalized by CT, because all three findings are more consistantly detected (approximately 78%) by this method (Kirchmayr et al, 2005; Ayantunde & Agarwal, 2007; Chou et al, 2007).

The clinical presentation of gallstone ileus has not changed in the past 40 years. In patients with intestinal obstruction, preoperative diagnostic accuracy is approximately 75% (Glenn et al, 1981). Preoperative diagnostic accuracy has contributed to an improved outcome of therapy (Deitz et al, 1986). The increased use of CT in patients with symptoms of intestinal obstruction has led to additional improvement in the diagnostic accuracy of gallstone ileus and has resulted in a decrease in the high mortality rate encountered with this disease (Delabrousse et al, 2000; Lassandro et al, 2004; Reimann et al, 2004; Ayantunde & Agarwal, 2007; Chou et al, 2007).

The overriding consideration in patients presenting with gallstone obstruction of the intestine should be relief of the life-threatening cause of obstruction (i.e., enterolithotomy). This surgical emergency should be approached expeditiously and without a period of waiting in the hope that a suspected stone will pass; it will not. The only reason for delay should be to provide adequate preoperative fluid and electrolyte resuscitation of these critically ill patients and, if possible, to assess the presence of other gallstones in the gallbladder and common duct by means of sonography or CT. The use of nasogastric decompression and preoperative antibiotics is strongly recommended to minimize the risks of aspiration and postoperative wound infection.

The terminal ileum is the site of obstruction in 70% of cases (see Figs. 42B.2B and 42B.4B). Unless the obstructed segment is ischemic or has perforated and requires a small bowel resection, the obstructing calculus can be manipulated proximally to a healthy section of bowel, where a safe enterotomy and stone removal may be executed. Jejunal impaction, often by stones larger than 4 cm, occurs approximately 15% of the time, and enterotomy may be made at the site or just proximal to it. Duodenal obstruction, usually in the bulb, is known as *Bouveret syndrome* (Argyropoulos et al, 1979; Bhama et al, 2002; Cooper & Kucharski, 1978; Koulaouzidis & Moschos 2007; Frattaroli et al, 1997; Maglinte et al, 1987; Thomas et al, 1976), which occurs in 10% of patients and may be handled by duodenostomy or pyloroplasty. It occasionally may be possible to manipulate the stone back into the stomach and remove it via gastrotomy. Rarely, a gastroenterostomy is necessary to protect a duodenotomy or severely traumatized duodenum at the site of impaction.

Bouveret syndrome and other cases of gallstone impaction high in the jejunum have been managed successfully by a combination of endoscopy and electrohydraulic lithotripsy (Fujita et al, 1992; Holl et al, 1989; Moriai et al, 1991; Sackmann et al, 1991). We are aware of one case report of a failed endoscopic extraction that led to spontaneous uneventful passage of the stone (Wagholikar & Ibrarullah, 2004). In rare instances, the sigmoid colon is the site of obstruction of a calculus that has managed to pass through the terminal ileum or enter the colon via a cholecystocolic fistula (Anseline, 1981; Clavien et al, 1990). Almost invariably, some other pathologic process, such as diverticulitis, has produced an area of colonic narrowing. A colostomy is necessary to decompress the proximal bowel. If the impacted stone cannot be manipulated proximally to a transverse colostomy, consideration should be given to exteriorization of the impacted segment with a Hartmann closure of the bowel distal to it (Milsom & MacKeigan, 1985).

Open exploration and enterolithotomy has always been the standard surgical approach for the treatment of classical gallstone ileus. It not only allows removal of the obstructing stone but also permits careful palpation of the entire bowel and gallbladder region, to determine whether other gallstones are in transit more proximally or if any still reside in the diseased gallbladder (see Fig. 42B.2B). These calculi may be poised for passage through the fistula, possibly to induce a recurrent episode of gallstone ileus, a phenomenon estimated to occur in 5% of cases; however, by simple maneuvers, this can be prevented (Clavien et al, 1990; Haq et al, 1981; Levin & Shapiro, 1980). More recently, some authors have described laparoscopic or laparoscopic-assisted treatment for patients with gallstone ileus (Allen et al, 2003; Malvaux et al, 2002; Moberg & Montgomery, 2007; Owera et al, 2008). Because of the limited number of laparoscopically treated patients, it is unclear wherther this approach will reduce the associated high mortality and morbidity rates. Therefore it is our opinion that an open surgical approach should remain the standard of practice and that laparoscopic treatment needs further evaluation.

Considerable debate in the surgical literature surrounds whether cholecystectomy or common duct exploration or both, with dismantling and closure of the cholecystenteric fistula, should accompany enterotomy and relief of the obstruction or await a second operation (Kirchmayr et al, 2005; Muthukumarasamy et al, 2008; Zuegel et al, 1997). Historical data of published reports from the years 1953 through 1993 (Reisner &

Cohen, 1994) showed a lower mortality rate of 11.7% in the enterolithotomy-alone group compared with 16.7% for patients who underwent a one-stage operation. Several published reports indicated that operative mortality is lower in these critically ill, elderly patients when only the gallstone obstruction is relieved (Muthukumarasamy et al, 2008; Tan YM et al, 2004; Heuman et al, 1980; Kasahara et al, 1980; VanLandingham & Broders, 1982). This has lead to the general agreement that enterolithotomy alone should be done for fragile patients with significant comorbidities and that the single-stage procedure should be reserved for young, fit, and low-risk patients.

Although some centers have recently published impressively low perioperative mortality rates (0%) for surgical treatment of gallstone ileus, other centers still report rates in the traditional high range (23%; Muthukumarasamy et al, 2008; Tan et al, 2004; Ayantunde & Agarwal, 2007). In a case series from the United Kingdom (Anyantunde & Agarwal, 2007), five deaths occurred in 22 patients; four of the five deaths were patients treated with enterolithomy alone. Seven of 19 patients from YM Tan and colleagues' (2004) series were clinically unstable and underwent enterolithotomy alone; on long-term follow-up, these patients did not have further complications.

Indeed, careful follow-up of patients treated with enterolithotomy alone indicates that one third to one half will have minimal or no symptoms after relief of the gallstone ileus, and no further treatment will be necessary (Clavien et al, 1990; van Hillo et al, 1987; Tan YM et al, 2004). If a patient has jaundice and intestinal obstruction at the outset, common duct exploration, or at least tube decompression of the common duct, may also be necessary as a lifesaving procedure. For patients who continue to be symptomatic after relief of gallstone ileus, careful preoperative evaluation and bowel preparation can precede a later operation, adding to its safety.

Because common duct stones are found in 40% of patients with biliary-enteric fistula, it is likely that patients who continue to be symptomatic would require endoscopic or open surgical removal of their common duct stones in addition to cholecystectomy and repair of the fistula. As mentioned, operative mortality rate slowly declined to 15% to 25% in large reported series until the early 1970s. Further reductions in operative mortality rates have been possible by limiting treatment to enterotomy and stone removal alone without further surgical therapy in high-risk patients (Ayantunde & Agarwal, 2007; Glenn et al, 1981; Muthukumarasamy et al, 2008; Rodriguez-Sanjuan et al, 1997; Tan YM et al, 2004).

Cholecystoduodenal Fistulae

Most cholecystoduodenal fistulae do not result in gallstone ileus (see Fig. 42B.1A). Rather they are asymptomatic or occur in association with the usual digestive complaints consistent with gastric or biliary tract disease. They may be found during an upper GI barium study or under less welcome circumstances, such as at the time of abdominal surgery for an unrelated problem.

If an asymptomatic or mildly symptomatic cholecystenteric fistula is diagnosed preoperatively, many of the management decisions regarding gallstone ileus discussed previously may apply. Elective surgery may never be necessary in a completely asymptomatic individual, and surgery may present an unfavorable risk-to-benefit ratio in an elderly, minimally symptomatic patient. Along with dismantling of the fistula and common duct exploration, other alternatives to cholecystectomy must be considered, such as a period of expectant management with careful observation, endoscopic papillotomy and stone extraction with the gallbladder left in situ, or interval cholecystectomy if symptoms of pain or cholangitis persist after endoscopic biliary surgery. In a relatively healthy patient younger than 70 years, we believe that open surgical extirpation of the gallbladder, closure of the fistula, and treatment of any common duct pathology promise the best long-term therapeutic result, although some authors advocate laparoscopic treatment of preoperatively diagnosed biliary-enteric fistulae (Chikamori et al, 2001; Crouch & Kuhnke, 2000; Kwon & Inui, 2007; Lee et al, 2004; Rohatgi & Singh, 2006).

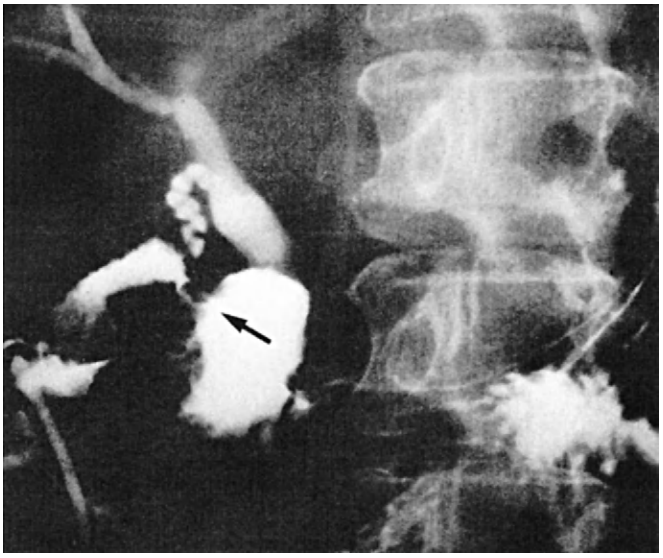


FIGURE 42B.7. Cholecystoduodenal fistula (*arrow*) shown by cholecystostomy tube cholangiogram 1 month after operation for acute cholecystitis.

If an incidental cholecystoduodenal fistula is discovered at the time of surgery, the major intraoperative decision revolves around the patient's need for, and ability to tolerate, additional surgical manipulations. If the patient is judged an unsound risk, or if the biliary tract pathology is not believed to be pertinent to the major indication for operation, nothing need be done. Rarely, a cholecystostomy (Fig. 42B.7) and extraction of large calculi can be accomplished with little additional risk. Usually, the gallbladder is shrunken and barely palpable, however, because it is stuck to the duodenum. If the patient can tolerate additional surgery, and sufficient indication exists to proceed at the present operation, rather than at a subsequent one, an attempt should be made to show the biliary-enteric anatomy and state of the common duct by an operative cholangiogram before proceeding with a definitive procedure.

Cholecystocolic Fistulae and Choleric Enteropathy

A cholecystocolonic fistula may develop acutely in patients with long-standing mild or moderately symptomatic biliary tract disease and may be heralded by a sudden change in bowel habits with multiple, loose stools and the development of fever, chills, and other signs of cholangitis from colonic bacterial reflux into the biliary tract. Many elderly patients either weather or ignore these symptoms without seeking medical attention, and some develop signs and symptoms that may incriminate the entire GI tract. Increased stool frequency persists, particularly

after ingestion of food, and bouts of fever and malaise subside. Other characteristic symptoms then appear, such as eructation, nausea, weight loss, and increasing diarrhea and steatorrhea. These latter symptoms precede the onset of choleric enteropathy, a dramatic complication of cholecystocolonic fistula. This enteropathy also is seen in other major disturbances of bile acid metabolism, such as with major ileal resection or blind loop syndrome (Brandt, 1984).

Choleric enteropathy comprises of a wide spectrum of anatomic, physiologic, and biochemical changes produced by a significant alteration of the enterohepatic circulation of bile acids. The malabsorption syndrome secondary to cholecystocolonic fistula was clinically documented first by Augur and Gracie (1970) and has since been studied by others (Rau et al, 1980). Ordinarily, 95% of bile acids are passed down the jejunum, aiding in fat and cholesterol absorption, before being largely reabsorbed in the terminal ileum as part of an efficent enterohepatic circulation. Two or three cycles of the bile acid pool per meal occur, with further metabolism of bile acids in the colon and very little lost. With a cholecystocolonic fistula, however, a large part of all of the primary bile acid pool is shunted directly into the colon, resulting in a high luminal concentration of bile acids. In the colon, the primary bile acids undergo deconjugation and dehydroxylation by fecal bacteria, and this increased concentration of bile acids causes a water secretory diarrhea.

Interestingly, only the two natural bile acids with two α-hydroxy groups, chenodeoxycholic acid and deoxycholic acid, induce colonic secretion (Keely et al, 2007). Depending on the amount of bile still passing via the common duct into the small bowel, fat absorption is affected, which over time may result in fatty acid diarrhea. More immediately, however, colonic secretion of water and electrolytes is maximally stimulated by the dihydroxy bile acids. Chenodeoxycholic acid gains access to the colon in large quantities, and massively increased amounts of deoxycholic acid are formed by bacterial dehydroxylation of cholic acid. The primary bile acids and their metabolites are no longer actively absorbed and are lost from the body, eventually causing a chronically lowered bile salt pool beyond the liver's capacity to synthesize new bile acids to replete it. At this point, even with a partial shunt to the colon, the bile acid concentration still normally passing down the common duct and through the small intestine may be too small to effect micellar solubilization of dietary fat. In contrast to a blind loop syndrome, in which bacterial overgrowth contributes to the choleric enteropathy and can be largely corrected by antibiotics, at least temporarily, cholecystocolonic fistula does not respond adequately to antibiotics. Until the fistula is dismantled, massive shunting of bile acids to the intestine persists and promotes continued watery diarrhea, diminished bile salt pool, and a variable degree of fat malabsorption.

Cholangitis seems to be a more prominent feature of cholecystocolonic fistula, when the fistula is narrow and prone to intermittent obstruction of bile flow (Edell et al, 1981; Safaie-Shirazi et al, 1973), whereas diarrhea with a lesser incidence of fever and chills is more common with a wide-open fistula (Lygidakis, 1981); we are also aware of one case report of a patient with a cholecystocolonic fistula who was seen with massive lower GI hemorrhage (Kunasani et al, 2003). In any instance, a fistula to the colon is more likely than other biliary-enteric fistulae to have associated cholangitis; if it does, the serum levels of bilirubin, alanine aminotransferase, and γ-glutamyltransferase may be slightly elevated and may direct attention to the biliary and upper digestive tract.

Because of the unusual initial complaints, full investigations for malabsorption that include upper GI studies, GI sonography, and jejunal biopsy may be undertaken but usually do not clarify the diagnosis. A pathognomonic triad consisting of pneumobilia, chronic diarrhea, and vitamin K malabsorption was recently suggested by Savvidou and colleagues (2009) to aid in the diagnosis of cholecystocolonic fistula. Diversion of bile acids into the colon results in malabsorption of fat and fat-soluble vitamins. In particular, vitamin K deficiency can be clinically significant and is easily detected by a prolonged prothrombin time (PT), and it can be corrected by parenteral supplementation (Savvidou et al, 2009). Although the condition of bile acid malabsorption can be easily diagnosed by the selenium-75-homocholic acid taurine (SeHCAT) test, this study is time consuming and is not widely available (Pattni & Walters, 2009). Plain abdominal radiographs have been reported to reveal air in the biliary tree in only 50% of cases, however, the diagnosis becomes evident only if a barium enema examination is done, preferably with air contrast, because barium (Fig. 42B.8) and air fill the gallbladder and extrahepatic bile ducts. In a recent report, a barium enema showing contrast filling of the biliary tract was used to diagnose a patient with a rare choledochocolonic fistula causing severe diarrhea (Anees et al, 2008). Failure of even a barium enema to show a cholecystocolonic fistula has been reported, but this is quite rare. In such cases, the cholecystocolic fistula is diagnosed by ERCP (Arvanitidis et al, 2004; Schoeters et al, 2002).

There is little controversy about the appropriate treatment for cholecystocolic fistulae. Except in the most extenuating circumstances, the fistulae should be dismantled because of the ever-present risk of sepsis. If the diagnosis can be made preoperatively, suitable mechanical and antibiotic bowel preparation reduces the chance of infectious complications of surgery and aids primary closure of the large bowel. Cholecystectomy and, if indicated, common duct exploration should be done at the same time. Centers with significant expertise in laparoscopic surgery have reported successful treatment of preoperatively diagnosed cholecystocolonic fistulae by this method (Chatzoulis et al, 2007; Gentileschi et al, 1995; Hida et al, 1999; Lee et al, 2004; Wang et al, 2006). Regardless of the choice of surgical treatment, preoperative ERCP with sphincterotomy and stone extraction may obviate the need to explore the CBD and, in rare cases, might result in spontaneous closure of the fistula, obviating surgery altogether (Marshall et al, 1990).

Cholecystocholedochal Fistula, Including Mirizzi Syndrome

The pathogenesis of cholecystobiliary fistula is similar to the mechanism of fistula formation between the gallbladder and other adjacent segments of the alimentary tract: the offending calculus remains impacted in the ampulla of the gallbladder or cystic duct, and the resultant inflammation causes adherence and then perforation into the adjacent structure (see Fig. 42B.1D) In 1948, Mirizzi described the clinical picture in detail and called it *functional hepatic syndrome*. It is now commonly referred to as *Mirizzi syndrome* (see Chapters 29 and 43). The mechanism of jaundice was postulated by Mirizzi to be due to spasm of the hepatic sphincter secondary to inflammation in the region of the cystic duct junction with the common hepatic duct (Mirizzi, 1948); however, extensive histologic studies have failed to disclose a "sphincter" in the common hepatic duct.

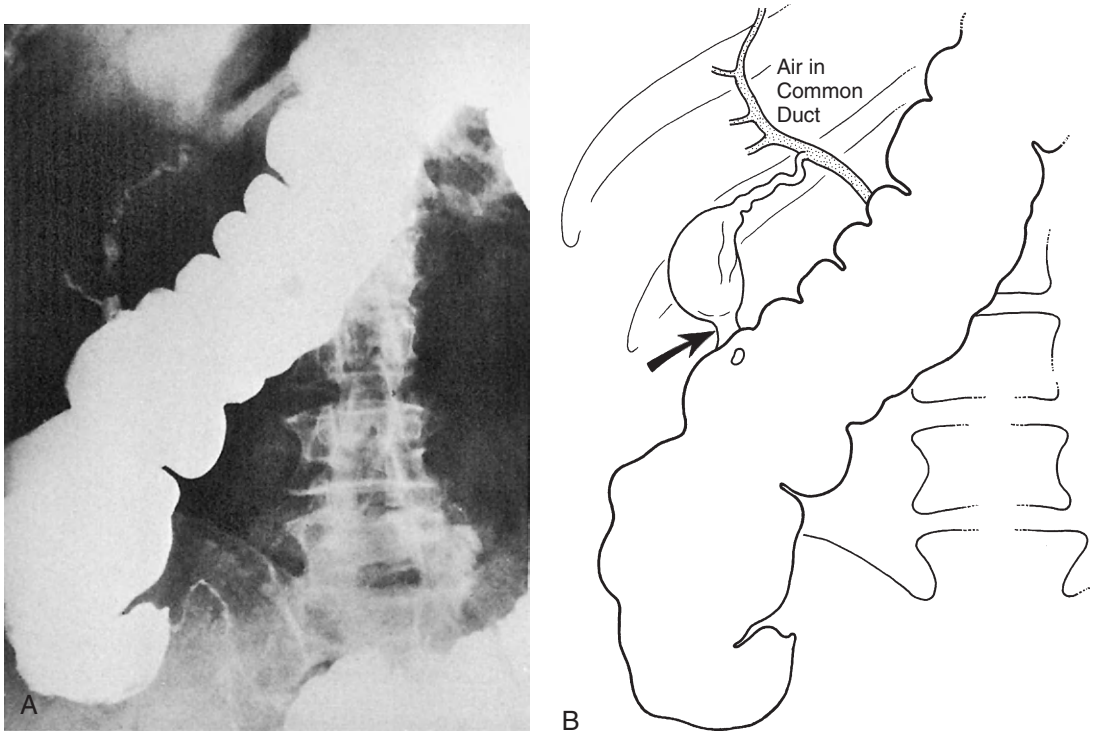


FIGURE 42B.8. **A** and **B,** Cholecystocolic fistula seen by barium enema.

The large size of the stone and the acute cholecystitis with marked pressure necrosis and inflammatory reaction at the site of stone intrusion into the common hepatic duct combine to produce jaundice with variable components of extrinsic compression and intrinsic calculous blockage of bile flow.

The early phase of this cholecystobiliary fistula presumably exists when a large gallstone is impacted in the ampulla of the gallbladder or in the intramural segment of the cystic duct, which often courses parallel to the common duct. The jaundice that occurs as a consequence of this pathologic anatomy is clinically indistinguishable from choledocholithiasis. McSherry and colleagues (1982) suggested that this classic picture (Fig. 42B.9) of Mirizzi's "functional hepatic syndrome" be subclassified as type 1. With progression of the disease, extrusion of the stone into the common hepatic duct may occur, and a fistula may form between the gallbladder and the hepatic duct. This is classified as type 2 (see Fig. 42B.1D), which is characteristically diagnosed intraoperatively by observing a gush of bile on removal of the impacted stone, indicating a biliobiliary fistula. Csendes and colleagues (1989) further subclassified type 2 patients into three categories based on the percentage of the wall of the common duct that was eroded by the offending calculus. In this subclassification, type II is a fistula involving less than one third of the circumference of the bile duct, type III involves two thirds, and type IV is a fistula with complete bile duct destruction. This classification scheme was recently updated to include a type V, which describes cholecystoenteric fistula, with or without gallstone ileus, coexisting with any of the other types (Csendes et al, 2007).

The large and solitary nature of the ampullary and cystic duct stones may be a hint to the preoperative diagnosis. The classic findings on ultrasonography include dilation of the biliary system that includes the common hepatic duct above the gallbladder neck, a stone impacted in the gallbladder, and an abrupt change in the caliber of the common duct below the stone (Hayek et al, 1988). Because most of these patients present with jaundice or some abnormalities on LFTs, a preoperative ERCP or PTC frequently is performed. These imaging studies permit a precise delineation of the condition, markedly altering surgical strategy. Cornud and others (1981) showed the appearance of biliobiliary fistulae at PTC, whereas Heil and Belohlavek (1978) relied on ERCP. In the six patients documented by McSherry and colleagues (1982), PTC and ERCP were equally effective in elucidating the cause of common duct obstruction. Although MRCP has been shown to diagnose Mirizzi syndrome preoperatively, it is limited, because it rarely shows the fistula and does not afford therapeutic stenting (Rappeport, 2002).

Biliobiliary fistulae have been referred to as a "trap" in the surgery of cholelithiasis (Corlette & Bismuth, 1975). This term is appropriate, because the presence of such a fistula frequently is not recognized until the time of surgery, often not soon enough to prevent injury to the common duct in an attempt to dissect the ampulla of the gallbladder or the cystic duct. Lygidakis (1981) emphasized the technical problems in operating on these patients. Other authors (Baer et al, 1990; Dewar et al, 1990, 1991; Yip et al, 1992) emphasized the importance of preoperative direct cholangiography. In patients with jaundice, biliary drainage may be necessary in the preoperative management.

If a large adherent mass about the gallbladder and CBD is encountered at surgery, operative cholangiography, although difficult, may delineate the presence of true choledocholithiasis or of the impacted stone without fistula (Mirizzi type 1) or the biliary fistula itself (Mirizzi type 2). In any event, it is unwise to attempt complete cholecystectomy; it is much better to

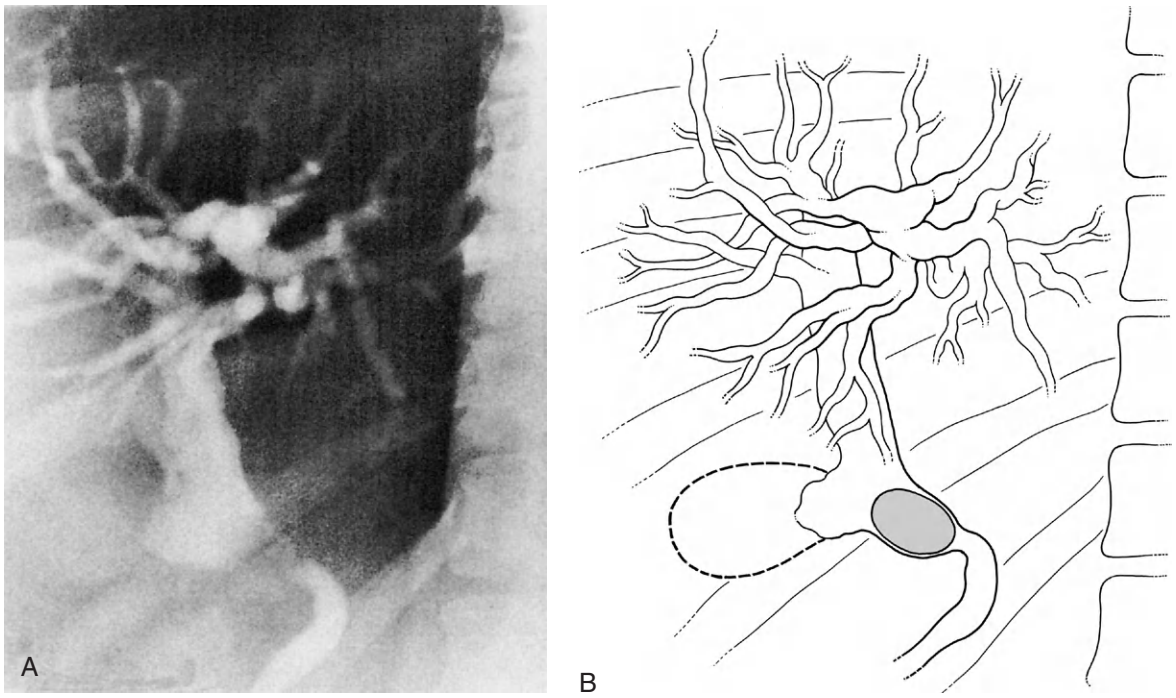


FIGURE 42B.9. **A** and **B,** Mirizzi syndrome type 1 (without cholecystocholedochal fistula). Percutaneous transluminal cholangiography shows an impacted cystic stone with extrinsic compression of the proximal hepatic ducts.

open the gallbladder, remove the stones, and directly assess the presence or absence of a fistula. A portion of the gallbladder wall is sent for frozen section histology to exclude concomitant malignancy, but choledochotomy is seldom necessary, because multiple stones are infrequent in this disease. For Mirizzi type 2 disease, direct choledochotomy may be done, but the obstructing stone usually can be removed via the opened gallbladder. The gallbladder may be dissected 1 to 2 cm proximal to the fistula, between the ampulla and the common hepatic duct, at which point it is transected and sutured closed. T-tube drainage of the common duct may be achieved through the longitudinal choledochotomy, but this is often unnecessary. Alternatively, the opened gallbladder may be anastomosed to the duodenum as described by Hadjis and colleagues (1987) and later advocated by Baer and others (1990) and Mishra and others (1990). Stenosis of the biliary tree often resolves spontaneously in the postoperative period, and choledochotomy is seldom indicated.

Since the introduction of laparoscopic approaches to surgery of the gallbladder and the bile ducts, several cases and small series of laparoscopic treatment of Mirizzi syndrome have been reported (Bagia et al, 2001; Binnie et al, 1992; Chowbey et al, 2000; Paul et al, 1992; Rust et al, 1991; Schafer et al, 2003; Silecchia et al, 1995; Vezakis et al, 2000; Yeh et al, 2003; Rohatgi & Singh, 2006; Kwon & Inui, 2007). To address the utility of laparoscopic treatment of Mirizzi syndrome, Antoniou and colleagues (2010) recently conducted a comprehensive systematic review of the literature on this topic, a query confined to the English and German literature. Because of the strict study criteria, the authors identified only 10 of 66 articles for comparison in the years between 1989 and 2008. The total number of patients treated by laparoscopy was 124, of which 73 (59%) were sucessfully completeted. Conversion to open operation was necessary in 51 (41%) patients. Interestingly, patients from studies reporting a high preoperative diagnosis rate (>80%) had a significantly lower risk for conversion. The main reasons for conversion included technical failure as a result of dense adhesions in the triangle of Calot, unclear anatomy, and unsuccessful stone retrieval. The analysis showed a complication rate of 16%, with residual stones and bile duct injury the most common complications. The authors concluded, and we agree, that laparoscopic treatment of Mirizzi syndome cannot be recommended as a standard procedure because of the high failure rate (Antoniou et al, 2010).

Paul and others (1992) described successful laparoscopic treatment of Mirizzi syndrome by adhering to a luminal approach to the problem, as advocated by Dewar and associates (1991). This approach includes preoperative ERCP and placement of a biliary stent, followed by use of a flexible choledochoscope introduced into the cystic duct high from the open neck of the gallbladder. Stone extraction from the dilated cystic duct via the choledochoscope may avoid carrying the dissection too far down and injuring the common duct. Although such successful laparoscopic approaches to Mirizzi syndrome have been reported, we believe an open approach should be used when the diagnosis is made preoperatively, or a procedure should be converted to open when encountered during laparoscopy. Open technique affords the use of tactile senses, allowing easier removal of the impacted stone and sampling of the gallbladder wall to exclude a coexisting carcinoma (see Chapter 49); an open approach also minimizes the risk of bile duct injury.

Proximal Choledochoduodenal Fistulae Secondary to Peptic Ulcer Disease

Patients with proximal choledochoduodenal fistulae secondary to peptic ulcer disease may be asymptomatic, or they may present with GI complaints suggesting peptic ulcer (see Fig. 42B.1E). Biliary tract symptoms are usually absent, and these

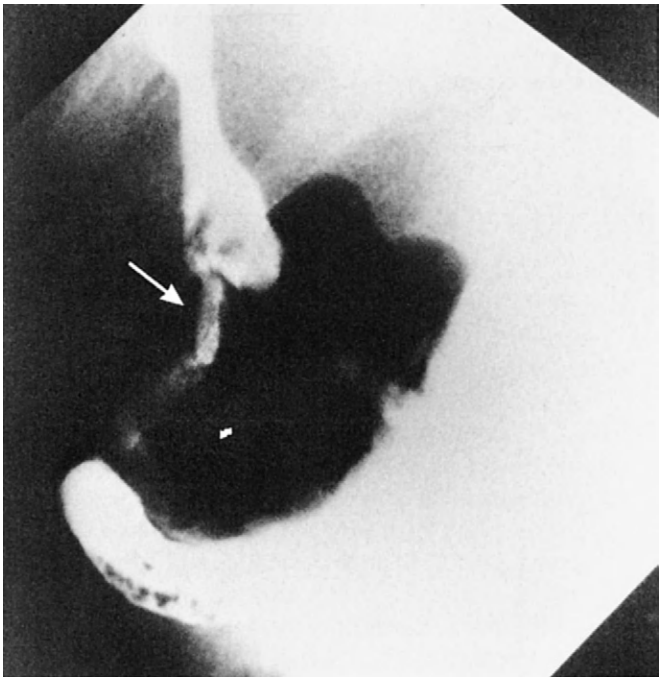


FIGURE 42B.10. Choledochoduodenal fistula secondary to gallstone disease shown by endoscopic retrograde cholangiopancreatography.

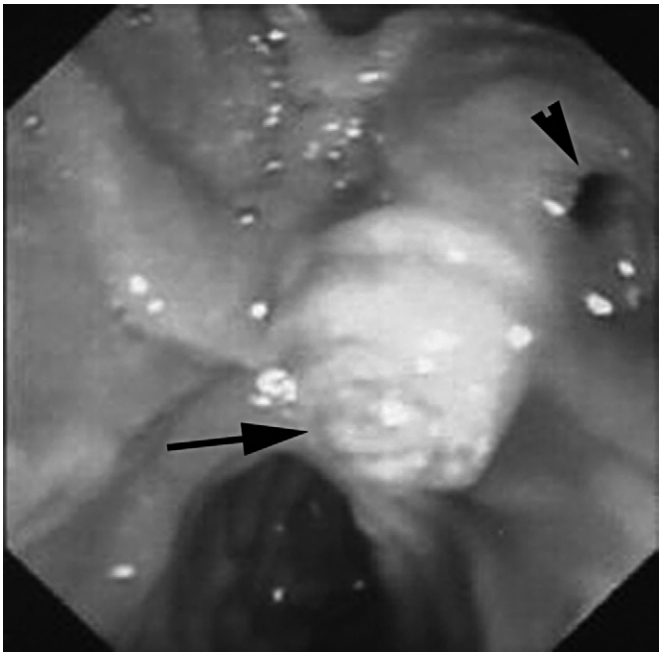


FIGURE 42B.11. Duodenoscopy showing the papilla of Vater (*arrow*) and a distal or peripapillary choledochoduodenal fistula (*arrowhead*). *(Courtesy Dr. Melih Karincaglu.)*

patients generally do not have associated cholelithiasis. In rare instances, cholangitis, jaundice, or abnormal LFTs are part of the clinical picture and indicate concomitant biliary tract infection and obstruction. The diagnosis may be suggested by pneumobilia in 15% to 60% of patients. More often, the diagnosis is made as contrast material from a barium meal refluxes up the common duct to outline a normal-sized, functioning gallbladder. Endoscopy with direct visualization of the ulcer and fistula and ERCP are the best studies to confirm the diagnosis and evaluate the extent of disease (Fig. 42B.10).

Given the paucity of reported experiences with choledochoduodenal fistula (Kourias & Chouliaras, 1964) and longstanding differences of opinion about the correct approach to peptic ulcer disease, it is not surprising that, until recently, treatment recommendations have been controversial. Excellent discussions of the natural history, clinical presentation, and management of these fistulae have been reported by Constant and Turcotte (1968), Feller and colleagues (1980), and Sarr and colleagues (1981). Most authors now agree that treatment should be directed at the ulcer diathesis and not at the biliary tract or the fistula itself. Medical management with proton-pump inhibitors and therapy for *Helicobacter pylori* is often sufficient to control the ulcer disease and even bring closure of the fistula.

More recent high success rates of medical management for peptic ulcer disease have resulted in a drastic reduction in the number of case reports of patients with proximal choledochoduodenal fistulae compared with years before 1990 (H'ng & Yim, 2003; Jaballah et al, 2001; Wong et al, 2004). Although choledochoduodenal fistula as a result of peptic ulcer is now extremely rare, clinicians should remain aware of this clinical entity, especially in symptomatic patients with refactory peptic ulcer disease. In such patients, surgery is indicated to prevent major complications such as hemorrhage and death (La Greca et al, 2008). Otherwise, surgery is not generally indicated for severe ulcer disease, except in the presence of uncontrollable hemorrhage, free perforation, obstruction, or intractability.

Many types of ulcer operations have been performed successfully; however, if technically possible, an exclusion type of gastric resection or duodenal bypass procedure, such as a Billroth II gastrectomy or gastroenterostomy, should be performed in addition to a vagotomy. There is no need to close the fistula, and doing so may injure the duodenum or bile duct. Cholecystectomy and biliary enteric reconstruction may be done, but these are reserved in cases of biliary stricture; such patients are younger and healthier than patients with biliary-enteric fistulae secondary to calculous biliary tract disease, and the results of medical and surgical treatment are usually good.

Distal Parapapillary Choledochoduodenal Fistula

Whether caused by spontaneous gallstone erosion or by iatrogenic damage to the distal common duct, parapapillary fistulae have a clinical presentation similar to that of other advanced calculous biliary tract diseases. In the series reported by Tanaka and Ikeda (1983), the following observations were made: a history of biliary symptoms longer than 10 years' duration in 46%; pain and/or jaundice in 88% and 69%, respectively; prior biliary surgery in 54%; air or barium in the biliary tree in 41%; cholelithiasis in 71%; and choledocholithiasis in 38%. The anatomic diagnosis rests on meticulous endoscopic observation and expertise in the technique of ERCP (Fig. 42B.11; see Fig. 42B.1F). In Japan, the incidence of primary intrahepatic stone disease is reported to be 17% to 30% (Tanaka & Ikeda, 1983; see Chapter 39). Particularly in Japanese patients with parapapillary fistulae, careful and complete evaluation of the intrahepatic ductal system is important.

The management of these biliary fistulae is still evolving, and a variety of endoscopic techniques have been advocated

(Osnes & Kahrs, 1977; Ramsey et al, 1992; Schapira & Khawaja, 1982; Urakami & Kishi, 1978; Van Linda & Rosson, 1984). These techniques involve using endoscopic sphincterotomy to widen the choledochal fistula enough to permit free drainage or to create a common channel between the fistula and natural ampullary orifice. When necessary, open surgical procedures, such as hepaticodochojejunostomy, have been used (Hunt & Blumgart, 1980).

Fistula to the Hepatic Veins or Portal Veins

Biliary-venous fistula is a rare occurrence that results in bilhemia, a condition that can be dangerous (see Chapter 105), and such a fistula can also be associated with interventional transhepatic maneuvers. When a large caliber intrahepatic bile duct is transected, the creation of a transjugular intrahepatic portosystemic stent-shunt (TIPSS) may be complicated by a biliary-venous fistula. The resulting biliary leak plays an important role in the stenosis and occlusion of the portosystemic shunt (Jalan et al, 1996).

EXTERNAL BILIARY FISTULAE

Most clinically significant external biliary fistulae follow some type of surgical procedure on or in the neighborhood of the biliary system. Causes of external biliary fistulae include invasive radiologic procedures, cholecystostomy, cholecystectomy (with or without common duct exploration), liver surgery or injury, intentionally created surgical biliary-intestinal anastomosis, and other abdominal operations. The persistent biliary drainage is the result of some unrecognized disease affecting the bile ducts, a complication of the surgical procedure, or, more importantly, the result of a surgical error. Bile duct injuries and fistulae are always significant, because they can be associated with considerable morbidity or mortality.

Etiology and Prevention

External biliary fistulae are best considered according to the type of previous intervention performed. The following are the more commonly associated surgical antecedents of fistulae.

Fistulae After Cholecystostomy

The first open cholecystotomy was done by Bobbs in 1867 (Sparkman, 1967), but open cholecystostomy is infrequently performed today. Historically, the procedure was used in high-risk patients with acute cholecystitis. In selected cases, cholecystostomy also was used as the first step of a two-stage operation for obstructive jaundice secondary to malignancy (see Chapter 62). Percutaneous cholecystostomy, a less invasive procedure that requires only local anesthesia, is currently the procedure of choice in high-risk elderly patients (Byrne et al, 2003; Ito et al, 2004; Winbladh et al, 2009). Percutaneous placement of a catheter into the lumen of the gallbladder can be performed and can even be done under US guidance at the bedside of critically ill patients (see Chapters 28 and 32). A persistent fistula denotes distal biliary obstruction (e.g., a retained gallstone lodged within a Hartmann pouch).

Biliary Fistulae After Invasive Radiologic Procedures

Biliary leak and fistulae may follow any invasive radiologic procedure involving the hepatobiliary system. Usually these are due to distal biliary tract obstruction, a result of either a retained bile duct stone or an unrecognized malignancy (Fig. 42B.12). Published rates for biliary leak after interventional radiologic procedures vary significantly and depend on patient selection and individual practitioner experience. Complications result from suboptimal puncture location, incorrect selection of biliary catheter size, and inadequate postprocedural tube care (Winick et al, 2001). Burke and colleagues (2003) classified bile leakage, sepsis, and infected biloma as major complications that occur at rates of 2% after PTC and biliary drainage procedures (see Fig. 42B.5). The risk of an internal fistula after radiologic intervention resulting in bilhemia was referred to earlier.

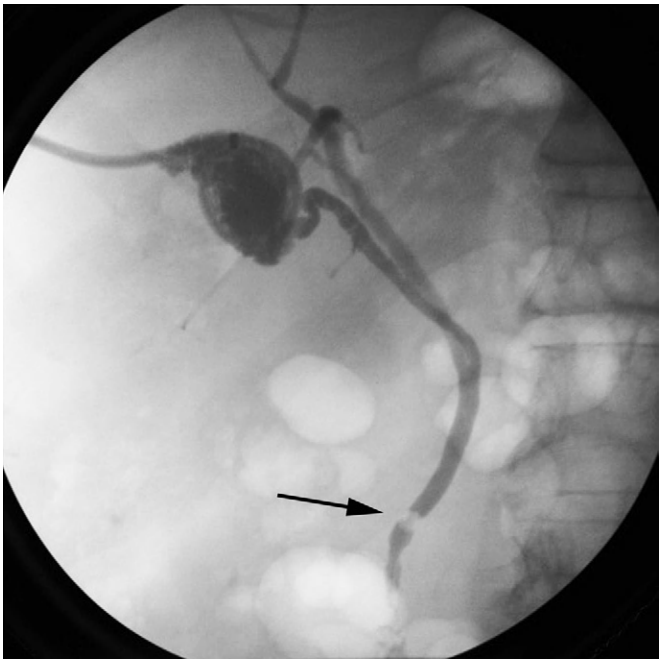


FIGURE 42B.12. An 85-year-old man with severe cardiomyopathy (unfit for surgery) was treated by percutaneous cholecystostomy tube drainage. Six weeks after tube insertion, a cholecystogram shows a retained gallstone impacted in the distal common bile duct (*arrow*). The patient was treated definitively by endoscopic retrograde cholangiopancreatography and papillotomy.

Fistulae After Abdominal Operations

LAPAROSCOPIC CHOLECYSTECTOMY. Laparoscopic cholecystectomy is currently the standard procedure for symptomatic cholelithiasis and for all forms of cholecystitis, including acute cholecystitis, and it is performed even in instances of gangrenous cholecystitis (Kiviluoto et al, 1998; Gharaibeh et al, 2002; Borzellino et al, 2008). However, laparoscopic cholecystectomy is associated with an increased incidence of bile duct injuries, including fistulae, which are reported in 1.3% to 5.5% of cases (see Chapter 34; Adamsen et al, 1997; Kum et al, 1996). Under these difficult circumstances, the procedure should be performed, or at least supervised, by an experienced surgeon. A high conversion rate of 40% in instances of gangrenous cholecystitis should be expected (Eldar et al, 1998; Gharaibeh et al, 2002; Borzellino et al, 2008).

As mentioned previously, the operative treatment of Mirizzi syndrome now includes a laparoscopic option. In accordance with others, however, we believe that when the presence of Mirizzi syndrome, particularly type 2, is suspected or realized,

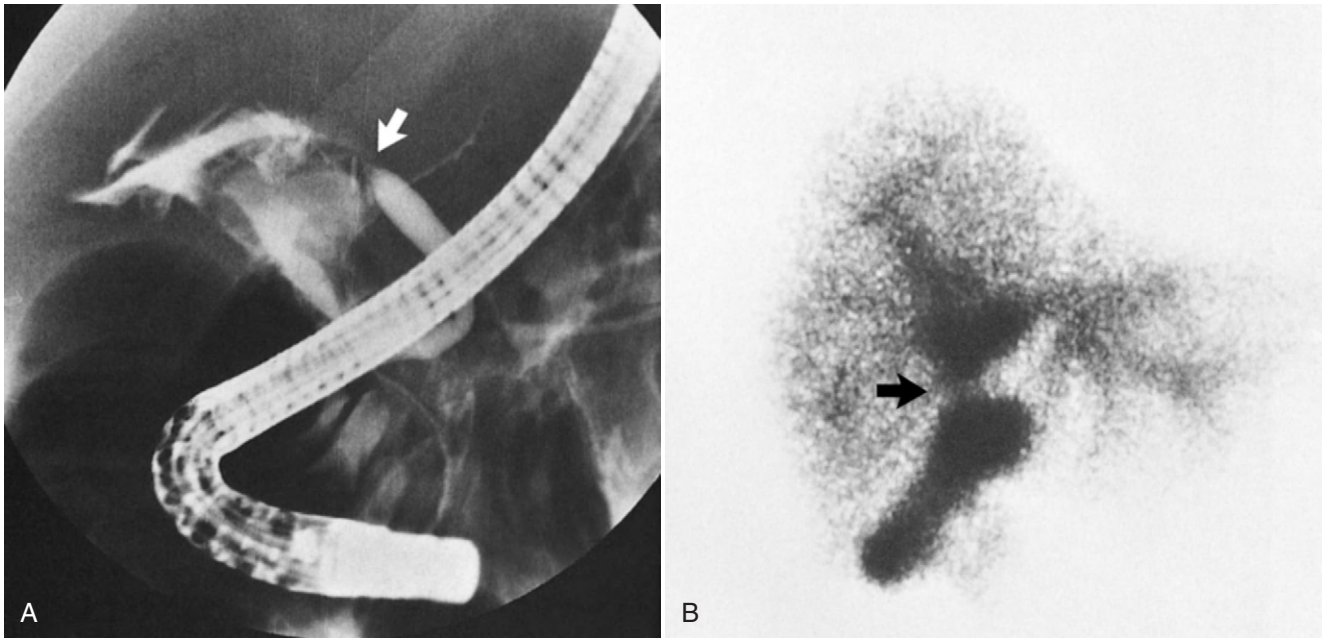


FIGURE 42B.13. Injury to the bile duct at laparoscopic cholecystectomy. The common bile duct was misidentified for the cystic duct, resulting in transection of the common bile duct between the clips. **A,** Endoscopic retrograde cholangiopancreatography shows a transected bile duct at the level of a clip (*arrow*) with extravasation of contrast material. **B,** Hepatobiliary iminodiacetic acid scan shows a total uncontrolled fistula originating from the proximal cut end of the choledochus (*arrow*).

safety demands that the laparoscopic procedure be converted to open laparotomy (Moser et al, 1993; Yeh et al, 2003; Antoniou et al, 2010).

Small amounts of bile leakage may occur occasionally in the immediate postoperative period after inadvertent damage to a subvesical duct (Viikari, 1960), which is present in normal subjects in 20% to 50% of cases (Kune & Sali, 1980). Removal of an intrahepatic gallbladder also may cause damage to tiny bile ducts in the liver around the gallbladder fossa.

Biliary fistula after laparoscopic cholecystectomy may occur as a result of injury to the extrahepatic biliary tree, or it may originate from the cystic duct stump. A leak from the cystic duct stump may occur from burn injury, from pressure necrosis of a metal clip, or in most instances from distal bile duct obstruction caused by a retained stone, resulting in a buildup of pressure and a resultant blowout of the cystic stump. It is important to differentiate patients at risk of having choledocholithiasis. Patients having deranged LFTs or dilated bile ducts on US should undergo imaging of the biliary tree before cholecystectomy. Sphincterotomy and stone extraction should be performed if choledocholithiasis is established.

Most ductal injuries are not recognized during the initial laparoscopic cholecystectomy (Lillemoe et al, 1997) or in the immediate postoperative period, mainly because drains usually are not left in the abdomen, and the patient typically leaves the hospital within 24 hours. The resulting uncontrolled biliary fistula becomes evident within days or sometimes weeks after the operation, with the clinical presentation of abdominal pain, fever, jaundice, and the demonstration of an intraabdominal fluid collection that produces bile on puncture.

Compared with open cholecystectomy, laparoscopic cholecystectomy is associated with an increased rate of bile duct injury (see Chapter 42A; Davidoff et al, 1992; Waage & Nilsson, 2006). Such injuries are common to most reported series of laparoscopic cholecystectomy and may reach an incidence of 0.9%. Reviews by Strasberg and colleagues (2001) and Vecchio and colleagues (1998) that encompass more than 100,000 patients found the incidence of major bile duct injury to be around 0.5%, and this incidence has reached a "steady state" (Walsh et al, 1998; Wherry et al, 1996; Waage & Nilsson, 2006). A large retrospective cohort analysis of nearly 1.6 million Medicare patients in the United States undergoing laparoscopic cholecystectomy from 1992 through 1999 confirmed the incidence rate of bile duct injury at 0.5% (Flum et al, 2003), and a Swedish population-based study of more than 150,000 patients showed a similar bile duct injury rate of 0.4% (Waage & Nilsson, 2006).

The mechanisms resulting in bile duct injuries are now well recognized (see Chapter 42A). The most common injury is caused by misidentification of the common duct for the cystic duct, resulting in complete transection of the common duct, often with some portion of the biliary tree (Fig. 42B.13). A traction injury results from inadvertent lateral traction of the gallbladder and "tenting" of the cystic duct–common duct junction. In this instance, the clip intended for the cystic duct may occlude the CBD, or a portion of the CBD may be removed between clips. An unrecognized anomalous biliary system—in particular, a cystic duct that empties directly into the right hepatic duct or a low-entry right hepatic sectoral duct—may result in similar damage (Fig. 42B.14; see Chapters 1B and 42A; Davidoff et al, 1992; Lillemoe et al, 1997). Other, less common mechanisms include thermal injury resulting from excessive use of the cautery or laser and the application of excessive clips to control bleeding in the triangle of Calot.

The role of operative cholangiography (see Chapter 21) in the prevention of bile duct injuries remains controversial despite two large, population-based studies demonstrating a protective effect (Flum et al, 2003; Waage & Nilsson, 2006).

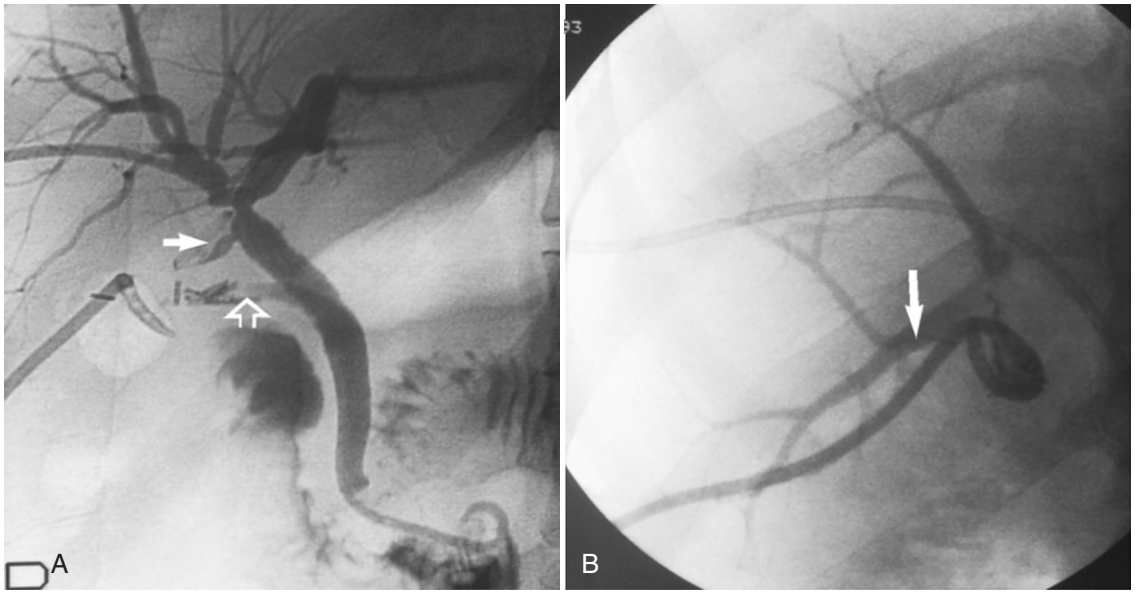


FIGURE 42B.14. Injury to a right sectoral hepatic duct at laparoscopic cholecystectomy. **A,** Percutaneous transluminal cholangiography. Note the remnant of the duct draining into the common bile duct (*solid arrow*) and cystic stump (*open arrow*). Note the low entry of this duct into the common bile duct. **B,** Tube fistulography. The biliary ductal system of the cut sectoral duct is outlined.

Intraoperative cholangiography (IOC) may supply information regarding the presence of unsuspected choledocholithiasis and unexpected anomalous anatomy, and its routine use is recommended by several authors (Fletcher et al, 1999; Flum et al, 2003; Kohn et al, 2004; Stuart et al, 1998; Waage & Nilsson, 2006). The use of IOC has not increased; in reports of laparoscopic cholecystectomy in the United States, IOC was performed in about 40% of cases (Flum et al, 2003; MacFadyen et al, 1998). In a population-based study by Flum and colleagues (2003), the rate of bile duct injury was found to be significantly higher when IOC was not used (0.39% vs. 0.58%). The more recent study by Waage and Nilsson (2006) showed that IOC reduced the risk of bile duct injury by 37%.

Before these reports, evidence that IOC prevented major bile duct injury did not exist (Wright & Wellwood, 1998). In a national survey of American surgeons performing laparoscopic cholecystectomy, Archer and colleagues (2001) found that IOC was helpful for intraoperative detection of bile duct injury. Interestingly, of the 1600 surgeons surveyed in the United States, one third had experienced this complication. A single institutional study by Kohn and associates (2004) examined the use of routine versus selective cholangiography among surgeons performing laparoscopic cholecystectomy. This study found that surgeons performing selective cholangiography were less likely to attempt IOC, even if indications arose resulting in significantly worse adverse events. Regardless of surgeon preference for routine or selective IOC, we recommend a low threshold for early conversion to laparotomy, if the ductal anatomy remains unclear or for any other concern. IOC remains the gold standard to define biliary anatomy, but it cannot prevent all bile duct injuries; and in some rare cases, it may even be the cause.

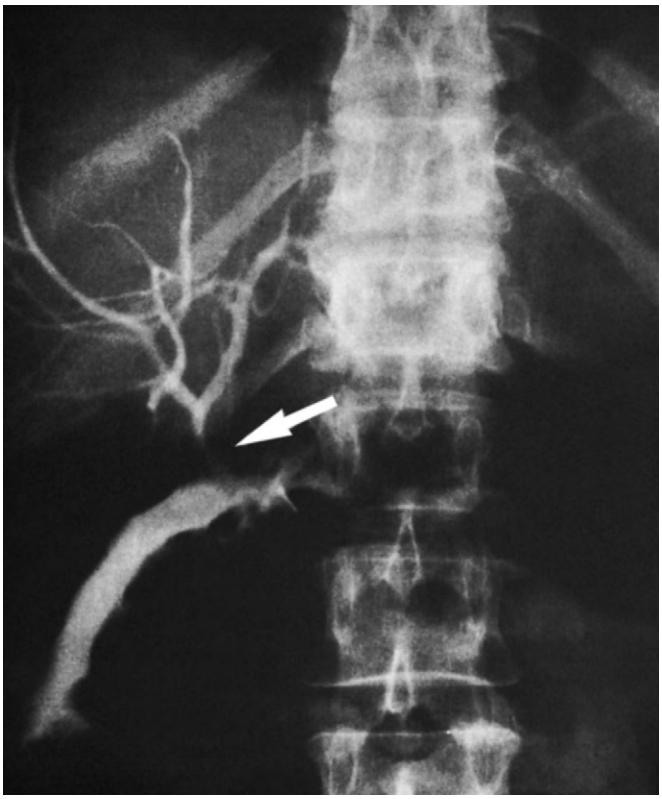


FIGURE 42B.15. Postcholecystectomy fistulography. Biliary fistula caused by accidental transection of the common hepatic duct (*arrow*), the most common cause of a persistent external biliary fistula.

OPEN CHOLECYSTECTOMY. The occurrence of unexpected biliary fistulae after cholecystectomy almost always indicates operative injury to a major bile duct. Such fistulae may arise from damage to the CBD (Fig. 42B.15) or to an anomalous sectoral right hepatic duct (see Chapter 42A). A 0.21% incidence of bile duct injuries was found in a study of 42,474 patients who underwent an open cholecystectomy (Roslyn et al, 1993). Bile duct injury is recognized at the time of cholecystectomy in only a few patients; in approximately 25% to 40% of

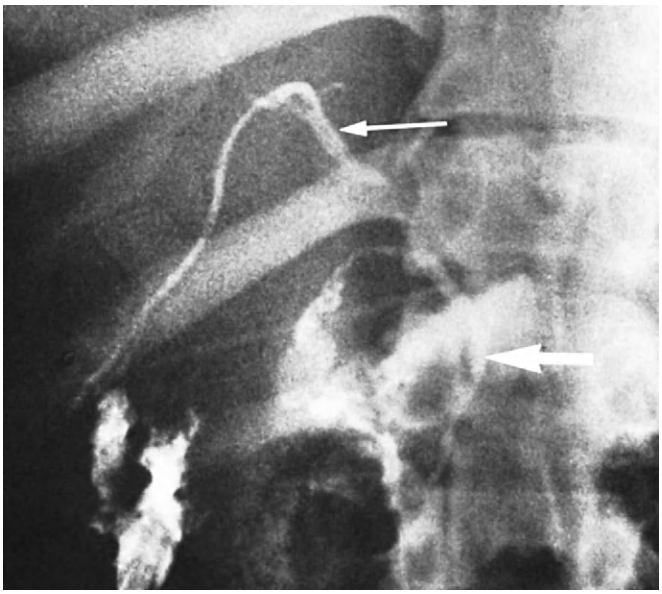


FIGURE 42B.16. Postcholecystectomy fistulography outlining large irregular cavity (*thick arrow*) and connecting with a faintly outlined, but apparently normal, biliary ductal system (*thin arrow*).

patients with unrecognized bile duct injury, the injury becomes apparent only when the presence of a biliary fistula is recognized (Andren-Sandberg et al, 1985a, 1985b). In the remaining patients, the injury is recognized only later, when a biliary stricture develops (Blumgart et al, 1984). The recognition of biliary ductal anomalies and prevention of biliary injury at cholecystectomy are discussed in detail in Chapters 1B and 42A. Inadequately ligated or sloughed ligatures on the cystic duct are rarely responsible for biliary fistulae, and for this reason, transfixion suturing of the cystic stump is recommended. However, the presence of an unrecognized significant distal obstruction may be followed by a blowout of the cystic duct stump, resulting in a biliary fistula or bile peritonitis.

Cholecystectomy is sometimes performed under difficult circumstances, as in the presence of a gangrenous gallbladder associated with fibrosis and inflammation in the region of the triangle of Calot. In these instances, proper identification and transfixion of the cystic stump may not be possible, and the patient is left with a temporary biliary fistula (Fig. 42B.16). As described previously, type 2 Mirizzi syndrome may pose significant technical difficulties, and specific surgical techniques have been devised to deal with this situation (Baer et al, 1990).

If a defect in the bile duct is found during operation, and if immediate repair is impossible, it may be better to end the procedure with adequate drainage, expecting a future controlled fistula. In all these difficult instances in which a biliary fistula is anticipated, it is important to ensure controlled and adequate drainage of bile and to exclude the presence of a distal obstruction to biliary-enteric bile flow. Under these circumstances, most fistulae close spontaneously after conservative treatment.

COMMON DUCT EXPLORATION. The classic open common duct exploration is now less frequently performed, having been replaced by laparoscopic and endoscopic techniques (see Chapter 35; Csendes et al, 1998). Whether it occurs after open or laparoscopic exploration of the CBD or persists after removal of a T-tube, a biliary fistula is almost always due to a residual



FIGURE 42B.17. Postcholecystectomy T-tube cholangiography shows a retained stone obstructing the distal bile duct (*arrow*). The stone was removed 6 weeks after surgery via instrumental basket extraction through the T-tube tract, preventing a persistent external biliary fistula.

common duct gallstone (Fig. 42B.17). It is essential to perform cholangiography and rule out the presence of retained stones before removal of a T-tube or biliary stent.

Less commonly, an overlooked malignant distal obstruction is the causative factor (Fig. 42B.18). In addition, the passage of metal bougies through the papilla during common duct exploration may result in the creation of false tract, which may result in a choledochoduodenal fistula and may cause jaundice, ascending cholangitis, and acute or chronic recurrent pancreatitis. Treatment may be by endoscopic papillotomy or sphincterotomy, joining the fistulous orifice with the papillary opening (Chung & Roberts-Thomson, 2000; Jorge et al, 1991; Karincaoglu et al, 2003b), but a surgical approach may be necessary (Hunt & Blumgart, 1980).

BILIARY-INTESTINAL ANASTOMOSIS. A major biliary fistula after biliary-intestinal anastomosis occasionally occurs, although this is uncommon. Anastomoses created well below the hilus, such as choledochoduodenostomy or choledochojejunostomy, are rarely associated with fistulae (Parrilla et al, 1991), whereas a biliary fistula after hepaticojejunostomy is more common, with a reported incidence of 0.4% to 8% (de Castro et al, 2005). When fistulae do occur, a technical error must be suspected, such as suture line disruption or failure to incorporate a significant bile duct within the anastomosis. Failure of the surgeon to appreciate ductal anatomy is particularly likely to occur in the hilar region, where the mode of confluence of the right and left ducts and caudate lobe ducts is extremely variable (see Chapter 1B). In these instances, the fistula becomes evident immediately after surgery. Meticulous technique with

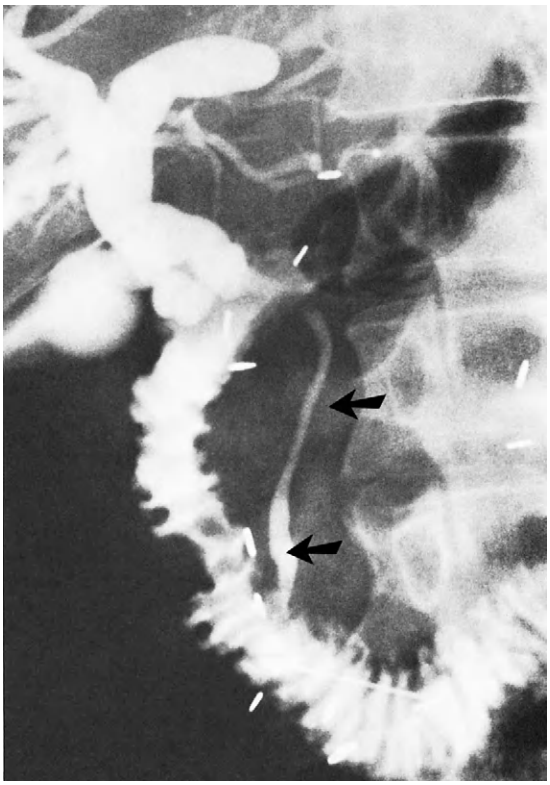


FIGURE 42B.18. Postcholecystectomy fistulography shows the external biliary fistula, which was caused by an extrinsic compression of the pancreatic portion of the bile duct (*arrows*). At reoperation, choledochal compression was shown to be due to cancer of the head of the pancreas.

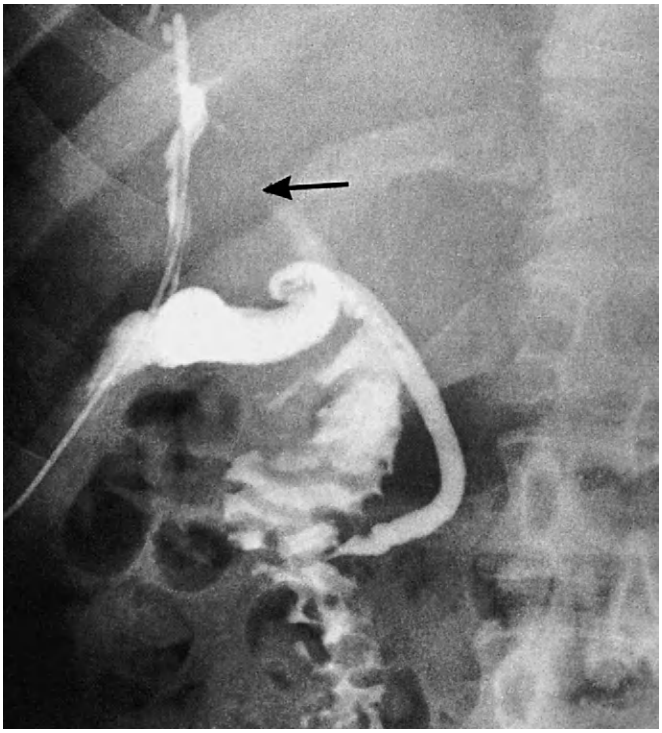


FIGURE 42B.19. External biliary fistula after blunt injury to the right lobe of the liver and subsequent drainage of a large right intrahepatic hematoma. The injury was associated with damage to the right hepatic duct and a subsequent intrahepatic stricture (*arrow*). After external drainage, a high-output biliary fistula developed. The tubogram illustrated was obtained after anastomosis of the fistulous tract issuing from the liver to the adjacent mobilized gallbladder. The cavity within the liver has collapsed, and the gallbladder fills and subsequently outlines the common bile duct. The tube was removed, and postoperative recovery was uneventful. The patient remained symptom free and with normal liver function test results 5 years after surgery. *(From Smith EE, et al, 1982: The management of post-traumatic intrahepatic cutaneous biliary fistulas. Br J Surg 69:317-318.)*

mucosa-to-mucosa anastomosis (see Chapter 29) prevents most such leaks. Alternatively, suture line disruption also may be caused by local factors, such as abscess or ischemic necrosis of the bile duct or bowel wall, and such fistulae may become evident days after surgery. It is important to ascertain whether the fistula is purely biliary or whether it also contains duodenal or pancreatic juice or both.

Fistula After Liver Injury, Liver Resection, and Liver Transplantation

LIVER INJURY. Liver injury (see Chapter 102) may be followed by the formation of biliary fistulae. Such fistulae may occur in association with damage to the liver (Fig. 42B.19) and the bile ducts or may follow sequestration and infection of areas of liver necrosis. Blunt or penetrating grade III or IV liver trauma may be complicated by bile collections and biliary fistulae in 0.5% to 14% of patients (Glaser et al, 1994; Goldman et al, 2003; Gourgiotis et al, 2007; Shahrudin & Noori, 1997; Vassiliu et al, 2004; Wahl et al, 2005). Emergency partial hepatectomy for major liver trauma may result in injury to the bile ducts at the confluence with an early biliary leak and, later, a biliary stricture (Bismuth et al, 1986). Complete transection of the CBD requires immediate hepaticojejunostomy, whereas lacerations of the main biliary channel may be sutured after placement of a T-tube.

Although nonoperative management of blunt liver injury is now firmly established as standard therapy for hemodynamically stable patients (Malhotra et al, 2000; Pachter & Hofstetter, 1995; Christmas et al, 2005), caution should be exercised, because this approach can be hazardous sometimes and demands close observation to avoid delayed surgical treatment of potentially fatal complications (Goldman et al, 2003). Most posttraumatic biliary fistulae can be expected to heal spontaneously (Vassiliu et al, 2004); however, in a case series of 32 patients treated nonoperatively, Carrillo and colleagues (1999) found severe biliary complications in up to 85% of patients with a liver abbreviated injury score (AIS) of grade IV or higher. A study specifically examining the diagnosis and management of bile leaks after liver injury by Wahl and colleagues (2005) confirmed that patients with liver injuries higher than grade IV are more likely to develop bile leaks, especially if treated by arterial embolization. These authors proposed a treatment algorithm for blunt liver injury associated with a bile leak, which includes laparoscopic washout for a diffuse leak. Laparoscopic evacuation and lavage as a new treatment option for bile collections has also been advocated by others to prevent the inflammatory sequelae of bile peritonitis (Franklin et al, 2007). Persistent biliary fistulae may occur from a segment of the liver isolated by the injury. Management of this situation is difficult, particularly when the fistula is associated with a distal stricture. Rarely, the fistula can be identified at operation and oversewn. Alternatively, a well-developed fibrous fistulous tract

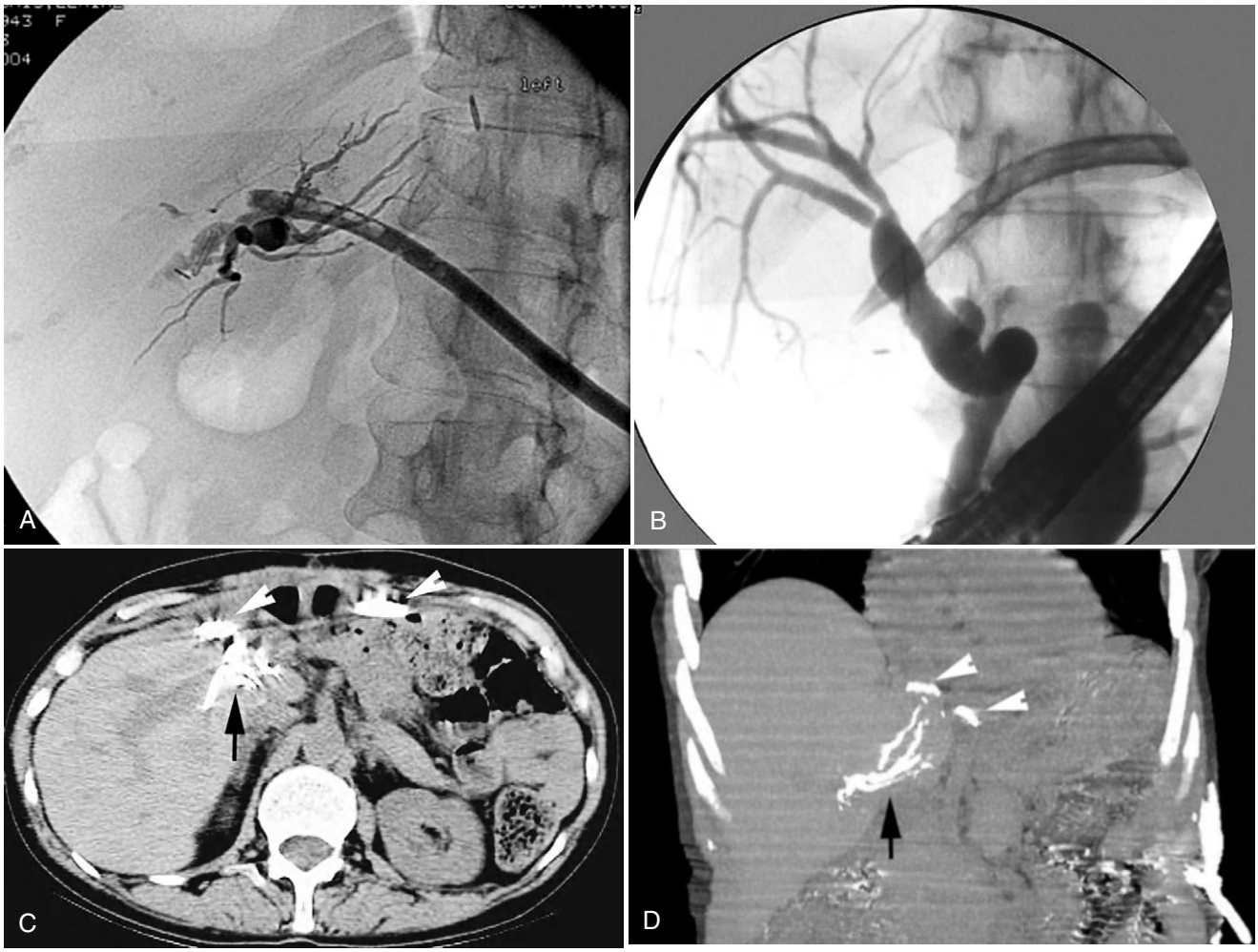


FIGURE 42B.20. A 61-year-old woman with isolated metastatic ovarian cancer underwent a left hepatic lobectomy and developed a persistent postoperative biliary fistula. **A,** Tube cholangiogram shows biliary segments without communication to the main biliary tree. **B,** Endoscopic retrograde cholangiopancreatography confirms noncommunication of the biliary segments. **C** and **D,** Computed tomography shows retained contrast medium within operative drain (*arrowheads*) and accessory segment VI and caudate duct branches (*arrow*). *(Courtesy Dr. Jeanne Laberge.)*

may be anastomosed to a jejunal loop or to the gallbladder (see Fig. 42B.19; Smith et al, 1982).

Biliovenous fistula with subsequent leakage of bile into the venous system (bilhemia) is a rare but serious complication of liver trauma. After the formation of a necrotic cavity within the liver, an open connection between a vein and an intrahepatic bile duct may occur, allowing bile to leak into the venous circulation (see Chapter 105; Haberlik et al, 1992). Rarely, transjugular intrahepatic portosystemic shunting (TIPS; see Chapter 76E) has been reported to be a direct cause of bilihemia (Jawaid et al, 2003; Singh et al, 2007; Singal et al, 2009).

LIVER RESECTION. The incidence of bile leak after hepatic resection ranges from 1.7% to 12% in large series (Lo et al, 1998; Capussotti et al, 2006; Nagano et al, 2003; Vigano et al, 2008; Tanaka et al, 2002; Yamashita et al, 2001; see Chapters 25 and 90). In most patients, bile leak resolves spontaneously, but sometimes a persistent fistula requires reoperation (Honore et al, 2009). Liver resection done for tumor (see Chapter 90) may be followed by biliary fistula, which may result from inadequate ligation of the bile ducts at the cut liver surface (Thompson et al, 1983) or from failure to secure the bile ducts at the hilus (Fig. 42B.20). This failure is more likely after right hepatectomy, in which the anatomy of the right sectoral ducts is variable in the hilar region. Extended left hepatic lobectomy also has been associated with a high incidence of biliary fistula (see Chapter 90; Starzl et al, 1982). In Japan, Yamashita and colleagues (2001) reported a biliary fistula rate of 4% (31 of 781) after hepatic resection. Their analysis identified operative procedures exposing the major Glisson capsule and including the hilum—anterior sectorectomy, central hepatectomy, and caudate resections—to be high-risk operations for development of postoperative bile leakage. Other factors that may contribute to a persistent bile fistula may include underlying cirrhosis or chronic hepatitis that impair wound healing (Tanaka et al, 2002). Once a posthepatecomy biliary fistula is established, if the drainage output exceeds 100 mL per day 10 days after diagnosis, interventional or endoscopic procedures should be considered to promote definitive closure (Vigano et al, 2008).

Operative injury to the biliary tract that is likely to result in fistula is more common after resection of lesions involving or close to the hilar structures (Fig. 42B.21). It also is more likely to occur after resection of lesions involving the caudate lobe ducts, because the anatomy of these ducts is significantly



FIGURE 42B.21. Fistulography obtained via a tube drain shows a biliary fistula after extended left hepatic lobectomy for primary hepatocellular cancer. The tumor was large and involved the hilar ducts; tumor extension was shown within the left hepatic duct. The fistula was managed conservatively, and it closed within 4 weeks. *Arrows* indicate the fistula and the course of the right hepatic duct and common bile duct.

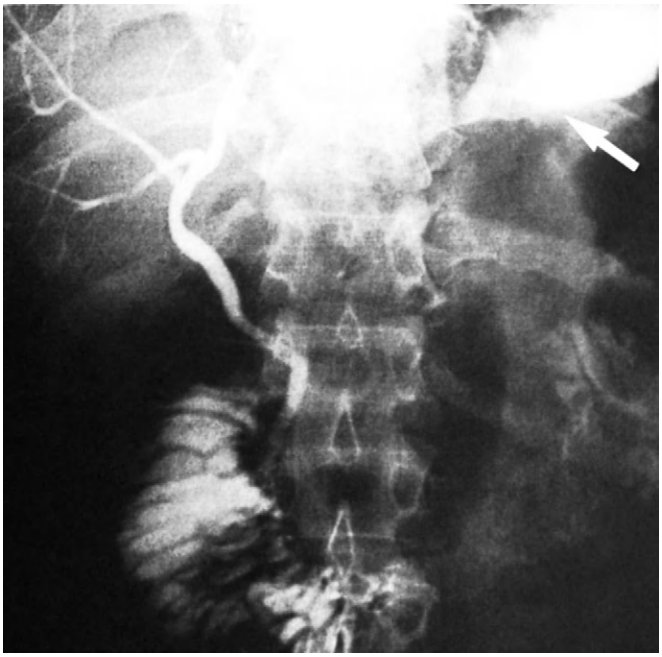


FIGURE 42B.22. Persistent external biliary fistula after external drainage of a hydatid cyst cavity (*arrow*) in the left lobe of the liver. Fistulography shows clear communication between the cyst cavity and the left hepatic duct.

variable in the hilar region. Using major hepatic resection, resection of cholangiocarcinoma combined with biliary-enteric reconstruction may be complicated by a biliary fistula originating from the caudate lobe ducts or from the biliary-enteric anastomosis (see Chapter 90). Hepatic cryotherapy (see Chapter 85B), which may be used at the cut liver surface after hepatectomy or for ablation of deep intrahepatic lesions, may also be complicated by biliary fistula (Sarantou et al, 1998). It may be prudent to leave a drain in situ after this procedure.

LIVER TRANSPLANTATION. Biliary leaks and fistulae are a continuing source of morbidity and mortality after liver transplantation. Pathogenesis usually is related to technical and vascular considerations and, in particular, to hepatic artery thrombosis (see Chapter 100).

GASTRECTOMY. Injury to the bile duct may occur during gastrectomy, particularly when the pyloric region or the first part of the duodenum is grossly distorted and inflamed (Florence et al, 1981). Such an injury becomes apparent either as a biliary fistula or at a later stage with the development of a stricture (see Chapter 42A).

SURGERY FOR HYDATID DISEASE. Surgery is an important treatment option for patients with hydatid disease (Dziri et al, 2004). Operative options include pericystectomy and hepatic resection or simply unroofing of the cyst and treatment of the residual cavity. Patients treated by these methods are prone to all the known complications associated with liver resection. Hydatid disease of the liver (see Chapter 68) is associated with biliary involvement by the disease in approximately 10% of instances (Erguney et al, 1991). An expanding liver cyst results in compression and stretching of adjacent liver tissue, including the bile ducts. It may erode into a stretched bile duct, with the establishment of continuity between the cyst cavity and the biliary system. Hydatid material may enter into the biliary tree, or bile may leak into the cyst. As with other hepatobiliary conditions, a laparoscopic surgical management option for hepatic hydatid disease has been introduced, but it is limited to those few centers where the disease is endemic (Duttaroy et al, 2008; Palanivelu et al, 2006; Sharma et al, 2009).

Biliary fistula may develop after operation for hydatid disease in certain situations. First, a communication between the cyst cavity and the biliary system is missed at operation and is not directly secured (Fig. 42B.22). It is prudent to drain all cyst cavities, particularly those of multiloculated hydatid cysts, to ensure that if a biliary fistula were to develop, it would be controlled. Unless a distal obstruction is present, these fistulae usually close spontaneously. Second, and rarely, the presence of hydatid material within the biliary tract produces biliary ductal obstruction (Fig. 42B.23) that results in a persistent biliary fistula that is relieved only when the hydatid material passes or is removed. Removal is achieved by exploration of the CBD with or without a bypass procedure (Ozmen et al, 1992) or by endoscopic methods (Iscan & Duren, 1991).

Assessment of the biliary tree, preferably by endoscopic cholangiography, should be performed before surgery in patients with a history of jaundice or cholangitis or in the presence of a large cyst located centrally and abutting the hilar structures. Kayaalp and colleagues (2003) in a series of 113

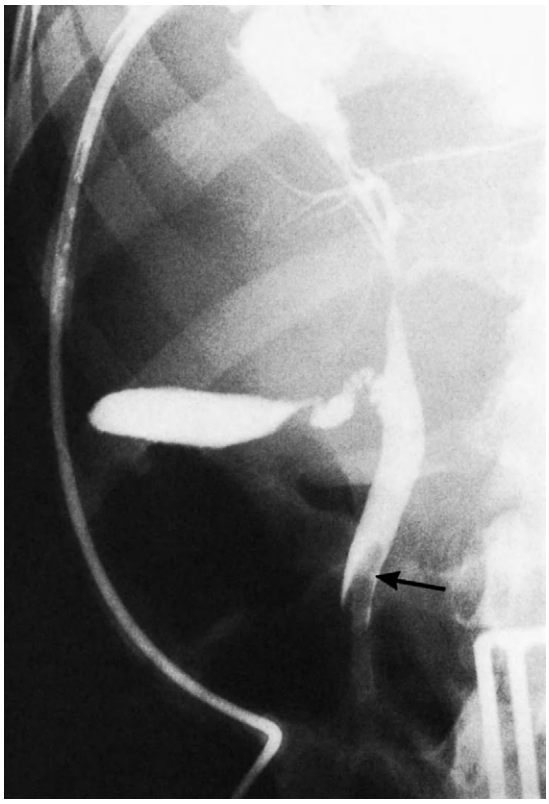


FIGURE 42B.23. Fistulography obtained after excision of a right hepatic hydatid cyst. Note the persistent fistula as a consequence of retained hydatid material in the common bile duct (*arrow*). Treatment was by exploration of the common bile duct and surgical removal of the retained hydatid material. The fistula rapidly closed.

patients showed that the location of the hydatid cyst near the hilum is a risk factor for the development of a cystobiliary communication and cavity-related complications. When a cystobiliary communication is shown, the biliary system should be cleared of all debris and cyst remnants, and endoscopic sphincterotomy should be performed before surgical intervention (Kornaros & Aboul-Nour, 1996). Percutaneous treatment of hydatid cysts is associated with a 10% incidence of biliary fistula (Men et al, 1999). Such fistulae usually close spontaneously after any biliary distal obstruction is relieved.

Clinical Presentation

The clinical presentation of a biliary fistula may be of an excessive, abnormal biliary drainage from the drain site or wound or, alternatively, of a localized or generalized peritonitis resulting from an intraabdominal collection of bile. After a diagnosis of biliary fistula has been established, it is most important to assess clinically the adequacy of bile drainage. In controlled fistulae, external biliary drainage is adequate, with no signs of localized or generalized peritonitis, and the adverse pathophysiologic features associated with cholestasis are not present.

In uncontrolled biliary fistula, biliary drainage is inadequate, resulting in an intraabdominal bilious collection. Because the bile is usually or soon becomes infected, the presentation is mostly of a subphrenic or subhepatic abscess or generalized peritonitis. The situation may be complicated further by cholangitis with or without intrahepatic abscess and septicemia that demands urgent treatment. In some patients with sterile bile, huge volumes may accumulate within the peritoneal cavity with minimal clinical findings apart from a distended abdomen (Fig. 42B.24). A high index of suspicion is important, because minimal abdominal symptoms and slightly deranged LFTs may be the only indicators of biliary damage. The presence of skin excoriation and digestion implies that activated digestive enzymes are present in the fistula effluent, because bile alone contains no digestive enzymes.

Pathologic Consequences of External Biliary Fistulae

The important pathophysiologic effects of an external biliary fistula depend on the volume of bile drained daily, the length of time the fistula has been present, and the degree to which bile is diverted from the GI tract. Consequences of biliary fistulae are mainly due to depletion of electrolytes and fluid, to the absence

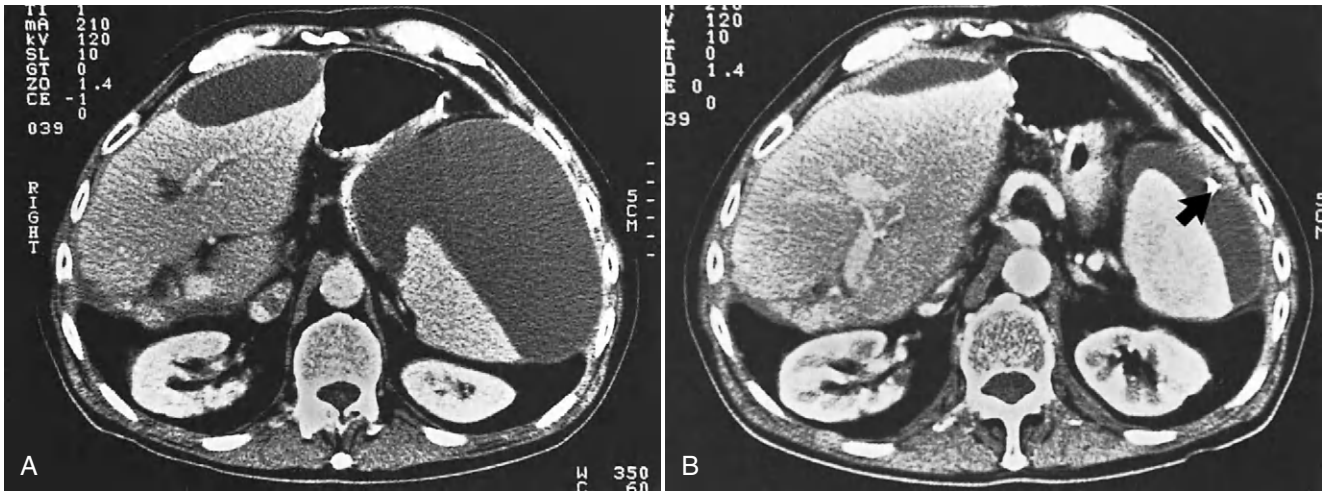


FIGURE 42B.24. **A,** Huge, asymptomatic biloma 3 weeks after partial hepatectomy for hepatocellular cancer. The patient reported abdominal distension only. **B,** Computed tomographic–guided puncture and drainage (*arrow*) converted the uncontrolled fistula into a controlled one. The fistula closed spontaneously after 17 days.

of bile from the gut, and to the possibility of ascending, exogenously acquired biliary infection. The important practical considerations are that the volume of bile secreted daily by the liver is on the order of 1000 mL, and the electrolyte composition of bile is equal to that of blood.

Total biliary loss for short periods (≤3 weeks) may not result in a serious depletion of electrolytes and fluid, because the body is able to compensate for this loss. Long-term total external biliary fistula results in fluid and electrolyte disturbances if replacement therapy is not instituted. Sodium loss is usually greater than chloride loss, leading to metabolic acidosis (Cass et al, 1955). The serum potassium level is initially lowered, but the accompanying fluid loss may lead to a decrease in plasma volume, low-output renal failure, and hyperkalemia (Knochel et al, 1962). Absence of bile from the GI tract causes interference in the absorption of fat-soluble vitamins A, D, and K. Vitamin A and D deficiencies are associated with long-term total biliary fistula and are rarely seen today, whereas vitamin K deficiency is evident earlier and can be easily diagnosed by a prolonged PT. Other adverse effects of total biliary loss are disruption of intestinal barrier function and bacterial translocation (Slocum et al, 1992). These findings are supported by an observation that bile replacement restored intestinal barrier function in patients with malignant obstruction undergoing external biliary drainage (Kamiya et al, 2004). Even in the short term, patients with an external biliary fistula feel unwell, weak, and lethargic. In advanced and neglected cases, caloric and protein malnutrition results in gradual weight loss, whereas the electrolyte changes may result in stupor and vasomotor collapse.

Diagnostic Procedures and Initial Treatment

The presence of a biliary fistula may first become apparent at reoperation. More commonly, and particularly after laparoscopic cholecystectomy, the biliary fistula becomes apparent at ERCP or after percutaneous drainage of a perihepatic collection. Reoperation is usually required for peritonitis or for drainage of an intraabdominal collection that is not amenable to percutaneous treatment. Such collections may be a complication from a previous surgery on the hepatobiliary system, the pancreas, or, rarely, the stomach or duodenum. Rarely, they may follow a spontaneously occurring pathologic process, such as hemorrhagic pancreatitis or rupture of a liver cyst. When the presence of an uncontrolled biliary fistula has been realized, initial management demands conversion of the fistula into a controlled one, usually by means of tube drainage. No attempt at definitive repair should be made at this early stage, because the involved bile ducts are collapsed, friable, and usually embedded within a severe local inflammatory reaction; it is virtually impossible to expose healthy bile ducts for any form of long-lasting definitive repair, and any attempt to do so is bound to fail and renders further operation more difficult (see Chapter 42A; Czerniak et al, 1988).

The early demonstration of an uncontrolled biliary fistula within 24 to 48 hours of laparoscopic cholecystectomy together with a transected or completely occluded CBD is an indication for early surgical intervention. A decision regarding definitive repair is based on operative findings. Rarely, removal of a misplaced clip intended for the cystic duct stump that has caused complete obstruction of the CBD is all that is necessary.

Alternatively, percutaneous CT- or US-guided drainage of a subphrenic or infrahepatic fluid collection may be followed by the establishment of an external biliary fistula. It is important to ensure adequate drainage and to see that the fistula is well controlled. Biliary drainage is ideally carried out using a sealed drainage-bag system (Blenkharn et al, 1981). Drainage initially should be done using a low-pressure, closed-suction system, which is valuable in reducing the cavity of the intraabdominal bile collection or in reducing the abscess of a fistula tract. Improvement of the clinical picture and repeated US or CT studies eventually should show proper positioning of the drain and reveal no residual collection or abscess. HIDA scintigraphy (see Chapter 15) and tubography are helpful in this respect (see Fig. 42B.18).

After the fistula is controlled, conservative treatment is instituted, the patient is nourished, deficits of electrolytes and vitamins (mostly vitamin K) are corrected, and infection is treated. It is important to know whether the biliary fistula contains bile only or whether it also contains duodenal, pancreatic, or intestinal juice; when the latter is present, appropriate measures to protect the skin should be taken. Parenteral nutrition is an essential element in the management of significant duodenal and pancreatic fistulae, in which total prohibition of oral intake is important to allow healing to occur. It has been shown that treatment with somatostatin can reduce bile secretion significantly (Nyberg, 1990; Sahin et al, 1999), and somatostatin has been used successfully in the management of pancreatic and small intestine fistulae (Draus et al, 2006); it may also be valuable in the management of combined biliary-pancreatic-duodenal fistulae. However, the benefit of somatostatin therapy in promoting closure of biliary fistulae arising entirely from the biliary tree remains unproven (Hesse et al, 2002). We are aware of three case reports that describe successful use of octreotide, a somatostatin analogue, in the treatment of bronchobiliary fistulae (Ong et al, 2004; Petrolati et al, 2009; Singh et al, 2002).

After the establishment of a controlled fistula, various radiologic investigations are performed with the aim of assessing the 1) origin of the fistula, 2) presence and extent of an injury to the extrahepatic biliary system, 3) adequacy of drainage, and 4) presence of biliary-enteric bile flow. The anatomy of the entire intrahepatic and extrahepatic biliary tree should be shown, and this is achieved by a variety of radiologic studies. All contrast examinations should be covered with antibiotic prophylaxis to minimize the risk of bacteremic episode.

Tube cholangiography should be performed routinely before removal of cholecystostomy or choledochostomy tubes or tube drainage across biliary-enteric anastomoses. Whenever an obstruction to free biliary-enteric bile flow is present, it should be treated. Removal of a tube in the presence of a distal stricture or a retained bile duct stone invariably results in a persistent biliary fistula.

Fistulography is a simple and effective means of determining whether biliary drainage is adequate and whether a fistulous cavity has converted to a fistulous tract. The site and underlying cause of the biliary fistula often can be clearly shown by fistulography (Fig. 42B.25; see Figs. 42B.13, 42B.14, 42B.19, 42B.21, and 42B.23). PTC is used when the findings of fistulography are equivocal, and the intrahepatic biliary tract, the right system in particular, is not fully shown. Iatrogenic damage to a right sectoral hepatic duct is an example of this problem, and PTC is the only diagnostic modality to yield accurate definition.

ERCP is a useful diagnostic and therapeutic tool where there is a continuity of the extrahepatic biliary system (Davids et al,

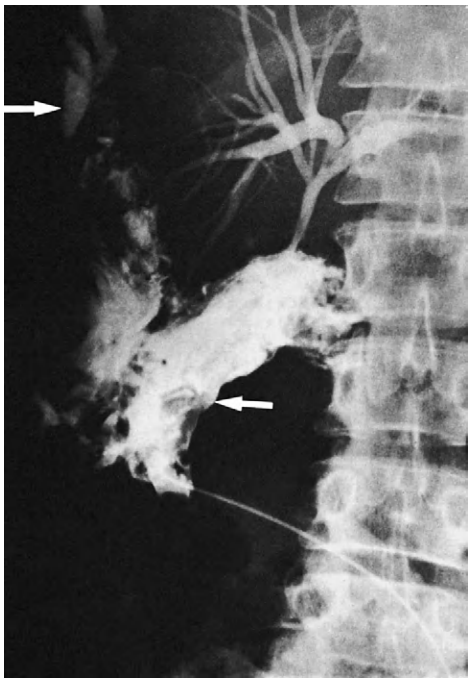


FIGURE 42B.25. Fistulography in a patient with neglected postcholecystectomy biliary fistula caused by accidental transection of the common hepatic duct with associated subphrenic (*top arrow*) and subhepatic (*bottom arrow*) collections of infected bile.

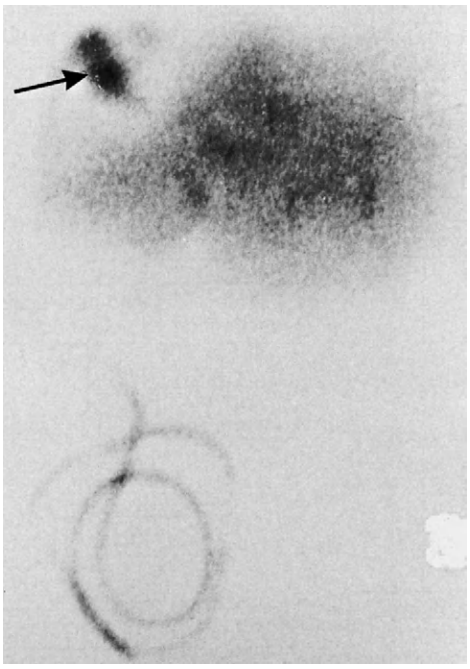


FIGURE 42B.26. Hepatobiliary iminodiacetic acid scan showing a fistula issuing from the liver surface (*arrow*). This is the same patient as is Figure 42B.23. The drainage tube also is shown. *(From McPherson GA, et al, 1984: The role of HIDA scanning in the assessment of external biliary fistulae. Surg Gastroenterol 3:77-80.)*

1992), particularly after laparoscopic cholecystectomy (Agarwal et al, 2006) and after liver transplantation (Sherman et al, 1993). The value of ERCP is limited in fistulae arising at the hilus of the liver and resulting from iatrogenic bile duct injury (see Chapters 18 and 27).

HIDA scintigraphy, as mentioned earlier (see Chapter 15), is a useful noninvasive method of evaluating liver function and bile secretion (Holbrook et al, 1991). Although it may not supply accurate anatomic details, information such as the presence of a fistula, its origin (liver or extrahepatic biliary system; see Figs. 42B.3 and 42B.24), and adequacy of its drainage (controlled or uncontrolled; Figs. 42B.26 and 42B.27; McPherson et al, 1984) can be clearly obtained.

MRCP and CT allow excellent assessment in hepatic biliary, arterial, and portal venous anatomy. In particular, use of CT after fistulography can help verify maturation of a fistula tract and define perihepatic bile collections or isolated liver segments (see Figs. 42B.5 and 42B.20).

Treatment

The principles of management of postoperative biliary fistulae are essentially the same regardless of the initial surgical procedure; these principles are outlined in Figure 42B.28 and are modified slightly according to the initial surgical procedure and the individual patient. ERCP and endoscopic techniques play an integral and indispensable role in the management of biliary fistulae. The individual treatment plan should be made and agreed on jointly by all members of the team involved in the treatment of the patient.

As stated earlier, it is important to establish a controlled fistula; this can be achieved initially by US- or CT-guided drainage of the abscess or collection. Operation is indicated when nonoperative measures are not suitable, such as in a patient

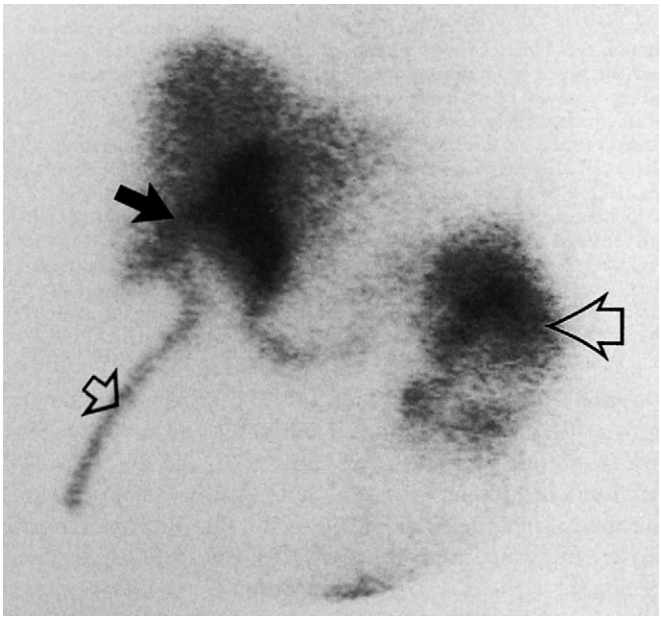


FIGURE 42B.27. Hepatobiliary iminodiacetic acid scan (*right lateral view*) showing a controlled biliary fistula (*small open arrow*) resulting from an incomplete closure of a wide cystic stump (*solid arrow*) at laparoscopic cholecystectomy. Free biliary-enteric bile flow is shown (*large open arrow*). The fistula closed spontaneously after 2 weeks.

with diffuse bile peritonitis, a septic patient with an intraabdominal abscess too large to be drained by the percutaneous route, or a patient with necrotic material and debris within the abscess. Early surgery also is indicated when percutaneous drainage has failed. During the operation, the temptation to

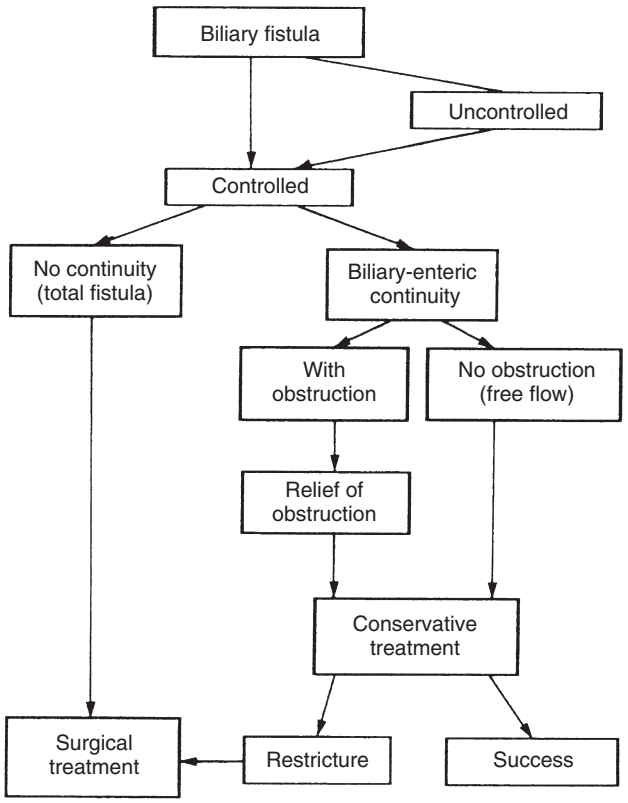


FIGURE 42B.28. Proposed management plan for postoperative biliary fistula. The initial treatment is most important and includes the establishment of a controlled fistula. This is achieved radiologically, by percutaneous drainage of a collection, or surgically, at which time no attempt at primary repair is made. The fistula is evaluated for biliary-enteric continuity. When a total fistula has been diagnosed, it is most important to ensure that it is controlled. Definitive surgical repair is attempted after a reasonable period of conservative treatment. When biliary-enteric continuity is present with free biliary-enteric bile flow, conservative treatment is instituted and results in spontaneous closure in most cases. The presence of biliary-enteric continuity with distal obstruction calls for some form of treatment to relieve the obstruction, and this is done endoscopically or, preferably, percutaneously by balloon dilation. After the establishment of free biliary-enteric bile flow, patients are treated conservatively. In suitable cases, nasobiliary intubation is followed up carefully after fistula closure for early signs of stricture. Highly complex hilar fistulae are treated conservatively with prolonged periods of drainage. The fistula is expected to close, and this usually occurs together with the development of stricture. After a stricture develops, it is treated surgically.

attempt primary repair at this stage must be resisted; only good drainage should be established. Occasionally, drainage of large amounts of bile with significant fluid and electrolyte loss may necessitate early operation, when the external fistula may be converted to an internal fistulojejunostomy using a mobilized and approximated Roux-en-Y jejunal loop (see Fig. 42B.19; Smith et al, 1982). In this procedure, the drainage tube is led from the fistula origin through the jejunal loop to the exterior; this allows control, but it creates an almost certain necessity to reoperate for restenosis at a later stage.

It is important to identify the presence or absence of biliary-enteric bile flow, which differentiates a total biliary fistula from a partial fistula with some residual biliary-enteric continuity. Subsequent management is influenced significantly, because operation is usually unavoidable in the former, and a nonoperative approach may be successful in the latter. A total biliary fistula rarely closes spontaneously when an internal fistula develops between the divided upper duct and the gut (Collins & Gorey, 1984).

When biliary-enteric continuity is present, and bile flow is not obstructed distal to the origin of the fistula, a prolonged period of conservative treatment is indicated, because spontaneous closure of the fistula is common. Fistula closure may be facilitated by temporary placement of a stent across the fistulous opening in the bile duct, excluding bile flow through the fistula. This method may be attempted where the CBD is intact above the fistula origin, and the defect in the common duct is not too large. Stenting may be achieved by endoscopic placement of an endoprosthesis or a nasobiliary tube with its tip above the origin of the fistula. When a short period of stenting is anticipated, nasobiliary intubation is preferred, because it enables follow-up cholangiography, damage to the papilla is minimal, and a second endoscopic procedure is avoided (Barthel & Scheider, 1995; Grala et al, 2009). Using this method, some fistulae close within 2 weeks (Toriumi et al, 1989). It is also useful in patients with liver transplant who have undergone duct-to-duct biliary reconstruction. In patients with concomitant CBD stones or stricture, a papillotomy is indicated. Nasobiliary tubes are cumbersome for the patient, and they may occasionally dislodge; if used for prolonged periods, they may enhance metabolic acidosis resulting from bile loss.

Endoscopic treatment of fistulae with intact biliary-enteric flow by sphincterotomy, stenting, or both is effective in most patients (Agarwal et al, 2006; Rauws & Gouma, 2004). In most instances, a biliary endoprosthesis is used and is left in place for several weeks, until the fistula closes. Closure is verified by HIDA scan before removal of the stent. If standard endoscopic therapy fails, an alternative endoscopic technique using n-butyl-2-cyanoacrylate glue occlusion of the fistula has been shown to be effective and helps avoid the need for surgery (Seewald et al, 2004).

Some authors recommend endoscopic sphincterotomy alone with the intention of reducing the pressure gradient between the biliary system and the duodenum (Ponchon et al, 1989). This procedure is unnecessary, because the fistula will close if no distal obstruction is present. Sphincterotomy may also be associated with short-term and long-term septic and obstructive complications (Kracht et al, 1986), therefore it should be avoided unless specifically indicated (e.g., in patients with a papillary stricture). It also has been shown that stenting is more effective than sphincterotomy alone in the resolution of biliary fistulae (Marks et al, 1998). As stated earlier, we believe that although endoscopic approaches are useful, they generally should be delayed for days to a few weeks to allow spontaneous closure of the fistula, which obviates the need for further intervention and its attendant complications.

After an obstruction distal to the fistula has been diagnosed, it should be dealt with, because until it has been managed, the fistula will not close spontaneously. Obstruction is usually caused by a retained stone or a stricture: retained stones usually are removed by endoscopic means, and relief of a benign stricture can be achieved using balloon dilation, applied either endoscopically or by interventional radiology after PTC. The patient is treated conservatively and expectantly for fistula closure or for restricture, and fistula closure can be facilitated

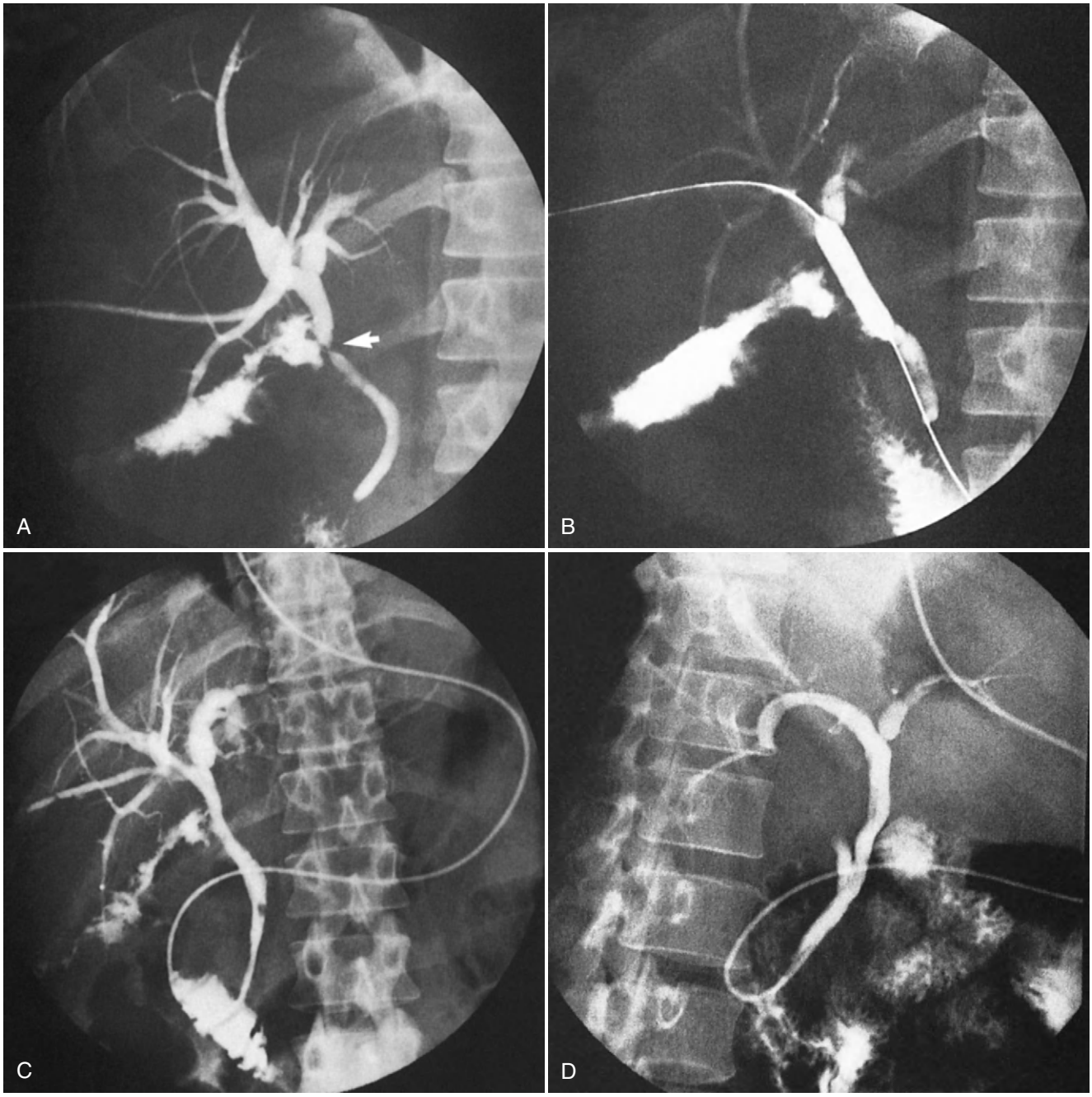


FIGURE 42B.29. Combined surgical/endoscopic/radiologic management of a biliary fistula diagnosed 3 weeks after an open cholecystectomy. **A,** Percutaneous transluminal cholangiography shows a biliary fistula with a significant distal stricture (*arrow*). **B,** Percutaneous transhepatic balloon dilation of the stricture. **C,** Percutaneous transhepatic guide is exchanged for a nasobiliary tube, which is placed endoscopically with its tip above the origin of the fistula. Free biliary-enteric bile flow is obtained. The fistula is still present but is smaller. **D,** Check-up cholangiography (lateral view) after 2 weeks of nasobiliary drainage shows fistula closure. The nasobiliary drain was removed.

by temporary stenting (Fig. 42B.29), if the location and the size of the defect in the bile duct are suitable, and restricture is treated operatively.

The use of temporary stenting is limited in highly complex hilar fistulae combined with stricture, particularly fistulae with separation of a right and left ductal system. Some authors place an endoprosthesis across the stricture and leave it for months (Ponchon et al, 1989), even for more than 1 year, with periodic replacements (Davids et al, 1992). This practice is not only unnecessary but is often harmful, resulting in obstruction and septic complications; the endoprosthesis should be removed when the fistula has closed.

Management of biliary fistula after laparoscopic cholecystectomy follows the same principles. Because early recognition of the biliary fistula or bile duct damage significantly affects treatment, a high index of suspicion is important. Initial evaluation includes abdominal US and HIDA scan to rule out the presence of an abnormal collection and to establish the presence of free biliary-enteric bile flow. Abnormal findings at either study call for ERCP. Treatment of biliary fistula with or without

biliary-enteric continuity follows the guidelines outlined. A biliary fistula associated with malignant distal obstruction is treated with reoperation and surgical excision of the neoplasm or the creation of an appropriate biliary-enteric bypass.

After closure of the fistula, patients are followed up carefully with regular LFTs and HIDA scans to detect early signs of the development of a biliary stricture, which may take months and sometimes years. Stricture is most likely to occur where a stricture has already been present or where a fistula is associated with an injury to a major bile duct (Blumgart et al, 1984). The proposed plan may involve relatively prolonged management, but it improves the chances of a successful and long-lasting bile duct repair, especially after injury at cholecystectomy. In this situation, early and untimely surgical attempts at definitive repair carry a high risk of biliary leak and anastomotic stricture.

Management of the rare patient with excluded or "orphaned" segemental bile ducts following hepatectomy is extremely challenging. This complication results from unrecognized anatomic biliary variations (see Chapter 1B), or when normal anatomic planes are ignored during hepatic transection. The end result is that a portion of liver tissue remains well perfused but entirely disconnected from the biliary tract (see Fig 42B.20). Multiple interventional treatments have been described, the majority consisting of sclerotic agents that are injected directly into the fistula tract. These substances include tetracycline, ethanol, and acetic acid, (Shaw et al, 1989; Shimizu et al, 2006; Park et al, 2005). Other agents such as fibrin glue, thrombin, and n-butyl cyanoacrylate have been used with variable success (Saad & Darcy, 2008; Vu et al, 2006). We are aware of one successful case report of a patient who was treated by percutaneous intraductal laser ablation after failing other treatments (Eicher et al, 2008). When these nonoperative treatments fail, repeat liver resection is necessary and usually definitive (Honore et al, 2009). The authors have successfully used ablation of the liver tissue containing the orphaned biliary segement to treat persistent biliary fistulae.

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CHAPTER 50B

Cancer of the bile ducts: extrahepatic biliary tumors

Michael G. House, Michael I. D'Angelica, and William R. Jarnagin

OVERVIEW

Primary tumors arising from the extrahepatic biliary tree are uncommon, typically malignant in nature, and show up with clinical manifestations associated with obstructive jaundice. Bile duct tumors continue to be challenging disease entities that require expertise for proper evaluation and treatment. This chapter focuses on the etiology of bile duct neoplasia, namely cholangiocarcinoma, the appropriate imaging modalities for diagnosing and staging malignant biliary strictures, and the available options for treating resectable and unresectable extrahepatic biliary cancer.

INCIDENCE AND ETIOLOGY

Worldwide, cholangiocarcinoma accounts for approximately 3% of all gastrointestinal cancers. In the United States, where approximately 5000 new cases (gallbladder cancers excluded) are diagnosed each year, the annual incidence of bile duct cancer is estimated at 1 to 2 per 100,000 (Carriaga & Henson, 1995; Greenlee et al, 2001; Khan et al, 2005). Over the past 3 decades, a trend has been seen toward older patient age (median range, 65 to 70 years) at the time of diagnosis and a relative increase in the ratio of intrahepatic to extrahepatic cholangiocarcinoma (see Chapter 50A; Carriaga & Henson, 1995; Endo et al, 2008a; Patel, 2001; Weber et al, 2007).

The molecular changes associated with the pathogenesis of cholangiocarcinoma are poorly characterized (see Chapter 8B). Multiple *KRAS* oncogene mutations at codon 12 have been identified in almost all resected specimens (Levi et al, 1991). These mutations most likely occur at some point along a stepwise progression to malignancy but probably are not the inciting genetic lesion. There are wide epidemiologic variations in the incidence of *KRAS* mutations (Lee et al, 1995; Levi et al, 1991; Nakamura et al, 1981). Many studies have reported differences in various genetic abnormalities according to location within the biliary tree, suggesting anatomic differences in pathogenesis. An in-depth review of the molecular biology of biliary cancer is beyond the scope of this chapter; the interested reader is referred to selected review articles (Rashid, 2002) and to Chapter 8B.

The majority of patients with cholangiocarcinoma have no obvious risk factors, although several conditions are associated with an increased incidence of cholangiocarcinoma. In the United States, the most common risk factor for cholangiocarcinoma is primary sclerosing cholangitis (PSC), an autoimmune disease characterized by periductal inflammation resulting in multifocal strictures of the intrahepatic and extrahepatic bile ducts (see Chapter 41; Broome et al, 1996; Katoh et al, 1988; Pitt et al, 1995a, 1995b). Approximately three quarters of patients with PSC have underlying ulcerative colitis (Broome et al, 1996). The natural history of PSC is quite variable, and the true incidence of cholangiocarcinoma is difficult to calculate but appears to depend on disease duration. In a Swedish series of 305 patients followed for more than 5 years, 8% of patients eventually developed cancer (Broome et al, 1996), and occult cholangiocarcinoma has been reported in 40% of autopsy specimens and 36% of liver explants from patients undergoing orthotopic liver transplantation for PSC (Broome et al, 1996; Katoh et al, 1988; Pitt et al, 1995a). Unfortunately, cholangiocarcinoma arising in the setting of PSC frequently is not amenable to operative resection because of advanced underlying hepatic parenchymal disease or multifocal malignancy. Medical or surgical treatment of coexisting ulcerative colitis in patients with PSC does not alter the subsequent risk of developing cholangiocarcinoma (Broome et al, 1996; Katoh et al, 1988; Pitt et al, 1995a).

Choledochal cysts are associated with an increased risk for cholangiocarcinoma (see Chapter 46; Hewitt et al, 1995; Vogt, 1954). The incidence of bile duct cancer in patients with congenital biliary cystic disease is substantial (15% to 20%), especially in patients who are not treated until after age 20 years and in patients previously treated by cyst drainage (Lipsett et al, 1994; Vogt, 1954). The hypothetical risk for malignant transformation of choledochal cysts may be related to an anomalous pancreatobiliary junction, which is commonly found in these patients and predisposes them to reflux of pancreatic juice into the biliary tree and chronic inflammation of the bile ducts (Lipsett et al, 1994; Jeng et al, 1994; Tanaka et al, 1998a; Vogt, 1954). By similar mechanisms, transduodenal sphincteroplasty and endoscopic sphincterotomy may be associated with an increased risk for cholangiocarcinoma (Tanaka et al, 1998b). In a series of 119 patients subjected to sphincteroplasty for benign disease (sphincter of Oddi dysfunction), Hakamada and associates (1997) found a 7.4% incidence of cholangiocarcinoma over 18 years.

Recurrent pyogenic cholangiohepatitis and hepatolithiasis resulting from chronic portal bacteremia and portal phlebitis are prevalent in Japan and parts of Southeast Asia (see Chapters 39 and 44). Although most cholangiocarcinomas in these patients arise within the intrahepatic ducts, cases of extrahepatic cholangiocarcinoma have been reported (Chen et al, 2004; Chu et al, 1997; Kubo et al, 1995; Meade et al, 1994; Winslet et al, 1990). Biliary parasites—specifically, *Clonorchis sinensis* and *Opisthorchis viverrini*—are endemic in parts of Asia and are associated with an increased risk of cholangiocarcinoma (Pitt et al, 1995a, 1995b). In Thailand, where approximately 7 million people are chronically infected with *Opisthorchis*, the

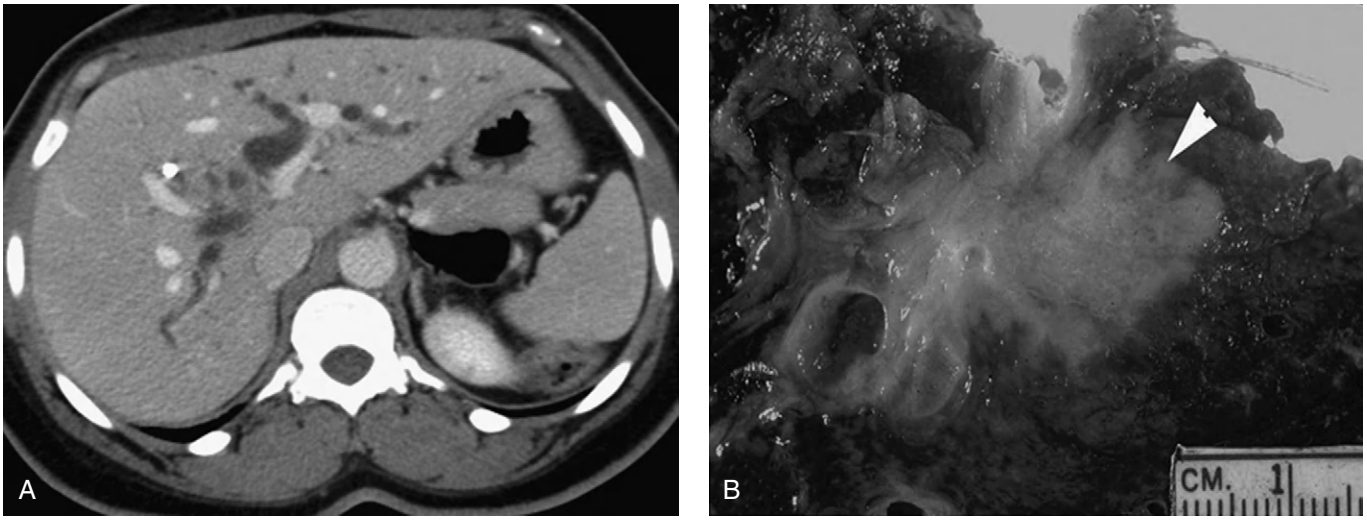


FIGURE 50B.1. A, Contrast-enhanced computed tomographic scan showing hilar bile duct tumor involving the right and left hepatic ducts. **B,** Gross appearance of a nodular-sclerosing tumor invading the hepatic parenchyma.

annual incidence of cholangiocarcinoma is 87 per 100,000 (see Chapter 45; Watanapa, 1996). In addition, several radionuclides and chemical carcinogens may be associated with an increased risk of cholangiocarcinoma, including thorium, radon, nitrosamines, dioxin, and asbestos.

TUMOR LOCATION AND HISTOPATHOLOGY

Adenocarcinoma is the most common neoplasm arising from the biliary tract and accounts for more than three fourths of all bile duct tumors (Are et al, 2006; Jarnagin et al, 2001). Benign neoplasms and strictures occasionally will mimic many of the clinical, radiographic, and operative findings associated with malignant biliary strictures. Other reported tumors of the extrahepatic bile ducts include adenoma, leiomyoma, paraganglioma, lipoma, granular cell tumor, and carcinoid (Felekouras et al, 2009; Holzinger et al, 1999). Benign strictures resulting from autoimmune pancreatitis, granulomatous disease, and PSC can masquerade as biliary neoplasms and should be treated as such (see Chapter 42A; Corvera et al, 2005; Hadjis & Blumgart, 1985). Malignant strictures of the extrahepatic biliary tree may represent secondary involvement from cancers arising from the gallbladder, pancreas, and periportal lymph nodes (see Chapter 49).

Cholangiocarcinoma can arise anywhere within the biliary tree, but tumors involving the biliary confluence are the most common. Retrospective reviews from high-volume centers reveal that between 40% and 60% of cholangiocarcinoma cases involve the perihilar bile ducts (Burke, 1998; Nagorney et al, 1993; Nakeeb et al, 1996a, 1996b; Tompkins et al, 1981). Tumors of the lower bile duct are classified according to their anatomic location, although there may be considerable overlap. Distal bile duct tumors typically arise within the pancreatic portion of the common bile duct (Tompkins et al, 1981) and represent approximately 20% to 30% of all cholangiocarcinomas and 5% to 10% of all periampullary tumors (Fong et al, 1996; Nakeeb et al, 1996a, 1996b; Wade et al, 1997; Yeo et al, 1997). Tumors of the mid–bile duct are rare and arise below the confluence of the hepatic ducts, usually between the upper border of the pancreas at the level of the cystic duct. The majority of such malignant strictures are caused by gallbladder cancer or cystic duct–based tumors.

Cholangiocarcinomas can present with extensive ductal involvement alone or with early metastatic spread to the liver, regional lymph nodes, or peritoneum (Jarnagin et al, 2005; Tsuzuki et al, 1983). Most bile duct cancers demonstrate characteristic invasive spread along ductal subepithelial histologic planes. Perineural and lymphovascular involvement is common, as is direct invasion into the liver or perihepatic structures (Weinbren & Mutum, 1983).

Three distinct macroscopic subtypes of cholangiocarcinoma have been described: 1) sclerosing, 2) nodular, and 3) papillary (Weinbren & Mutum, 1983). *Sclerosing tumors* account for most cases and are more common at the hilus than in the distal bile duct. They are firm and cause an annular thickening of the bile duct, often with diffuse infiltration and fibrosis of the periductal tissues (Fig. 50B.1). *Nodular tumors* are characterized by a firm, irregular nodule of tumor that projects into the lumen of the duct. Features of both types are often seen, hence the frequently used descriptor *nodular-sclerosing.* The *papillary tumors* account for approximately 10% of all cholangiocarcinomas, and although occasionally seen at the hilus, these are more common in the distal bile duct (Weinbren & Mutum, 1983). These tumors are soft and friable and may be associated with little transmural invasion; a polypoid mass that expands the duct, rather than contracting it (Fig. 50B.2), is a characteristic feature. Although papillary tumors may grow to a significant size and appear surgically unapproachable on radiographic studies, they often arise from a well-defined stalk and can be minimally invasive. The bulk of the tumor frequently is mobile within the bile duct. Recognition of this variant is important, because they appear to be more often resectable and have a more favorable prognosis than the sclerosing type (Jarnagin et al, 2005; Pitt et al, 1995a).

Longitudinal spread along the duct wall and periductal tissues is an important pathologic feature of cholangiocarcinomas (Endo, 2008b; Sakamoto et al, 1998; Weinbren & Mutum, 1983). There may be substantial extension of tumor beneath an intact epithelium, and it can extend as much as 2 cm proximally and 1 cm distally (Sakamoto et al, 1998; Shimada et al, 1988).

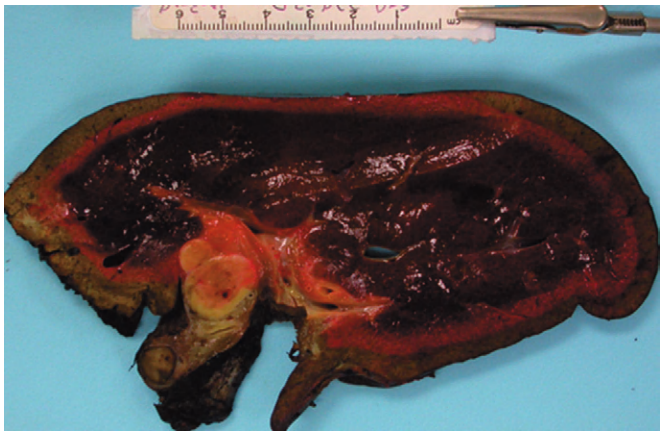


FIGURE 50B.2. Gross appearance of a papillary-type cholangiocarcinoma within the right hepatic duct. Note the expansion of the duct lumen.

The full tumor extent may be underestimated by radiographic studies and may not be appreciated on palpation. This predilection for submucosal extension underscores the importance of frozen-section analysis of the duct margins during resection, although its utility has been called into question (Endo et al, 2008b). Although most of these tumors are adenocarcinomas, in rare instances other malignant cell types may arise primarily in the biliary tree and cause biliary obstruction, such as carcinoid tumors (Jutte et al, 1987; Rugge et al, 1992; Sankary et al, 1995).

CLINICAL PRESENTATION

The early symptoms of hilar and distal cholangiocarcinoma are nonspecific. Abdominal pain, anorexia, weight loss, and pruritus are the most common symptoms, but these are seen only in about one third of patients. Fever is rarely seen at initial presentation but is common once biliary manipulation is initiated (Farley et al, 1995; Katoh et al, 1988; Meade et al, 1994; Nakeeb et al, 1996b; Pitt et al, 1995a; Vatanasapt et al, 1990b). Most patients have few symptoms and come to attention because of jaundice or abnormal liver function tests. Although most patients eventually become jaundiced, this finding is not present initially in cases of incomplete biliary obstruction (i.e., right or left hepatic duct) or segmental ductal obstruction. Segmental obstruction may go unrecognized for a long time, resulting in ipsilateral lobar atrophy without overt jaundice (see Chapter 5). These patients often are further evaluated and diagnosed because of an elevated serum alkaline phosphatase.

The clinical presentation of distal bile duct cancer generally is indistinguishable from that of other periampullary malignancies. Progressive jaundice is seen in 75% to 90% of patients. Abdominal pain, weight loss, fever, or pruritus occur in one third of patients or fewer (Fong et al, 1996; Nakeeb et al, 1996a, 1996b).

In some patients, pruritus precedes jaundice by some weeks; this symptom should prompt an evaluation, especially if associated with abnormal liver function test results. Patients with papillary tumors of the hilus may have a history of intermittent jaundice. Small fragments of tumor may detach from a friable papillary tumor of the right or left hepatic duct and pass into the common hepatic duct. Alternatively, if mobile within the lumen, the main tumor may cause a ball-valve effect at the hepatic duct confluence.

In jaundiced patients, the total bilirubin level may suggest an etiology. In patients with obstruction from cholangiocarcinoma, the serum bilirubin level is often greater than 10 mg/dL and averages 18 mg/dL, whereas patients with obstruction from choledocholithiasis have bilirubin levels 2 to 4 mg/dL and rarely greater than 15 mg/dL (Way, 1994); however, there is likely to be considerable overlap. Furthermore, the degree of jaundice may suggest the level of bile duct obstruction. Hilar obstruction is typically associated with higher levels of serum bilirubin compared with distal tumors. In patients with cholangiocarcinoma and no previous biliary intervention, cholangitis is uncommon at initial presentation despite a 30% incidence of bactibilia (see Chapter 43; Hochwald et al, 1999; Meade et al, 1994). The incidence of bactibilia is nearly 100% after biliary intubation, and cholangitis is also more common (Hochwald et al, 1999). Gallstones or common bile duct stones may coexist with bile duct cancer. In the absence of certain predisposing conditions (PSC, choledochal cyst, hepatolithiasis), however, it is uncommon for choledocholithiasis to cause obstruction at the biliary confluence. It is imperative to investigate fully and delineate the level and nature of any obstructing lesion causing jaundice to avoid missing the diagnosis of carcinoma.

Physical examination findings are usually nonspecific but may provide some useful information. The liver may be enlarged and firm as a result of distal biliary tract obstruction, whereas the gallbladder usually is decompressed and nonpalpable with hilar obstruction. Rarely, patients with long-standing biliary obstruction or portal vein involvement or both may have findings consistent with portal hypertension.

Bactibilia is relatively common in patients with hilar cholangiocarcinoma; however, in the absence of prior biliary manipulation, frank cholangitis is uncommon at initial presentation (McPherson et al, 1984).

DIAGNOSTIC STUDIES

The diagnosis of hilar and distal cholangiocarcinoma usually follows targeted studies for the evaluation of obstructive jaundice or elevated liver enzymes. Most patients are referred after having had some studies done elsewhere, usually computed tomography (CT) and often some form of direct cholangiography, such as percutaneous transhepatic cholangiography (PTC) or endoscopic retrograde cholangiopancreatography (ERCP). In our view, histologic confirmation of malignancy is not mandatory before exploration. In the absence of previous biliary tract surgery, the finding of a focal stenotic lesion combined with the appropriate clinical presentation is sufficient for a presumptive diagnosis of hilar cholangiocarcinoma, which is correct in most instances (Wetter et al, 1991).

Although most patients with hilar strictures and jaundice have cholangiocarcinoma, alternative diagnoses are possible in 10% to 15% of patients (Wetter et al, 1991). The most common of these are gallbladder carcinoma, Mirizzi syndrome, and benign focal strictures, such as lymphoplasmacytic sclerosing pancreatitis/cholangitis, granulomatous disease, and PSC (see Chapters 42, 48, and 49). Distinguishing gallbladder carcinoma from hilar cholangiocarcinoma can be difficult. A thickened, irregular gallbladder wall with infiltration into segments IV and V of the liver, selective involvement of the right portal pedicle, and obstruction of the mid–bile duct with occlusion of the



FIGURE 50B.3. Endoscopic retrograde cholangiopancreatography findings of a mid–common bile duct stricture are typically associated with carcinoma of the gallbladder or cystic duct.

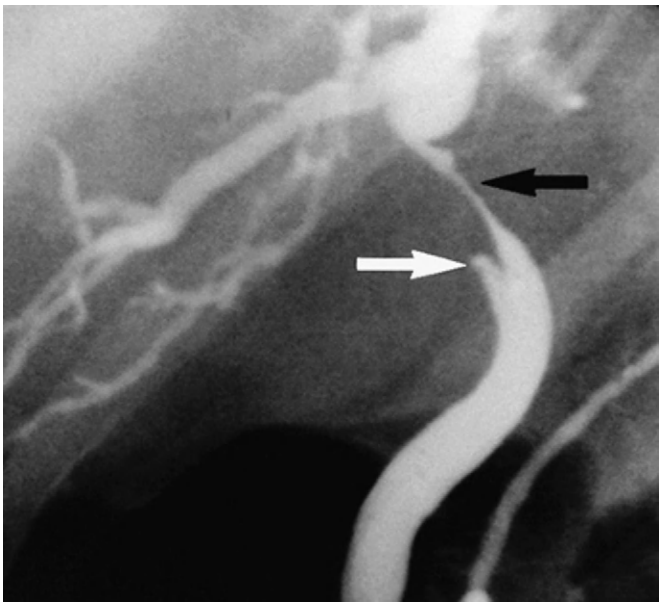


FIGURE 50B.4. Endoscopic retrograde cholangiopancreatography from a patient with a benign stricture of the proximal bile duct. The smooth, tapered appearance (*black arrow*) is in contrast to the irregular stricture typical of a sclerosing tumor. Nonfilling of the cystic duct (*white arrow*) is an important finding, and in the appropriate setting, it should raise the suspicion of gallbladder carcinoma (see Fig. 50B.3). In this patient, the chronic inflammatory process had involved the hepatic duct and cystic ducts. Most cases of benign strictures of the proximal bile duct spare the cystic duct.

cystic duct on endoscopic cholangiography all suggest gallbladder carcinoma (Fig. 50B.3).

Mirizzi syndrome is a benign condition resulting from a large gallstone impacted in the neck of the gallbladder (see Chapters 29 and 42A). The ensuing pericholecystic and periductal inflammation and fibrosis can obstruct the proximal bile duct, which is often difficult to distinguish from a malignant obstruction (Baer et al, 1990; Callery et al, 1997; Cabooter et al, 1990). Other benign focal strictures (malignant masquerade) can occur at the hepatic duct confluence but are uncommon (Fig. 50B.4; Hadjis et al, 1985; Saldinger & Blumgart, 2000; Verbeek et al, 1992; Wetter et al, 1991). The finding of a smooth, tapered stricture on cholangiography suggests a benign stricture. Diagnostic assessments based on the cholangiographic appearance of the stricture are unreliable, and hilar cholangiocarcinoma must remain the leading diagnosis until definitively disproved with operative exploration. The alternative conditions that one may encounter are best assessed and treated at operation. Relying on the results of percutaneous needle biopsy or biliary brush cytology is dangerous, because they often are misleading, and the surgeon may miss the opportunity to resect an early cancer (Enjoji et al, 1998; Rabinovitz et al, 1990). In the absence of clear contraindications, exploration is indicated in all patients with suspicious hilar lesions with concordance of clinical and radiographic findings.

Many tumors express carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9). Serum levels of these markers, although elevated in some patients, have had little diagnostic value (Pitt et al, 1995a). It has been suggested that CEA levels in hepatic bile may help distinguish between benign and malignant strictures in patients with premalignant conditions (Nakeeb et al, 1996a).

Radiographic studies are pivotal in selecting patients for resection. In the past, CT, PTC, and angiography were considered standard investigations; however, magnetic resonance cholangiopancreatography (MRCP) may provide equal anatomic information with less risk.

Direct cholangiography (see Chapter 18) shows the location of the tumor and the biliary extent of disease, both of which are crucial in surgical planning. When performed skillfully, ERCP provides useful duct detail and can effectively drain functional liver segments prior to operative planning. Although invasive, PTC outlines the extent of intrahepatic bile duct involvement reliably and has been the preferred study in the past (Pitt et al, 1995a, 1995b). High-quality cholangiograms are often thought to be essential for accurately diagnosing the extent of cancer (Kondo et al, 2004; Nimura, 1997). In many centers, particularly in Japan, surgeons extend the diagnostic process by performing detailed cholangiography with one or more percutaneous catheters placed in the intrahepatic ducts, often combined with percutaneous cholangioscopy along a mature transhepatic drain tract (Ohkubo et al, 2004; Ozden, 2002). PTC with biliary drainage should be considered not only an effective method of relieving jaundice but also an important diagnostic modality.

MRCP is a powerful investigative tool that has almost replaced endoscopic and percutaneous cholangiography as the initial preoperative assessment of hilar cholangiocarcinoma (see Chapter 17). Several studies have shown its utility in evaluating patients with biliary obstruction (Guthrie et al, 1996; Lee et al, 1997; Schwartz et al, 1998). MRCP may not only identify the tumor and the level of biliary obstruction, but it also may reveal

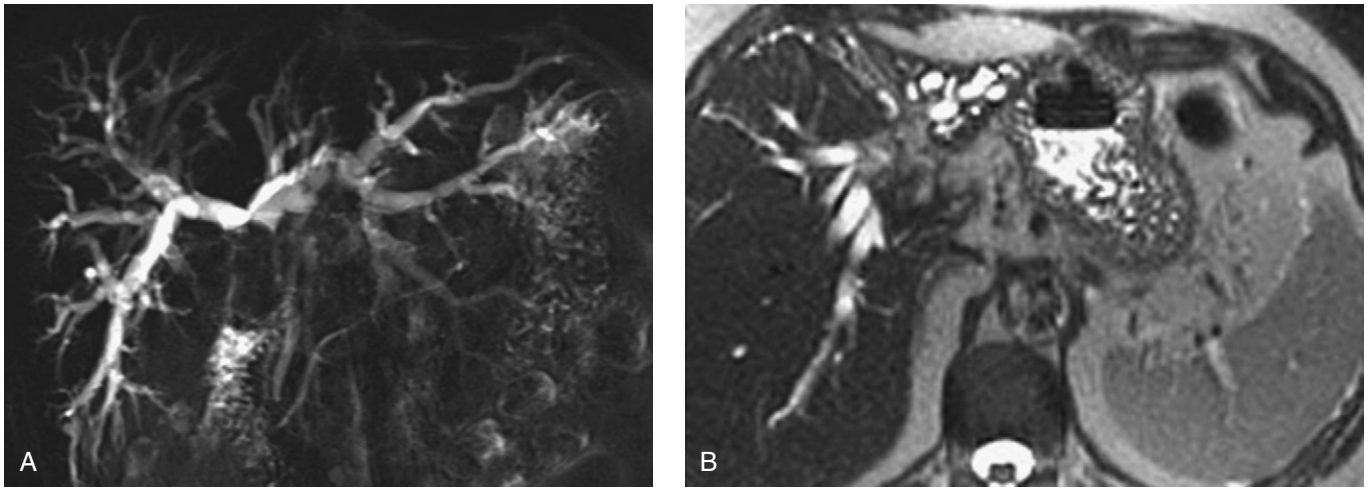


FIGURE 50B.5. Coronal (**A**) and axial (**B**) magnetic resonance cholangiopancreatographic images of a patient with hilar cholangiocarcinoma. The tumor involves the right and the left hepatic ducts. The bile ducts in this study appear white.

obstructed and isolated ducts not appreciated at endoscopic or percutaneous study (Fig. 50B.5). MRCP also provides information regarding the patency of hilar vascular structures, the presence of nodal or distant metastases, and the presence of lobar atrophy (Fig. 50B.6).

CT is an important study for evaluating patients with biliary obstruction. A high-quality CT scan can provide valuable information regarding the level of obstruction, vascular involvement, and liver atrophy (Fig. 50B.7; see Chapter 16). Advances in CT technology permit the acquisition of three distinct circulatory phases—the *arterial*, *pancreatic*, and *portal venous* phases—in the hilar and pancreatobiliary region with 1-mm collimation. These isotropic volume data allow generation of high-quality three-dimensional images—such as CT arteriography, CT cholangiopancreatography, and CT portography—in a single scanning session (Itoh et al, 2005).

Although it is operator dependent, ultrasound (US) is a useful noninvasive diagnostic study (see Chapter 13). When utilized by experienced centers, it often delineates tumor extent accurately. US can not only show the level of biliary ductal obstruction, but it can also provide information regarding tumor extension within the bile duct and in the periductal tissues (Gibson et al, 1986; Hann et al, 1997; Okuda et al, 1988). Duplex US is firmly established as a highly accurate predictor of vascular involvement and resectability (Fig. 50B.8). In a series of 19 consecutive patients with malignant hilar obstruction, US with color spectral Doppler technique was equivalent to angiography and CT portography in diagnosing lobar atrophy, level of biliary obstruction, hepatic parenchymal involvement, and venous invasion (Hann et al, 1997). Duplex US is particularly useful for assessing portal venous invasion. In a series of 63 consecutive patients from Memorial Sloan-Kettering Cancer

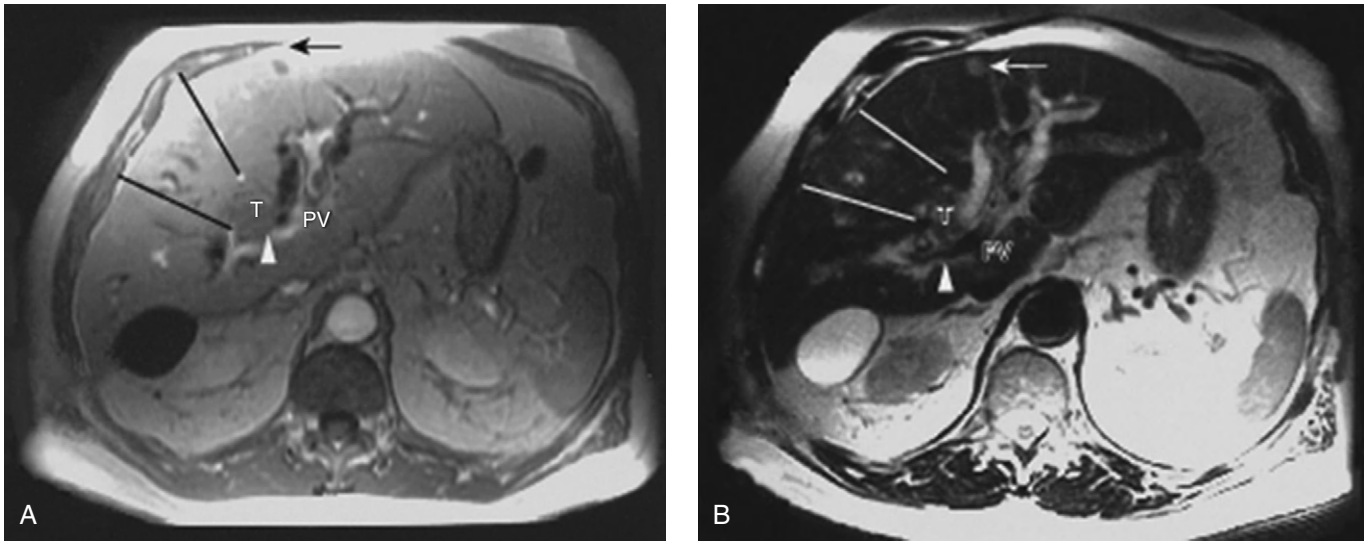


FIGURE 50B.6. **A**, T1-weighted, gadolinium-enhanced magnetic resonance image of a patient with hilar cholangiocarcinoma. The bile ducts appear black. A hilar tumor is seen (*T*), apparently adherent to or encasing the right portal vein branch (*PV; arrowhead*). The tumor has occluded the right anterior sectoral branch of the portal vein, and the anterior sector appears atrophic (*black lines*) with crowded, dilated ducts. The *arrow* points to intrahepatic metastases. **B**, Magnetic resonance cholangiopancreatography cut through the same area of the liver. Similar findings are indicated in this image, in which the bile ducts appear white.

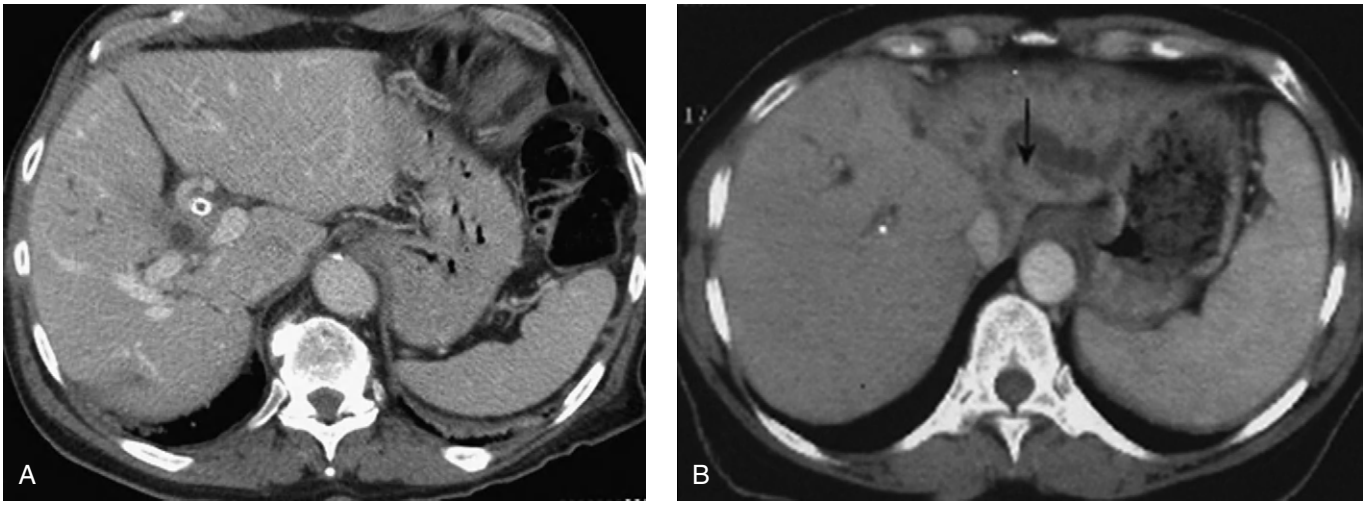


FIGURE 50B.7. Computed tomographic images from a patient with hilar cholangiocarcinoma and jaundice. **A,** The right portal vein is invaded by tumor, and there is right-sided lobar atrophy with compensatory left hemiliver hypertrophy. **B,** The left portal vein is occluded, causing left lobar atrophy with crowding of dilated ducts (*arrow*). Note that there is no defined mass in either image.

Center (MSKCC), duplex US predicted portal vein involvement in 93% of cases, with a specificity of 99% and a positive predictive value of 97%. In the same series, angiography with CT angioportography had a 90% sensitivity, 99% specificity, and 95% positive predictive value (Bach et al, 1996).

The diagnosis of malignancy in patients with bile duct strictures can be challenging and depends on accurate interpretation of ERCP and/or PTC as well as cross-sectional imaging (MRCP and CT) findings. ERCP in particular is a useful tool for assessing biliary tract strictures, as it permits visualization of the biliary tree with the opportunity for therapeutic intervention (biliary drainage) and collection of specimens for cytopathologic and histopathologic evaluation (Fig. 50B.9). Although highly specific, biliary brush cytology is limited by low to moderate sensitivity (15% to 68%; Fritcher et al, 2009). As a result, adjunctive diagnostic techniques including mutation analysis, DNA ploidy analysis, and fluorescence in situ hybridization (FISH) have been studied clinically and experimentally to improve tumor detection sensitivity (Kipp et al, 2010). Two

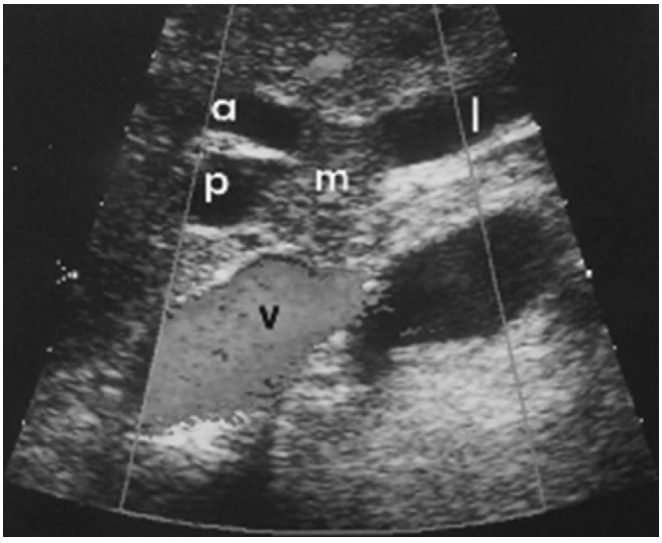


FIGURE 50B.8. Transverse color Doppler ultrasound of the biliary confluence shows a papillary cholangiocarcinoma (*m*) extending into the right anterior (*a*) and posterior (*p*) sectoral ducts and the origin of the left duct (*l*). The adjacent portal vein (*v*) is not involved and has normal flow. *(From Hann LE, et al, 1996: Malignant hepatic hilar tumors: can ultrasonography be used as an alternative to angiography with CT arterial portography for determination of resectability? J Ultrasound Med 15:37-45.)*

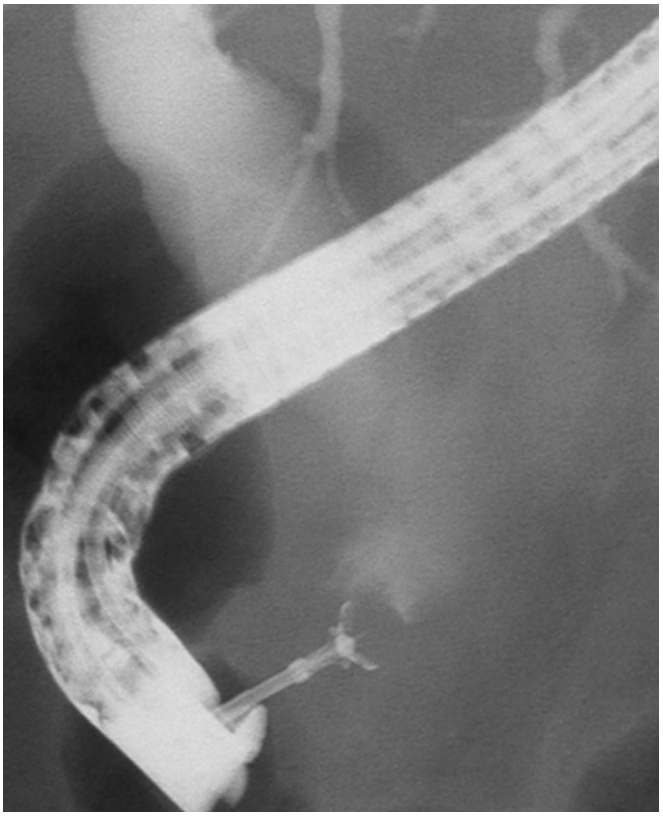


FIGURE 50B.9. Endoscopic retrograde cholangiopancreatography–guided grasp biopsy of a distal bile duct tumor in a patient presenting with obstructive jaundice and requiring biliary drainage. Cross-sectional imaging had previously staged the patient with metastatic disease, and a tissue diagnosis was sought.

types of chromosomal abnormalities are frequently identified with a clinical FISH probe set, namely polysomy and trisomy 7. Polysomy has been defined as a gain of two or more of the four probes in five cells. A large clinical study recently demonstrated that FISH was more sensitive than cytology for detecting biliary tract cancer and was able to detect 49 (22%) of 227 cancers that routine cytology interpreted as nonmalignant, without compromising test specificity (Fritcher et al, 2009).

Distal bile duct tumors frequently are mistaken for adenocarcinoma of the pancreatic head, the most common periampullary malignancy. In a series of 119 periampullary tumors, the site of origin was diagnosed incorrectly in 28% of patients preoperatively and in 20% of patients intraoperatively (Jones et al, 1985). Nevertheless, ERCP can provide valuable information regarding the level of obstruction and may show clearly that the obstruction is arising from the bile duct and does not involve the pancreatic duct. ERCP also may be useful in cases in which choledocholithiasis is suspected and may be therapeutic in these patients. PTC is generally less useful for tumors of the distal bile duct. A good quality cross-sectional imaging study also is required, usually CT, to assess for vascular involvement and metastatic disease. CT commonly does not reveal a mass, however, because these tumors are frequently small at the time of presentation. MRCP increasingly is being used to evaluate periampullary tumors. As is true for hilar lesions, it can provide images of the distal bile duct previously obtainable only with direct cholangiography and without the need for invasive procedures (Georgopoulos et al, 1999). A dilated extrahepatic bile duct terminating abruptly at its distal aspect without a concomitantly dilated pancreatic duct suggests a distal bile duct carcinoma.

In patients with a stricture of the distal bile duct and a clinical presentation consistent with cholangiocarcinoma, histologic confirmation of malignancy is generally unnecessary, unless nonoperative therapy is planned. Benign strictures occur in the lower bile duct, but these are difficult to differentiate definitively from malignant strictures without resection. Percutaneous needle biopsy is difficult, often impossible, because of the small size of these tumors. In addition, endoscopic brushings of the bile duct have an unacceptably low sensitivity, making a negative result virtually useless (Ryan, 1991). Reliance on the results of percutaneous endoscopic US-guided fine needle aspiration or endoscopic brush biopsy serves only to delay operative therapy.

PREOPERATIVE EVALUATION AND MANAGEMENT

When a biliary tract malignancy is suspected on clinical and radiographic grounds, patient evaluation should turn toward an assessment of tumor resectability and of hepatic and overall physiologic reserve. The presence of significant comorbid conditions, chronic liver disease, or portal hypertension generally precludes resection. In patients not fit for operation, biliary drainage is an appropriate intervention to consider, and the diagnosis should be confirmed histologically if palliative therapies focused on local and systemic disease control are anticipated. Patients with potentially resectable tumors occasionally present with biliary tract sepsis, frequently after instrumentation of the biliary tree. These patients require resuscitation and treatment of the infection before operation can be considered. The preoperative evaluation must address the four crucial determinants of resectability: 1) extent of tumor within the biliary tree, 2) vascular involvement, 3) hepatic lobar atrophy, and 4) metastatic disease (Burke, 1998; Jarnagin et al, 2005).

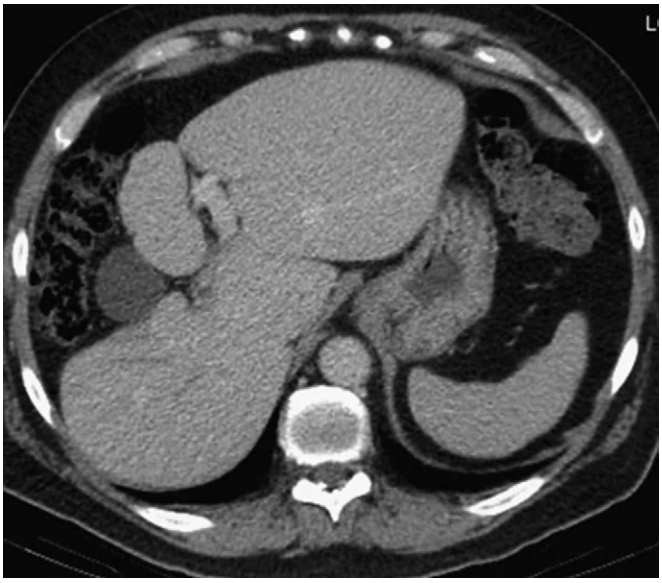


FIGURE 50B.10. Axial computed tomographic imaging demonstrates severe atrophy of the right anterior sector in a patient with a Bismuth type IV hilar cholangiocarcinoma that had invaded the respective sectoral portal vein selectively.

Lobar atrophy is an often overlooked or underappreciated finding in patients with hilar cholangiocarcinoma; however, its importance in determining resectability cannot be overemphasized, because it often influences therapy (Hadjis & Blumgart, 1987; see Chapter 5). Long-standing biliary obstruction may cause moderate atrophy, whereas concomitant portal venous compromise induces rapid and severe atrophy of the involved segments. On cross-sectional imaging, atrophy is characterized by a small, often hypoperfused lobe with crowding of the dilated intrahepatic ducts (Figs. 50B.10 and 50B.5B). The crucial determinants of resectability, including lobar atrophy, can be assessed with noninvasive studies that include cross-sectional imaging. Tumor involvement of the portal vein is usually present if compression, narrowing, encasement, or occlusion is seen on imaging studies.

Preoperative Biliary Drainage

Typically, patients with hilar cholangiocarcinoma will require major liver resection, so their preoperative management must be optimized carefully. Obstructive jaundice associated with perihilar cholangiocarcinoma differs from that associated with middle or distal bile duct cancer. In distal bile duct cancer, a single catheter is enough for biliary drainage, whereas in perihilar cholangiocarcinoma, multiple biliary drainage catheters of the future liver remnant may be necessary. Experienced centers have demonstrated excellent results with endoscopic biliary drainage, but controversy exists as to whether this technique should replace percutaneous transhepatic biliary drainage (Gholson & Burton, 1991; Polydorou et al, 1992; Speer et al, 1987). Endoscopic retrograde biliary drainage offers several advantages, including low procedure-related morbidity and mortality, shorter hospital stay, and improved patient comfort.

The limitations of endoscopic retrograde biliary drainage include a high incidence of cholangitis, especially when multiple obstructed ducts are instrumented but not subsequently drained (Andersen et al, 1989; Chang et al, 1998; Liu et al, 1998; Rerknimitr et al, 2004), and the difficulty in follow-up assessment of the extent of segmental duct involvement once an endobiliary stent is placed. Furthermore, control of which exact segmental ducts are cannulated is imperfect when performed endoscopically. For both endoscopic and percutaneous biliary drainage, a few guiding principles should be followed. The intrahepatic bile duct of the predicted future liver remnant (FLR) is intubated or punctured (Kawasaki et al, 2003; Seyama et al, 2003) and subsequently drained. If the FLR cannot be predicted with certainty in the preoperative setting, the left hepatic duct should be manipulated and drained (Fig. 50B.11). When the intrahepatic bile ducts are isolated into segmental units, PTC and multiple direct segmental transhepatic drainages may be necessary (Nagino et al, 1992; Nimura et al, 1995). If segmental cholangitis develops in patients with endoscopic or transhepatic biliary drainage catheters, urgent drainage of affected ducts should be attempted (Iyomasa et al, 1994; Sakamoto et al, 1995).

Clinical studies of biliary decompression have shown that external drainage has limited benefit, and that by preserving intestinal bile flow, the internal drainage is associated with more advantages (Clements et al, 1993). Superiority of internal drainage was shown in experimental studies, which showed that rat liver regeneration after partial hepatectomy is suppressed under external drainage but not under internal drainage (Saiki et al, 1999; Suzuki et al, 1994). Ogata and colleagues (2003) investigated bacterial translocation in bile duct–ligated rats, finding that bile replacement is essential to maintain intestinal barrier function. Impaired intestinal barrier function does not recover by percutaneous biliary drainage (PBD) without bile replacement. Bile replacement can restore the intestinal barrier function primarily as a result of repair of physical damage to the intestinal mucosa. Bile replacement during external biliary drainage should be recommended for planned hepatectomy for hilar cholangiocarcinoma because of the substantial infectious morbidity associated with these resections.

Many retrospective reports (Denning et al, 1981; Gundy et al, 1994; Nakayama et al, 1978; Norlander et al, 1982) support preoperative biliary drainage, whereas several older, prospective randomized studies (Hatfield et al, 1982; McPherson et al, 1984; Pitt et al, 1985) concluded that drainage did not reduce overall morbidity and mortality following management of proximal cholangiocarcinoma. The pertinence of the these cited randomized studies is questionable, as few major hepatectomies were included in these trials, and preoperative biliary drainage procedures were associated with unexpectedly high morbidity and mortality rates. In addition to accurate assessment of bile duct involvement, preoperative biliary drainage improves cholestatic liver disease and affords safer performance of hepatectomy for hilar cholangiocarcinoma. Lastly, the volume of the future liver remnant should be assessed prior to drainage, because with an atrophic hemiliver, very little functional liver may be removed with the resection, and performance of the operation without drainage should be considered (Kennedy et al, 2009).



FIGURE 50B.11. A percutaneous transhepatic cholangiogram (PTC) shows a left hepatic duct stricture with no apparent isolation of the segment IV and left lateral ducts. PTC guides safe placement of a percutaneous biliary drain, which can permit internalization of bile flow.

Three-Dimensional Computed Tomography

Advances in helical CT technology, such as multiple simultaneous detectors and subsecond rotation, have shown unparalleled capabilities for fast data acquisition and narrow collimation (see Chapter 16). Multidetector CT permits the acquisition of three distinct circulatory phases—arterial, portal, and late venous—in the pancreatobiliary and intrahepatic regions with 1-mm collimation. These isotropic volume data allow generation of high-quality three-dimensional images with CT arteriography, CT cholangiopancreatography, and CT portography in a single scanning session (Itoh et al, 2005).

CT is now a mainstay in the preoperative diagnostic evaluation for patients with perihilar cholangiocarcinoma, and it provides information on resectability and planning of the operation. Three-dimensional understanding of the main hepatic artery distribution may facilitate skeletonization of the hepatoduodenal ligament, and understanding of the intrahepatic artery branching is helpful during resection of the segmental or subsegmental bile ducts as the final step of resection. Hepatobiliary surgeons must appreciate two variations of the hepatic artery distribution: One is the left hepatic artery running right to the umbilical portion of the left portal vein, the other is a posterior branch of the right hepatic artery running cranially to the right portal trunk. Careful attention should be paid to the former variant in extended right hepatectomy with caudate lobectomy, and the same applies to the latter variant in extended left hepatectomy with caudate lobectomy (see Chapter 1B).

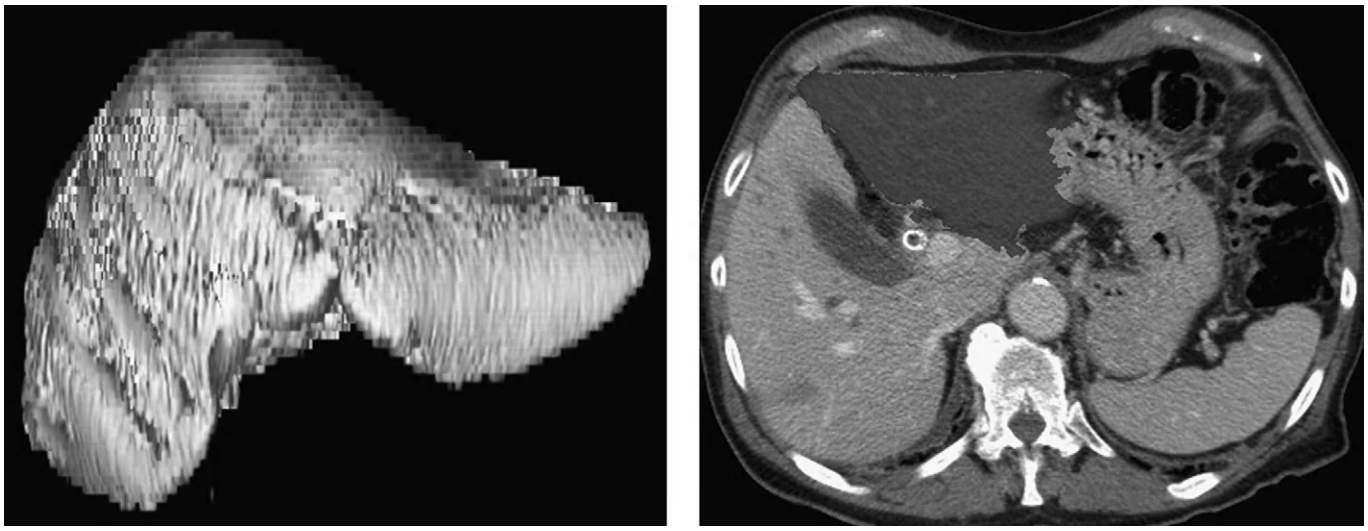


FIGURE 50B.12. Thin-slice, contrast-enhanced computed tomographic imaging can be reformatted into volume-averaged three-dimensional models. Operative planning for the future liver remnant (FLR) allows a calculation of the residual functional liver parenchyma, following hepatic resection, as a percentage of the total liver volume. Here a right trisectorectomy with caudate resection is planned with the FLR consisting of segments II and III only (*shaded area*). In this patient, the FLR represented 22% of the total liver volume prior to portal vein embolization.

Unilateral involvement of the hepatic artery is compatible with resection (Williamson et al, 1980). Bilateral involvement of the hepatic artery usually is associated with nonresectability, when the tumor is located mainly on the right. Hepatic arterial reconstruction to accomplish a complete resection should be reserved for highly selected patients with potentially curable disease. Similarly, although not an absolute contraindication for resection of hilar cholangiocarcinoma, main portal vein invasion will preclude a complete resection with long-term benefit for the majority of patients (Blumgart et al, 1984; Hoevels & Ihse, 1979; Launois et al, 1979; Williamson et al, 1980). Despite the poor prognosis associated with main portal vein invasion in general, several groups have reported reasonable long-term outcomes with portal vein resection for advanced biliary cancer (Ebata et al, 2003; Miyazaki et al, 1998a; Nimura et al, 1991a; Sakaguchi & Nakamura, 1986).

Three-dimensional CT also offers the capacity to generate volumetric models of the total liver for planned hepatic resection and FLR (Fig. 50B.12). Because patients subjected to resection of more than 75% of functional liver parenchyma have substantially higher risk of postoperative liver failure regardless of existing cholestatic liver disease, routine preoperative volumetry may help to identify and select candidates for biliary drainage and portal vein embolization (PVE) who may be at considerable risk for postoperative morbidity and mortality.

Portal Vein Embolization

Devised by Makuuchi and colleagues (1990) and Kinoshita and colleagues (1986), PVE has become important in the presurgical management of patients who are to undergo extensive liver resection (see Chapter 93). The purpose of PVE is to increase the functional liver mass by inducing compensatory hypertrophy in the FLR. The ultimate goal of PVE is to minimize postoperative liver dysfunction, which contributes to mortality. PVE may be approached in two ways: the *percutaneous approach*, or *percutaneous transhepatic portal vein embolization* (PTPE) (Baere et al, 1993; Kinoshita et al, 1986), and the *transileocolic approach*, or *transileocolic PVE* (Makuuchi et al, 1990). PTPE can be accomplished with coil and/or microparticle embolization (Fig. 50B.13) and has established itself as the superior technique for several reasons, two of which are the avoidance of a laparotomy and avoidance of general anesthesia.



FIGURE 50B.13. Portal vein embolization can be utilized to induce hypertrophy of the planned functional liver remnant (*FLR*) after major hepatectomy for hilar bile duct cancer. Percutaneous transhepatic embolization is the most widely used technique. In this patient, right portal vein branches were coil embolized 4 weeks prior to a planned right hepatectomy. Three-dimensional volumetric calculations of the planned FLR were analyzed before and after embolization.

PTPE can produce a sizable compensatory hypertrophy of the nonembolized segments of the liver (Baere et al, 1993; Kawasaki et al, 1994; Nagino et al, 1995; Nagino, 2006). In right PVE, the volume of the left lobe increases by 130 cm^3 on average within 2 weeks after embolization, and the estimated resection volume decreases by an average of approximately 10% (Nagino et al, 1995). Many case series have reported the clinical value of PVE (Abdalla et al, 2002; Elias et al, 2002; Farges et al, 2003; Hemming et al, 2003; Kawasaki et al, 2003; Nagino, 2006). A single prospective trial in patients undergoing right hemihepatectomy demonstrated a benefit in patients with chronic liver disease, but no benefit was reported in patients with normal livers (Farges et al, 2003), thus indications for PVE remain somewhat arbitrary.

Preoperative Staging

Historically, no clinical staging system was available to stratify patients preoperatively into subgroups based on potential for resection. The modified Bismuth-Corlette classification stratifies patients based on the extent of biliary duct involvement by tumor alone (Fig. 50B.14; Bismuth et al, 1992). Although useful to some extent, it does not predict resectability or survival. The American Joint Commission for Cancer (AJCC) tumor-node-metastais (TNM) staging system (Table 50B.1) is based largely on pathologic criteria and has little relevance to preoperative staging, because it can only be determined after resection. The ideal staging system should accurately predict resectability, the need for hepatic resection, and survival. Such a system would assist the surgeon in formulating a treatment plan, and it would help the patient understand the treatment options and likely outcome. Jarnagin and colleagues (2001) proposed such a system, one that improves characterization of tumor extent by taking into account all of the available preoperative data related to local tumor extent including 1) extent of tumor within the biliary tree, 2) vascular involvement, and 3) lobar atrophy. Using such an approach, it is possible to stage tumors preoperatively in a way that correlates with resectability and outcome. This preoperative T-staging system is based on the extent of local disease regardless of N or M status (Table 50B.2; Jarnagin et al, 2001). Longitudinal ductal tumor extension can be assessed by either MRCP, ERCP, or PTC. Duplex US and CT may be useful for assessing radial spread of tumor (Hann et al, 1997, 1998; Voyles et al, 1983).

This preoperative clinical staging system has been compared with the AJCC classification in a series of 87 patients with cholangiocarcinoma, with no correlation seen between AJCC stage and resectability or median survival (Burke, 1998; Jarnagin et al, 2001). By contrast, the proposed staging system correlated closely with resectability, which was highest in the T1

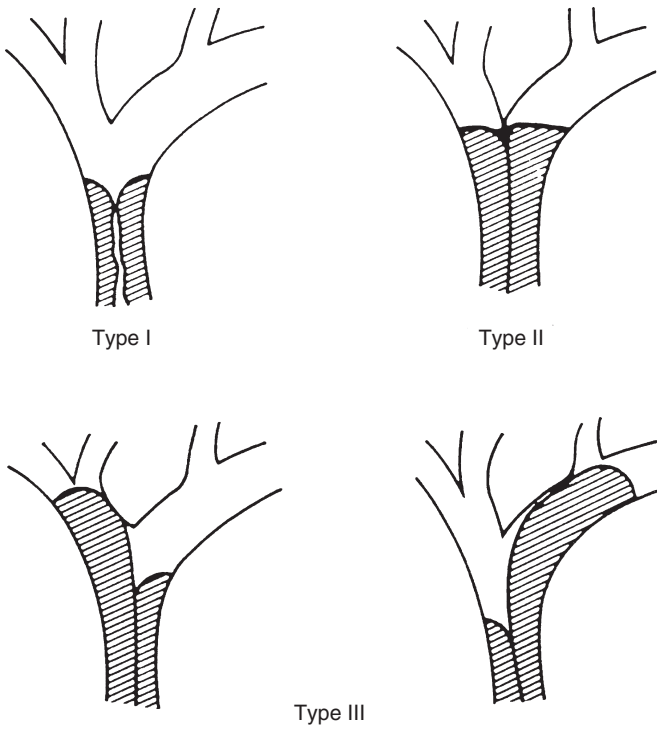


FIGURE 50B.14. Bismuth-Corlette classification scheme of biliary strictures.

Table 50B.1

AJCC Staging System (Seventh Edition) of Hilar Bile Duct Cancer

Primary Tumor (pT)

pTX:	Cannot be assessed
pT0:	No evidence of primary tumor
pTis:	Carcinoma in situ
pT1:	Tumor confined to the bile duct with extension up to the muscle layer or fibrous tissue
pT2a:	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
pT2b:	Tumor invades adjacent hepatic parenchyma
pT3:	Tumor invades unilateral branches of the portal vein or hepatic artery
pT4:	Tumor invades main portal vein or its branches bilaterally; or the common hepatic artery; or the second-order biliary radicals bilaterally; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement

Regional Lymph Nodes (pN)

pNX:	Cannot be assessed
pN0:	No regional lymph node metastasis
pN1:	Regional lymph node metastasis (including nodes along the cystic duct, common bile duct, hepatic artery, and portal vein)
pN2:	Metastasis to periaortic, pericaval, superior mesentery artery, and/or celiac artery lymph nodes

Distant Metastasis (pM)

pMx:	Cannot be assessed
pM1:	Distant metastases present

Stage Groupings

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a or T2b	N0	M0
Stage IIIa	T3	N0	M0
Stage IIIb	T1, T2, or T3	N1	M0
Stage IVa	T4	N0 or N1	M0
Stage IVb	Any T	N2	M0 or M1
	Any T	Any N	M1

AJCC, American Joint Commission on Cancer

Table 50B.2

Preoperative Tumor Staging System for Hilar Cholangiocarcinoma

Stage	Criteria
T1	Tumor involving biliary confluence ± unilateral extension to two biliary radicles
T2	Tumor involving biliary confluence ± unilateral extension to two biliary radicles and *ipsilateral* portal vein involvement ± ipsilateral hepatic lobar atrophy
T3	Tumor involving biliary confluence + bilateral extension to two biliary radicles or unilateral extension to two biliary radicles with contralateral portal vein involvement or unilateral extension to two biliary radicles with contralateral hepatic lobar atrophy or main or bilateral portal venous involvement

From Jarnagin WR, et al, 2001: Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg 234:507-519.

group (59%) and decreased progressively to 0 in the T3 group (nonresectable because of extent of local disease). Other related variables also correlated with T stage, including the likelihood of an R0 resection, presence of metastatic disease, the need for partial hepatectomy, and survival (Table 50B.3). The clinical T-stage grouping was an independent predictor not only of resectability but also of the likelihood of achieving an R0 resection. The proposed clinical staging scheme underscores the importance of considering portal vein involvement and liver atrophy in relation to the extent of ductal cancer spread. Ipsilateral involvement of vessels and bile ducts is usually amenable to resection, whereas contralateral involvement is not.

Despite advances in imaging technology, a large proportion of patients with hilar cholangiocarcinoma are found to have unresectable disease at the time of exploration. Hilar cholangiocarcinoma previously was considered more of a locally invasive disease uncommonly associated with metastases. However, in a report of 225 patients, 73 (32%) had unresectable disease; of the 160 patients submitted to exploration, 47 (29%) had metastases discovered intraoperatively that precluded a curative resection (Jarnagin et al, 2001). Given the high rate of nontherapeutic laparotomy, staging laparoscopy has been investigated as a means of improving resectability and seems to have a defined role.

Early studies examined the role of laparoscopy combined with laparoscopic US in a mixture of hepatobiliary and pancreatic malignancies and detected occult metastases in 30% to 35% of patients (Callery et al, 1997; D'Angelica et al, 2003; Jarnagin et al, 2000), but these studies included a small proportion of patients with hilar cholangiocarcinoma. Two studies showed the utility of staging laparoscopy in patients with biliary tract cancer. In a study that included 23 patients with hilar and distal cholangiocarcinoma, Vollmer and colleagues (2002) reported that laparoscopy identified 57% of patients with unresectable disease and improved resectability by 14%. Another study analyzed 56 patients, all with hilar cholangiocarcinoma, and showed similar benefit; it further showed that the yield of laparoscopy is greatest in patients with more locally advanced tumors (i.e., clinical stage T2 and T3; Weber et al, 2002). Whether fluorodeoxyglucose positron-emission tomography (FDG PET) has a role in preoperative staging is unclear (see Chapter 15). Several studies have suggested that FDG PET may identify occult metastatic disease or advanced regional lymphadenopathy (N2 disease) in a significant proportion of patients (Anderson et al, 2004; Fritscher-Ravens et al, 2001; Kluge et al, 2001); however, larger confirmatory studies are necessary before FDG PET can be recommended as routine.

As mentioned earlier, both direct cholangiography of segmental ducts and percutaneous cholangioscopy have been used to increase resectability rates for hilar cholangiocarcinoma (Kondo et al, 2004; Nimura et al, 2000). Definition of proximal and distal cancer extent and early detection of small lesions and multiple foci of cancer can be accomplished by cholangioscopic observation followed by biopsy and histologic confirmation (Nimura et al, 1988).

TREATMENT

Most patients with unresectable bile duct cancer die within 6 months to 1 year of diagnosis. Death usually results from liver failure or infectious complications secondary to biliary obstruction (Burke, 1998; Kuwayti et al, 1957; Okuda et al, 1977; Sako et al, 1957). In patients with unresectable disease, the prognosis has been considered worse for tumors affecting the confluence of the bile ducts and better for distal tumors close to the papilla. This difference in prognosis may reflect the relatively later presentation and the complexity of managing hilar biliary obstruction rather than a difference in biologic behavior. It has been shown that location within the biliary tree (proximal versus distal) has no impact on survival, provided complete resection is achieved (Allen et al, 2008; Nagorney et al, 1993).

Complete resection is the only effective therapy for cancers of the lower bile duct (Fong et al, 1996; Nagorney et al, 1993;

Table 50B.3

Correlation of Proposed Clinical Tumor Staging System with Resectability, Metastatic Disease, and Survival

T Stage	No. Patients	Explored with Curative Intent	Resected	R0 Resection	Hepatic Resection*	Metastatic Disease	Median Survival (mo)†
1	87	73 (84%)	51 (59%)	38 (44%)	33 (65%)*	18 (21%)	20
2	95	79 (83%)	29 (31%)	24 (25%)	29 (100%)*	40 (43%)	13
3	37	8 (22%)	0	0	0	15 (41%)	8
Total	219	160 (71%)	80 (37%)	62 (28%)	62 (78%)*	73 (33%)	16

*Percentage figures for hepatic resection represent the proportion of all resections; all other percentage figures represent the proportion of the total number of patients within each stage group.

†Median survival for all patients within each stage group, including patients not submitted to resection

From Jarnagin WR, et al, 2001: Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg 234:507-519.

Nakeeb et al, 1996b; Tompkins et al, 1981; Wade et al, 1997; Yeo et al, 1997). Meaningful experience with these relatively uncommon tumors has been limited to a few centers. In reports containing significant numbers of patients, 5-year survival rates of 40% have been reported after complete resection. In most studies, survival beyond 1 year was uncommon in patients subjected to palliative bypass or biliary intubation (Fong et al, 1996; Nakeeb et al, 1996b; Tompkins et al, 1981; Wade et al, 1997).

Operative Resection for Hilar Cholangiocarcinoma

The two objectives in the therapy of hilar cholangiocarcinoma are complete tumor excision with negative margins if possible and restoration of biliary-enteric continuity from an adequate liver remnant. Patients should be evaluated fully for possible curative resection before any intervention is performed, because stent-associated infection and inflammation renders assessment and exploration difficult. If resection is clearly not feasible, biliary drainage with some form of endoluminal or transhepatic stenting offers satisfactory palliation, and this can be combined with nonoperative measures to control local tumor growth.

Orthotopic liver transplantation has been attempted for hilar cholangiocarcinoma considered unresectable (see Chapter 97E). Klempnauer and colleagues (1997b) reported four long-term survivors out of 32 patients who underwent transplantation for hilar cholangiocarcinoma. The same group also reported a 5-year survival of 17% for their overall transplant group (Pichlmayr et al, 1996). Iwatsuki and colleagues (1998) reported comparable results. Data from the Mayo Clinic suggest good results with transplantation in highly selected patients with no metastatic disease on imaging or at laparotomy when combined with an intensive pretransplant treatment regimen that includes chemoradiotherapy (Heimbach et al, 2004; Rea et al, 2005). Although the data are compelling, this approach is applicable to only a small fraction of patients because of the high incidence of lymph node metastases and distant occult metastases.

In patients with potentially resectable tumors based on preoperative imaging, the primary goal should be complete resection with intent to cure. Our criterion for curative resection is complete removal of all gross disease with clear histologic margins (R0 resection). Achieving an R0 resection almost always requires a partial hepatectomy for hilar cholangiocarcinoma (Jarnagin et al, 2001). Bile duct excision with en bloc partial hepatectomy, often with en bloc caudate lobectomy (Nimura et al, 1990), is frequently necessary to achieve negative histologic margins.

Several studies show a parallel between the number of patients undergoing partial hepatectomy and negative resection margins (Table 50B.4). We routinely use hepatic resection but perform caudate resection selectively in cases with suggested tumor extension into the ducts of the caudate lobe. The principal caudate lobe ducts drain into the left hepatic duct, and tumors extending into the left hepatic duct almost always involve the caudate duct and usually require caudate resection (Mizumoto & Suzuki, 1988). A dilated caudate duct suggestive of tumor involvement may occasionally be seen on preoperative imaging. In some cases, intraoperative frozen section of the caudate duct margin may help in making the decision to proceed to caudate resection. The importance of negative resection margins for long-term survival is confirmed by the results of several studies (see Table 50B.4). In the MSKCC experience, survival after an R1 resection (histologically involved resection margins) is similar to survival in patients with unresectable, locally advanced tumors identified at exploration (Fig. 50B.15; Endo et al, 2008b; Jarnagin et al, 2001).

Table 50B.4

Influence of Partial Hepatectomy on Histologic Margins in Patients Who Underwent a Potentially Curative Resection for Hilar Cholangiocarcinoma

Reference	Potentially Curative Resection (No.)	Hepatectomy (%)	Negative Margins (%)
Cameron et al, 1990	39	20	15
Tsao et al, 2000	25	16	28
Hadjis et al, 1990	27	60	56
Neuhaus et al, 1999	95	85	61
Jarnagin, et al 2001	80	78	78
Klempnauer et al, 1997a, 1997b	147	79	79
Nimura et al, 1990	55	98	83

Distinguishing resectable from nonresectable tumors demands careful consideration of all available clinical and imaging data. Bilateral tumor extension to second-order intrahepatic biliary radicles and, in many patients, encasement or occlusion of the main portal vein preclude a resection. The individual determinants of resectability must be considered within the context of all of the imaging findings. Ipsilateral involvement of the portal vein and bile ducts may be amenable to resection, whereas contralateral involvement usually is not. Likewise, ipsilateral lobar atrophy does not preclude resection, whereas atrophy of the contralateral lobe does. Other factors that influence resectability include the presence of significant comorbid medical conditions, significant hepatic parenchymal disease, and distant metastatic spread of tumor (Table 50B.5).

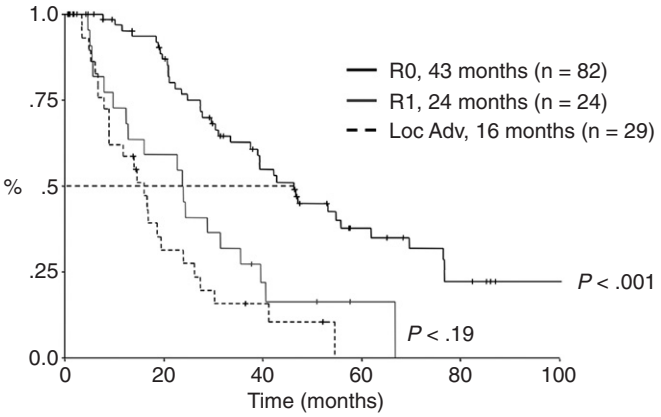


FIGURE 50B.15. Actuarial survival curves after resection of hilar cholangiocarcinoma. *R0* indicates complete resection with histologically negative resection margins (median survival, 43 months). *R1* indicates histologically involved resection margins (median survival 24 months; $P < .001$ R0 vs. R1). *Loc Adv* indicates a patient explored but found to have unresectable tumors owing to local invasion (no metastatic disease; median survival, 16 months; $P < .19$ R1 vs. Loc Adv).

Table 50B.5

Criteria of Nonresectability in Patients with Hilar Cholangiocarcinoma

Patient Factors
Medically unfit for operation
Cirrhosis/portal hypertension
Local Factors
Hepatic duct involvement up to secondary radicles bilaterally
Encasement or occlusion of the main portal vein proximal to its bifurcation
Atrophy of one lobe with encasement of contralateral portal vein branch
Atrophy of one lobe with contralateral involvement of secondary biliary radicles
Distant Disease
Histologically proven metastases to lymph node groups beyond the hepatoduodenal ligament (celiac, paraaortic, retropancreatic)
Histologically proven metastases to liver, lung, or peritoneum

Invasion of the main portal vein or its branches by tumor is a major determinant of resectability. The preoperative assessment of vascular involvement and ductal extension of tumor is an essential part of operative planning and gives valuable information to the surgeon with respect to the extent of operation and operative strategy. Limited tumor involvement of the portal venous confluence or the main portal vein may be amenable to resection and portal vein reconstruction (see Chapter 91B).

Several technical steps during the exploration and resection of hilar cholangiocarcinoma are crucial to the success of the operation. Local resection—that is, resection of the extrahepatic biliary apparatus without concomitant partial hepatectomy—for small Bismuth-Corlette type I tumors not involving the major vessels may be possible. In this situation, resection must include removal of the entire supraduodenal bile duct, gallbladder, cystic duct, and extrahepatic hepatic ducts with clearance of the supraduodenal tissues, including the related lymph nodes. Even if a complete resection can be achieved without an en bloc partial hepatectomy, such local resections seem to be inferior with respect to long-term survival. In 106 resections at MSKCC, 19 were local resections, and 9 of these were considered complete or R0; however, no patient submitted to an R0 bile duct resection was among the 5-year survivors (Jarnagin et al, 2005). In most patients, the option of a local resection does not exist, however, because of intrahepatic extension of the tumor, right or left portal vein involvement, or both. In these cases, en bloc liver resection, often with caudate lobectomy, is necessary to achieve tumor clearance. In some patients, tumor adherence to the portal vein can be managed by segmental portal vein resection and reconstruction (Blumgart et al, 1984; Neuhaus et al, 1999; Nimura et al, 1991b). This procedure can be done only if intraoperative assessment shows that a tumor-free remnant with intact biliary drainage and blood supply can be left in situ. Some centrally located tumors may be amenable to a more limited hepatic resection. Such resections, which include segments IV and V or IV and I, are limited in their application (Grune et al, 1991; Miyakawa et al, 1996; Miyazaki et al, 1998a, 1998b) and are inappropriate in the face of lobar atrophy and involvement of a main portal vein branch, both of which are common findings.

Operative exploration is carried out through a right subcostal incision with proximal extension to the xiphoid, a so-called "hockey stick" incision. The exploration should begin with a thorough inspection of the peritoneal cavity and distant nodal sites, because metastatic disease is common in patients with hilar cholangiocarcinoma. In our experience, 73 (50%) of 145 unresectable patients had metastases to regional lymph nodes or distant sites (Jarnagin et al, 2001). These findings are supported by results from other series (Cameron et al, 1990; Lai et al, 1987). Careful bimanual palpation of the liver and intraoperative US are performed to rule out unsuspected masses in the liver. Palpation of the caudate lobe is performed after incision of the lesser omentum, allowing access to the lesser sac. A Kocher maneuver is performed to allow access to the retroduodenal lymph nodes, and the ligamentum teres is elevated, exposing the undersurface of the liver and allowing thorough examination of the subhilar and retroduodenal area. Precise assessment of tumor extension and biopsy of any suspicious lesions or distant lymph nodes with frozen-section analysis should be performed. Evidence of intrahepatic metastases, multicentricity within the liver, or spread to distant sites precludes resection. With any of these findings, the patient should be considered for palliative biliary drainage.

Although a segmental bile duct resection and biliary reconstruction are possible in some patients, most require partial hepatectomy to achieve complete tumor clearance. In all cases, the surgeon must be prepared to perform a liver resection. The general principles of intraoperative management are discussed in detail in other chapters within this text (see Chapters 90 and 91). Preparation for surgery includes suitable intraoperative monitoring and the possibility for rapid transfusion. The patient's central venous pressure is kept at less than 5 mm Hg during the operation to keep blood loss from hepatic veins at a minimum during retrohepatic dissection, dissection of the hepatic veins, and parenchymal transection (Cunningham et al, 1994; Melendez et al, 1998).

The following description summarizes the initial steps of dissection, exposure of the hilar structures, dissection and resection of the hilar structures, and subsequent biliary-enteric reconstruction as performed for a segmental bile duct resection. The specifics of en bloc liver resection, including caudate lobectomy, are discussed in other chapters.

To reach the confluence of the bile ducts and assess its relationship to the portal vein, the common bile duct first must be transected above the duodenum and turned upward. The liver hilus is fully exposed anteriorly by taking down the gallbladder and lowering the hilar plate by incising the Glisson capsule along the base of segment IV. Exposure of the left hepatic duct is improved by dividing the bridge of liver tissue that often connects the base of segment IV and the left lateral segment; this may be quite substantial in some patients. The entire extrahepatic biliary apparatus and adjacent lymphatic tissues are turned upward to expose the portal vein. A plane can be developed easily between the posterior aspect of the bile duct tumor and the portal vein, provided no tumor has invaded into the vessels (Fig. 50B.16). The dissection is continued upward toward the hilus, skeletonizing the portal vein and hepatic artery.

At this point, the surgeon should assess the proximal extent of tumor by palpation and, if necessary, by biopsy. Segmental bile duct resection is possible only if an adequate length of the hepatic ducts can be achieved beyond the tumor, and if no vascular involvement is evident. If the tumor extends to the

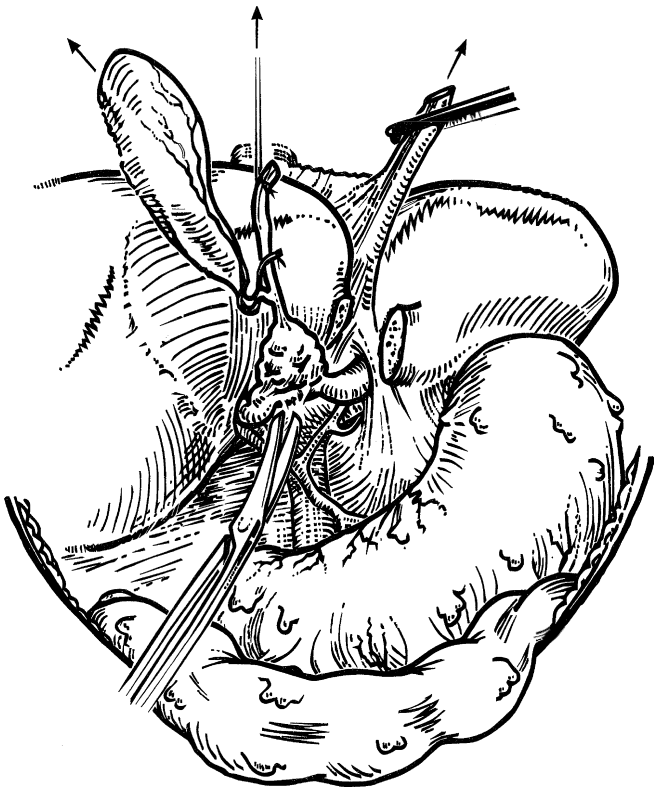


FIGURE 50B.16. The entire extrahepatic biliary apparatus is elevated together with associated portal connective tissue and nodes to allow dissection anterior to the bifurcation of the portal vein and elevation of the tumor, which is now completely mobilized. The hepatic artery and portal vein are skeletonized.

second-order biliary radicles unilaterally such that clearance cannot be achieved, or if the ipsilateral portal vein branch is involved, partial hepatectomy must be performed. Tumors extending well into the left hepatic duct may involve the caudate ducts as well and require en bloc caudate lobectomy (Mizumoto et al, 1986; Mizumoto & Suzuki, 1988). If partial hepatectomy is required, inflow control is obtained by ligation and transection of the ipsilateral branch of the portal vein and hepatic artery. Extrahepatic control and division of the ipsilateral hepatic vein are performed before parenchymal transection.

When it has been established that segmental bile duct excision is feasible and will result in an R0 resection, the left and right hepatic ducts are divided above the tumor. Occasionally, unresectability as a result of main portal vein invasion or extensive bilateral intrahepatic duct involvement (see Table 50B.5) will not be determined until the extrahepatic biliary tree has been divided and mobilized. In both of these situations, biliary-enteric continuity is restored by hepaticojejunostomy to a Roux-en-Y loop of jejunum. When residual disease remains at the final level of the transected duct, appropriate consideration should be made for placement of retrograde transhepatic biliary stents (Fig. 50B.17). After removal of the tumor, the surgeon may be faced with multiple exposed duct orifices, all of which require suitable drainage (see Chapters 29 and 42A). Frequently, removal of the tumor results in discontinuity of the right anterior and posterior sectoral ducts, separation of one or more caudate ducts from the left hepatic duct, or both. The sidewalls of adjacent ducts can be brought into apposition with sutures and regarded as a single duct for purposes of anastomosis. In cases of multiple exposed ducts, it is often possible to make it so that no more than two or three separate ducts need to be anastomosed. A Roux-en-Y loop of jejunum is prepared and brought up, usually in a retrocolic fashion, and anastomosis is carried out in an end-to-side fashion between the exposed ducts and the side of the jejunal loop using a single layer of 4-0 interrupted polyglactin 910 (Vicryl) sutures (Blumgart & Kelley, 1985; Voyles & Blumgart, 1982). Anastomotic techniques are illustrated and discussed in more detail in other chapters.

High biliary anastomoses to multiple ducts can be exceedingly difficult and require careful planning. Multiple disconnected ducts that cannot be approximated should be similarly viewed as a single duct for purposes of the anastomosis. It is usually impossible to perform sequential anastomoses in this location. The safest and most reliable method is to place the entire anterior row of sutures to all exposed ducts and separately place the entire posterior row of sutures to the duct and jejunum. The jejunum is railroaded up on the posterior sutures so that the back wall of the duct is flush with the back wall of the jejunum. The posterior layer of sutures to all exposed ducts is tied first, and the previously placed anterior sutures are passed sequentially through the anterior jejunal wall to complete the anastomosis. We routinely employ dependent drainage near the anastomosis.

Operative Resection for Distal Cholangiocarcinoma

Resection of most distal bile duct cancers requires pancreatoduodenectomy (see Chapter 62A). Compared with patients with pancreatic cancer, those with distal bile duct cancer are more often amenable to resection, less often have microscopic disease at the resection margin, and less frequently have spread of tumor to adjacent lymph nodes (Fong et al, 1996; Nakeeb et al, 1996a, 1996b; Yeo et al, 1997). In addition to completeness of resection, lymph node status is a crucial determinant of outcome. Fong and colleagues (1996) found that lymph node status was the only independent predictor of long-term survival in resected patients, with positive nodes conferring a 6.7 times greater likelihood of recurrence and death. Similarly, Wade and colleagues (1997) identified no survivors beyond 3 years with involved regional lymph nodes, and Nakeeb and colleagues (1996a, 1996b) found that lymph node status and tumor differentiation were independent predictors of outcome.

OUTCOMES AFTER OPERATION

Long-term survival can be achieved with an acceptable operative mortality (Ahrendt et al, 1998; Baer et al, 1993; Hadjis et al, 1990; Hasegawa et al, 2007; Haswell-Elkins et al, 1991; Hemming et al, 2005; Jarnagin et al, 2001; Klempnauer et al, 1997a; Kondo et al, 2004; Nagata et al, 1990; Nagorney et al, 1993; Nakeeb et al, 1996a, 1996b; Neuhaus et al, 1999; Nimura et al, 1990, 2000; Parc et al, 1997; Pichlmayr et al, 1996; Rosen et al, 1991; Sano et al, 2006; Wolber et al, 1991). Five-year survival rates range from 25% to 40%, and status of the resection margins is crucial to obtaining such results. Several studies have shown that patients resected with negative histologic margins survive significantly longer than those with involved

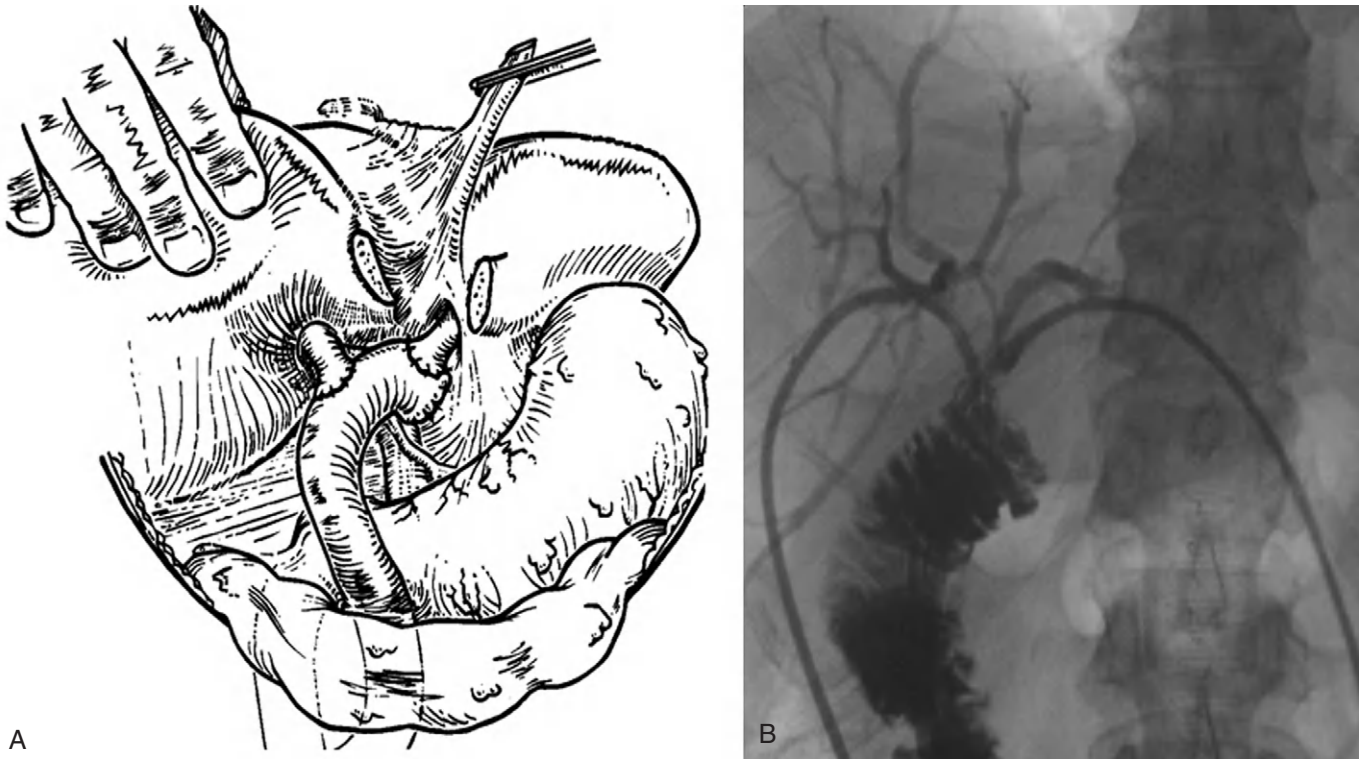


FIGURE 50B.17. A, In rare circumstances, the extrahepatic biliary tree can be excised alone with curative intent without the need for partial hepatectomy. In other situations, tumor unresectability may not be determined until the extrahepatic bile ducts are divided. The exposed right and left hepatic ducts are anastomosed individually to a retrocolic Roux-en-Y loop of jejunum. **B,** Retrograde transhepatic biliary stents can be passed at the time of operation to provide long-term palliation of obstructive jaundice and facilitate photodynamic therapy.

margins (Ahrendt et al, 1998; Endo et al, 2008b; Hadjis et al, 1990; Jarnagin et al, 2001; Lupi et al, 1990; Pichlmayr et al, 1996).

Since the 1980s, the use of hepatic resection in patients with hilar cholangiocarcinoma has increased steadily. We believe this increase is responsible for the increase in the percentage of R0 resections (negative histologic margins) and the observed improvement in survival after resection (Saldinger & Blumgart, 2000). In addition to status of the resection margin, many other variables have been shown to have an impact on outcome, including tumor involvement of regional lymph nodes, tumor grade or differentiation, and tumor morphology (e.g., papillary versus nodular sclerosing) (Ebata et al, 2003; Jarnagin et al, 2005). The issue of lymph node metastases, their impact on outcome, and extent of lymphadenectomy remain points of some controversy. Some authors have reported long-term survivors, even with involved paraaortic lymph nodes, and have argued for extended lymphadenectomy as a routine part of the resection procedure (Kitagawa et al, 2001). Examination of several series in which 5-year survival is documented suggests, however, that involved lymph nodes are a powerful adverse prognostic variable. We do not advocate extended lymph node dissection, and we consider metastatic involvement of distant lymph node basins (N2 disease) to represent unresectable disease.

In many prior studies, the operative mortality associated with hilar cholangiocarcinoma, including partial hepatectomy, was on the order of 10%. In an effort to improve these figures, numerous centers have adopted an approach that combines extensive preoperative biliary drainage and PVE, as discussed previously. Using such an approach, Sano and colleagues (2006) reported 102 consecutive resections without operative mortality. A major rationale for using these preoperative procedures is to reduce the incidence of postoperative hepatic failure associated with extended resections in the setting of biliary obstruction.

The combined data from the literature suggest that survival after resection of adenocarcinoma of the distal bile duct is at least as good as and probably better than that for pancreatic cancer (Fong et al, 1996; Wade et al, 1997). It has long been assumed that survival after resection of distal bile duct tumors is greater than after resection of hilar cholangiocarcinomas (Tompkins et al, 1981). This assumption is almost certainly erroneous and likely evolved from older reports that did not take into account the status of resection margins in patients with hilar tumors. If adjusted for stage and completeness of resection, the survival rates seem to be comparable (Allen et al, 2008; Nagorney et al, 1993).

ADJUVANT THERAPY AFTER OPERATIVE RESECTION

Several single-arm studies have investigated the benefit of postoperative adjuvant radiation therapy in patients with hilar cholangiocarcinoma. Two separate reports from Johns Hopkins (Cameron et al, 1990; Pitt et al, 1995b) showed no benefit of adjuvant external beam and intraluminal radiation therapy. Kamada and associates (1996) suggested that radiation might improve survival in patients with histologically positive hepatic duct margins. Additionally, in a small series of patients (five

with hilar cholangiocarcinoma), resectability was reportedly greater in patients given neoadjuvant radiation therapy before exploration (McMasters et al, 1997). None of these studies was randomized, however, and most consist of a small, heterogeneous group of patients. At present, no data are available to support the routine use of adjuvant or neoadjuvant radiation therapy except in the context of a controlled trial.

Takada and associates (2002) reported results of a Phase III multicenter randomized study evaluating the potential benefit of adjuvant systemic chemotherapy after resection of pancreatobiliary tumors. This study found no benefit of adjuvant systemic 5-fluorouracil (5-FU) and mitomycin C compared with surgery alone for patients with bile duct carcinoma. Whether newer agents, such as gemcitabine and/or oxaliplatin, have a role in the adjuvant setting remains to be determined.

Adjuvant therapy (chemotherapy and/or radiation therapy) after resection has not been shown to improve survival for distal bile duct cancer, although this issue has not been evaluated in a prospective fashion for a homogeneous population of patients with distal cholangiocarcinoma only (Nakeeb et al, 1996b).

PALLIATIVE THERAPY

Most patients with hilar cholangiocarcinoma are not suitable for resection. In this setting, management options include some form of biliary decompression or supportive care. Jaundice alone, without pruritus or cholangitis, is not an indication for biliary decompression. For biliary decompression in inoperable patients, our current indications are to relieve intractable pruritus, treat cholangitis, gain access for intraluminal radiotherapy, and allow recovery of hepatic parenchymal function in patients who are potential candidates for chemotherapy. Supportive care alone is probably the best approach for elderly patients with significant comorbid conditions, provided that pruritus is not a major feature. Patients who are found to be unresectable at operation represent a different group, and operative biliary decompression usually is performed successfully (Burke, 1998) and can be constructed to provide access to the biliary tree for postoperative irradiation (see Fig. 50B.17; Kuvshinoff et al, 1995).

Assessment of palliative biliary drainage procedures is difficult, because the spectrum of patients ranges from those critically ill and unresectable to those in relatively good health with potentially resectable tumors. All patients should be assessed properly by experienced personnel with a view toward possible resection. This point cannot be overemphasized: ***If the patient is deemed unresectable, the diagnosis should be confirmed with a biopsy.*** Biliary decompression can be achieved by percutaneous transhepatic puncture or by endoscopic stent placement (see Chapters 27, 28, and 50D). Hilar tumors are more difficult to traverse with the endoscopic technique, which should only be approached by skilled endoscopists with extensive ERCP experience. The failure rates and incidence of subsequent cholangitis after endoscopic drainage can be high (Liu et al, 1998). For this reason, initial endobiliary drainage, even in the palliative setting, should utilize plastic stents. Exchange for metallic stents can be considered after close monitoring for adequate palliative biliary drainage with plastic stents in the short and intermediate term.

Percutaneous transhepatic biliary drainage and subsequent placement of a self-expandable metallic endoprosthesis can be performed successfully in most patients with hilar obstruction. Satisfactory results, even with experienced interventional radiologists, are more difficult to achieve in patients with hilar tumors than in patients with distal biliary obstruction (Becker et al, 1993; Cheung & Lai, 1995; Miyazaki et al, 1998a, 1998b; see Chapters 28 and 50D). Satisfactory drainage of only 25% to 30% of functional hepatic parenchyma is required for resolution of jaundice. Still, hilar tumors frequently isolate all three major hilar ducts—left hepatic, right anterior sectoral hepatic, and right posterior sectoral hepatic—and two or more uncovered stents must be placed for adequate drainage (Fig. 50B.18;



FIGURE 50B.18. Unresectable hilar cholangiocarcinoma tends to isolate all major hilar bile ducts from one another. In this patient, two expandable metallic stents were required for adequate biliary drainage. Self-expanding metal stents are shown here on plain radiography and coronal computed tomographic imaging.

Schima et al, 1997). Bilateral drainage is not better or more effective than unilateral drainage, provided that an adequate volume of liver parenchyma can be decompressed (De Palma et al, 2001). It also must be considered that jaundice may result from hepatic dysfunction secondary to portal vein occlusion. Jaundice in this setting, without intrahepatic biliary dilation, is not correctable with biliary stents. In addition, lobar atrophy is an important factor when considering palliative biliary procedures. Percutaneous drainage through an atrophic lobe does not relieve jaundice and should be avoided. The presence of multiple intrahepatic metastases or ascites also may add to the technical difficulty of the procedure.

The median patency of metallic endoprostheses at the hilus is approximately 6 months (Glattli et al, 1993), significantly less than that reported for similar stents placed in the distal bile duct. Becker and colleagues (1993) reported 1-year patency rates of 46% and 89% for metal stents placed at the hilus and at the distal bile duct. Similarly, Stoker and Lameris (1993) documented occlusion in 36% of patients at the hilus compared with 6% of patients with self-expanding metal stents (SEMS) in the distal bile duct. In most series of SEMS placed for hilar obstruction, documented stent occlusion requiring reintervention occurs in 25% of patients (Becker et al, 1993; Bergquist et al, 1998; Glattli et al, 1993; Hurlimann & Gardiol, 1991; Rossi et al, 1994; Schima et al, 1997; Stoker & Lameris, 1993). This percentage concurs with our findings of a mean patency of 6.1 months in 35 patients palliated for malignant high biliary obstruction by placement of expandable metallic endoprostheses. The periprocedural mortality was 14% at 30 days, and seven patients (24%) had documented stent occlusion that required repeated intervention (Glattli et al, 1993). In a recent prospective trial, patients presenting for percutaneous biliary drainage for malignant biliary obstruction had a dismal survival and experienced no improvement in quality of life with drainage. The exception in this trial was an improvement in pruritus-related quality of life, which was significantly better (Robson et al, 2010).

Palliating distal biliary obstruction in unresectable patients can be achieved with an operative bypass (hepaticojejunostomy or choledochojejunostomy) or with placement of a biliary stent. Endoprostheses for distal biliary obstruction are typically easy to place and have a greater long-term patency than endoprostheses placed for hilar obstruction (Becker et al, 1993). Operative biliary-enteric bypass, either open or laparoscopic, will provide excellent relief of jaundice and can be done with an acceptably low morbidity and mortality. Patients who are found to have unresectable disease at the time of operative exploration should undergo biliary-enteric bypass. Planned palliative operative bypass should be reserved for patients expected to survive greater than 6 months (van den Bosch et al, 1994), and endoscopic SEMS should be used in patients with clear-cut metastatic disease on cross-sectional imaging or discovered with staging laparoscopy.

Patients with hilar tumors who are found to be unresectable at operation may be candidates for hepaticojejunostomy or intrahepatic biliary-enteric bypass. The segment III duct usually is the most accessible and is our preferred approach, but the right anterior or posterior sectoral hepatic ducts also can be used (Jarnagin et al, 1998; see Chapter 42A). Typically, a segment III bypass is used to restore biliary-enteric continuity after the bile duct has been divided and a locally invasive, unresectable tumor has been discovered. Segment III bypass provides excellent biliary drainage and is less prone to occlusion by tumor than a SEMS (Stoker & Lameris, 1993), because the anastomosis can be placed some distance away from the tumor (Fig. 50B.19). Relief of jaundice is achieved if at least one third of the functioning hepatic parenchyma is adequately drained. Communication between the right and left hepatic ducts is unnecessary, provided the undrained lobe has not been percutaneously drained or otherwise contaminated (Baer et al, 1994). In this circumstance, there is a high risk of persistent biliary fistula and cholangitis. Bypass to an atrophic lobe or a lobe heavily involved with tumor is ineffective. In a report of 55 consecutive bypasses in patients with malignant hilar obstruction, segment III bypass in patients with hilar cholangiocarcinoma (n = 20) yielded the best results. The 1-year bypass patency in this group was 80%, with no perioperative deaths (Jarnagin et al, 1998).



FIGURE 50B.19. Transhepatic cholangiography obtained via a temporary percutaneous drainage tube shows a widely patent anastomosis from the segment III duct to a Roux-en-Y loop of jejunum (*arrows*).

Patients with unresectable, locally advanced tumors but without evidence of widespread disease may be candidates for palliative radiation therapy. A combination of external beam radiation (5000 to 6000 cGy) and intraluminal iridium-192 (2000 cGy) delivered percutaneously is typically used. Several authors have shown the feasibility of this approach, but improved survival compared with biliary decompression alone has not been documented in a controlled study (Bowling et al, 1996; Cameron et al, 1990; Kuvshinoff et al, 1995; Nagano et al, 1990; Vallis et al, 1996; Vatanasapt et al, 1990a). In a group of 12 patients treated with this regimen over 3 years at MSKCC, the median survival was 14.5 months. Episodes of cholangitis and intermittent jaundice were relatively common, but the incidence of serious complications was low, and there

were no treatment-related deaths (Kuvshinoff et al, 1995). Cameron and colleagues (1990) reported improved survival in irradiated patients compared with a group of patients not irradiated; however, the median survival in both groups was less than 1 year. Other investigators reported no benefit and questioned the routine use of radiation, given the increased incidence of complications and greater time spent in the hospital (Bowling et al, 1996). Radiation therapy is inappropriate in patients with widespread disease. Systemic chemotherapy is the only option for these patients, but response rates are low (Patt et al, 1996).

Ortner and colleagues (1998) evaluated the efficacy of photodynamic therapy in unresectable hilar cholangiocarcinoma. This method has been used in the treatment of tumors of the esophagus, colon, stomach, bronchus, bladder, and brain. It is a two-step procedure. First, a photosensitizer is injected; second, direct illumination via cholangioscopy activates the compound, causing tumor cell death. Ortner and colleagues (1998) treated nine patients in this fashion who had not responded to endoscopic stenting. They reported zero mortality for the procedure; however, a 25% mortality rate was related to the initial endoscopic stenting, which must be considered. These investigators did not mention their indication for biliary drainage. This information is important to assess the extent of disease before therapy. Detailed reasons for nonresectability were not discussed, and the reported median survival of 439 days is difficult to interpret. The data presented in this report, including decrease in bilirubin and some improved quality of life, are insufficient to advocate routine use of this method. Two randomized studies in patients with unresectable cholangiocarcinoma suggested improved survival with biliary stenting combined with photodynamic therapy compared with biliary stenting alone (Ortner et al, 2003; Zoepf et al, 2005). The improved survival observed with photodynamic therapy is likely related to better biliary decompression and avoidance of early segmental duct isolation and subsequent cholangitis, rather than any significant reduction in tumor burden (Quyn et al, 2009).

Palliative systemic chemotherapy has been investigated. Two phase II studies analyzing the effect of 5-FU combined with interferon alfa-2b and the effect of paclitaxel failed to show any benefit (Jones et al, 1996; Patt et al, 1996). In more recent studies, gemcitabine and irinotecan seemed to have limited efficacy, although they may offer a higher response rate than that seen with 5-FU–based regimens, (Alberts et al, 2005; Park et al, 2005; Sanz-Altamira et al, 2001). A recent Phase III study by the investigators of the Advanced Biliary Cancer (ABC) 02 trial randomized 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer to receive either cisplatin followed by gemcitabine or gemcitabine alone for up to 6 months (Valle et al, 2010). This study showed an improvement in median survival from 8.2 to 11.7 months for patients receiving cisplatin plus gemcitabine without the addition of substantial toxicity.

SUMMARY

Improvements in high-resolution cross-sectional imaging have permitted better patient selection and enhanced preoperative planning and preparation prior to the safe performance of operations for hilar cholangiocarcinoma. Long-term disease-free survival, rather than palliation, is now the primary goal of operative resection. Judicious use of adjunctive preoperative interventions that include biliary drainage and portal vein embolization may help to improve outcomes, especially when major perioperative and postoperative complications are anticipated. Selection of appropriate nonoperative therapies for palliation of unresectable tumors arising from the proximal and distal bile ducts should be tailored, according to the patient's expected longevity and technical expertise of the multidisciplinary team charged with treating bile duct cancer.

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CHAPTER 50C

Cancer of the bile ducts: perihilar cholangiocarcinoma with emphasis on presurgical management

Tomoki Ebata and Masato Nagino

OVERVIEW

Perihilar cholangiocarcinoma is often diagnosed as advanced disease at initial presentation and is difficult to treat (de Groen et al, 1999). Hepatobiliary resection represents the definitive surgery and most effective treatment for this disease (Bismuth et al, 1992; Blumgart et al, 1984; Burke et al, 1998; Hemming et al, 2005; Kawasaki et al, 2003). Combined portal vein resection (Ebata et al, 2003; Nimura et al, 1991a), combined hepatic artery resection, or hepatopancreatoduodenectomy (Ebata et al, 2007; Nimura et al, 1991b) have also been aggressively used at leading hepatobiliary centers in Japan, Korea, Europe, and the United States (Igami et al, 2010; Lee et al, 2010; Miyazaki et al, 2010; Rocha et al, 2010; Unno et al, 2010; Young et al, 2010). However, hepatobiliary resection for perihilar cholangiocarcinoma is well known to result in higher morbidity or mortality rates than those for simple hepatectomy because of impaired liver function with cholestasis or cholangitis (Belghiti et al, 2000; Nagino et al, 1993, 2001). To eradicate the involvement of the hilar duct, extensive hepatectomy should be designed based on tumor extension and individual liver functional reserve. It is of particular importance that the presurgical management is optimized. Perioperative management and surgical techniques have evolved over the past 30 years, which has succeeded in reducing postoperative complications. Current methods and recommendations for the presurgical management of perihilar cholangiocarcinoma are outlined in this section.

BASIC ANATOMIC PATHOLOGY DICTATES SURGICAL STRATEGY (SEE CHAPTER 47)

According to the Johns Hopkins classification for cholangiocarcinomas (Nakeeb et al, 1996), *perihilar cholangiocarcinomas* are defined as cholangiocarcinomas involving or requiring resection of the hepatic duct conference. Because the boundary between the intrahepatic and extrahepatic bile duct is unclear, perihilar tumors are potentially composed of two types of tumors: *extrahepatic hilar cholangiocarcinomas,* which arise from the large hilar bile duct, and *intrahepatic hilar cholangiocarcinomas,* which have an intrahepatic component and involve the hepatic hilum. These two tumors exhibit the same clinical presentation, demonstrate similar radiologic features, require an identical surgical intervention, and have comparable histologic characteristics (Ebata et al, 2009). In addition, they can be well classified by the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging for extrahepatic bile duct cancer (Greene et al, 2002), providing well-stratified survival (Ebata et al, 2009). Thus these two tumor categories overlap considerably, as already suggested by Klatskin (1965); therefore both tumors should be treated under the banner of perihilar cholangiocarcinoma (Ebata et al, 2009; Nakeeb et al, 1996).

Cholangiocarcinoma microscopically infiltrates the surrounding tissue beyond the macroscopic tumor extent (main tumor) (Ebata et al, 2002; Sakamoto et al, 1998). The lateral extension of invasive cancer is limited within 1 cm in both directions beyond the main mass in most tumors, and noninvasive cancer extension is limited within 2 cm in 90% of tumors (Ebata et al, 2002). These observations indicate that a 1-cm margin and a 2-cm margin of the duct are recommended for eradication of invasive and noninvasive cancer cells, respectively.

However, in perihilar cholangiocarcinomas, it is often difficult to obtain a satisfactory margin length that meets the above requirements because of the anatomy of the liver, especially in the proximal direction. Therefore a proximal resection line is set at the farthest proximal point as technically possible, and pathologic assessment with frozen sections of the ductal stump is widely used to confirm a negative ductal margin. Flaws in the results of intraoperative frozen section have been reported, including 1) the diagnostic difficulty of differentiation between intraepithelial neoplasm and reactive/regenerative epithelial changes, 2) the absence of a standard histologic classification (Konishi et al, 2008), 3) difficulty in obtaining sufficient material for diagnosis because of crushing and exfoliation resulting from manipulation (Konishi et al, 2008), and 4) relatively low diagnostic accuracy, ranging from 25% to 57% (Okazaki et al, 2002; Yamaguchi et al, 2005). These limitations suggest an inherent limitation of frozen-section examination. When the ductal margin is positive by intraoperative frozen-section diagnosis, several factors must be taken into account. First, prognostic indicators after surgery are nodal metastasis, poor histologic grade, portal vein invasion, and positive surgical margins (Ebata et al, 2003, 2009). Of these predictors, nodal involvement is observed most frequently, in more than 50% of patients (Ebata et al, 2003; Igami et al, 2009; Kitagawa et al, 2001). Second, a positive ductal margin with noninvasive cancer, unlike invasive cancer, may not have a negative impact on survival (Igami et al, 2009; Nakanishi et al, 2010; Sasaki et al, 2007; Wakai et al, 2005). It has been noted that residual in situ carcinoma does not result in early fatal recurrence; however, over time, it steadily and insidiously progresses to an anastomotic tumor mass (Nakanishi et al, 2010). Third, additional resection of more than 5 mm of the proximal duct is difficult, practically, after maximal or near-maximal resection of the duct. Such limited resection of a margin-positive proximal duct

does not improve survival, even when a negative margin can be achieved after additional resection (Shingu et al, 2010). Overall, the clinical value of additional resection of the proximal duct in perihilar cholangiocarcinoma is limited.

A right hemihepatectomy or trisectionectomy with en bloc resection of the caudate lobe is generally recommended for perihilar cholangiocarcinomas (Kawasaki et al, 1994; Neuhaus et al, 1999). This right-sided resection satisfies the nontouch technique, en bloc resection, and wide tumor-free margins and consequently leads to good local control and a favorable prognosis (Jonas et al, 2008). However, the optimal procedure (extensive vs. limited surgery) for Bismuth type I and II tumors is still under debate. Tumor configuration is classified into *papillary, nodular,* or *diffusely infiltrating* tumors (Henson et al, 2000). Papillary tumors display less invasive behavior and, accordingly, they have a more favorable survival than other tumor types (Albores-Saavedra et al, 2000; Jarnagin et al, 2005). Recently, the surgical strategy for Bismuth type I and II tumors were reappraised based on gross tumor type (Ikeyama et al, 2007). When optimizing by the gross tumor configuration, right-sided hepatectomy is suitable for nodular or flat tumors that display an infiltrating nature in the advancing margin; whereas a limited surgery—including resection of S1, S1+4, or bile duct resection alone—is acceptable for papillary tumors, provided the surgical margin is negative (Ikeyama et al, 2007).

In addition, there is a specific tumor type called *superficial spreading type cholangiocarcinoma* (Igami et al, 2009; Nakanishi et al, 2008; Sakamoto et al, 1998), which is defined as cholangiocarcinoma with superficial spread; that is, a noninvasive cancer extension longer than 2 cm. The mean length of the superficial spread is 54 mm, suggesting that this tumor often requires extensive resection to obtain a negative ductal margin. In contrast, superficial spreading-type cholangiocarcinomas are also characterized by less advanced pT and pN classifications and a more differentiated histologic grade, which leads to a favorable prognosis (Igami et al, 2009; Nakanishi et al, 2008). In such patients, complete eradication of the superficial spreading lesion (in situ carcinoma) is necessary. Taken together, these findings suggest that a patient with this specific tumor may benefit from extensive surgery, such as hepatopancreatoduodenectomy (Ebata et al, 2007; Nimura et al, 1991b).

Hepatobiliary surgeons should keep the possibility of multiple synchronous cancers in mind. Multiple tumors are more common than previously thought: the incidence ranges from 5% to 9% (Gertsch et al, 1990; Kozuka et al, 1984; Kurosaki et al, 1997). Thus, multiplicity is a feature of biliary neoplasia that may be clinically relevant in some patients. Gertsch and colleagues (1990) proposed three criteria for multiplicity: 1) no direct continuity between the two tumors, 2) a growth pattern typical of a primary tumor, and 3) clear histologic differences between the two tumors. However, a true synchronous tumor and metastatic tumor originating from a biliary site elsewhere cannot always be clinically distinguished. Interestingly, a second tumor may not be identified by the preoperative radiologic workup but rather by pathologic assessment. Most second biliary tumors are an incidental early stage gallbladder cancer (Gertsch et al, 1990; Kurosaki et al, 1997). This indicates a need for intraoperative surveillance, meticulous inspection of the specimen immediately after resection, and appropriate sampling of the tissue for pathology.

The concept of *field cancerization* potentially explains the multiplicity of biliary tumors. Recently, pathoepidemiologic evidence for multiple biliary tumors has been reported (Henson et al, 2009). The age-specific incidence of biliary tract and gallbladder tumors in the United States demonstrates a parallel incline pattern, indicating that the rate of cancer development is identical and that the sequential molecular/cellular events toward the carcinogenesis among multiple isolated lesions share common pathways.

BILIARY DRAINAGE IN THE PREOPERATIVE SETTING (SEE CHAPTERS 7 AND 18)

It is well known that chronic obstruction of the bile duct causes hepatic fibrosis, secondary biliary cirrhosis, and portal hypertension. When biliary obstruction is appropriately relieved, the fibrosis and portal hypertension can be ameliorated (Hammel et al, 2001). Furthermore, prolonged obstruction often induces acute obstructive suppurative cholangitis (Glenn & Moody, 1961), which can only be treated by biliary drainage (Berliner & Burson, 1973). The purposes of biliary drainage are summarized as follows: 1) treatment of biliary sepsis (Kanai et al, 1996), 2) relieving jaundice and recovery of functional capacity, 3) diagnosis of lateral tumor extension (Nimura et al, 1989), 4) liver function assessment using bile samples (Higuchi et al, 2005; Kurumiya et al, 2003; Maeda et al, 1999; Takeuchi et al, 1997; Uesaka et al, 1996), and 5) improvement of poor food intake (Padillo et al, 2001).

Obstructive jaundice associated with perihilar cholangiocarcinoma differs from jaundice associated with distal tumors. In the latter, a single catheter is enough for biliary decompression of the entire liver; in the former, multiple drainage catheters are necessary because perihilar cholangiocarcinomas frequently isolate the intrahepatic biliary tree into several subunits (Klatskin, 1965). Under such difficult conditions, it remains controversial which method is better: an endoscopic approach versus a percutaneous approach or unilateral versus bilateral drainage. Several authors (Gholson & Burton, 1991; Polydorou et al, 1991; Speer et al, 1987) have stressed the advantages of endoscopic retrograde biliary drainage (ERBD) because it is associated with low procedure-related morbidity and mortality rates, a shorter hospital stay, and good quality of life (external tube free). However, ERBD is associated with a high incidence of cholangitis because of catheter occlusion and/or inability to perform multiple drainages (Andersen et al, 1989; Chang et al, 1998; Liu et al, 1998; Rerknimitr et al, 2004). Hence, percutaneous transhepatic biliary drainage (PTBD), rather than ERBD, may be indicated for perihilar cholangiocarcinomas (Nomura et al, 1997).

Recently, endoscopic nasobiliary drainage (ENBD) has been recommended as a preoperative drainage procedure for perihilar cholangiocarcinomas (Arakura et al, 2009; Maguchi et al, 2007). Arakura and colleagues (2009) reported that a single ENBD was enough to relieve jaundice in 46 of 62 patients (74%) with perihilar cholangiocarcinoma, and additional PTBD was necessary in only eight patients. Early complications, such as acute cholangitis, dislodgement, and hemobilia, occur 14.5%, 0%, and 0% of the time, respectively, indicating the low morbidity associated with ENBD. Furthermore, ENBD carries no risk of seeding metastases along the catheter tract, which could compromise the results of curative resection (Fig. 50C.1). In our experience, seeding metastases are encountered in up to 5% of patients with cholangiocarcinoma who underwent resection after PTBD.

Obstructive jaundice appears when more than 75% of the liver is involved (Abraham et al, 2002), and based on the

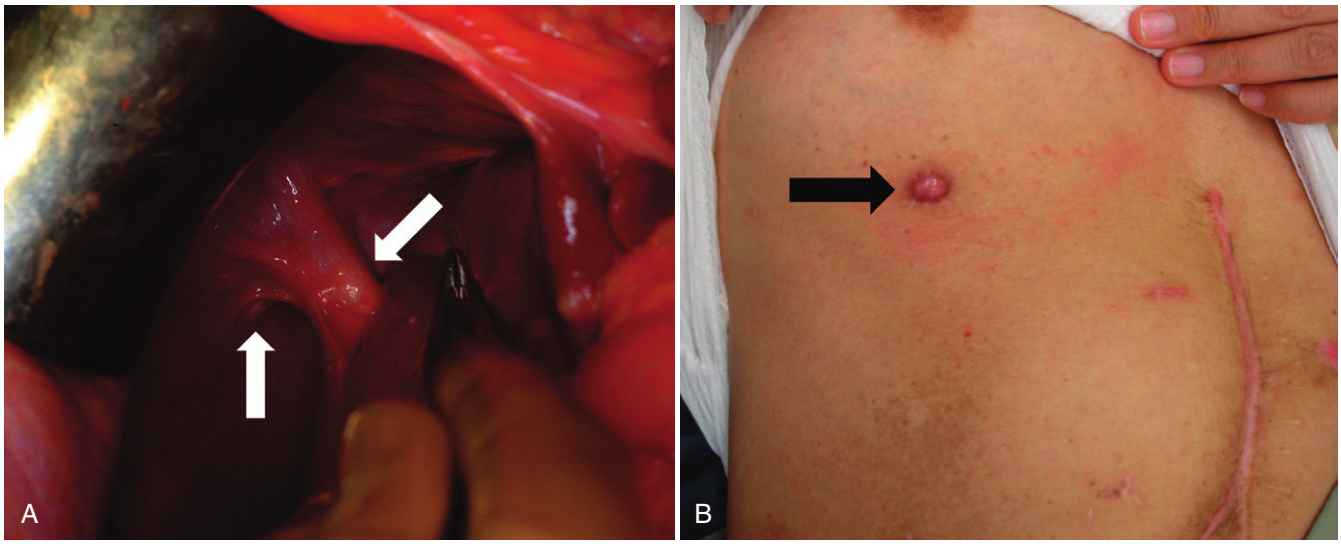


FIGURE 50C.1. Percutaneous transhepatic biliary drainage (PTBD)-related seeding metastasis from perihilar cholangiocarcinoma. **A,** At laparotomy, peritoneal dissemination is observed at the sinus tract of PTBD catheter (*arrows*). **B,** A skin nodule emerges (*arrow*) just at the PTBD wound scar 6 months after curative surgery.

experience of palliative biliary drainage, it is usually relieved by drainage of a single liver segment (Abraham et al, 2002; Ballinger et al, 1994; Van Laethem et al, 2003). In addition, unilateral drainage promotes hypertrophy of the future liver remnant (FLR), which leads to a good functional reserve (Ishizawa et al, 2007). Thus the current strategy of preoperative biliary drainage for perihilar cholangiocarcinoma is summarized as follows: first, all ducts in the FLR should be drained; second, ENBD is superior to PTBD. Previously, we preferred PTBD (Nagino et al, 1992; Nimura, 1993; Nimura et al, 1995, 1998) but have not changed the policy for preoperative drainage since 2007. The first-line treatment is currently a single ENBD placed in the FLR alone, irrespective of the Bismuth tumor type. PTBD is performed as a second-line procedure only when 1) multiple, separated ducts are present in the FLR; 2) total liver drainage is necessary for prolonged cholestasis or segmental cholangitis of the undrained lobe; or 3) the ENBD tube is dislodged or kinked. As a result, the proportion of patients treated with ENBD has recently increased, but PTBD has decreased, although it is still needed for approximately half of the patients (Table 50C.1).

Table 50C.1

Type of Biliary Drainage in Patients with Perihilar Chlangiocarcinoma Who Underwent Surgery from 2001 to 2009

	2001–2005 (n = 164)	2006–2007 (n = 83)	2008–2009 (n = 93)
PTBD	131 (80%)	55 (66%)	48 (52%)
ERBD	3 (2%)	3 (4%)	2 (2%)
ENBD	4 (2%)	12 (15%)	35 (38%)
Without drainage	26 (16%)	13 (16%)	8 (9%)

PTBD, percutanenous transhepatic biliary drainage; ERBD, endoscopic retrograde biliary drainage; ENBD, endoscopic nasogastric biliary drainage

The current role of PTBD is mainly to salvage the procedure if ENBD fails. In this difficult scenario, multiple PTBD is frequently required to decompress the whole liver, except for the caudate lobe (Nagino et al, 1992; Nimura et al, 1995). Our favorite method for PTBD is Takada's direct anterior approach (Takada et al, 1976), using a Takada needle, approximately 3 mm in diameter, which is composed of an internal metallic needle and an outer Teflon sheath (Fig. 50C.2). First, the target duct is opacified with a fine needle; next, the needle is advanced parallel to the radiograph into the duct; and finally, a 6-Fr soft catheter is installed through the sheath. Previously, the intrahepatic bile duct of the FLR was directly punctured; however, vascular injury is possible with such an approach (Fig. 50C.3). A large series of PTBD between 1991 and 2006 (Dowsett, 1989; Fidelman et al, 2008) showed that the risk of

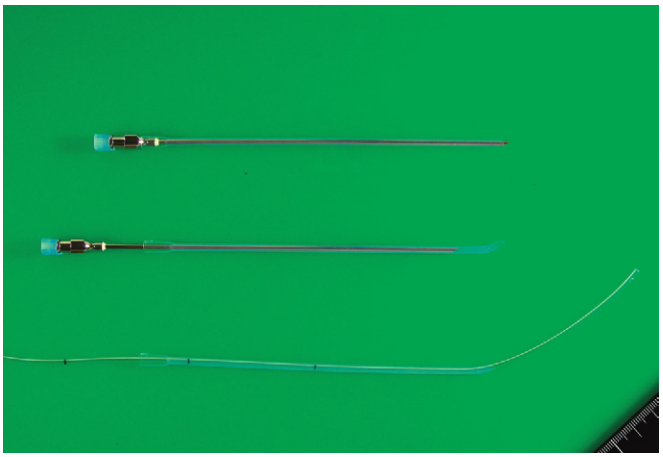


FIGURE 50C.2. Needle device specific for percutaneous transhepatic biliary drainage, Takada's direct anterior approach. The needle consists of an inner metallic needle and outer Teflon tube (*top*). The tip of the outer tube is curved; consequently, a 6-Fr catheter is easily introduced into the duct via the outer tube (*bottom*).

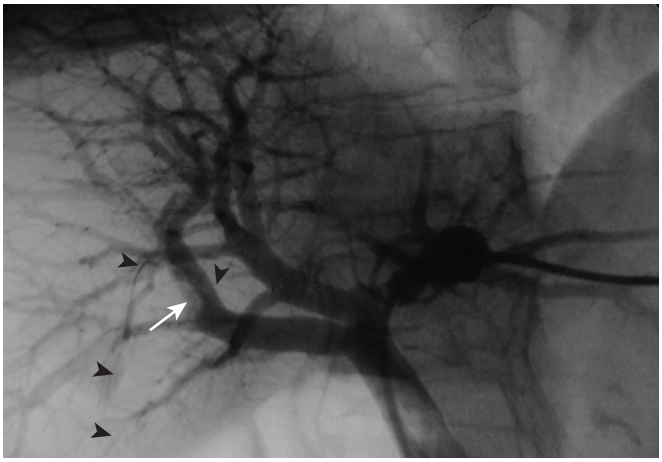


FIGURE 50C.3. Percutaneous transhepatic biliary drainage (PTBD)-related vascular injury. The PTBD catheter is introduced to the right posterior sectorial duct (*arrowheads*), because the patient is scheduled for left trisectionectomy. Portogram reveals a small thrombus (*arrow*) in the right poster portal vein as a result of PTBD-related injury.

procedure-related arterial injury is 2.2%, and the incidence has not changed since the 1970s and 1980s. To prevent accidental vascular injury, the ipsilateral approach, similar to portal vein embolization (Nagino et al, 1996), is recommended when it is possible. In this approach, the bile duct in the sector to be removed is punctured, and the straight single catheter is introduced into the duct in the FLR via the hilar duct, which is stenotic as a result of tumor. Although this procedure requires a meticulous searching technique using a flexible guidewire, it offers complete bilateral drainage with the least numbers of single catheters (Fig. 50C.4). PTBD with the ipsilateral approach should be considered when total liver drainage is necessary.

Although biliary drainage is the routine preoperative management strategy for jaundiced patients in Japan (Nagino et al, 2008), randomized control trials (RCTs) conducted in Western countries have raised questions about the effectiveness of preoperative biliary drainage (see Chapters 7 and 50B). The results of these trials showed no significant difference in postoperative morbidity and mortality among patients who received preoperative biliary drainage and those who did not. These RCTs concluded that, considering the potential risk related to PTBD, preoperative biliary drainage has no advantage (Hatfield et al, 1982; McPherson et al, 1984; Pitt et al, 1985). However, these studies involved patients undergoing bypass surgeries or palliative small resections. In addition, PTBD-related complications were very common. These flaws in the previous RCTs made it difficult to accept their conclusions. In Western centers, preoperative biliary drainage is performed in selected patients (Laurent et al, 2008; Kennedy et al, 2009). Over time, the bile is contaminated after biliary drainage (Nomura et al, 1999): the incidence of bacterobilia and fungobilia is 85% and 40%, respectively (Jethwa et al, 2007), leading to surgical site infection, cholangitis, and bacteremia after hepatectomy (Hochwald et al, 1999; Jethwa et al, 2007; Nomura et al, 1999; Shigeta et al, 2002). These observations may partly support the limited indications for biliary drainage; however, the mortality rate after extended hepatectomy for jaundiced patients is still high at near 10%, and the cause of death is mainly hepatic failure (Nagino et al, 1993b, 2001). Therefore, preoperative biliary drainage followed by portal vein embolization is recommended before extended hepatectomy, in spite of a lack of clear evidence based on previous RCTs. This is the Japanese standard of care (Henson et al, 2000; Kawasaki et al, 2003).

CHOLANGIOGRAPHY (SEE CHAPTER 18)

Cholangiograms precisely delineate the segmental anatomy of the intrahepatic bile duct (Ohkubo et al, 2004), the tumor configuration, and the extent of the tumor border. To avoid misinterpretation related to overlap of segmental ducts, cholangiograms should be taken in various projections (Fig. 50C.5). Most perihilar cholangiocarcinomas are infiltrating tumors, in which cancer cells are likely to extend predominantly in the submucosal layer rather than in the mucosal layer. Histologically, direct and lymphatic invasion are common routes of invasion to the ductal wall, evoking reactive fibrosis (Sakamoto et al, 1998; see Chapter 47). These changes cause rigidity,

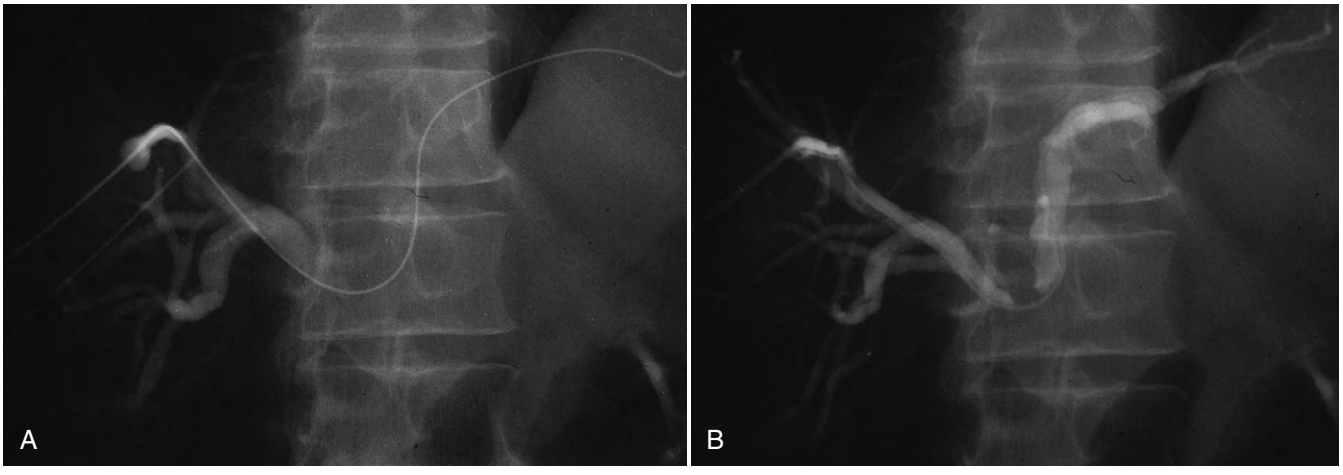


FIGURE 50C.4. Bilateral biliary drainage using ipsilateral approach. Patient has a Bismuth type II tumor, requiring biliary drainage of the left liver. **A,** The right anterior sectorial duct is targeted for puncture. A guidewire is advanced to the left lateral superior sectional duct (*B2*) through the hilar stenosis. **B,** Bilateral drainage is completed. Theoretically, unilateral drainage of the left liver is enough; however, this approach will decrease the risk of the vascular injury of the left liver.

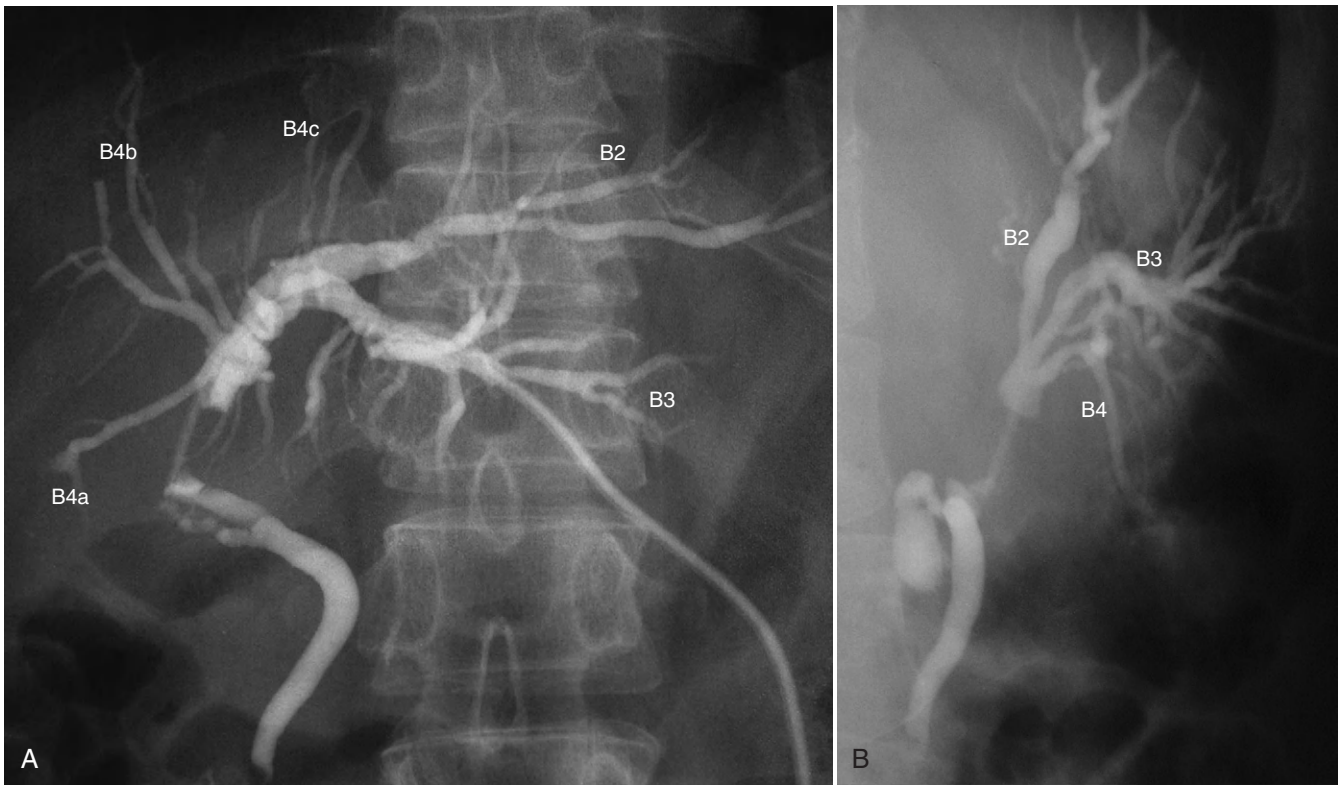


FIGURE 50C.5. Cholangiography specific for right-sided hepatectomy. **A,** In a routine spine position, the nodular tumor is demonstrated at the hepatic bifurcation, but the definitive information for lateral tumor extension is not obtained. **B,** Right anterior oblique position with cranial tilting clearly demonstrates the confluence of segment II duct (*B2*), segment III duct (*B3*), and segment IV duct (*B4*).

narrowing, tapering, and obstruction of the duct on the cholangiogram. The border of these findings on cholangiograms correspond to the leading edge of cancer infiltration (Sakamoto et al, 1998).

In hilar biliary obstruction, direct cholangiography frequently shows insufficient opacification of the proximal ductal system. However, MR cholangiography (MRC) delineates the whole biliary system, and its ability to diagnose the Bismuth classification is superior, with an accuracy of 81% (Yeh et al, 2000). Overestimation is a common pitfall of MRC, which may preclude patients from potentially curative surgery (Otto et al, 2004). The limitations of MRC include lower spatial resolution, longer acquisition time, and sensitivity to motion.

CHOLANGIOSCOPY

Despite the advent of new diagnostic modalities, cholangioscopic examination with biopsy sampling plays an important role in the diagnosis of biliary malignancies (see Chapter 28). Differentiation between malignant and benign lesions, evaluation of proximal and distal cancer extent, and early detection of small lesions and multiple cancer foci can be accomplished by cholangioscopic observation with biopsy sampling (Nimura et al, 1989). Irregularly dilated and tortuous vessels are characteristic of malignancy. A fine granular/papillary mucosa extending continuously from a main lesion is a characteristic finding of superficial spread (Nimura & Kamiya, 1998). Papillary tumors are often associated with the superficial spread of carcinoma (Igami et al, 2009; Sakamoto et al, 1998), and mucosal extension is easily detectable by cholangioscopy. Therefore, cholangioscopy should be considered for patients with papillary tumors. Attention should be paid not only to the intrahepatic extension but also to the distal extension of the tumor.

Percutaneous transhepatic cholangioscopy (PTCS) is performed through the PTBD sinus tract. One week after PTBD, the drainage catheter is replaced by a 9- or 10-Fr PTCS catheter, and then the sinus tract is gradually dilated by replacing the preceding catheter with a larger catheter two or three times a week. A small-caliber cholangioscope (Olympus XP-20) can be used via the sinus tract of the 12-Fr catheter; a standard-type cholangioscope (Olympus, P-20) requires placement of a 15-Fr catheter. This preparation process for PTCS is time consuming and painful; therefore PTCS has recently been replaced by peroral cholangioscopy (POCS). With technical advances in endoscopy, POCS with biopsy gives a high diagnostic accuracy of the extent of the superficial spreading lesion (Kawakami et al, 2009).

MULTIDETECTOR ROW COMPUTED TOMOGRAPHY

Recent advances in helical CT technology, such as multislice detectors and subsecond rotation, have dramatically reduced scanning times in comparison with single-slice CT and have provided unparalleled capability for fast data acquisition and narrow collimation. Thus, multidetector row computed tomography (MDCT) permits the acquisition of three distinct circulatory phases, consisting of the arterial, pancreatic, and portal venous phases in the pancreatobiliary region with 1-mm

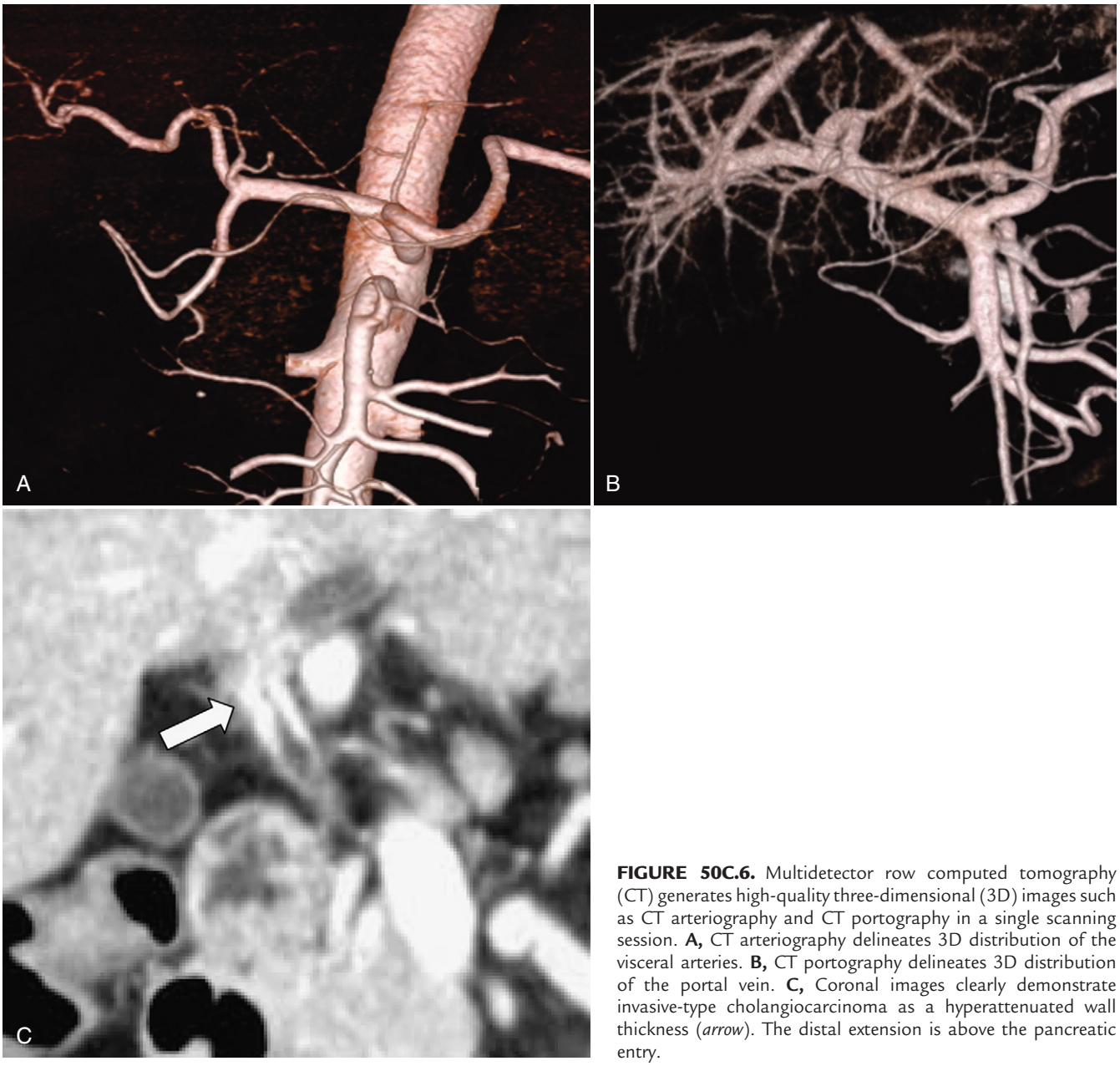


FIGURE 50C.6. Multidetector row computed tomography (CT) generates high-quality three-dimensional (3D) images such as CT arteriography and CT portography in a single scanning session. **A,** CT arteriography delineates 3D distribution of the visceral arteries. **B,** CT portography delineates 3D distribution of the portal vein. **C,** Coronal images clearly demonstrate invasive-type cholangiocarcinoma as a hyperattenuated wall thickness (*arrow*). The distal extension is above the pancreatic entry.

collimation (Itoh et al, 2003; see Chapter 16). These isotropic volume data allow multiplanar reformation (MPR), which can demonstrate complex anatomic relationships and three-dimensional volume rendering (3DVR) images, such as CT arteriography and CT portography, in a single scanning session (Fig. 50C.6). These postprocessing techniques enhance the diagnostic capability of CT (Choi et al, 2007). In patients with perihilar cholangiocarcinoma, preoperative MDCT is used to diagnose 1) distant metastasis, including dissemination, liver metastasis, and nodal metastasis; 2) tumor lateral extension or Bismuth classification; 3) vascular invasion with or without lobar atrophy; 4) anatomic variation of the vascular system; and 5) the liver volume of each sector. MDCT is now a pivotal element of the preoperative staging of perihilar cholangiocarcinoma, and it provides definitive information about resectability and design of resectional procedure. Previously, we used PTCS, celiac angiography, and percutaneous transhepatic portography (PTP) for staging (Nimura, 1993; Nimura et al, 1995, 1998; Nishio et al, 1999). However, these procedures are invasive in nature and have been replaced by MDCT.

With MDCT, cholangiocarcinoma can be correctly identified in nearly 100% of patients, and the accuracy in prediction of resectability has improved to 75% to 100% (Chen et al, 2006; Lee et al, 2006). MDCT with or without enhancement prior to biliary drainage often displays the tumor as a ductal thickness. To evaluate the value of MDCT on longitudinal extension in one study, the authors analyzed 73 patients with cholangiocarcinoma who underwent MDCT prior to biliary drainage (Senda et al, 2009). Of the 73 patients, 40 showed a hyperattenuated tumor, and the remaining 33 had a hypoattenuated tumor; in the latter group, it was difficult to identify the border between normal and thickened duct. Hence, the

extent of lateral extension could be assessed in only those 40 patients (55%) with a hyperattenuated tumor. The diagnostic accuracy of the extent of ductal cancer infiltration was 76% and 82% in the proximal and distal direction, respectively. The extent of cancer was underestimated by 24% and 15% at the proximal and distal border, respectively, because of superficial spread, minimal invasive cancer extension, or both. Thus the ability of MDCT to diagnose lateral extension is limited, and cholangiography is still the standard tool.

A belief has persisted that involvement of the main portal trunk denotes irresectability of the cholangiocarcinoma (Blumgart et al, 1984; Lee et al, 2006). Hoevels and Ihse (1979) emphasized that a portography showing portal vein invasion suggests irresectability. Launois and colleagues (1999) also reported that the main reason for irresectability of hilar cholangiocarcinomas is invasion of the portal bifurcation; however, several surgeons have recently reported portal vein resection for advanced biliary cancer (Kondo et al, 2004; Miyazaki et al, 2007; Nimura et al, 1991a; Sakaguchi & Nakamura, 1986). We have carried out combined portal vein and hepatobiliary resection in nearly 200 patients with advanced perihilar cholangiocarcinoma and have demonstrated significantly better survival in patients who underwent portal vein resection than in those with unresectable disease (Ebata et al, 2003; Igami 2010; Nimura et al, 1991a). Currently, portal vein resection and reconstruction are more or less routine in leading centers. Some surgeons have reported the clinical significance of prophylactic portal vein resection for all patients, irrespective of invasion of the portal vein, based on the nontouch technique (Kondo et al, 2004; Neuhaus et al, 1999). We do not think that this strategy improves survival, and they emphasize that portal vein resection should be performed only in patients with gross invasion of the portal vein.

We assessed the value of MDCT on *portal vein invasion,* defined as absence of a visible hypoattenuated layer between the portal bifurcation and the adjacent tumor on an MPR image. The diagnostic accuracy for macroscopic portal vein invasion (i.e., the requirement for portal vein resection) was 98%, showing the high sensitivity of MPR images for macroscopic portal vein invasion. Meanwhile, 3D portography clearly demonstrates the portal branch anatomy and the site and length of the portal vein invasion. Three-dimensional portography facilitates the design of the resection and the reconstruction procedure: wedge versus segmental resection and direct end-to-end anastomosis versus autologous vein grafting. In practical terms, the presence or absence of portal vein invasion should be first assessed by using MPR images; 3DVR images should then be used to plan the surgical procedure. When the right portal vein is markedly involved, if contralateral involvement does not reach the umbilical portion of the left portal vein, curative resection is possible by using a right-sided hepatectomy with portal vein resection and reconstruction (Fig. 50C.7). In contrast, when the left portal vein is considerably involved, if contralateral involvement is limited within the right portal trunk, a left hepatectomy with portal vein resection and reconstruction is indicated (Fig. 50C.8). If the bifurcation of the right anterior and posterior portal veins is involved, a left trisectionectomy with portal vein resection and reconstruction may be required.

Three-dimensional understanding of the hepatic artery distribution expedites skeletonization resection of the hepatoduodenal ligament; 3D understanding of the intrahepatic artery branching is helpful when the segmental or subsegmental bile ducts are divided as the final step of hepatobiliary resection. Hepatobiliary surgeons must appreciate two variations of the hepatic artery distribution that may be associated with potential injury (Fig. 50C.9): one is the left hepatic artery (LHA) running *right* to the umbilical portion of the left portal vein; and the other is a posterior branch of the right hepatic artery (RHA) running *cranially* to the right portal trunk. Careful attention

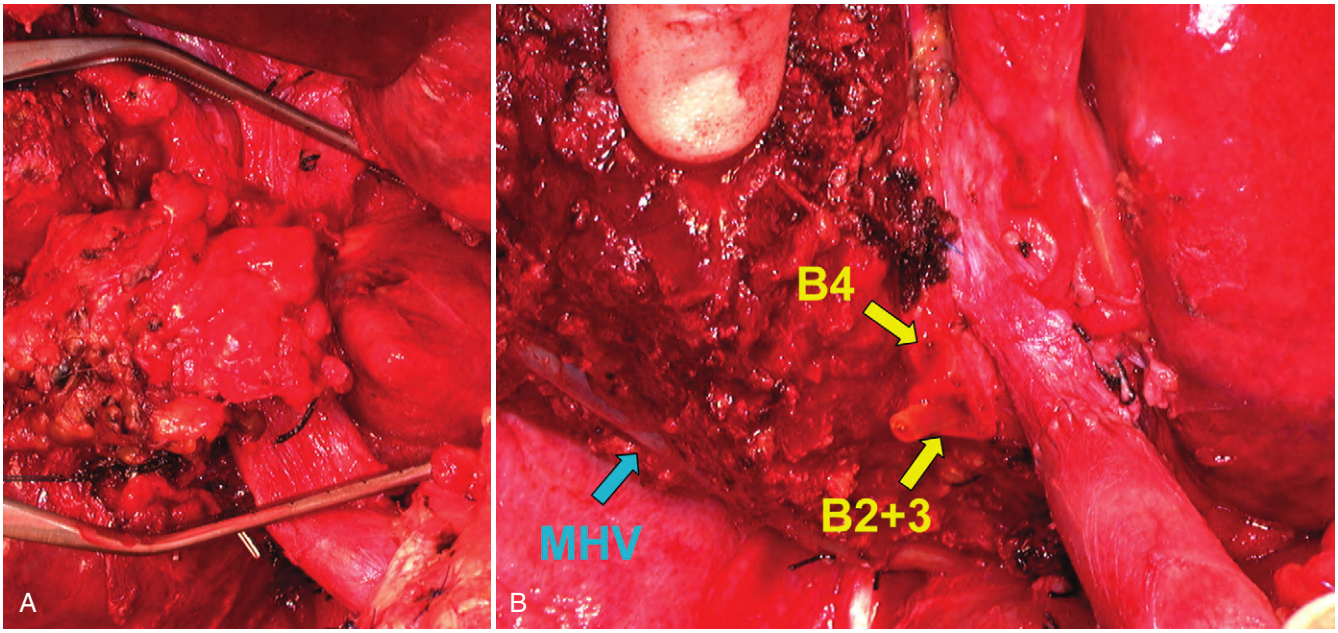


FIGURE 50C.7. A patient with perihilar cholangiocarcinoma involving the portal bifurcation. **A,** The vascular clamps are placed on both sides of the involved portal bifurcation. **B,** Completion photograph after a right hepatectomy, caudate lobectomy, and portal vein resection/reconstruction. *MHV,* middle hepatic vein; *B4,* resected stump of the left medial segmental bile duct; *B2+3,* resected stump of the left lateral segmental bile duct.

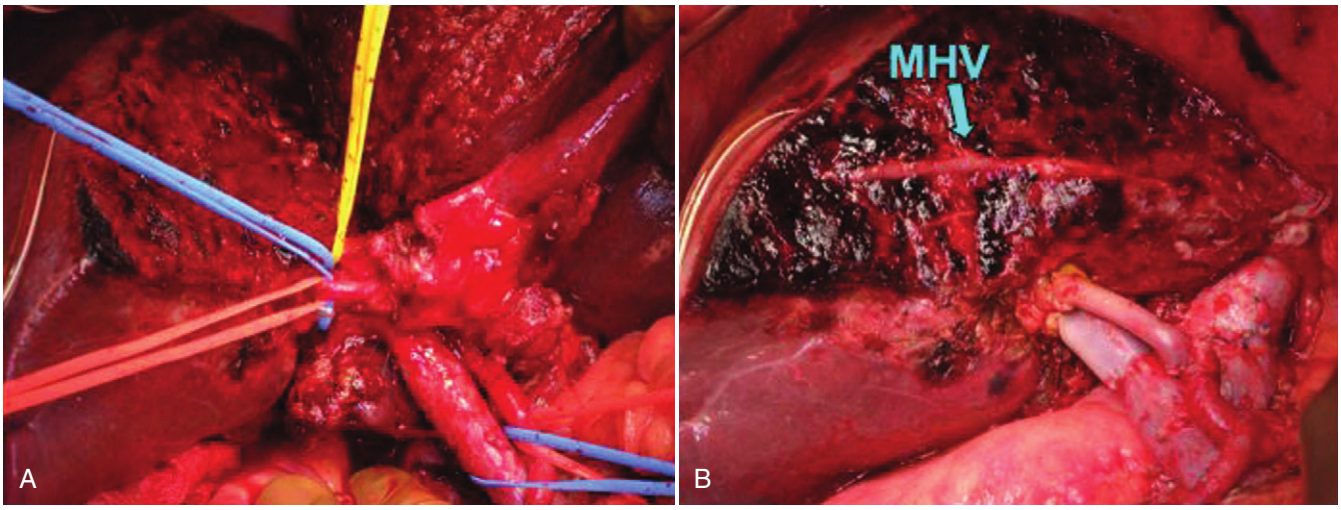


FIGURE 50C.8. A patient with perihilar cholangiocarcinoma involving the portal bifurcation. The tumor was curatively resected by a left hepatectomy and caudate lobectomy with simultaneous resection and reconstruction of the portal vein and the hepatic artery. **A,** Tumor involved the portal bifurcation and the right hepatic artery. The right hepatic duct, the right portal vein, and the right hepatic artery are encircled by tape, from the top. **B,** Completion photograph after resection. The portal vein is reconstructed using an external iliac vein graft, and the hepatic artery is also reconstructed using the greater saphenous vein graft. *MHV,* middle hepatic vein.

should be paid to the former variant in right hepatic trisectionectomy (extended right hepatectomy) with caudate lobectomy (Nagino et al, 2006a) and to the latter variant in left hepatic trisectionectomy (extended left hepatectomy) with caudate lobectomy. These variations can be clearly identified on a CT arteriography prior to surgery.

In general, unilateral involvement of the hepatic artery is compatible with resection. Because the RHA is usually just behind the common hepatic duct, it is likely to be involved by a cancer of the hepatic bifurcation. In cases of a right-sided tumor, bilateral involvement signifies local irresectability, because the LHA runs along the left border of the hepatoduodenal ligament. However, when the tumor is located on the left side, a left-sided hepatectomy with resection and reconstruction of the RHA can be performed in selected patients (see Fig. 50C.8; Fig. 50C.10). Hepatic artery reconstruction using microscopy is now well established and safely performed by experienced cosmetic or vascular surgeons; however, it remains unclear whether combined hepatic artery and liver resection offers a better chance of long-term survival. From 2001 to 2008, Igami and colleagues

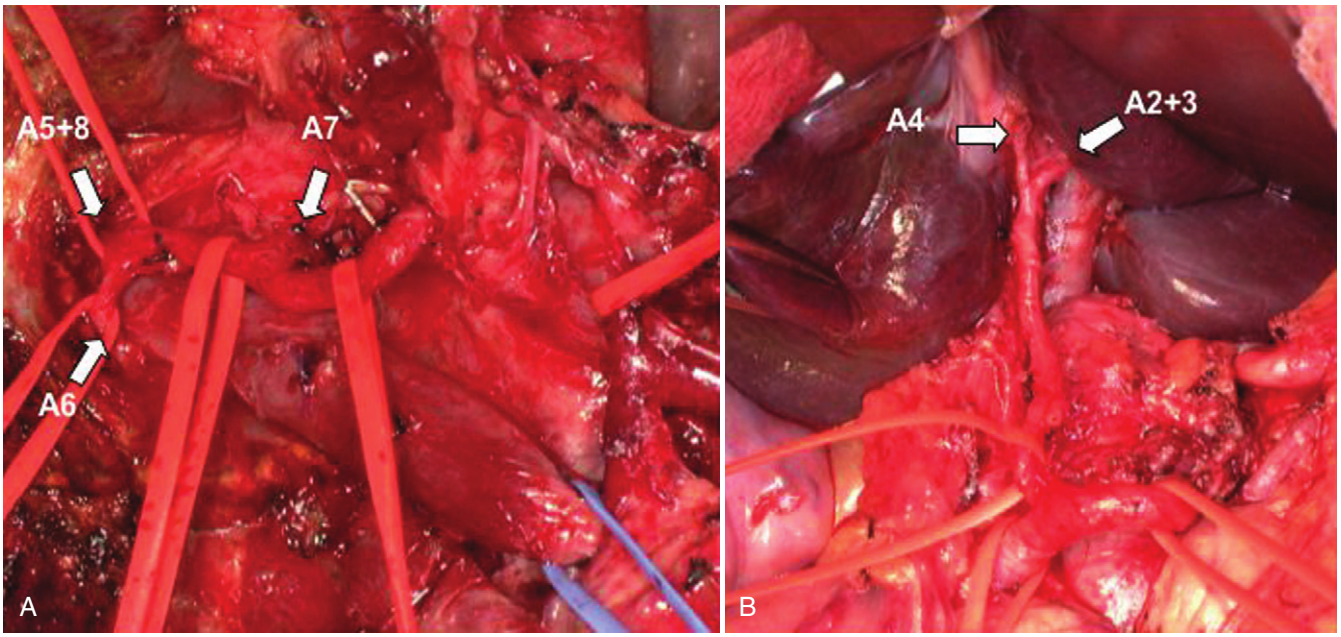


FIGURE 50C.9. Intraoperative view of two different variations of the hepatic artery distribution. **A,** The superior branch of the right posterior hepatic artery (*A7*) runs cranially to the right portal trunk. The inferior branch (*A6*) runs caudally to the right portal trunk. **B,** The left hepatic artery runs right to the umbilical portion of the left portal vein.



FIGURE 50C.10. A patient with perihilar cholangiocarcinoma invading bilateral hepatic arteries. The tumor was curatively resected by a left hepatectomy and caudate lobectomy with resection and reconstruction of the right hepatic artery. **A,** Three-dimensional volume-rendered image showing encasement of the right hepatic artery (*arrow*). **B,** Multiplanar reconstruction image showing the right hepatic artery eroded by tumor (*arrow*). **C,** Microscopic image of the resected specimen demonstrating cancer cells around the right hepatic artery.

(2010) performed combined hepatic artery resection and reconstruction in 53 patients. Despite the risky nature of this procedure, only one of the 53 patients died of complications, and the 5-year survival rate was 33%. This satisfactory result may encourage hepatobiliary surgeons to attempt this aggressive surgery.

PORTAL VEIN EMBOLIZATION

Portal vein embolization (PVE), introduced by Makuuchi and Kinoshita in the 1980s (Kinoshita et al, 1986; Makuuchi et al, 1990), can induce hypertrophy of the nonembolized lobe, has the potential to enhance the safety of extended hepatectomy, and has been considered the standard of care in preoperative management (see Chapter 93). Some authors have reported that PVE can be safely performed without serious complications, and it can minimize postoperative liver dysfunction. A recent meta-analysis involving 37 highly selected reports from the literature also supports the utility of PVE (Abulkhir et al, 2008). However, because no RCT has been conducted, the indication for PVE still remains undefined. The choice of device, technique, or embolic agent is generally based on the operator's preference.

Belghiti (2004) summarized the indication for PVE as follows: 1) a percentage of FLR of 25% or less in normal liver; 2) scheduled concomitant extrahepatic surgery or complex hepatectomy; and 3) any major hepatectomy in patients with underlying chronic diseases or with an injured liver (chemotherapy, major steatosis, or cholestasis). In this context, most patients with perihilar cholangiocarcinoma may be candidates for preoperative PVE because they require extensive hepatectomy, frequent vascular resection, and have a cholestatic liver requiring biliary drainage. In our department, PVE is

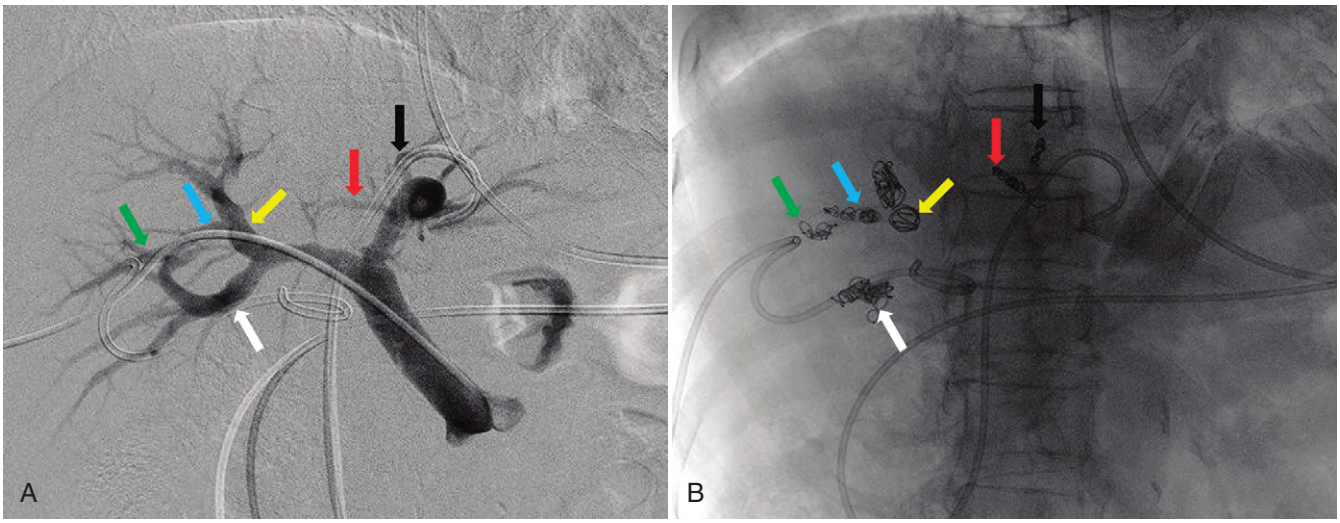


FIGURE 50C.11. Right trisegment portal vein embolization. **A,** The right anterior portal vein was punctured. The right oblique position clearly demonstrates the portal bifurcation. *Arrows* show the site of the placed steel coil. **B,** Plain film after completion of portal vein embolization.

performed when the estimated FLR is below 40% (Nagino et al, 2006b).

The two most common techniques for PVE are *transileocolic portal vein embolization* (TIPE) (Makuuchi et al, 1990) and *percutaneous transhepatic portal vein embolization* (PTPE) (Kinoshita et al, 1986). Many surgeons prefer TIPE to PTPE (Imamura et al, 1999; Makuuchi et al, 1990) for three main reasons: First, surgeons can perform a minilaparotomy. Second, catheterization is easier because of the straightforward ramification of the portal branches. Third, a diagnostic laparotomy and intraoperative ultrasound provide further accurate staging of the disease (Imamura et al, 1999). However, TIPE has some disadvantages; it requires general anesthesia, and it comes with a theoretical higher risk of postoperative complications such as ileus (Imamura et al, 1999). In contrast, PTPE can be performed in the radiologic suite with the patient under local anesthesia and conscious sedation. Because general anesthesia is avoided, cost is reduced, and recovery time is short. Overall, PTPE is superior to TIPE and, accordingly, TIPE should be used only when interventional radiologic facilities are not available.

As an alternative to the conventional transhepatic contralateral approach, in which the umbilical portion of the left portal vein is punctured for right-sided PTPE access, we developed a different approach for PTPE, termed the *ipsilateral approach* (Nagino et al, 1996). In this approach, the portal branch of the sector to be resected is punctured, thereby minimizing the risk of vascular injury in the FLR. This is the main advantage of the transhepatic ipsilateral approach. Furthermore, there is no risk of portal bleeding after removal of the catheter sheath. As PTPE is indicated in patients who are to undergo right hemihepatectomy or right or left trisectionectomy, the right anterior sector will always be resected. Hence, the right anterior portal branch is recommended for puncture using any type of PVE. Importantly, to confirm the individual anatomy of the portal system, a portogram is obtained with at least three different projections: 1) supine position, 2) right anterior oblique projection, and 3) right anterior oblique projection tilting caudally 20 degrees (Nishio et al, 2003). The third projection provides the best visualization of the right anterior/posterior portal vein and the left portal vein. Selective catheterization of the right portal branches is also important for complete occlusion without migration of the embolic material. In the case of a right PVE, a proximal segment at least 1 cm long must remain unembolized to facilitate the division and closure of the right portal vein during surgery.

We have developed an extensive PTPE procedure called *trisegment portal vein embolization* (Madoff et al, 2005; Nagino et al, 1995, 2000a). Right or left trisectionectomy is the most extensive hepatectomy performed and is often associated with major sacrifice of parenchyma (Nagino et al, 1995). The ipsilateral approach through the right anterior portal vein makes trisegment PVE possible (Fig. 50C.11). It allows catheterization of the segment IV branch (P4) in the case of right trisegment PVE (P4 plus right anterior and posterior portal vein) and of the left portal vein in the case of left trisegment PVE (left and right anterior portal vein). The use of a coaxial catheter system or a curved catheter adjusted for the angulation helps to advance the catheter into P4, which often has two to three branches (Takayasu et al, 1985). Although additive P4 embolization prior to right trisectionectomy still remains controversial, the volume gain of the left lateral segment is larger in patients with right trisegment PVE than in those with conventional right PVE (Madoff et al, 2005; Nagino et al, 2000a). On the other hand, left trisectionectomy is a technically demanding and challenging procedure with higher morbidity than other anatomic hepatectomies (Nishio et al, 2005). With left trisegment PVE, a demarcation between the right anterior and posterior sector appears on the liver surface just after temporary clamping of the RHA. This is simple and useful in patients with locally advanced perihilar cholangiocarcinoma requiring combined hepatic artery and portal vein resection, in which hilar dissection cannot be completed before liver resection. Therefore, we recommend use of left trisegment PVE before this complex surgery.

From 1991 to 2005, we performed PTPE in 240 patients with biliary cancer, which included 150 perihilar cholangiocarcinomas and 90 gallbladder cancers involving the hepatic hilus (Nagino et al, 2006b). All patients were scheduled to undergo

Table 50C.2

Type of Planned Hepatectomy and Embolized Portal Vein

Planned Hepatectomy	Embolized Portal Vein	No. Patients
Right trisectionectomy	Right and left medial	23
	Right	4
Left trisectionectomy	Left and right anterior	26
Left		5
Right anterior		8
Right hepatectomy	Right	160
Right anterior		9
Right posterior		5
Total		240

extended major hepatectomy, and all procedures were performed using the ipsilateral approach. The PTPE was done 2 to 4 weeks before surgery, when the total serum bilirubin levels were lower than 5 mg/dL. Details of the PTPEs performed are listed in Table 50C.2. From 1991 to 2000, fibrin glue mixed with iodized oil was injected thorough two different types of triple-lumen balloon catheters (Nagino et al, 1993a). Recently, absolute ethanol injection followed by placement of steel coil has been used. Because absolute ethanol is not radiopaque, and it permeates into the peripheral portal system and induces endothelial injury/thrombosis, it must be carefully and slowly administered in 0.5- to 2.0-mL increments, meeting the extent of the liver volume fed by the target portal branch. After ethanol injection, steel coils are placed at the second- or third-order portal branch for permanent and complete occlusion. Although the rate of recanalization was slightly higher with fibrin glue (8.3%) than with ethanol and coils (5.1%), no significant difference was reported in either the hypertrophy ratio of the nonembolized lobe or the atrophy ratio of the embolized lobe. No procedure-related serious complications requiring a blood transfusion or interventions occurred. In addition, unexpected tumor growth after PVE was not observed.

Our strategy for unsatisfactory volume gain of the nonembolized liver after PVE is straightforward. In the case of revascularization, repeat PVE should be performed. When sufficient hypertrophy cannot be achieved despite complete PVE, second-line interventions should be considered for further hypertrophy. Sequential hepatic artery embolization of the ipsilateral liver or hepatic vein embolization may be useful to boost liver regeneration (Hwang et al, 2009; Nagino et al, 2000b). Selective intrahepatic biliary ablation with absolute ethanol can also be applied for this purpose, when the biliary duct in the embolized lobe is completely separated from the duct of the FLR (Kyokane et al, 2001). Because all of these optional interventions are empiric, technically demanding, and still experimental, the indication should be strictly selective.

OTHER SPECIFIC MANAGEMENTS

Internal Drainage and Bile Replacement

The superiority of internal biliary drainage is shown in experimental and clinical studies that have demonstrated that liver regeneration after partial hepatectomy is suppressed under external drainage but not under internal drainage (Clements et al, 1993; Saiki et al, 1999; Suzuki et al, 1994). Ogata and colleagues (2003) investigated bacterial translocation in bile duct–ligated rats and found that bile replacement is essential to maintain intestinal barrier function. Recently, we studied the effect of bile replacement on intestinal permeability, integrity, and microflora in 25 biliary cancer patients who underwent PTBD as a part of presurgical management (Kamiya et al, 2004). Impaired intestinal barrier function did not recover using PTBD without bile replacement, but bile replacement did restore intestinal barrier function. Our results strongly support that bile replacement during external biliary drainage is beneficial in preoperative patients with perihilar cholangiocarcinoma, because this type of hepatectomy is complicated and still a high-risk procedure. We ask all patients to drink their own externally drained bile juice.

Inchinkoto and Ursodeoxycholic Acid

Plants contain abundant bioactive materials. In Japan, oriental herbal medicines are now manufactured under modern scientific quality controls and have been empirically administered to many kinds of patients for more than 30 years. Inchinkoto, one such medicine, has been traditionally recognized as a "magic bullet" for jaundice. In experimental rat models, inchinkoto attenuates gene expression for inflammatory cytokines and inducible nitric oxide synthase and also upregulates antioxidants genes (Kawai et al, 2010). We confirmed the choleretic effect of inchinkoto in a prospective controlled trial involving 27 patients with cholangiocarcinoma (Watanabe et al, 2009). The biliary concentration of total bilirubin and total bile acids were significantly increased after administration of inchinkoto, and the protein levels of MRP2, a bilirubin transporter expressed in the canalicular membrane of hepatocytes, was also significantly higher in patients treated with inchinkoto. Thus, inchinkoto has a therapeutic potential in obstructive cholestasis associated with cholangiocarcinoma.

Ursodeoxycholic acid (UDCA) is a major primary bile acid in some species of bear (Hagey et al, 1993). For centuries, dried bear bile has been used in traditional Chinese medicine as a remedy for liver disorders. In humans, UDCA is considered a minor secondary bile acid that is formed in the gut by intestinal bacteria and accounts for less than 3% of the whole bile acid pool (Hofmann, 1994). Pathophysiologically, UDCA has several effects on hepatocytes: protection against oxidative stress, inhibition of apoptosis, stimulation of bile flow, detoxification of cholephilic compounds, and immunomodulation (Perez & Briz, 2009). Therefore, UDCA is widely used for cholestatic liver disease. In our department, UDCA and Inchinkoto are routinely used in jaundiced patients undergoing biliary drainage.

Synbiotic Administration

Infections in immunocompromised hosts often arise from their intestinal microflora (Tancrede & Andremont, 1985; Wang et al, 1993). Indigenous enteric gram-negative bacteria, such as the *Enterobacteriaceae*, are among the leading causes of infections. Lilly and Stillwell first introduced the term *probiotics* for bacteria that benefit the host by improving the intestinal microbial balance. *Lactobacilli* and *Bifidobacteria* are widely used as probiotics (Fuller, 1991). In addition, *prebiotics* are nondigestive food

Table 50C.3

Supplemental Protocol for Preoperative Patients Who Are to Undergo Hepatobiliary Resection in Nagoya University Hospital (14 Days to 1 Day Before Surgery)

Regular diet
Replacement of bile
Inchinkoto 7.5 g/3 × 1
Ursodeoxycholic acid 600 mg/3 × 1
Prebiotics: oligomate 15 mL/3 × 1
Probiotics
Yakult 400 1 pack/day
Bifile 1 pack/day

Oligomate, galactooligosaccharides; Yakult 400, *Lactobacillus casei* strain Shirota 400 × 108; Bifile, *Bifidobacterium breve* strain Yakult 100 × 108 plus galactooligosaccharides 0.6 g

constituents that selectively alter the growth and/or activity of a limited number of beneficial bacteria in the colon, thus potentially improving the health of the host (Collins & Gibson, 1999; Fuller, 1991; Gibson et al, 1995). Several types of ingredients, such as fructooligosaccharides, galactooligosaccharides, and inulin, are used as prebiotics. The combined use of probiotics and prebiotics is called *synbiotics* (Collins & Gibson, 1999). Synbiotic combinations have beneficial effects on human health, but their clinical value in surgical patients remains unclear because, to date, only a few clinical studies have been conducted on synbiotics (Rayes et al, 2002a, 2002b). We investigated the effect of postoperative synbiotics, combined with early enteral nutrition, in biliary cancer patients undergoing hepatectomy (Kanazawa et al, 2005). The primary result of this RCT was that the incidence of infection was 19% in the synbiotics group and 53% in the control group ($P < .05$), demonstrating that synbiotics can reduce postoperative infections. This beneficial effect encouraged us to schedule the next RCT, which investigated the benefit of perioperative use of synbiotics compared with postoperative use only (Sugawara et al, 2006). The incidence of postoperative infection was 30% in the former group and 12% in the latter group ($P < .05$), showing that perioperative synbiotics can decrease postoperative infections. Our latest protocol for perioperative supplementation is presented in Table 50C.3.

References are available at expertconsult.com.

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CHAPTER 50D

Cancer of the bile ducts: interventional techniques in hilar and intrahepatic biliary structures

Karen T. Brown

OVERVIEW

Malignant disease resulting in high bile duct obstruction (Fig. 50D.1)—that is, obstruction above the junction with the cystic duct—is not uncommon. Although frequently related to primary tumors of the biliary tree (see Chapters 49, 50A, and 50B), hilar obstruction, and even intraductal tumor, can be seen with other common malignancies such as breast, pancreatic, and colorectal cancers. Significant technical progress has occurred in both endoscopic and percutaneous biliary drainage, allowing safer palliative treatment of patients with such obstructions. Because these patients are often asymptomatic at presentation, the goals of treatment should be clearly defined prior to committing the patient to even a minimally invasive procedure. First and foremost, whether the patient is a surgical candidate should be determined. With the exception of patients who are clearly in a palliative situation, we prefer to discuss these patients in a multidisciplinary group with hepatobiliary surgeons, interventional radiologists, oncologists, and gastroenterologists to outline a plan of treatment. A thorough understanding of this plan and of the patient's prognosis facilitates the development of a strategy for drainage. Accepted indications for palliative biliary drainage in these patients include intractable pruritus, cholangitis, the need to restore liver function to allow for administration of chemotherapeutic agents with biliary metabolism/excretion, access for intraluminal brachytherapy or choledochoscopy, and diversion for bile leak. Given the availability of high-quality magnetic resonance cholangiopancreatography (MRCP), direct cholangiography as a diagnostic tool is rarely warranted (see Chapters 17 and 18; Choi et al, 2008; Park et al, 2008).

INDICATIONS FOR BILIARY DRAINAGE

Neither hyperbilirubinemia alone nor the computed tomographic (CT) or ultrasound finding of dilated bile ducts is an indication for biliary drainage. Pruritus, cholangitis, and the need to lower the bilirubin to administer certain chemotherapeutic agents, on the other hand, are all accepted indications for biliary drainage. Patients who have undergone biliary-enteric bypass as part of curative resection for a benign or malignant lesion may develop postoperative bile leaks that require drainage for diversion. In some cases, access to the biliary tree may be undertaken as a method of delivering local treatment for primary bile duct cancer, such as brachytherapy or photodynamic therapy. Many physicians have the impression that patients feel better and have improved performance status after relief of jaundice; however, this has not been confirmed in clinical studies. Indeed, in a prospective trial, we have shown that in patients with malignant biliary obstruction, percutaneous drainage does not significantly improve quality of life (QOL), except for improving pruritus (Robson et al, 2007). Controversy remains in regard to the role of biliary drainage prior to surgery (Johnson & Ahrendt, 2006; Mezhir et al, 2009; Wang et al, 2008).

ENDOSCOPIC VERSUS PERCUTANEOUS DRAINAGE (SEE CHAPTERS 18, 27, AND 28)

Patients with low bile duct obstruction are typically treated endoscopically. Patients with high bile duct obstruction, particularly when the obstruction extends above the hilus, have traditionally been treated percutaneously. This is because the success rate of percutaneous drainage has been higher, and the complication rate lower, when compared with endoscopic methods (Rerknimitr et al, 2004). This perspective is evolving as endoscope technology becomes more advanced, and endoscopists become better trained and more experienced in wire-guided procedures and have better guidewires and stents with which to work.

The two biggest drawbacks to endoscopic drainage for high bile duct obstruction have been the lack of ability to reliably target a specific area of the liver for drainage and the risk of contamination, by retrograde injection of contrast, of parts of the biliary tree that will not be drained. It is not uncommon to see a patient who is thought to have undergone successful endoscopic stenting of the right and left liver only to find, upon repeat imaging, that is not the case at all (Fig. 50D.2). Despite this, endoscopic management is indicated in some cases of high bile duct obstruction. This is particularly so when the risk of the patient having a permanent exteriorized catheter is high or when a patient has a higher risk of contaminating the entire biliary tree if approached percutaneously.

One exciting new endoscopic approach is the placement of a transgastric segment III stent using endoscopic ultrasound. This procedure is considered when a patient is best treated by draining the left lateral segment, and the percutaneous approach is technically difficult, or where the risk of contaminating the right-sided bile ducts is thought to be high with or without being able to cross the obstruction. This is particulary indicated when draining the right liver would be of no clinical benefit, either because of replacement of right liver by tumor or occlusion of the right portal vein (Fig. 50D.3). When technically feasible, this procedure can be gratifying for the patient, with relief of pruritus and lowering of bilirubin without the added burden of a percutaneous catheter. Endoscopic drainage is almost never indicated in patients with papillary intraductal tumor because it can easily grow into a metallic stent and result

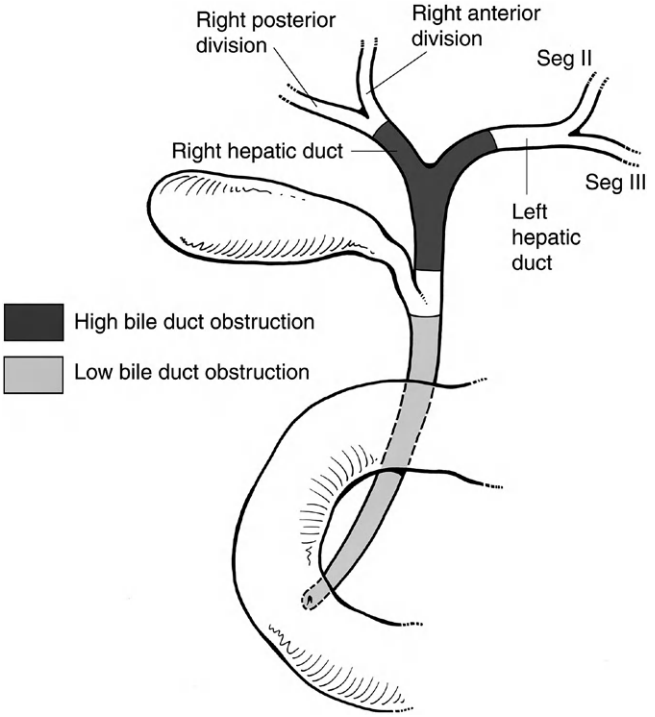


FIGURE 50D.1. High bile duct obstruction refers to obstruction at or above confluence (*dark gray area*); low bile duct obstruction occurs below the common hepatic duct (*light gray area*). Seg, segment. *(Courtesy Memorial Sloan-Kettering Cancer Center Medical Graphics.)*

in early stent occlusion. Intraductal tumor can be seen from cancers other than papillary cholangiocarcinoma. When intraductal tumor occurs in the setting of metastatic colorectal cancer, it is usually the direct extension of a parenchymal metastasis into the duct. Patients with intraductal tumor often require permanent indwelling catheter drainage. The indwelling multiple sidehole catheter allows bile to drain around the intraductal tumor, and it can be changed every 10 to 12 weeks to maintain catheter patency (Fig. 50D.4). Having a realistic idea of what is feasible endoscopically and percutaneously is very important when making the initial decision regarding who will treat the patient. This depends on a thorough understanding of the goal of treatment as well as knowledge of the skill level of the interventional radiologists and endoscopists available to care for the patient.

Preprocedure Preparation

Imaging

The importance of excellent preprocedure imaging in patients with bile duct obstruction cannot be overemphasized. This imaging should include at a minimum a contrast-enhanced CT scan of the abdomen. Ultrasound is often used to establish the presence of dilated bile ducts, identify the level of obstruction, evaluate portal vein patency, and demonstrate intraductal tumor, but ultrasound is not adequate for drainage planning. Although MRCP provides an excellent three-dimensional (3D) rendering of the obstructed bile ducts and is excellent at delineating intraductal abnormalities and depicting isolated bile duct (Fig. 50D.5), it excludes certain things that can serve as targeting aides at the time of drainage, such as surgical clips, dystrophic calcifications, and bone landmarks. CT scans performed on multislice scanners in a picture archiving and communication system (PACS) environment allow the development of a 3D understanding of the anatomy while identifying relevant landmarks that can be used for targeting, and it also demonstrates other structures that should be avoided, such as liver lesions and bowel. Of course, as with MRI, one may also identify ascites, hepatic atrophy, and portal vein occlusion or encasement. All of this information is important in making prognostic assessments and in determining the best approach for drainage.

When planning drainage in patients with high bile duct obstruction, it is important to determine the amount of functional parenchyma that can be drained. Functional parenchyma is the part of the liver that is not replaced by tumor, and it has an intact portal venous supply. If 75% of the hepatic parenchyma is replaced by tumor, even if it were possible to drain the entire biliary tree, it is unlikely that normal hepatic function or normalization of serum bilirubin level would be restored. The portal vein provides the trophic blood supply to the liver, and occlusion results in atrophy of the affected segment or segments, particularly when the ipsilateral bile duct is also occluded (see Chapter 5; Hann et al, 1996). Atrophy may be recognized by the diminutive size of the involved part of the liver, accompanied by crowding of the bile ducts (Fig. 50D.6; see also Chapter 50B and Figs. 50B.6 and 50B.7). When portal vein occlusion causes atrophy, drainage of the atrophied liver does not improve liver function. In addition, it is frequently difficult to cross out of the obstructed/atrophied portion of the liver. The end result is an external drainage catheter that provides no clinical benefit to the patient but degrades QOL.

Central tumors frequently obstruct the right and left biliary tree, isolating them from one another. Obstruction may extend even higher, isolating the ductal system at the sectoral, segmental, or subsegmental level. When drainage is undertaken for relief of pruritus, draining even a segment of the liver may result in relief of symptoms (Abraham et al, 2002; Van Laethem et al, 2003). When isolation is present, and drainage is undertaken to lower the serum bilirubin, it is important to estimate how much functional parenchyma can be drained with one catheter. *Functional liver parenchyma* is defined as hepatic parenchyma with intact portal venous inflow and hepatic venous drainage. Analogous to a surgeon resecting no more than 75% of the liver to ensure an adequate liver remnant, it seems that at least 30% of functional hepatic parenchyma must be drained to improve liver function for chemotherapy, returning the serum bilirubin to normal or near-normal levels. In some cases, this goal may be impossible to achieve, unless more than one drainage catheter or stent is placed. Recognition of this allows for informing both the patient and referring physician about the potential need for more than one catheter or stent.

Cholangitis is rarely the primary indication for drainage in patients with malignant bile duct obstruction, except in patients who have undergone instrumentation and in those who have reason to have a contaminated biliary tree by virtue of previous biliary-enteric bypass, cross ampullary stenting, or sphincterotomy (Ozden et al, 2005). When draining a hemiliver or a segment, either percutaneously or endoscopically, it is possible to contaminate functionally "isolated" parts of the biliary tree. In this case, subsequent cholangitis may drive the placement of additional catheters. Widespread contamination of a severely isolated biliary tree with drainage of only part of the obstructed system can result in chronic recurrent cholangitis. Whether induced by endoscopic or percutaneous means, this situation

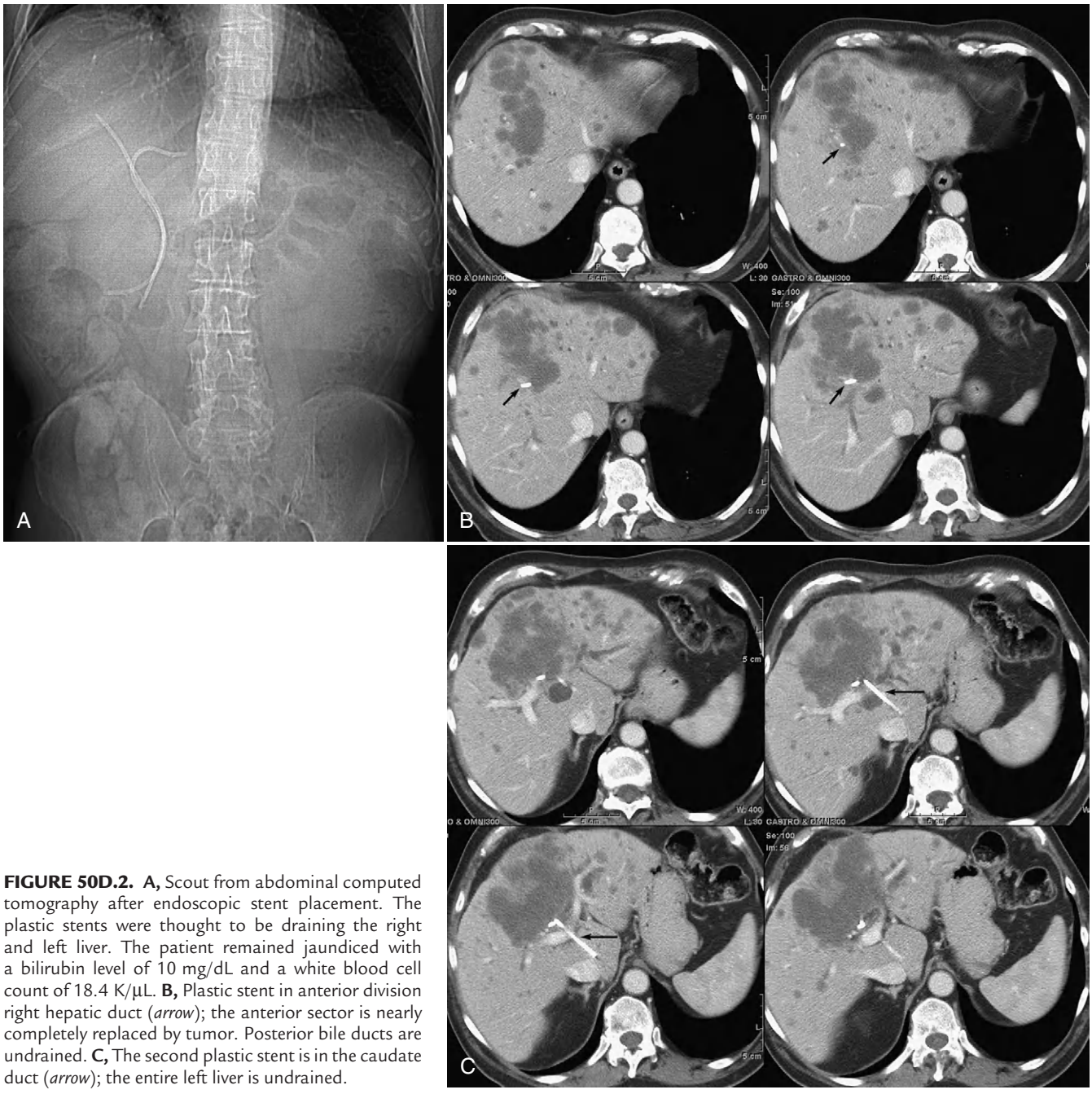


FIGURE 50D.2. **A,** Scout from abdominal computed tomography after endoscopic stent placement. The plastic stents were thought to be draining the right and left liver. The patient remained jaundiced with a bilirubin level of 10 mg/dL and a white blood cell count of 18.4 K/μL. **B,** Plastic stent in anterior division right hepatic duct (*arrow*); the anterior sector is nearly completely replaced by tumor. Posterior bile ducts are undrained. **C,** The second plastic stent is in the caudate duct (*arrow*); the entire left liver is undrained.

can be difficult to manage and should be anticipated and avoided if possible.

Laboratory Studies

Patients undergoing biliary drainage need a complete blood count, hepatic function panel, and coagulation studies. The serum bilirubin can change rapidly when patients become obstructed. Because decisions regarding the need for further drainage in high obstruction and isolated bile ducts depend in part on the serum bilirubin, it is important to draw this reference laboratory value within 24 hours prior to drainage. Because this value is typically increasing at the time of drainage, it is common for the serum bilirubin to be higher the morning after the drainage procedure than it was the morning of the procedure. Serum bilirubin values drawn 48 hours after drainage more accurately predict effectiveness of drainage. Poor hepatic synthetic function may result in elevation of the prothrombin time (PT) and international normalized ratio (INR) and the partial thromboplastin time (PTT). If needed, underlying coagulopathy may be corrected by the administration of vitamin K or fresh frozen plasma, depending on the urgency of drainage.

Antibiotics

Preprocedure antibiotic prophylaxis is given to all patients undergoing biliary drainage, even if the patient does not have an elevated white blood cell count or fever, as bactibilia is present in 30% to 40% of patients without these signs (see Chapter 11;

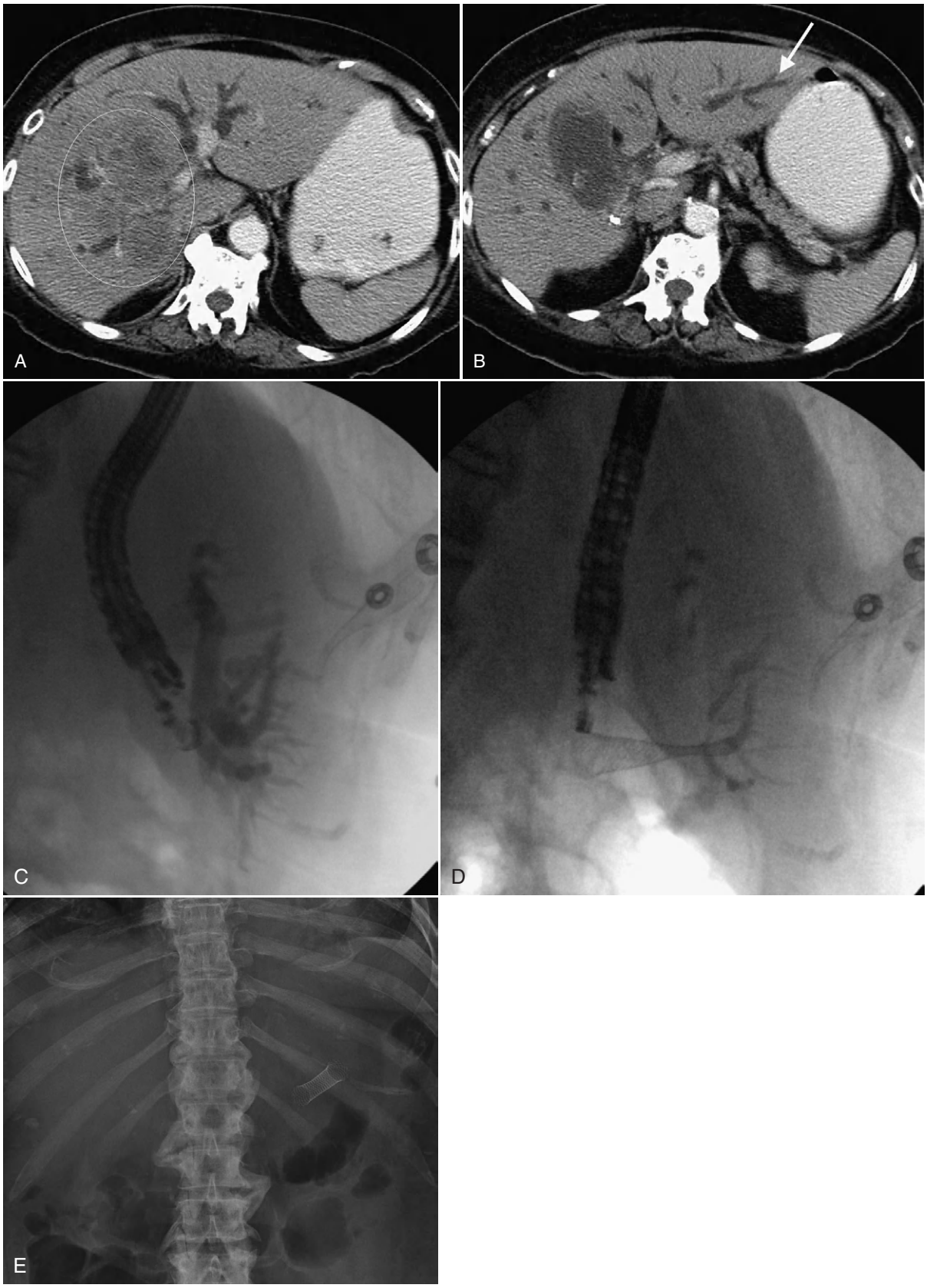


FIGURE 50D.3. A, Central mass in right liver (*circled*) encasing the right portal vein and isolating right anterior and posterior bile ducts. **B,** Segment III duct (*arrow*) in close proximity to the stomach. **C,** Endoscopic image after puncture into segment III duct and injection of contrast. **D,** Image following placement of transgastric segment III stent. **E,** Image of the kidney, ureter, and bladder the next day demonstrates a well-expanded stent between the lesser curvature of the stomach and the segment III bile duct.

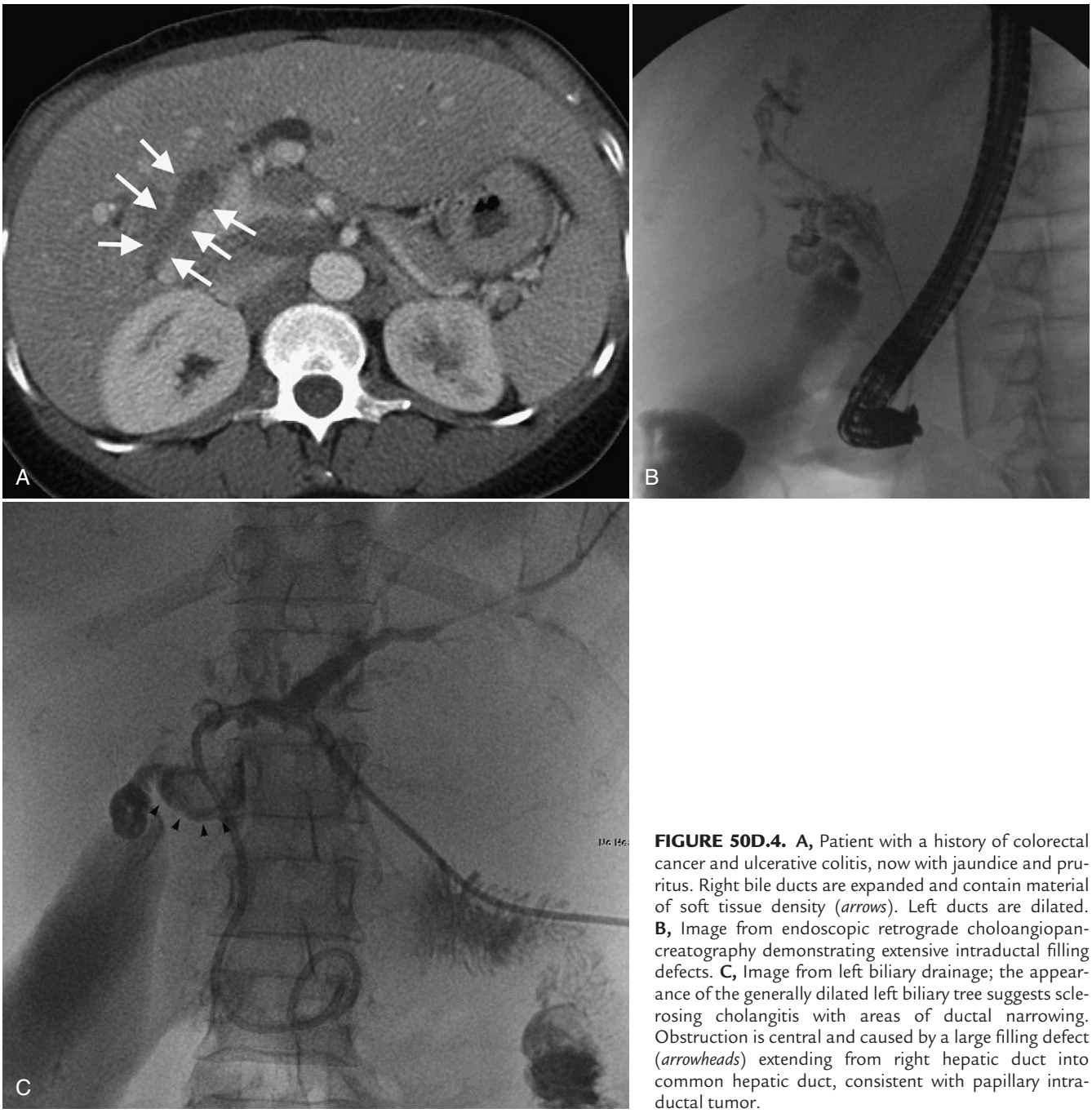


FIGURE 50D.4. A, Patient with a history of colorectal cancer and ulcerative colitis, now with jaundice and pruritus. Right bile ducts are expanded and contain material of soft tissue density (*arrows*). Left ducts are dilated. **B,** Image from endoscopic retrograde choloangiopancreatography demonstrating extensive intraductal filling defects. **C,** Image from left biliary drainage; the appearance of the generally dilated left biliary tree suggests sclerosing cholangitis with areas of ductal narrowing. Obstruction is central and caused by a large filling defect (*arrowheads*) extending from right hepatic duct into common hepatic duct, consistent with papillary intraductal tumor.

Brody et al, 1998). Many patients become bacteremic during the procedure, even in the absence of preintervention signs or symptoms of infection. Generally, patients receive broad coverage with an agent such as ticarcillin-clavulanate or ceftriaxone. When cholangitis is not present, administration of intravenous antibiotics beyond 24 hours is not warranted. Patients with a history of cholangitis or sepsis or those presumed to have a contaminated bilary tree related to transampullary stenting, biliary-enteric bypass, sphincterotomy, or recent instrumentation should receive prophylactic coverage with an agent such as piperacillin-tazobactam (Zosyn), which is excreted into the bile. Appropriate postprocedure coverage should be determined based on bile cultures obtained at the time of drainage.

Psychological Preparation

A thorough discussion of possible outcomes is particularly important prior to biliary drainage in patients with high bile duct obstruction. Patients should understand that, although every effort will be made to establish internal drainage with stents, this may not be straightforward. Although it is usually possible to cross an obstructing lesion into the common bile duct, internalization might be precluded by extensive isolation of the biliary tree, intraductal tumor, concomitant duodenal obstruction, or other factors. Two or more catheters or self-expanding stents may be required when the tumor extends beyond the secondary confluence on one side or the other, depending on the clinical objective. Such a discussion is not

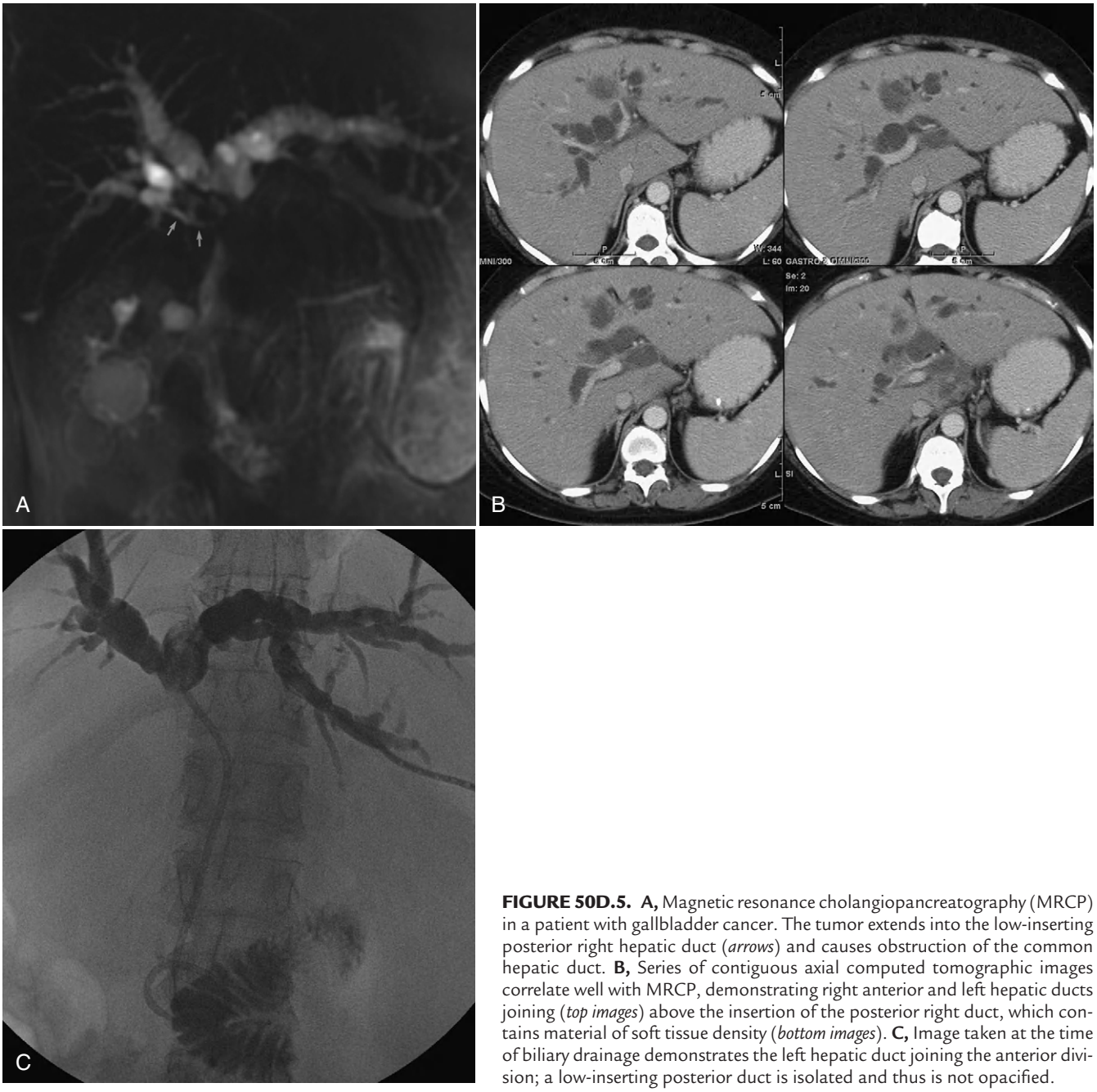


FIGURE 50D.5. **A,** Magnetic resonance cholangiopancreatography (MRCP) in a patient with gallbladder cancer. The tumor extends into the low-inserting posterior right hepatic duct (*arrows*) and causes obstruction of the common hepatic duct. **B,** Series of contiguous axial computed tomographic images correlate well with MRCP, demonstrating right anterior and left hepatic ducts joining (*top images*) above the insertion of the posterior right duct, which contains material of soft tissue density (*bottom images*). **C,** Image taken at the time of biliary drainage demonstrates the left hepatic duct joining the anterior division; a low-inserting posterior duct is isolated and thus is not opacified.

intended to frighten the patient but rather to promote an understanding of the complexity of the situation to mitigate sentiments of surprise or anger if stent placement is not possible at the initial encounter and subsequent procedures are necessary.

Even in the presence of segmental isolation, pruritus often resolves following biliary drainage. Unfortunately, it is not always possible to lower the serum bilirubin, particularly to levels that would allow for the administration of certain chemotherapeutic agents. In certain situations, two or more biliary drainage catheters may be placed without a significant decrease in bilirubin; sometimes, the bilirubin may even increase. It is possible that a single biliary drainage catheter may drain one portion of the liver well, while converting near-complete obstructions in other areas to complete obstructions (Fig. 50D.7). It also is conceivable that intervening cholangitis or progression of disease may play a role. Patients who have realistic expectations and some understanding of these issues before the initial biliary drainage procedure are less likely to become distressed if multiple procedures are required, or if the ultimate outcome is less than satisfactory.

INTRAPROCEDURAL ISSUES

Approach

Many interventional radiologists prefer a right-sided approach to the biliary tree. The right side of the liver is larger and more accessible than the left. Approach from the right side more

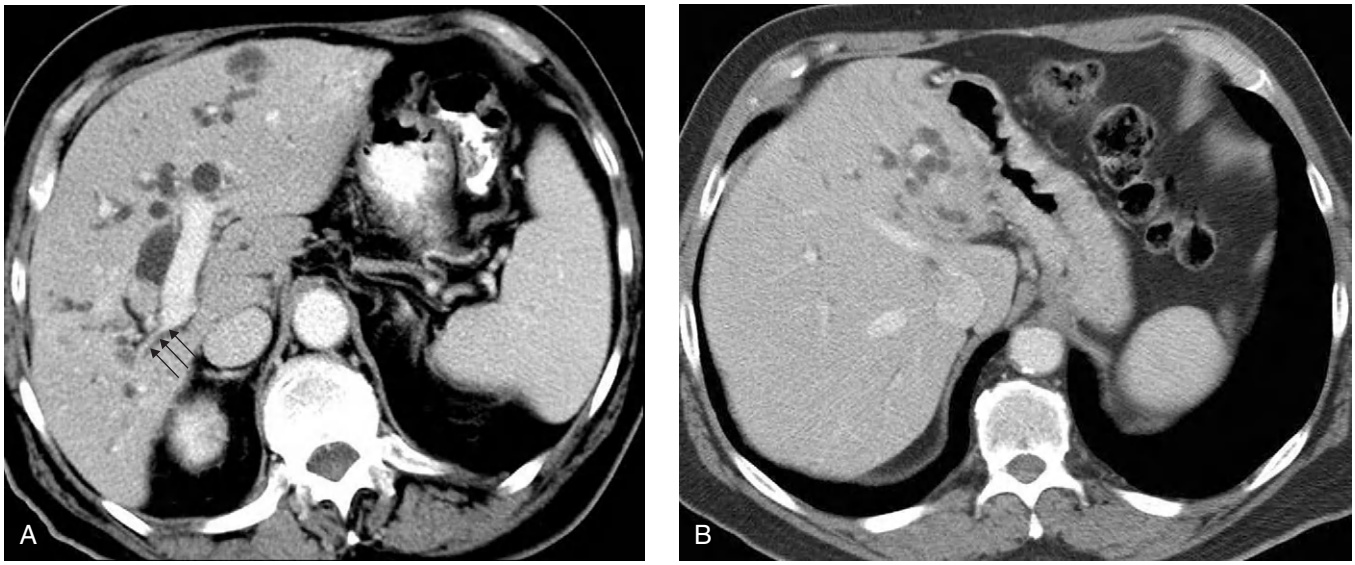


FIGURE 50D.6. A, Right hepatic atrophy. Volume of the right hemiliver is markedly diminished, with severe attenuation of the right portal vein (*arrows*). **B,** Left hepatic atrophy. Note the small size of the left hemiliver (anterior to middle hepatic vein) and crowding of dilated bile ducts.

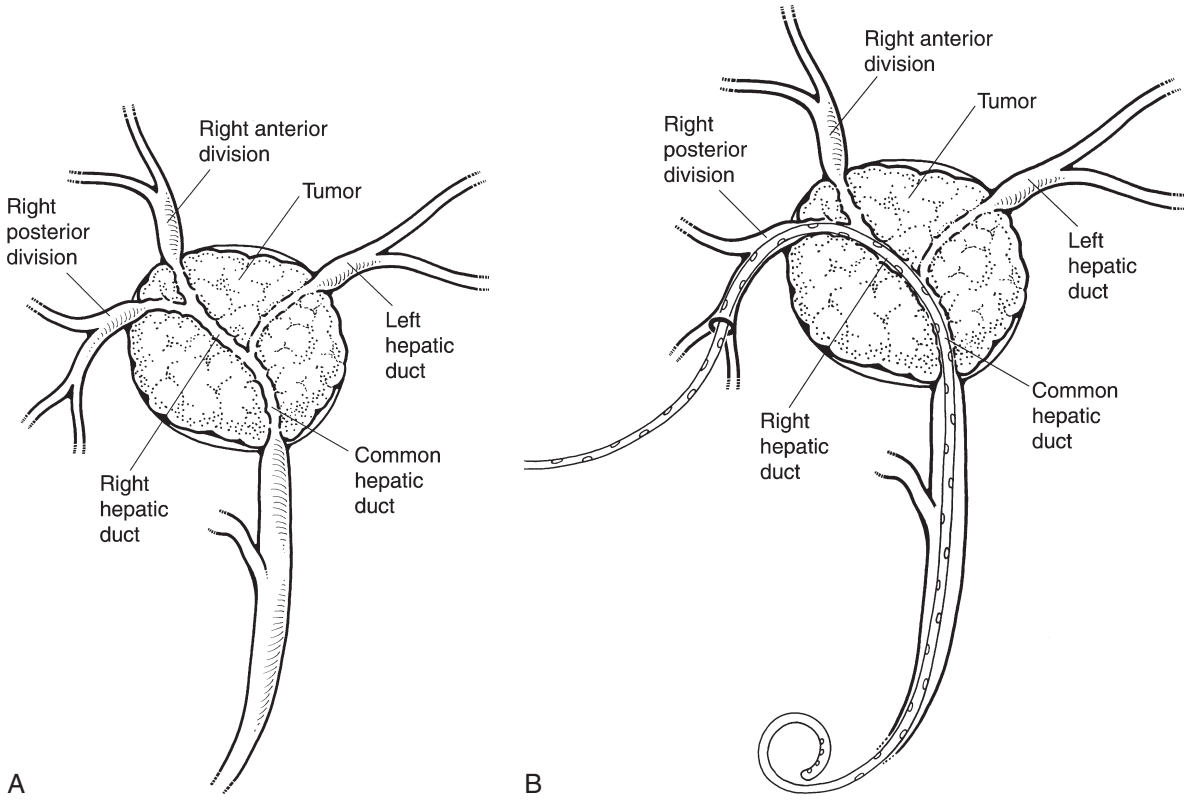


FIGURE 50D.7. A, Obstruction caused by tumor severely narrows the biliary tree up to the secondary confluence on right. **B,** After placement of a multiple sidehole catheter, the right posterior sector is well drained by the catheter, which converts near-complete obstruction of the right anterior division duct and left hepatic duct into complete obstruction by further compromising an already narrowed lumen. *(Courtesy Memorial Sloan-Kettering Cancer Center Medical Graphics.)*

easily avoids direct x-ray exposure to the hands of the operator and allows a direct approach to the hepatic hilus and common bile duct, making catheter and guidewire manipulations easier and often more successful. In addition, the approach from the right side is thought to be safer, because there are fewer structures between the skin and right liver that may be injured. Patients with low bile duct obstruction that cannot be drained endoscopically may be approached from either side.

The direct approach from the right is sometimes complicated, when the site of puncture is the right posterior duct, and that duct enters the left hepatic duct. This anatomic variant is often evident on preprocedure imaging studies (see Chapter 1B); it occurs in 20% of patients and may add a 180-degree turn to the approach to the hepatic hilum, making it more difficult to traverse the obstruction. On the other hand, when the obstruction extends to the left-right confluence but no higher, approach from the posterior right duct will drain the right posterior sector as well as the entire left liver. The main disadvantages to a right-sided approach are the discomfort associated with intercostal catheters, leaking of ascites around a more gravity-dependent right-sided catheter, and the fact that tumors are more likely to extend to the secondary confluence on the right.

A left-sided approach to the biliary tree is preferred in several instances. When an obstructing tumor extends above the biliary confluence, it may isolate the right and left bile ducts and may extend toward a secondary confluence or higher. As alluded to above, the right hepatic duct is typically shorter than the left (see Chapter 1B); as a result, tumor is more likely to extend to and isolate the right anterior and posterior sectoral ducts, while the left medial and lateral sectors continue to communicate. In such cases it may be possible to drain more functional hepatic parenchyma by placing a single catheter or stent on the left. Patients with ascites are less likely to leak around a left anterior catheter, so a left approach is preferred when possible. When atrophy or compromise of the portal vein is present, the patient will always derive more benefit from drainage of the contralateral functional liver, as previously discussed.

Image Guidance

In most cases, biliary drainage is performed with fluoroscopic guidance. Ultrasound is often used for duct puncture from a left-sided approach; a right-sided approached is used less often because bile duct orientation and the need to image through an intercostal space make the use of ultrasound more challenging and therefore less useful. Careful review of a high-quality CT scan is helpful for identifying radiopaque landmarks that may be used to target a specific region of the biliary tree or even a specific bile duct. This review is particularly important when isolation is suspected and the objective is to target a specific duct. If the right anterior duct is the target, it would be unfortunate to enter a segment IV duct by being too anterior or medial. Previously placed stents, surgical clips, or other radiopaque landmarks can frequently be used to facilitate targeting.

Sedation

In most cases, general anesthesia is not warranted, and biliary drainage can be performed with conscious sedation, often with midazolam (Versed) combined with a narcotic. For this reason, patients receive only a clear liquid diet for 4 hours before the procedure. Patients should be well hydrated and have functional venous access, particularly if cholangitis is part of the clinical picture; these patients can become septic and hypotensive, requiring rapid administration of intravenous fluids.

Technical Aids

The most significant technical development to facilitate biliary drainage and other fluoroscopically guided procedures in recent years has been the advent of multidetector CT scans (MDCT), particularly when used within a PACS environment. The ability to scan the liver in a single breath hold and then cine through the images facilitates identification of the level of obstruction and the likelihood of isolation. It also enables the formulation of a three-dimensional mental image of the biliary tree much more easily than looking at hard copy scans, and understanding the biliary anatomy facilitates a successful, uncomplicated procedure. It is frequently possible to anticipate normal variants of bile duct anatomy, which can have a significant impact on preprocedure planning (see Chapter 1B). In addition, most PACS workstations allow cross-reference to the axial images (Fig. 50D.8A) with the "scout" image (Fig. 50D.8B), which is a simulated frontal radiograph used for programming the extent of the scan. In this way, targeting of a specific region, or even a specific duct, is made much easier—and the final catheter resides within the planned segment of the liver (Fig. 50D.8C). Although this degree of sophistication is unnecessary for obstruction below the hepatic hilum, MDCT facilitates drainage in patients with complex high bile duct obstruction such that it is sometimes worth performing MDCT, even when the patient has had a recent hard copy CT scan from the referring institution.

Drainage Catheter Versus Primary Stent Placement

The suitability of a patient for primary stent placement is determined at the time of biliary drainage based on the indication for the drainage, evidence of infected bile, presence of blood or tumor within the biliary tree, and cholangiographic findings. The goal of biliary drainage is to solve the patient's clinical problem by placing as few catheters or stents as possible, intending that the bile should drain internally when the intervention is complete. Patients with obstruction below the common hepatic duct without cholangitis may be stented primarily, at the time of the initial drainage procedure, provided significant blood is not present within the biliary tree. Blood clot within the intrahepatic bile ducts impairs drainage and can cause stent obstruction that may result in bile leaking into the peritoneal cavity from the site of duct puncture. When hemobilia occurs (see Chapter 105), a drainage catheter is placed until the bile clears, at which time the patient can be easily stented. Patients undergoing drainage for cholangitis cannot be stented primarily in most cases. Catheter manipulation in this group of patients is kept to a minimum to diminish the risk of procedure-related sepsis. Once the biliary tree is drained and cholangitis resolves, a stent can be placed.

Having dispensed with the straightforward decisions regarding patients who clearly can or cannot be stented, the more difficult situations that occur in patients with high bile duct obstruction must be addressed. In 1975, Bismuth and Corlette (1975) classified obstruction of the hepatic confluence as types

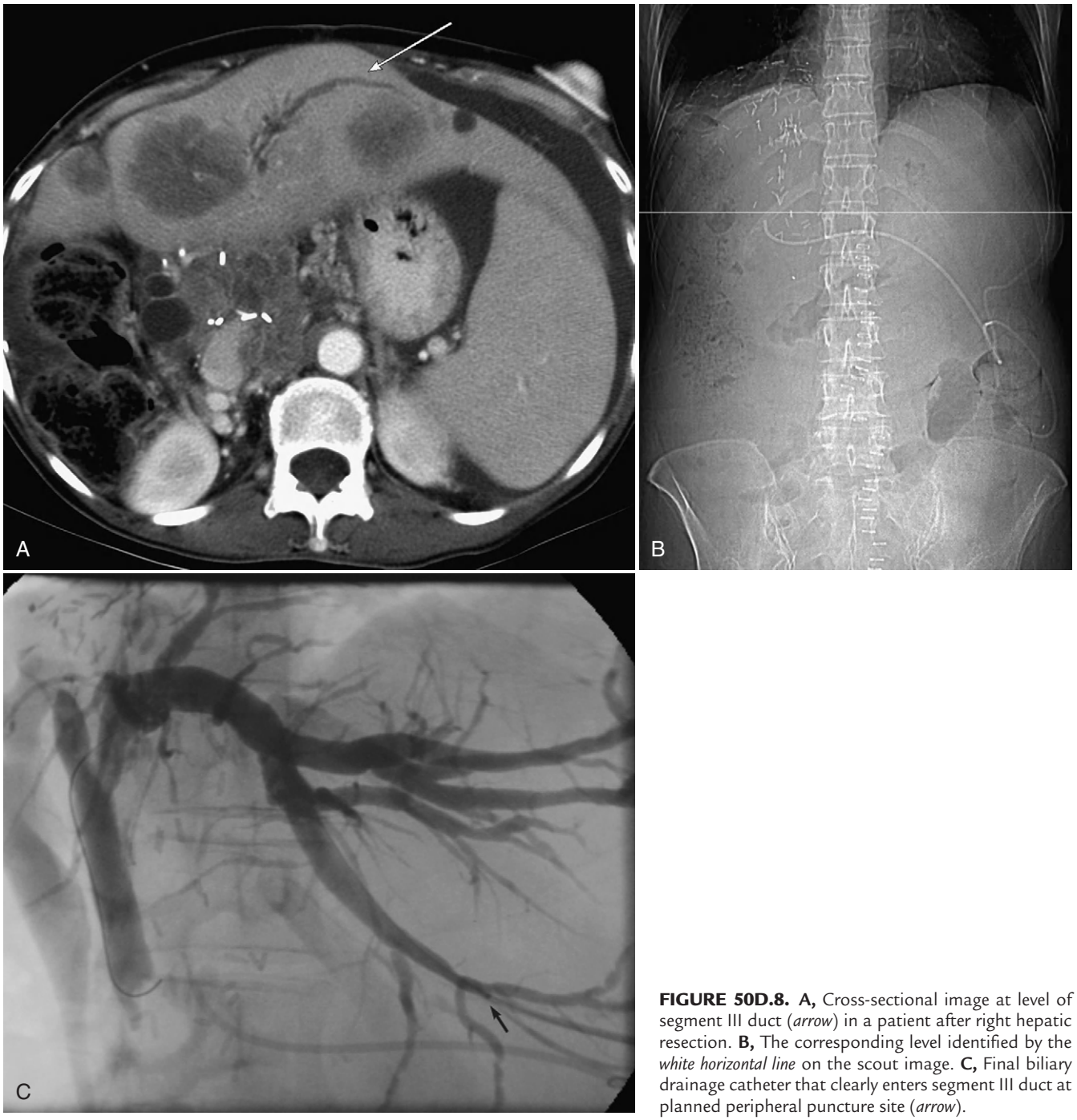


FIGURE 50D.8. **A,** Cross-sectional image at level of segment III duct (*arrow*) in a patient after right hepatic resection. **B,** The corresponding level identified by the *white horizontal line* on the scout image. **C,** Final biliary drainage catheter that clearly enters segment III duct at planned peripheral puncture site (*arrow*).

I through IV (Fig. 50D.9; see Chapter 42A). Predictions about the level of obstruction and degree of isolation of the biliary tree can be made based on the preprocedure imaging studies. These predictions are not always accurate, however, and it is sometimes necessary to modify the stenting approach based on cholangiographic findings; in rare instances, it may be necessary to abandon the procedure altogether. Patients with type I obstruction can have the entire liver drained with one catheter or stent, because right and left ducts communicate freely. Barring one of the previously mentioned contraindications, these patients have a primary stent placed.

Patients with type II obstruction cannot be completely drained with one catheter, although it is sometimes possible to opacify ducts in both sides of the liver. Some suggest that survival is better when both sides of the liver are drained (Chang et al, 1998), although even in Bismuth type II and III hilar obstructions, Inal and colleagues (2003a) saw no significant difference in clinical response to treatment or stent patency rate with unilobar versus bilobar drainage.

When contrast material enters the obstructed side opposite the puncture, it usually does not drain effectively, and that side is considered contaminated. These patients can be stented from

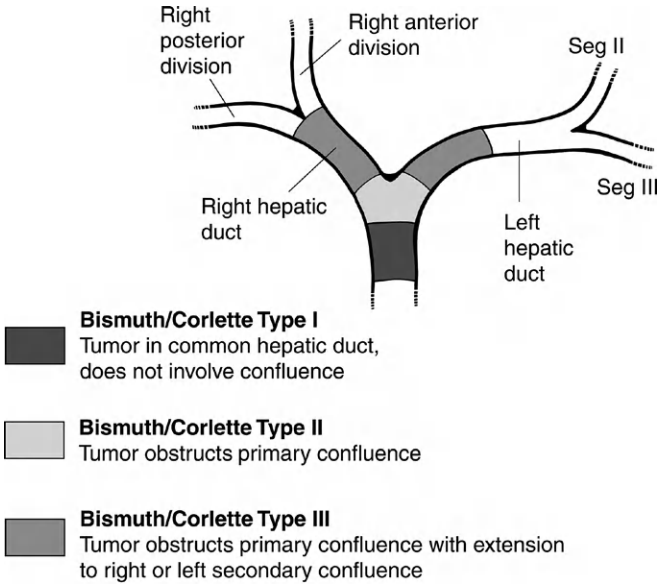


FIGURE 50D.9. Bismuth-Corlette classification for high malignant bile duct obstruction. Type IV involves both right and left ducts to secondary confluence. Seg, segment. *(Courtesy Memorial Sloan-Kettering Cancer Center Medical Graphics.)*

the ipsilateral approach by inserting one stent from the ipsilateral side to the contralateral side and a second stent from the ipsilateral side into the common bile duct or duodenum (Fig. 50D.10), in a T-shaped configuration. The other option is to puncture the contralateral side and place side-by-side stents (Fig. 50D.11), in a Y-shaped configuration. In either case, we prefer to stent into the common bile duct and not into the duodenum if possible so as to preserve function of the sphincter of Oddi. Barring any contraindication, this could be done primarily at the time of initial drainage, as advocated by Inal and colleagues (2003b). These authors found that whether stents were placed primarily or at a second sitting, patients without cholangitis at the time of stenting did not develop cholangitis subsequently, and in all patients with a type I or II obstruction, the serum bilirubin decreased to 2 mg/dL or less. One advantage of the more anatomic Y-shaped configuration stent placement is that if stent occlusion occurs, both stents are approachable endoscopically. In addition, the patency rate of the Y-shaped configuration may be better in patients with type IV obstruction (Inal et al, 2003a). Specially constructed stents have been developed that allow placement of one stent through an opening in the midbody of the other (Kim et al, 2004).

Sometimes the contralateral biliary tree is not opacified, precluding knowledge of the type of obstruction, or the ipsilateral obstruction is a type III obstruction or worse. In this case, and in the absence of some other contraindication, a patient being drained for pruritus alone might have a primary stent placed,



FIGURE 50D.10. A, Patient with cholangiocarcinoma that resulted in Bismuth-Corlette type II obstruction, with near-complete isolation of right and left hepatic ducts. **B,** Same patient treated with side-by-side T-shaped configuration. Wallstents were placed simultaneously, with one stent placed from the left hepatic duct to the right hepatic duct and the other from the left hepatic duct into the common bile duct. The stent from the left hepatic to common bile duct ends well short of the duodenum but extends several centimeters on either side of the obstructed segment.

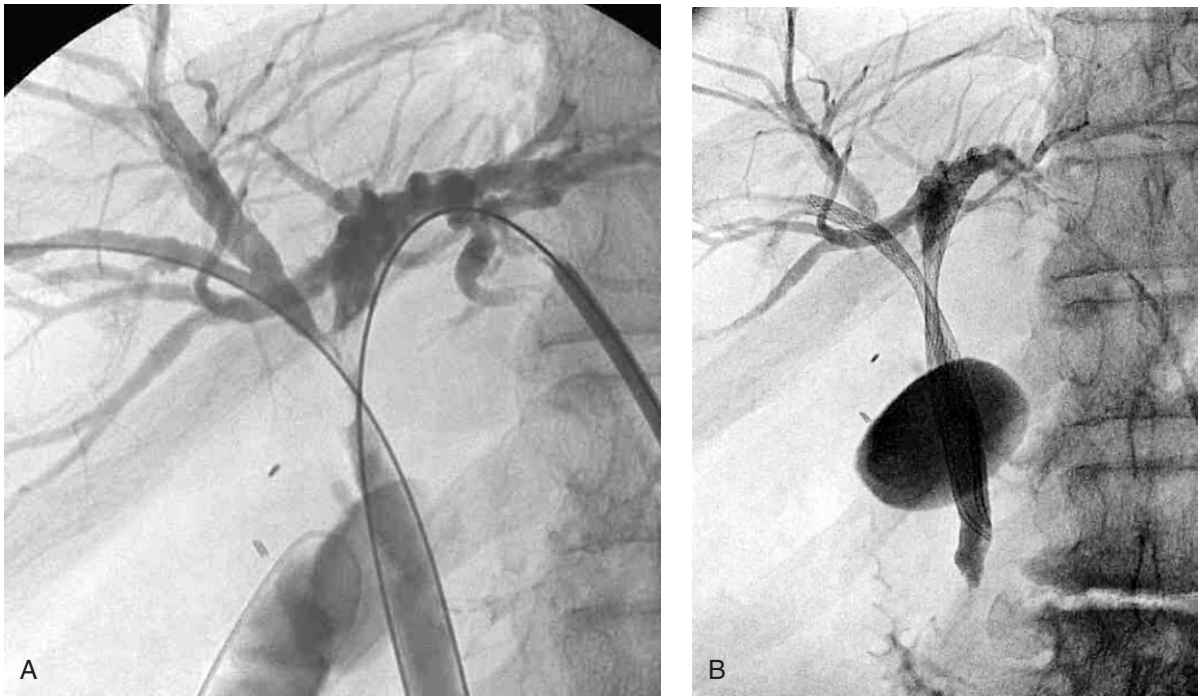


FIGURE 50D.11. **A,** Patient with history of pancreatic cancer after a Whipple procedure with recurrence at the biliary-enteric anastomosis and type II obstruction. **B,** Same patient after simultaneous placement of side-by-side Y-shaped configuration stents.

because only a small portion of the liver need be drained to alleviate pruritus. If the patient is being drained in an attempt to lower the bilirubin level for chemotherapy, a stent should be considered, if it is thought that 30% or more of the liver will be drained. We use this as a rule of thumb, despite the fact that in a series of 149 patients drained at Memorial Sloan-Kettering Cancer Center, we found only a marginally significant difference in the number of patients attaining a bilirubin less than 2 mg/dL based on the estimated volume of liver drained. In this analysis, 6 (29%) of 21 patients with less than a third of the liver drained attained a bilirubin level below 2 mg/dL, whereas this was achieved in 65 (51%) of 128 patients with more than one third of the liver drained ($P = .06$; Ulrich et al, 2009). Following stent placement, if the bilirubin fails to fall to the desired level, a second drainage procedure can be performed. Given the QOL issues for the patient, as well as the risk of contaminating an undrained part of the liver by having an externalized catheter in place, the slight inconvenience of working through a previously placed stent seems warranted.

If an internal/external drainage catheter is placed, and subsequently the serum bilirubin normalizes without evidence of cholangitis, the patient can undergo stenting of that portion of the liver drained by the catheter. If an internal-external catheter has been placed, and the bilirubin does not fall to a level that allows treatment or cholangitis develops, it will be necessary to drain more of the isolated undrained liver before stent placement.

When the initial drainage has been on the right side, and the tumor has extended up the right hepatic duct so as to isolate the anterior and posterior divisions from each other and from the left hepatic duct, side-by-side self-expanding metallic stents can be placed on the right to drain both the anterior and posterior ducts. Alternatively, when the left side of the liver is functional, a left drainage can be performed as the next step; then one stent can be placed from the left, and another can be placed from the right. If instead of a stent, a second catheter has been placed on the left, and the serum bilirubin still does not decrease to an appropriate level or cholangitis develops, stents can be placed from the right to the common bile duct, from the left to the common bile duct, and from the left to the residual undrained right system (Fig. 50D.12). Although a significant difference in patency is reported when more than one stent is placed in a noncoaxial fashion (Maybody et al, 2009), the mean patency is almost 6 months, which justifies stent placement. Even when one part of the liver is not functional, drainage may be necessary to eliminate a source of ongoing cholangitis.

The concepts of biliary drainage are simple, but when high bile duct obstruction is present, the planning is complex, and execution can be difficult. The patient must have enough of the liver drained to be free of cholangitis and pruritus and to effect a reduction in serum bilirubin to receive chemotherapy if indicated. Given the fact that no difference in stent patency is reported if the stent is inserted for proximal or distal obstruction, a significant difference in patency is seen when more than one stent is placed, and lower complication rates are reported when stents are placed primarily, primary stent placement should be considered whenever possible (Inal et al, 2003a, 2003c; Maybody et al, 2009). Additional stents can be placed later if necessary. Patients with Bismuth type I or II obstructions may be treated with a single stent, whereas patients with type III or IV obstructions may ultimately require placement of additional stents (Inal et al, 2003a).



FIGURE 50D.12. Stents placed from right anterior hepatic duct to the common bile duct, from the left hepatic duct to the common bile duct, and from the left hepatic duct to the residual undrained posterior right duct. **A,** Without contrast. **B,** After injection of contrast.

POSTPROCEDURE CARE

Patients are monitored carefully for the first 24 hours after drainage for signs of bleeding or sepsis. With proper technique, including peripheral bile duct puncture, serious bleeding complications are uncommon. Because the hepatic artery, portal vein, and bile duct travel side by side within portal triads, it is common for blood to enter the bile duct during catheter exchanges, resulting in hemobilia in the immediate postprocedure period (see Chapter 105). Hemobilia usually clears within 24 hours, and new or recurrent hemobilia within the first few days of drainage typically is related to catheter malposition. If the catheter is pulled out from its original position, it is possible for a catheter sidehole to become positioned adjacent to a portal vein branch; this problem can be corrected by simply repositioning the catheter, but the catheter is often upsized as well. Significant arterial bleeding during this period is rare. No matter where the initial puncture is performed to opacify the biliary tree, attempts are always made to puncture a peripheral bile duct for catheter placement, preferably a fourth-order or fifth-order branch. The more peripheral the bile duct punctured, the smaller the accompanying hepatic artery branch, and the lower the risk of arterial injury and postprocedure bleeding.

When bleeding occurs a week or more after biliary drainage—especially when the event is sudden in onset, and not only hemobilia but bleeding also occurs around the catheter entry site—arterial injury should be suspected, and the patient should be studied angiographically (see Chapter 19). Although a pseudoaneurysm or extravasation of contrast is sometimes seen, as in any other case of vascular trauma, any abnormality of a hepatic arterial branch adjacent to the biliary drainage catheter should be taken as presumptive evidence of injury to the branch, and the vessel should be selectively embolized (Fig. 50D.13). If the clinician is determined to demonstrate extravasation of contrast material angiographically, it is sometimes necessary to remove the biliary drainage catheter over a guidewire during the angiogram. In the correct clinical setting, empiric superselective embolization of the arterial branch corresponding to the bile duct punctured is acceptable. There is little down side to this approach, and the patient's bleeding is stopped; the biliary catheter is exchanged at this point, because it is usually at least partially occluded by thrombus.

Despite prophylactic antibiotic coverage, sepsis may occur immediately after or within several hours of drainage and should be treated appropriately (Smith et al, 2004). This is most commonly manifested by the development of rigors with normal or low body temperature, but hypotension and fever may also occur. Sepsis is managed with continued administration of appropriate antibiotics, expansion of intravascular volume, and pressor support if necessary. Blood cultures should be drawn to identify organisms responsible for the bacteremia. Cultures of bile obtained at the time of drainage are routinely sent in for all patients. This is particularly important for those with preprocedure fever, biliary-enteric anastomosis or sphincterotomy, previous endoscopic retrograde cholangiopancreatography, or



FIGURE 50D.13. A, Proper hepatic angiogram in patient with hemobilia and bleeding around biliary drainage catheter 1 week after drainage. Note spasm of right hepatic artery branch (*small arrows*) adjacent to catheter at site of duct puncture. **B,** Right hepatic angiogram after coil embolization (*arrows*) of right hepatic artery branch.

an indwelling stent or catheter. Although positive bile cultures are more common in patients with benign bile duct obstruction, cultures are positive in more than half of patients with malignant obstruction. Five percent of patients without fever, previous biliary surgery, or endoscopic or percutaneous intervention have positive bile cultures (Brody et al, 1998).

Bile may leak around a biliary drainage catheter. Leaking is most commonly related to the catheter becoming malpositioned so that one or more sideholes are no longer within the biliary tree but are in the catheter tract or even outside the patient. This problem is easily managed by repositioning the catheter. Leakage may also be seen with lack of adequate sideholes above the level of obstruction. Anything that impedes the flow of bile from above the obstruction, either through the catheter to below the obstruction or into a drainage bag, will result in bile leaking back along an established tract. For a properly positioned catheter with an appropriate number of sideholes, the problem is easily remedied by catheter exchange. Patients with capped internal-external catheters may have bile leak back along the catheter tract when egress of bile is obstructed internally. Distal sidehole occlusion is the most common cause, and this problem is easily remedied by catheter exchange. Patients with duodenal obstruction or impaired small bowel motility may be relegated to obligate external drainage.

Ascites may leak around the catheter and may be mistaken for bile. This occurs most often in the presence of jaundice, when the ascitic fluid is bile colored. Leaking of ascites can be difficult to manage. The best treatment is to establish internal biliary drainage with stent placement as expeditiously as possible. If the patient cannot be stented, the catheter may be upsized to tamponade the site more effectively. In addition, ascites can be tapped frequently or drained by a Tenckhoff catheter in an attempt to allow time for tract maturation. These strategies often fail eventually, and as a last resort, a stoma is created around the entry site to contain the ascites.

SUMMARY

Treatment of malignant high bile duct obstruction presents unique challenges to the interventional radiologist. The outcome depends on the condition of the underlying hepatic parenchyma, the degree of isolation of the biliary tree, and the technical skills of the operator. A thorough understanding of functional biliary anatomy and the availability of high-quality imaging are necessary to optimize outcome. Although pruritus may be palliated by draining even one segment of the liver, lowering the serum bilirubin to normal or near-normal requires adequate drainage of at least 30% of the liver, assuming the underlying parenchyma is relatively normal. Contamination of undrained parts of the biliary tree may occur as a result of drainage catheter placement, with ongoing or recurrent cholangitis becoming a problem. For this reason, primary stent placement should be considered when 30% or more of the liver can be drained at the time the initial procedure.

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CHAPTER 55B

Management of chronic pancreatitis: conservative, endoscopic, and surgical

Werner Hartwig, Oliver Strobel, Markus W. Büchler, and Jens Werner

OVERVIEW

Chronic pancreatitis (CP) is a progressive, destructive, inflammatory process that ends in total destruction of the pancreas and results in malabsorption, diabetes mellitus, and severe pain. Incidence and prevalence of CP varies between continents and countries. Most studies from Western countries show comparable incidence and prevalence rates of around 7 per 100,000 and 28 per 100,000, respectively (Lankisch et al, 2002; Levy et al, 2006). The numbers reported from Asia are markedly higher with a rapidly rising incidence (Otsuki & Tashiro, 2007; Wang et al, 2009). The etiologic factors associated with CP are commonly summarized using the TIGAR-O classification: ***t***oxic–metabolic (in the West, alcohol and tobacco are associated in approximately 80% to 90% of cases), ***i***diopathic, ***g***enetic (*PRSS1, CFTR,* or *SPINK1* gene mutations), ***a***utoimmune, ***r***ecurrent and severe acute pancreatitis, or ***o***bstructive (pancreas divisum, sphincter of Oddi dysfunction, or neoplasm) (Etemad & Whitcomb, 2001). Tropical CP is a common entity in India, southern Africa, and parts of South America and typically affects younger patients. Tropical CP is often classified as idiopathic but may in fact have a mixed etiology that includes nutritional, metabolic, and genetic factors (Mohan et al, 2003). Current evidence suggests that a combination of predisposing factors—environmental, toxic, and genetic—is likely involved in most cases rather than a single factor. The sentinel acute pancreatitis event (SAPE) hypothesis proposes a sentinel event of acute pancreatitis that initiates the inflammatory process, which is then sustained by a combination of the mechanisms mentioned above (Whitcomb, 1999).

Repeated episodes of inflammation initiated by autodigestion, oxidative stress, one or more episodes of severe pancreatitis, and toxic-metabolic factors can lead to activation and continued stimulation of pancreatic stellate cells. Histologically, CP is characterized by inflammatory infiltration, acinar atrophy, formation of metaplastic ductal lesions (tubular complexes and pancreatic intraepithelial neoplasia), extended fibrosis, and in some cases by focal necrosis and cysts (Klöppel, 2007). Furthermore, neural hypertrophy and perineural inflammation can frequently be observed and are the correlate of neuropathic pain (Ceyhan et al, 2009a).

Clinically, the course of CP is characterized by recurrent episodes of upper abdominal pain, which represents the most common indication for endoscopic and surgical intervention. Although pain attacks and intensity might decrease over time, the so called "burnout" of the gland does not regularly occur, and more than 50% of patients will come to medical attention with persistent pain even 15 years after initiation of the disease. Furthermore, patients may be seen with symptoms of endocrine insufficiency (diabetes mellitus) and exocrine insufficiency (diarrhea, steatorrhea, malnutrition, and weight loss).

In the natural course of CP, endocrine and exocrine insufficiency frequently develops secondary to the fibrotic changes of the pancreas. As a result of morphologic changes of the pancreas, patients frequently develop local complications. Inflammatory ductal changes and intraductal calculi (pancreatolithiasis) may result in obstruction of the pancreatic duct or of the intrapancreatic portion of the bile duct. An inflammatory mass of the pancreatic head, as it is regularly observed in European and American series (Beger et al, 1999; Jimenez et al, 2000), frequently results in obstruction of the duodenum and affects the splenic, superior mesenteric, or portal vein with subsequent thrombosis. Development of pancreatic pseudocysts represents another local complication, which results in obstruction, abscess formation, or in ascites or pleural effusions in cases of rupture (see Chapter 54). A rare but severe local complication of CP is vascular erosion presenting as gastrointestinal hemorrhage or, less frequently, as intraabdominal bleeding (see Chapter 19). Finally, CP is a risk factor for the development of pancreatic cancer (see Chapter 58); patients with CP have a fourfold higher risk of cancer than individuals without it. Especially in the management of patients with an "inflammatory mass," this differential diagnosis has to be considered (Pedrazzoli et al, 2008).

The treatment of CP is complex; in the majority of cases, an interdisciplinary approach is indicated that includes conservative, endoscopic, and surgical therapy.

CONSERVATIVE TREATMENT

Pancreatic Exocrine Dysfunction

In Western countries, the number of patients suffering from pancreatic exocrine insufficiency has increased. The most common cause is an increase in alcohol consumption with a concomitant increase of CP (FitzSimmons, 1993). The main goal of therapy for pancreatic exocrine dysfunction is to avoid fat maldigestion. Reasons for earlier and more severe impairment of fat digestion, compared with protein and carbohydrate digestion, in patients with pancreatic insufficiency are that 1) impairment of pancreatic lipase synthesis and secretion occurs earlier; 2) more rapid and complete inactivation of lipase occurs in the acidic duodenum as a result of impaired bicarbonate output; 3) proteolytic degradation of lipase occurs earlier during aboral transit than with amylase and proteases; 4) impairment of pancreatic bicarbonate secretion decreases duodenal pH,

resulting in precipitation of glycine-conjugated bile acids and further deterioration of fat digestion; and 5) extrapancreatic sources of lipase are unable to compensate for loss of pancreatic lipase activity.

For all of the reasons listed, steatorrhea is the leading symptom in patients with pancreatic exocrine insufficiency.

Pancreatic Exocrine Enzyme Supplementation

When weight loss or steatorrhea (≥15 g/day) or both develop, supplementation of pancreatic enzymes is indicated. Dyspepsia, diarrhea, meteorism, and malabsorption of proteins and carbohydrates also have been cited as indications. Another interesting indication for pancreatic enzyme supplementation, although not formally studied, is in the treatment of pain (discussed in the next section). The main goal of the treatment of pancreatic exocrine dysfunction is to ensure that optimal amounts of lipase reach the duodenum with the delivered food. With the currently available pancreatic enzyme supplement preparations, azotorrhea (protein malabsorption) can be eliminated (Brady et al, 1991), whereas steatorrhea usually can be reduced but not totally corrected.

Four different types of pancreatic exocrine enzyme preparations are available. *Uncoated preparations* show only poor effects because of their inactivation by gastric acid. Huge doses of enzymes are required to have any effect on fat malabsorption. These preparations should be used only in patients with pancreatic exocrine insufficiency and hypochlorhydria or achlorhydria. The use of *enteric-coated tablets* is strongly discouraged, because these preparations are ineffective for decreasing fat excretion owing to erratic enzyme release. The superiority of *enteric-coated microsphere preparations* over conventional enzyme preparations with regard to decrease in stool fat excretion has been firmly established (Layer & Holtmann, 1994). Pancreatic enzymes in these preparations are protected at low pH by a special polymer coating. The release of the enzymes occurs only at a pH of at least 4.5. Simultaneous administration of antacids, H2-receptor antagonists, or proton pump inhibitors is unnecessary. Unfortunately, microencapsulation results in a considerable increase in costs. Another problem concerning enteric-coated microspheres might be considerable differences in the diameter of the microspheres and in their physical nature as a result of differences in the manufacturing process; however, clinical differences in the various enteric-coated microsphere preparations have not yet been proofed.

The use of *enzyme preparations in combination with acid-reducing compounds* also is not justified for many reasons, although additional administration of proton pump inhibitors or H2-receptor antagonists reduces fecal nutrient loss. These preparations are expensive, there is a variability of the effects owing to the acid-reducing therapy, and especially in children, the safety of long-term administration has not been firmly established (Lebenthal et al, 1994).

Certain *bacterial and fungal lipases* have shown no benefit in the treatment of pancreatic steatorrhea, although they are resistant against acid denaturation and proteolytic digestion. Decreased lipolytic activity of fungal lipase in the presence of bile acids could explain the fact that no superiority over enteric-coated microsphere preparations has been demonstrated to date (Griffin et al, 1989; Zentler-Munro et al, 1992).

Although rare, possible side effects of pancreatic exocrine enzyme supplementation are sourness of the mouth, perianal irritation, abdominal pain, diarrhea, constipation in infants, allergic reactions to pork proteins, hypersensitivity reactions after inhalation, and fibrosing colonopathy in cystic fibrosis patients (Lebenthal et al, 1994; Loser & Folsch, 1995). In regard to fibrosing colonopathy, it has been recommended that the maximum dose of lipase should not exceed 10,000 IU/kg body weight per day, or 2500 IU/kg body weight per meal.

Substitution Therapy in Chronic Pancreatitis

Approximately 80% of patients with CP can be managed by dietary means and pancreatic enzyme supplements. Some patients (10% to 15%) need oral supplements (polymeric or semielemental), 5% need enteral tube feeding, and approximately 1% need total parenteral nutrition (TPN). Reduction of steatorrhea and supplementation of calories are the main goals of nutritional therapy in CP. Treatment of exocrine insufficiency starts with dietary therapy and pancreatic enzyme supplementation (DiMagno, 1979).

Total abstinence from alcohol and partaking of frequent meals are basic dietary recommendations. The diet should be rich in proteins (1.0 to 1.5 g/kg body weight/day) and carbohydrates, although carbohydrates must be limited when diabetes mellitus is present. In addition, 30% to 40% of calories should be in the form of fats. Medium-chain triglycerides may be used to increase fat absorption, because they are absorbed directly across the small bowel into the portal vein, even in absence of lipase, co-lipase, and bile salts. Vitamins should be supplemented if serum levels indicate a deficiency (Havala et al, 1989). Patients with protein maldigestion and steatorrhea must be supplemented individually with exogenous pancreatic enzymes. Weight control, symptomatic relief of diarrhea, and a decrease in 72-hour fecal fat excretion are practical end points of therapy.

Enteral nutrition (EN) is indicated when a patient is unable to eat, has progressive weight loss despite an adequate dietary regimen, or develops acute complications; EN may also be indicated preoperatively and postoperatively. Only rarely is TPN indicated in patients with CP, such as when gastric emptying is blocked, when the patient needs gastric decompression, when the feeding tube cannot be introduced into the jejunum, or when a complicated fistula is present. In most cases, surgical intervention can solve these problems.

Conservative Treatment of Pain

Pain significantly reduces patients' quality of life, and pain relief should be one of the main goals of conservative treatment in CP. Pain also may be treated interventionally or surgically, but medical treatment is generally the first-line therapy in patients with painful CP.

Different medical treatment options and therapeutic interventions are available, and these must be integrated into an individualized treatment plan. The pathogenesis of pain especially influences the therapeutic procedure. Two mechanisms are suggested for the generation of pain in the absence of local complications: 1) inflammatory changes of pancreatic parenchyma with intrapancreatic and peripancreatic neural alterations (Bockman et al, 1988; Ceyhan et al, 2009a, 2009b; Di Sebastiano et al, 1997), and 2) ductal and intraparenchymal hypertension (Di Sebastiano et al, 2003; Ebbehoj et al, 1990).

As for the second mechanism, options that reduce the intrapancreatic pressure may lead to a significant reduction of

pancreatic pain. In the case of inflammation, a significant number of inflammatory mediators in pancreatic parenchyma and pancreatic nerves are detected in patients with pain (Ceyhan et al, 2009b; Di Sebastiano et al, 2000). Several medical, analgesic, and antiinflammatory treatment options are available, which may be combined with or supported by interventional methods.

Alcohol Abstinence and Diet

Besides alcohol abstinence, no specific dietary measures have been found to be effective in preventing pancreatic pain. Even total abstinence from alcohol may achieve pain relief in only 50% of patients with moderate to mild CP (Gullo et al, 1988).

Suppression and Inhibition of Pancreatic Secretion

The effect of pancreatic enzyme preparations on pain is uncertain. A meta-analysis of six studies on enzymes for pain treatment concluded that there is no positive effect, but this conclusion is unreliable because of the heterogeneity of the study groups and significant differences in drug preparations (Brown et al, 1997). A more recently published review that also included data from studies published in abstract form came to a similar conclusion (Winstead & Wilcox, 2009). Further studies are needed to prove whether somatostatin and its analogue octreotide have any impact on pain in patients with CP. A proper placebo randomized controlled trial (RCT) must be performed, which should include 1) the classification of patients as to the etiology of their CP, 2) the systematic assessment of quality of life of patients prior to the initiation of therapy and at regular intervals throughout the study, 3) a priori power analysis estimating a placebo response rate of at least 25%, and 4) multiple planned subgroup analysis (Winstead & Wilcox, 2009).

Analgesics

Guidance for analgesic treatment in patients with CP is based on the consensus report of the German Society of Gastroenterology (Mössner et al, 1998) and the recommendation of the World Health Organization (WHO, 1990). One physician should be responsible for the administration of analgesics. For the first step in pain management, nonnarcotic agents, such as acetaminophen or nonsteroidal antiinflammatory drugs (NSAIDs), are recommended. Opioids are often necessary further along. Every patient requires an individualized type and dose of analgesic drug, starting with the lowest dose necessary to control pain. In patients with pain mainly caused by inflammation and by invasion of inflammatory cells, antiinflammatory drugs such as NSAIDs may be helpful. Some patients with CP have depression, which lowers the visceral pain threshold. An additional antidepressant therapy may have an effect on pain and generally increases the effects of opiates.

Interventional Procedures to Treat Pancreatic Pain

Of patients with pancreatic pain, 40% to 70% seem to benefit from medical treatment (Ammann et al, 1984). This percentage may increase by combining medical therapy and interventional procedures (van der Hule et al, 1994). Pancreatic pain may also be improved by the combination of interventional endoscopy and lithotripsy, although a recent RCT demonstrated increased costs but no outcome benefit when systematic endoscopy was added to lithotripsy (Dumonceau et al, 2007). Some studies showed a significant difference in improvement of pain among patients with successful or unsuccessful lithotripsy (Delhaye et al, 1992; Costamagna et al, 1997; Johanns et al, 1996; Ohara et al, 1996; Sauerbruch et al, 1992; Schneider et al, 1994; Smits et al, 1996). Other studies did not report this difference (Adamek et al, 1999).

Celiac plexus neurolysis and celiac block involve injecting an agent at the celiac axis, with the aim of either selectively destroying the celiac plexus or temporarily blocking visceral afferent nociceptors. Agents most commonly used for this purpose include alcohol or phenol for neurolysis and bupivacaine and triamcinolone for a temporary block. Methods to administer such agents to the celiac ganglion include CT imaging, percutaneous ultrasound, fluoroscopy, or endoscopic ultrasound (EUS). Whereas the EUS-guided technique may be superior compared with the other methods, response rates in general are relatively low (Gress et al, 1999; Noble & Gress, 2006; Santosh et al, 2009).

Autoimmune Pancreatitis

A type of CP that might be caused by an autoimmune mechanism was first described by Sarles and collegues (1961) and was termed *primary inflammatory sclerosis of the pancreas.* Since then, a growing body of evidence suggests that autoimmune pancreatitis (AIP) is distinct from obstructive or calcifying forms of CP. Two clinical and histologic patterns of AIP can be distinguished (Park et al, 2009). Type 1 is characterized by the histologic key features of dense periductal lymphoplasmacytic infiltrate, swirling or storiform fibrosis, and obliterative venulitis; serum levels of the immunoglobulin G4 (IgG4) subclass of IgG are typically increased (Hamano et al, 2001). Type 1 AIP fits the classic description of the disease reported in Japan, also known as *lymphoplasmacytic sclerosing pancreatitis.* Type 1 AIP appears to be the pancreatic manifestation of a systemic disease that may also affect other organs, including the bile duct, retroperitoneum, kidney, lymph nodes, and salivary glands. Type 2 AIP is typically characterized by a duct-destructive pathology with infiltrating neutrophils, lymphocytes, and plasma cells. Typical serologic markers seen in type 1 AIP are not elevated in type 2 AIP (Park et al, 2009). Typical imaging features—a diffuse, sausage-shaped, enlarged pancreas with delayed and peripheral enhancement—only show up in about 50% of patients. Furthermore, classic features of lymphoplasmacytic sclerosing pancreatitis are found in just 20% of core biopsies, and false-positive IgG4 immunostaining has also been reported in the setting of cancer. Thus the preoperative differentiation from pancreatic carcinoma is a diagnostic challenge. In highly suspected or histologically confirmed cases of AIP, steroid therapy (prednisolone, initially 30 to 40 mg/day) may ameliorate symptoms and imaging findings within two weeks. Importantly, the similarity to pancreatic carcinoma and the absence of specific diagnostic parameters may result in surgical treatment of this disease. Because reports about patients misdiagnosed as having AIP are increasingly encountered, surgery should always be considered in doubtful cases (Gardner et al, 2009).

ENDOSCOPIC TREATMENT IN CHRONIC PANCREATITIS

Pancreatic ductal obstruction by fibrotic stenoses and/or calculi are the most frequent indications for endoscopic therapy.

Interventional treatment modalities aim to decompress and drain the pancreatic ductal system. Endoscopic interventions (see Chapters 14 and 27)—such as stone extraction, dilations, and stenting—have to be repeated on a regular basis in almost all patients. As a consequence, patients suffer from frequent rehospitalizations.

Two recent RCTs demonstrated the superiority of surgical versus endoscopic therapy in primary success rate, pain relief, and quality of life in patients with duct obstruction in the pancreatic head (Cahen et al, 2007; Dite et al, 2003). On the other hand, a large multicenter study in 1018 patients reported success of endoscopic therapy (multiple sessions) in 65% of patients, with the necessity for surgery in only 24% (Rösch et al, 2002). A study of 61 patients with CP and bile duct stenosis reported a 1-year success rate of 59% with endoscopic stenting and stent replacement every 3 months, but failure of endoscopic therapy occurred in the majority of cases with presence of calcifications, with a success rate of only 7.7%; moreover, 49% of patients who had an unsuccessful interventional therapy underwent surgery within a year (Kahl et al, 2003). In patients with symptomatic pseudocysts and no ductal obstruction, endoscopic drainage procedures may be as safe and effective as surgical drainage but superior to external drainage, as reported in a recent retrospective study (Johnson et al, 2009). However, this result needs confirmation in a larger-scale randomized trial.

Available data suggest recommendations concerning endoscopic versus surgical treatment in CP as follows:

1) Patients with proximal stenosis and no calcifications or inflammatory mass may be treated endoscopically. If two to three repetitive endoscopic treatments fail, the option of surgery must be evaluated.

2) In patients with distal duct obstruction, calcifications, or local complications, surgery is superior to endoscopic treatment. Patients should undergo surgery early in the course of the disease to prevent further deterioration of exocrine or endocrine function.

3) Pancreatic pseudocysts may be treated endoscopically. If endoscopic treatment fails, a surgical drainage procedure is recommended.

Endoscopic treatment options and their possible indications are summarized in Table 55B.1. Endoscopic therapy for pancreatic pseudocysts and common bile duct stenosis associated with CP is discussed in detail here.

Table 55B.1

Interventional and Endoscopic Therapy: Options and Indications

Options	Indications
Interventional External Drainage	Temporary treatment of a pancreatic abscess or an infected pseudocyst Frequently followed by definitive surgical treatment If internal drainage is not possible
Internal Drainage	Effective therapy of pseudocysts; no RCTs with comparison to surgery
Endoscopic cystogastrostomy/ cystroduodenostomy	If anatomically possible: less invasive than surgery Problems with recurrence and catheter dislocation
Endoscopic Ductal Drainage	
ePT	Pancreas divisum, sphincter of Oddi dysfunction
ePT plus dilation + stenting of pancreatic duct	Proximal stenosis of pancreatic duct
ePT plus lithotripsy and stone extraction	Pancreatolithiasis
ePT plus bile duct stenting	Bile duct stenosis
Indicators of Poor Outcome	
Distal stenosis of pancreatic duct	
Parenchymal calcifications	
Unsuccessful management after 1 year	

RCT, Randomized, controlled trial; ePT, endoscopic papillotomy

Decompression of Pancreatic Pseudocysts

Pancreatic pseudocysts are a late complication of CP. The main techniques for decompression of pancreatic pseudocysts include *transgastric* and *transduodenal* approaches (Sahel, 1990; Dohmoto & Rupp, 1992); these require a clear bulging of the cyst into the gastric or duodenal cavity to ensure a short distance between the cystic wall and the intestinal tract. In this context, endosonography has been shown to reduce the risk of cyst perforation and hemorrhage (Binmoeller et al, 1994; Etzkorn et al, 1995; Grimm et al, 1992).

The technical success rate appears to be better for cystoduodenostomy than for cystogastrostomy owing to a higher complication rate (Binmoeller et al, 1994; Sahel, 1991). In more recent articles, the mortality appears to be almost zero, whereas morbidity rates are reported between 3% and 11% (Binmoeller et al, 1994; Dohmoto & Rupp, 1992; Etzkorn et al, 1995; Grimm et al, 1992; Sahel, 1990, 1991). A more recent approach to access the cystic cavity is indirectly via the papilla and the ductal system (Pinkas et al, 1994). For this reason, a selective endoscopic pancreatic sphincterotomy and a retrograde pancreatography must be performed to introduce a guidewire, over which the dilation of the cannulation can be performed. A double-pigtail endoprothesis should be inserted through the papilla into the cyst. No deaths (Dohmoto & Rupp, 1992; Pinkas et al, 1994; Sahel, 1990) and very low morbidity (2% to 7%) have been reported. A major problem of this approach is its nonfeasibility in patients with strictures or stones located between the papilla and the pseudocyst. Because these procedures call for a highly specialized endoscopist, cases with poor anatomic conditions or with contraindications determined by preliminary endosonography should be referred to a specialized center.

Common Bile Duct Stenting

Common bile duct stenosis is a mechanical complication of CP. A team approach that includes endoscopists and surgeons should guide the treatment of common bile duct stenosis in patients with CP. The decision for either interventional or surgical treatment depends on the patient's age, comorbidities, the course of CP, and the cause of the stricture. A subgroup of patients has been reported to benefit from endoscopic stenting, with permanent regression of the stenosis reported after stent removal. Endoscopic stenting should be performed as first-line therapy in those patients with CP-induced acute cholestasis, when malignancy can be excluded. Especially for patients who

refuse surgery or those who have significant comorbidities, the endoscopic approach might be the therapy of choice. Kahl and associates (2003) reported in a prospective follow-up study that endoscopic drainage of biliary obstruction provides excellent results in the short term but offers only moderate long-term results. Patients without calcifications of the pancreatic head benefit from biliary stenting; patients with calcifications were identified to have an increased risk of failure within a 12-month course of endoscopic stenting. Major limitations, such as plastic stent clogging, migration, and cholangitis, frequently occur in the long-term follow-up. Alternatively, self-expanding Wallstents may improve the results, and metal stents that cannot migrate offer a stent effectiveness greater than 80% (Ng & Huibregtse, 1998). At present, long-term follow-up data to clarify the role of endoscopic approaches and to identify the preferred stent for the management of cholestasis in CP are unavailable. The placement of Wallstents used to be irreversible, but results with the latest generation of stents that are covered, and therefore removable, are awaited. However, for young patients with CP and no comorbidity, adequate and definitive therapy for recurrent cholestasis is provided by a surgical drainage procedure or pancreatic head resection (Eickhoff et al, 2001).

SURGERY

The surgical treatment of CP is based on two main concepts: *preservation of tissue via drainage* aims to protect against further loss of pancreatic function, and *pancreatic resection* is performed for nondilated pancreatic ducts, pancreatic head enlargement, or if a pancreatic carcinoma is suspected in the setting of CP. An overview on the common surgical procedures and the indications for surgery are listed in Table 55B.2.

Drainage Procedures

Pancreatic duct sphincterotomy was one of the first surgical procedures proposed for patients with CP and stenosis at the papilla of Vater. This procedure was recognized as a dangerous approach, however, with lower success rates for amelioration of pain, indicating that a stenosis at the papilla Vater is not the cause of pain in CP. The original Puestow procedure, and its modification by Partington and Rochelle (1960), proved more successful in patients with CP and a dilated pancreatic duct. The procedure includes resection of the tail of the pancreas, followed by a longitudinal incision of the pancreatic duct along the body of the pancreas and an anastomosis with a Roux-en-Y loop of jejunum. The modification by Partington and Rochelle abandons the resection of the pancreatic tail. Preservation of tissue and reduction of mortality to less than 1% and of morbidity to less than 10% are the advantages of this operation (Evans et al, 1997; Izbicki et al, 1999; Prinz & Greenlee, 1981; Proctor et al, 1979). Although these ductal drainage operations have good primary success rates (Duval, 1956; Partington, 1952), their long-term outcome is poor (Markowitz et al, 1994). Moreover, these procedures are only promising if the duct is substantially dilated (>7 mm), which is the case in about 25% of patients (Büchler & Warshaw, 2008), and in patients who do not show a dominant mass in the head of the pancreas. For these reasons, pure drainage procedures have been replaced by techniques that combine resection and drainage for the majority of patients.

Table 55B.2

Surgical Therapy: Techniques and Indications

Indications for Surgery in Chronic Pancreatitis

- Intractable pain
- Symptomatic local complications
- Unsuccessful endoscopic management
- Suspicion of malignancy

Surgical Techniques	Indications and Recommendations
Pure Drainage Operations	
Cystojejunostomy (see Fig. 55B.1A)	Surgical procedure of choice for isolated pseudocysts*
Laterolateral pancreatojejunostomy	Ductal dilation >7 mm without inflammatory mass
Partington-Rochelle procedure (see Fig. 55B.1B)	
Caudal drainage/Puestow procedure	Rare indications, replaced by other procedures
Resection Procedures	
Pancreatic head resection (see Fig. 55B.2)	Always include a ductal drainage
	Procedure of choice if inflammatory mass is in the head of the pancreas
	All techniques have comparable results
PD and ppPD (see Fig. 55B.2A)	Procedure of choice in suspected malignancy and in irreversible duodenal stenosis
DPPHR Techniques†	
DPPHR, Beger (see Fig. 55B.2B)	Procedures of choice if inflammatory mass in the head of the pancreas
DPPHR, Bern (see Fig. 55B.2D)	Technically less difficult than Beger but equal in long-term outcome
DPPHR, Frey (see Fig. 55B.2C)	Patients with ductal obstruction in the head and tail and a smaller inflammatory mass in the head of the pancreas
V-shaped excision	Small duct disease (diameter of pancreatic duct <3 mm)
Pancreatic left resection	Rare cases, such as isolated chronic pancreatitis in the tail (e.g., posttraumatic)
	Rare cases of large psudocysts in the tail
Segmental resection	Rare cases, such as isolated ductal stenosis in the body (e.g., posttraumatic) in patients without diabetes
Total pancreatectomy	Rare cases with severe changes in the entire pancreas and preexisting IDDM

**Caution:* intraoperative frozen section must be done to exclude a cystic neoplasm.
†*Caution:* intraoperative frozen section must be done to exclude malignancy.
PD, pancreatoduodenectomy; ppPD, pylorus-preserving pancreatoduodenectomy; DPPHR, duodenum-preserving pancreatic head resection; IDDM, insulin-dependent diabetes mellitus

In patients with isolated pancreatic pseudocysts, and often in those with a history of a severe episode of acute pancreatitis, a drainage procedure in the form of a cystojejunostomy with Roux-en-Y reconstruction (Fig. 55B.1) is still the surgical procedure of choice.

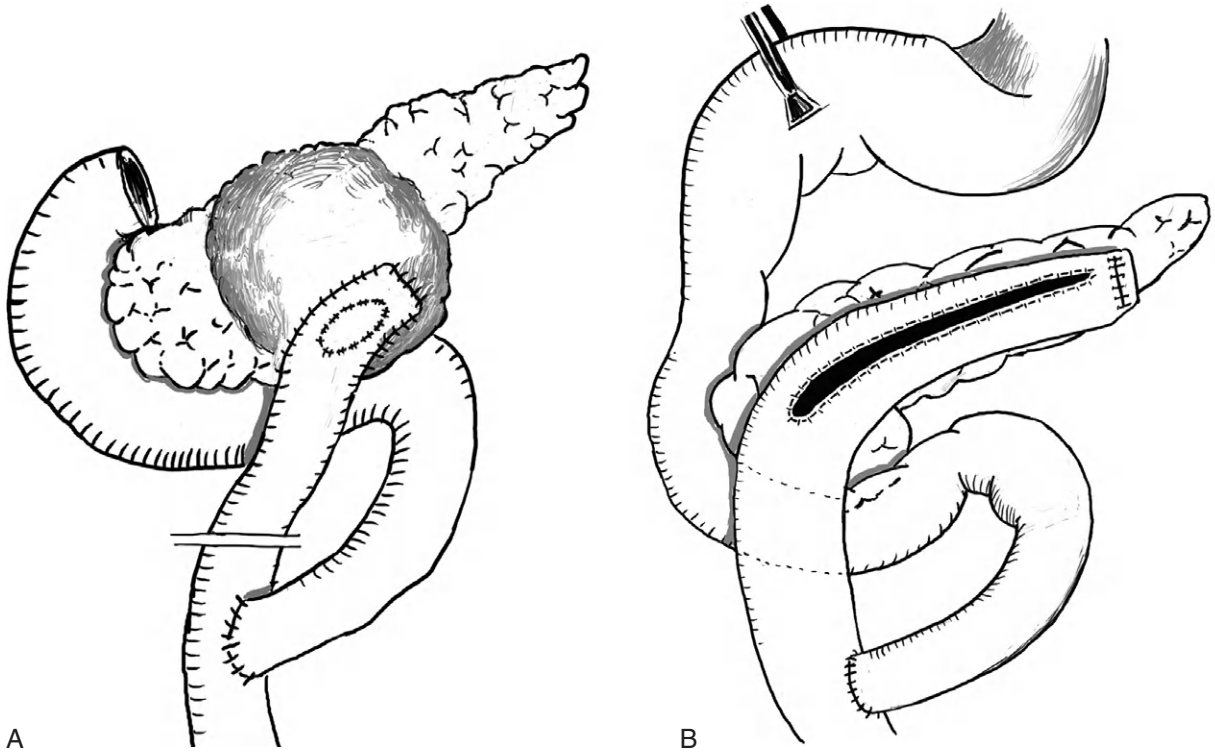


FIGURE 55B.1. Drainage procedures in chronic pancreatitis. **A,** If the cyst wall is thick enough, a pancreatic pseudocyst can be safely and effectively treated by drainage with a cystojejunostomy and Roux-en-Y reconstruction. **B,** In rare patients with a dilation of the pancreatic duct >7 mm and no inflammatory mass, a laterolateral pancreatojejunostomy (Partington-Rochelle procedure) may be performed.

Resective Procedures

The vast majority of patients are seen with a ductal obstruction in the pancreatic head, frequently associated with an inflammatory mass. In these patients pancreatic head resection is the procedure of choice; the available techniques are shown in Figure 55B.2. The partial pancreatoduodenectomy, or Kausch-Whipple procedure, in its classic or pylorus-preserving variant, has been the procedure of choice for pancreatic head resection in CP for many years (Jimenez et al, 2000, 2003). The duodenum-preserving pancreatic head resections and its variants—the Beger (Beger et al, 1985), Frey (Frey & Smith, 1987), and Bern procedures (Gloor et al, 2001)—represent less invasive, organ-sparing techniques with equivalent long-term results (see Table 55B.2).

Only very few patients come to medical attention with small duct disease (diameter of the pancreatic duct <3 mm) and no mass in the pancreatic head. In these cases, a V-shaped excision of the anterior aspect of the pancreas is a safe approach and offers effective pain management (Yekebas et al, 2006). In the rare case of a patient seen with segmental CP in the pancreatic body or tail, such as that seen as a result of posttraumatic ductal stenosis, a middle segment pancreatectomy or a pancreatic left resection may be the best approach. The most frequently applied resection techniques are detailed here.

Partial Pancreatoduodenectomy: Kausch-Whipple Procedure (See Chapter 62)

The most frequent indications for a pancreatoduodenectomy in patients with CP and pain are 1) the head of the pancreas is enlarged, often containing cysts and calcifications; 2) a previous endoscopic intervention or drainage procedure was ineffective; or 3) a malignancy is present in the head of the gland. Concerning the latter subgroup, it is commonly accepted that the distinction between benign and malignant disease remains an unsolved dilemma in some patients (up to 6% to 8%) (Büchler & Warshaw, 2008). The extent of resection in the classic Kausch-Whipple pancreatoduodenectomy (PD) includes the pancreatic head with duodenum and the lower third of the stomach. PD was initially designed for malignancies in the pancreatic head and was associated with high morbidity and mortality rates. With increasing safety the procedure has also been used for patients with CP (Traverso & Kozarek, 1993).

With the pylorus-preserving pancreatoduodenectomy (ppPD), a less invasive procedure for resection of cancer or CP was introduced, in which the stomach is preserved (see Fig. 55B.2A) (Traverso & Longmire, 1978). Today, PD and ppPD are safe and effective procedures in experienced hands, with an operative mortality of 2% to 5% and lasting pain relief in about 80% of patients (Büchler & Warshaw, 2008; Jimenez et al, 2000).

With regard to quality of life, the data after the Kausch-Whipple procedure are promising, although poor postoperative digestive function has been reported, including gastric dumping, diarrhea, peptic ulcer, and dyspeptic complaints in some patients. In up to 20% of the patients with CP, the Kausch-Whipple resection results in diabetes mellitus and subsequently in increased late postoperative morbidity and mortality (Izbicki et al, 1998).

The drawbacks of the Kausch-Whipple procedure may be ameliorated by the ppPD. The rate of gastric dumping, marginal ulceration, and bile-reflux gastritis can be reduced by

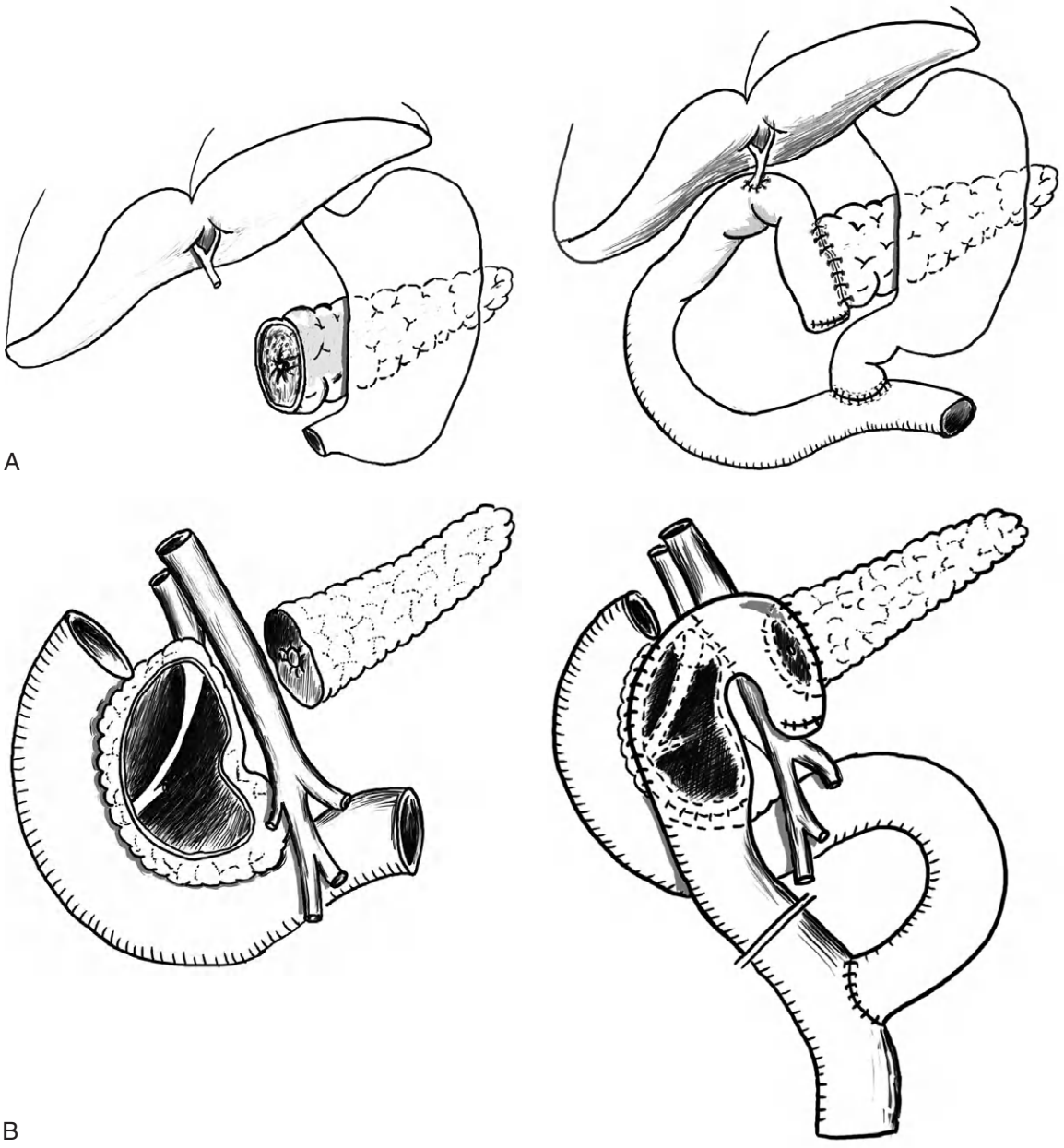
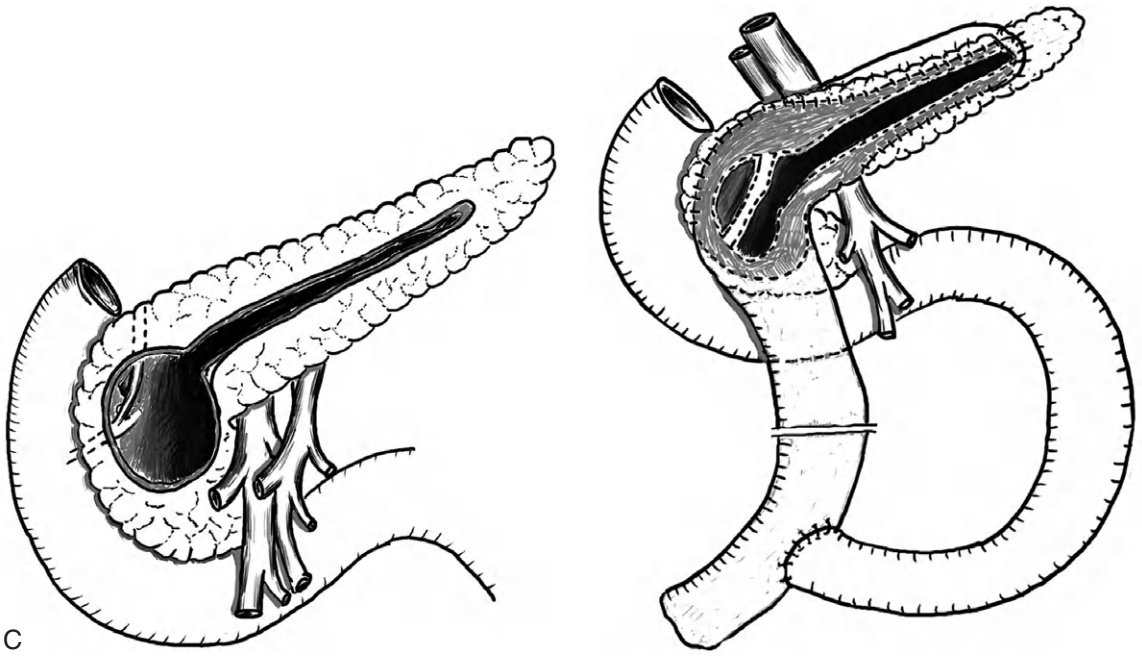
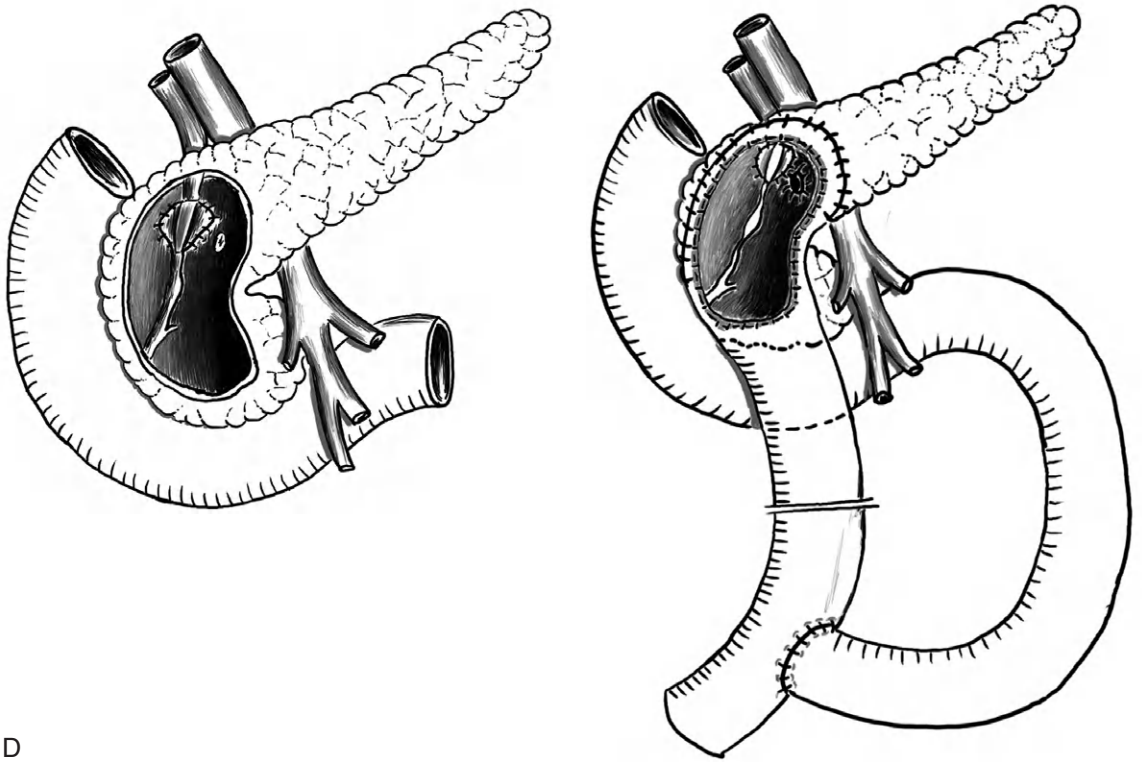


FIGURE 55B.2. Techniques of pancreatic head resection for chronic pancreatitis. Resections are shown on the left side, reconstructions on the right side. **A,** Partial pancreatoduodenectomy; the pylorus-preserving procedure is shown. The pancreatic head and duodenum are removed, reconstruction is performed by pancreatojejunostomy, hepaticojejunostomy, and a duodenojejunostomy. **B,** Duodenum-preserving pancreatic head resection (DPPHR)-Beger procedure. The pancreas is dissected on the level of the portal vein, the pancreatic head is excavated, and the duodenum is preserved with a thin layer of pancreatic tissue. If the bile duct is obstructed, it can be opened, and an internal anastomosis with the excavated pancreatic head can be performed (not shown). The reconstruction is performed with a Roux-en-Y jejunal loop, including two anastomoses, one to the pancreatic tail remnant and one to the excavated pancreatic head. *Continued*



C



D

FIGURE 55B.2, cont'd C, DPPHR-Frey procedure. A circumscript excision in the pancreatic head is combined with longitudinal dissection of the pancreatic duct toward the tail. Reconstruction is performed with an anastomosis to a Roux-en-Y jejunal loop. Compared with the Beger procedure, pancreatic head resection is less extensive; reconstruction is easier, because only one anastomosis to the pancreas is required. **D,** DPPHR-Bern modification. A technical simplification of the Beger procedure, the extent of resection of the pancreatic head is comparable, except the pancreas is not dissected on the level of the portal vein. Thus reconstruction can be performed with a single anastomosis of the pancreas to a Roux-en-Y jejunal loop. The bile duct may be opened if necessary, with an internal anastomosis to the loop (shown). The pancreatic duct toward the tail is probed to rule out distal stenosis.

preserving the stomach, pylorus, and the first part of the duodenum. Regarding quality of life, the ppPD provides better results than the classic PD, specifically with weight gain in around 90% of patients postoperatively. Furthermore, the operation leads to long-lasting pain relief in 85% to 95% of patients during the first 5 years postoperatively (Martin et al, 1996). The postoperative sequelae of transient delayed gastric emptying, which is observed in 30% to 50% of patients, and the risk of cholangitis and long-term occurrence of exocrine and endocrine pancreatic insufficiency seen in more than 45% of patients represent the possible drawbacks of this operation in CP patients (Müller et al, 1997). The relevant studies (level I and II) concerning delayed gastric emptying comparing classic Kausch-Whipple and ppPD could not show a clear advantage of the classic Whipple procedure (van Berge Henegouwen et al, 1997; Büchler et al, 2000; Di Carlo et al, 1999; Izbicki et al, 1998; Jimenez et al, 2000; Klempa et al, 1995; Lin & Lin, 1999; Roder et al, 1992). Although three studies favored the ppPD, two showed no difference, and two showed lower delayed gastric emptying rates after a classic Whipple procedure compared with the ppPD.

It should be kept in mind that both the classic PD and the ppPD resection were originally introduced to radically resect malignant pancreatic or periampullary tumors. Therefore for a benign disorder such as CP, other than the occasional inability to exclude pancreatic cancer definitively, there is no reason to remove organs adjacent to the pancreas—part of the stomach, the duodenum, and the extrahepatic bile duct; these may just be secondarily involved in the disease.

Duodenum-Preserving Pancreatic Head Resection: Beger Procedure

The duodenum-preserving pancreatic head resection (DPPHR) was introduced by Beger and colleagues as a less radical, organ-sparing procedure designed specifically for patients with CP and an inflammatory mass in the head of the pancreas (Beger et al, 1985, 1989, 1999). Similar to PD, the pancreas is divided at the level of the portal vein (see Fig. 55B.2B). In contrast to PD, the pancreatic head is excavated with preservation of the duodenum and a layer of pancreatic tissue. In most cases, it is possible to free the bile duct from surrounding scar tissue. In patients with biliary obstruction (approximately 24%), the common bile duct must be opened so that the bile drains into the cavity of the resected pancreatic head (Beger et al, 1985). The mesoduodenal vessels should be respected, while removing the uncinate process. The standard reconstruction consists of a pancreatojejunostomy to the pancreatic tail and a side-to-side pancreatojejunostomy to the remnant of the pancreatic head using a Roux-en-Y loop of proximal jejunum. In about 10% of patients, DPPHR is combined with lateral pancreatojejunostomy as a consequence of multiple stenoses of the pancreatic main duct; the mortality rate is lower than 1%, and the morbidity rate is approximately 15% (Beger et al, 1985).

Compared with the Kausch-Whipple procedure, the DPPHR offers the advantage of preserving the duodenum. Its superiority over pylorus-preserving resection has been demonstrated in prospective studies (Beger et al, 1985; Büchler et al, 1995; Müller et al, 1997, 2008a). Patients who underwent DPPHR had greater weight gain, better glucose tolerance, and a higher insulin-secretion capacity (Büchler et al, 1995; Müller et al, 1997, 2008a). Over long-term follow-up, 20% of the patients developed new-onset diabetes mellitus. Compared with the natural course of CP, with normal glucose metabolism in 17% of patients (Lankisch et al, 1993), preserved endocrine function is seen in 39% following DPPHR.

With regard to pain status, DPPHR promotes the transformation of clinically manifest CP into a silent disease in around 91% of patients. In terms of quality of life, 69% of the patients were professionally rehabilitated, 26% retired, and only 5% were still in the status of disease after DPPHR (Köninger et al, 2004). Taking into account the better pain status, lower frequency of acute episodes of CP, decreased need for further hospitalization, low early and late mortality rates, and the restoration of quality of life, DPPHR seems to be able to delay the natural course of CP.

Duodenum-Preserving Pancreatic Head Resection: Frey Procedure

Frey and colleagues developed a modification of the DPPHR that represents a hybrid technique between the Beger and the Partington–Rochelle procedures (Frey & Amikura, 1994; Frey & Smith, 1987). Compared with the Beger procedure, the resection in the pancreatic head in the Frey modification is smaller and is combined with a laterolateral pancreatojejunostomy to drain the entire pancreatic duct toward the tail (see Fig. 55B.2C). Unlike the Beger procedure, the reconstruction can be performed with a single anastomosis. This procedure appears advantageous in patients with less severe inflammation in the head of the pancreas that is combined with an obstruction in the left-sided pancreatic duct.

Duodenum-Preserving Pancreatic Head Resection: Bern Modification

The Bern modification of the DPPHR represents a technical simplification of the Beger procedure with equal outcome (Gloor et al, 2001; Köninger et al, 2008; Müller et al, 2008b). The excavation of the pancreatic head can be performed to the same extent as the Beger procedure (see Fig. 55B.2D). However, unlike the Beger procedure, the pancreas is not divided at the level of the portal vein, which is often difficult because of inflammation and portal hypertension. In patients with portal hypertension, the risk of intraoperative bleeding is reduced by this modification (Gloor et al, 2001). The reconstruction after pancreatic head excavation can be performed by a single anastomosis between a jejunal loop and the pancreatic resection rim (Gloor et al, 2001). As in the Beger procedure, a bile duct obstruction can be managed by internal bile duct anastomosis. Thus the Bern modification of the DPPHR appears ideal for patients with an inflammatory mass and no stenosis in the left-sided duct. Adequate drainage of the pancreatic tail has to be verified by probing of the duct. If a stenosis is discovered, the resection can be extended toward the left, similar to the Frey and Partington-Rochelle procedures, until adequate drainage is achieved. In our collective experience, we have found this to be necessary in about 2% to 3% of patients (Strobel et al, 2009).

Left Pancreatic Resection in Chronic Pancreatitis

As long as the pancreatic head is the pacemaker of CP, the DPPHR or the two variants of the pancreatoduocenectomy are the favored surgical treatment options. However, for a small and carefully selected group of patients, pancreatic left resection can be a viable alternative. Good indications for pancreatic left resection are inflammatory complications, such as pseudocysts and fistulae, and main pancreatic duct stenosis in the tail of the

pancreas. Furthermore, the suspicion of a left-sided neoplasm may indicate pancreatic left resection. Overall, less than 5% of all patients who have surgical interventions for CP may benefit from distal pancreatectomy.

Pancreatic left resection can be performed with and without splenectomy. Distal pancreatectomy with conservation of the splenic artery and vein is time consuming. The advantage of avoiding a postsplenectomy syndrome and the importance of the spleen for the host defense system should be taken into consideration. If no clear indication for splenectomy is present, such as perisplenic pseudocyst or inflammatory or fibrotic encasement of the splenic vessels, preservation of the spleen may be appropriate (Aldridge & Williamson, 1991; Bauer et al, 2002; Warshaw, 1988). Importantly, in patients with spleen-preserving distal pancreatectomy in whom the splenic vessels have been resected or in whom the splenic vein showed postoperative thrombosis, the development of left-sided portal hypertension with subsequent formation of gastric varices and potential variceal bleeding demands close follow-up (Balzano et al, 2007; Miura et al, 2005).

The surgical approach concerning the optimal closure technique of the pancreatic remnant after distal pancreatectomy includes stump closure by sutures or stapler application or by creating a Roux-en-Y pancreatojejunostomy. Because the postoperative outcome is similar in both groups (Shankar et al, 1990), the drainage procedure should be reserved for patients with a dilated duct and/or a stricture in the pancreatic head (Aldridge & Williamson, 1991). Distal resection should not exceed 40% to 60% of the pancreatic gland to avoid postoperative insulin-dependent diabetes mellitus (IDDM) (Eggink et al, 1983). IDDM seems to be more of a long-term complication after pancreatic left resection, however, and it is difficult to differentiate whether this is due to pancreatic resection or simply the natural course of the disease.

Evidence-Based Surgery in Chronic Pancreatitis: Pancreatoduodenectomy and DPPHR

Irrespective of the technique, if carried out by experienced personnel, pancreatic head resection is a safe and effective therapy with good short- and long-term results in patients with CP and an inflammatory mass in the head of the pancreas. Various techniques of pancreatic head resection were compared in several RCTs (Table 55B.3; Büchler et al, 1995; Izbicki et al, 1995, 1997, 1998; Klempa et al, 1995; Köninger et al, 2008; Müller et al, 2008a; Strate et al, 2003, 2008), in which their safety and efficacy were confirmed. The RCTs that compared PD and DPPHR (Büchler et al, 1995; Izbicki et al, 1998; Klempa et al, 1995; Müller et al, 2008a; Strate et al, 2008), as well as a recent meta-analysis (Diener et al, 2008), demonstrated comparable mortality and efficacy rates in terms of pain relief and endocrine insufficiency. The less invasive DPPHR was superior in terms of duration of hospital stay, exocrine insufficiency, weight gain, and quality of life in medium-term follow-up. In recent studies with long-term follow-up, these metabolic advantages appear to decrease over time, and long-term results of PD and DPPHR are equal in terms of pain management, quality of life, and endocrine and exocrine function (compare results reported in the initial trials and the latest follow-ups in Table 55B.3). Of interest, the resection techniques remain effective in terms of pain relief and quality of life but may not stop the progress of exocrine and endocrine insufficiency in the long term (Müller et al, 2008a; Strate et al, 2008). One explanation may be that resection effectively treats duct obstruction and hypertension but does not completely stop continued cellular damage and parenchymal loss (Büchler & Warshaw, 2008). Certainly these observations stress the importance of continued postoperative therapy, including the reduction of etiologic factors, substitution of exocrine and endocrine insufficiency, and possibly antioxidant therapy (Bhardwaj et al, 2009).

The RCTs that compared the various techniques of DPPHR demonstrated equal outcomes regarding pain control, quality of life, and metabolic parameters after the Beger procedure versus

Table 55B.3

RCTs Comparing Techniques for Pancreatic Head Resection in CP

Reference	Technique	N	Results
ppPD vs. DPPHR			
Klempa, 1995	Beger ppPD	21 22	Shorter hospital stay, less exocrine insufficiency, less need of analgesics
Büchler, 1995	Beger ppPD	20 20	Less-impaired glucose metabolism, greater weight gain, more frequent pain relief
Follow-up			
Müller, 1997	Beger ppPD	10 10	More frequent delayed gastric empting, more frequent pathologic secretion of enteral hormones
Follow-up			
Müller, 2008b	Beger ppPD	20 20	Equal in pain relief, exocrine, and endocrine function Equal in QoL
Izbicki, 1998	Frey ppPD	31 30	Lower morbidity, better QoL Better professional rehabilitation, equal in pain relief
Follow-up			
Strate, 2008	Frey ppPD	23 23	Equal in pain relief and QoL, equal in exocrine and endocrine function
Different Techniques of DPPHR			
Izbicki, 1995	Beger Frey	20 22	Comparable in pain relief, QoL, exocrine and endocrine function, management of local complications
Follow-up			
Izbicki, 1997	Beger Frey	38 36	Comparable in pain relief, QoL, professional rehabilitation, exocrine and endocrine function
Follow-up			
Strate, 2005	Beger Frey	34 33	Comparable in pain relief, QoL, exocrine and endocrine function
Köninger, 2008	Beger Bern	32 33	Shorter operative time and hospital stay, comparable in QoL

RCT, randomized, controlled trial; PD, pancreatoduodenectomy; ppPD, pylorus-preserving pancreatoduodenectomy; DPPHR, duodenum-preserving pancreatic head resection; QoL, quality of life

the Frey and Bern procedures (see Table 55B.3; Izbicki et al, 1995, 1997; Köninger et al, 2008; Strate et al, 2005). However, the trial by Köninger and colleagues (2008) demonstrated that the Bern modification of the DPPHR represents a technically simpler alternative, as reflected by a significantly shorter operative time (by 46 minutes) and a significantly shorter hospital stay (11 vs. 15 days). Thus the Bern technique represents a modification of the DPPHR that will find a broader acceptance in the future because of technical and economic advantages.

CONCLUSIONS

The adequate therapy of CP is adjusted to the symptoms of the patient, the stage of the disease, and the morphology of pathologic changes of the pancreas. Conservative therapy is the basis of treatment in all patients, and it must accompany both interventional and surgical therapy. Endoscopic therapy appears to be effective for internal drainage of pseudocysts and for proximal ductal stenosis in patients without calcifications. Importantly, endoscopic therapy requires frequent reinterventions, and if not sufficiently effective after a year of treatment, the patient should be referred to surgery. The surgical technique must be adjusted to the pathomorphologic changes of the pancreas. For patients with CP and an inflammatory mass in the head of the pancreas, the DPPHR is less invasive than a pancreatoduodenectomy and is associated with comparable long-term results. The Bern modification of the DPPHR represents a technical variation that is equally effective but technically less demanding. Surgical therapy provides effective long-term pain relief and improvement of quality of life, but it may not stop the decline of endocrine or exocrine pancreatic function. Strategies to improve or maintain endocrine and exocrine function in CP remain an interesting field of research.

References are available at expertconsult.com.

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CHAPTER 58B

Pancreatic cancer: clinical aspects, assessment, and management

Eugene P. Kennedy and Charles J. Yeo

CLINICAL PRESENTATION

The diagnosis of pancreatic cancer is typically a devastating experience for patients. These malignancies often arise silently, invade locally, and spread distantly prior to any clinical signs or symptoms. The symptoms that bring these tumors to clinical attention vary, based upon the location of the tumor within the pancreas and the stage at presentation. The majority of resectable pancreas cancers occur in the right side of the pancreas, in the head or uncinate process of the gland. Classic symptoms from these right-sided tumors include jaundice from biliary obstruction, often accompanied by pruritis, and epigastric pain radiating to the back from tumor involvement of the celiac plexus. Less commonly, persistent nausea or vomiting as a result of gastric outlet obstruction from tumor narrowing at the duodenal C-loop is the initial symptom. Additionally, pancreatitis in the absence of cholelithiasis or ethanol abuse should arouse suspicion for cancer in patients age 60 years or older. Tumors arising in the left side of the pancreas typically cause few symptoms until they are locally advanced or metastatic. For such left-sided tumors, pain is the most common presenting symptom, and jaundice is rare.

Nonspecific symptoms often occur in association with pancreatic cancer. Nausea, anorexia, weight loss, and fatigue are commonly reported and often are present for some time before diagnosis. Because of the generalized and quite common nature of these symptoms, they rarely lead directly to a diagnosis unless they become profound. Significant weight loss without gastric outlet obstruction is often indicative of advanced disease.

Typically, jaundice is the only physical finding in "early" stage pancreatic cancer. The classic physical findings of left supraclavicular adenopathy (Virchow node), periumbilical adenopathy (Sister Mary Joseph node), or a firm circumferential rim of tumor at the top of the rectum on digital rectal examination (Blumer shelf from drop metastases) are found only with advanced, disseminated disease. Less specific findings that also typically indicate advanced disease include temporal wasting, ascites, hepatomegaly from metastatic disease, or a palpable abdominal mass.

Laboratory analysis is of limited benefit in the diagnosis of pancreatic cancer. Elevated liver function tests are nonspecific and require imaging to investigate their etiology. It is not uncommon to have hyperbilirubinemia with marked increases in the alkaline phosphatase and γ-glutamyl transpeptidase (GGT), with mild elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). New-onset diabetes mellitus is often associated with pancreatic cancer. However, such new-onset diabetes has a low sensitivity and specificity for the diagnosis of pancreatic cancer, and significant overlap is found between the typical age of onset of diabetes mellitus and pancreatic cancer. The incidence of diabetes mellitus is also much greater than that of pancreatic cancer, further limiting its utility as a diagnostic sign.

Ongoing research has produced a multitude of potential biomarkers for pancreatic cancer (Harsha et al, 2009). The only biomarker that has recognized clinical utility is carbohydrate antigen 19-9 (CA19-9); however, its usefulness has two significant limitations. First, it is not specific for pancreatic cancer because it can be elevated in benign conditions, particularly those that cause obstructive jaundice. Second, its sensitivity is reduced by the fact that patients who test negative for Lewis blood group antigens A and B are unable to synthesize CA19-9 and therefore do not express it in their serum. The percentage of pancreatic cancer patients who fall into this group has been reported to range from 10% to 34% (Berger et al, 2008; Tempero et al, 1987). Thus CA19-9 best serves as a marker of treatment response and recurrence in patients who have a pathologic diagnosis of pancreatic cancer.

DIAGNOSIS

Once suspicion is sufficient for pancreatic cancer, high-quality imaging is critical for diagnosis and treatment planning. Many patients initially undergo an abdominal ultrasound (US) or a limited computed tomography (CT) scan of the abdomen. These modalities will suggest processes in the pancreas that require appropriate evaluation. Currently, the best diagnostic modality for imaging the pancreas is a pancreas protocol multidetector CT with dedicated arterial and venous phases and three-dimensional (3D) reconstruction (see Chapter 16; Buchs et al, 2010; Horton & Fishman, 2002). Water is given orally, and contrast is given intravenously. Such scans typically demonstrate the tumor as a low-density (hypodense) lesion within the pancreas, best seen during the venous phase of contrast enhancement. Importantly, these high-quality imaging studies show the important relationship between the tumor and the surrounding visceral vessels, including the superior mesenteric vein, portal vein, splenic vein, superior mesenteric artery (SMA), and the branches of the celiac axis. Such high-quality CT imaging can reliably predict visceral vessel involvement, and thereby surgical respectability, approximately 80% to 90% of the time (House et al, 2004; Karmazanovsky et al, 2005). Additionally, the arterial phase with 3D reconstruction can assist in surgical planning by identifying variations in hepatic arterial anatomy and other vascular anomalies preoperatively, most notably a "replaced" right hepatic artery originating from the SMA, which is seen in one of six patients (see Chapter 1B).

Continuing improvement in the technology that produces magnetic resonance imaging (MRI) has resulted in image quality and resultant diagnostic sensitivities that approach those of CT (see Chapter 17). A recent meta-analysis of 68 articles calculated an overall diagnostic sensitivity of 91% for CT, compared with 84% for MRI, and reported diagnostic specificities of 85% and 82%, respectively (Bipat et al, 2005). Regarding determination of resectability, CT had a sensitivity and specificity of 81% and 82% compared with MRI at 82% and 78%, respectively. No advantage has been demonstrated by obtaining both CT and MRI for uncomplicated patients who display classic symptoms of pancreatic cancer, and this practice should be discouraged. We typically reserve the use of MRI for patients with renal impairment or sensitivity to the intravenous contrast used for CT. The use of MR cholangiopancreatography (MRCP) is valuable in evaluating and following small cystic lesions of the pancreas, but a detailed discussion of these lesions is outside the scope of this chapter (see Chapters 17 and 57).

Endoscopic evaluation of patients with classic symptoms of pancreatic cancer is appropriate in specific situations. Esophagogastroduodenoscopy (EGD) is appropriate in cases of gastric outlet obstruction to assess the anatomy and presence of other diagnoses. In the presence of metastatic or unresectable disease, or when a patient is not physiologically appropriate for immediate surgical intervention, a therapeutic EGD combined with duodenal stenting can be of some benefit, allowing the patient to return to oral intake (see Chapter 27). Endoscopic retrograde cholangiopancreatography (ERCP) was once commonly used as a diagnostic modality for patients with a suspected periampullary pancreatic cancer. With the improvement of cross-sectional imaging, the use of strictly diagnostic ERCP is currently unsupported. Therapeutic ERCP with stenting of biliary strictures can be of benefit in the same patient population (metastatic, unresectable, or physiologically unfit) as therapeutic EGD (see Chapters 14, 18, and 27). However, the routine placement of a biliary endoprosthesis for all patients seen with jaundice without cholangitis should be discouraged. Multiple studies have shown a doubling of the wound infection risk and a slight increase in overall complication risk with preoperative biliary stenting (Pisters et al, 2001a; Sohn et al, 2000). For most patients seen initially with a pancreatic mass and jaundice, early surgery is preferable to endoscopic stenting and delayed surgical resection (Kennedy et al, 2010).

Endoscopic ultrasound (EUS) is a relatively new imaging and diagnostic technology compared with those previously discussed (see Chapter 14). Well established at specialty referral centers, it is rapidly becoming more widely available. Interpretation of EUS imaging is operator dependent, a factor that may account for the wide range of diagnostic sensitivities reported in the literature and encountered in real-world clinical settings (Ahmad et al, 2000; Gress et al, 1999; Hunt & Faigel, 2002; Palazzo et al, 1993; Rösch et al, 1991; Varadarajulu & Eloubeidi, 2010). Reported sensitivities for the diagnosis of pancreatic neoplasia have ranged from 69% to 94%. Several studies have found EUS to be superior to CT for the detection of lesions smaller than 2 cm. EUS is of particular utility when a patient has a presentation consistent with pancreatic cancer (biliary or pancreatic duct obstruction) but no evidence of mass on cross-sectional imaging. The ability of EUS to accurately estimate T-stage decreases compared with CT for larger lesions. Additionally, EUS has shown some superiority over CT for the detection of venous invasion, but it is less useful for the determination of arterial involvement (Varadarajulu & Eloubeidi, 2010). An important additional advantage of EUS is the ability to obtain tissue via fine needle aspiration (FNA) for diagnostic purposes at the time of evaluation. This can be of great benefit to unresectable or marginally resectable patients who need a confirmed tissue diagnosis prior to the initiation of chemotherapy. However, for the vast majority of patients with a symptomatic pancreatic mass that appears completely resectable by CT or MR imaging, EUS with FNA is not needed; in most cases the mass will require resection regardless of the EUS and FNA results.

^{18}Fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET) is a functional imaging modality based on the observation that neoplastic cells exhibit accelerated glucose uptake and metabolism (see Chapter 15). Once transported into the cell and phosphorylated by hexokinase, the first step in glycolysis, ^{18}FDG remains trapped within the cell. Although studies suggest ^{18}FDG-PET is sensitive for the detection of pancreatic cancer, the precise role of this technique in the diagnosis and staging of patients with localized pancreatic cancer is limited. Its use is confounded by the difficulty ^{18}FDG-PET has in distinguishing benign from malignant masses as a result of localization, both to sites of inflammation and infection and to neoplasms. ^{18}FDG-PET is of greater utility in evaluating indeterminate masses in the liver that are not amenable to biopsy. A tissue diagnosis of a primary mass made by EUS, when combined with a PET-positive liver lesion, is adequate to initiate palliative chemotherapy at many centers.

DIAGNOSTIC BIOPSY

As mentioned above, in low-risk patients with resectable lesions suspicious for periampullary cancer, a tissue diagnosis is not required prior to surgical resection, because a negative or inconclusive biopsy result will not affect the decision to operate. Pancreatic biopsy should be reserved for patients with locally unresectable or metastatic disease or for those clinical situations in which a true diagnostic or management dilemma is present. Such situations would include patients with a history of other cancers that have a realistic chance of having a metastasis to the periampullary region (renal cell cancer, melanoma) or patients with marginal physiologic reserves at prohibitive risk for surgical intervention.

Whenever possible, biopsy of a pancreatic lesion should be performed endoscopically with EUS-FNA. Percutaneous US- or CT-guided pancreatic biopsy should be discouraged, and patients should be referred to centers where EUS-FNA is available. Percutaneous biopsy should be reserved for evaluation of suspected metastatic lesions, typically liver metastases. In the presence of suspected metastatic disease, biopsy of the distant lesion if accessible is preferred over biopsy of the primary pancreatic lesion.

STAGING

Pancreatic cancer is staged by the seventh edition (2010) of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, according to clinical parameters that are available from high-quality CT imaging (Edge, 2010). Classic T, N, and M parameters are used for tumor size, nodal involvement, and distant metastases, but stage grouping is performed according to resectability. Patients are classified as having localized

Table 58B.1

AJCC Staging of Pancreatic Cancer

Stage	Primary Tumor (T)	Regional Lymph Nodes (N)	Distant Metastases (M)	Description
0	Tis	N0	M0	Carcinoma in situ, includes PanIN3
IA	T1	N0	M0	Tumor limited to the pancreas, ≤2 cm in greatest dimension
IB	T2	N0	M0	Tumor limited to the pancreas, >2 cm in greatest dimension
IIA	T3	N0	M0	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
IIB	T1, T2, T3	N1	M0	Regional lymph node metastasis
III	T4	Any N	M0	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)
IV	Any T	Any N	M1	Distant metastasis

AJCC, American Joint Commission on Cancer; PanIN3, pancreatic intraepithelial neoplasia.

From Edge SB (2010): American Joint Committee on Cancer. AJCC Cancer Staging Manual, 7th ed. New York, Springer.

resectable disease (stages I and II), locally advanced unresectable disease (stage III), or distant metastatic disease (stage IV; Table 58B.1). A resectable tumor is characterized on CT by no evidence of metastatic disease, a clear tissue (fat) plane between the tumor and the visceral arteries (celiac axis and SMA), and 180-degree or less circumferential involvement of the superior mesenteric vein–portal vein confluence (Fig. 58B.1). In contrast, patients with unresectable disease exhibit distant metastases, ascites, or involvement of the celiac axis or SMA (Fig. 58B.2). Venous vascular involvement is considered potentially resectable in the AJCC system and is therefore categorized as stage II disease, and arterial involvement is considered unresectable and is categorized as stage III disease. A small subset of patients with complete occlusion of the superior mesenteric vein–portal vein confluence and significant collateralization that precludes safe venous resection and reconstruction are typically deemed unresectable but are still classified as stage II in the current AJCC system. This system has been validated by correlation to overall survival (OS) using the National Cancer Database (Table 58B.2; Bilimoria et al, 2007a).

LAPAROSCOPY

Diagnostic laparoscopy for suspected or confirmed pancreatic cancer has the potential to detect small surface liver or peritoneal metastases (see Chapter 21). It is limited, however, in its ability to evaluate locally advanced disease. Prior to the development of current imaging techniques, namely three-dimensional MDCT, unresectability rates at laparotomy exceeded 30%. Modern cross-sectional imaging has reduced that rate considerably, as discussed above.

Disagreement exists in the literature about the role of diagnostic laparoscopy in the evaluation of pancreatic cancer.

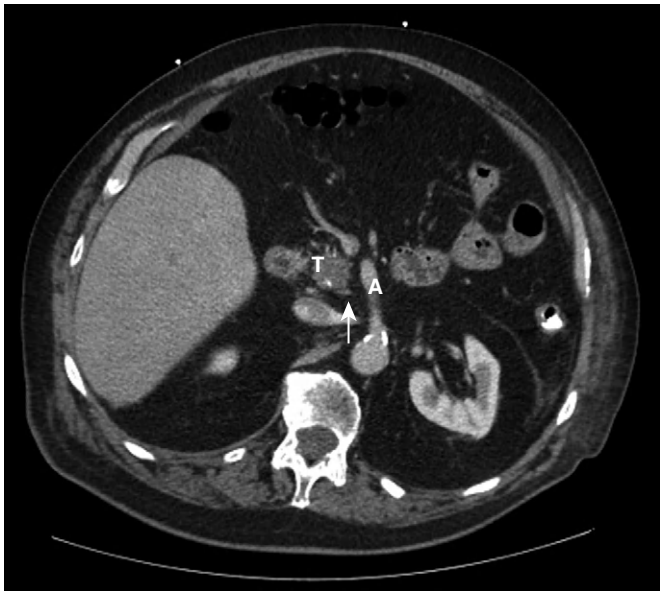


FIGURE 58B.1. Resectable pancreatic adenocarcinoma in the head and uncinate process, showing well-preserved fat plane (*arrow*) between tumor (*T*) and superior mesenteric artery (*A*).

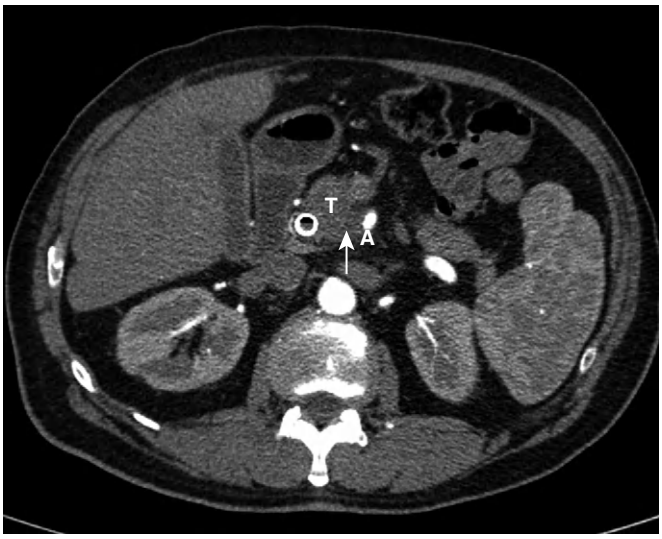


FIGURE 58B.2. Unresectable pancreatic adenocarcinoma in the head and uncinate process, showing loss of fat plane (*arrow*) between tumor (*T*) and superior mesenteric artery (*A*). A metallic endoprosthesis is seen as a hyperintense circular structure in the distal common bile duct.

Table 58B.2

Median Survival by Surgical Treatment and AJCC Stage in Months

Stage	Nonresected Patients	Resected Patients	All Patients
Ia	6.8	24.1	10.0
1b	6.1	20.6	9.1
IIa	6.2	15.4	8.1
IIb	6.7	12.7	9.7
III	7.2	10.6	7.7
IV	2.5	4.5	2.5
Total	**3.5**	**12.6**	**4.4**

AJCC, American Joint Commission on Cancer.

Data from Bilimoria KY, et al, 2007a: Validation of the 6th edition AJCC pancreatic cancer staging system: report from the National Cancer Database. Cancer 110(4):738-744.

Multiple authors have reported series evaluating the utility of diagnostic laparoscopy. The rate at which diagnostic laparoscopy alters subsequent management is reported at between 4% and 40% (Pisters et al, 2001b; Shah et al, 2008; Stefanidis et al, 2006). Taking the data as a whole, diagnostic laparoscopy seems best reserved for selected patients, in whom an increased likelihood of intraabdominal dissemination exists. Such cases include tumors greater than 4 cm, particularly those on the left side of the pancreas; ascites; markedly elevated CA19-9 (>1000 U/mL); and small, indeterminate liver or peritoneal lesions seen on CT, which are too small to investigate with percutaneous biopsy or PET imaging. We rarely use diagnostic laparoscopy for right-sided lesions, and our use of diagnostic laparoscopy for left-sided tumors has declined in recent years, as CT staging has become more accurate.

SURGICAL TREATMENT

Resectable Disease (See Chapters 62A and 62B)

The goal of the initial evaluation process for patients with pancreatic cancer is classification into one of three broad groups: *resectable*, *locally advanced/borderline resectable*, or *unresectable*. This determination should be made in consultation with an expert in pancreatic surgery. Standards as to what constitutes resectable disease have broadened, as more experience is gained with pancreatic resection. A 2007 study by Bilimoria and colleagues revealed that of the more than 9500 U.S. patients identified in the National Cancer Database as having clinical stage 1 pancreatic cancer, more than 70% did not undergo surgery. In this group, the reason for not undergoing surgery could not be identified in more than 50% of patients, and a minority were deemed too old or unfit for pancreatectomy. This represents a gross underutilization of surgical intervention for potentially curable pancreatic cancer in the United States, which the authors postulate may be due to a nihilistic attitude toward pancreatic cancer care.

Surgical resection of pancreatic cancer remains the only potentially curative therapy. Unfortunately, only a minority of patients (approximately 20% to 30%) diagnosed with pancreatic cancer are candidates for curative resection at the time of diagnosis. Hopefully, as early detection schemes improve and gain widespread use, and our ability to identify high-risk groups improves, the percentage of patients who are candidates for resection will increase. Resectional approaches are based on tumor location and extent. Resection of right-sided tumors typically requires pancreatoduodenectomy, most often performed with pylorus preservation. Distal pancreatectomy is used to resect left-sided tumors. In a small group of patients with extensive parenchymal involvement of the pancreas, total pancreatectomy may be required. The specific techniques of such resectional procedures can be found in Chapter 62.

Results

Recurrent controversies have persisted over the effectiveness of surgical resection for pancreatic cancer (Crile, 1970; Gudjonsson, 1995). The preponderance of recent data that have emerged from large specialized centers refute claims of futility and lack of long-term survival. A recent publication by Riall and colleagues (2006) examines the actual 5-year survival rates after pancreatoduodenectomy, all stages combined, for pancreatic and periampullary cancer and reports actuarial 10-year survival. The actual 5-year survival for resected pancreatic cancer (all stages combined) was 17%, but the actuarial 10-year survival was 9% (Fig. 58B.3). This analysis included a positive lymph node rate of 48% and a positive margin rate of 8% in the overall periampullary cohort. A similar study by Ferrone and colleagues (2008) revealed an actual 5-year survival rate of 23% for resected stage Ia disease, and all-stage actual 5-year and 10-year survival rates of 12% and 5%, respectively, were reported (Ferrone et al, 2008).

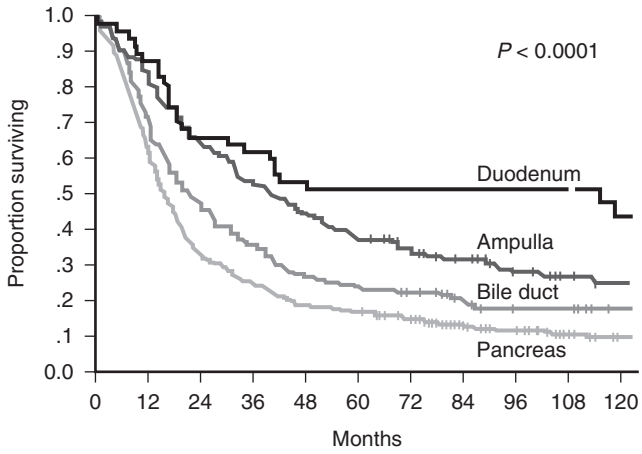


FIGURE 58B.3. Kaplan-Meier actuarial 10-year survival by site of tumor origin after right-sided pancreatectomy for pancreatic and periampullary adenocarcinoma. Results from a cohort of 890 patients treated by pancreatoduodenectomy (pancreas, n = 564; ampulla, n = 144; bile duct, n = 135; duodenum, n = 47). The first 5 years of the curve represent the actual 5-year survival because no patients were censored during that time. Five-year actual survival rates were 17% for pancreas, 37% for ampulla, 23% for bile duct, and 51% for duodenum. Ten-year actuarial survival rates were 9% for pancreas, 25% for ampulla, 17% for bile duct, and 44% for duodenum. All patients were censored after 5 years, so all 890 were at risk for recurrence. Censoring points are shown. *(Modified from Riall et al, 2006: Resected periampullary adenocarcinoma: 5-year survivors and their 6- to 10-year follow-up. Surgery 140[5]:764-772.)*

Table 58B.3

Randomized Adjuvant Chemotherapy and Chemoradiotherapy Trials in Pancreas Cancer

Reference	No. Patients	EBRT Dose (Gy)	Chemotherapy	SURVIVAL				
				Median	1 yr	2 yr	3 yr	5 yr
GITSG (Kalser & Ellenberg, 1985)	22 Surgery alone	None	None	11 mo	49%	15%		NR
	21 Adjuvant tx	40 split course	5-FU bolus	20 mo	63%	42%		NR
EORTC (Klinkenbijl et al, 1999)	54 Surgery alone	None	None	12.6 mo	40%	23%		10%
	60 Adjuvant tx	40	5-FU CI	17.1 mo	65%	37%		20%
ESPAC-1 (Neoptolemos et al, 2004)	69 Surgery alone	None	None	16.9 mo				11%
	75 Chemo tx	None	5-FU bolus	21.6 mo				29%
	73 Chemorad tx	40 split course	5-FU bolus	13.9 mo				7%
	72 Chemorad plus additional chemo	40 split course	5-FU bolus	19.9 mo				13%
RTOG (Regine et al, 2008), pancreatic head subset	221 5-FU arm	50.4	5-FU CI	NR	68%	33%		
	221 Gem arm	50.4	Gem + 5FU CI	NR	69%	39%		
	194 5-FU arm	50.4	5-FU CI	16.9 mo			32%	
	187 Gem arm	50.4	Gem + 5FU CI	20.6 mo			21%	
CONKO-001 (Neuhaus et al, 2008)	175 Surgery alone	None	None	20.2 mo	72.5%	42%	20.5%	11.5%
	179 Gem arm	None	Gem	22.8 mo	72.5%	47.5%	34%	22.5%
ESPAC-3 (Neoptolemos et al, 2009)	551 5-FU/LV arm	None	5-FU/LV	23.0 mo				
	537 Gem arm	None	Gem	23.6 mo				
JSAP-02 (Ueno et al, 2009)	60 Surgery alone	None	None	18.4 mo	75%	40%		11%
	58 Gem arm	None	Gem	22.3 mo	78%	48%		24%

EBRT, external-beam radiation therapy; 5-FU, 5-fluorouracil; CI, continuous infusion; Gem, gemcitabine; LV, leucovorin; tx, treatment.

ADJUVANT THERAPY

Because of the great propensity of pancreatic cancer to recur or persist even after optimal surgical resection, clinicians have used adjuvant chemotherapy with or without radiotherapy in an attempt to prolong disease-free survival and increase OS (see Chapter 63A). The most noteworthy of the early trials was a prospective, randomized trial from the Gastrointestinal Tumor Study Group (GITSG) using split-course irradiation (40 Gy) with concurrent bolus 5-fluorouracil (5-FU) followed by maintenance 5-FU for a duration of up to 2 years (Kalser & Ellenberg, 1985). Patients were randomized to treatment versus a no-treatment control arm. The trial showed a survival advantage for adjuvant chemoradiotherapy (median survival, 20 months) compared with surgery alone (median survival, 11 months; $P = .01$). Although criticized for its small numbers (43 total patients), slow accrual, and failure to meet accrual targets, the GITSG trial was the first trial to document a survival advantage for adjuvant therapy in pancreatic adenocarcinoma.

Subsequent to this initial study, six additional randomized adjuvant chemotherapy or chemoradiotherapy trials have been published (Table 58B.3; Klinkenbijl et al, 1999; Neoptolemos et al, 2004, 2009; Neuhaus et al, 2008; Regine et al, 2008; Ueno et al, 2009). A randomized controlled trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) showed a trend toward improved survival with adjuvant 5-FU–based chemoradiation compared with surgery alone in patients with periampullary and pancreatic cancer (Klinkenbijl et al, 1999). However, this study was statistically underpowered and initially reported as a negative trial.

The results of the European Study Group for Pancreatic Cancer (ESPAC-1) trial were met with controversy (Neoptolemos et al, 2004). In this randomized controlled trial of adjuvant therapy for pancreatic cancer, patients were assigned to one of four groups: treatment with 5-FU–based chemoradiation alone, chemotherapy alone (5-FU plus leucovorin), chemoradiation followed by chemotherapy, or observation. Using a two-by-two factorial design, the authors concluded that adjuvant chemotherapy conferred a survival benefit, whereas adjuvant chemoradiation had a deleterious effect on survival. This study is often criticized for methodologic problems, such as a high rate of nonadherence for the patients assigned to receive chemotherapy, and for radiation therapy quality control issues (Choti, 2004). Because of the study design, statistical power was insufficient to compare each of the four treatment groups individually. However, when compared to the observation group, patients who received chemoradiation alone appeared to have a worse median survival, suggesting a possible role for treatment-related toxic radiation effects.

The Radiation Therapy Oncology Group (RTOG) protocol R97-04 was designed to determine whether the addition of gemcitabine to postoperative adjuvant 5-FU chemoradiotherapy improved survival for patients with resected pancreatic adenocarcinoma (Regine et al, 2008). This phase III multi-institution trial randomized resected pancreatic adenocarcinoma patients to either one cycle of continuous infusion 5-FU, followed by continuous infusion 5-FU during radiotherapy (50.4 Gy), followed by two additional cycles of continuous 5-FU or one cycle of gemcitabine, followed by continuous infusion 5-FU during radiotherapy (50.4 Gy), followed by three additional cycles of gemcitabine. Patients with pancreatic head tumors had a median survival of 20.5 months and a 3-year survival of 31% in the gemcitabine group versus 16.9 months and 22% in the 5-FU group (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.65 to 1.03; $P = .09$). After adjusting for the protocol-specified stratification variables of nodal status,

which strongly affected survival (P = .001), tumor diameter, and surgical margin status, the multivariate analysis for patients with pancreatic head tumors treated with gemcitabine yielded an HR of 0.80 (95% CI, 0.63 to 1.00; P = .05), reflecting improved survival for the gemcitabine group.

The Charité Onkologie study (CONKO-001) compared adjuvant gemcitabine therapy to no postoperative anticancer therapy in patients undergoing surgical resection of pancreatic cancer (Neuhaus et al, 2008). Patients in the treatment arm received six cycles of gemcitabine therapy over 6 months with acceptable toxicity. Overall, 368 patients were randomized and 354 were included in the intention-to-treat analysis. Patients in the treatment arm had a statistically significant increase in OS on final analysis, with a median OS of 22.8 months and a 5-year survival of 21% compared with a 20.2-month median survival and a 5-year survival of 9.0% for the control arm (P = .005).

ESPAC-3 is the largest randomized trial of adjuvant postresection treatment of pancreas cancer to date (Neoptolemos et al, 2009). The trial randomized patients who had undergone either an R0 or R1 resection to adjuvant 5-FU plus leucovorin versus adjuvant gemcitabine. Radiation therapy was not used. Over a 6.5-year period, 1088 patients from 16 countries were randomized. Median survival for the 5-FU/leucovorin arm was 23.0 months, and median survival for the gemcitabine arm was 23.6 months. The authors concluded that no significant difference in survival was evident between the two treatment arms.

A study recently published by the Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer (JSAP) ran concurrent with the CONKO-001 trial and was of similar design (Ueno et al, 2009). It also randomized resected pancreas cancer patients to either observation or adjuvant gemcitabine therapy. OS was extended in the gemcitabine group (22.3 months vs. 18.4 months in the control arm), but the difference did not reach statistical significance. The authors reported their belief that their study was underpowered to detect a difference, given its smaller enrollment than the CONKO-001 trial.

Taken together, the preponderance of evidence indicates that adjuvant therapy for pancreatic cancer has a survival benefit. Controversy remains, however, as to the optimal chemotherapeutic regimen and the role of radiotherapy; RTOG-0848 has been designed to address these questions. Opened in November 2009, it has a target enrollment of 950 patients. This Phase III trial is a double-randomization design, assigning patients first to either adjuvant gemcitabine or adjuvant gemcitabine plus erlotinib. Patients receive five cycles of chemotherapy and are then assessed by cross-sectional imaging for evidence of disease progression. Patients without progression then undergo a second randomization to continue chemotherapy alone or to proceed to chemoradiotherapy. All patients receive one additional cycle of the chemotherapy they received under the first randomization. Patients randomized to receive chemoradiotherapy then receive external beam radiotherapy to a dose of 50.4 Gy in 28 fractions. This radiotherapy is given in combination with either oral capecitabine or infusional 5-FU. The organizers hope to have evaluable data by April 2015.

NEOADJUVANT THERAPY AND BORDERLINE RESECTABLE DISEASE

When preoperative imaging reveals either tumor encroachment with significant compromise of the mesenteric venous structures that is not amenable to reconstruction or encroachment on the superior mesenteric artery or celiac axis, patients are classified as borderline resectable. A skilled pancreatic surgeon can often remove such tumors safely, however, it is statistically unlikely that an R0 resection can be accomplished in such settings. Therefore, neoadjuvant chemotherapy or chemoradiotherapy is usually initiated with the goal of downstaging the tumor such that an R0 resection is possible. In theory, therapy administered in the preoperative neoadjuvant versus the postoperative adjuvant setting offers several potential advantages: the therapy would be given up front, eliminating the risk of delayed or incomplete treatment postoperatively; patients who manifest metastatic disease following neoadjuvant therapy would avoid an operation unlikely to be beneficial; and, because radiation efficacy is dependent on oxygenation, it may be more effective given before tissues are devascularized by surgery. The M.D. Anderson group has recently published reports of two phase II trials of either gemcitabine-based neoadjuvant chemoradiotherapy or preoperative gemcitabine and cisplatin chemotherapy in addition to chemoradiation (Evans et al, 2008; Varadhachary et al, 2008). They report resection rates of 74% and 58%, respectively, for patients entered into each protocol. Median survival for the subset of patients who actually underwent resection is promising, at 34 months and 31 months, respectively.

Another report from the same group described three types of borderline patients: *type A* is borderline resectable by objective anatomic criteria; *type B* is borderline resectable because of findings suggestive but not diagnostic of metastatic disease; and *type C* is borderline operable because of marginal performance status or extensive comorbidity (Katz et al, 2008). The 160-patient group was composed of 84 type A, 44 type B, and 32 type C patients classified as borderline resectable. After neoadjuvant treatment and restaging, 66 patients (41%) underwent pancreatectomy. The median survival was 40 months for the 66 borderline patients who completed all therapy but only 13 months for the 94 patients who did not undergo pancreatectomy (P < .001).

PALLIATIVE THERAPY

Unresectable Disease (see Chapters 63A and 63B)

The first goal in treating patients with unresectable and/or metastatic disease is to provide adequate palliation for symptoms related to their diagnosis, particularly obstructive jaundice, gastroduodenal obstruction, and abdominal pain. A more detailed discussion of these topics is provided in Chapters 63A and 63B. Modern endoscopic therapy and interventional radiology procedures can often provide substantial palliation of biliary obstruction and gastric outlet obstruction. When patients cannot be palliated in this fashion, surgical palliation through gastrojejunostomy and Roux-en-Y hepaticojejunostomy is indicated to relieve symptoms of duodenal and biliary obstruction and allow physiologic improvement such that patients can subsequently receive palliative chemotherapy or chemoradiotherapy. Additionally, when patients are determined to be unresectable at the time of exploration with curative intent, the opportunity exists to provide surgical palliation of duodenal obstruction or tumor-associated pain, two symptom complexes that can cause suffering and interrupt other cancer-directed therapies. Prophylactic gastrojejunostomy at the time of initial exploration has been shown to predispose to symptomatic

duodenal obstruction in this population of patients (Lillemoe et al, 1999).

Another beneficial intervention that can be provided at the time of exploration is celiac plexus nerve block. This simple intervention has been shown to decrease pain and postoperative narcotic use, and, in the subset of unresectable patients who present with pain, to prolong survival (Lillemoe et al, 1993). The procedure is simple and carries minimal risk and expense when done during surgical exploration. It can also be done endoscopically or percutaneously, with pain relief that is often superior to that suggested by the stepwise analgesic ladder provided by the World Health Organization (WHO) (Wong et al, 2004).

Palliative Chemotherapy

Chemotherapy is provided in the unresectable and metastatic setting with the intention of prolonging life while preserving or improving quality of life. The current standard of care for advanced pancreatic cancer was set in 1997 by Burris and colleagues in their landmark study, which showed a significant prolongation in OS, as well as a concurrent clinical benefit response, in patients with advanced pancreatic cancer treated with gemcitabine compared with the previous standard chemotherapy (5-FU). The efficacy measure was clinical benefit response, which was a composite of measurements of pain, specifically, analgesic consumption and pain intensity; Karnofsky performance status; and weight. Clinical benefit required a sustained (≥4 weeks) improvement in at least one parameter without worsening in any others. Since that time, only one other chemotherapeutic, erlotinib, has been granted a Food and Drug Administration (FDA) therapeutic indication for use against pancreatic cancer (Moore et al, 2007). Of note, the inclusion of erlotinib as standard of care has been controversial, given the minimal improvement in OS (only 0.33 months) when evaluated in the context of the drug's expense and side effects.

Multiple studies continue to be done in this area that examine combination therapies involving currently available chemotherapeutics and investigational agents (Stathis & Moore, 2010). Most have failed to show any evidence of benefit to patients with advanced pancreatic cancer, although recently, some enthusiasm attended the preplanned interim analysis of the PRODIGE 4/ACCORD 11 trial, presented at the Spring 2010 American Society of Clinical Oncology meeting (Conroy et al, 2010). This randomized Phase III trial compared a combination of 5-FU, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) versus gemcitabine as first-line therapy for advanced pancreas cancer. At the preplanned interim analysis, the median OS for the FOLFIRINOX group was 10.5 months compared with 6.9 months for the gemcitabine group ($P < .001$). FOLFIRINOX is the first therapy not containing gemcitabine that has shown a significantly longer OS, progression-free survival, and higher response rate than gemcitabine alone. Determination of the role of this regimen as standard of care will await the full results of the trial and detailed reporting of the toxicity associated with FOLFIRINOX therapy.

Multiple targeted therapies that focus on matrix metalloproteinas, farnesyl transferase in the RAS pathway, epidermal growth factor receptor, and vascular endothelial growth factor, as well as a host of novel strategic targets, have shown promising preliminary results. However, with the exception of erlotinib, these have not been translated to usual care. The rational use of these powerful and potentially beneficial agents awaits the development of appropriate predictive biomarkers that can guide therapy. As promising biomarkers are validated, they can be used to guide future therapy. Then, the treatment of pancreatic cancer can evolve into a future of individualized patient care based on the combined efforts of the hundreds of investigators working worldwide.

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CHAPTER 62A

Resectional techniques: pancreaticoduodenectomy, distal pancreatectomy, segmental pancreatectomy, total pancreatectomy, and transduodenal resection of the papilla of Vater

Jens Werner and Markus W. Büchler

OVERVIEW

The previous chapters in this section have outlined the definition, classifications, pathogenesis, clinical aspects, diagnostic assessment, and management of acute pancreatitis, chronic pancreatitis, and periampullary and pancreatic tumors that include pancreatic cancer and cystic and endocrine tumors. This chapter describes the different pancreatic resection procedures available today and is mainly focused on technical aspects.

Pancreatic resection ranks as one of the most, if not *the* most, complicated and technically challenging surgical procedures known to surgeons. It is not only a demanding technical exercise, it also exerts a substantial logistical strain on health care resources. Add to this equation the typical surgical candidate, who may already be profoundly jaundiced and malnourished preoperatively, not to mention the heavy physiologic toll any operation will take on such patients, let alone pancreatic surgery.

The modern surgeon can certainly appreciate the trepidations felt by early surgical pioneers faced with such a clinical situation. Early series on pancreatic operations for cancer published in the late 1960s reported postoperative morbidity rates of 60% and mortality rates approaching 25%, with dismal long-term outcomes. Consequently, Crile (1970) opined that patients would be better served by a bypass procedure rather than putting them through a futile and risky resection. Such a nihilistic view was the prevailing attitude prior to the 1980s, to the point that surgeons asked themselves whether pancreatoduodenectomy (PD) should be abandoned as treatment for pancreatic cancer (van Heerden et al, 1981).

In the ensuing decades, however, a dramatic decline was seen in surgical mortality and morbidity rates. High-volume pancreatic surgical centers are consistently reporting mortality rates of less than 2% and morbidity rates of 36% (Büchler et al, 2003; Cameron et al, 2006; Wagner et al, 2004). Certainly, continual improvements in surgical technique have played a role, but credit cannot be claimed solely by the surgical profession; significant advances were achieved in tandem in other fields that included better understanding of pancreatic diseases, advances in diagnostics, better patient selection, and improvements in perioperative care. Perhaps one of the main contributors to this phenomenon was the establishment of high-volume centers (Birkmeyer et al, 2003; Fong et al, 2005). Such centers tend to boast larger facilities and therefore have a broader range of specialist- and technology-based services, with better staffed intensive care units. This also implies that complications are better recognized and managed.

Although the question of the safety of pancreatic resection has been effectively addressed, the long-term outcome is more controversial as far as pancreatic adenocarcinoma is concerned. The concept of cure following "curative" resection has recently been challenged (Gudjonsson, 1995), but surgical resection is the only therapy that offers significantly increased survival. A randomized multicenter trial affirmed the superior results of resection on survival compared with various forms of nonsurgical therapy (Imamura et al, 2004). The median survival following resection was 14.3 months, whereas patients who did not undergo surgery died at 4.9 months (Conlon et al, 1996); 10% to 30% of patients will be true 5-year survivors (Cameron et al, 2006; Wagner et al, 2004). Furthermore, although pancreatic cancer is the most common of the periampullary tumors, cancers of the ampulla, duodenum, and distal bile duct, as well as intraductal papillary mucinous neoplasm–associated adenocarcinoma, have a better long-term survival following curative PD (Poultsides et al, 2010). In addition, more and more cystic pancreatic and endocrine tumors are diagnosed today, and simple enucleation or segmental resection of the tumors at the appropriate stage can cure the disease. Even with advances in multimodal treatment, surgery remains the centerpiece of the treatment algorithm for pancreatic cancer because no truly effective chemotherapeutic agents for treating nonresectable disease have been developed (Gillen et al, 2010; Postier, 2003).

Technical refinements have led to a variety of surgical techniques that have allowed a more individualized, disease-directed approach. These modifications were partly responsible for the decline in surgical morbidity. This chapter focuses on some of these surgical techniques, as practiced in our institution, as well as some of the more pertinent perioperative issues for patients subjected to pancreatic resection. Surgical techniques specific

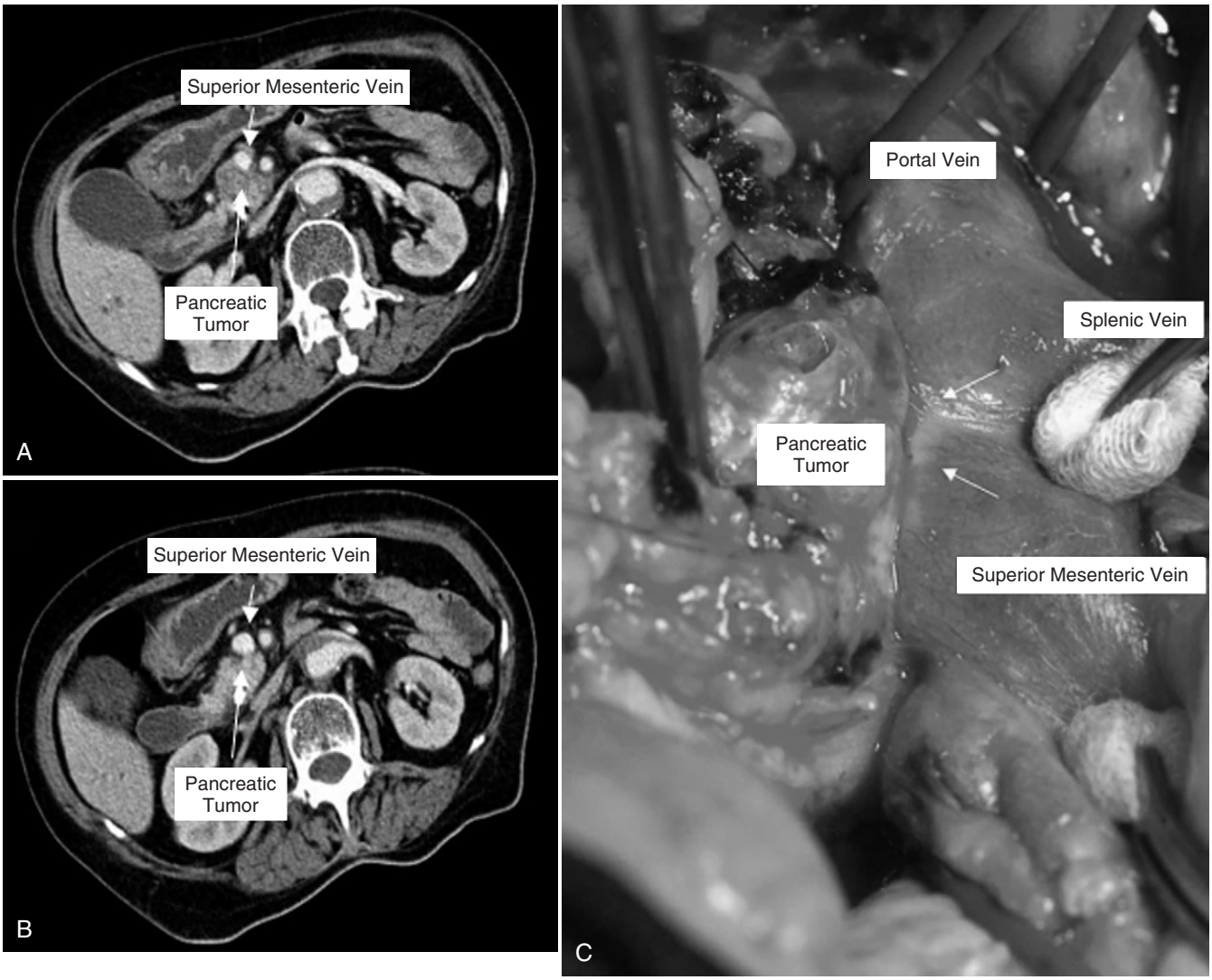


FIGURE 62A.1. **A** and **B,** Computed tomographic scan with axial cuts showing a pancreatic head carcinoma with involvement of less than 50% of the circumference of the superior mesenteric vein without involvement of the superior mesenteric artery (note the rim of fat tissue around the artery). **C,** Intraoperative findings confirm the scan findings with tumor infiltration of the superior mesenteric vein (*arrows*). Subsequently, a portal vein resection and reconstruction with a venous graft was carried out.

for the treatment of acute pancreatitis (open and minimally invasive necrosectomy) and chronic pancreatitis (duodenum-preserving pancreatic head resection) are described in detail in Chapters 54 and 55B.

PREOPERATIVE WORKUP AND MANAGEMENT

Diagnosis and Staging of Disease

Clinical staging should reliably define the extent of disease, thereby avoiding unnecessary intervention and the accompanying morbidity, mortality, and diminished quality of life in patients with advanced disease (Spanknebel & Conlon, 2001). Although the tumor-node-metastasis (TNM) staging system is most often used in clinical trials, physicians in practice typically classify patients as having resectable, locally unresectable, or metastatic disease (Haller, 2002). *Resectable pancreatic cancer* is universally defined as a pancreatic tumor without evidence of involvement of the superior mesenteric artery (SMA) or the celiac axis and no evidence of distant metastasis. Tumors with infiltration of one of these central arteries are defined as *locally irresectable,* but those with infiltration of the superior mesenteric vein or abutment of visceral arteries are defined as *borderline resectable* (Adler et al, 2007; Katz et al, 2008). Portal vein (PV) involvement, although somewhat controversial, should not be a contraindication for surgery; today, this is still center dependent. In general, PV involvement does not preclude an R0 resection (Fig. 62A.1).

Imaging

Imaging is now the mainstay in diagnosis and staging of pancreatic tumors, unlike the traditional approach of surgical exploration and a hands-on intraoperative examination to determine resectability.

Helical computed tomography (CT) scanning has been established as the single most effective initial staging study (Freeny, 2001; Klauss et al, 2008) and is often used as the entry

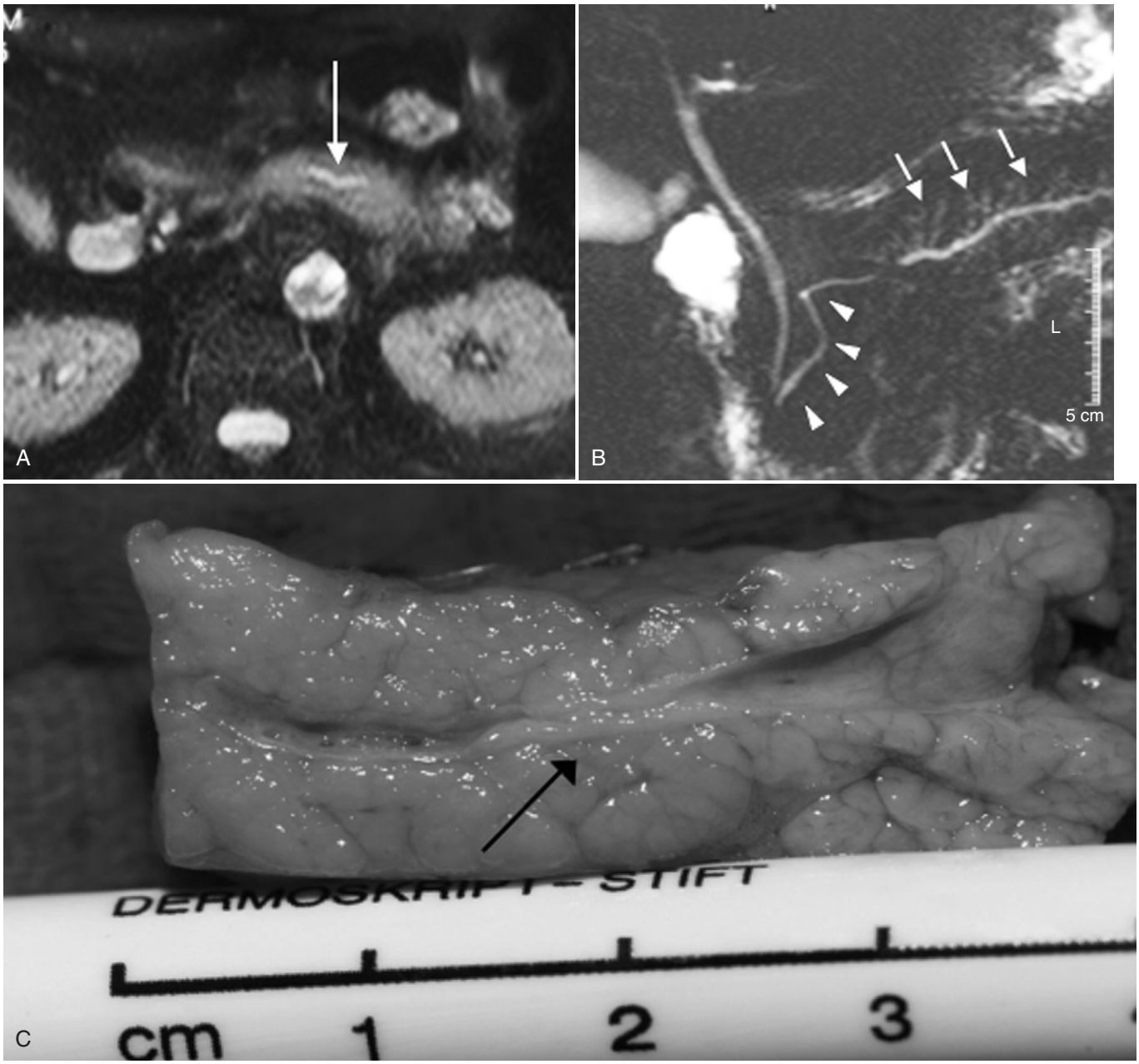


FIGURE 62A.2. A, Magnetic resonance image showing a dilated pancreatic duct (*arrow*) secondary to a small tumor. **B,** Magnetic resonance cholangiopancreatography shows a clearer delineation of the pancreatic duct. It demonstrates a normal pancreatic duct in the pancreatic head (*arrowheads*), a filling defect in the pancreatic body, and distal dilation of the pancreatic duct in the tail with appearance of first- and second-order side branches (*arrows*). **C,** Specimen photograph. The cause of the ductal obstruction was later shown to be a T1 pancreatic ductal adenocarcinoma (*arrow*) in the final histology.

point to a management algorithm. The findings then dictate the subsequent management, including additional diagnostics (see Chapter 16).

The previous selling point of magnetic resonance imaging (MRI) (see Chapter 17) was its being a one-stop modality that combines pancreatography, cholangiography, and angiography and also assists in the evaluation of tumors. However, MRI is being progressively overshadowed with the advent of the multidetector CT, which has nearly the same offerings. As such, MRI offers no added benefit over CT for evaluating pancreatic cancer, except perhaps in patients in whom a contrast-enhanced CT cannot be performed (White et al, 2003), and MRI seems to be superior for the differential diagnosis of pancreatic cystic lesions (see Chapter 57).

MR cholangiopancreatography (MRCP) offers a noninvasive delineation of the pancreatic and biliary ducts. It detects pancreatic or ampullary carcinoma by demonstrating the effect of a space-occupying lesion on the ducts, namely obstruction or displacement (Fig. 62A.2). The classic feature is the "double-duct" sign. However, even a strictly defined double-duct sign is only 80% to 85% specific for malignancy (Menges et al, 2000). More recent applications include secretin-enhanced MRCP,

which can improve pancreatic duct and side-branch delineation. Furthermore, such pharmacologic stimulation of pancreatic juice secretion can potentially allow the evaluation of pancreatic flow dynamics and assessment of pancreatic exocrine function (Kalra et al, 2003).

Endoscopic ultrasonograpy (EUS) allows a sonographic transducer to be placed in close proximity to the pancreas (see Chapter 14). In doing so, interference from overlying bowel gas is eliminated, thus allowing higher frequencies to be used and resulting in markedly improved resolution of the imagery. Consequently, EUS is more sensitive in detecting smaller lesions (<20 mm), with a sensitivity in the range of 93% to 100% (Tamm et al, 2003). In a meta-analysis of studies comparing staging by EUS to results with other modalities, EUS without fine needle aspiration (FNA) more accurately predicted T stage, N stage, and PV involvement than did CT scanning. EUS also allows image-guided FNA of the primary tumor and the regional lymph nodes without the possible risk of tumor seeding along the needle tract, unlike FNA via the percutaneous route (Gress et al, 2001).

EUS-guided FNA biopsy has been reported to have a high sensitivity (93%) and specificity (100%) (Wiersema, 2002); however, EUS with FNA is only of diagnostic value if histology confirms a pancreatic tumor. The major limitations of this technology are operator dependence and a limited field of visualization for the detection of distant metastasis. In fact, in resectable pancreatic cancer, but also in cystic or endocrine tumors, preoperative biopsies are of no value (Hartwig et al, 2009a). Therefore, we use this modality on a highly selective basis, such as in obtaining tissue biopsy for patients scheduled for neoadjuvant therapy with locally advanced pancreatic cancer, or before palliative chemotherapy is applied in metastatic disease.

With the advent of MRCP, EUS, and multidedector CT with multiplanar three-dimensional (3D) reconstruction, the role of endoscopic retrograde cholangiopancreatography (ERCP) as a diagnostic tool has become increasingly limited. Furthermore, it has potentially high complication rates compared with other procedures (Ciocirlan & Ponchon, 2004). Such concerns have been summarized in a recent report by the American Society of Gastrointestinal Endoscopy (ASGE, 2003). In light of these data, the current view is that purely diagnostic uses of ERCP should be limited, a view affirmed by the National Institutes of Health (NIH) State of the Science Conference Statement (Cohen et al, 2002), which recommended that for patients with pancreatic or biliary cancer, the principal advantage of ERCP is palliation of biliary obstruction when surgery is not elected.

General Preoperative Patient Assessment

Pancreatic resections exert a significant physiologic stress on patients, many of whom are elderly; the peak incidence of pancreatic cancer falls in the 65- to 75-year age group (Lankisch et al, 2002). With the improvement of the safety profile of pancreatic operations, many centers have offered surgery to octogenarians, although in such patients the incidence of comorbidities is higher.

In our center, we found that systemic complications, chiefly cardiopulmonary complications, have become the main cause of operative death (Büchler et al, 2003). As such, we routinely subject our patients to a rigorous preoperative assessment of their cardiac, pulmonary, and renal functions. Cardiopulmonary exercise testing has been shown to more accurately evaluate the ability of the cardiorespiratory system to deliver oxygen under stress (Davies & Wilson, 2004). We have also included a pulmonary function test in our algorithm. Optimization of afterload and myocardial contractility take equal importance, and pulmonary artery catheters are occasionally inserted to facilitate this. The operation will only proceed when we can achieve an optimal hemodynamic profile.

Perioperative Management (See Chapters 22, 23, and 24)

Perioperative Anticoagulation

Meta-analysis of the role of low-molecular-weight heparin (LMWH) in the prevention of venous thromboembolic events in general surgery has shown that LWMH can significantly reduce the incidence of asymptomatic deep vein thrombosis (DVT), clinical venous thromboembolism, and pulmonary embolism, with a trend toward a reduction in overall mortality rate (Mismetti et al, 2001). Consequently, we routinely administer LMWH in a prophylactic dose to our patients, starting the evening before the day of surgery, until the patient is ambulant postoperatively. In addition, our patients are prescribed compression stockings to wear intraoperatively and for their entire inpatient stay because such stockings reduce pooling of blood in deep veins by mechanically preventing venous distension (Morris & Woodcock, 2004) and are thus a simple and cost-effective method of DVT prophylaxis.

Antibacterial Prophylaxis

Antibacterial prophylaxis is instrumental in the reduction of infection-related morbidity with clean-contaminated procedures (de Lalla, 2002); as such, it is recommended for all patients who undergo hepatobiliary or pancreatic surgery (Sganga, 2002). Drugs with antianaerobic activity are added if anaerobe encounter is anticipated during the procedure, in particular procedures involving the gastrointestinal (GI) tract. The general guideline is to use the highest licensed dosage of the chosen antimicrobial agent, administered at induction of anesthesia so as to achieve high peak tissue concentration at the site of the wound before the first incision, which should be maintained until the time of closure (Polk et al, 2000). For our pancreatic operations, in addition to 500 mg metronidazole, we routinely give 4 g mezlocillin, an ureidopenicillin with activity against both gram-positive and gram-negative organisms, including enteric bacilli. We generally do not give postsurgical doses unless the patient has had a recent bout of cholangitis or if the bile was found to be turbid or purulent intraoperatively. In any event, in all procedures that require entry into the biliary tract, bile is sent for microbiologic examination to guide postoperative antimicrobial treatment if the need arises.

Octreotide Analogues

The pancreatoenteric anastomosis is considered the Achilles heel of PD, a testimonial to the potentially disastrous sequelae of life-threatening intraabdominal sepsis and hemorrhage (Stojadinovic et al, 2003) in the event of a pancreatic leak. The secretion capacity of the remnant gland has been found to be a determining factor for the development of a leak because continuous pancreatic secretion has been hypothesized to hinder healing of the pancreatic stump. This led to the hypothesis that

by reducing exocrine secretion, perhaps the incidence of pancreatic fistula could be reduced accordingly.

Octreotide, the octapeptide analogue of somatostatin, is a powerful inhibitor of pancreatic exocrine secretion. A number of randomized prospective trials have examined the role of prophylactic, perioperative octreotide and its impact on outcome after pancreatic surgery. The results seemed to display an intercontinental difference: level 1 studies from Europe generally showed that perioperative somatostatin has a protective effect, whereas all the North American studies failed to demonstrate any benefit. A recent systematic review of this topic came to the conclusion that the prophylactic administration of somatostatin or its analogue does not uniformly reduce the incidence of pancreatic anastomotic leak, overall morbidity, or mortality after pancreatic resection (Li-Ling & Irving, 2001). Based on the findings of the trials conducted by our center (Büchler et al, 1992; Friess et al, 1995), we believe that some benefits may still be reaped from the use of prophylactic somatostatin in high-risk patients (soft pancreas, small duct), in whom a PD is performed. If the pancreas is deemed to be high risk by the surgeon, because of a soft consistency and a pancreatic duct size of less than 2 mm in diameter, somatostatin is applied intraoperatively (200 μg subcutaneously), followed by three daily doses of 200 μg octreotide for 5 days. Other indications for applying somatostatin are when segmental resections or enucleations must be performed in patients with a soft pancreas, as is frequently observed with cystic or endocrine lesions.

Preoperative Biliary Drainage

Patients with pancreatic cancer who have jaundice are also at risk for associated coagulopathy, malabsorption, malnutrition, and immune dysfunction. Using a multiple-variant regression analysis, we had previously determined that jaundice (bilirubin level >5.8 mg/dL) is a significant risk factor for postoperative hemorrhage (Martignoni et al, 2001). This calls into question the role of preoperative biliary drainage (PBD) in reducing surgical morbidity through the normalization of liver function and the correction of coagulopathy. Sewnath and colleagues (2002) found in a meta-analysis no difference in the overall death rate among patients who had PBD and those who had surgery without PBD. Instead, the overall complication rate was adversely and significantly affected by PBD, and the hospital stay was also prolonged, so they concluded that PBD carries no benefit. Recent studies also demonstrate that routine PBD should not be performed because of the high rate of procedure-associated complications (Mezhir et al, 2009; van der Gaag et al, 2010). We concur with the opinion that ERCP should only be undertaken with therapeutic intent and believe that PBD as a routine practice should be halted. We would refer a patient for PBD in the presence of cholangitis or other severe complication of jaundice that would preclude a safe, early resection. An absolute indication for PBD is jaundice that requires induction therapy prior to surgical extirpation.

Fast-Track Surgery

Studies on so-called *fast-track GI surgery* have shown that epidural analgesia, combined with an intensive and standardized regimen of early feeding and mobilization, can reduce hospital stay (Basse et al, 2002). Epidural analgesia has been found to have many attributes, including a shorter duration of postoperative ileus, attenuation of the stress response, fewer pulmonary complications, improved postoperative pain and mobility, and patient perception of a quicker recovery (Fotiadis et al, 2004). Thoracic epidural analgesia is of particular benefit to patients with a high risk of cardiac or pulmonary morbidity, and it can reduce hospital stay and costs in this subgroup of patients.

Attracted by the promising results published in the literature,and encouraged by the concept of fast-track surgery, we have since recommended thoracic epidural analgesia to all our patients who undergo pancreatic resection. We use a combination of local anesthetic and opioids; the former blocks sympathetic outflow, resulting in less cardiac stress, and at the same time promotes the return of bowel motility. The addition of opioids allows adequate analgesia with less local anesthetic, thereby reducing local anesthetic–related hypotension and motor deficits. Alternative methods of analgesia can be used when epidural analgesia is contraindicated or declined. We have also established postoperative pain teams to assist in patient care and monitoring and have realized some of the published benefits, including earlier and better tolerance of oral feeding, less postoperative pain, and earlier mobilization.

RESECTIONAL TECHNIQUES

Pancreatoduodenectomy

Ductal adenocarcinoma is by far the most prevalent tumor of the pancreas, with a predominant localization within the pancreatic head (78%) (see Chapters 58 and 59; Schäfer et al, 2002). Furthermore, adenocarcinoma of the body or tail is seldom resectable on presentation. It is thus not surprising that PD is the best-studied pancreatic surgical procedure.

Technique

In thin patients, we prefer a midline incision beginning from the xiphoid process, but we perform a rooftop incision in patients with a short torso and a wide abdominal girth. After we have ruled out liver metastasis, the peritoneal surfaces are carefully inspected for metastatic deposits. Particular attention is paid to the pelvis for drop metastasis and to the root of the mesentery for evidence of tumor extension or matted nodes. A wide Kocher maneuver is then performed to assess the retroperitoneum and appraise the tumor and its relationship to the SMA (Fig. 62A.3). The mesenteric artery is inspected from the ligament of Treitz and dissected on its right hemicircumference to exclude any tumor infiltration of the artery. This technical approach, the so-called *artery-first approach* (Fig. 62A.4; Weitz et al, 2010), helps avoid R2 resections because any infiltration of the central arteries can be diagnosed early during exploration. We proceed with the resection only if we find no evidence of infiltration of the celiac trunk and SMA.

Access to the lesser sac is achieved by division of the gastrocolic ligament. On the left side, we divide the gastrocolic ligament only as far as the most medial branch of the short gastric vesssls. This is to ensure an alternative venous egress for the splenic blood flow in the event of any venous resection of the SMV-PV trunk. Moving to the right, the hepatic flexure is mobilized caudally. Careful dissection in the avascular plane between the hepatic flexure and the duodenum and extension of the Kocher maneuver will allow the third part of the duodenum to be freed from the colonic mesentery. The gastroepiploic vein is then divided where it empties into the gastrocolic trunk, and the SMV is traced to the inferior margin of the pancreas. Two stay sutures are then placed at the inferior border of the

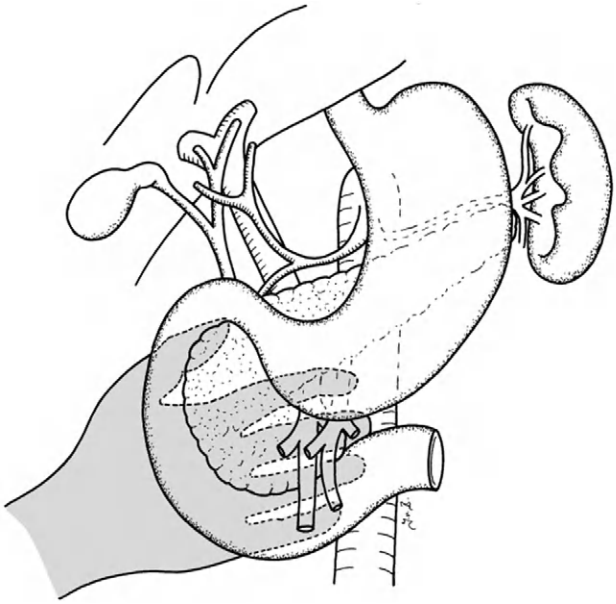


FIGURE 62A.3. Adequate kocherization to facilitate assessment of the retroperitoneum and the relation of the tumor to the vascular structures.

pancreas to aid in the creation of the tunnel between the pancreatic neck and the SMV-PV trunk. Attention is now turned to the supraduodenal compartment.

Cholecystectomy is performed in a typical fashion. The cystic duct is traced to its origin from the common bile duct (CBD), which is transected just cephalic to this point. Extreme care must be taken to avoid any iatrogenic injury to the right hepatic artery, which usually runs posterior to the hepatic duct (see Chapter 1B; Skandalakis et al, 2004). In addition, it is important to assess for an aberrant right hepatic artery, present in 20% of patients, by palpation of the posterior aspect of the hepatoduodenal ligament. The cystic artery is isolated and closed with ligation.

The lymphadenectomy of the hepatoduodenal ligament is performed with great caution and completed along the common hepatic artery toward the celiac trunk. The distal end of the CBD and its adjoining fibrous fatty tissues are then dissected free from the rest of the hepatoduodenal ligament and retracted caudally. A small, noncrushing clamp is then applied to the proximal bile duct stump to prevent any further bile spillage for the rest of the operation. The proper hepatic artery is identified and looped then traced proximally toward the common hepatic artery. The right gastric artery (RGA) and the gastroduodenal artery (GDA) can be isolated during this dissection. Nodal tissues surrounding the proper hepatic artery and the common hepatic artery are excised. The RGA and GDA are then divided near the origin of the GDA. A potential pitfall here is the misidentification of a replacing common hepatic artery or even a replacing right hepatic artery as the GDA. A technique to avoid this mistake is to place a vascular clamp across the presumed GDA and check for pulsations at the porta hepatis before this vessel is divided.

If preservation of the pylorus is planned, which is our usual practice, the right gastric and right gastroepiploic arteries are divided and the duodenum is skeletonized 2 cm beyond the pylorus. The suprapancreatic portion of the PV will now be widely exposed, and two stay sutures are similarly placed on the superior border of the pancreas; these sutures at the superior and inferior pancreatic borders also serve to ligate the superior and inferior pancreatic vessels respectively, running longitudinally in the parenchyma. Hence bleeding from the cut edges is reduced after transection. A tunnel is cautiously created between the SMV-PV trunk posteriorly and the pancreatic neck anteriorly. A silicon drain is then insinuated into this tunnel to loop up the neck (Fig. 62A.5).

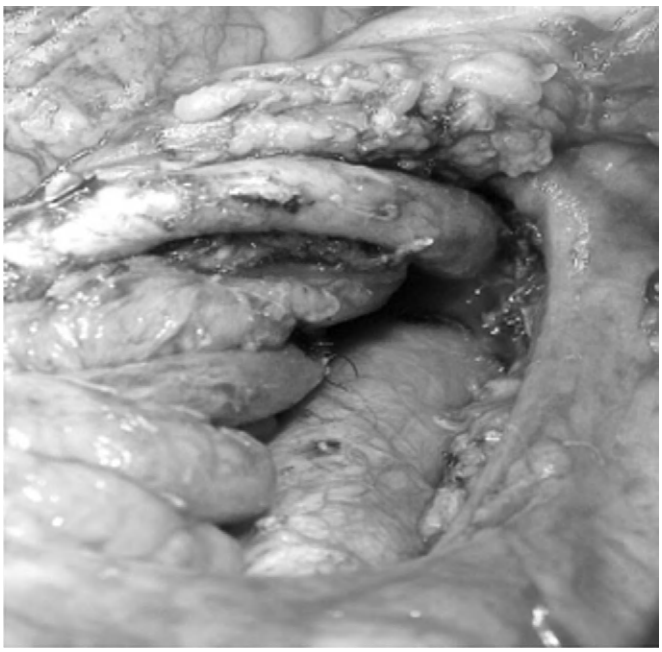


FIGURE 62A.4. Artery-first approach. The superior mesenteric artery is dissected, and infiltration of the artery is ruled out as one of the first steps of the operation.

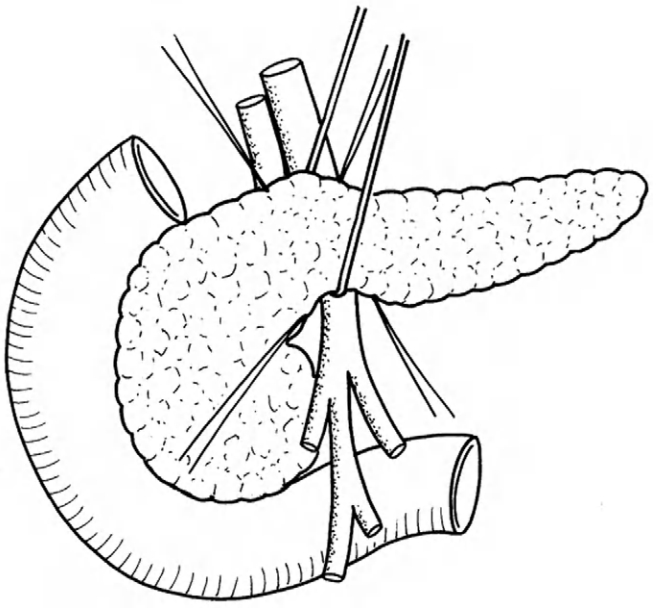


FIGURE 62A.5. Clearance of the surrounding fibrofatty tissues around the pancreatic stump for a distance of 2 cm allows adequate visualization of the pancreatic capsule. Cannulation of the pancreatic duct facilitates subsequent ductal sutures.

Because the medial margin is the most crucial with regard to tumor infiltration and the R status of the resection (Esposito et al, 2008), we now perform the uncinate process–first approach (Hackert et al, 2010). After having exposed and evaluated the SMA, the ligament of Treitz is mobilized, and the mesenteric branches to the fourth part of the duodenum are divided to allow it to be delivered into the inframesocolic compartment under the SMA. The mesenteric window is extended to the proximal jejunum, which is transected at a point that allows a tension-free loop of jejunum to be brought into the supramesocolic compartment in a retrocolic fashion through a window created on the right side of the middle colic pedicle. The dissection is performed along the SMA and SMV with bipolar cautery and clips.

If venous resection is required, it is reserved as the last step in the extirpative phase. The PV is then gently retracted medially to expose the underlying tissues, and any venous branches are divided. At the same time, the specimen is retracted to the right. The tissue and branch arteries arising from the SMA are serially clamped, divided, and clipped or stitch ligated. During this step, the specimen that comprises the pancreatic head, duodenum, and proximal jejunum is cupped in the surgeon's nondominant hand, and the fingers continuously appraise the position of the SMA to avoid any injuries to it. The anterolateral aspect of the SMA is completely skeletonized of its investing tissues.

After complete transection of the pancreatic mesentery along the SMA and SMV, a scalpel is used to transect the neck of the pancreas. Bleeding vessels from the transected pancreatic ends are ligated using nonabsorbable monofilament polybutester sutures. We do not use any form of electrical cautery on the pancreas for hemostasis; we believe this to be an insecure form of hemostasis when used on the pancreatic parenchyma. We also suspect that this will be detrimental to the tissues and that it may compromise the subsequent anastomosis. The venous trunk is then examined for any tumor involvement on its posterolateral aspect, and margins are harvested from the proximal pancreatic stump and bile duct for margin analysis by frozen section.

At last, the duodenum is transected by using a linear stapler. The stomach is then retracted to the left upper quadrant of the abdomen, and the specimen is sent for histologic examination. The pancreatic stump is cleared over a distance of 2 cm from the cut end to provide a clear, all-around visualization of the pancreatic capsule and to allow a safe pancreatojejunostomy; this also facilitates the subsequent construction of the pancreatoenteric anastomosis. Next, hemostasis is ensured, and the operative field is washed with warm water before proceeding to the reconstructive phase.

Standard Pancreatoduodenectomy Versus Pylorus-Preserving Pancreatoduodenectomy

In addition to the known postoperative complications associated with PD, the performance of a distal gastrectomy in the standard procedure also brings with it the possible long-term morbidities of gastric dumping, marginal ulceration, and bile-reflux gastritis (Poon & Fan, 2001). First introduced by Kenneth Watson (1944), it was not popular until 1978, when Traverso and Longmire (1978) reintroduced it. They hypothesized that the preservation of the stomach and pyloric function would improve GI function and hence reduce the morbidities associated with a gastroenterostomy. Indeed, better long-term digestive function and quality of life have been found after pylorus-preserving pancreatoduodenectomy (PPPD) in some retrospective studies. To retain a functioning pylorus, the entire stomach, 2 cm of the first part of the duodenum, and the neurovascular supply to both are preserved. Following the division of the right gastric and right gastroepiploic arteries at their origin, the duodenum is skeletonized 2 cm distal to the pylorus (Farnell et al, 2001), taking care to preserve the nerve of Latarjet. The duodenal bulb is then transected.

A recent meta-analysis demonstrated that the classical Kausch-Whipple procedure and the pylorus-preserving Whipple procedure are comparable with regard to perioperative morbidity and mortality and long-term outcome (Diener et al, 2008b). Hence, in the light of the available evidence, PPPD should be designated the "standard" procedure for pancreatic and periampullary neoplasm because no study to date has demonstrated any advantage to the removal of the stomach and the proximal duodenum (Bell, 2004). Hemigastrectomy should be performed only when gastric or proximal duodenal invasion or grossly abnormal peripyloric nodes are evident.

Vascular Resection

Over 30 years ago, Fortner (1973) reasoned that a more radical resection should improve survival by improving tumor clearance, specifically that tumor adherence to the PV or SMV, often regarded as a criterion of unresectability, could be overcome by en bloc resection of the involved vessels. Randomized evaluation of portal and superior mesenteric vein resection in patients with tumors adherent to these vessels is difficult because considerable intersurgeon variation in the interpretation of adherence is likely. Thus no randomized trial evaluates this topic.

A recently published systematic review (Siriwardana & Siriwardena, 2006) evaluated 52 manuscripts with 6333 patients in whom pancreatic resection was performed for pancreatic cancer; 1646 of these patients (26%) underwent synchronous portal and superior mesenteric vein resection. The median number of resections per publication evaluated was 82; of those, 23 patients underwent portal and superior mesenteric vein resection. The proportion of portal and superior mesenteric vein resection per publication varies widely, ranging from 2% to 77%, which mirrors the various treatment approaches of pancreatic cancer in different institutions today.

Information on the operation was available in 39 studies with 1334 patients. The operations performed included PD (71%), total pancreatectomy (24%), subtotal pancreatectomy (3%), and distal pancreatectomy (2%). The median operation time was 513 minutes (range, 168 to 1740 minutes), median blood loss was 1750 mL (range, 300 to 26,000 mL), and the median time for PV occlusion was 20 minutes (range, 7 to 302 minutes). The perioperative mortality rate was 5.9%, varying between 0% and 33%, and postoperative morbidity rate was 42%, ranging from 9% to 78%. PV invasion was detected in 64% of all portal and superior mesenteric vein resection specimens, and the range varied widely between 3% and 86% in the different series, and 67% of all patients with portal and superior mesenteric vein resection had positive lymph nodes detected on histology. The long-term survival was 13 months (range, 1 to 109 months) after portal and superior mesenteric vein resection. The 1-, 3-, and 5-year overall survival rates of 1351 patients undergoing portal and superior mesenteric vein resection was 50%, 18%, and 8%, respectively.

The assessment of pooled data is critically influenced by the quality of the single reports. The reports included have been published over the last 25 years, and the standards of perioperative care, surgical technique, and adjuvant therapy have developed dramatically. Thus the wide variations of outcome parameters—perioperative death, operative time, blood loss—mirror the nonhomogenous collective included in this review. However, the long-term survival rate demonstrates that resection of the portal or superior mesenteric vein is a potentially curative operation. It seems that patients who need a portal or superior mesenteric vein resection for cure include a high percentage of patients with a positive nodal stage. Because adjuvant treatment has been proven to increase survival but has only recently been introduced as standard care for patients with pancreatic cancer, the survival rates of patients with portal or superior mesenteric vein resection today should be even better than those reported in this review (Neoptolemos et al, 2004; Oettle et al, 2007).

In addition, surgical expertise has improved over the past few decades, and the quality of high-volume centers—especially for technically demanding surgeries, such as pancreatic resection—has been proven (Birkmeyer et al, 2003; Büchler et al, 2003). Thus it is not surprising that perioperative morbidity and mortality rates reported for pancreatic resections with portal or superior mesenteric vein resection are identical to those without it (Bachellier et al, 2001; Carrere et al, 2006; Leach et al, 1998; Nakao et al, 2006; Riediger et al, 2006; Wagner et al, 2004).

These latest reports also demonstrate that extended resections with portal or superior mesenteric vein resection improve long-term survival. However, histologically confirmed tumor infiltration into the tunica media of the PV has a worse prognosis and a long-term survival of less than 2 years.

Tumor infiltration of the SMA, celiac trunk, or hepatic arteries are well-accepted criteria for unresectability of pancreatic adenocarcinoma. However, because adherence of tumors to the arteries does not automatically mean infiltration—in fact, the arterial wall is resected much longer than the venous wall—several published series of pancreatic resections included resection and reconstruction of visceral arteries (Hartwig et al, 2009a; Li et al, 2004; Sasson et al, 2002; Varadhachary et al, 2006). A recent review states that in 15% of pancreatic operations in which portal or mesenteric vein resection had to be performed, arteries were also resected. These included the common hepatic artery (50%), SMA (20%), celiac axis (10%), and other arteries (Siriwardena & Siriwardena, 2006).

In summary, resection of the portal and superior mesenteric vein should be performed when adherence or infiltration of the tumor is present, because perioperative morbidity, mortality, and long-term survival are identical to those patients in whom an R0 resection can be performed without PV resection. Moreover, the long-term survival of patients who have had pancreatic resection in combination with PV resection is far superior compared with those in whom only palliative surgical management was performed. In contrast, with arterial adherence of the pancreatic tumor, arteries can only rarely be resected in a curative way. Although resection of the SMA, celiac trunk, or hepatic arteries is technically feasible, no data suggest that this leads to any improvement of long-term outcome. Thus, resections of arteries during pancreatic resections are an experimental approach that cannot be recommended as a standard technique today.

Multivisceral Resections

The benefit of radical surgical resection of contiguously involved structures for locally advanced pancreatic cancer has been addressed in several reports (Hartwig et al, 2009; Sasson et al, 2002). In fact, about 35% of patients are seen initially with locally advanced pancreatic cancers with involvement of surrounding structures and organs. Although several reports in the past showed that morbidity of extended resection was increased and survival benefit limited, more recent publications demonstrate that en bloc resection of contiguously involved organs can be performed safely (Sasson et al, 2002). No difference was reported with regard to perioperative morbidity (35%) and mortality (3%) compared with standard resection. Although operation time is clearly longer because of the extended resection—which includes mesocolon, colon, adrenal glands, liver, and stomach—blood loss and hospital stay are not different from what is observed after the standard procedure. The main aim of the extended procedure must be an R0 resection because this is the most important predictor of long-term survival (Wagner et al, 2004). The survival rate after resection of mesocolon and colon, as well as stomach, is not significantly decreased compared with the standard procedure (Sasson et al, 2002). The 5-year survival rate was 16%, and the median survival of 26 months is much better than the 6 to 9 months reported for patients who are not resected at all.

Similarly, another study demonstrated that patients with pancreatic adenocarcinoma of the body or tail need extended resection for contiguous organ involvement more frequently because these tumors are generally detected later and have therefore reached a greater size than cancers of the pancreatic head by the time of diagnosis. The median survival in these patients was 15.9 months, and the survival at 5 and 10 years was 22% and 18%, respectively. In our series of more than 100 patients with multivisceral resections, we showed that perioperative mortality rate and long-term outcome are similar to those of standard resections (median survival, 20 months), but that the morbidity is increased. Thus these patients need careful postoperative observation in an experienced pancreatic center (Hartwig et al, 2009).

In summary, patients undergoing extended resection for adenocarcinoma of the pancreas have long-term survival rates similar to those undergoing standard resection. The main aim is to achieve a curative (R0) resection, and resected patients have improved survival compared with patients with advanced disease who are not resected or considered unresectable; thus extended pancreatic resection for contiguous organ involvement is justified.

Lymphadenectomy

The rationale for extended lymphadenectomy is that lymph node studies have confirmed positive lymph nodes may be found outside the confines of the standard dissection (Cubilla et al, 1978). Even for small cancers, lymph nodes of the paraaortic region, between the celiac trunk and the origin of the inferior mesenteric artery, frequently harbor metastases; it has been suggested that these should be dissected en bloc during radical resections (Nagakawa et al, 1993). These revelations initiated a movement of extended lymphadenectomy among Japanese surgeons. A few studies reported similar surgical morbidity and mortality rates, but improved survival results were seen with extended surgery compared with the standard PDs

(Ishikawa et al, 1993). However, these were all retrospective, nonrandomized studies.

What constitutes extended lymphadenectomy is still widely debated; this is epitomized by the multitude of terminologies used in the literature. In an attempt to harmonize this subject, a consensus conference on the surgical treatment of pancreatic cancer took place in Castelfranco Veneto, Italy (Pedrazzoli et al, 1999). This consensus provided a standardized definition of the different extent of lymphadenectomy that used the Japanese Pancreas Society rules for the study of pancreatic cancer to define the lymph node stations to be removed for the various procedures (Japan Pancreas Society, 1993). The three stages of radicality for PD have been named *standard, radical,* and *extended radical,* depending on the nodal stations removed. For cancers of the body or tail, according to the extent of lymphadenectomy, two different procedures are identified: standard and radical. It is hoped that this standardization of surgical procedures will facilitate comparison of results between different centers.

Between 1988 and 1999, eight retrospective studies were published on the extent of lymphadenectomy for PD. The data on survival are largely heterogeneous, but neither morbidity nor mortality seems to be altered. Altogether, two studies reported on morbidity rates, whereas five studies reported perioperative mortality rates. Especially in Japan, extended lymphadenectomy was widely used in the late 1980s and 1990s because of the initial reports of Ishikawa and colleagues (1988) and Manabe and colleagues (1989), who advocated an extension of the PD. In these studies, survival rates were significantly increased in the extended lymphadenectomy groups. Interestingly, some long-term survivors were seen in the extended lymphadenectomy groups, but none (Manabe et al, 1989) or very few (Ishikawa et al, 1988) of the patients in the standard lymphadenectomy arm survived for more than 5 years.

In terms of operative techniques, total pancreatectomies were used in many patients, which may have also altered the outcome. Interestingly, the largest retrospective studies (Hirata et al, 1997; Mukaiya et al, 1998), which together included 1330 patients, did not reproduce these results. The 1- and 3-year survival rates were comparable in the standard lymphadenectomy and extended lymphadenectomy groups, but data on morbidity and mortality were not provided. A study by Kawarada and colleagues was the only one to reproduce the results of Manabe and Ishikawa. However, patients included in the standard lymphadenectomy arm had been operated on between 1976 and 1981, whereas extended lymphadenectomy was performed between 1981 and 1993. Because the perioperative outcomes were significantly improved in the late 1980s, the survival benefit shown for extended lymphadenectomy may be due solely to generally advanced perioperative management. Hence, it cannot be concluded from the retrospective studies that extended lymphadenectomy provides a survival benefit.

Six prospective, nonrandomized studies have been published on this topic. A prospectively conducted study from Henne-Bruns and colleagues (1998), in which the decision to perform a standard or extended lymphadenectomy was made based on the clinical status of the patient, revealed no significant differences in mortality rate and long-term survival but did show a trend toward a better outcome in the standard lymphadenectomy group. This may be due to a higher percentage of patients with advanced-stage tumors in the extended lymphadenectomy group. Furthermore, extended lymphadenectomy was associated with an increased rate of severe diarrhea in the early postoperative phase. Gazzaniga and colleagues (2001) showed that morbidity, mortality, and long-term survival were unaltered between standard and extended lymphadenectomy. Interestingly, a third group of patients received extended lymphadenectomy and additional adjuvant chemoradiation and fared significantly better, with a 5-year survival rate of 17.6%. However, this promising concept of multimodal therapy was not confirmed by randomized trials. Another retrospective study from Italy showed a tendency toward increased survival rates with an extended lymphadenectomy, but morbidity was comparable (Iacono et al, 2002). Studies from both Popiela and colleagues (2002) and Capussotti and colleagues (2003) confirmed the results of the previous reports with unchanged morbidity, mortality, and survival rates. However, for node-negative cancer, extended lymphadenectomy significantly improved the 5-year survival rates (Popiela et al, 2002), and a slight improvement in short-term survival was also seen for patients in the extended lymphadenectomy group (Capussotti et al, 2003). Overall, the number of resected lymph nodes was significantly higher in the extended lymphadenectomy groups.

Four randomized controlled trials have been conducted so far and were summarized in a meta-analysis (Farnell et al, 2005; Michalski et al, 2007; Nimura et al, 2004; Pedrazzoli et al, 1998; Yeo et al, 2002). Interestingly, these four level I studies are from centers on three different continents. The first study by Pedrazzoli and colleagues did not reveal any differences with regard to morbidity, mortality, and survival between the standard and extended lymphadenectomy groups. Standard lymphadenectomy included the dissection of lymph nodes at the anterior and posterior pancreatoduodenal side, at the pylorus, bile duct, and superior and inferior part of the pancreatic head and body. For the extended procedure, additional lymph nodes were dissected within the complete circumference at the aorta, the inferior and superior mesenteric arteries, and the celiac trunk. Interestingly, a retrospective subgroup analysis revealed a significantly prolonged survival for node-positive patients who received an extended lymphadenectomy. This statement has since been intensively discussed because of the small difference in the number of resected lymph nodes between the standard and extended lymphadenectomy groups (13.3 vs. 19.8).

The largest study on this subject enrolled 294 patients; it was published in 2002 and updated in 2005 by Yeo and colleagues and was preceded by a preliminary evaluation in 1999. The authors randomized 294 patients into standard and extended lymphadenectomy arms after intraoperative frozen section with tumor-negative margins. However, the study encompasses the different entities of periampullary malignancies, and only 57% of the tumors were of pancreatic origin. Thus conclusions with regard to survival have to be critically reviewed because ampullary and distal bile duct tumors were also included. A pylorus-preserving PD was performed in 86% of the patients in the standard lymphadenectomy group; in the extended lymphadenectomy arm, the classic Whipple operation was mainly used. Mortality and survival rates were unaltered, whereas a significant increase in morbidity was reported in the extended lymphadenectomy group (29% vs. 43%; $P < .01$), which was mainly due to higher rates of delayed gastric emptying and pancreatic fistula.

Considering the large number of patients and the detailed analysis of many variables, the conclusion that extended lymphadenectomy does not improve survival but may increase

morbidity is to be supported. These data and conclusions are underlined by their follow-up publication and a study on quality of life (QOL) of the same patient group (Riall et al, 2005). Additional studies from the Mayo Clinic by Farnell and colleagues (2005) and from Japan by Nimura and colleagues (2004) supported those results. The Mayo Clinic trial included 79 patients randomized in two groups (lymphadenectomy: standard [n = 40] vs. extended [n = 39]). When performing an extended lymphadenectomy, the number of lymph nodes resected was greater (36 vs. 15), but morbidity and mortality rates were comparable. No significant differences were observed for the 1-, 3-, and 5-year survival rates. However, at 4 months postoperatively, diarrhea was significantly increased, and bowel control and body appearance were worse in the extended lymphadenectomy group. The multicenter trial from Nimura and colleagues revealed similar results with comparable mortality and survival rates but increased morbidity, which was due to severe diarrhea in 48% of the patients (Nimura et al, 2004). Of interest, the number of lymph nodes resected varies considerably between the studies. For examples, Nimura and colleagues resected about twice as many lymph nodes in the extended lymphadenectomy group as did Pedrazzoli and colleagues, which may reflect different operative techniques as well as differences in pathologic analysis.

In summary, none of the randomized, controlled trials (RCTs), except for a retrospective subgroup analysis within the study of Pedrazzoli and colleagues, showed any survival benefit for extended lymphadenectomy, whereas overall morbidity with diarrhea and delayed gastric emptying as particular complications tended to occur more frequently. Interestingly, both Yeo and colleagues and Farnell and colleagues particularly report a reduction in QOL in the extended lymphadenectomy group, primarily because of high rates of postoperative diarrhea with subsequent development of malnutrition (Michalski et al, 2007). Thus mortality and morbidity may be at best unaltered for the extended radical operation compared with the standard procedure. The randomized studies are altogether underpowered and lack standardization with regard to the actual extent of the performed lymphadenectomy. As for the potential survival benefit, further adequately powered randomized studies will need to be impractically large, thus precluding their realization. Therefore, the current standard of surgery for pancreatic head tumors remains PPPD without extended lymphadenectomy.

Reconstruction After Pancreatic Resection and Management of the Pancreatic Remnant

A pancreatic leak is the major cause of procedure-related death. Simply occluding the duct has been shown to result in higher fistula rates in addition to increasing the risk of pancreatic exocrine and endocrine insufficiency (Tran et al, 2002). Hence, drainage of the pancreatic remnant to the GI tract remains a crucial step, but it runs the risk of anastomotic breakdown. It is thus not surprising that the pancreatoenteric anastomosis has fascinated surgeons, motivating them to search for a more reliable technique to avoid this dreaded complication. Many techniques have been described, and the literature will continue to report novel techniques that promise to be even safer. However, more so than the choice of the variant used, successful management of a pancreatic anastomosis is most dependent on the surgeon's concentration on meticulous execution of the chosen technique (Trede et al, 2001). For as long as the basic tenets of a safe anastomosis are met—namely, careful handling of the pancreatic tissues, a tension-free adaptation, good perfusion, and no distal obstruction—any pancreatoenteric anastomotic technique can have a good outcome.

One of the most commonly used techniques is a pancreatojejunal anastomosis, which can be performed by invaginating the transected pancreas into the end of the jejunum, the so-called *dunking procedure*. Another variant is to anastomose the pancreatic duct directly to a proper opening in the jejunum, the so-called *duct-to-mucosa technique*. The technique of pancreatojejunal anastomosis—whether end-to-side or end-to-end, duct-to-mucosa or dunking—does not seem to significantly influence the anastomotic leak rate. Another strategy is to anastomose the pancreatic stump to the stomach, and proponents of pancreatogastrostomy (PG) have cited various reasons to choose this method (Zenilman, 2000); it is easier to perform given the close proximity of the stomach to the pancreas, and the anastomosis is less prone to ischemia because of the rich gastric perfusion. Because the exocrine enzymes enter an acidic environment, it was once thought that the leak rate would be lower because the enzymes do not get activated, but this idea has since been debunked. In a prospective randomized trial comparing pancreatojejunostomy (PJ) to PG, the leak rates were not significantly different (PJ, 11%; PG, 12%) (Yeo et al, 1995).

The authors' institution uses a standardized technique of PJ performed in an end-to-side fashion with a retrocolic jejunal limb (Z'graggen et al, 2002). The anastomosis is performed in two layers with duct-to-mucosa adaptation using monofilament absorbable polydioxanon sutures (PDS 5/0) with an atraumatic JRB-1 (5/8) needle. The first step is the placement of the ductal sutures, first anteriorly from the outside in, then posteriorly from the inside out (Fig. 62A.6). We endeavor to place at least three ductal sutures on each side. This is generally no problem, because the duct is dilated in cases of pancreatic head tumors. Only in patients with very small ducts that cannot be cannulated with a small ductal probe, the duct sutures should be omitted to avoid obstruction of the duct.

Because the pancreatic stump is dissected over 2 cm toward the left, good visualization of the posterior capsule can be achieved. A row of interrupted sutures is then placed through the dorsal capsule, with the needle entering the pancreatic

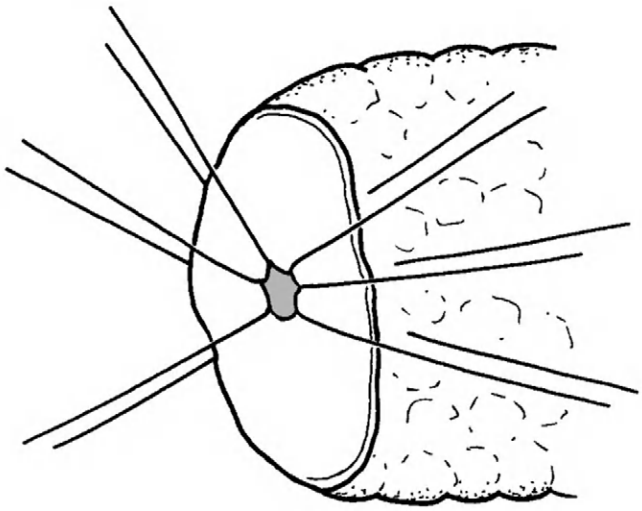


FIGURE 62A.6. Three anterior and three posterior ductal sutures.

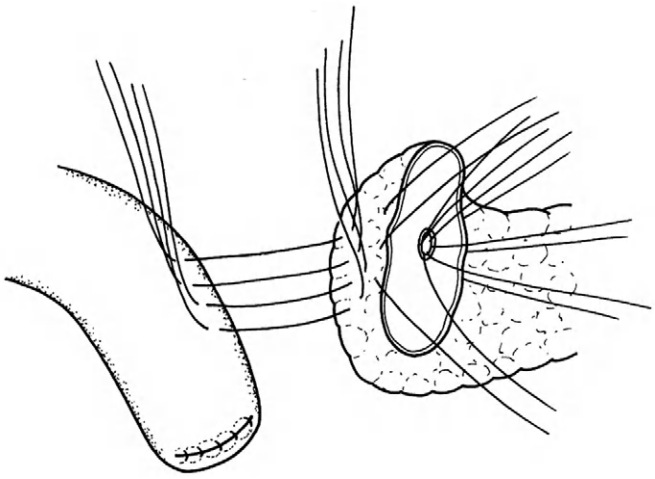


FIGURE 62A.7. The first layer of the posterior suture row performed in an interrupted fashion.

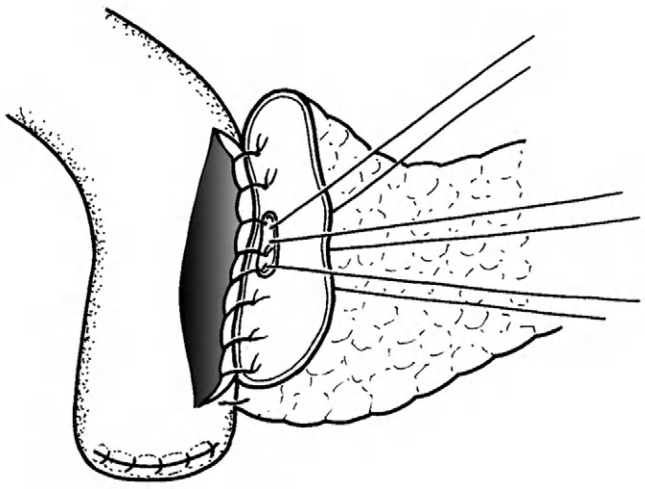


FIGURE 62A.9. The completed second layer of the posterior suture row demonstrates the integration of the previously placed ductal sutures into the suture row.

tissues about 1 cm from the cut end of the stump and taking an adequate bite of the parenchyma. The needle is then driven through the seromuscular layer of the jejunal limb about 1 to 2 mm from the mesenteric border. The intersuture distance is about 4 to 6 mm (Fig. 62A.7). The jejunum is carefully adapted to the pancreas following meticulous and gentle tying of the knots. A longitudinal enterotomy is then performed about 5 mm from the posterior row of sutures (Fig. 62A.8) with the width of the opening tailored to the size of the pancreatic stump.

The posterior inner row of sutures is then constructed, first catching the pancreas in an inside-out fashion, ensuring an adequate bite of the parenchyma, and exiting just at the cut edge of the remnant pancreas. The suture is then driven through the posterior edge of the enterotomy in an outside-in fashion, ensuring a full-thickness bite. The previously placed ductal sutures are integrated in order, and each suture is clipped with an artery clamp (Fig. 62A.9). All knots are tied after completion of the suture row.

This is followed by the anterior inner row of sutures, which is driven through the pancreas in an outside-in manner, entering just at the anterior cut edge of the stump and ensuring an adequate bite of the pancreatic parenchyma. The suture is then placed through the anterior edge of the enterotomy in an inside-out fashion with a full-thickness bite (Fig. 62A.10). All knots are, again, only tied following completion of the suture row.

The final step is the second row of anterior sutures, the aim of which is to cover the inner suture line by imbricating the jejunal serosa over it (Fig. 62A.11). The suture first catches the anterior capsule of the pancreas close to the anterior inner row. A seromuscular bite is then taken of the jejunum at a point that will allow a fold of the jejunal wall to cover the inner row of sutures in a tension-free manner (Fig. 62A.12).

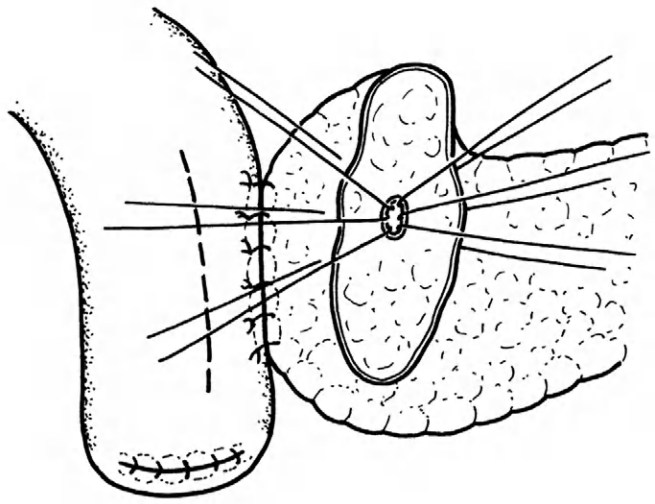


FIGURE 62A.8. Following apposition of the pancreas to the jejunal limb via the posterior serocapsular suture row, a longitudinal enterotomy is planned, tailored to the width of the pancreatic stump.

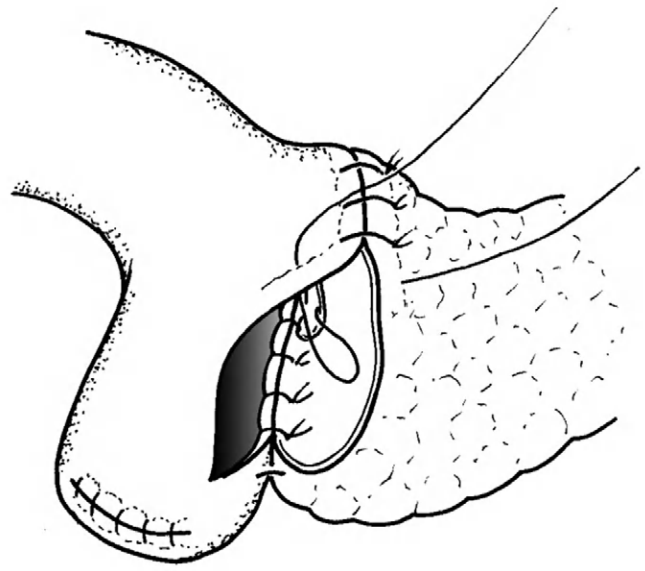


FIGURE 62A.10. Placement of the first layer of the anterior suture row.

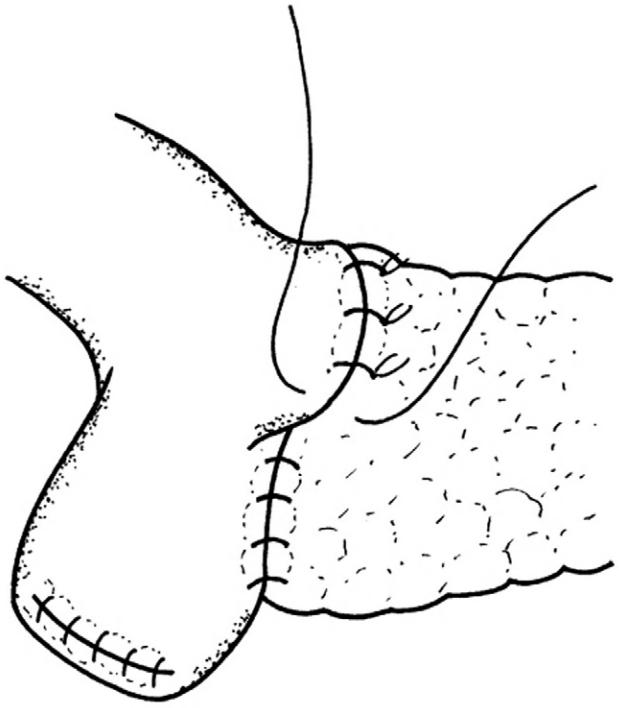


FIGURE 62A.11. The second layer of the anterior suture row, which serves to imbricate the first layer.

The end-to side technique allows the adaptation of the jejunal opening to the specific requirements of the pancreatic remnant. Separate duct-to-mucosa adaptation also keeps the duct orifice open, thereby ensuring the unobstructed flow of pancreatic secretions through the anastomosis. Consequently we see no need for the placement of any pancreatic stents. This technique was used in 93% of patients undergoing pancreatic head resection, with an overall leak rate of 3.2% (Büchler et al, 2003).

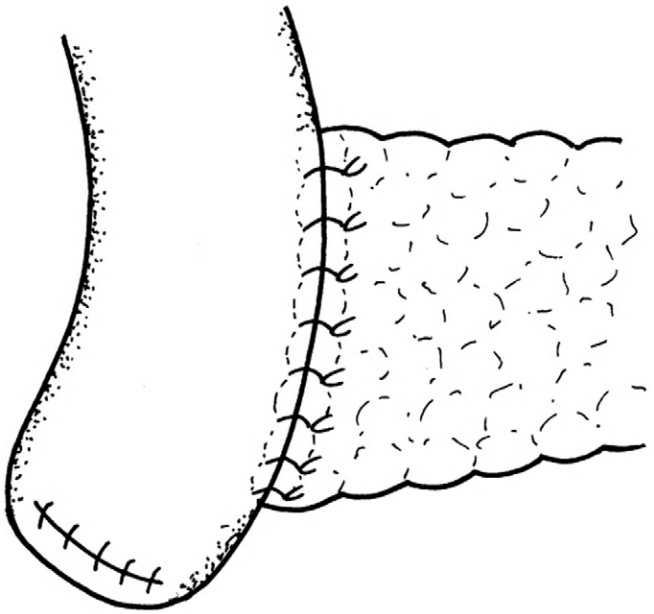


FIGURE 62A.12. Completion of the pancreatojejunostomy.

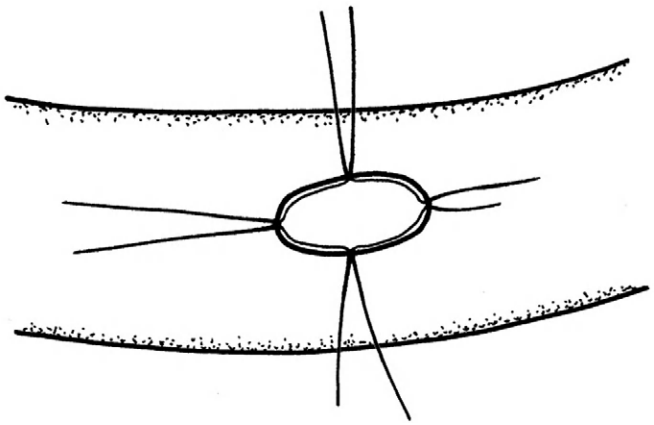


FIGURE 62A.13. Jejunal mucosal fixation stitches.

Bilioenteric Anastomosis

Unlike the pancreatoenteric anastomosis, fewer variations are used for a bilioenteric anastomosis, which is usually constructed in an end-to-side fashion with a single layer of sutures using monofilament absorbable sutures (PDS 5/0) with a C1 needle. This needle, with its smaller rounding radius, enables easier handling, especially within the confines of the bile duct, particularly when the caliber of the duct is small.

We position this anastomosis about 10 to 15 cm downstream from the PJ. The cut edge of the bile duct is freshened to obtain well-perfused healthy tissues, after which a small enterotomy is made at the antimesenteric border of the jejunal loop, with removal of a small cuff of mucosa. The protruding mucosa is then fixed at four quadrants of the enterotomy using 6/0 PDS sutures (Fig. 62A.13). These mucosa-fixation sutures ensure a full-thickness bite in the subsequent suture placement and thus guarantee a secured duct-to-mucosa coadaptation. The posterior suture layer is first constructed, with each individual suture held in clamps, until the entire suture row is completed and before knotting begins (Fig. 62A.14). This is then followed by the anterior suture row (Fig. 62A.15), and the final step is closure of the mesocolic opening around the jejunal limb.

Reconstitution of Gastrointestinal Continuity

Depending on whether a distal gastrectomy or PPPD is performed, the reconstruction ends either with a gastrojejunostomy or a duodenojejunostomy, respectively. Some concern has surrounded the question of whether an intact pylorus will lead to higher delayed gastric emptying (DGE) rates postoperatively following a PPPD; however, this controversy seems to have been finally laid to rest following the results of several controlled trials that to which we have previously alluded. Therefore, based on evidence available in 2004, it is apparent that pylorus preservation does not seem to increase the frequency of DGE (Horstmann et al, 2004).

The technique used to reconstitute GI continuity may have an impact on the incidence of DGE, however. One group speculated that a retrocolic reconstruction predisposes the jejunal limb to venous congestion and bowel edema, which can consequently retard recovery of jejunal peristalsis at the duodenojejunostomy (Park et al, 2003). Postoperative gastroparesis may also lead to temporary gastric distension, which can lead to angulation of the anastomosis because it lies relatively fixed through its retrocolic position (Horstmann et al, 2004).

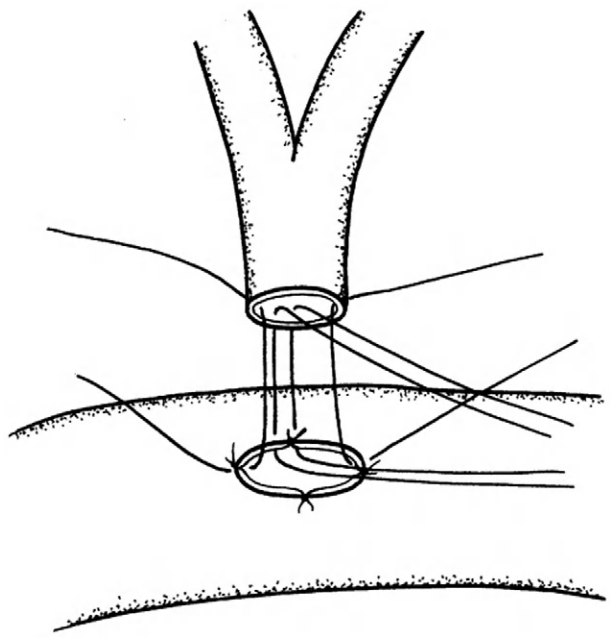


FIGURE 62A.14. Posterior suture row of the biliojejunal anastomosis in interrupted fashion.

Additionally, the close proximity of the duodenojejunostomy to the PJ also predisposes the occurrence of DGE in the event of a small PJ leak or transient postoperative remnant pancreatitis. Opponents to this theory have suggested that the real culprit is an antecolic reconstruction (Riediger et al, 2003) that predisposes the relatively fixed stomach to angulation or torsion. The risk of DGE caused by local inflammation is reduced by placing the duodenojejunstomy in the infracolic compartment through a separate mesenteric window, away from the pancreatic and biliary anastomoses, which lie in the supracolic compartment.

Our unit's philosophy is more in line with the first group, substantiated by the results of a retrospective review conducted in our center, in which we compared the outcomes following retrocolic placement of the duodenojejunostomy with those following an antecolic placement of the anastomosis. We found that the incidence of DGE was lower after using the second surgical strategy. After PPPD, we now routinely perform an antecolic end-to-side duodenojejunostomy about 50 cm downstream from the hepaticojejunostomy, using the transverse colon to splint the duodenojejunostomy away from the PJ. The anastomosis is constructed in two layers using monofilament absorbable sutures in a continuous fashion (PDS 4/0 or 5/0) (Fig. 62A.16).

Abdominal Drains and Nasogastric Tubes

Intraperitoneal drains have been placed in relation to the biliary and pancreatic anastomoses with the intention of controlling leakage of blood and biliary, lymphatic, or pancreatic secretions. Such a practice has been prophylactic in nature, and the reason for it stems more from habit than evidence. But this has been challenged by a randomized trial that addressed the value of drains following pancreatic resection and found that placement of drains did not translate into a reduction in surgical morbidity (Conlon et al, 2001). Rather, a significantly higher proportion of patients randomized to the drain group developed intraperitoneal sepsis, fluid collection, or fistula, although this trial was not sufficiently powered to determine whether the drain was the cause of these intraabdominal complications. Consequently, based on this trial alone, our unit has not found sufficient evidence for us to abandon this practice.

Our hesitancy to embrace a no-drain policy is further vindicated by the findings of a recently published meta-analysis of prophylactic drainage after GI surgery (Petrowsky et al, 2004). This evidence-based review found that drains do not reduce

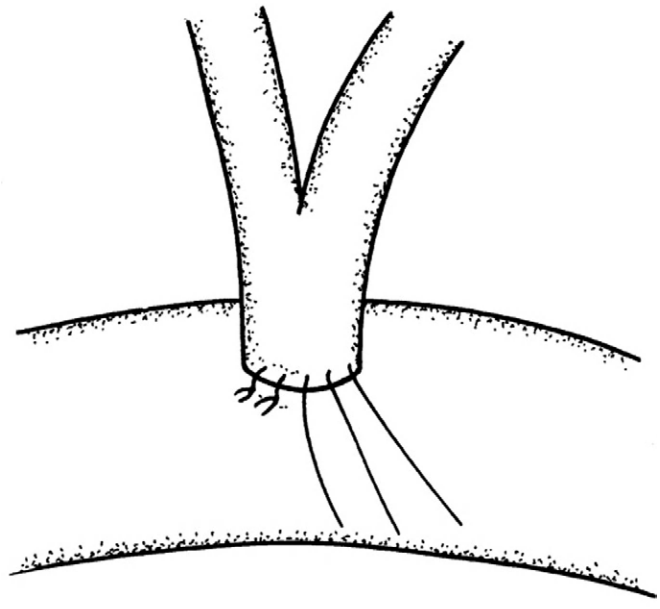


FIGURE 62A.15. Anterior suture row of the choledochojejunostomy.

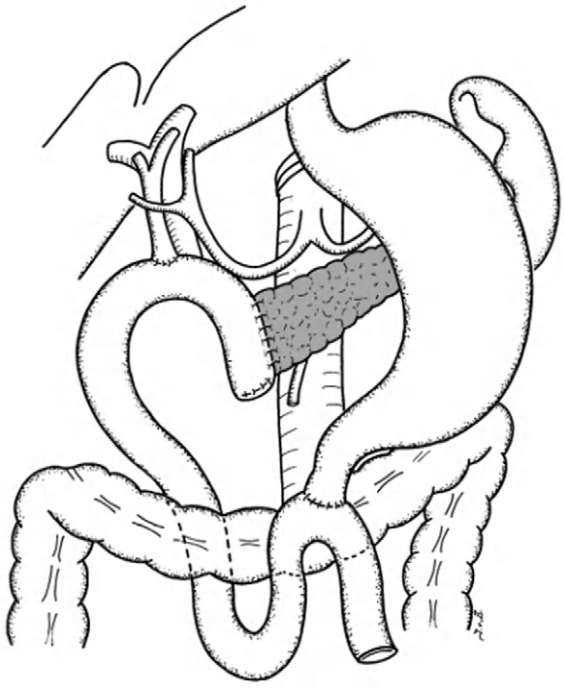


FIGURE 62A.16. Completion of the reconstruction following the pylorus-preserving pancreatoduodenectomy.

complications following hepatic, colorectal, or rectal resection with primary anastomosis, and drains should not be used following such procedures. With regard to many other GI procedures, including pancreatic resections, the jury is still out, and we have concluded that more well-designed trials are needed to clarify the role of prophylactic drainage. For our participation in a multicenter randomized (PANDRA) trial evaluating this issue, we routinely place two passive drainage tubes (Easy-flow; Dahlhausen & Company, Cologne, Germany): one below the diaphragm and the other in close proximity to the hepaticojejunostomy and the PJ.

We also routinely place nasogastric (NG) suction tubes for our patients during the operation and anesthesia, which are immediately removed at extubation. A meta-analysis on the need for NG decompression has quashed the long-held belief that routine NG decompression decreases the risk of postoperative nausea, vomiting, aspiration, wound dehiscence, and anastomotic leak (Cheatham et al, 1995). Instead, it was found that fever, atelectasis, and pneumonia were significantly less common, and days to first oral intake were significantly fewer, in patients managed without NG tubes. Although patients may develop abdominal distension or vomiting without an NG tube, this does not necessarily translate into an increase in complications or length of stay.

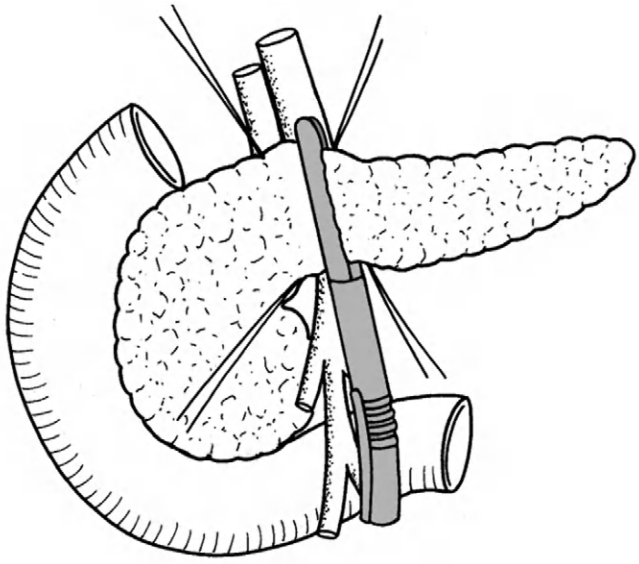


FIGURE 62A.17. Staple transection of the pancreas.

Distal Pancreatectomy

The surgical procedure of choice for tumors arising in the body or tail of the pancreas is the distal pancreatectomy. This operation entails the removal of that portion of the pancreas extending to the left of the midline, not including the duodenum and distal bile duct. The pancreas is usually divided to the left of the SMV-PV trunk, the exact line of transection depending on the location of the tumor.

Technique

Following a thorough examination of the peritoneal cavity, the gastrocolic ligament is divided sufficiently to allow full visualization of the pancreas to its tail and the hilum of the spleen. Extreme care is taken here to preserve the short gastric vessels and the gastroepiploic arcade. The point of division is selected in the proximal normal pancreas, and the overlying peritoneum is divided along the superior and inferior borders of the pancreas. Stay sutures are then placed on either side of the planned transection line on both the superior and inferior borders. A plane is then developed posterior to the pancreas by blunt dissection, aided by upward tension on the stay sutures, until the splenic vein (SV) is identified. The splenic vein is situated posterior to the pancreas and lies fairly deep in the pancreatic parenchyma distally. Therefore, if problems in identifying the SV are encountered, one suggestion is to identify the SV-PV junction under the pancreatic neck, which is technically easier, and subsequently follow the SV toward the spleen. The splenic artery can usually be located along the superior border of the pancreas. The artery and the vein are then individually encircled with vascular loops. Following vascular control, our preference is early division of the pancreas.

Management of the Pancreatic Remnant

Pancreatic fistula remains the most common surgery-related complication after distal pancreatectomy (Benoist et al, 1999; Ferrone et al, 2008). Many techniques have been described in the literature with regard to the management of the residual transected pancreatic parenchyma and the divided pancreatic duct to lower the risk of leak. These include direct duct ligation, enteric drainage, prolamine injection, sealing with fibrin glue, and transection with linear stapling devices. The plethora of surgical strategies described in the medical literature simply underlies the fact that no one technique has been convincingly shown to reduce the incidence of pancreatic leak consistently.

When the pancreas has a soft texture and is not too thick, we transect it with a linear stapling device (Fig. 62A.17). This device gives a staple line consisting of a triple row of closely placed staples. In all other cases, the pancreas is dissected by a knife, and the resection margin is closed with single PDS stitches; the pancreatic duct should be identified and closed by separate sutures. A meta-analysis comparing the safety of hand-sewn sutures versus staple closure of the pancreatic remnant after pancreatic left resection did not show a significant difference with regard to morbidity, including postoperative fistula (Knaebel et al, 2005). Results of a European multicenter randomized trial comparing the two techniques over the last several years will be available shortly (Diener et al, 2008a).

Alternatives to these standard techniques are to cover the pancreatic remnant with omentum, small bowel, or the falsiform ligament and to perform a PJ to the left remnant. However, none of these techniques has been evaluated in larger randomized trials.

Splenic Preservation

Conventionally, the spleen has been removed en bloc with distal pancreatectomy. This was believed to be necessary because of the close relationship of the splenic artery and vein to the body of the pancreas; splenic preservation might compromise the oncologic resection (Shoup et al, 2002). Furthermore, this was thought to be technically simpler. Splenic preservation can be performed either with the division of the splenic artery and vein or with preservation of the entire length of both vessels. The paramount prerequisite in the former surgical approach is preservation of the gastrosplenic vessels to ensure splenic perfusion

and allow venous drainage. In the latter technique, the splenic artery and vein must be uninvolved by tumor. Because of the important immune function of the spleen, it is not surprising that the incidence of infectious complications that require intervention is significantly higher in the splenectomy group (Shoup et al, 2002). More importantly, Schwarz and colleagues (1999) found that in their patients undergoing resection of pancreatic adenocarcinoma with curative intent, the median actuarial survival was 12.2 months with splenectomy versus 17.8 months without splenectomy. Such an adverse effect of splenectomy on survival was also evident when it accompanied surgical resection for gastric and colon cancer. Based on the available evidence, we concur with Conlon and colleagues (2001) in concluding that splenic preservation should be attempted in patients with low-grade malignancies or other more indolent tumors of the pancreatic body/tail, but we feel that splenic preservation may compromise oncologic clearance if performed for pancreatic adenocarcinoma.

Our preference is to attempt to preserve the splenic artery and splenic vein to reduce the risk of splenic necrosis and abscess formation; because splenic perfusion based on the short gastric vessels alone has been shown to be potentially inadequate (Gurleyik et al, 2000). Following division of the pancreas, the distal stump is elevated and rotated gently to the left. Multiple small, short branches of the splenic artery and vein are then identified and clipped serially with hemostatic clips and cut. The dissection proceeds from the proximal to distal pancreas, until the tail of the pancreas can be separated from the splenic hilum (Fig. 62A.18). This separation of the splenic vein from the pancreas can only proceed in the direction of the spleen because the vein has already divided into small vessels that can easily be injured at the level of the hilum. On the other hand, isolation of the pancreas from the splenic artery is described to be easier when performed from the hilum toward the pancreatic head (Jovine et al, 2004). This is also a less tedious task because there are fewer branches from the splenic artery, and they are all on one side. Any vessel injuries can be repaired by suturing with monofilament 5/0 vascular sutures. If attempts at hemostasis of such vascular injuries are unsuccessful, we divide the splenic pedicle. We avoid mobilizing the spleen medially into the operative field, as this step is unnecessary and carries the risk of iatrogenic splenic injury.

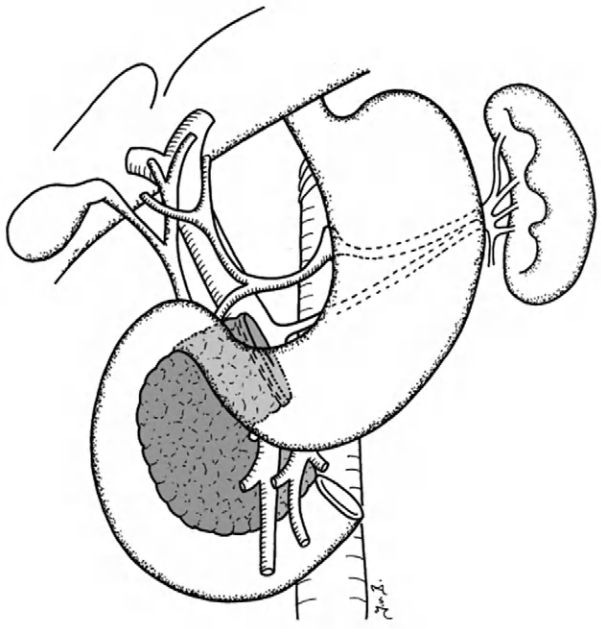


FIGURE 62A.18. Spleen-preserving distal pancreatectomy.

Distal Pancreatectomy with Splenectomy

The division of the gastrocolic ligament is extended to include the division of all the short gastric vessels. The splenic artery is then identified and divided close to its origin, thereby removing the surrounding fibro-fatty tissues. Based on the surgeon's discretion, the subsequent dissection can be performed in either a retrograde or antegrade fashion. For the former approach, the lienorenal ligament is cut and the spleen is retracted inferiomedially. The surgical specimen is then dissected off the retroperitoneum in a plane just superficial to the left renal vein and the left adrenal gland. If the planned transection margin lies very medially, the inferior mesenteric vein may have to be ligated and divided. The pancreas is then transected with a stapling device. For an antegrade approach, the peritoneum overlying the superior and inferior borders of the pancreas is incised. A plane is then developed by blunt dissection to create a tunnel deep to the SV, after which the jaws of the stapling device are insinuated across the gland, encompassing the SV to transect the gland and the vein en masse. The distal stump is then elevated to allow the separation of the specimen off the retroperitoneum as the dissection proceeds to the left. Drains are then placed near the pancreatic remnant, and the abdomen is closed.

We routinely perform lymphadenectomy when the indication for the operation is a malignant tumor of the body or tail. This involves excision of the nodal tissues along the common hepatic artery, left gastric artery, celiac axis, and along the SMV, as well as the peripancreatic and retroperitoneal lymph nodes and the left adrenal gland (Kleeff et al, 2007). A similar approach called the *radical antegrade modular pancreatosplenectomy* (RAMPS) allows a more comprehensive lymphadenectomy of the N1 nodes and reduces the risk of positive posterior resection margins (Strasberg et al, 2003).

Segmental Pancreatectomy

Letton and Wilson (1959) were the first to describe the technique of segmental pancreatectomy for two cases of traumatic transection of the pancreatic isthmus. Following a central segmental resection, the cephalic stump was oversewn, and a Roux-en-Y jejunal limb was constructed and anastomosed to the distal stump. Pancreatic surgeons were quick to recognize the versatility of this procedure and have since adapted it to the treatment of benign or borderline lesions of the pancreas situated in the neck. Benign or low-malignancy tumors arising from this region present a unique challenge. Conventionally, if the lesion is small, enucleation would be the optimal strategy. However, if the lesion measures more than 2 cm, or when it is situated deep within the parenchyma such that damage to the pancreatic duct becomes a real risk, the surgeon may have to resort to either an extended distal pancreatectomy or PD simply to remove the lesion. Such operative strategies for a small lesion come at the cost of a significant waste of normal tissue, not to mention the inherent risk of morbidity and mortality that accompanies such extended pancreatectomies.

Segmental pancreatectomy represents an organ-preserving extirpation technique that offers the advantages of avoiding the morbidity and mortality associated with PD; preserving splenic function by avoiding splenectomy, which often accompanies distal pancreatectomy; and preserving maximal pancreatic endocrine and exocrine function (Efron et al, 2004). Perhaps the most beneficial attraction seems to be the excellent preservation of endocrine function. This is not surprising because the risk of diabetes is proportional to the extent of resection and length of follow-up observation (Warshaw et al, 1998). On the other hand, the prime concern was whether pancreatic fistula rates would be significantly higher with two possible sources of pancreatic leakage. In the literature, the frequency of pancreatic leak in segmental pancreatectomy ranged from 14% to 30%, whereas in distal pancreatectomy, it ranged from 5% to 15%. These findings notwithstanding, in almost all reports patients do well with conservative management.

Iacono and colleagues (1998) succinctly summarized the prerequisites that allow segmental pancreatectomy to be considered as a reasonable approach: small lesions (<5 cm in diameter) (1) that are benign or low-grade malignant tumors (2) located in the neck or its contiguous portion (3), and a distal pancreas stump of at least 5 cm in length (4). A critical adjunct is the availability of frozen-section examination to confirm that the lesion is benign and to verify a free resection margin (Müller et al, 2006).

Technique

The lesser sac is entered, and the anterior aspect of the pancreas is widely exposed by dividing the adhesions between the posterior surface of the stomach and the pancreas. This is followed by intraoperative pancreatic ultrasonography to better delineate the lesion and to exclude concomitant lesions that may necessitate a change of plan. The pancreas is then elevated off the SMV-PV trunk. Stay sutures are placed in the superior and inferior pancreatic margins to indicate the proximal and distal limits of division and to aid in the subsequent dissection of the pancreas from the splenic vein. The pancreas is then divided proximally with a vascular stapler at least 1 cm from the lesion. The distal stump is then gently retracted toward the left to allow the cautious and tedious process of freeing the splenic vein from the posterior surface, clipping and cutting all the fine venous tributaries lying between the splenic vein and the pancreas. The pancreas is then divided distal to the lesion with a blade (Fig. 62A.19), and a specimen is sent for analysis and margin assessment.

Our usual technique of reconstruction follows that described in most other series and consists of the closure of the proximal stump and a Roux-en-Y PJ for the distal stump as described. The duct in the proximal pancreatic stump is closed by PDS single stiches, and the resection margin is covered by a serosal patch by apposing the serosa of the jejunal limb to the stump and taking seromuscular bites of the jejunum and the pancreatic capsule (Figs. 62A.20 to 62A.24).

However, in cases in which stenosis or obstruction of the proximal pancreatic duct is suspected, we prefer to perform jejunal anastomosis for both the proximal and distal stumps. Such proximal ductal abnormalities can be rather prevalent in patients with chronic pancreatitis; therefore, by anastomosing the proximal stump to the jejunum, an alternative outflow route is created for the pancreatic secretions. We also prefer a double anastomosis when we have doubts about obtaining a secured stapled closure, such as when the proximal pancreas is found to be large and bulky.

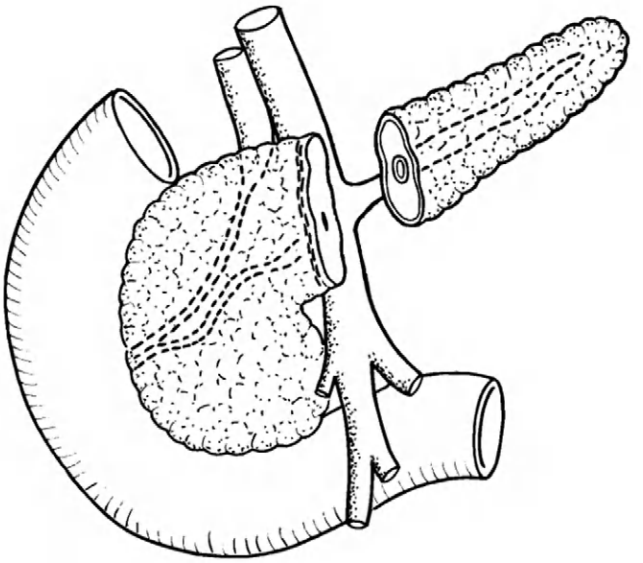


FIGURE 62A.19. Excision of a segment of the pancreas with identification of the underlying splenic vein prevents iatrogenic injury to the vein.

A jejunal Roux limb is created by dividing the proximal jejunum 15 to 20 cm past the ligament of Treitz. This is then brought to the supracolic compartment in a retrocolic fashion, through a mesenteric window created on the left side of the middle colic vessels. The distal pancreatojejunal anastomosis is

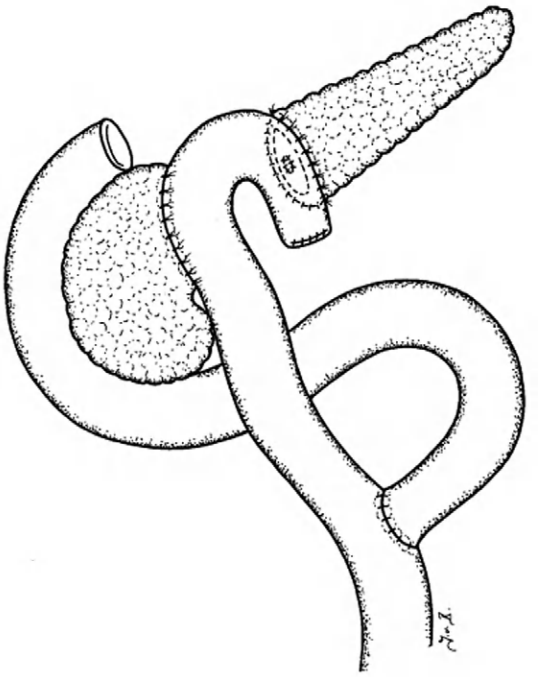


FIGURE 62A.20. Following a two-layer pancreatojejunostomy to the distal stump, a serosal patch is performed on the stapled end of the proximal stump.

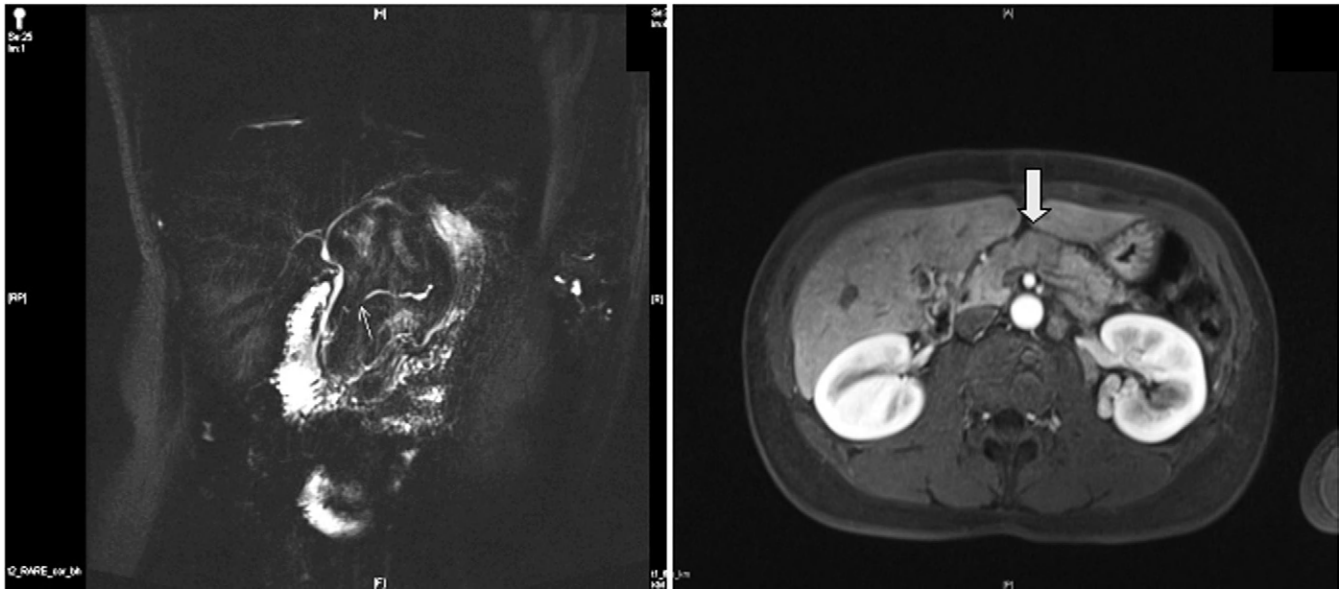


FIGURE 62A.21. Segmental chronic pancreatitis secondary to trauma with stenosis of the pancreatic duct. The patient presented with recurrent pancreatitis.

constructed first in the same two-layer fashion as previously described (see Management of the Pancreatic Remnant). This is then followed by the proximal anastomosis using the same jejunal Roux limb. The reconstruction is completed by an end-to-side jejunojejunostomy, and drains are placed.

Total Pancreatectomy

In the 1960s and 1970s, dissatisfaction with the early results of PD for cancer of the head of the pancreas led surgeons to look for an alternative operation. Total pancreatectomy (TP) was proposed by some to be a rational choice for several reasons: It can eliminate multifocal disease, achieve wider resection margins, and achieve a more extensive lymphadenectomy. It also avoids complications emanating from the pancreatic remnant. However, recent evidence has shown that multicentric disease is actually uncommon, seen only in perhaps 9% of cases (Karpoff et al, 2001). Furthermore, randomized trials on extended lymphadenectomy have shown that no tangible benefits could be reaped from such procedures, especially because the lymph nodes around the body and tail of the gland are rarely involved with metastatic disease from a cancer of the pancreatic head. Conversely, removal of the entire pancreas is associated with severe metabolic consequences as a result of the loss of pancreatic endocrine and exocrine functions. One of the more serious metabolic aftermaths is brittle diabetes and severe recurrent hypoglycemia. Indeed, Yeo and associates (1995) have shown that the median survival for patients who had TP performed for pancreatic head cancer was 10 months, as opposed to 16 months in the PD group. Likewise, researchers at Memorial Sloan-Kettering

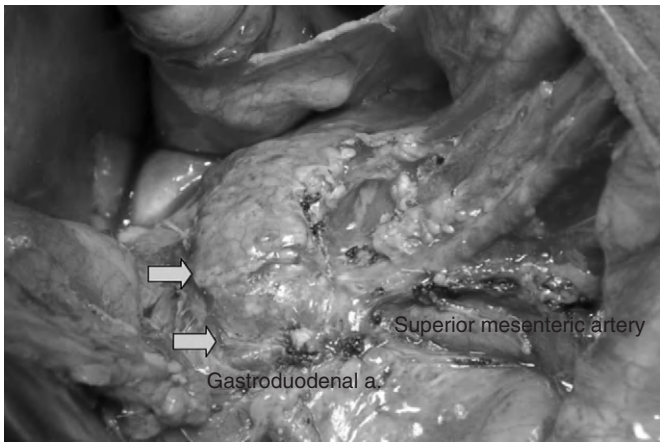


FIGURE 62A.22. Intraoperative finding of segmental inflammation secondary to trauma. The gastroduodenal artery (*a.*) and the superior mesenteric vein are demonstrated. The *arrows* indicate the margin of the inflamed area.

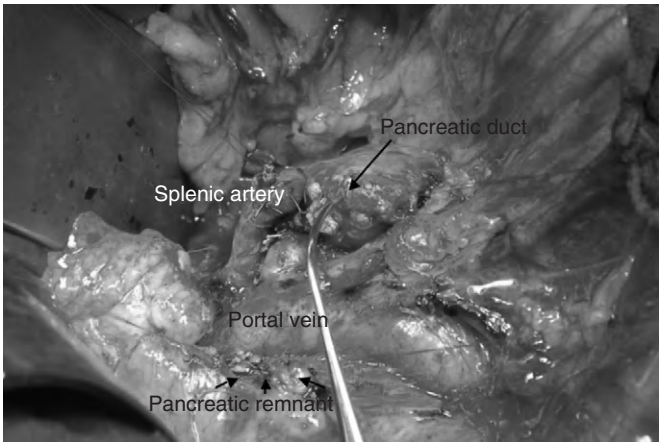


FIGURE 62A.23. Intraoperative finding after the segmental resection has been performed. The resection margin on the right has been closed with monofilament absorbable polydioxanon single stitches; the pancreatic duct is to the left.

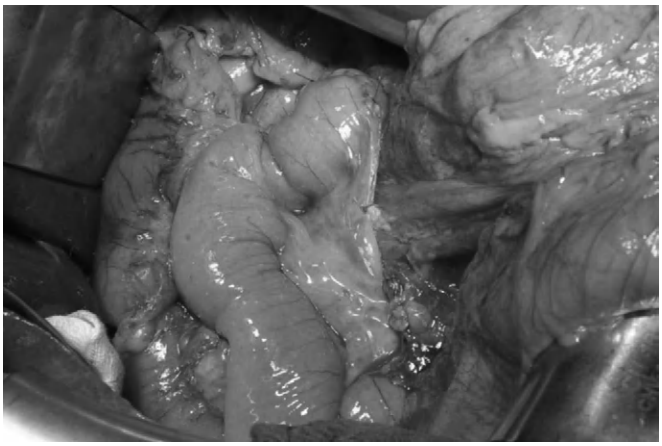


FIGURE 62A.24. After reconstruction, the end-to-side pancreatojejunostomy and the coverage of the resection margin at the pancreatic head with a serosal layer with the same jejunal loop can be seen.

Cancer Center (MSKCC) have shown that patients with TP had a significantly lower overall survival compared with a contemporary cohort of patients who underwent PD and distal pancreatectomy (Karpoff et al, 2001). The length of stay was markedly prolonged, emphasizing the greater morbidity of this procedure. No apparent effect of positive margins on outcome was shown, and hence it was concluded that a positive margin of resection at the time of PD should not compel the extension of the resection to a TP.

We are of a different opinion, as we had previously shown that a curative resection (R0) is the single most important factor in determining outcome in patients with pancreatic adenocarcinoma (Wagner et al, 2004). Hence, positive resection margins on frozen-section surgical margin analysis remains one of the few indications for us to proceed with a TP. Similarly, longitudinal involvement of the pancreatic duct in cases of intraductal papillary mucinous neoplasm (IPMN) is another reason to cut back until lesion-free margins are obtained; on some occasions, TP becomes necessary (see Chapter 57). Recent evidence has also shown that the presence of atypia or carcinoma in situ at the ductal resection margin was not associated with a poor outcome (D'Angelica et al, 2004), suggesting abandonment of this obsession with clear margins in cases of IPMN. However, our center and others (Gigot et al, 2001) have held that surgical resection should be tailored to the longitudinal spreading into the pancreatic duct as established by routine frozen section of the surgical margins. It will be interesting to follow this debate as more evidence emerges. Another indication for TP is the presence of an atrophic, soft, friable pancreatic remnant that does not hold sutures. Most recent reports demonstrate that morbidity and mortality of TP have decreased dramatically and that the perioperative and oncologic long-term outcome are comparable to standard pancreatic resections (Müller et al, 2007; Reddy et al, 2009).

Besides rendering a patient diabetic, TP also has a nutritional toll as a consequence of the loss of exocrine function, leading to persistent diarrhea and steatorrhea. If TP is accompanied by gastric resection by a standard Whipple procedure, further nutritional compromise will ensue from decreased dietary intake as a result of the loss of gastric reservoir function. It is our center's policy to preserve the pylorus whenever we perform a TP, unless tumor infiltrates into the proximal duodenum or suspicious peripyloric nodes are present that preclude an R0 resection if left in situ. This philosophy is the result of a study comparing patients who had a pylorus-preserving TP with those who had a classic TP in which a distal gastrectomy was performed. Patients in the first group showed a significantly faster rate of recovery of body weight compared with those in the second group, and no difference in survival was reported between these two groups (Wagner et al, 2001). Sugiyama and Atomi (2000) also demonstrated improved recovery of body weight and serum albumin at 6 months after surgery following pylorus-preserving TP, with a low incidence of persistent diarrhea and lower hyperalimentation requirements. Not surprisingly, the postoperative QOL was somewhat better in the pylorus-preserving group than in those who had a standard TP (Sugiyama & Atomi, 2000).

Technique

In cases of main duct IPMN, an en bloc total pancreatectomy without transaction of the pancreas may be necessary. In this case, the mobilization of the pancreatic head and the transection of the jejunum and duodenum are performed first. The pancreatic tail is mobilized together with the spleen, and the dissection of the pancreatic mesentery along the PV and the SMA is the last step of resection (Werner & Büchler, 2010).

In cases with a positive pancreatic resection margin, we would already have resected the pancreatic head along with the adjoining duodenal loop and the distal CBD. The distal duodenum is then delivered into the infracolic compartment after taking down the ligament of Treitz, and the proximal jejunum is transected to complete the resection of the duodenum. The pylorus is preserved in the same manner as in a PPPD. If a TP is necessary because of cancer involvement of the distal stump, we would resect the pancreas together with the spleen to ensure radicality. The short gastric vessels are divided, the splenic artery is divided at its origin, and the splenic vein is divided at its confluence with the SMV-PV trunk with a vascular stapler or suture closure. The distal pancreatic stump and underlying splenic vein are retracted to the left, and the specimen is dissected off the retroperitoneum toward the spleen. The inferior mesenteric vein is ligated and divided, and the lienorenal ligament is divided.

For more low-grade tumors, such as IPMNs, we would attempt to preserve the spleen. In this case, we would preserve all the short gastric vessels in the event that the splenic vessels need to be divided. This is followed by the tedious process of ligating or clipping and cutting the multiple branches that connect the splenic vein and the splenic artery to the pancreas in an attempt to preserve both splenic artery and vein. Reconstruction after TP consists of an interrupted end-to-side, single-layer hepaticojejunal anastomosis with a retrocolic jejunal limb. An antecolic end-to-side duodenojejunostomy is then constructed about 50 to 60 cm downstream from the bilioenteric anastomosis (Kulu et al, 2009).

Transduodenal Resection of the Papilla of Vater

All ampullary tumors should be resected. Such a sweeping statement governing the strategy of managing such neoplasia stems from several observations. The most common benign tumors of the ampulla of Vater are villous and tubulovillous adenomas, and although they are classified as benign, they are truly premalignant neoplasms whose malignant transformation

can only be confidently prevented by their complete removal. These tumors are also highly deceptive; consequently, distinguishing adenoma from carcinoma becomes an exceedingly difficult problem. Adenomas are known to harbor occult foci of carcinoma, with a reported incidence of coexistent carcinoma in duodenal or ampullary tumors ranging from 35% to 60% (Martin & Haber, 2003). Furthermore, preoperative endoscopic diagnosis is notoriously unreliable. False-negative results from endoscopic biopsies have been described in 25% to 60% of patients with carcinoma (Posner et al, 2000); thus complete excision is the only sure way of establishing whether an ampullary adenoma harbors undetected foci of carcinoma. Finally, among the various types of periampullary cancers, overall 5-year survival is greatest for ampullary cancers and duodenal cancers (Sarmiento et al, 2001). A recent series from de Castro and associates (2004) reported that overall 5-year actuarial survival of patients with adenocarcinoma after PD was 37%, which is considerably superior to that of patients with pancreatic adenocarcinoma. Another recent series echoed this finding; the authors found that survival after resection of ampullary cancer was far better than that after resection of other periampullary cancers, with a 5-year survival rate of 36% as opposed to 14% in the other group (Bettschart et al, 2004). Furthermore, the resectability rate of ampullary carcinoma is higher than the other periampullary tumors, with a 92% resection rate reported in this series. Adopting an aggressive approach toward ampullary tumors therefore appears justifiably warranted.

Although it is generally agreed that PD is the operation of choice for ampullary adenocarcinoma, the ideal treatment for benign neoplasms, with or without dysplasia, and lesions with microinvasion remains controversial. Some have argued that a radical resection should also be applied to benign lesions, citing a high incidence of malignancy in ampullary tumors and an increased tendency for these lesions to recur after local excision. Recurrence of villous tumors after transduodenal excision (TDE) is reportedly 32% at 5 years and 43% at 10 years; more importantly, it may recur as invasive cancer (Farnell et al, 2001). An added bonus is that PD obviates the need for endoscopic surveillance during the postoperative follow-up in cases of sporadic adenomas. Detractors, however, believe that TDE is an acceptable and adequate form of treatment with markedly decreased morbidity and mortality rates compared with radical resection. Posner and colleagues (2000) have shown that TDE of benign ampullary tumors, even those with varying degrees of dysplasia, can have low recurrence rates. Beger and colleagues (1999) also observed that TDE of lesions with only submucosal invasion does not compromise long-term survival. The transduodenal approach is also associated with a significantly shorter operation time, a significantly lower incidence of surgery-related morbidity and, consequently, a significantly shorter postoperative hospital stay (de Castro et al, 2004). Even after recurrence, most benign lesions do not lead to the patient's demise, and many can be treated endoscopically or with reexcision.

The emergence of endoscopic ampullectomy has added a new dimension to the issue of local resection. It is an attractive alternative for patients unfit for general anesthesia as a result of prohibitive comorbidities or for those who refuse surgery. The main limitation is that this option is restricted to a few select centers with expertise in interventional endoscopy. With the low incidence of ampullary adenomas, combined with the more widespread and established availability of surgical resection at most medical centers, the number of endoscopists who have accumulated a sizable experience in this technique will remain low. Therefore, at least in the near future, TDE is unlikely to be relegated as a result of the emergence of endoscopic ampullectomy.

We have established certain indications for which TDE would be a reasonable option (Paramythiotis et al, 2004), such as large (≥2 cm) villous or tubulovillous adenomas of the papilla, adenomas of the papilla with high-grade dysplasia, and adenomas with carcinoma in situ. Beger and colleagues (1999) have also offered TDE for pT1N0M0/G1 and G2 cancer of the mucosa with the caveat of additional lymphadenectomy of the anterior and posterior nodal groups of the pancreatic head and the supraduodenal lymph nodes. However, even in pT1 tumors, lymph node involvement has been observed in 6% to 10% of patients (Klein et al, 1996). Hence, we would recommend PD even for superficially invasive cancer of the ampulla, especially with the good safety profile of this procedure in experienced hands. However, in patients who are unfit for PD, we concede that TDE offers a chance for good palliation and even cure.

As with military operations, good planning prior to surgical operations requires good intelligence. We consider the ERCP critical in the preoperative workup. Besides being able to obtain tissues for histologic diagnosis, the endoscopic visualization may give some clues as to the biologic behavior of the lesion. Reliable endoscopic signs that indicate the likelihood of malignant transformation have been described such as induration and rigidity of the papilla on probing, ulceration, and a submucosal mass effect suggestive of tumor extension into the duodenal wall (Martin & Haber, 2003). Although not conclusive, the presence of such signs will certainly raise the index of suspicion. With its ability to clearly delineate the layered anatomy of the duodenal wall, EUS can identify the depth of tumor invasion with an accuracy of 75% to 85% (see Chapter 14; Posner et al, 2000). If a T2 tumor (invasion of duodenal wall) or involvement of contiguous structures is clearly demonstrated on EUS despite a negative biopsy, we would proceed with a radical procedure.

Technique

Because the ampulla is absent in nearly two thirds of patients (Sarmiento et al, 2001), it would be more often correct anatomically to use the term *TDE of the papilla of Vater.* The abdomen is entered through a midline incision in case a conversion to a more radical procedure is required. A generous Kocher maneuver is then performed to completely mobilize the second part of the duodenum, and three to four stay sutures are placed alongside the antimesenteric border on its anterior aspect to help elevate the duodenum toward the abdominal wound to facilitate the duodenotomy. A 6- to 8-cm long longitudinal duodenotomy is then made in a lazy-S fashion along the antimesenteric border opposite the pancreas; the incision is kept open with stay sutures (Fig. 62A.25). Circumferential stay sutures, using monofilament absorbable PDS (5/0), are placed about 1 cm beyond the gross border of the lesion and are kept long. Excision of the lesion is undertaken with electrocautery to minimize bleeding, along a resection margin just inside the circle formed by the circumferential stay sutures. A heavy stay suture is placed through the tumor mass to allow the tumor and the papillary region to be drawn upward. The dissection is carried around the tumor area in a stepwise fashion, and the incision must allow a full-thickness excision of the tumor that includes the biliopancreatic ductal junction. Ductal resection can be safely performed up to 1 cm (Nikfarjam et al, 2001); this is to

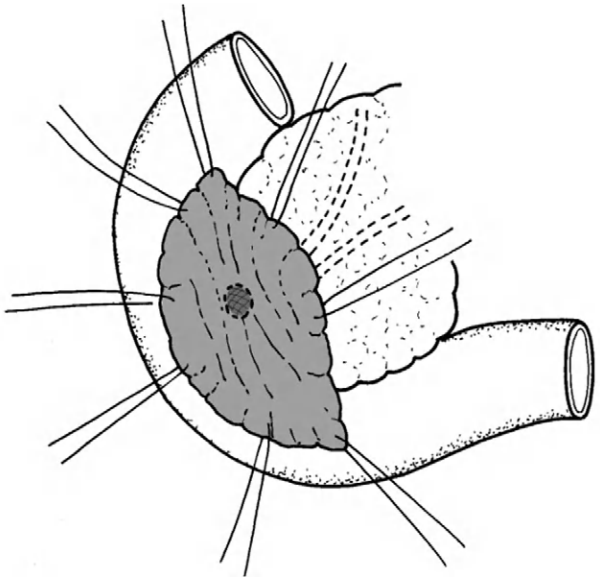


FIGURE 62A.25. A generous duodenotomy and the use of stay sutures allow good access to the papilla.

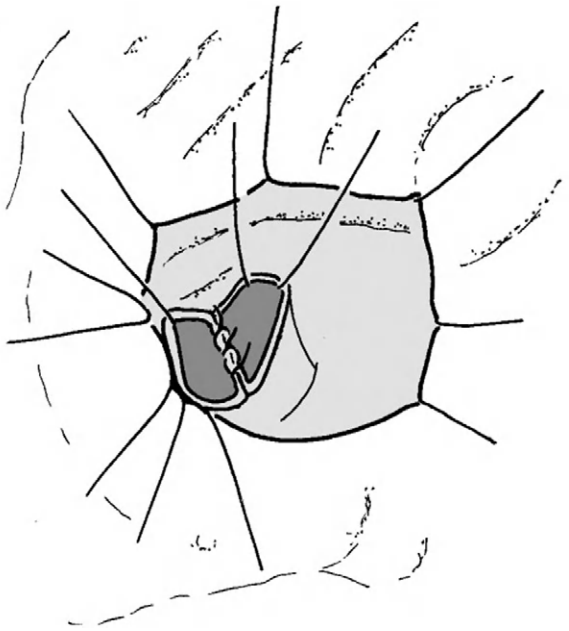


FIGURE 62A.27. Apposition of the pancreatic duct and bile duct to form a common septum.

safeguard against any possible tumor infiltrations of the bile and pancreatic ducts. As each duct is identified, stay sutures are placed through the ductal wall following complete transection (Fig. 62A.26). Following complete excision, the specimen is carefully oriented for the pathologist to facilitate frozen-section examination. If clear margins are reported, we would proceed with the reconstruction, which begins with the suturing together of the pancreatic and common bile ducts in a common septum (Fig. 62A.27). This is followed by the reimplantation of this new common channel back into the duodenal wall with 5/0 monofilament absorbable sutures to approximate the duodenal wall to the joined pancreatic and bile duct openings (Fig. 62A.28). Patency of the ducts is ensured before closure of the duodenotomy. The duodenal opening is then closed in two layers (Fig. 62A.29), and drains are routinely placed in the vicinity of the duodenotomy.

Postoperative Management

Following operation, we routinely monitor our patients in the intensive care unit or the high-dependency unit for the first 24 hours. The NG tube is usually removed at extubation or, at the latest, within the first 12 hours after extubation, when the patient has regained a reasonable level of consciousness and has an intact cough reflex. Intravenous antiemetics are given prophylactically. The abdominal drains are usually removed within the first 3 days after operation, based on the volume and the amylase/lipase content (Bassi et al, 2005; Molinari et al, 2007).

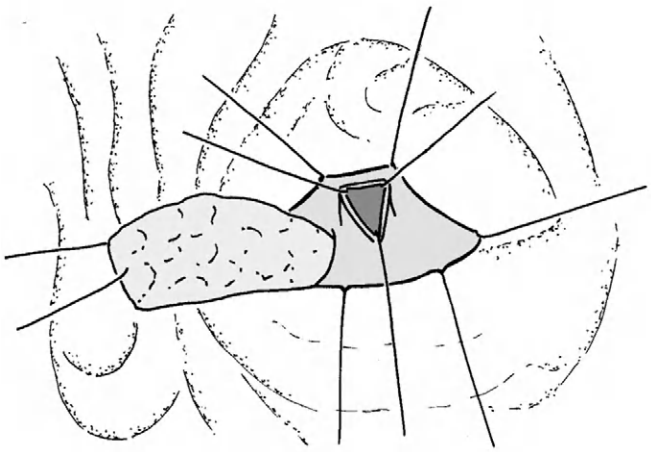


FIGURE 62A.26. Ductal sutures are placed once each duct is identified.

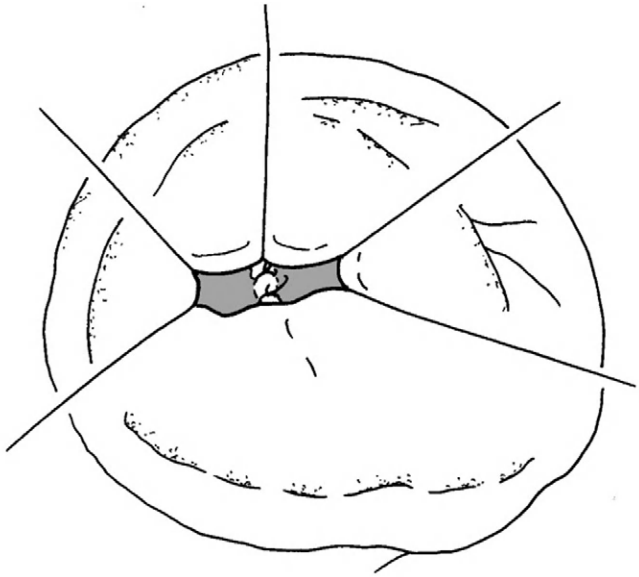


FIGURE 62A.28. Reimplantation of the ducts to the duodenal mucosa.

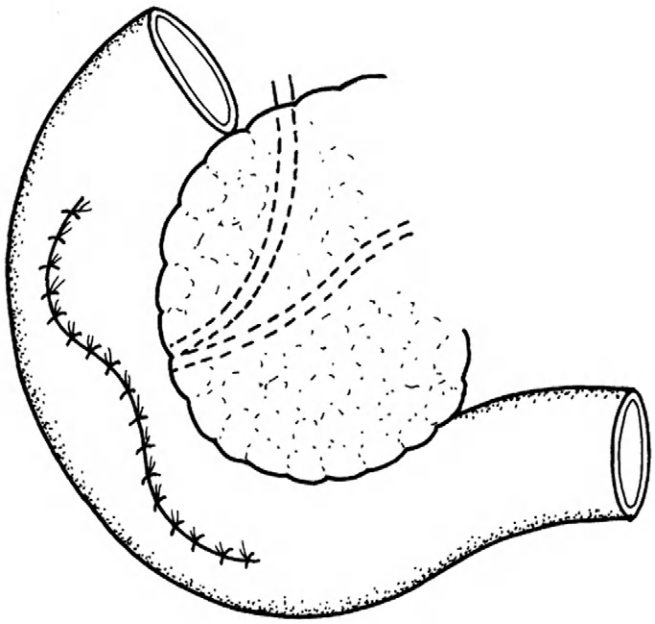


FIGURE 62A.29. Closure of the lazy S–shaped duodenotomy in two layers.

However, if the volume is excessive (>700 mL/day), the drains should be kept in place. If the fluid amylase level is three times the serum amylase level or higher, the drains are kept in and the patient is treated as for a pancreatic leak.

The issue of postoperative nutritional support has been a popular topic for research, which seems justified, since many patients with pancreatic disease present with significant weight loss. Two issues are critical with regard to the provision of nutrients postoperatively: *timing* and *method* of administration. Lewis and colleagues challenged the long-held practice of "nil by mouth" after GI surgery and conducted a systematic review of the topic and a meta-analysis of controlled trials. They showed that early feeding within 24 hours after surgery, whether by mouth or directly into the small bowel, can significantly reduce both the risk of any type of infection and the mean length of hospital stay. Risk reductions were also seen for anastomotic dehiscence, wound infection, pneumonia, intraabdominal abscess, and mortality, but these failed to reach significance.

On the question of the ideal route of administration, investigators at MSKCC conducted a prospective randomized trial of early enteral feeding (EEN) with an immune-enhancing formula in patients with upper GI malignancies. They found that EEN via a jejunostomy tube did not provide any benefit over postoperative crystalloid support in well-nourished patients (Heslin et al, 1997). A more recent publication echoed similar findings. Braga and colleagues (2001) observed that EEN did not improve outcome compared with total parenteral nutrition (TPN) in the overall population; however, they did find that in a subgroup of malnourished patients, EEN was associated with a significantly shorter length of stay. This was probably secondary to a lower overall complication rate, particularly the rate of infectious complications—noted in the EEN group compared with the TPN group. The prevalence of glucose and electrolyte disturbances was also lower during EEN than during TPN. In addition, researchers were able to demonstrate better gut oxygenation with EEN, not to mention significant cost savings compared with TPN. This makes EEN the ideal method for nutritional support, albeit in a selective manner.

EEN is not without risks, however. We previously demonstrated a significantly higher incidence of DGE in the enteral nutrition (EN) group compared to the no-EN group (Welsch et al, 2010). Furthermore, the use of a feeding jejunostomy tube is itself subject to the risk of adverse events, including tube dislocation, blockage, and leakage. Looking at the risk/benefit ratio, we agree with Braga and colleagues that the use of EEN should be targeted selectively at the group of patients with malnourishment, defined as the involuntary weight loss of more than 10% of the patient's usual body weight in the preceding 6 months. In general, 25 to 30 kcal/kg/day and 1.2 to 1.5 g/kg/day of protein are reasonable goals in these patients (Sampliner, 2001). TPN is used when nutritional goals cannot be met with enteral feedings because of GI dysfunction.

On the other hand, positive effects have been demonstrated by mere institution of early oral intake. In the group randomized to clear liquids *ad lib* after surgery, followed by a soft diet for patients who can tolerate 500 mL of liquid. Steed and colleagues (2002) showed that length of stay was significantly reduced, but the rates of ileus, emesis, and morbidity remained identical with the control group.

Clear liquids may be served to the patient following extubation on the first postoperative day. Thereafter, the amount and type of oral intake is progressively tailored, according to the patient's tolerance. Most of our patients are able to tolerate solids by the third or fourth postoperative day. Oral feeding is suspended or reverted back to a liquid-only diet if the patient vomits, and the NG tube is reinserted if the patient vomits on more than one occasion.

Blood glucose level must be closely monitored, with 4 to 6 hourly blood glucose level measurements for the first 24 to 48 hours. For patients who had a TP, blood glucose was regulated with intravenous administration of insulin. After starting oral food intake, patients received either semi–long-acting insulin or a combination of long-acting insulin as baseline therapy with premeal short-acting insulin. This must be done in consult with an endocrinologist and it may entail transfer of the patient to the endocrine unit once surgically fit for discharge. Patients should also be taught self-monitoring of their blood sugar and self-administration of insulin by the diabetic nurse educator.

Following TP, pancreatic enzyme substitutes are also be prescribed to this group of patients to treat their expected exocrine insufficiency. Although many patients complain of some form of diarrhea, this symptom resolves rapidly with high-dose enzyme substitution (Müller et al, 2007; Wagner et al, 2001).

Epidural analgesia or patient-controlled analgesia is continued for the first 72 hours. Oral analgesia is started concurrently once the patient can tolerate oral intake. Active chest physiotherapy with incentive spirometry should commence on the first postoperative day. Abdominal binders are occasionally provided for patients to minimize wound pain during deep-breathing exercises. Patients must be assisted to sit out of their beds on the first postoperative day, and a graded mobilization exercise regimen will allow the patient to begin limb exercises before progressing to supervised mobilization and finally to independent mobilization. Urinary catheters are removed following the discontinuation of the epidural analgesia. All patients who had their spleen removed should be vaccinated against *Streptococcus pneumoniae* and *Hemophilus influenzae* type B.

CONCLUSION

In the short but illustrious history of pancreatic surgery, pancreatic resection has evolved from a procedure synonymous with high mortality rates and poor quality of life for the survivors to one that is now recognized as the standard of care because of its vastly improved safety profile and efficacy. Modern pancreatic resection is one in which the extent of resection can be tailor made to the individual needs of the patient based on the disease process. All these are the fruits of hard work and research over the last century in the areas of surgical technique refinements, perioperative care, and diagnostics, just to name a few. The management of patients with pancreatic diseases will continue to require a multispecialty approach, with the surgeon in a central and coordinating role.

Pancreatic resection is now an accepted form of therapy for a large spectrum of pancreatic diseases, both benign and malignant. In sharp contrast with the nihilistic views that permeated the profession during the 1970s, the medical profession and patients alike have now recognized that pancreatic resection is a worthwhile undertaking, and that it is able to cure sometimes, and with regard to pancreatic cancer, to relieve often.

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CHAPTER 63B

Palliation of pancreatic and periampullary tumors

Dirk J. Gouma

OVERVIEW

Pancreatic and periampullary tumors are the fifth most common cause of cancer-related death in the Western world (DiMagno et al, 1999; Greenlee et al, 2000). The incidence in the United States is approximately 10 per 100,000 persons per year. Most of these tumors are pancreatic adenocarcinoma, and the survival is poor (DiMagno et al, 1999; Greenlee et al, 2000; Gudjonsson, 1995, 2009; Kuhlmann et al, 2004). Despite surgical treatment with or without radiotherapy and chemotherapy, the overall 5-year survival is approximately 4% and has barely improved over the last few decades (Fig. 63B.1; Gudjonsson, 2009; Kuhlmann et al, 2004). Most patients are seen initially with "incurable" disease, owing to extensive local disease or metastases at the time of diagnosis (Sener et al, 1999). Confusion surrounds the terminology, however, with the words *incurable, inoperable,* and *unresectable* having a variety of interpretations. Use of the term *unresectable* partly depends on the local surgical philosophy (e.g., accepting a resection of the mesenteric artery portal vein and macroscopically nonradical R2 resections). This surgical philosophy is not only a country-related or regional pattern, it also may be influenced by the experience at the center and the local tradition of the surgeons. The strong relationship between outcome and hospital mortality may play a role in the indication for resection and acceptance of palliative resections (Alexakis et al, 2004; Birkmeyer et al, 2003; Gouma et al, 2000).

It has been questioned whether cure is possible at all in patients with pancreatic cancer (Gudjonsson, 1995, 2009). Gudjonsson summarized the literature, and after adjusting for calculations and duplications, suggested that the total number of 5-year survivors is hardly more than 700 to 800.

There is consensus, however, that patients who undergo resection have the best chance for long-term survival (Alexakis et al, 2004). A recent study showed up to 20 years survival after resection (Adham, 2008). Survival data for patients with distal bile duct carcinoma do not differ from data for patients with pancreatic cancer. Patients with ampullary tumors have a 5-year survival of 20% to 45%, and only a few go straight to palliative treatment (de Castro et al, 2004).

Overall, most patients have palliative treatment, and palliation of symptoms is still the major focus. According to the World Health Organization (WHO, 2002), palliative care is aimed at the improvement of the quality of life (QOL) of patients who face a life-threatening illness and at the prevention or relief of pain and symptoms. The three most important symptoms that should be treated in advanced pancreatic and periampullary cancer are 1) obstructive jaundice, 2) duodenal obstruction, and 3) pain.

The decision to aim for palliative treatment can be made at two different points during the disease (Nakakura & Warren, 2007). The first decision generally is made after staging procedures, and a selection is made for potential curative surgery, palliative surgery, or nonsurgical (endoscopic) palliation. Recently, another option, preoperative radiochemotherapy and subsequent exploration, has been introduced for patients with borderline resectable lesions in an attempt to reduce local tumor ingrowths (Abrams et al, 2009; Bjerregaard et al, 2009).

The second decision is the selection of treatment strategy made during surgery, which can be an attempt for a resection with curative intent (R0/RI), a resection for palliation (RII), or other surgical procedures for palliative treatment, such as drainage.

Accurate initial staging is the crucial step for the selection of surgical and nonsurgical (palliative) treatment. Radiologic imaging techniques have evolved rapidly in the last decade. Various methods, such as contrast-enhanced spiral computed tomography (CT) and endoscopic ultrasonography (EUS), have enhanced the accuracy of radiologic staging, and noninvasive staging procedures are currently the first choice (Alexakis et al, 2004; McMahon et al, 2001; Phoa et al, 2000). Recent evaluation has identified the "new group" of patients, the borderline resectable patients, for pretreatment assessment, and criteria have been described (Callery et al, 2009). Endoscopic retrograde cholangiopancreatography (ERCP) is no longer used as a diagnostic procedure.

The role of diagnostic laparoscopy in combination with laparoscopic sonography has been studied extensively in the past (Bemelman et al, 1995; Friess et al, 1998; Nieveen van Dijkum et al, 2003; Pisters et al, 2001; Tilleman et al, 2004), but its role has diminished. A review showed that no data justify the routine use of staging laparoscopy (Pisters et al, 2001). In a recent series, however, metastasis or local ingrowth was found in 27%. Some authors therefore suggest that it should be used selectively for patients with larger tumors and tumors located in the body and tail (Chang, 2009).

Depending on local philosophy, patients who are found to have a resectable tumor at preoperative noninvasive diagnostic workup should undergo an exploratory laparotomy immediately without preoperative biliary drainage (van der Gaag et al, 2010). Patients with unresectable or incurable disease found during exploration (11% to 50%) are generally considered to be best treated with surgical palliation (Nieveen van Dijkum et al, 2003; Pisters et al, 2001; Sohn et al, 1999). This chapter evaluates the current knowledge of different aspects of surgical and nonsurgical palliative treatment for the symptoms

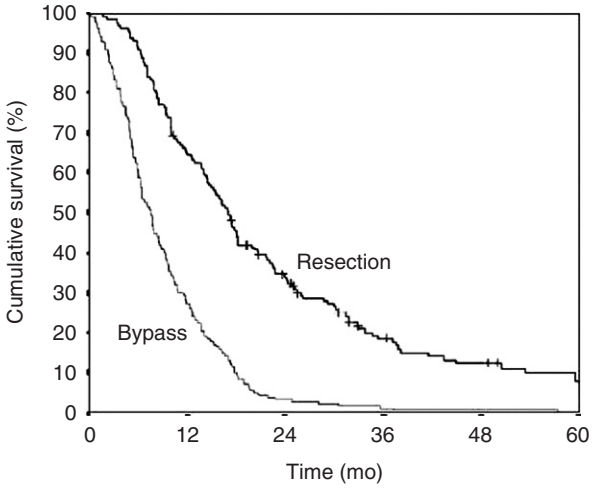


FIGURE 63B.1. Kaplan-Meier survival curves of patients who underwent a resection (n = 160) or a palliative bypass (n = 183) between 1992 and 2002. The median survival after resection and bypass were 17 and 7.5 months, respectively ($P < .01$). *(Modified from Kuhlmann KF, et al, 2004: Surgical treatment of pancreatic adenocarcinoma: actual survival and prognostic factors in 343 patients.* Eur J Cancer *40:549-558.)*

mentioned above: obstructive jaundice, duodenal obstruction, and pain.

OBSTRUCTIVE JAUNDICE

At the time of diagnosis, 90% of patients with pancreatic and periampullary tumors present with obstructive jaundice. Obstructive jaundice is associated clinically with jaundiced skin and sclerae, nausea, pruritus, dark-colored urine, and decoloring of the stool. More severe consequences are liver dysfunction and eventually hepatic failure secondary to bile stasis and cholangitis, which is found more frequently in patients with ampullary lesions compared with patients with pancreatic cancer. Relief of obstructive jaundice causes a dramatic increase in the QOL of patients and should always be achieved (Abraham et al, 2002; Crippa et al, 2008).

Biliary drainage can be achieved nonsurgically by placement of a biliary stent (endoscopic or percutaneous; see Chapter 18) or surgically by performing a biliary bypass (see Chapter 29). The success rate for short-term relief of biliary obstruction is comparable for surgical and nonsurgical biliary drainage procedures and ranges from 80% to 100%.

In the past, endoscopic biliary drainage was widely performed with plastic stents (polytef [Teflon] and polyethylene). Plastic stents can cause complications such as migration and occlusion, reported in 40%. A new stent type for endoscopic treatment is the self-expandable, covered metallic stent. Compared with plastic stents, expandable stents have a longer patency, but they generally cannot be removed after placement (Davids et al, 1992; Kaassis et al, 2003; Weber et al, 2009).

A surgical bypass can be performed by a hepaticojejunostomy alone or by a double bypass including a gastroenterostomy. In earlier studies, surgical bypass was associated with high rates of morbidity and mortality (Watanapa & Williamson, 1992).

Surgical Palliation of Obstructive Jaundice

Different surgical approaches can be used to obtain adequate biliary drainage. External biliary drainage by a T-tube has been used in the past but results in loss of appetite, and electrolyte and fluid imbalances frequently accompany external drainage. Internal biliary drainage generally is preferred and is performed by a cholecystojejunostomy, choledocho(hepatico)jejunostomy or choledochoduodenostomy (Watanapa & Williamson, 1992). In the past, cholecystojejunostomy was preferred because it is a relatively simple procedure (Rappaport & Villalba, 1990). In an extensive review, the success rate of cholecystojejunostomy to relieve obstructive jaundice was lower, however, compared with choledochojejunostomy (Watanapa & Williamson, 1992). A randomized controlled trial by Sarfeh and colleagues (1988) also showed that the technically more difficult choledochojejunostomy is preferred over a cholecystenterostomy, owing to the lower rate of recurrent jaundice and cholangitis and better patency of the bypass.

A choledochoduodenostomy is not recommended because it is generally believed that this drainage procedure frequently results in recurrent jaundice from local tumor ingrowth into the duodenum and the distal common bile duct, including the entrance of the cystic duct. A few cohort studies show low procedure-related complication rates and low rates of recurrent jaundice after choledochoduodenostomy (Di Fronzo et al, 1999).

At our institution, a side-to-side Roux-en-Y choledochojejunostomy is routinely performed after removal of the gallbladder in case of detection of advanced disease or metastases. According to the extension of dissection, in an attempt to prove locally advanced disease by ingrowth at the proximal portal vein, the common bile duct may be transected in an early phase of the procedure, and an end-to-side anastomosis is made by a one-layer running suture. This procedure can be performed with a low mortality rate and acceptable morbidity. The mortality rate in earlier studies, as well as most "outdated" randomized controlled trials from the 1990s (see below), was high and varied between 15% and 24%. However, recent studies showed mortality rates between 1% and 8%, morbidity rates between 21% and 29%, and shorter hospital stay (10 to 17 days) with a relatively low incidence of recurrent jaundice. The mean survival varied between 7 and 9 months (Table 63B.1).

Surgical or Endoscopic or Percutaneous Drainage of Obstructive Jaundice

Five prospective, randomized controlled trials have been performed, four of which compared surgical biliary drainage and endoscopic drainage (Andersen et al, 1989; Bornmann et al, 1986; Nieveen van Dijkum et al, 2003; Shepherd et al, 1988; Smith et al, 1994). In the first trial by Bornmann and associates (1986), percutaneous biliary drainage was used, and no differences were found between percutaneous and surgical palliation (Table 63B.2). The other studies were performed between 1988 and 1994, except for the study done by Nieveen van Dijkum and colleagues (2003), in which patients underwent a diagnostic laparoscopy as a final staging procedure, and randomization was performed after pathology had proven metastasis. The small number of patients randomized hampered the studies by Shepherd and associates (1988) and Andersen and colleagues (1989). Shepherd and colleagues predominantly used 7-Fr endoprotheses, which are known to have a higher occlusion rate than 10- or

Table 63B.1

Results of Biliary Bypass Procedures With or Without Gastric Enterostomy for Advanced Pancreatic Cancer

First Author	No. Patients	Gastric Bypass	Mortality (%)	Morbidity (%)	Hospital Stay (Days)	Recurrent Jaundice (%)	Survival (mo)
Lillemoe et al (1993)	118	107	2.5	—	14	3	7.7
Park et al (1997)	61	0	8	21	10	8	7
Van Wagensveld et al (1997)	126	124	2.5	—	17	—	7
Lesurtel et al (2006)	83	83	5	27	16	2	9
Müller et al (2008)	136	109	4	29	11	—	8.3
Singh et al (2008)	204	167	1	27	—	—	—
Mann et al (2009)	102	102	—	—	—	2	—

12-Fr endoprotheses or Wallstents currently used (Davids et al, 1992). A study by Shepherd and colleagues (1988) had a relatively high rate of recurrent jaundice and cholangitis. The length of follow-up in both studies was unclear, and the registration of complications and the readmission rate were limited. In the study by Smith and coworkers (1994), 201 patients were randomized. A higher procedure-related mortality rate was found after bypass compared with stenting (14% vs. 3%), and the 30-day mortality rate was not significantly different (8% vs. 15%) but was still relatively high. Major complications after bypass versus stenting were significantly different (29% vs. 11%), but minor complications were comparable (29% vs. 18%). The recurrence of jaundice and cholangitis during follow-up was significantly higher after stenting (36% vs. 2%), but survival was comparable between groups (Smith et al, 1994).

Taylor and associates (2000) conducted a meta-analysis using the three above-mentioned studies of endoscopic stenting and concluded that more treatment sessions were required after stent placement than after surgery, with a common odds ratio (OR) estimated to be 7.23. This ratio indicates a more than sevenfold increased risk of additional treatment sessions after stenting. No significant difference between the two treatment strategies was found concerning 30-day mortality rate.

The more recent randomized study by Nieveen van Dijkum and colleagues (2003) analyzed the value of diagnostic laparoscopy for patients with a periampullary carcinoma. Patients who were found to have incurable disease owing to pathology-proven metastases were allocated to either surgical (double bypass) or endoscopic palliation by a Wallstent. No difference was found in procedure-related morbidity or number of readmitted patients between the surgically and endoscopically palliated patients (see Table 63B.2). The survival was 192 days and 116 days in the surgical and endoscopic groups, respectively ($P = .05$; Fig. 63B.2). This study concerns a select group of patients who were believed to have a resectable tumor after conventional radiologic staging, leading to a low (zero) procedure-related mortality.

So far, a few general conclusions can be drawn from the available studies. Surgical treatment of biliary obstruction in unresectable pancreatic cancer is associated with higher early morbidity, a longer hospital stay, and probably a higher initial mortality rate, but long-term results are better. Endoscopic treatment is associated with lower initial mortality and morbidity, but it more frequently leads to late biliary complications and reinterventions resulting from clotting of the stent, infection, and gastric outlet obstruction (GOO).

Table 63B.2

Prospective Randomized, Controlled Trials Comparing Percutaneous or Endoscopic Drainage with Surgical Biliary Drainage

	BORNMANN ET AL (1986)		SHEPHERD ET AL (1988)		ANDERSEN ET AL (1989)		SMITH ET AL (1994)		NIEVEEN VAN DIJKUM ET AL (2003)	
	Percutaneous Stent (n = 25)	Bypass (n = 25)	Stent (n = 23)	Bypass (n = 25)	Stent (n = 25)	Bypass (n = 25)	Stent (n = 100)	Bypass (n = 101)	Wallstent (n = 14)	Bypass (n = 13)
Success (%)	84	76	80	92	96	88	95	93	100	100
Morbidity (%)	28	32	30	56	36	20	29	58	7	8
30-Day mortality (%)	8	20	9	20	20	24	15	8	0	0
Hospital stay (days)	18	24	5	13	26	27	19	26	3	12
Readmission(s) (%)	NS	NS	43	12	NS	NS	NS	NS	65	56
Recurrent jaundice or cholangitis (%)	38	16	30	0	0	0	36	2	NS	NS
Gastric outlet obstruction (%)	14	0	9	4	0	0	19	11	NS	NS
Survival (weeks)	19	15	22	18	12	14	21	26	17	27

NS, not stated in the article.

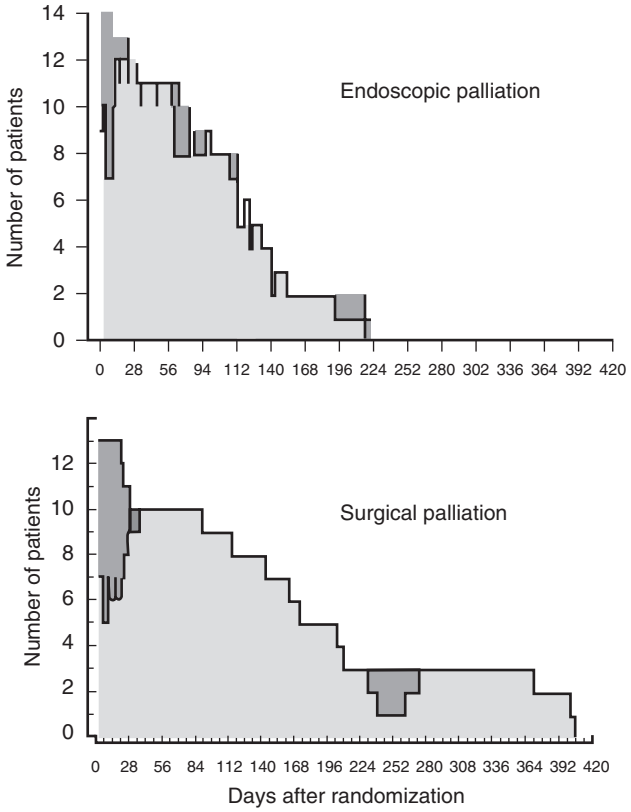


FIGURE 63B.2. Survival in patients with unresectable peripancreatic carcinoma allocated to endoscopic (n = 14) or surgical palliation (n = 13). *Dark gray areas* under the curve represent the time spent in the hospital. *(Modified from Nieveen Van Dijkum EJ, et al, 2003: Laparoscopic staging and subsequent palliation in patients with peripancreatic carcinoma.* Ann Surg *237:66-73.)*

GASTRIC OUTLET OBSTRUCTION

Symptoms of GOO, such as nausea and vomiting, are reported in 11% to 50% of patients with pancreatic cancer at the time of diagnosis (DiMagno et al, 1999). For the optimal palliative treatment, it is important to determine the origin of these symptoms. The first cause is motility dysfunction of the stomach and duodenum secondary to tumor infiltration of the celiac nerve plexus (Thor et al, 2002) or probably dysfunction of the small bowel owing to tumor infiltration around the mesenteric artery. The second cause of GOO is mechanical obstruction of the duodenum from direct tumor ingrowth into the duodenum or secondary to compression of the duodenum by a tumor in the direct vicinity. At presentation, mechanical obstruction is reported in only approximately 5% of patients with pancreatic or periampullary tumors.

Surgical palliation should be performed only when GOO has a mechanical cause. When there is no mechanical cause, pharmaceutical treatment options should be investigated (Yeo et al, 1993). It is important to confirm mechanical GOO radiologically or endoscopically. Approximately 3% to 20% of patients with unresectable pancreatic cancer eventually develop mechanical GOO (Espat et al, 1999; Lillemoe et al, 1999). In a review by Watanapa and Williamson (1992) that included 1086 patients, 17% developed mechanical GOO, and an additional gastrojejunostomy was performed on these patients. In patients who are found to have an unresectable tumor at laparotomy, a gastrojejunostomy, in addition to a biliary bypass, is often performed and is not associated with increased morbidity and mortality (see Table 63B.1).

Endoscopic duodenal stenting also is accepted as a nonsurgical palliative treatment of duodenal obstruction (Holt et al, 2004; Telford et al, 2004). In a multicenter study, the success rate after stent placement was 84%, and oral intake in patients with successful stent placement resumed for a median time of 146 days (Telford et al, 2004). Recently, a systematic review was performed to analyze medical outcome and costs of gastrojejunostomy and stent placement. No difference was found in technical success rate (96% vs. 100%), early and late major complications (7% vs. 6% and 18% vs. 17%, respectively), and persisting symptoms (8% vs. 9%). Hospital stay was longer after surgical gastrojejunostomy, 13 versus 7 days after stent placement. The mean survival time after gastrojejunostomy was 164 days versus 105 days after stenting. The authors concluded that a stent should be used for patients with a relatively short life expectancy, and gastrojejunostomy should be performed for patients with a prolonged prognosis (Jeurnink et al, 2007).

Among surgeons and gastroenterologists, it is debated whether a prophylactic gastrojejunostomy should be performed. This is an important topic because only 40% to 80% of patients with pancreatic cancer who initially undergo an exploratory laparotomy with the intention to perform a pancreatoduodenectomy undergo a resection (Alexakis et al, 2004; Kuhlmann et al, 2004; Pisters et al, 2001; Sohn et al, 1999). Two randomized controlled trials evaluated the role of a prophylactic gastrojejunostomy in patients who were found to have an unresectable periampullary or pancreatic tumor during exploratory laparotomy (Lillemoe et al, 1999; Van Heek et al, 2003). Lillemoe and colleagues (1999) analyzed 87 patients who were found to have an unresectable tumor and were believed to not be at risk for duodenal obstruction. These patients received either a prophylactic retrocolic gastrojejunostomy and a biliary (double) bypass or a biliary (single) bypass alone. Both groups also underwent a chemical splanchnicectomy during the laparotomy. The addition of a prophylactic gastrojejunostomy did not increase procedure-related mortality and morbidity rates and did not extend hospital stay (Table 63B.3). None of the patients who received a gastrojejunostomy developed late GOO during follow-up compared with 19% of patients who did not undergo a gastrojejunostomy in the initial procedure, which was a significant difference. No significant difference in survival was found between both groups.

Van Heek and colleagues (2003) also randomly assigned patients found to have a resectable tumor during exploration to either a single bypass or a double bypass in a multicenter trial. The outcome of the interim analysis after 50% (n = 70) of the inclusion was comparable with the outcome of the study by Lillemoe and colleagues (1999), and it was decided to discontinue the trial. During follow-up, clinical GOO was diagnosed in 5.5% of patients after double bypass and in 41.4% of patients after single bypass, which was a significant difference (Fig. 63B.3). The study by Van Heek and colleagues (2003) also longitudinally evaluated the QOL of these two patient groups using the EORTC-C30 and Pan 26 questionnaires. Overall, no major differences were observed in the QOL between the two surgical treatment groups (Fig. 63B.4). After surgery, most QOL scores deteriorated temporarily and were restored to their preoperative levels within 4 months. This

Table 63B.3

Two Prospective Randomized, Controlled Trials Analyzing Prophylactic Gastrojejunostomy in Patients Who Underwent Hepaticojejunostomy for Unresectable Periampullary Cancer

	LILLEMOE ET AL (1999)		VAN HEEK ET AL (2003)	
	Double Bypass (n = 44)	Single Bypass (n = 43)	Double Bypass (n = 36)	Single Bypass (n = 29)
Morbidity (%)	32	33	31	28
Mortality (%)	0	0	3	0
Hospital stay (days)	8.5	8	11	9
Late gastric outlet obstruction (%)	0	19	5.5	41.4
Survival (mo)	8.3	8.3	7.2	8.4

pattern of a temporary deterioration of the different domains of QOL score and restoration after a few months also was found in patients undergoing a Whipple procedure and was comparable to the temporary deterioration of QOL after bypass surgery (Nieveen van Dijkum et al, 2005).

The results of a recent meta-analysis also favor prophylactic gastroenterostomy. The chance of GOO during follow-up was significantly lower (OR, 0.06; 95% CI, 0.02 to 0.21; $P < .001$) with no difference in postoperative morbidity and mortality rates (Hüser, 2009). In these studies, endoscopic stenting of duodenal obstruction during follow-up was not attempted routinely, which could influence the outcome in the near future. A new trial should focus on nonsurgical palliation, including stenting of the common bile duct and the duodenum and adding a celiac plexus block by EUS versus the "optimal" surgical palliation described above, including the double-bypass procedure.

PAIN MANAGEMENT

At the time of diagnosis, approximately 40% to 80% of patients report pain. As the disease progresses, more than 90% of patients eventually have moderate to severe pain. The pain of advanced pancreatic cancer is located most frequently in the upper abdomen (epigastric region) and the back and may be caused by tumor ingrowth into the mesenteric and celiac nerve plexus.

Another phenomena, such as neurogenic inflammation, well known from patients with chronic pancreatitis, could also lead to pain generation in this group of patients. These different

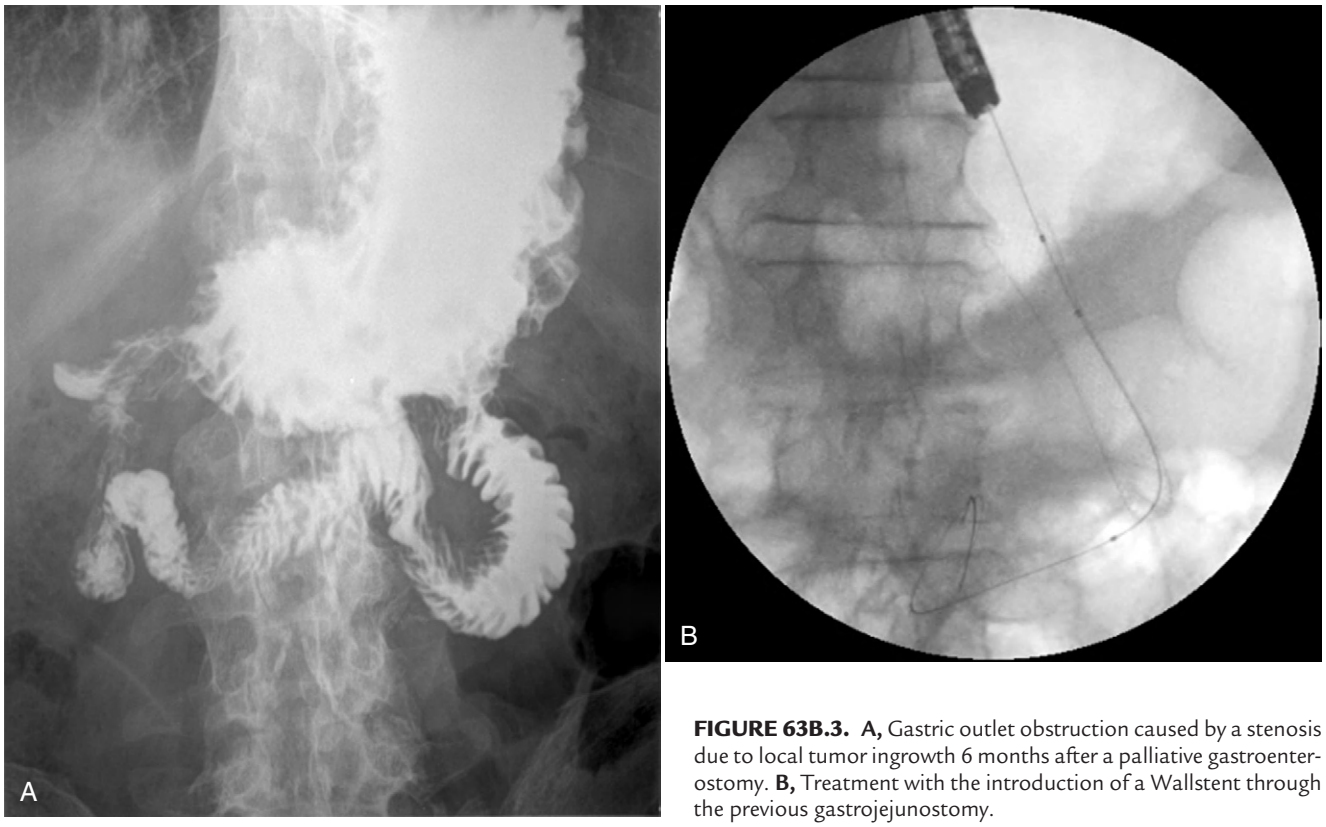


FIGURE 63B.3. A, Gastric outlet obstruction caused by a stenosis due to local tumor ingrowth 6 months after a palliative gastroenterostomy. **B,** Treatment with the introduction of a Wallstent through the previous gastrojejunostomy.

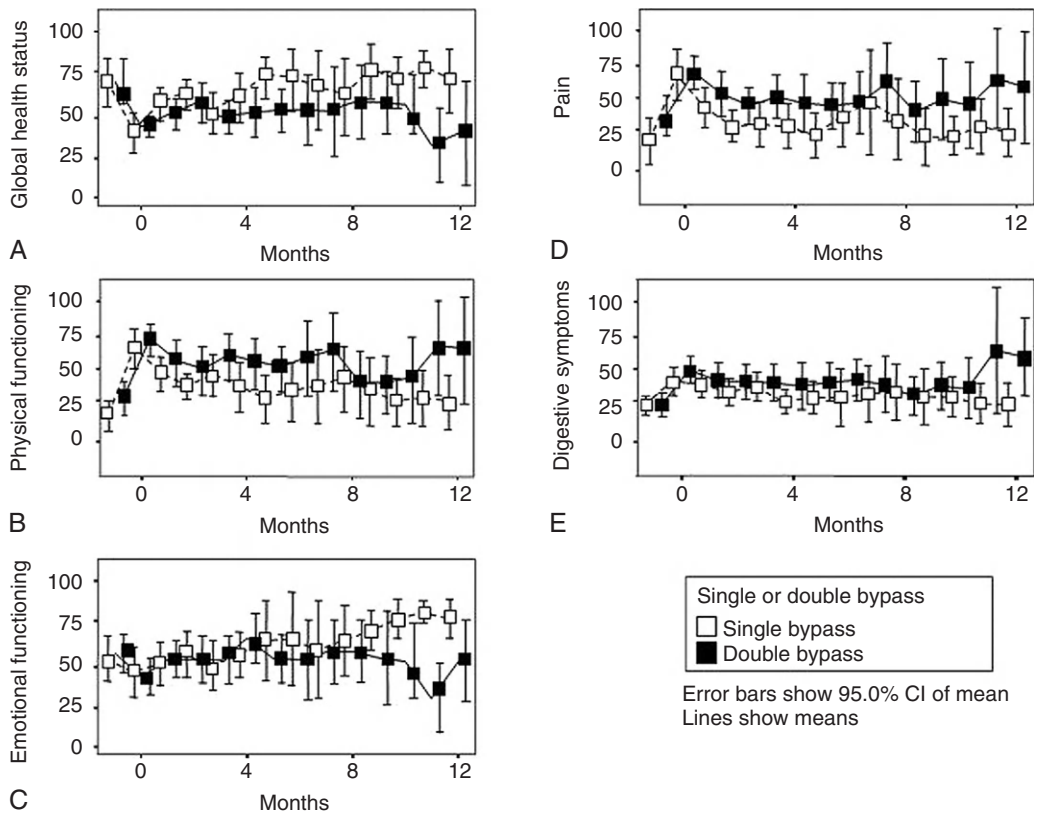


FIGURE 63B.4. Quality of life graphs representing the 12 months after surgery of patients randomized to receive a double or single bypass. The *left side* of the graph represents the time of the operation. The nonimputated subscales of the following subscales are presented: **A,** Global health status. **B,** Physical functioning. **C,** Emotional functioning. **D,** Pain. **E,** Digestive symptoms. *(Modified from van Heek NT, et al, 2003: The need for a prophylactic gastrojejunostomy for unresectable periampullary cancer: a prospective randomized multicenter trial with special focus on assessment of quality of life.* Ann Surg *238:894-902.)*

mechanisms have been summarized nicely in a recent report on pain generation (di Mola & di Sebastiano, 2008). Initial pain management should be pharmacologic and should be composed of analgesics such as nonsteroidal antiinflammatory drugs (NSAIDs) and oral or transdermic narcotic analgesics (Cruciani & Jain, 2008). Side effects of these drugs are frequently reported, however, and eventually pharmaceutical pain management alone may be insufficient (Caraceni & Portenoy, 1996). The next step is a celiac plexus nerve block, which was first described by Kappis in 1914. The nerve block interrupts the innervation of the pancreas and prevents painful stimuli from reaching the brain. This is a relatively straightforward procedure, but it can cause side effects, such as diarrhea and orthostatic hypotension, in approximately 40% of patients (Eisenberg et al, 1995). Currently, the celiac plexus block can be performed percutaneously, by EUS, or during laparotomy. Permanent paraplegia is uncommon (0.15%) but is the most dramatic complication of this procedure, which results from an infarct/occlusion of the art spinalis anterior (Abdalla & Schell, 1999).

Percutaneous Celiac Plexus Block

The percutaneous route to block the celiac plexus has been investigated extensively. It can be performed under fluoroscopic, CT, or US guidance. Multiple studies, mostly uncontrolled, have evaluated the accuracy and techniques of percutaneous celiac plexus block. In a meta-analysis of 24 publications that included 1145 patients treated with a percutaneous neurolytic celiac plexus block (NCPB) for cancer pain (63% pancreatic cancer), 70% to 80% of patients had long-lasting benefit from the procedure (Eisenberg et al, 1995).

Only a few randomized controlled trials on NCPB have been done (Ischia et al, 1992; Polati et al, 1998; Wong et al, 2004). The best evidence is in the most recent study by Wong and associates (2004), who randomly assigned 100 patients with unresectable pancreatic cancer to receive either NCPB or a sham NCPB procedure. After the randomized procedure, both groups could receive systemic analgesic therapy according to the WHO guidelines. End points were pain relief, QOL, and survival. The major findings were that NCPB significantly improved pain relief in patients with pancreatic cancer compared with optimized analgesic therapy, but it did not affect QOL or survival. NCPB had no effect on the consumption of analgesics, and significantly more patients needed a rescue NCPB in the analgesic therapy group (10 vs. 3 patients; $P = .01$).

These results suggest that the application of an aggressive pain management protocol, regardless of NCPB, can effectively control pain, although NCPB can provide significantly better analgesia than optimized analgesic therapy alone. Polati and colleagues (1998) performed a small, randomized, controlled

trial (n = 24) comparing percutaneous NCPB with pharmacologic therapy; mean analgesic consumption was lower, and drug-related side effects—constipation, nausea, and vomiting—were significantly less frequent in the group that underwent a nerve block. Ischia and colleagues (1992) randomized 61 patients to receive either a transaortic block, a classic retrocrural block, or a bilateral chemical splanchnicectomy. In 60% to 75% of patients, both techniques abolished pain until the patient's death.

Endoscopic Ultrasound-Guided Celiac Plexus Block

More recently, EUS-guided fine needle injection therapy has been developed (Giovannini, 2004; Klapman & Chang, 2005), and various techniques have been described. Generally, 5 to 10 mL of 1% lidocaine and 15 to 20 mL of 95% alcohol are injected at two areas of the celiac trunk. Results from nonrandomized studies showed a significant reduction of pain in 85% to 90% of the patients. Studies and follow-up are limited, however, and trials comparing the efficacy of this endoscopic procedure with the other techniques should be performed.

Celiac Plexus Block During Surgery

Celiac plexus block during surgery has been performed for many years. Lillemoe and colleagues (1993a) conducted a double-blind, randomized, controlled trial that compared a chemical splanchnicectomy during laparotomy with alcohol versus saline placebo. Chemical splanchnicectomy was performed perioperatively by injection of 20 mL of either 50% alcohol or saline solution on each side of the aorta at the level of the celiac axis. No differences were observed between the two groups concerning mortality rate, procedure-related complications, and hospital stay. Long-term complications and side effects were not investigated. Compared with the placebo group, alcohol injection significantly reduced the mean pain score for surviving patients at 2, 4, and 6 months (Fig. 63B.5). In the alcohol group, significantly more patients never reported pain (56% vs. 34%). However, the analgesic effect was not permanent: 10% of patients in the alcohol group required an additional percutaneous celiac axis block compared with 12% in the saline group. The time interval between the initial operative and additional percutaneous block varied significantly (11.8 ± 3.2 vs. 4 ± 1.1 months) in the alcohol group and saline group, respectively. Actuarial survival was improved in the subgroup of patients who reported significant preoperative pain and underwent a splanchnicectomy with alcohol ($P < .001$). The authors suggested that the difference could be caused by the progressive physical deterioration secondary to persistent pain, which eventually leads to impaired survival. These findings confirm other reports that state the presence of pain is associated with a poor prognosis (Kelsen et al, 1997).

The Amsterdam group retrospectively analyzed pain in 74 patients who underwent a palliative bypass for pancreatic adenocarcinoma (Van Geenen et al, 2002). The investigators found a significant difference in survival between patients who reported preoperative pain and patients who did not (4.9 vs. 9.5 months, respectively; $P = .01$; Fig. 63B.6). The association of persistent pain with a more advanced stage of the tumor could also explain this difference.

Another strategy to palliate pain is the thoracoscopic splanchnicectomy. A bilateral thoracoscopic splanchnicectomy or a unilateral left-sided thoracoscopic splanchnicectomy can be performed. Ihse and colleagues (1999) performed a prospective study analyzing the follow-up of patients with pancreatic cancer (n = 23) or chronic pancreatitis (n = 21) who underwent a bilateral thoracoscopic splanchnicectomy. Within 1 week, the average pain scores were reduced by more than 50% and remained stable throughout the follow-up period of 4 months.

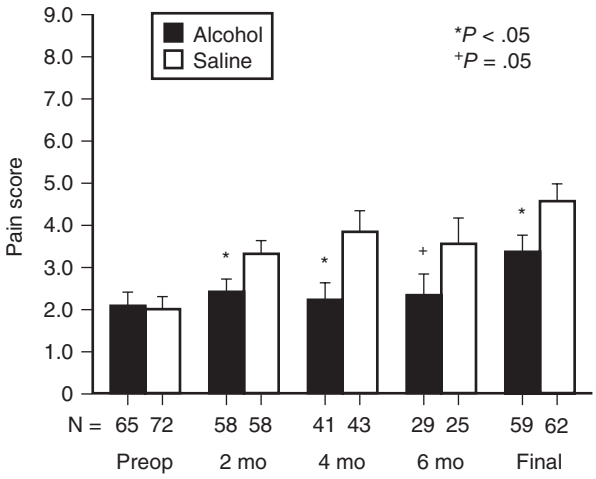
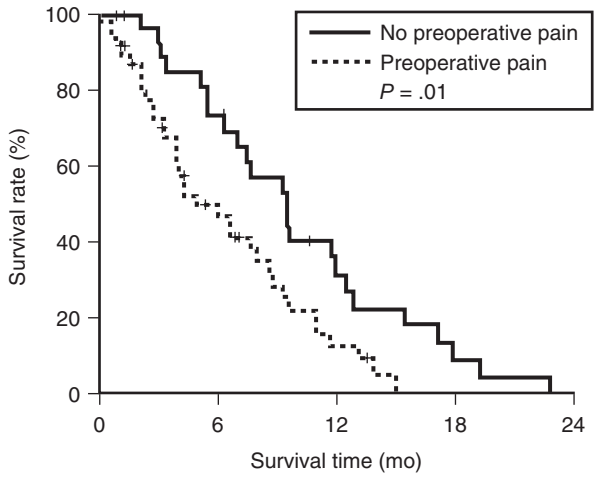


FIGURE 63B.5. Mean pain scores (visual analog scale) measured preoperatively at 2, 4, and 6 months with final assessments for all randomized patients surviving at each point. *(Modified from Lillemoe KD, et al, 1993: Chemical splanchnicectomy in patients with unresectable pancreatic cancer: a prospective randomized trial.* Ann Surg *217:447-455.)*



Number of patients alive/number of patients evaluable

28/28	19/26	7/24	2/24	No preoperative pain
46/46	17/39	4/37	0/36	Preoperative pain

FIGURE 63B.6. Survival of 74 patients with or without preoperative pain who underwent a palliative bypass for nonresectable pancreatic adenocarcinoma. *(Modified from Van Geenen RC, et al, 2002: Pain management of patients with unresectable peripancreatic carcinoma.* World J Surg *26:715-720.)*

Four patients (9%) required a thoracotomy because of a bleeding complication. Leksowski (2001) showed adequate and consistent pain relief in 26 patients who underwent a unilateral splanchnicectomy. Follow-up was also limited to 6 months, and recurrent pain after that period was not analyzed.

Radiotherapy can also be applied to reduce pancreatic cancer pain. It may take several weeks before pain relief is achieved, however, and side effects are common. Most studies are limited because of small patient numbers and poor pain assessment methods. Ceha and colleagues (2000) investigated the feasibility of high-dose conformal radiotherapy (70 to 72 Gy, 35 to 36 fractions) in 44 patients with nonresectable pancreatic cancer. Pain relief was experienced in 68% of patients, with a median duration of 6 months to pain progression.

In accordance with the results from previous studies, a chemical splanchnicectomy should be considered during the initial double-bypass procedure for patients with nonresectable pancreatic carcinoma. In other patients, pharmacologic pain management as described earlier is the first step, followed by percutaneous or US-guided celiac plexus block. For recurrent pain problems, radiotherapy and incidental thoracoscopic splanchnicectomy are performed.

PANCREATODUODENECTOMY FOR PALLIATION

Several reports have discussed the indications to perform a pancreatoduodenectomy as a palliative treatment option (Fusai et al, 2008; Gouma et al, 1999; Köninger et al, 2008; Lavu et al, 2009; Lillemoe et al, 1996; Reinders et al, 1995; Schniewind et al, 2006). This controversial question results from the observation of reduced morbidity and mortality associated with pancreatoduodenectomy in high-volume centers (Cameron et al, 1993; Kuhlmann et al, 2004; Lillemoe et al, 1996). This decreased mortality rate is partly due to improved management of severe complications (de Castro et al, 2005), but mainly to a hospital volume effect (Alexakis et al, 2004; Cameron et al, 1993; Gouma et al, 2000).

Frequently, the term *palliative resection* has been used to describe patients in whom the palliative resection was regarded as a macroscopically radical resection, which appeared to be microscopically nonradical after pathologic examination, a so-called *R1 resection* (Table 63B.4). Although the resection was undertaken with a curative intention, it can be considered palliative (Fig. 63B.7). In this case, the resection is called *palliative in retrospect*. The percentage of these patients from cohort studies depends heavily on the quality of the pathology examination of the specimen. It is debatable whether these patients should be included, if the role of a palliative resection per se is discussed, because these patients underwent a resection with a *curative* intent. The term *palliative resection* probably should be used only for R2 resections, those with macroscopically residual tumor. In a few of these situations, the tumor is found to be nonresectable after a point of no return (e.g., after transection of the pancreatic neck), or resection is required because of preoperative tumor bleeding. As a result of improved staging strategies by CT and MRI, and the nonsurgical management of bleeding by selective embolization, this indication is limited in current practice (Alexakis et al, 2004; de Castro et al, 2005; Phoa et al, 2000; WHO, 2002). However, some authors consider this an optimal palliative treatment (Köninger et al, 2008). No prospective studies in which a resection was performed or planned as a palliative procedure after adequate preoperative staging showed advanced disease leading to R2 resection.

The benefit of surgical resection in the subset of patients with advanced pancreatic cancer, including those with vascular ingrowth in portal vein and/or mesenteric vein, should be balanced against the potential benefits and complications of palliative chemoradiotherapy. Because no randomized controlled trials have been done, a decision analysis was provided comparing the survival after pancreatic resection, including portal vein resection, for locally advanced pancreatic cancer with survival after palliative chemoradiotherapy. It was concluded that surgical resection might confer a survival advantage over palliative chemoradiotherapy in selected patients with presumed local venous ingrowth. However, it was also found that if the probability of an R1 or R2 resection is greater than 77%, resection is no longer the favored strategy (Abramson et al, 2009). Another group of patients is a very small, well-selected group in which (palliative) resection is performed: patients with metastatic disease, mainly patients with solitary (small) liver metastasis, limited peritoneal metastasis, or interaortacaval/intermesenteric lymph node metastasis. A few small studies have been published that show combined pancreatic resection with hepatic resection is technically possible and relatively safe (Gleisner et al, 2007; Shrikhande et al, 2007). These studies showed no long-term survival, and it might be questioned whether survival in this highly selected group of patients is better compared with that of patients who receive other palliative procedures. The study from

Table 63B.4

Studies Comparing Palliative Resection (R) and Bypass Surgery (B)

Reference	Type and Resection*	Patients (n) (R/B)	Morbidity (%) (R/B)	Mortality (%) (R/B)	Survival (mo) (R/B)
Reinders et al (1995)	R1/R2	36/24	42/32	3/0	10.2/7.8
Lillemoe et al (1996)	R1/R2	64/62	44/33	2/2	12/9
Kuhlmann et al (2006)	R1/R2	80/90	41/31	0/2	15.8/9.5
Schniewind (2006)	R1/R2	38/129	58/42	8/3	7/6
Fusai et al (2008)	R1/R2	40/32	12/32	3/3	18/9
Köninger (2008)	R2	38/46	47/22	8/2	12.5/10.5
Lavu et al (2009)†	R1	37/24	49/33	0/0	15.6/6.5

*R1 resection, microscopically irradical after pathologic examination; R2 resection, macroscopically residual tumor.
†Bypass including patients with metastasis.

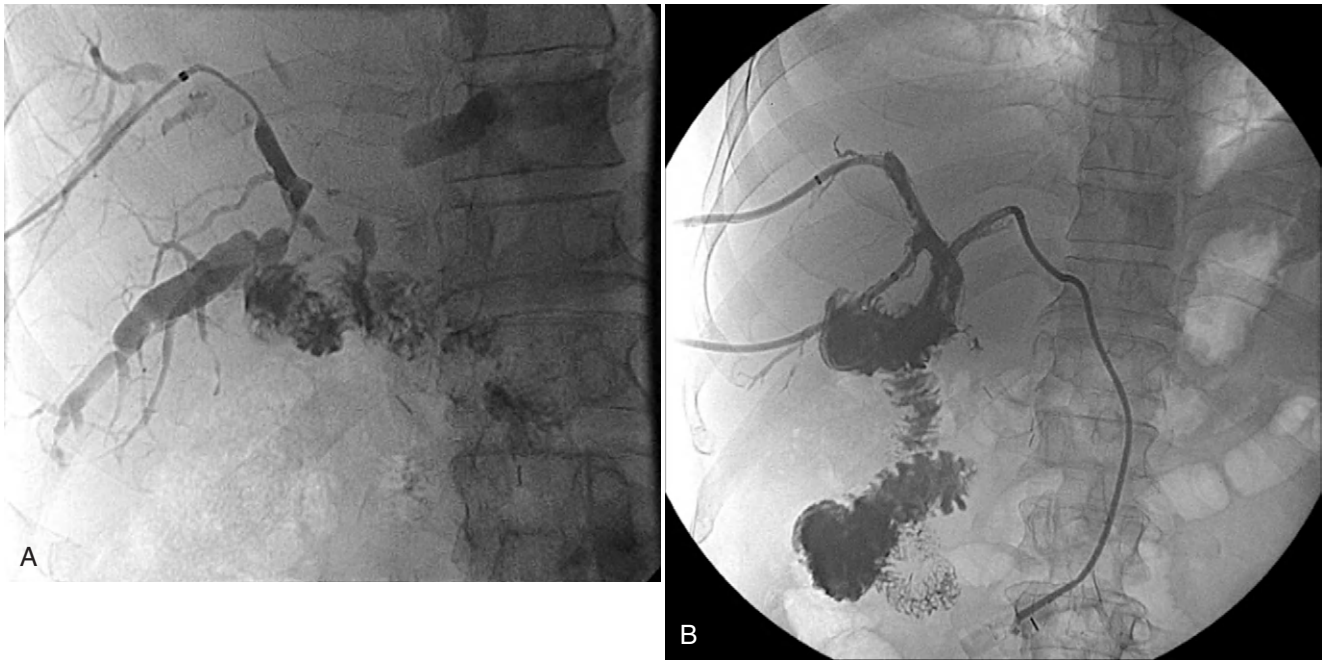


FIGURE 63B.7. Obstructive jaundice after a palliative pylorus-preserving pancreaticoduodenectomy. **A,** Stenosis occurred secondary to recurrence at the bifurcation. **B,** Palliative treatment was given for another 4 months by a percutaneous Wallstent and three percutaneous drainage catheters. Eventually the patient died as a result of recurrent cholangitis.

Hopkins (Fleiser, 2007) showed similar overall survival of the combined resection, compared with palliative bypass alone, but increased morbidity and hospital stay.

It can be concluded that controversy remains regarding the role of pancreatic resection for palliation. The available data confirm that, in the case of questionable radical resectability, a resection will offer relatively good palliation and longer survival compared with chemoradiotherapy, so a more aggressive approach can be advocated in patients whose tumor resectability is doubtful. R2 resections should only be performed in a highly select patient group and after passing the point of no return because no data prove a survival benefit. In addition, no data support resection in patients who are found to have liver metastasis at the preoperative diagnostic workup.

LAPAROSCOPIC PALLIATION

Diagnostic laparoscopy has been frequently used in the diagnostic workup for patients with suspected pancreatic tumors. The use of diagnostic laparoscopy also facilitated the introduction of the minimally invasive approach for subsequent palliation if metastases or local ingrowth of tumors is found. The procedures include palliation of obstructive jaundice by cholecystojejunostomy or choledochojejunostomy and palliation of GOO by gastroenterostomy.

Although a cholecystojejunostomy as a biliary bypass is considered to be less suitable because of the higher incidence of recurrent jaundice, this strategy is easier and safer compared with a hepaticojejunostomy (see Chapter 29). To prevent short-term obstruction of the cholecystojejunostomy, the tumor status in relation to the cystic junction anatomy always should be assessed by performing cholangiography; otherwise, a laparoscopic common bile duct exploration and bypass is indicated. The available data from five relatively small studies showed that laparoscopic double bypass can be performed safely with acceptable morbidity and low mortality rates (Table 63B.5). The long-term follow-up concerning recurrent jaundice and GOO is highlighted only briefly in these studies, however (Hamade et al, 2005; Kuriansky et al, 2000; Rhodes et al, 1995; Rothlin et al, 1999; Suzuki et al, 2007). As previously mentioned, new endoscopic techniques, including duodenal stenting for GOO (Mittal et al, 2004; Nassif et al, 2003; Wong et al, 2002), should be compared with new, minimally invasive laparoscopic approaches.

Table 63B.5

Result of Combined Laparoscopic Biliary and Gastric Bypass for Advanced Pancreatic Cancer

Reference	No. Patients	Operating Time (min)	Mortality (%)	Morbidity (%)	Hospital Stay (Days)	Survival (Days)
Rhodes et al (1995)	16	75	0	13	4	201
Rothlin et al (1999)	14	129	0	7	9	NA
Kuriansky et al (2000)	12	89	8	33	6	85
Hamade et al (2005)	21	130	5	14	4	120-390
Suzuki et al (2007)	8	191	0	0	7	NA

NA, not available.

CONCLUSION

Although new treatment modalities for pancreatic cancer are being continuously developed, survival remains poor. Because symptoms develop late in the course of the disease, more than 80% of patients are not eligible for treatment with a curative intent. Survival of patients with unresectable tumors is even worse, and the best efforts must be made in the optimal palliative treatment of these incurable patients. The most common symptoms that must be palliated are obstructive jaundice, GOO, and pain.

To palliate obstructive jaundice, a biliary bypass should be performed in relatively fit patients. Compared with endoscopic biliary stenting, a biliary bypass provides optimal long-term prevention of biliary obstruction, but it is associated with higher initial morbidity. Stents are preferred in patients in whom survival is expected to be relatively short (3 to 6 months). In addition to biliary bypass, gastric bypass should be performed routinely to prevent GOO secondary to tumor ingrowth or compression of the duodenum. Novel techniques for palliation of GOO are being developed, such as endoscopic duodenal stenting. These techniques still must be validated, however.

More than 90% of patients have severe pain during the course of their disease. Initial treatment may be analgesic, but when the disease progresses, this is insufficient. NCPB can be performed percutaneously or during laparotomy. When the tumor is found to be unresectable during exploration, a plexus block is a relatively straightforward procedure. Radiotherapy also can be applied to treat pain, but data are limited. Palliative R1 resections for patients with borderline resectable tumors are generally accepted now as palliative care; however, so far the role for R2 palliative resection and resection for patients with metastatic disease is limited.

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CHAPTER 69B

Simple cysts and polycystic liver disease: surgical and nonsurgical management

Olivier Farges and Béatrice Aussilhou

OVERVIEW

Most patients with simple cysts or polycystic liver disease (PCLD) are asymptomatic and require no treatment. When indicated, the aim of treatment in patients with single cysts is to either destroy the epithelial lining of the cyst with sclerotherapy or create a communication between the cyst lumen and the peritoneal cavity by fenestration. In patients with PCLD, treatment aims at promoting the regeneration of noncystic liver (hepatectomy) or at replacing the entire liver (transplantation). For patients with PCLD, the treatment is a major procedure, and medical alternatives are under development.

SINGLE CYSTS

Asymptomatic liver cysts, even when large, need no treatment and do not require surveillance. A small percentage of patients have symptoms related to an increase in the size of cysts (see Chapter 69A). Caution must be exercised when considering whether a simple cyst is symptomatic when it is smaller than 8 cm or when it does not protrude outside of the liver surface. If this is not the case, or if symptoms are vague, ultrasound-guided aspiration of the cyst may be attempted as a therapeutic test. If this does not result in improvement of symptoms, further treatment is not required. When aspiration is effective at relieving symptoms, the cyst is symptomatic. Improvement, however, is transient, as the cyst inevitably recurs after simple aspiration (Saini et al, 1983), and more radical treatment, such as sclerotherapy or fenestration, can be considered.

It is unclear whether treatment is indicated in patients who are asymptomatic but nevertheless have evidence on imaging of compression of the bile ducts, or of portal or hepatic veins, by the cysts. If these anomalies are unilateral—that is, at least one hemiliver has normal biliary drainage and normal inflow and outflow—our opinion is that treatment is not required, as the stenosis is not always reversible (Fig. 69B.1).

Treatment of symptomatic cysts relies on the destruction of the epithelial lining (sclerotherapy) or on the creation of a communication between the cyst and the peritoneal cavity (unroofing, also known as fenestration). Sclerotherapy is performed under ultrasound (US) guidance, whereas unroofing is currently mostly performed by laparoscopy. Hence symptomatic patients today are most likely to undergo a minimally invasive procedure. This should not lead to an extension of the indications because complications, occasionally severe ones, may occur. It is also important to warn patients early on that these treatments aim at transforming a large, symptomatic cyst into a small, asymptomatic one, and that they should not worry if some anomalies persist on imaging after the procedure.

Sclerotherapy

Method

Sclerotherapy aims at destroying the epithelium lining the inner surface of the wall to stop intracystic fluid secretion (see Chapter 28). Under US guidance, the cyst is located and punctured, and a small drainage catheter is introduced by the Seldinger technique. Injection of water-soluble contrast media ensures that no communication with the bile duct exists and that no leak into the peritoneal cavity is present, both of which are contraindications (Tikkakoski et al, 1996).

The most frequently used sclerosing agent is 95% ethanol, as for renal cysts. Minocycline hydrochloride, otherwise used for pleurodesis or, more recently, ethanolamine oleate (Miyamoto et al, 2006; Nakaoka et al, 2009) have been proposed as alternatives. Radiofrequency ablation (RFA) has also been performed, although reports are only anecdotal.

The amount of ethanol injected should be limited because alcohol sclerotherapy is associated with an increase in blood alcohol concentration, peaking 3 to 4 hours after treatment (Yang et al, 2006). As massive ethanol intoxication leading to coma has been reported after injection of 240 mL in a 3500 mL cyst (Wernet et al, 2008), the volume of alcohol should not exceed 100 to 120 mL. To ensure that the sclerosant comes in contact with the entire surface, the patient is rolled in different positions. Alcohol is then aspirated and the catheter removed. The procedure is performed with the patient under light general anesthesia because it is painful.

Several protocols have been designed that differ in the duration of alcohol retention in the cyst (from 10 to 240 minutes) and in the number of sessions (single or multiple) (Larssen et al, 2003; Simonetti et al, 1993; Tikkakoski et al, 1996; Yang et al, 2006). Comparative studies are lacking, but a single study showed that 120- and 240-minute retention times yield comparable results (Yang et al, 2006).

Recently, prolonged catheter drainage with negative pressure of the cyst without sclerotherapy has been shown to be as effective as alcohol injection in a randomized study (Zerem, 2009). This result mainly shows that an important aspect of percutaneous treatments in general is to achieve collapse of the cystic cavity.

Limitations

Although the alcohol injected should not exceed a certain amount, the size of the cyst in itself is not a limitation. Provided the cyst collapses after aspiration, the sclerosant will come into contact with the epithelial lining. It is also possible to repeat the procedure if required.

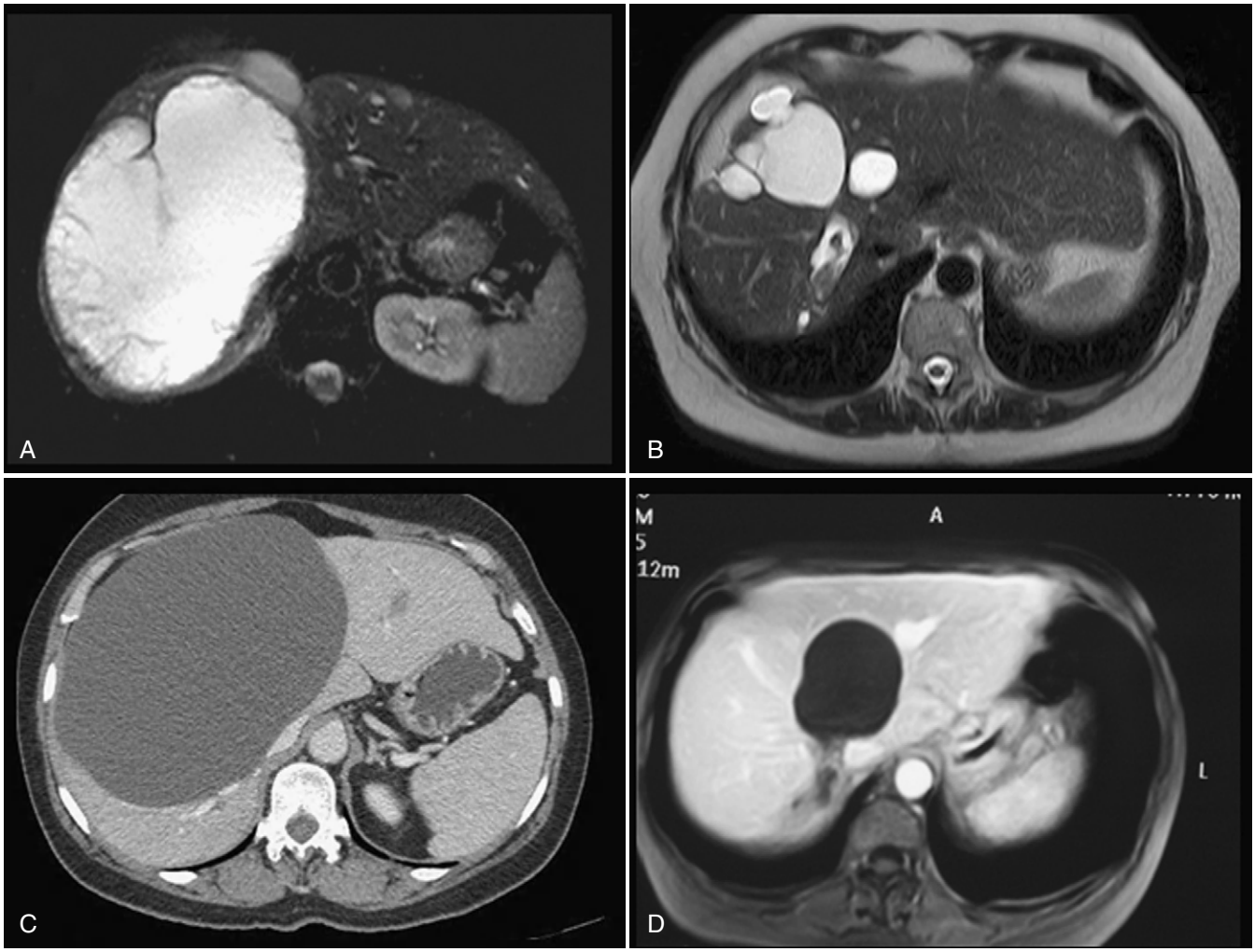


FIGURE 69B.1. Biliary cysts before (**A** and **C**) and after (**B** and **D**) alcohol sclerotherapy. In the first patient (**A** and **B**), vascular pedicles were compressed, and marked atrophy persisted despite reduction in the size of the cyst. In the second patient (**C** and **D**), hepatic vein compression persisted despite size reduction.

An absolute contraindication, which should be formally and completely excluded before the injection, is the presence of a communication between the cyst and the biliary tract. Simple cysts do not normally communicate, but fistulization may occur, presumably by erosion. Recent intracystic bleeding with fresh blood in the cyst is also a contraindication for most physicians; in such cases, sclerotherapy should be delayed.

Complications

Although the injection is painful, pain resolves rapidly and most patients are discharged the following day. Transient neuropsychic disorders secondary to diffusion of alcohol through the cyst wall have been reported. Intracystic bleeding is rare but potentially severe (Fig. 69B.2). It should be realized that vessels are compressed at the periphery of enlarged cysts because of the high intracystic pressure and are therefore not visible; however, bleeding may occur once the cysts have emptied if a vessel has been inadvertently punctured.

Inflammatory changes are frequent after sclerotherapy and may interfere with follow-up. They may also increase the difficulty of subsequent fenestration if sclerotherapy has been ineffective.

Long-Term Outcome

A systematic literature review published in 2001 identified 112 patients treated by alcohol sclerotherapy and 17 treated with minocycline hydrochloride instillation (Moorthy et al, 2001). In most patients, a complete or partial regression of the cyst was seen, but follow-up was short overall. Although the reported experience since then has been limited, the efficacy has been confirmed, with a symptomatic recurrence rate requiring additional treatment of less than 5% (Erdogan et al, 2007).

An early morphologic assessment, usually by US, is frequently performed. However, patients should be warned that this is likely to show the persistence of the cyst, although at a smaller size; this is not predictive of symptomatic recurrence. In practice, several months—perhaps up to a year—may be required to achieve optimal efficacy after alcohol sclerotherapy (Fig. 69B.3).

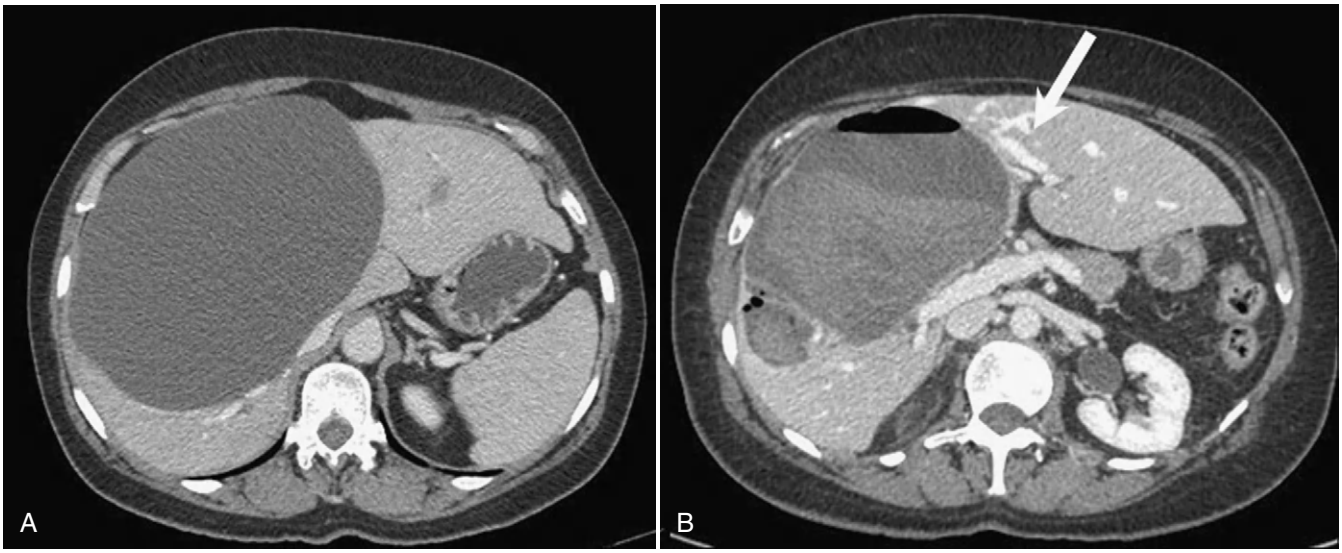


FIGURE 69B.2. Biliary cyst before (**A**) and after (**B**) sclerotherapy by ethanol. Sclerotherapy was complicated by hemorrhage (dense content). Note the presence of hepatic vein collateral circulation adjacent to the cyst that could have been inadvertently injured during sclerotherapy (*arrow*).

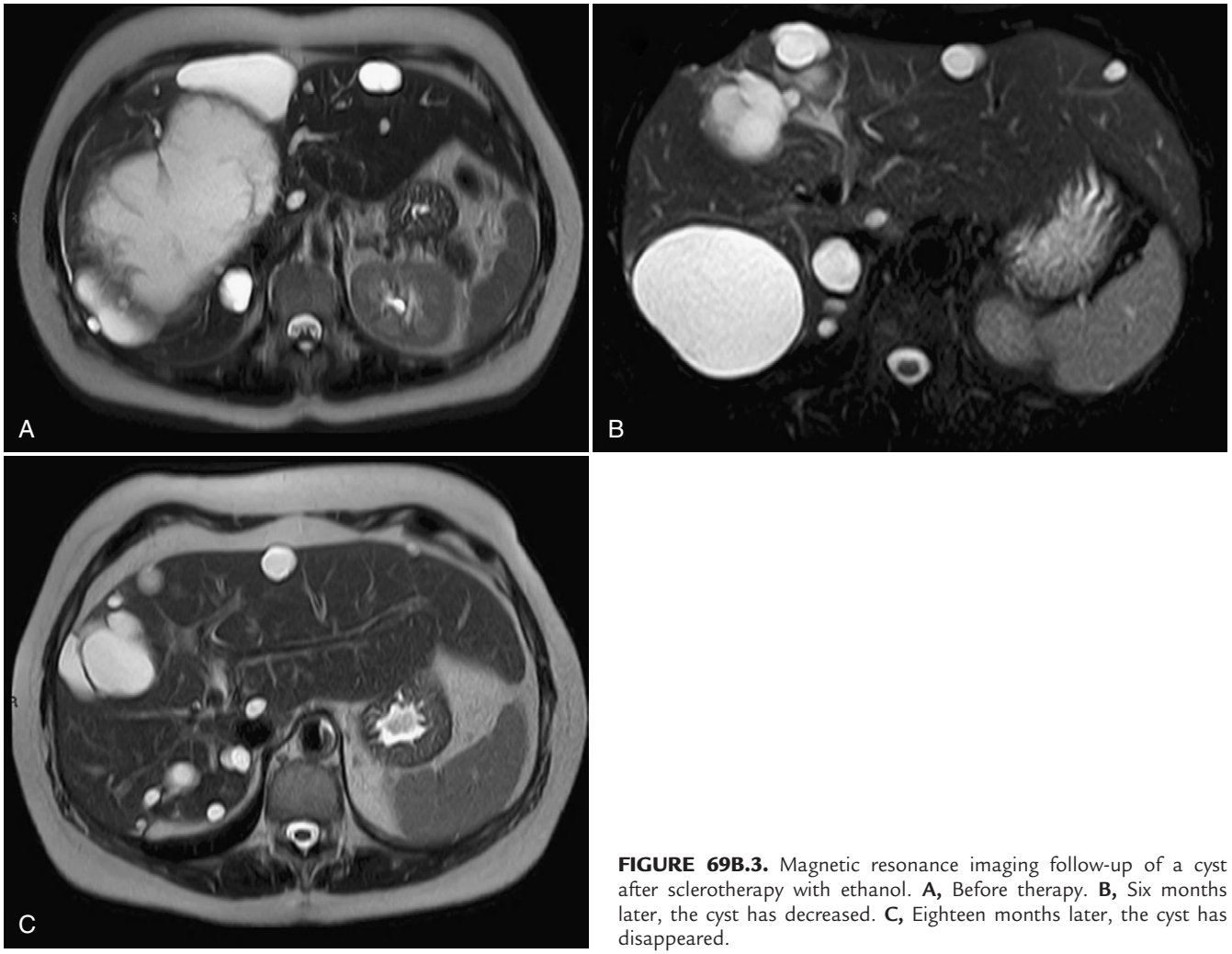


FIGURE 69B.3. Magnetic resonance imaging follow-up of a cyst after sclerotherapy with ethanol. **A,** Before therapy. **B,** Six months later, the cyst has decreased. **C,** Eighteen months later, the cyst has disappeared.

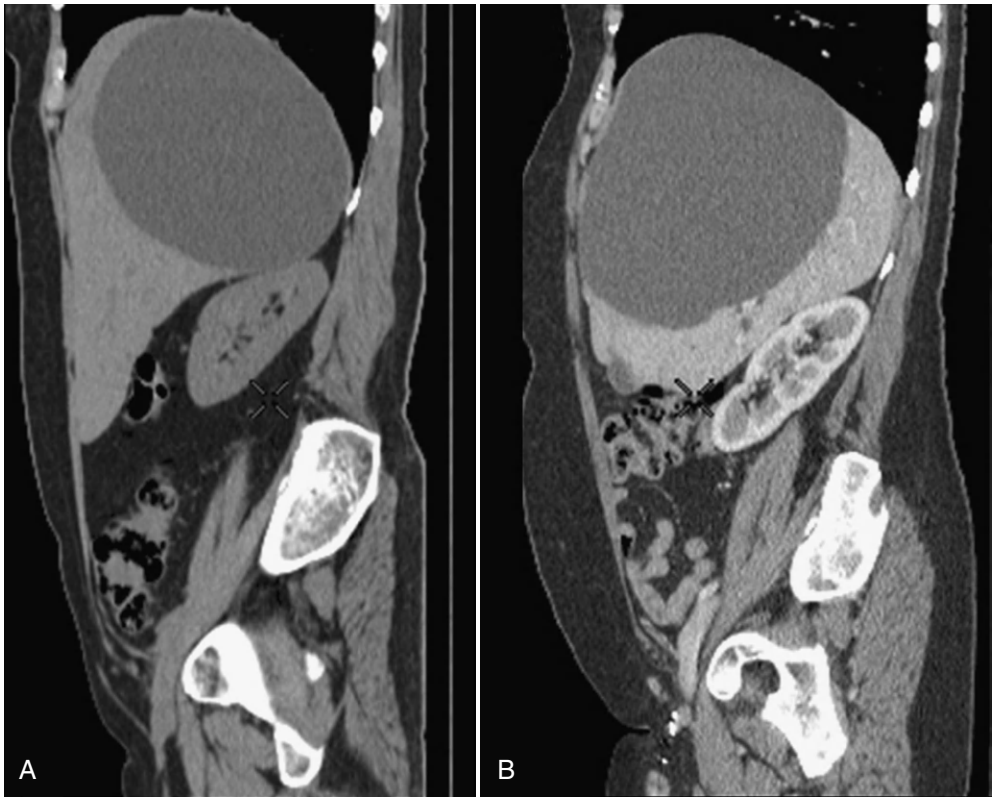


FIGURE 69B.4. Two examples of large cysts located in the right liver (transverse view). A cyst with a predominantly posterior development (**A**) may be more difficult to fenestrate by laparoscopy than an anterior cyst (**B**), and sclerotherapy may be more successful.

Fenestration

Method

The surgical treatment of choice for a single, large, symptomatic cyst is fenestration that consists of an excision of the roof of the cyst to establish a large communication between the cyst and the peritoneal cavity. Fluid continues to be produced by the epithelial lining, but it is reabsorbed by the peritoneum and the cyst cavity collapses. This treatment is extremely simple because symptomatic cysts are virtually always large and have a protrusion of part of their wall outside the liver. Only the protruding part of the cyst wall should be excised; there is no need to enter the liver parenchyma, which is the main cause of intraoperative and postoperative bleeding of biliary leaks, nor is there a need to remove the cyst completely.

The procedure has been described by laparotomy but is currently most often performed by laparoscopy, which offers the advantage of being less invasive and ensuring a quicker recovery. A pneumoperitoneum is established, the cyst is punctured and incised with either scissors or electrocautery, and the cyst wall is widely excised. If transection is performed along a thin part of adjacent parenchyma to ensure a wider opening—that is, if the protruding part of the cyst is small—endovascular staplers may occasionally be used to secure vasculobiliary structures that are compressed at the periphery of the cyst wall. The internal lining of the cyst is examined, and if a biliary communication is suspected, intraoperative cholangiography should be performed. Some investigators have advocated treating the remnant cyst epithelium by argon laser beam coagulation or electrocoagulation to destroy the epithelium. In any case, the excised portion of the cyst is sent for pathologic analysis. Suction drainage is optional.

Limitations

Cysts protruding into segments VII or VIII are not formal contraindications to laparoscopic fenestration, but the procedure is unlikely to be very successful in such a case because limited access will prevent wide unroofing. In addition, the margins of the opening may adhere to the diaphragm, and the risk of cyst recurrence is increased as a result of contained secretion (Fig. 69B.4). Open fenestration is a wise alternative in this circumstance.

Complications

The most severe intraoperative complication is bleeding, and transfusion has occasionally been required (Loehe et al, 2010). This occurs when the liver parenchyma, not the cyst wall, is opened. Conversion, the most frequent indication for which is bleeding, is required in less than 5% of patients.

Postoperative complications are rare, and patients are usually discharged after 1 to 3 days. No deaths have been reported, and morbidity ranges between 0% and 15% (Gall et al, 2009; Loehe et al, 2010). The most severe complications include biliary leak and hemorrhage, which result from reexpansion of biliary and vascular structures that were compressed at the interface between the cyst wall and the parenchyma and that were inadequately secured. If the periphery of the opened cyst is thick, it should be closed with running sutures; an alternative is to use an endovascular stapler on these portions of the cyst wall because it allows wide fenestration while maintaining hemostasis. Ascites is very rare after fenestration of simple cysts, unlike PCLD (see below).

Long-Term Outcome

Long-term efficacy of fenestration for simple cysts is still somewhat unclear. Reported experience is limited, follow-up is usually short, and results are not always stratified according to the number of cysts (i.e., simple cysts vs. PCLD). Furthermore, cyst recurrence, symptomatic recurrence, and the need for additional treatment are not always distinguished. It is usually assumed that although cysts may recur in one third to one half of patients, symptomatic recurrence occurs in less than 5% (Hansman et al, 2001; Morino et al, 1994; Tan et al, 2005); however, higher figures of symptomatic recurrence (15% to 20%) have been reported (Erdogan et al, 2007; Gall et al, 2009; Martin et al, 1998).

A more precise comparison of preoperative and postoperative symptoms has recently been published (Loehe et al, 2010). Abdominal pain was improved in 91% of patients and disappeared in 68%. Other symptoms—including impaired gastrointestinal transport, early satiety, nausea, vomiting, and acid reflux—disappeared in 53% of the patients. Overall, within 1 year of surgery, 32% of the patients developed or had persistent subjective symptoms in this series, but this rate decreased to 7% and 2% after 3 and 5 years, respectively. During follow-up, 9% required reoperation.

Persistent symptoms may be related to technical failure or reflect inaccurate selection, with some patients undergoing surgery for non–cyst-related symptoms (see Chapter 69A).

Sclerotherapy Versus Fenestration

Although both techniques have been used for years, no randomized or prospective comparative analysis has been done. As a rule, the severity of symptoms that leads to treatment has not been standardized, and recurrence is poorly defined. It would seem that both methods are almost as effective (Erdogan et al, 2007; Furuta et al, 1990; Moorthy et al, 2001). Our policy is to systematically attempt sclerotherapy first; fenestration is indicated in cases of recurrence, but location of the protruding part of the cyst may influence this choice (see Fig. 69B.4).

POLYCYSTIC LIVER DISEASE

Symptoms in PCLD are related mainly to the volume of the entire liver rather than to the volume of a specific cyst. Although palliation with percutaneous alcohol sclerotherapy or laparoscopic fenestration has been reported, neither proves effective in the long term in the most frequent forms of PCLD (Robinson et al, 2005). The aim of treatment is instead to decompress and reduce the size of the entire liver or to remove as many cysts as possible. In highly symptomatic patients, these objectives can be achieved by open fenestration, liver resection, or liver transplantation. Patients should be carefully informed of the limitations and risks of these procedures. Medical alternatives have been recently introduced, although larger studies are required to confirm their clinical impact.

Nonsurgical Treatments

Medical Treatment

AVOIDANCE OF ESTROGEN REPLACEMENT THERAPY. Avoidance of estrogen replacement therapy (ERT) would seem logical as medical treatment for PCLD because hepatic cystic disease may worsen under the influence of hormones of pregnancy or exogenous female steroid hormones (Shrestha et al, 1997). However, proof that avoidance is effective is lacking, and the benefits and drawbacks should be discussed on an individual basis.

SOMATOSTATIN ANALOGUES. Cyclic adenosine monophosphate (cAMP) is a potent mediator of cholangiocyte proliferation and secretion of fluid into cysts (see Chapter 69A). Somatostatin receptors are expressed on cholangiocytes; when triggered, this activates a signaling cascade that suppresses cAMP. Somatostatin blunts hepatic cyst expansion by blocking secretin-induced cAMP generation (Masyuk et al, 2007). It also suppresses the expression of insulin-like growth factor 1 (IGF-1), vascular endothelial growth factor (VEGF), and other cystogenic growth factors and downstream signaling from their receptors (Pyronnet et al, 2008). Two randomized controlled trials have recently demonstrated that 6 or 12 months of treatment with lanreotide, a long-acting somatostatin analogue, was associated with a significant reduction of liver volume in patients with PCLD, with or without autosomal dominant polycystic kidney disease (ADPKD), compared with placebo-treated controls (Hogan et al, 2010; van Keimpema et al, 2009). This was especially the case in patients with larger livers; however, this decrease in volume was limited overall, on average 3% to 5%. Severity of abdominal symptoms was not improved (Van Keimpema et al, 2009), although some features of quality of life scores were.

MTOR INHIBITORS. Although mTOR-mediated signaling has been shown to play a role in cyst expansion (see Chapter 69A), sirolimus inhibits this pathway and promotes apoptosis. Follow-up of transplant recipients with ADPKD whose immunosuppression contained sirolimus has shown that both the native kidney (Shillingford et al, 2006) and liver volume (Qian et al, 2008) decreased compared with those of patients who received the more classic calcineurin inhibitor immunosuppression. The clinical impact of this size reduction was not assessed. Trials have been lauched in ADPKD patients to halt the progression of kidney disease (Perico et al, 2010), but long-term efficacy and safety studies are required. This treatment should not be used outside these trials.

ARTERIAL EMBOLIZATION. Transcatheter embolization, also known as *renal contraction therapy,* has been advocated in Japan since the mid-1990s for patients with ADPKD (Ubara et al, 2002), and it has been applied to PCLD since the early 2000s (Takei et al, 2007). The rationale is that kidney cysts are supplied by well-developed arteries, but hepatic cysts in ADPKD patients are mostly supplied from hepatic arteries but not from portal veins. Embolization may use microcoils or polyvinyl alcohol particles, ranging in size between 150 and 250 μm, and targets hepatic artery branches supplying the hepatic segments mainly replaced by the cysts (Park et al, 2009;Takei et al, 2007). Considering the extent of the disease and the number of small-branch arteries to occlude, the procedure is demanding. Reported experience is limited, but the largest series includes 30 patients in whom intrahepatic cyst volume was significantly reduced (from $6.667 \pm 2.978\ cm^3$ to $4.625 \pm 2.299\ cm^3$), whereas the volume of hepatic parenchyma increased (Takei et al, 2007). Improvement of symptoms was observed in most patients but required several months to be optimal. No major complications were related except for classic but occasionally severe postembolization syndrome (Takei et al, 2007; Park et al,

2009). Because targeted segments are those that also have an occluded portal flow, it is possible that the procedure acts as a hepatectomy, favoring regeneration of noncystic parenchyma.

Cyst-Targeted Treatments

As a rule, percutaneous sclerotherapy and laparoscopic fenestration are futile in highly symptomatic patients with massive, diffuse involvement of the liver. However, some patients may have one to five large cysts coexisting with a varying number of very small cysts. In these patients, symptoms are related only to the large cysts, which should be treated individually, as if they are a single cyst. The small cysts, which are often located deep in the liver, should not be treated.

PERCUTANEOUS SCLEROTHERAPY. Percutaneous sclerotherapy is usually considered ineffective in patients with PCLD because symptoms are related to the multiplicity of the cysts, which cannot all be targeted. Furthermore, the rigid architecture of the parenchyma, as well as the presence of smaller adjacent cysts, prevents cyst collapse. Symptomatic recurrence requiring additional treatment occurs in most patients (Erdogan et al, 2007); however, a small subset of patients have one or a few strategically located large cysts (>6 cm) that may account for at least part of the symptoms and can be managed as simple cysts (see Fig. 69B.3). The technique and results do not differ from those for simple cysts. Cyst resolution is gradual and may only be optimum within 1 year of therapy.

Fenestration

Technique and Indication

Initially described by Lin and colleagues (1968), the aim of fenestration is to unroof as many cysts as possible, starting with superficial cysts and proceeding stepwise to the deeper cysts. Open fenestration was historically the standard therapy, but a laparoscopic approach has also been used recently; with few exceptions, this does not allow sufficient and safe access to the deeper cysts and, as a rule, a laparoscopic approach is contraindicated (Kabbej et al, 1996; Morino et al, 1994). The exceptions are patients with a limited number of large and superficial cysts that can be individually treated as single cysts (Fig. 69B.5).

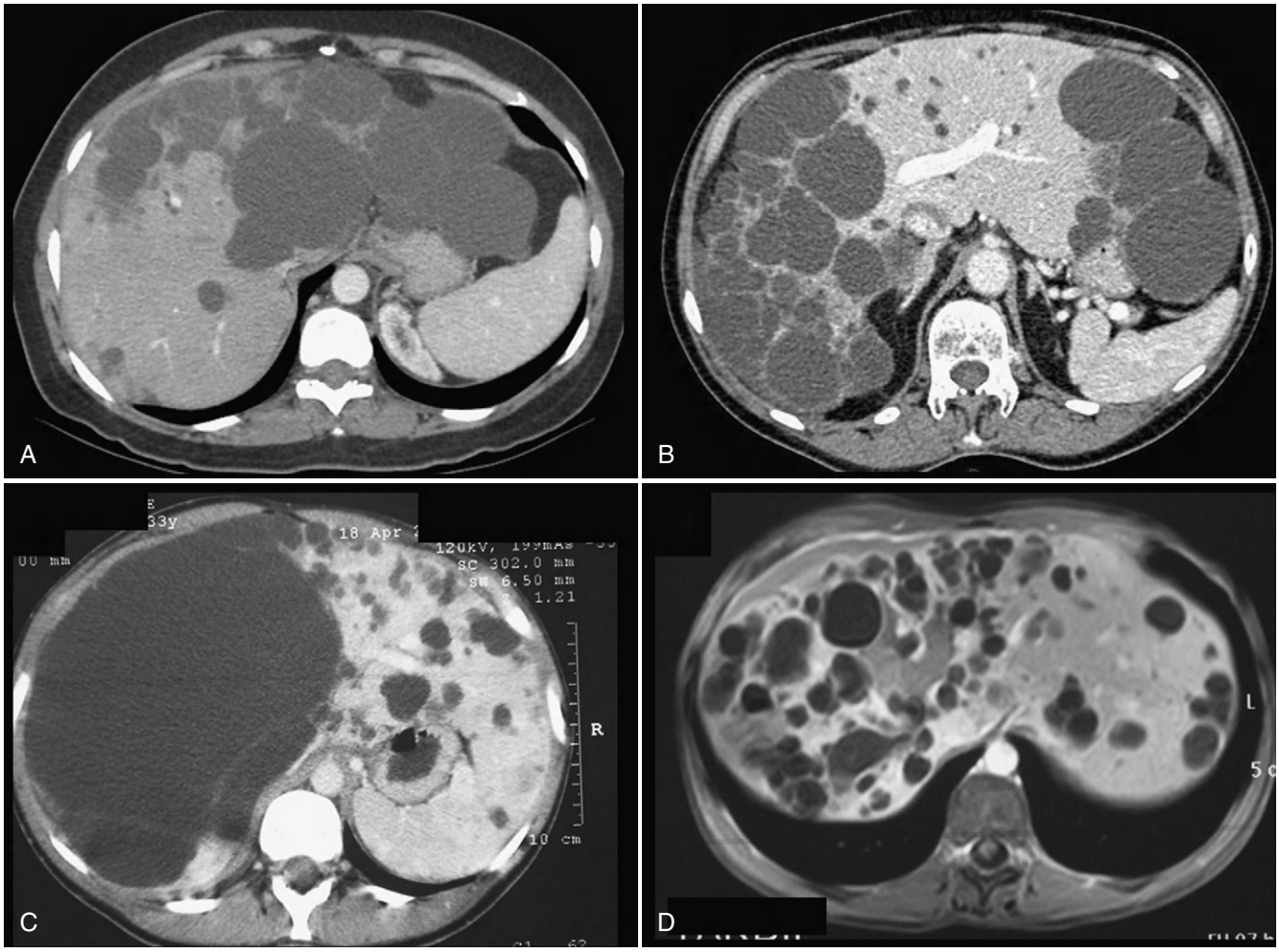


FIGURE 69B.5. Examples of patients with polycystic liver disease but with limited cyst involvement, in whom laparoscopic fenestration of the cysts could be considered. **A,** Cysts are mainly located in the left lateral section. **B,** Fenestration of the cysts in the left lateral section is likely to be effective, whereas fenestration of those in the right liver is not because the cysts are small and deeply located. **C** and **D,** The same patient before and after fenestration of a large cyst in the right liver. Note that the large cysts collapses, small cysts remain, and the obstruction of the termination of the hepatic vein persists, which can account for some persisting symptoms of congestion.

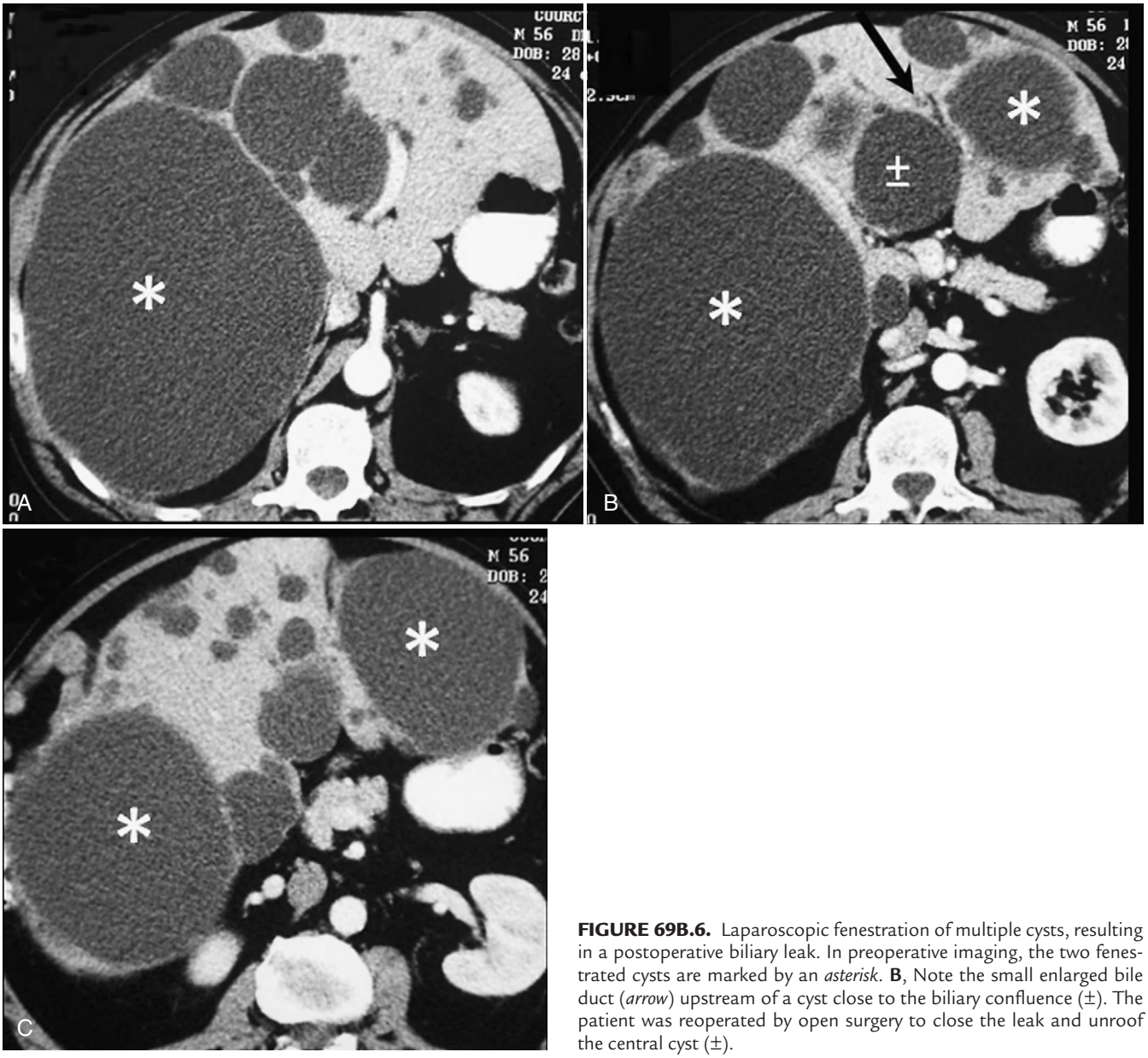


FIGURE 69B.6. Laparoscopic fenestration of multiple cysts, resulting in a postoperative biliary leak. In preoperative imaging, the two fenestrated cysts are marked by an *asterisk*. **B**, Note the small enlarged bile duct (*arrow*) upstream of a cyst close to the biliary confluence (±). The patient was reoperated by open surgery to close the leak and unroof the central cyst (±).

Complications

The main intraoperative hazard is inadvertent injury of vascular structures that are compressed at the periphery of the cysts. What looks like a simple membrane between two cysts may in fact be a large hepatic vein; therefore it may be wise to puncture it with a fine needle before widely opening it. Hemorrhage from hepatic vein injury can be massive in patients with PCLD because the termination of the hepatic vein is frequently compressed by cysts, resulting in outflow obstruction. Biliary injury may also occur when cysts located around the biliary confluence are approached. As for hepatic veins, the biliary confluence may be compressed between adjacent cysts, thus becoming unrecognizable. Most complications occur when deeper, localized cysts are treated.

Fenestration for PCLD is associated with a higher incidence of postoperative biliary leak compared with fenestration for simple cysts. This occurs particularly when cysts are left untreated around the biliary confluence (Fig. 69B.6). Performing intraoperative cholangiography to ensure that biliary drainage of both hemilivers is normal at the end of the procedure is advisable.

Postoperative ascites is also a frequent complication. It may result in delayed wound healing or in ascites superinfection. The mechanism is probably multifactorial and includes persistent secretion by the epithelial lining, relative outflow obstruction, or impaired kidney function.

Mortality, although at low rates, has been reported, and morbidity averages 31% (Table 69B.1).

Outcome

The incidence of symptomatic recurrence overall is 35% (see Table 69B.1). Results are largely influenced by morphologic aspects of the disease.

Table 69B.1

Treatment of PCLD by Fenestration in Clinical Series

Reference	No. Patients (Open/Laparoscopic)	Deaths (n)	Morbidity (n)	Recurrent Symptoms (n)	Follow-up
Van Erpecum et al (1987)	9 (9/0)	1	0	1	<12 mo
Turnage et al (1988)	5 (5/0)	1	1	2	10 mo
Sanchez et al (1991)	7 (7/0)	0	NA	4	18 mo
Farges & Bismuth (1995)	13 (13/0)	0	9	3	84 mo
Morino et al (1994)	9 (9/0)	0	4	4	NA
Kabbej et al (1996)	13 (0/13)	0	6	10	26 mo
Gigot et al (1997)	10 (8/2)	0	6	2	71 mo
Koperna et al (1997)	39 (34/5)	0	NA	7	75 mo
Martin et al (1998)	13 (6/7)	0	4	7	37 mo
Marks et al (1998)	7 (0/7)	0	4	0	NA
Katkhouda et al (1999)	8 (0/8)	0	3	1	NA
Hansman et al (2001)	2 (2/0)	0	0	2	NA
Fiamingo et al (2003)	6 (0/6)	0	3	1	34 mo
Robinson et al (2005)	11 (0/11)	0	2	6	41 mo
Konstadoulakis et al (2005)	9 (0/9)	1	0	2	26 mo
Barahona-Garrido et al (2008)	16 (12/4)	0	4	3	68 mo
Erdogan et al (2007)	4 (2/2)	0	2	3	15 mo
Van Keimpema et al (2008)	12 (0/12)	0	3	1	18 mo
Gall et al (2009)	24 (11/13)	0	8	17	77 mo
Loehe et al (2010)	22 (6/16)	0	5	—	76 mo
Schnelldorfer et al (2009)	10 (8/2)	0	0	—	96 mo
TOTAL	249	3	64 (31%)	76 (35%)	

Qualitative evaluation is detailed in the text.
PCLD, polycystic liver disease; NA, not available

HEPATECTOMY

Partial liver resection has been proposed, in combination with fenestration of the remnant liver, to reduce liver volume and increase regeneration of the noncystic liver (Que et al, 1995). This is made possible by the frequently asymmetric distribution of the cysts, with some areas being relatively spared (Fig. 69B.7). Regeneration is associated with expansion of these areas, whereas the volume of the remaining small cysts remains unchanged or progresses very slowly. Although this technique is highly successful in some patients, it is technically demanding, associated with a high morbidity rate, and its indications are becoming more selective and restrictive.

Technique

The site and extent of resection are dictated by the location of the cysts, and surgery aims at removing as much cystic liver as possible. Care should be taken, however, to leave a sufficient amount of functional remnant liver. In particular, evidence of congestion related to outflow obstruction should be ruled out. This can be done on imaging by carefully analyzing the termination of the hepatic veins after reconstruction and looking for a collateral circulation between hepatic veins, usually running close to the liver surface. A biopsy may also be useful, although the interpretation of results is not standardized.

The liver resection is most often a left lateral sectionectomy, a left hepatectomy, or a right hepatectomy. The main hazard is injury of the hepatic vein or of the biliary confluence, a danger compounded by the fact that the usual landmarks are displaced by the cysts and are hardly recognizable. Intraoperative US is of little help because vascular and biliary structures are compressed, and the presence of cysts interferes with visualization. Extensive fenestration of the larger cysts is performed first to decompress the liver, gain access to its dome, and mobilize the right or left triangular ligaments. Transection is performed either in the noncystic parenchyma or proceeding stepwise between the cystic cavities. When approaching the biliary confluence, the surgeon should always bear in mind that glissonian pedicles are compressed between the cysts, and that no cyst wall should be cut before being sure that this is not the case. The same holds true for the hepatic veins close to their termination.

After hepatectomy, the remnant liver is widely fenestrated (see Fig. 69B.7). Intraoperative cholangiography may be advisable to ensure that no bile duct injury has occurred and that bile drains freely (i.e., that a deeply situated cyst does not compress the remnant right or left duct). Considering the high rate of biliary leak, a leakage test should also be performed; it is also wise to place running sutures along the transected cyst walls. After right-sided resections, care should be taken to secure the remnant liver in a stable position, resulting in adequate venous outflow. A suction drain is frequently left in the abdomen.

Morbidity and Mortality

Hepatectomy for PCLD, although a benign disease, is a demanding procedure with a definite risk of mortality and high morbidity rates, even when performed by highly experienced

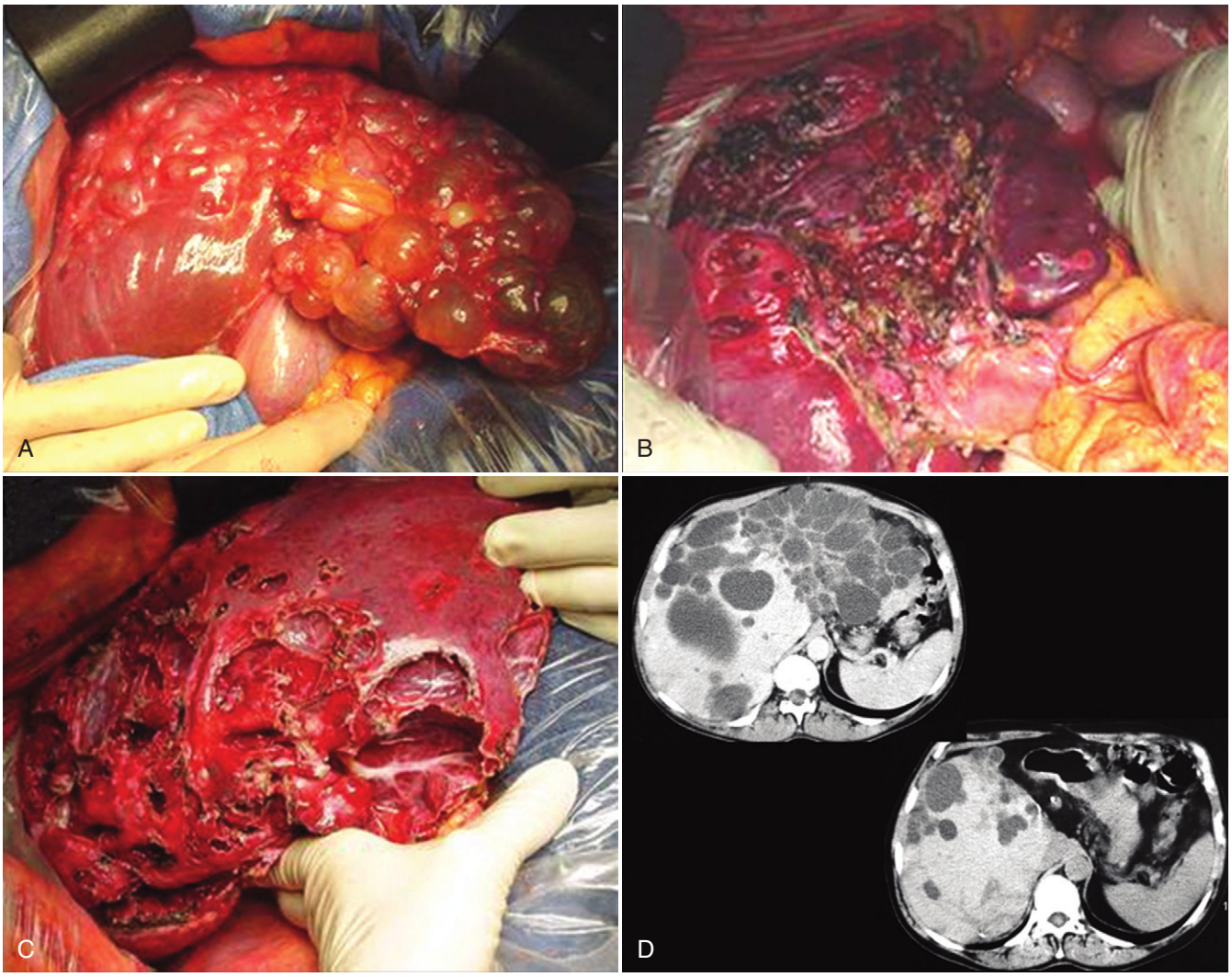


FIGURE 69B.7. Principle of liver resection for polycystic liver disease. **A,** The liver is massively enlarged, but some areas of noncystic liver remain. **B,** An extended left hepatectomy is performed. **C,** The remaining right liver is widely fenestrated. **D,** Preoperative and postoperative computed tomographic scan shows an expansion of the noncystic liver.

hepatopancreatobiliary surgeons. The main intraoperative risk is that of bleeding; and perioperative transfusions are required in 50% to 80% of the patients. Injury to the main bile duct within the liver remnant occurs in 5% (Aussilhou et al, 2010; Schnelldorfer et al, 2009).

Mortality rates in the literature average 4% (Table 69B.2) and has been related to abdominal sepsis, acute Budd-Chiari syndrome, and complications related to treatment of complications. Intracranial hemorrhage from ruptured aneurysms have also been described (see Chapter 69A).

Morbidity rates average 64% (see Table 69B.2), but some consider that it is virtually constant. The most frequent complications are ascites and pleural effusion, and the mechanism is likely the same as for fenestration: persistent fluid secretion by the remnant epithelial lining and relative outflow obstruction. However, increased portal pressure and lymphatic leakage associated with liver resection increase this risk. Furthermore, patients undergoing liver resection, rather than fenestration tend to have more severe PCLD with malnutrition. Although ascites resolves in most patients within 1 month, some have required stenting of the inferior vena cava or hepatic veins to resolve outflow obstruction (Grams et al, 2007; Schnelldorfer et al, 2009). The next most frequent complications are hemorrhage and biliary leak; approximately 10% of patients require reoperation for management of these. In contrast, liver failure is infrequent. Hepatectomy is usually not performed in patients with severe kidney failure. In those with moderate impairment, although a slight transient deterioration of kidney function may be observed, most patients have recovered their preoperative creatinine levels by the time of discharge.

Preoperative risk factors for complications include kidney dysfunction, ascites, and denutrition (Schnelldorfer et al, 2009). In the presence of these symptoms, liver transplantation is indicated.

Long-Term Outcome

Results are highly variable among series and among patients. This reflects the diversity of the clinical and morphologic situations as well as the extent of resection. The average reduction in hepatic volume achieved ranges between 50% and 75% (Aussilhou et al, 2010; Schnelldorfer et al, 2009), which results

Table 69B.2

Treatment of PCLD by Combined Resection and Fenestration

Reference	No. Patients	Mortality	Morbidity	Recurrent Symptoms	Follow-up
Turnage et al (1988)	3	2 (67 %)	2 (67 %)	33%	10 mo
Vauthey et al (1991)	5	0	5 (100 %)	0	14 mo
Newman et al (1990)*	9	1	5	1	17 mo
Henne-Bruns et al (1993)	8	0	3 (38%)	50%	15 mo
Madariaga et al (1993)	2	0	NA	0	>96 mo
Que et al (1995)*	31	1 (3%)	15 (48%)	3%	28 mo
Soravia et al (1995)	10	1 (10%)	2 (20%)	33%	68 mo
Koperna et al (1997)	5	0	NA	0	—
Martin et al (1998)	9	0	6	0	NA
Vons et al (1998)	12	1 (8%)	10 (83%)	2	34 mo
Hansman et al (2001)	2	0	0	0	NA
Yang et al (2004)	7	0	7 (100 %)	0%	20 mo
Li et al (2008)	21	0	16 (76%)	14%	61 mo
Schnelldorfer et al (2009)*	124	4 (3%)	78 (63%)	—	96 mo
Aussilhou et al (2010)	45	2 (4%)	32 (71%)	30%	41 mo
TOTAL	253	10 (4%)	161 (64%)		

*Studies held at the same institution.
PCLD, polycystic liver disease; NA, not available

in considerable objective and subjective improvement in more than 75% of the patients (Fig. 69B.8). Symptoms may recur because of the enlargement of some cysts that were left untreated, and such patients may benefit from targeted treatments, sclerotherapy in particular. In addition, other recurrences are related to the progressive reexpansion of the entire liver. It has recently been estimated that after 4 years of follow-up, the liver was on average 11% larger than the initial remnant volume after resection (Schnelldorfer et al, 2009). However, half of the patients have stable volumes, a difference that may also reflect the variable natural history of the disease.

TRANSPLANTATION

Because PCLD is a genetic disease, liver transplantation is the only curative treatment (see Chapter 97A). As for any benign disease, there is some reluctance to perform this high-risk procedure for this indication, considering that liver function is preserved. However, some patients with massive liver involvement have incapacitating symptoms that may be life threatening (ascites, denutrition); in this situation, and when liver resection is considered too high risk with little anticipated efficacy, liver transplantation is the only option (Fig. 69B.9). Quality of life is excellent after transplantation despite the need for long-term immunosuppression.

In countries where graft allocation is patient oriented, based on Model for End-Stage Liver Disease (MELD) criteria, exceptions have been implemented because patients with PCLD who do not have liver failure would otherwise have no chance to undergo transplantation (Arrazola et al, 2006).

Technique

Most transplantations have been performed with livers from brain-dead donors, although living donors have also been used (Mekeel et al, 2008). The technique is the same as that for other indications, but, as for hepatectomy, extensive fenestration is required first to gain access to the liver. The inferior vena cava can be preserved, which is important in the context of living donation, but transient clamping may be necessary to achieve this. A transient portocaval shunt is required in most instances because PCLD does not induce portal hypertension with spontaneous portosystemic shunts.

In patients with ADPKD (see Chapter 69A), simultaneous kidney transplantation is not necessary if the glomerular filtration rate is more than 60 mL/min (Martin et al, 2008) but is indicated if it is less than 30 mL/min. For values between 30 and 60 mL/min, single liver transplantation appears safe, provided renal-sparing immunosuppression is used. Secondary kidney transplantation may be required in half of the patients with the drawback of previous immunization through liver transplantation (Jeyarajah et al, 1998; Pirenne et al, 2001; Ueno et al, 2006).

Perioperative Risk

Liver transplant for PCLD is also technically demanding, particularly in patients who have undergone previous procedures. Virtually all patients require an intraoperative transfusion. Reported mortality rate is 16% overall (Table 69B.3) and is mainly related to sepsis. As for other indications of transplantation, perioperative mortality and morbidity, in particular from sepsis, are increased in patients with the most severe forms of the disease. Such severe forms are usually associated with malnutrition (Lang et al, 1997; Pirenne et al, 2001).

Long-Term Outcome

The 5-year survival rate in the registries is 80% to 84%, higher than for most other indications. Quality of life is excellent (Kirchner et al, 2006), and short- and long-term results are the same for liver transplantation as for combined transplantation of liver and kidney.

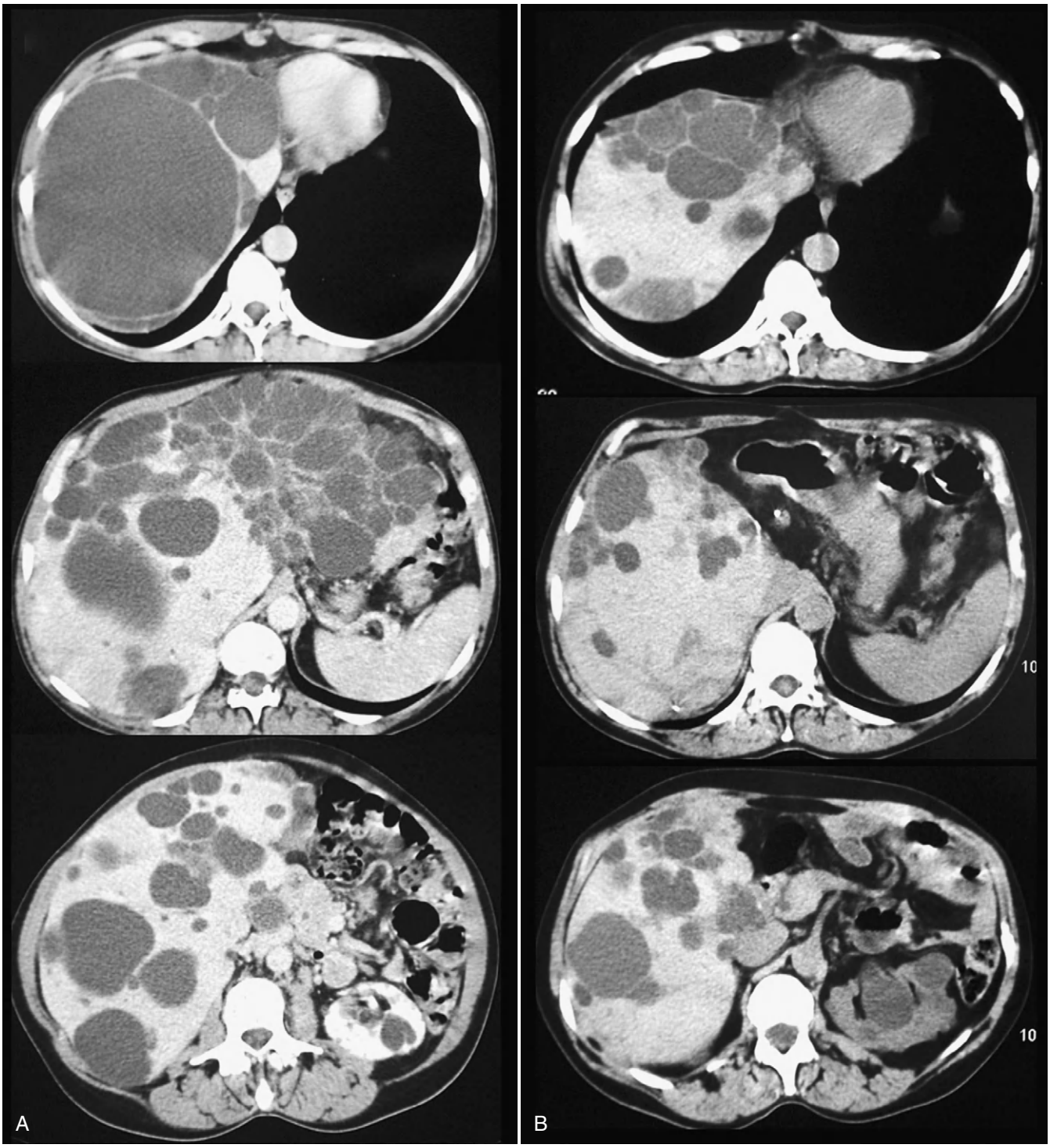


FIGURE 69B.8. Computed tomographic scan in a patient who had undergone left hepatectomy and fenestration of the right liver for polycystic liver disease. **A,** Preoperative view. **B,** View 24 months after surgery.

Choice of Surgical Treatment

PCLD covers a wide range of morphologic and clinical situations (see Chapter 69A), and three classifications have been proposed to help the clinician chose among the various treatment options. One classification was designed to identify under which circumstances fenestration of PCLD is indicated (Gigot et al, 1997). The two others have more recently aimed at defining the limits of resection (Li et al, 2008; Schnelldorfer et al, 2009), but all three classifications overlap to some degree (Fig. 69B.10).

Gigot's classification mainly relies on the number and size of the cysts. Type I is defined by a limited number (<10) of large cysts (>10 cm), in which each cyst can be treated as if it were a simple cyst. Laparoscopic fenestration is indicated in this

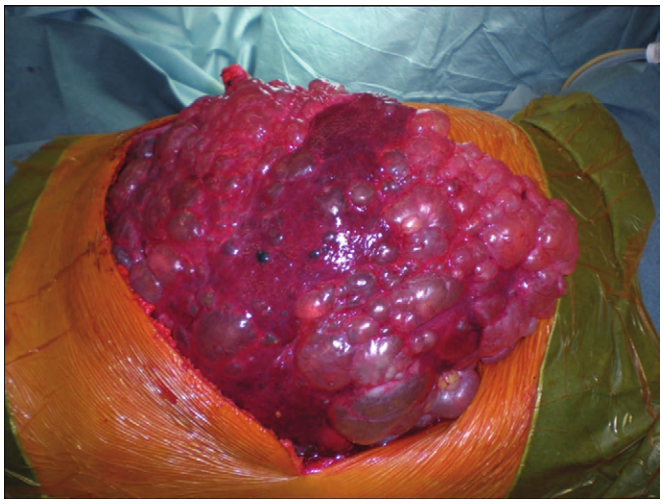


FIGURE 69B.9. Intraoperative view of a patient undergoing liver transplantation for polycystic liver disease. Note that the liver is massively enlarged, and there is hardly any spared area of noncystic liver.

Table 69B.3

Liver Transplantation with or Without Kidney Transplantation for Highly Symptomatic PCLD in the Literature and Reported Deaths

Reference	No. Patients	LT	LT + KT	Deaths
Starzl et al (1990)	4	2	2	1
Uddin et al (1995)	3	3	0	1
Klupp et al (1996)	10	5	5	1
Washburn et al (1996)	5	4	1	1
Lang et al (1997)	17	9	8	5
Swenson et al (1998)	9	6	3	1
Jeyarajah et al (1998)	6	3	3	2
Pirenne et al (2001)	16	15	1	2
Becker et al (2003)	17	0	17	3
Gustafsson et al (2003)	7	4	3	0
Kirchner et al (2006)	36	21	15	5
Ueno et al (2006)	14	9	5	1
Krohn et al (2008)	14	11	3	1
Taner et al (2009)	13	6	7	3
Schnelldorfer et al (2009)	7	4	3	2
Aussilhou et al (2010)	27	4	23	4
TOTAL	214	112	102	34 (16%)

PCLD, polycystic liver disease; LT, liver transplantation; KT, kidney transplantation

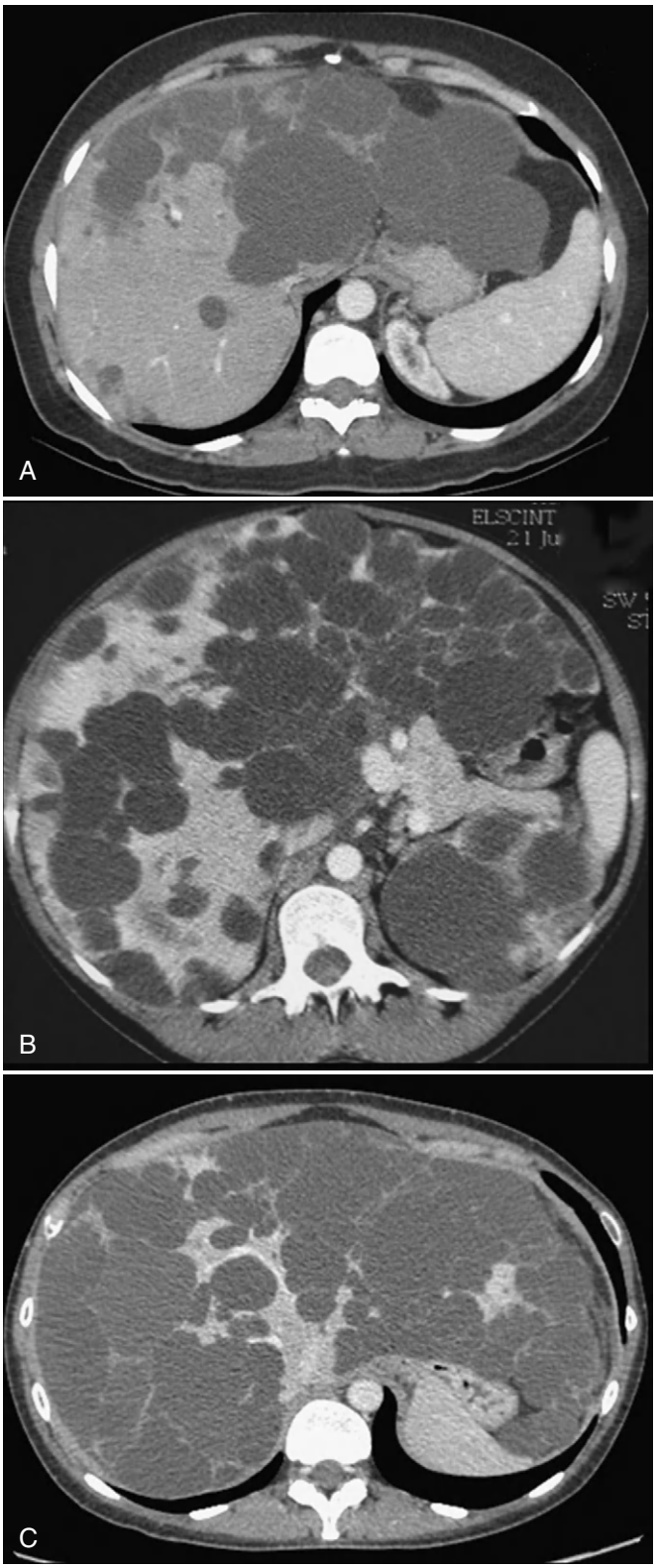


FIGURE 69B.10. Treatment according to severity of polycystic liver disease. **A,** A mild form can be treated by laparoscopic fenestration or hepatectomy. **B,** A moderate form in which fenestration is unlikely to be effective; left hepatectomy can be considered because the future remnant liver is large and has normal inflow and outflow. **C,** A severe form requiring liver transplantation.

situation, but these patients account for less than 10% of PCLD. Type II corresponds to diffuse involvement of liver parenchyma by multiple medium-sized cysts with remaining large areas of noncystic liver parenchyma; some patients with type II disease can benefit from open fenestration. Type III corresponds to the most severe form of adult polycystic liver disease with massive, diffuse involvement of liver parenchyma by small and medium-sized liver cysts, with only a few areas of remaining normal liver parenchyma between cysts; it is not an indication for fenestration.

Li's classification differs in that it also takes into account deeply located cysts that would be left in place in the remnant liver. Types A and B are defined as the presence of less than or more than 15 cysts, respectively. This classification is correlated with the outcome after resection.

Schnelldorfer's classification stratifies patients according to symptoms, number and size of the cysts, volume of relatively normal parenchyma, and whether this spared parenchyma has a normal vascular inflow and outflow. Fenestration is indicated in patients with moderate symptoms resulting from a limited number of large cysts, preserving more than two sectors with adequate inflow and outflow. Hepatectomy is indicated when symptoms are more severe and disease is more extensive, as long as the future remnant liver corresponds to more than one sector with normal vascularization. Highly symptomatic patients with insufficient remnant parenchyma in terms of volume of vascularization should undergo transplantation; patients with ascites or denutrition should undergo transplantation and not resection.

Although the natural history of PCLD is highly variable among patients, progression is fairly linear for any given patient (see Chapter 69A). Therefore age at the time of diagnosis, first symptoms, incapacitating symptoms, and kidney involvement are useful markers to predict the future need for transplantation. When transplantation will likely be indicated at some stage of the disease, fenestration and resection should be considered with caution to avoid increasing the risks of transplantation.

CONCLUSION

Treatment is only indicated when symptoms related to cysts are present. Single large cysts can be equally treated by sclerotherapy or laparoscopic fenestration. In patients with symptoms related to a limited number of large cysts, fenestration is the treatment of choice. In PCLD patients whose symptoms cannot be linked to one or a few large cysts, treatment may range from observation to transplantation, depending on the severity of symptoms and whether areas of noncystic parenchyma can be preserved. Liver resection, and to some extent fenestration, should be avoided if liver transplantation is anticipated, considering the likelihood of cyst progression and the added complexity of the liver transplant procedure, if prior cyst fenestration or resection has been performed.

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CHAPTER 70B

Nonhepatic surgery in the cirrhotic patient

Amelia J. Hessheimer, Truman M. Earl, and William C. Chapman

OVERVIEW

Chronic liver disease and cirrhosis were the twelfth leading cause of death in the United States and resulted in more than 30,000 deaths in 2009 (Kochanek et al, 2011). Chronic viral infection and alcohol abuse account for the majority of the disease burden globally, but the incidence of obesity-associated nonalcoholic fatty liver disease accounts for an ever-increasing proportion of cases, especially in Western societies. Furthermore, clinicians continue to gain knowledge and skills to care for patients with cirrhosis in the end stages of their disease. These facts explain why a significant increase has been seen in the number of patients with comorbid liver disease and cirrhosis encountered in both general and specialty surgical practice.

Cirrhosis can have dramatic effects on multiple organ systems, making surgery on the cirrhotic patient a complex and difficult undertaking. A recent, large, population-based study demonstrated that people with cirrhosis, in particular those with portal hypertension, have significantly worse outcomes after elective operations than those without (Fig. 70B.1; Csikesz et al, 2009). The mere act of opening the abdominal wall in a cirrhotic patient with portal hypertension causes collateral blood vessels to dilate and may lead to systemic hypotension and hepatic decompensation secondary to ischemia (Haskal et al, 1994; Norton et al, 2003).

Extrahepatic surgery in the cirrhotic patient may be a formidable undertaking. The objective of this chapter is to provide practical knowledge on how to evaluate these patients before surgery as well as current information on some of the most commonly performed procedures in this unique population.

EVALUATION AND STRATIFICATION OF LIVER DISEASE

The decision regarding whether a cirrhotic patient is medically fit to undergo an operation can be difficult to make. Many factors must be considered, but the most important are the magnitude and necessity of the proposed operation, the nonhepatic comorbidities of the patient, and the severity of the liver disease. Numerous factors have been correlated with poor outcome in patients with cirrhosis—including low albumin levels, blood transfusion requirements, abnormal coagulation, and ascites—and various scoring systems to gauge these have evolved. The first, most widely used scoring system is the Child-Turcotte-Pugh (CTP) system, which incorporates several objective and subjective variables to stratify severity of liver disease. Historically, patients with CTP scores of A, B, or C have been shown to have operative mortality rates of 10%, 30%, and 80%, respectively (Garrison et al, 1984; Mansour et al, 1997).

The Model for End-Stage Liver Disease (MELD) score was developed to predict death after transjugular intrahepatic portosystemic shunt (TIPS) in an effort to determine who was likely to progress toward needing liver transplantation. In an effort to improve on the tripartite CTP system, researchers have recently evaluated to ability of MELD to predict morbidity and death after nonshunt abdominal surgery (Befeler et al, 2005; Farnsworth et al, 2004). As with CTP, MELD correlates with risk of postoperative death (Figs. 70B.1 and 70B.3). Several reports have found that MELD is superior to CTP in predicting postoperative problems, although these improvements generally are modest (Perkins et al, 2004). Interestingly, the survival rates from the more recent series indicate a fairly dramatic improvement in survival compared with older series (Fig. 70B.3).

In addition to factors considered in MELD and CTP scoring, other factors have been identified for risk stratification and prediction in cirrhotic patients undergoing major operations. These include elevated creatinine level, chronic obstructive pulmonary disease (COPD), male gender, and an American Society of Anesthesiologists (ASA) class of IV or V (Ziser et al, 1999). Teh and colleagues (2007) demonstrated ASA classification as a useful marker to further stratify the comorbid illness in cirrhotic patients preoperatively. This case-control study of cirrhotic patients who underwent major nontransplant operations identified MELD score, ASA class, and age as predictors of perioperative death. An ASA class of IV was equivalent to the addition of 5.5 MELD points in added risk, and age greater than 70 years was equivalent to three additional MELD points. A single point increase in MELD score was associated with a 15% increase in perioperative death. Emergency surgery predicted in-hospital death, although patients undergoing emergency operations had a higher median MELD score. ASA class V was the strongest predictor of 7-day mortality, and MELD score was the most robust predictor beyond 7 days. The median survival of patients in this series was 4.8 years for a MELD score of 0 to 7, 3.4 years for a score of 8 to 11, 1.6 years for 12 to 15, 64 days for 16 to 20, 23 days for 21 to 25, and 14 days for 26 or greater.

PERIOPERATIVE MANAGEMENT AND OPTIMIZATION

The perioperative management of patients with cirrhosis involves aggressive attempts to control the various manifestations of their underlying disease. Much of this is covered at length in other chapters (see Part 3, Anesthetic Management: Preoperative and Postoperative Care). Nonetheless, a few considerations are worth mentioning here.

Most cirrhotic patients have protein-energy malnutrition, placing them at an increased risk for developing a variety of postoperative complications, such as wound dehiscence,

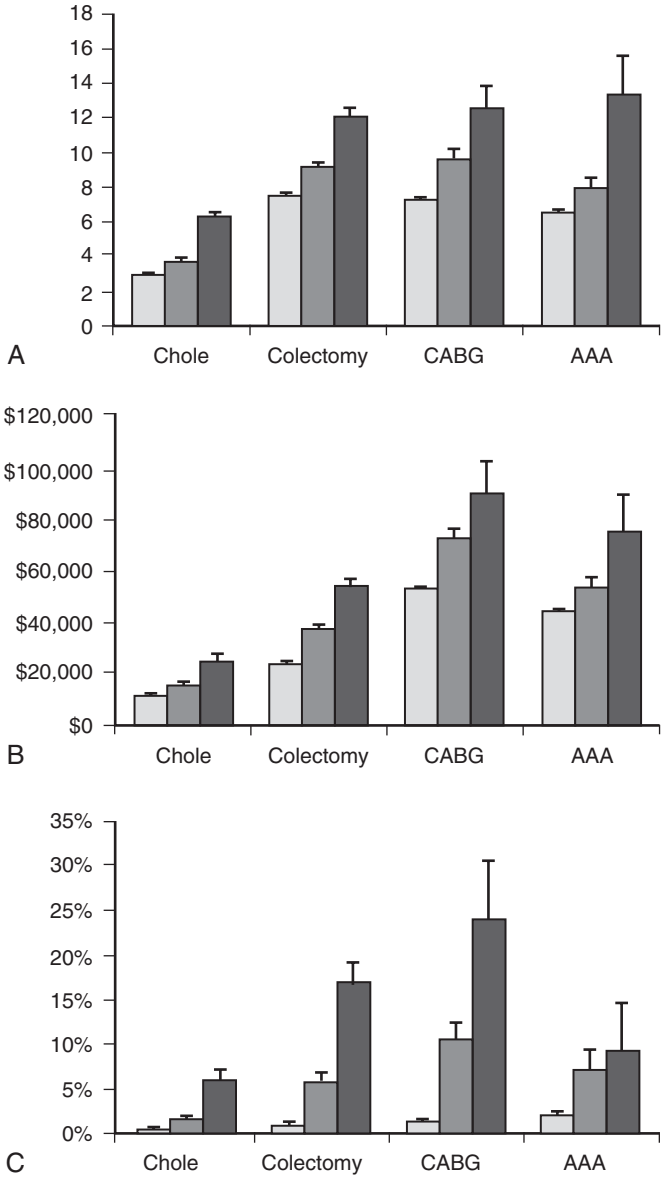


FIGURE 70B.1. Outcomes for patients who underwent four index operations (cholecystectomy [*Chole*], colectomy, coronary artery bypass grafting [*CABG*], and abdominal aortic aneurysm [*AAA*]). **A,** Length of stay. **B,** Total charges. **C,** Mortality rate. Normal, light gray; cirrhosis, medium gray; cirrhosis complicated by portal hypertension, dark gray. *(Modified from Csikesz NG, Nguyen LN, Tseng JF, 2009: Nationwide volume and mortality after elective surgery in cirrhotic patients. J Am Coll Surg 208:96-103.)*

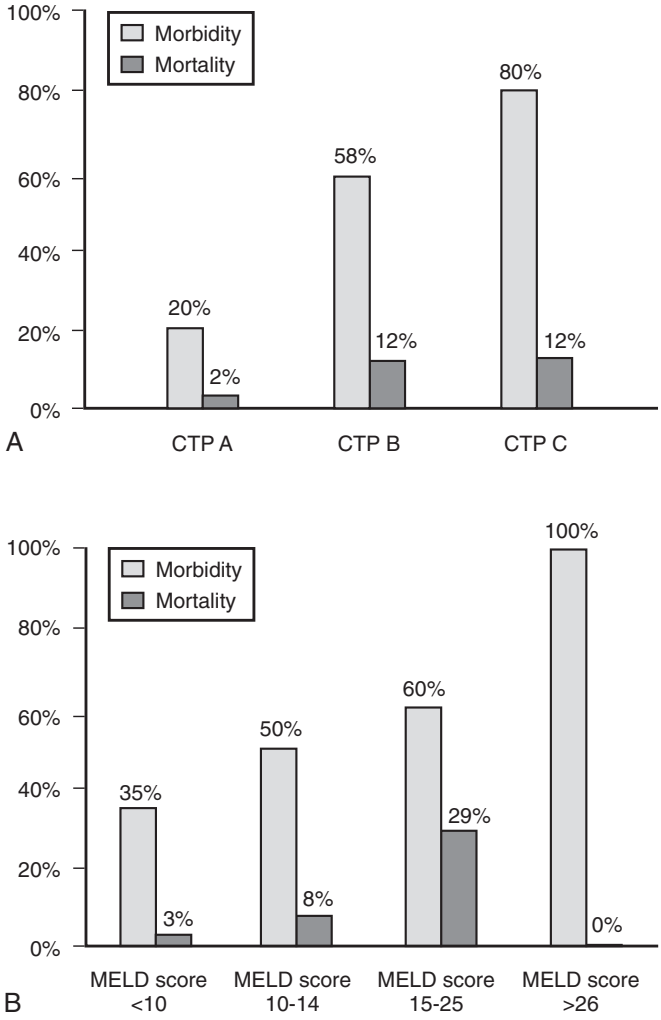


FIGURE 70B.2. Perioperative morbidity and mortality rates in a recent series of patients who underwent nonhepatic abdominal surgery. **A,** Stratified by Child-Turcotte-Pugh (*CTP*) class. **B,** Stratified by Model for End-Stage Liver Disease (*MELD*) score. *(Modified from Telem DA, Schiano T, Goldstone R, et al. 2010. Factors that predict outcome of abdominal operations in patients with advanced cirrhosis. Clin Gastroenterol Hepatol 8:451-457.)*

infections, reaccumulation of ascites, and death (Merli et al, 2002). Nutritional status should be evaluated preoperatively; when found to be deficient, efforts should be undertaken to improve it (see Chapter 24). Nasoenteric or parenteral feedings that use low-sodium formulas supplemented with trace elements and branched-chain amino acids are an option for patients who are unable to adequately nourish themselves.

Coagulopathy secondary to impaired hepatic synthesis of clotting factors and decreased vitamin K stores as a result of malnutrition and poor intestinal absorption may be present. Thrombocytopenia is also common in these patients secondary to splenic sequestration and bone marrow suppression. Preoperative transfusions of fresh frozen plasma and platelets lower the risk of bleeding. In the operating room, careful tissue handling and the maintenance of a low central venous pressure are other factors that can help to minimize blood loss (Alkozai et al, 2009). If significant bleeding arises, cryoprecipitate, diamino-8-D-arginine vasopressin, and recombinant factor VIIa are additional options to reverse coagulopathy and control hemorrhage (O'Leary et al, 2009).

In the perioperative period, altered mental status in a cirrhotic patient should be thoroughly evaluated. Only after all other potential causes have been ruled out can hepatic encephalopathy be diagnosed. With the acute onset of encephalopathy, protein intake may be briefly withheld. Lactulose should be administered and titrated for three soft bowel movements a day. Oral antibiotics, such as metronidazole or neomycin, may also be used to decrease the intestinal bacterial load (Muilenburg et al, 2009). Surgery should be postponed if encephalopathy arises preoperatively. Postoperatively, the administration of

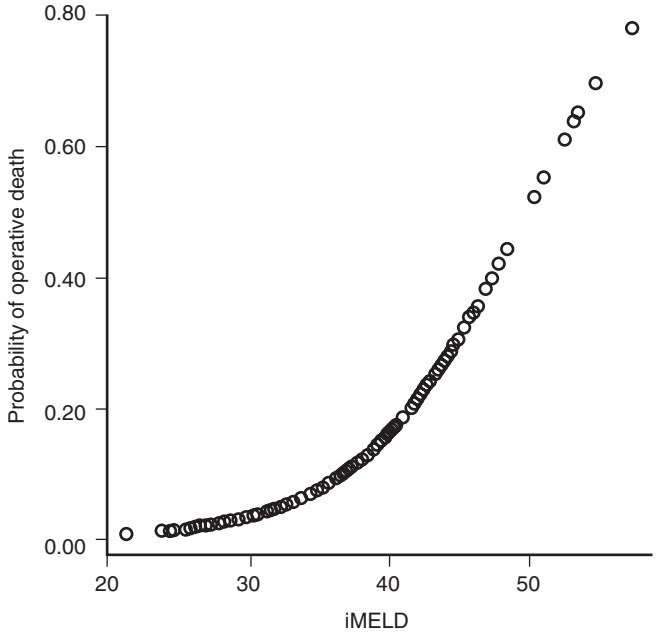


FIGURE 70B.3. Relationship between the predicted probability of operative death and Integrated Model for End-Stage Liver Disease (*iMELD*) in 190 patients with cirrhosis who underwent operation. *(Modified from Costa BP, 2009: Value of MELD and MELD-based indices in surgical risk evaluation of cirrhotic patients: retrospective analysis of 190 cases, World J Surg 33:1711.)*

narcotics and other sedating medications should be kept to a minimum. There is no role for prophylactic lactulose therapy for all cirrhotic patients undergoing surgery (O'Leary et al, 2009).

Perioperative fluid management in cirrhotic patients can be very difficult. Patients with cirrhosis should be adequately resuscitated to avoid hypotension and hepatic ischemia, but fluids should also be given judiciously to minimize the accumulation of ascites postoperatively. One center that performs a large volume of surgery on patients with end-stage liver disease limits the infusion of crystalloid solutions in the perioperative period (Telem et al, 2010b). Instead, all patients with advanced liver disease are placed on a postoperative sodium-poor albumin drip until they are able to resume oral intake.

Ascites increases the risk of postoperative renal failure, infections, and wound dehiscence. Even if ascites is drained at the time of surgery, it rapidly reaccumulates in the postoperative period. Medical therapy, which includes salt restriction and diuretics, is typically considered the first line of treatment. TIPS, however, may be considered a first-line treatment for refractory ascites and may be placed before elective surgery to help control ascites throughout the entire perioperative period (Azoulay et al, 2001; Gines et al, 2004; Schlenker et al, 2009). Moreover, TIPS may also reduce the risk of significant perioperative bleeding. In one of the largest series on the use of TIPS in patients undergoing major extrahepatic surgery, 25 cirrhotic patients with a mean MELD score of 15 ± 7.6 underwent TIPS at a median of 20 days before major abdominal and cardiothoracic operations. Blood transfusions were relatively minimal in the series, with a median of 3 units for abdominal operations (range, 0 to 21) and 4 units for cardiothoracic operations (range, 0 to 20). With a median follow-up of 33 months, actuarial 1-year patient survival was 74%, and the three postoperative deaths in the series occurred in patients with MELD scores higher than 24, all of whom underwent emergent surgery (Kim et al, 2009). Studies that compare outcomes after surgery with preoperative TIPS placement versus those with no TIPS, however, are lacking. Also, the optimal time interval between TIPS placement and elective surgery is unclear, but it is common for a period of several weeks to be required to see a clinical improvement in ascitic volume after TIPS; therefore shunts should probably be placed several weeks prior to planned operations.

SPECIFIC PROCEDURES

Cholecystectomy

The incidence of gallstones in patients with cirrhosis is twice that of the general population as a result of increased intravascular hemolysis and decreased gallbladder motility and emptying (Bouchier, 1969; Conte et al, 1991; Schwesinger et al, 1985). In the 1980s, rates of major morbidity and mortality in patients with cirrhosis undergoing cholecystectomy were as high as 35% and 25%, respectively (Aranha et al, 1982; Cryer et al, 1985; Garrison et al, 1984; Schwartz, 1981). Postoperative death occurred secondary to blood loss, sepsis, and liver failure. Almost invariably, these procedures were performed as open laparotomy. At that time, the presence of cirrhosis was considered a contraindication for the laparoscopic approach, based on the assumption that it would lead to increased rates bleeding and liver failure (Yerdel et al, 1993). However, as greater experience in laparoscopic surgery has been gained, this point of view has changed, and now many studies demonstrate favorable morbidity and minimal to no mortality in patients with early cirrhosis (CTP class A and B) undergoing laparoscopic cholecystectomy (Cucinotta et al, 2003; Fernandes et al, 2000; Ji et al, 2004; Morino et al, 2000; Poggio et al, 2000; Yeh et al, 2002). A recent meta-analysis comparing laparoscopic cholecystectomy in cirrhotic and noncirrhotic patients demonstrated significantly higher rates of morbidity (21% vs. 8%, respectively; $P < .001$), intraoperative bleeding (26% vs. 3%; $P < .001$), and open conversion (7% vs. 4%; $P < .05$), but no difference was reported in terms of wound infection and mortality rates between the two (Puggioni & Wong, 2003).

Laparoscopic cholecystectomy offers improved visualization for meticulous dissection and avoids the need for a large subcostal or upper midline incision. It is associated with less operative blood loss, shorter operative time, and decreased length of hospital stay versus the open procedure in cirrhotic patients (Puggioni & Wong, 2003). Furthermore, laparoscopic cholecystectomy leads to fewer adhesions in the right upper quadrant, which are associated with increased bleeding complications and longer operative times in patients who ultimately undergo liver transplant.

Some specific technical considerations must be considered when performing laparoscopic cholecystectomy in a cirrhotic patient. In placing the umbilical port, particular care must be taken to avoid venous collaterals and the umbilical vein. One approach may be to place one of the other ports first, such as the subxiphoid port, in order to then place the umbilical port under direct visualization. Transillumination of the abdominal wall helps the surgeon to avoid these and other venous collaterals during trocar placement. Furthermore, the subxiphoid port

should be placed off midline to avoid the falciform ligament and the recanalized umbilical vein. Careful traction on the gallbladder helps to avoid undue bleeding as it is dissected off the liver. Instruments such as the Harmonic Scalpel (Ethicon, Somerville, NJ) or LigaSure (Covidien, Mansfield, MA) may also be used to help control bleeding during the dissection (Curro et al, 2005; El-Awadi et al, 2009; Morino et al, 2000; Schiff et al, 2005; Tuech et al, 2002). A subtotal or supracystic cholecystectomy, leaving part of the gallbladder wall attached to the liver bed and ligating the cystic duct from within the gallbladder with a purse-string suture, is an option in patients with large pericholecystic venous collaterals (Bornman & Terblanche, 1985; see Chapter 33). Trocars should also be removed under direct visualization to ensure adequate abdominal wall hemostasis at the end of the procedure. Finally, if anatomy is unclear or any doubt exists as to the safety of continuing laparoscopically, the procedure should be converted to open.

In patients with advanced cirrhosis (CTP class C), cholecystectomy in general is associated with very poor outcomes. Despite the lack of controlled trials, the literature supports the use of alternatives to cholecystectomy, such as a percutaneous cholecystostomy, in this high-risk group (Cucinotta et al, 2003; Curro et al, 2005; Delis et al, 2010; Yeh et al, 2002). An endoscopically placed cystic duct stent is another option proposed by some (Gaglio et al, 1996; Shrestha et al, 1996, 1999).

In general, the CTP scoring system is used in the literature to stratify patients suitable for cholecystectomy. Although some evidence suggests that the MELD classification system may be more accurate in predicting postoperative complications, these data are inconsistent, and cutoff values vary among studies (Delis et al, 2010; Perkins et al, 2004). Therefore, until the MELD system has been further validated, CTP should be used for stratification. In CTP classes A and B patients with symptomatic cholelithiasis and/or acute cholecystitis, laparoscopic cholecystectomy should be performed by surgeons experienced in managing cirrhosis. In patients with class C cirrhosis, surgery should be deferred until liver disease is under better control, and alternate interventions, such as percutaneous cholecystostomy or endoscopic stenting, should be used.

Herniorrhaphy

Umbilical hernias occur in up to 20% of patients with cirrhosis. The pathogenesis of umbilical hernias in the setting of cirrhosis is multifactorial; ascites causes increased intraabdominal pressure, poor nutritional status leads to decreased abdominal muscle mass and fascial strength, and umbilical vein dilation results in enlargement of the preexisting supraumbilical fascial opening (Belghiti & Durand, 1997). In addition to the risks of bowel incarceration and strangulation that affect all patients with umbilical hernias, additional unique risks accompany having an umbilical hernia and cirrhosis. Skin ulceration over the hernia may be associated with the leakage of ascites, sac rupture, bacterial peritonitis, and even evisceration, with very high attendant rates of morbidity and mortality. Although rare, spontaneous umbilical rupture is associated with up to a 60% perioperative mortality rate and has been shown to correlate independently with an adverse outcome after emergent repair (Telem et al, 2010a).

Historically, mortality rates for umbilical hernia repair (UHR) in patients with cirrhosis were prohibitively high, and the prevailing opinion among surgeons was that uncomplicated hernias should be left untreated (Baron, 1960; O'Hara et al, 1975). UHR was only undertaken when complications, such as incarceration, strangulation, skin breakdown or impending rupture, or overt rupture, necessitated immediate intervention. In the present era, however, outcomes appear to be significantly improved for elective and even complicated UHR in patients with end-stage liver disease. Most series published in the literature since the early 1980s have reported little to no perioperative deaths and relatively low morbidity, although most of them have been relatively small retrospective studies (Belghiti et al, 1990; de la Pena et al, 2000; Ozden et al, 1998; Pescovitz, 1984; Runyon & Juler, 1985).

Marsman and colleagues (2007) looked at outcomes of elective UHR versus conservative management in patients with umbilical hernias, cirrhosis, and ascites. Seventeen patients with a median MELD score of 23 (range, 18 to 26) underwent elective UHR, and another 13 patients, also with a median MELD score of 23 (range, 18 to 27), were observed. In the elective UHR group, 3 patients (18%) had local wound complications, but there were no instances of hepatic decompensation or perioperative death. In contrast, in the group that was observed, 10 patients (77%) developed complications, including nine cases of incarceration and one spontaneous rupture with evisceration; these led to emergency UHR in six patients, and there were two perioperative deaths (15%). Although this was a retrospective study, and it is likely that some selection bias existed between the two groups, it is one of the few studies to compare early UHR versus watchful waiting in patients with comparable and relatively high MELD scores.

Another recent report, a retrospective review of the Veterans' Affairs National Surgical Quality Improvement Program (VA NSQIP) database, analyzed the results of UHR in 127 cirrhotic and 1294 noncirrhotic patients (Gray et al, 2008). It determined that UHR performed electively in patients with cirrhosis was associated with an outcome similar to that in patients without cirrhosis. When UHR was performed emergently, however, patients with cirrhosis had significantly worse outcomes than those without. One drawback of this study was that the authors were not able to classify the degree of hepatic impairment among the patients with cirrhosis.

In patients with ascites, UHR has been combined with peritoneovenous (PV) shunting, closed-system suction drainage, or temporary peritoneal dialysis catheters to help manage ascites as the repairs heal (Ammar, 2010; Belghiti et al, 1990; Leonetti et al, 1984; O'Connor et al, 1984). A meta-analysis compared UHR with concomitant interventions to control ascites, namely PV shunting, versus repair alone and determined that uncontrolled ascites was associated with a relative risk ratio of 8.51 (95% confidence interval, 2.69 to 26.9) for hernia recurrence (McKay et al, 2009). Although PV shunting cannot be recommended in the current era because of the associated complications and high incidence of shunt occlusion, TIPS has been used more recently to successfully reduce ascites in the period surrounding UHR (Fagan et al, 2004; Inturri et al, 1996; Telem et al, 2010a). No controlled studies have evaluated the perioperative use of TIPS in UHR in patients with ascites, and definitive recommendations regarding its use cannot be made. In addition, TIPS may lead to new onset of encephalopathy or worsening of existing encephalopathic symptoms. Nonetheless, it is an option to manage ascites in patients who are deemed suitable candidates.

Whether nonabsorbable mesh should be used for the repair in cirrhotic patients is another issue of debate. Traditionally,

the use of foreign material has been avoided in the repair of complicated hernias. However, some evidence suggests that nonabsorbable mesh may be used successfully, even when ascites is present (Ozden et al, 1998). A recent study prospectively randomized 80 CTP class A and B patients with cirrhosis and an umbilical hernia to either primary tissue repair with sutures or mesh repair with polypropylene onlay (Ammar, 2010). Surgical site infection occurred at a higher rate in the mesh group (16%) versus suture repair (9%), but the difference was not significant. Furthermore, all infections were successfully managed conservatively and did not require mesh removal. At a minimum of 6 months of follow-up, hernias recurred in 14% of patients in the suture repair group and in only 3% of patients in the mesh repair group ($P < .05$). Again, the dataset is small, but it does appear that mesh onlay may be used to lower the risk of recurrence in patients with cirrhosis who have umbilical hernias, in particular those with well-compensated disease.

In terms of inguinal hernia repair, results in this patient population are similar to those for umbilical herniorrhaphy (Inagaki et al, 2009; Lawson et al, 2009; Patti et al, 2008). Outcomes after elective repair do not vary between cirrhotic and noncirrhotic patients, although outcomes after emergent repair of an incarcerated or strangulated inguinal hernia are significantly worse in patients with cirrhosis (Carbonell et al, 2005). It appears that cirrhotic patients may safely undergo inguinal hernia repair with mesh; local wound complications, if they do arise, are usually easily treated (Inagaki et al, 2009; Lawson et al, 2009). In short, it is reasonable, and the data would suggest even advisable, to repair hernias electively in patients with cirrhosis. However, as with any elective operation, patients should be well compensated and medically optimized, and ascites should be controlled.

Colectomy

Compared with cholecystectomy and herniorrhaphy, considerably less data are available on colon resection in patients with chronic liver disease and cirrhosis. As in patients without cirrhosis, indications for colon resection include colon cancer, diverticular disease, and colonic ischemia. Colorectal surgery, which is associated with relatively high rates of morbidity and mortality when performed on the general population, is particularly high risk for those with cirrhosis. In fact, the mortality rate for patients with cirrhosis undergoing colectomy is around 20% to 25% (Metcalf et al, 1987; Meunier et al, 2008; Nguyen et al, 2009). Emergent colectomy is associated with an even higher mortality rate: up to 36% in patients with cirrhosis who have portal hypertension and 21% in those with portal hypertension who did not have cirrhosis (Nguyen et al, 2009). It is preferable to perform colorectal surgery in a cirrhotic patient on an elective basis whenever possible.

In a recent, large, population-based study, extraintestinal complications, such as pulmonary and wound complications, were increased in patients with cirrhosis and portal hypertension in particular. On multivariate analysis, total colectomy, malnutrition, and comorbid cardiac, pulmonary, and renal disease were the most significant predictors of postoperative morbidity (Nguyen et al, 2009). In another recent, retrospective, single-center study that included 41 cirrhotic patients undergoing colorectal surgery (CTP class A, 40%; class B, 49%; class C, 12%), the presence of preoperative ascites was significantly linked to postoperative morbidity (Meunier et al, 2008). When colectomy is performed on an elective basis, every effort should be made to optimize comorbid conditions and nutrition and to control ascites before surgery.

When feasible, the laparoscopic approach for colectomy may be advantageous in this patient population. Laparoscopy has significantly improved outcomes for gallbladder surgery in patients with cirrhosis, in particular in patients with well-compensated disease. Along these lines, a report on laparoscopic-assisted colectomy in 17 patients with compensated cirrhosis (CTP class A, 71%; class B, 29%) was notable for relatively minimal blood loss (mean, 245 mL; range, 100 to 250 mL), a 29% morbidity rate, and no operative deaths (Martinez et al, 2004). The study was small, and the group of patients was highly selected. Nonetheless, this research does offer some indication that laparoscopic colectomy, when performed at centers experienced in advanced laparoscopic surgery, may lead to improved outcomes in CTP class A and B patients versus the open approach.

Bariatric Surgery

Because of the high incidence of nonalcoholic fatty liver disease (NAFLD) and its association with the metabolic syndrome, chronic liver disease is not infrequent among patients being considered for bariatric procedures. The finding of overt cirrhosis is estimated to occur in 1.4% of patients undergoing these operations (Dallal et al, 2004). The majority of these patients are diagnosed with cirrhosis intraoperatively, and surgery is abandoned. Few reports exist as to the safety and efficacy of bariatric procedures in known cirrhotic patients. In the largest series to date, which includes 30 patients analyzed retrospectively, 27 were diagnosed intraoperatively (Dallal et al, 2004). All patients were classified as CTP class A, and there were no perioperative deaths.

Given the paucity of data, the decision of whether to proceed with operation in patients with well-compensated cirrhosis is unclear. Certainly, patients with more advanced disease and/or portal hypertension are at significant mortality risk. However, several reports document the reversal of even advanced liver disease after surgical weight loss (Dixon et al, 2004; Kral et al, 2004). Therefore it appears that bariatric surgery may be reasonable in patients with early fibrosis and possibly in those with well-compensated cirrhosis. As outlined earlier, the risk inherent to the procedure, severity of liver disease, and comorbid conditions must be considered individually along with the potential benefit of surgical weight loss.

The choice of weight loss procedure in those deemed candidates is also unclear (Baltasar, 2006; Sarr, 2006). Despite the histologic improvement in liver disease seen with biliopancreatic diversion, several case reports of hepatic failure after this procedure exist (Castillo et al, 2001; Grimm et al, 1992; Kral et al, 2004). The optimal procedure regarding weight loss remains under intense debate in the bariatric surgical community and is beyond the scope of this chapter. However, the suggestion has been made that sleeve gastrectomy may be the procedure of choice in patients with cirrhosis because of minimal bleeding complications, protection from malabsorption associated with other bariatric procedures, and potential improvement in transplant candidacy (Baltasar, 2006; Takata et al, 2008). No studies evaluating the use of adjustable gastric bands in cirrhotic patients are available.

Cardiac Procedures

Cardiovascular risk factors occur at greater rates among those with cirrhosis than among the general population (Hessheimer et al, 2010). Furthermore, although an uncommon cause, congestive heart failure may actually lead to hepatic congestion, fibrosis, and ultimately cirrhosis. Because of these and other factors, cardiac surgery is becoming increasingly more frequent in patients with end-stage liver disease, in particular those awaiting liver transplantation (Thielmann et al, 2010). Cardiac surgery, however, is extremely risky in patients with cirrhosis. Mortality rates are as high as 50% to 80% in patients with advanced liver disease undergoing cardiac surgery with cardiopulmonary bypass (CPB) because of high rates of infection, gastrointestinal complications, and bleeding (Bizouarn et al, 1999; Kaplan et al, 2002; Klemperer et al, 1998).

Outcomes for cirrhotic patients undergoing cardiac surgery have variably been associated with preoperative serum cholinesterase, serum bilirubin, and platelet count (An et al, 2007; Filsoufi et al, 2007; Hirata et al, 1999; Morisaki et al, 2010; Reinhartz et al, 1998). More consistently, however, outcomes have been linked to the preoperative CTP or MELD score. CTP class B and C and/or a MELD score greater than 13 to 15 have been shown to correlate with a significantly increased risk for postoperative complications and death in cirrhotic patients undergoing cardiac procedures, in particular those involving CPB (Ailawadi et al, 2009; An et al, 2007; Filsoufi et al, 2007; Hayashida et al, 2004; Klemperer et al, 1998; Morisaki et al, 2010; Thielmann et al, 2010).

CPB induces the production of inflammatory cytokines and other vasoactive substances and leads to further derangements in hemodynamics, coagulation, and immune function. Advanced cirrhosis (CTP class B and C) is considered a contraindication for CPB (An et al, 2007; Filsoufi et al, 2007; Hayashida et al, 2004). A few recent reports, however, have described successful on-pump valve procedures in patients with advanced liver disease (Iino et al, 2008; Nemati et al, 2008; Takahashi et al, 2006). By preoperative optimization of hepatic status, aggressive administration of platelets and fresh frozen plasma throughout the perioperative period, and dilutional ultrafiltration (DUF) during CPB, these investigators were able to curtail the negative effects of CPB in patients with decompensated disease. DUF in particular helps to minimize hemodilution and remove inflammatory mediators produced during CPB (Iino et al, 2008). Another option that has shown modest success in patients with moderate to severe cirrhosis in need of coronary artery bypass (CAB) is off-pump surgery (Ben Ari et al, 2006; Hayashida et al, 2004; Murashita et al, 2009). Off-pump CAB may reduce bleeding and transfusion requirements. Further investigations, however, are required to determine the true applicability of these techniques in this patient population.

Thoracic Procedures

The literature on thoracic surgery in patients with cirrhosis primarily describes thoracoscopic procedures for the treatment of refractory hepatic hydrothorax, a complication that occurs in approximately 5% of cirrhotic patients (Alberts et al, 1991). It is a symptomatic transudative pleural effusion that is believed to arise secondary to tiny defects in the diaphragm that allow ascites to flow from the high-pressure peritoneal cavity into the low-pressure pleural space (Huang et al, 2005; Nakamura et al, 1996; Zenda et al, 1998). Hepatic hydrothorax may result in significant respiratory compromise, and initial treatments include sodium restriction, diuretics, TIPS, and frequent thoracenteses. When these fail, video-assisted thoracoscopic surgery (VATS) with closure of obvious diaphragmatic defects and/or mechanical or chemical pleurodesis are options that may allow prolonged symptomatic relief (Assouad et al, 2003; Ferrante et al, 2002; Mouroux et al, 1996; Northup et al, 2009). Potential complications include empyema and persistent leakage of high volumes of ascites from the chest tube site. Nonetheless, the procedure is relatively well tolerated and is associated with success rates of up to 80%, even in patients with advanced cirrhosis (Cerfolio & Bryant, 2006).

Cirrhosis is present in approximately 4% to 7% of patients undergoing esophagectomy in some series (Fekete et al, 1987; Lu et al, 2005; Tachibana et al, 2000). Actual rates of cirrhosis in patients with esophageal neoplasms are likely higher than reported, based on the fact that alcohol plays an important role in the pathogenesis of both diseases; stage for stage, many more cirrhotics than noncirrhotics would be deemed unsuitable for surgery. Unlike gastric resection, esophagectomy in cirrhotic patients is actually associated with relatively few deaths as a result of postoperative liver failure, in theory because of the radical gastroesophageal devascularization and postoperative anorexia, which may lead to a significant reduction in alcohol consumption (Tachibana et al, 2000). Nonetheless, esophagectomy in cirrhotic patients is associated with much higher rates of surgical morbidity and mortality compared with noncirrhotics, in the range of 31% to 87% and 17% to 26%, respectively (Fekete et al, 1987; Lu et al, 2005; Tachibana et al, 2000). Perioperative bleeding, ascitic effusions, pneumonia, and sepsis are the most common complications and cause the majority of postoperative deaths. Significant preoperative coagulopathy, hyperbilirubinemia (>3 mg/dL), weight loss (>10% to 15% of body weight), and CTP classes B and C are associated with the highest rates of postoperative death and may be considered contraindications for surgery. For patients surviving the immediate postoperative period, however, overall survival appears to be similar to that of noncirrhotic patients undergoing the same procedures (Tachibana et al, 2000). Esophageal resection may play some role in well-selected patients with mild underlying liver disease.

Only four published reports from two centers have reported on pulmonary resection for non–small-cell lung cancer in patients with cirrhosis, the great majority of whom were CTP class A (Iwasaki et al, 2006; Iwata et al, 2007a, 2007b, 2008). Surgical morbidity rates were approximately 19% to 27%, and mortality rates were 5% to 13%. The most common complications were infection, bleeding, and acute liver failure. Based on the retrospective nature of the studies and the small number of patients they included, the authors were unable to conclude whether these operations had any impact on life expectancy in this patient population.

Trauma

Cirrhotic patients represent approximately 1% to 1.5% of the trauma population and an even greater proportion of those sustaining blunt trauma (Georgiou et al, 2009; Wutzler et al, 2009). In these patients, falls are the most common cause of injury (43%), followed by assault (Chen et al, 2007; Georgiou et al, 2009). Complications occur in up to 10% of patients and

primarily include acute respiratory distress syndrome, trauma-associated coagulopathy, pneumonia, and sepsis (Christmas et al, 2005; Georgiou et al, 2009). In-hospital mortality rates are high, in the range of 22% to 33%. The CTP classification appears to be associated with a stepwise increase in the risk of death: up to 15% in class A, 37% in class B, and 76% in class C (Christmas et al, 2005).

Cirrhotic trauma patients are significantly more likely than those without cirrhosis to undergo laparotomy, and splenectomy is one of the most common operations performed (Christmas et al, 2005; Georgiou et al, 2009). This is not surprising given the prevalence of portal hypertension and splenomegaly among these patients. Among cirrhotic patients, nonoperative management of splenic injury fails in up to 92% of patients (Fang et al, 2003). On the other hand, multivariate analyses from several studies have demonstrated that after laparotomy, 40% to 55% of cirrhotic patients ultimately die in the hospital, versus only 15% to 24% of those who avoid laparotomy (Christmas et al, 2005; Demetriades et al, 2004; Georgiou et al, 2009).

Obviously, management of these patients is highly complex. The American College of Surgeons recommends that trauma patients with a history of cirrhosis be transferred to a trauma center, if they are not at one already (Wahlstrom et al, 2000), and should be very carefully resuscitated and monitored in an intensive care setting. Bleeding complications are common, and coagulopathy and hypothermia should be aggressively corrected. Because these patients are almost routinely malnourished and hypoalbuminemia has been significantly linked with poor outcomes, nutritional support with solutions rich in branched-chain amino acids should be started early (Chiarla et al, 1997). It is imperative to promptly diagnose injuries in these patients, although interventions should be undertaken judiciously. Early consultation with hepatology and/or hepatobililary surgery, if possible, is strongly advised.

SUMMARY

In many instances, nonhepatic elective surgery may be safely performed in patients with cirrhosis. There is certainly almost always an increase in morbidity and mortality when compared with patients without chronic liver disease; however, often these are not prohibitive. The severity of liver failure as judged by the CTP or MELD scoring systems appears to be the most important factor in determining postoperative outcomes. CTP class A or B cirrhotic patients and those with a MELD score less than 15 are often suitable operative candidates, depending on the magnitude and necessity of the procedure. Emergency operations carry greater risk, as does comorbid illness and age. Perhaps most importantly, operations on cirrhotic patients should be performed only after medical optimization of liver disease and only by centers experienced in managing end-stage liver disease.

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CHAPTER 75B

Esophageal varices: acute management of portal hypertension

Joseph Awad and Julia Wattacheril

OVERVIEW

The most important aspect of care in patients with suspected variceal or other portal hypertensive hemorrhage is adequate resuscitation while directed diagnostic maneuvers and therapies are being coordinated. Although this chapter focuses on acute esophageal variceal bleeding, many of the principles and therapies may apply to other sources of portal hypertensive bleeding. Acute variceal hemorrhage is associated with a 15% to 20% mortality rate at 6 weeks (Abraldes et al, 2008; Villanueva et al, 2006). Although evidence supports the use of endoscopy for diagnosis and treatment, insufficient resuscitation can lead to significant periprocedural complications. Appropriate pharmacotherapy has proven equally effective in controlling variceal hemorrhage in some studies. More importantly, pharmacotherapy can be started immediately in any hospital, regardless of endoscopic staff availability.

The morbidity of patients who present with acute variceal hemorrhage is strongly influenced by their reason for recent decompensation. In most instances, early resuscitative measures followed by pharmacotherapy and endoscopy allow improvement in hepatic synthetic function and provide time to address more definitively the overall management of the patient and any recurrent bleeding. In patients with life-threatening exsanguination, balloon tamponade is a useful maneuver until the patient is stable enough for endoscopy. In patients with bleeding refractory to pharmacotherapy and endoscopic intervention, transjugular intrahepatic portosystemic shunting (TIPS) generally is the next option for short- and mid-term stabilization (see Chapter 76E). Shunt operations (see Chapters 76A through 76D) have traditionally been reserved for individuals for whom transplantation and TIPS are not an option but who have a reasonable chance of operative survival.

EMERGENCY MANAGEMENT

Before any diagnostic maneuvers can be performed (e.g., endoscopy), support of the circulating blood volume with adequate resuscitation is imperative. Isotonic crystalloid is the first replacement fluid of choice, but typed and cross-matched blood products are needed for the majority of patients with variceal hemorrhage. Evidence supports the use of colloids over crystalloid and packed red blood cells with the end points of optimal hemodynamics and oxygen transport (Shoemaker, 1987). Maintenance of hemoglobin values of approximately 8 g/dL are recommended; higher blood volumes are associated with increased portal pressures, higher rebleeding rates, and higher mortality rates. Other measures of the adequacy of resuscitation include systolic blood pressures of 90 to 100 mm Hg, central venous pressures of 9 to 16 mm Hg, and adequate urine output; pulmonary artery occlusion catheters may be a useful adjunct in some patients. When the adjusted prothrombin time is prolonged by more than 3 to 4 seconds, fresh frozen plasma is likewise recommended. Recombinant Factor VIIa has not been shown to benefit patients with cirrhosis with gastrointestinal (GI) hemorrhage over standard therapy (Bosch et al, 2008). For patients with significant bleeding or decreased consciousness, endotracheal intubation should be expedited.

Complications from variceal bleeding contribute to overall morbidity and mortality related to chronic liver disease. Preventing these complications can therefore have a significant impact on the short-term mortality rate associated with variceal bleeding. Antibiotic prophylaxis has been shown to decrease variceal rebleeding and bacterial infection (Bernard et al, 1999; Fernandez et al, 2006). Systematic reviews have shown decreased mortality rates with antibiotic prophylaxis in the setting of GI bleeding (Soares-Weiser et al, 2002). Consensus agreement supports norfloxacin use for 7 days (400 mg bid) in patients with two or more of the following: malnutrition, ascites, encephalopathy, or serum bilirubin level greater than 3 mg/dL. Ceftriaxone had better outcomes than norfloxacin when given intravenously in areas with known quinolone resistance according to randomized, controlled data (Fernandez et al, 2006). It may be that other antibiotics with similar spectra of activity would provide satisfactory substitutes in the event of problems with patient tolerance, local antibiotic availability, or susceptibility issues.

Controlling Acute Hemorrhage: Pharmacologic Agents

Coupling pharmacologic measures and endoscopy with the initiation of preventative measures provides the most sustainable results when attempting to control acute GI hemorrhage in patients with advanced liver disease. The specific drugs are widely available, generally safe, and can be initiated as soon as variceal hemorrhage is suspected. Drugs such as somatostatin or its analogues, octreotide and vapreotide, work by constricting arterial and thus venous splanchnic blood flow, thereby reducing portal hypertension acutely. In randomized controlled trials comparing these vasoactive agents with others, including vasopressin and terlipressin, no significant differences in bleeding control were reported, although vasopressin was associated with more adverse events (Banares et al, 2002; Villaneuva et al, 2006). Currently, an initial bolus dose of octreotide 50 µg IV followed by 50 µg/h is recommended. Duration usually extends

from 72 hours to 5 days, and recurrent bleeding should be treated with an additional bolus dose. Only octreotide and vasopressin are currently available in the United States.

Controlling Acute Hemorrhage: Endoscopic Therapy

The two main endoscopic therapeutic choices are endoscopic variceal ligation (EVL) and sclerotherapy. The strong preference remains for EVL, given its superior control of bleeding and decreases reported in rebleeding rates, mortality rates, and esophageal complications. Both techniques require a skilled endoscopist; however, when both groups were treated with somatostatin concomitantly, failure rates of EVL were estimated at 10% compared with 24% of sclerotherapy patients. Failure to control acute bleeding is also significantly more frequent in the sclerotherapy group (Villanueva et al, 2006).

After adequate sedation and diagnostic endoscopy, EVL should commence. The decision regarding whether to start with a standard 2.8-mm gastroscope versus a therapeutic endoscope is practitioner dependent given the potential for clot removal by irrigation. Once a variceal source has been identified, the endoscope should be removed and a multibanding kit should be applied with a standard gastroscope. Bands should be applied to any vessels actively spurting blood or displaying stigmata of recent hemorrhage, such as red wale marks, white nipples, and/or adherent blood clots. Other vessels should then be ligated, starting as close as possible to the esophagogastric junction. The varix is drawn into the ligator by applying suction, and a band is then applied as shown in Figure 75B.1.

Two techniques of sclerosant injection are in use, and the choice of which to use is somewhat institutionally and regionally influenced. Sclerosants can be injected into the varix itself (intravariceally) or adjacent to it (paravariceally); both techniques appear to be effective. Often a paravariceal injection results inadvertently from an intravericeal injection attempt, given the technical challenges in an acutely bleeding patient. Sodium morrhuate and sodium tetradecyl sulfate are the two sclerosants most commonly used in the United States, and each varix should be injected with 1 to 2 mL of sclerosant just above the esophagogastric junction and 5 cm proximal. Some endoscopists find sclerotherapy effective when active bleeding impairs visualization for EVL. On occasion, application of sclerotherapy sufficiently impedes bleeding enough to allow band ligation.

Balloon Tamponade

A correctly placed balloon tube can temporarily control acute variceal bleeding. The balloon tube is primarily used when patients have continued, active bleeding despite attempted control by emergency endoscopic therapy, but a balloon tube may also be inserted when massive variceal bleeding obscures visibility during emergency endoscopy; both are relatively uncommon circumstances. Balloon tube tamponade has also proved to be lifesaving during the transfer of patients to a tertiary care center, to control a subsequent major bleed while awaiting emergency endoscopy, and to stop variceal bleeding while preparing for alternative therapy when endoscopic therapy fails (e.g., a further major, acute variceal bleed after two emergency endoscopic treatments during a single hospital admission).

The balloon tube should be inserted by a practitioner familiar with the technique (details presented below). The tube should be left in place for as short a time as needed for resuscitation, endoscopic treatment, or TIPS placement. Bleeding that continues after tube insertion warrants additional assessment regarding correct placement and potential for repeat endoscopy. In these cases, a bleeding lesion below the balloon in the distal stomach or duodenum that was missed at the first diagnostic endoscopy is usually the culprit (Terblanche et al, 1994).

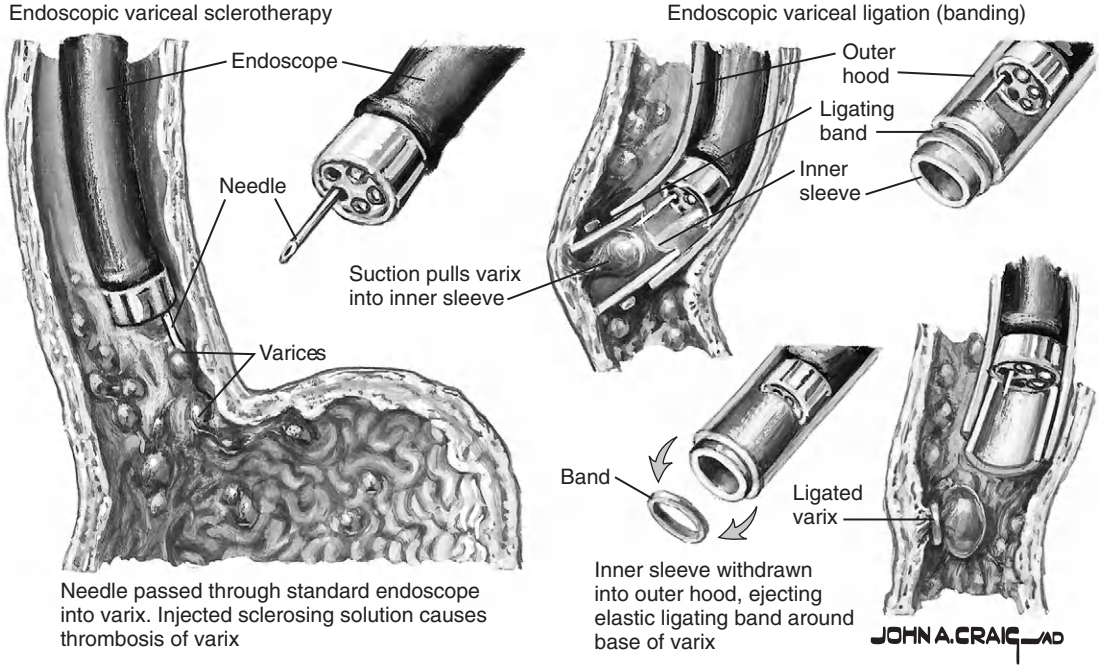


FIGURE 75B.1. Variceal bleeding ligation techniques. *(Netter illustration from www.netterimages.com. Copyright Elsevier, Inc. All rights reserved.)*

TECHNIQUE. After confirming a complete air seal underwater, the deflated lubricated tube is passed via the mouth through a bite guard placed between the teeth. The tube is inserted as far as possible. To confirm the balloon's position in the stomach, the epigastrium is auscultated while instilling air via the aspirating lumen of the gastric tube with a 50-mL syringe. Thereafter, the gastric balloon is cautiously inflated via its lumen with 50-mL increments of air until a total of 100 mL has been inserted. Air should be easy to insert; if the tube is curled in the esophagus, resistance is felt and the inflation must be stopped immediately; otherwise, the esophagus may be damaged. If the gastric balloon has been easily inflated, it is pulled up until it is seated firmly against the esophagogastric junction. Then the position of the tube is confirmed radiographically before another 150 to 200 mL of air is added to the balloon.

Tension on the tube is often maintained by taping it to the facemask of an American football helmet. Alternatively, a split tennis ball strapped to the tube at the mouth guard can be used to protect the patient's lips from the pressure of the tennis ball. Adequate tension on the gastric balloon can be checked regularly at the mouth. Inflation of the esophageal balloon is not usually necessary because traction on the gastric balloon is generally sufficient to compress gastric veins that feed esophageal varices. If esophageal balloon inflation is required, a three-way tap and a blood pressure manometer are used to inflate the esophageal balloon to 40 mm Hg before clamping the tube. This pressure needs to be checked regularly, and the balloon should be deflated hourly to prevent esophageal necrosis. The fourth lumen, which opens in the esophagus, is placed on constant suction; the gastric lumen is used for suction and to administer medication such as lactulose.

Patients with a balloon tube in place are monitored carefully in an intensive care unit (ICU). When the balloon tube has been inserted and fixed and bleeding has been arrested, resuscitation is continued, clotting abnormalities are corrected, and the patient is made as fit as possible for the necessary subsequent management. The balloon tube should usually be removed within 24 hours (Blumgart & Belghiti, 2007).

Gastric Varices

Approximately 20% of patients with cirrhosis have gastric varices, either in isolation or associated with esophageal varices. Bleeding from gastric varices carries greater risk and is associated with increased mortality rates (Ryan et al, 2004). In these cases, endoscopic variceal obturation (EVO) with cyanoacrylate has been demonstrated as superior to endoscopic variceal ligation in controlling initial hemorrhage as well as controlling rebleeding (Lo et al, 2001; Tan et al, 2006). TIPS is also effective in controlling acute hemorrhage from gastric varices. Decreased recurrent bleeding has recently been demonstrated in patients undergoing TIPS versus EVO (Lo et al, 2007). In the United States, where N-butyl-2-cyanoacrylate is not available and 2-octyl-cyanoacrylate has been used instead, adverse events have been noted. Its use requires specialized endoscopic training; in situations where this is not available, primary placement of TIPS is preferred (Garcia-Tsao & Lim, 2009).

Ectopic Varices

Ectopic varices are those in an atypical location (nonesophageal or nongastric). Bleeding from ectopic varices accounts for approximately 1% to 5% of variceal bleeding (Helmy et al, 2008). Most ectopic varices arise from global portal hypertension, but they may be related to regional thrombosis or prior surgery sites, where the healing process promotes venous connections between a high-pressure portal system and the lower pressure systemic circulation. Common sites include the duodenum, anorectal region, umbilicus, and ostomies. Patients typically bleed into the lumen of the GI tract, but peritoneal and retroperitoneal bleeding can occasionally occur. Given their relatively rare occurrence, treatment recommendations have been made on case reports, case series, and small reviews, not in randomized controlled trials.

Imaging and endoscopy techniques have allowed approximation of the prevalence of ectopic varices. Anorectal varices have been reported in 10% to 40% of patients with cirrhosis; duodenal varices have been reported in 40% of patients with portal hypertension as seen during angiography. Fortunately, bleeding from these lesions is quite rare.

Peristomal/stoma varices are seen in patients with ostomies who have, or later develop, portal hypertension such that alternatives to creating an ostomy should be considered in these patients. Although more common in those with significant intrahepatic portal hypertension, they are particularly insidious and can bleed at a hepatic venous pressure gradient (HVPG) of less than 12 mm Hg. Peristomal varices are most common on the skin near the stoma rather than deep within the stoma. Thus it is important to remove the skin covering around the stoma and apply direct pressure or local treatment to the bleeding vessel.

Initial management remains the same as in esophageal variceal bleeding, namely to provide adequate clinical assessment and resuscitative measures, hemodynamic support, and antibiotic prophylaxis. Vasoactive drugs are reasonable to use, and endoscopy should proceed with goals similar to those for therapy of variceal bleeding.

Band ligation of ectopic varices has been limited to a few reports and mainly involves varices in the rectum and duodenum. Banding can be performed when the diameter of the varix does not exceed the endoscope diameter. More studies have evaluated the role of sclerotherapy in ectopic varices, but the results were less than optimal. Colorectal varices respond less often to sclerotherapy, possibly as a result of the dilution of sclerosant to an ineffective concentration in these larger varices.

The argon-beam plasma coagulator (APC) has been used in the prevention and eradication of recurrent esophageal varices but should not be used in the acute management of variceal bleeding. It may be useful in bleeding ileocolonic varices, but evidence for its use in other ectopic variceal sites has not been sufficiently demonstrated.

Embolization with coils, gel foam, collagen, autologous blood clot, or thrombin has been effective in interventional radiology as an adjunct to band ligation or TIPS. Occlusion of the supplying vein decreases blood supply to the varix itself. Steel coils, placed via interventional techniques, are most effective in achieving total focal occlusion. Success rates for bleeding cessation are reported to be greater than 90%; however, the underlying portal hypertension is not treated.

Surgical treatment, including direct focal devascularization, is effective and usually performed in the presence of portal vein occlusion or advanced cirrhosis. Some of the direct approaches used are oversewing of varices via duodenotomy, duodenal dearterialization and stapling, circumferentially stapled anoplasty, and double-selective shunting. Nonselective portosystemic shunts (see Chapter 76D) are much more invasive and are therefore less commonly used (Helmy et al, 2008).

Portal Gastropathy and Gastric Antral Vascular Ectasia

Portal gastropathy is rarely a cause of rapid life-threatening bleeding, but it can be severe enough to require daily transfusion. This situation is most common in the presence of gastric antral vascular ectasia (GAVE), a condition well described by its name. GAVE can occur without portal hypertension but is especially difficult to manage in the presence of portal hypertension. The antrum often has a red, longitudinally striped appearance that gives this condition its alternative name, *watermelon stomach.* In the absence of portal hypertension, this cause of chronic blood loss and iron deficiency anemia can be treated with APC or antrectomy. However, APC in the setting of portal hypertension is much less effective and can even cause a worsening of bleeding. Unfortunately, TIPS shunting has also been of little benefit, and antrectomy is usually too risky to be considered.

Recently, banding of antral mucosa has been described as a treatment for this condition. Up to 12 bands can be placed per session with about three sessions required to complete the treatment course. Banded mucosa is sloughed and replaced by mucosa without ectatic blood vessels. Wider experience with this modality will help determine the place of banding in this difficult to manage condition (Wells et al, 2008).

RECURRENT BLEEDING

GI hemorrhage in patients with cirrhosis either recurs or cannot be controlled in approximately 10% to 20% of cases despite coordinated efforts with directed therapy. In these cases, shunt therapy is indicated. In Child-Turcotte-Pugh class A (compensated) cirrhotic patients, surgical shunts (see Chapters 76A through 76D) have proven efficacious. However, in most acute and later recurrences, TIPS is the preferred mechanism of portal decompression (see Chapter 76E). In addition to serving as a bridge to liver transplantation in patients not responding to pharmacologic and endoscopic therapy, TIPS is sometimes thought to be advantageous because of the lower portal pressures during transplantation. A TIPS functions as a nonselective shunt, and the development of encephalopathy or worsening of existing encephalopathy should be considered before implantation. Stenosis or occlusion may develop in up to 50% of patients within 1 year with bare metal stents; however, results appear to be improved when stents covered with polytetrafluoroethylene (PTFE) are used; both types of stents can be restored with angiographic interventions.

In the era of TIPS, an extensive gastric and lower esophageal devascularization together with transection of the lower esophagus is rarely required (see Chapter 75C). The extensive abdominothoracic Sugiura procedure popularized in Japan has been replaced by a transabdominal procedure in most institutions (Blumgart & Belghiti, 2007).

No Therapy: Observation Only

Patients with end-stage liver disease who are not candidates for transplantation and who present with major esophageal variceal bleeding complicated by multiorgan failure perhaps should not be subjected to the most invasive procedures described. Withholding treatment in these circumstances, in which the chances of meaningful survival is remote at best, is a difficult clinical and ethical decision but one that must be considered, discussed, and accepted in the appropriate clinical scenario.

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CHAPTER 75C

Esophageal varices: operative devascularization and splenectomy

Chung-Bao Hsieh and Kuo-Feng Hsu

TREATMENT OF ESOPHAGEAL VARICES

With the development of advanced vasoactive agents (see Chapter 75B), endoscopic therapies (Chapter 75B), and transjugular intrahepatic portosystemic shunting (TIPS; see Chapter 76E), the need for surgical treatment for esophagogastric varices has decreased (Cello et al, 1984). Most patients with esophagogastric varices have cirrhosis and portal hypertension; for patients in advanced stages of liver failure, liver transplantation (see Chapter 97) is the optimal treatment, although shunting (see Chapter 78) or nonshunting operations can be considered for treatment of bleeding complications. Rikkers (1998) reported that portosystemic shunts and esophagogastric devascularization have an important role in selected patients with bleeding related to portal hypertension.

Compared with the risk of postoperative hepatic encephalopathy in surgical shunts and TIPS, nonshunting procedures maintain postoperative portal perfusion and long-term hepatic and systemic hemodynamics in patients with cirrhosis, which results in a low incidence of postoperative encephalopathy (Lin et al, 1993; Vons et al, 1996). The applications of shunting operations are limited in patients with extensive thrombosis of the mesenteric venous system, but nonshunting operations do not have such limitations. In addition, nonshunting operations do not alter vascular anatomy and complicate future liver transplant surgery, although they can cause significant upper abdominal adhesions, which are associated with increased bleeding at the time of transplantation.

In the era of multimodalities for bleeding esophagogastric varices, the role of nonshunting operations is redefined as 1) an emergency procedure when medical treatment, endoscopic ligation or sclerotherapy, and TIPS have failed; 2) a part of combined therapies to achieve better outcomes in selected patients (Burroughs et al, 1989); and 3) a long-term bridge to liver transplantation, particularly in patients with splanchnic thrombosis or in the absence of a facility capable of TIPS (Selzner et al, 2001).

In general, nonshunting operations include the devascularization procedure, splenectomy, and esophagus transection. The devascularization procedure has been described as obliteration of varices or disconnection of the esophagogastric veins from the hypertensive portal tributaries. These approaches, known as the Hassab (Hassab, 1998) and Sugiura procedures (Sugiura & Futagawa, 1973), and other modified procedures are discussed.

EFFECTS OF DEVASCULARIZATION AND SPLENECTOMY FOR ESOPHAGEAL VARICES

The principle of devascularization procedures for variceal bleeding is based on anatomic features. The coronary vein and gastric veins are anastomosed with tributaries of the superior vena cava by collateral channels in the submucosa of the esophagus, between the two muscular layers, and in the periesophageal region. In portal hypertension, the increased venous pressure can produce varices throughout the length of the esophagus and down into the upper stomach. In the region of the esophageal hiatus, periesophageal vein dilation does not usually occur, and the most blood flow goes through the esophageal submucosal varices. Hence, most bleeding occurs in the distal segment of the esophagus, in the last 5 cm, usually at the esophagogastric junction (Spence, 1984).

Spence and colleagues (1983) applied a computerized image analysis system to study the venous anatomy of the esophagus; serial sections have shown that the large vessels in the lamina propria communicate directly with dilated intraepithelial blood channels via the epithelial papillae. These intraepithelial channels seen histologically represent the cherry-red spots viewed endoscopically (Spence & Terblanche, 1987). An ideal technique of control for bleeding varices would be permanent obliteration of the varices in the lower periesophageal vessels and intraepithelial dilated vessels.

Portal hypertension, however, is not decreased even with the ideal devascularization procedures. Some methods to reduce the portal hypertension include medication with β_2-blockers, octreotide, and vasopressin (Dell'Era et al, 2008) and surgical treatment. Liver transplantation is the most effective treatment to reduce portal hypertension, but splenectomy may also have benefit in this regard. Zhang and colleagues (2009) found a decreased portal venous pressure gradient, decreased portal venous flow, and increased hepatic artery flow after splenectomy with periesophagogastric devascularization, which resulted in short-term improvement in hepatic functional reserve. De Cleva and colleagues (2007) compared esophagogastric devascularization plus splenectomy with distal splenorenal shunt in hemodynamic evaluation and found similar improved hyperdynamic circulation in schistosomal portal hypertension.

HISTORY OF ESOPHAGEAL TRANSECTION, DEVASCULARIZATION, AND SPLENECTOMY

Crile (1950) proposed transthoracic ligation of esophageal varices, and subsequently many modifications of his technique have been devised. Boerema (1949) and Vosschulte (1957) introduced the simple button technique for transabdominal esophageal transection, but unfortunately, this method was a major source of stricture formation (Johnston & Kelly, 1976). Walker (1964) used a vertical incision for the muscle layers of the esophagus and a transverse division of the mucosa and

submucosa to reduce the risk of posttransection leakage. About the same time, Tanner (1961) proposed a subcardiac portoazygos disconnection with gastric transection. Hassab (1967) found that in patients with bleeding esophageal varices secondary to schistosomiasis, an adequate gastroesophageal devascularization procedure via the abdomen was possible. This technique, known as the *Hassab procedure,* included splenectomy but not esophageal or gastric transection, and Hassab (1998) reported a remarkably low rate of rebleeding with this method.

Japanese surgeons devised an extensive transthoracic paraesophageal devascularization and esophageal transection combined with an abdominal component consisting of splenectomy, devascularization of the upper stomach, vagotomy, and pyloroplasty (Sugiura & Futagawa, 1973). Thereafter, some Japanese surgeons modified this *Sugiura procedure* with a sole abdominal approach and achieved similar survival (Inokuchi, 1985).

In 1974, Vankemmel published the first report of the use of a circular stapling gun for esophageal transection. This technique removes approximately 1 cm of full-thickness esophageal wall, provides a safe suture line, and reduces the risk of stricture formation. Jin and Rikkers (1996) reported the American experience with a modified Sugiura procedure without esophagus transection as an effective method for treating variceal hemorrhage. Johnson and colleagues (2006) proposed that the same results could be achieved with a transabdominal modified devascularization procedure without esophageal stapler transection. Nakamura and colleagues (1996) simultaneously used the Hassab procedure and endoscopic injection sclerotherapy for esophageal varices. Hashizume and colleagues (1998) first applied the laparoscopic technique to perform the Hassab procedure and splenectomy successfully in 10 patients with cirrhosis and varices. Jiang and colleagues (2009) compared open and laparoscopic splenectomy with azygoportal devascularization and concluded that the laparoscopic procedure was a safe and effective method in carefully selected patients.

HASSAB PROCEDURE

Hassab (1967) proposed a method of gastroesophageal decongestion and splenectomy (GEDS) for management of bleeding varices. In this approach, the patient is in a supine position; a 30-degree, head-up tilt improves the exposure of the operative field. A midline epigastric incision is generally used. Occasionally, an extended left subcostal incision or L-shaped incision of the left upper abdomen is used for extreme splenomegaly. The left lobe of the liver is retracted. In case of left lobe hypertrophy in cirrhotic patients, division of the left lobe ligaments may be useful. Splenectomy was initially performed, and the splenic artery could be suture ligated from the upper part of the pancreatic body if pancreatic tail oozing persisted. Next, the gastrohepatic ligament is divided in the area where it is thin and usually transparent, exposing the right crus of the esophageal hiatus. The incision is carried out superiorly over the anterior aspect of the esophagus, dividing the reflection of the parietal peritoneum at the junction between the esophagus and the diaphragm. The incision is pursued down the left side of the esophagus until the left crus of the esophageal hiatus is identified. The abdominal esophagus is isolated by circumferential dissection and looped with a tape (Fig. 75C.1).

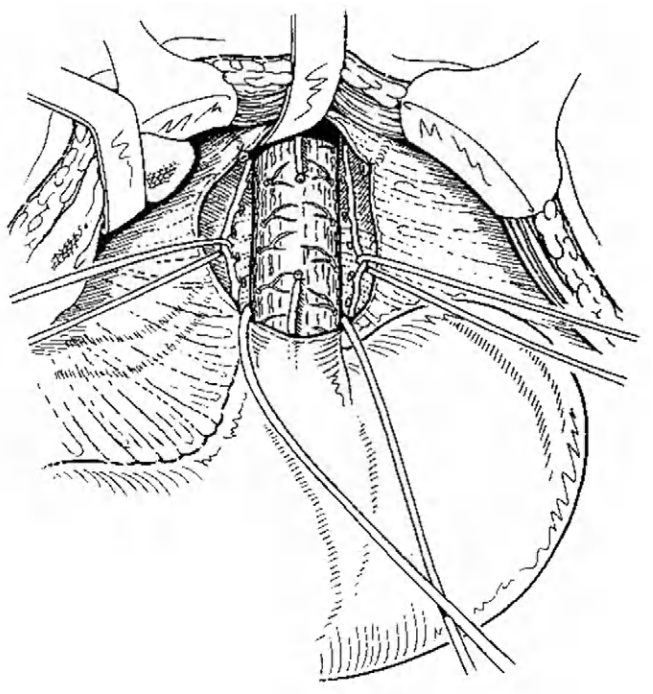


FIGURE 75C.1. Technique of esophageal exposure for devascularization. A tape has been placed around the esophagus, and the vagus nerves have been divided.

The Hassab procedure consists of splenectomy, perihiatal devascularization of the lower esophagus, ligation of the left gastric vessels, devascularization of the proximal half of the stomach, and separation of the stomach from its bed through the abdominal approach (Fig. 75C.2). The points of this technique are 1) perihiatal devascularization of the lower 3 to 4 inches of the esophagus with ligation of any vessels or vagus nerves ascending through the hiatus and diaphragm; 2) ligation of the left gastric artery branches to the stomach, taking care to avoid injury to any accessory left hepatic artery; 3) devascularization of the proximal half of the stomach, taking care to reperitonealize the greater curvature of the stomach to avoid rebleeding; and 4) aggressive pulmonary toilet, which is necessary to avoid basal collapse and chest infection. As an additional step, suction drainage of the splenic bed was suggested by Hassab (1998) to avoid subphrenic infection, although this is probably unnecessary.

Hassab (1998) suggested that combined sclerotherapy or endoscopic ligation could reduce rebleeding if there were missed obliterated esophageal perforators or if devascularization at operation was incomplete. Nakamura and colleagues (1992) applied endoscopic ultrasonography and reported that GEDS is effective for the extramural connections, but for the intramural connections, combination with sclerotherapy is necessary. Hassab (1998) reported that esophageal transection is unnecessary and instead disconnected the perigastroesophageal portoazygos connections; this is contrary to Sugiura and Futagawa (1973), who preserved them and interrupted gastroesophageal continuity with stapled transection and reanastomosis. Zhang (1991) compared treatment of variceal bleeding treated with GEDS or GEDS plus esophageal transection and found that the simple procedure without transection was effective in maintaining good quality of life with no encephalopathy. He reported maintenance of liver function and an upper gastrointestinal (GI)

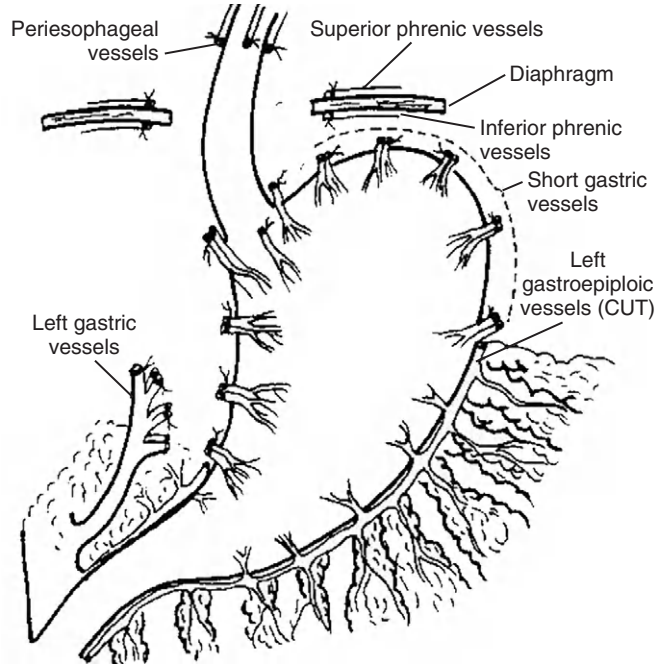


FIGURE 75C.2. Diagrammatic representation of the Hassab procedure. *(From Hassab MA, 1967: Gastro-esophageal decongestion and splenectomy in the treatment of esophageal varices in bilharzial cirrhosis: further studies with a report on 355 operations. Surgery 61:170.)*

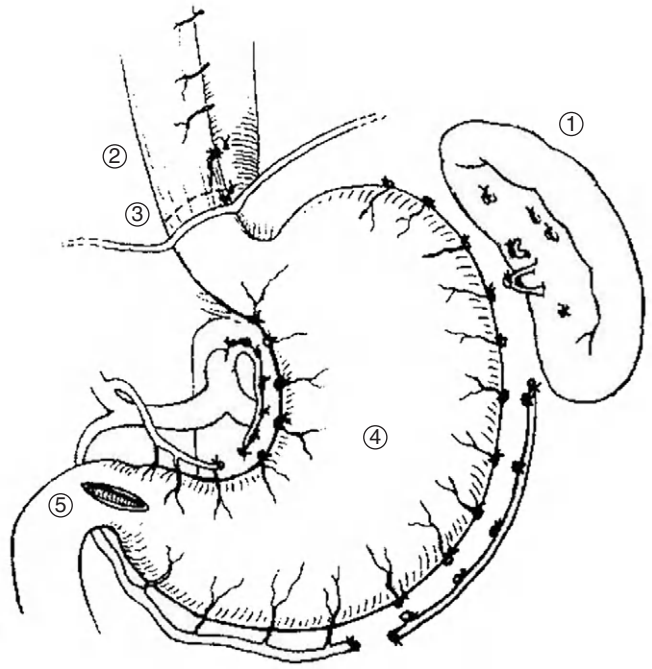


FIGURE 75C.3. Sugiura procedure includes *1,* splenectomy, *2,* devascularization of 8 to 10 cm of the esophagus, *3,* transection and end-to-end anastomosis of the lower esophagus 4 to 5 cm above the gastroesophageal junction, *4,* devascularization of the lesser and greater curvatures of the stomach, and *5,* pyloroplasty. *(From Selzner M, 2001: Current indication of a modified Sugiura procedure in the management of variceal bleeding. J Am Coll Surg 193:168.)*

bleeding rate of 3.1% within 2 years. The addition of esophageal transection did not change the bleeding rate and added more serious complications early after operation.

SUGIURA AND MODIFIED SUGIURA PROCEDURES

The Sugiura procedure is a nonshunting technique aimed at the eradication of esophageal varices. The operation consists of an extensive paraesophagogastric devascularization with esophageal transection and splenectomy through successive thoracic and abdominal incisions. The results obtained by Sugiura and Futagawa (1973, 1984) in Japan were impressive and led some authors to evaluate the efficacy of the operation in Western countries. In the West, the Sugiura procedure was believed to be technically complex and time consuming and was largely ignored or abandoned. Interest was renewed, however, when simplified procedures using an exclusive abdominal approach and stapled transection were described (Peracchia et al, 1980). The original procedure proposed by Sugiura and Futagawa (1973) and the modified procedure described by Ginsberg and colleagues (1982) and Umeyama and colleagues (1983), which is the procedure used routinely use today (Liao et al, 2009), are described.

Sugiura Procedure

The original Sugiura procedure (Fig. 75C.3) is performed in two steps; a thoracic approach is taken first, followed by an abdominal procedure 4 to 6 weeks later (Sugiura & Futagawa, 1973). The thoracic procedure is carried out through a left lateral thoracotomy using the sixth or seventh intercostal space. The mediastinal pleura over the esophagus is opened longitudinally. The lower part of the thoracic esophagus is surrounded by dilated (adventitial) veins that form a plexus. These adventitial veins run parallel to the esophageal wall and communicate with the submucosal veins (variceal channels) via large perforating veins. All these perforating veins must be completely and systematically ligated and divided to devascularize the esophagus; at the same time, great care must be taken not to damage the adventitial veins, which represent a spontaneous portacaval shunt. Usually, 30 to 50 perforating veins must be ligated over a 12- to 18-cm length of the thoracic esophagus. At the level of the hiatus, periesophageal channels are bulky and esophageal varices predominate. Thorough devascularization of this region is paramount because it prepares the area for esophageal transection. After completion of the devascularization, esophageal transection is performed at the level of the diaphragm. During this step, esophageal varices are electively occluded with sutures. A nasogastric tube is left in the stomach and the thorax is closed with appropriate drainage.

The abdominal procedure is subsequently performed through an upper midline or left subcostal laparotomy, and splenectomy is performed. The abdominal esophagus and the cardia are devascularized, as are the greater curvature and the posterior aspect of the stomach. The posterior vagus nerve is divided as in a selective vagotomy (Sugiura & Futagawa, 1973). Devascularization of the lesser curvature of the stomach follows, and the cardioesophageal branches of the left gastric vessels are ligated and divided. Devascularization is performed over more than 7 cm of gastric wall from the cardia (Sugiura & Futagawa,

1973), and the esophagus and the cardia are completely mobilized and freed from the adjacent anatomic structures. Devascularization is facilitated by the division of the anterior vagus nerve; because of this, pyloroplasty is performed, and the abdominal incision is closed. Both key steps of the abdominal procedure may be performed during the same operative session by using synchronous incisions. If such an option is elected, the abdominal procedure is carried out through a left subcostal incision.

Modified Sugiura Procedure

In this approach, the entire operation is performed through a one-stage transabdominal approach via a midline incision or extension of a left subcostal incision as an L-shaped incision. The patient is slightly rotated to the right, and strong mechanical retractors lift the costal margin cephalad to expose the left subphrenic space.

The procedure is initiated with splenectomy. Removal of the spleen, which is usually enlarged, dramatically improves the exposure of the abdominal esophagus and facilitates paraesophagogastric devascularization. Gastric devascularization is begun at the greater curvature of the stomach and continues along its upper part and is performed adjacent to the stomach wall. Completion of the greater curvature devascularization at the cardia is facilitated by placing a tape around the abdominal esophagus. This maneuver is not always easy in the presence of portal hypertension, especially when extrahepatic portal vein thrombosis is present, and it is difficult in patients who have undergone previous sclerotherapy. The posterior aspect of the upper part of the stomach is devascularized, including the esophagogastric branches of the left gastric vessels; devascularization is likewise pursued along the lesser curvature. The surgical technique used is similar to that of proximal gastric vagotomy. The heel of the crow's foot of the nerve of Latarjet nerve is divided, and devascularization is carried up to the esophagus.

To improve the exposure of the esophagus, the diaphragmatic orifice of the esophagus is opened. The pericardium is freed from the upper aspect of the diaphragm, which is divided sagittally. Esophageal devascularization is performed close to the esophageal wall by dividing only the vessels running transversely (perforating veins) and coursing to perforate the esophageal wall. Devascularization is pursued over a distance of 10 to 12 cm; this step of the operation is facilitated by using clips. In patients who have had previous sclerotherapy with periesophageal fibrosis, completely safe devascularization may be technically impossible; but at the very least, devascularization should be done within the limits of safety to avoid damaging the esophagus. The degree of difficulty during this step of the procedure most likely is linked to the type of sclerosant used and the number of sclerotherapy sessions carried out before surgery (Alam et al, 1996; Chaudhary & Aranya, 1991).

Esophageal transection is performed with a mechanical stapler introduced through a short gastrotomy (Fig 75C.4). In cases of previous sclerotherapy, thickness of the lower end of the esophagus and inflammatory changes preclude the use of a large stapler. A 29-mm circular stapler is optimal for this procedure; however, a smaller stapler (25 mm) may be required, especially in patients treated by previous sclerotherapy (Mariette et al, 1994).

In the postoperative period, it has been the tradition to start total parenteral nutrition for 7 days. On postoperative day 7, the patient is administered a meglumine diatrizoate meal or gastrografin swallow to check the patency of the transection line and confirm the lack of fistulae. Endoscopic examination of the esophagus is systematically performed 3 weeks postoperatively, and dilation of any stricture is performed as required.

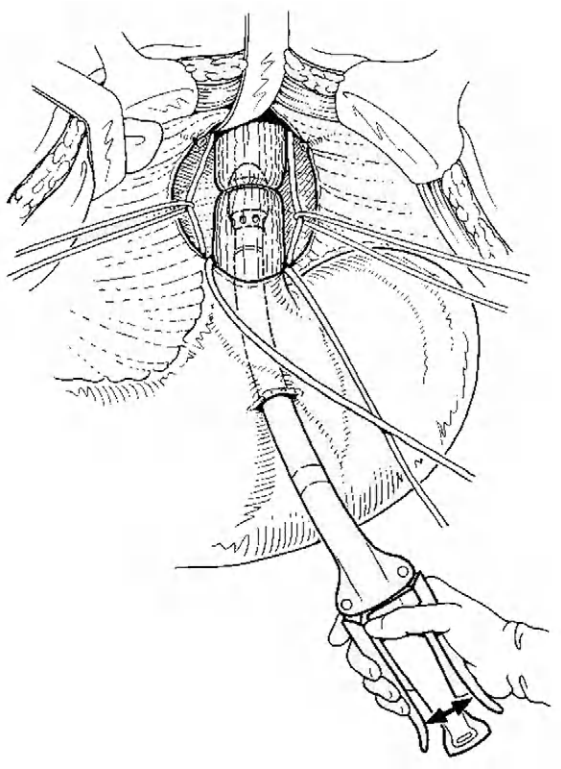


FIGURE 75C.4. Esophageal transection by a mechanical stapler. The head of the circular stapler has been closed, and the esophageal anastomosis has been completed.

The Sugiura operation includes five procedures, and only devascularization of the gastroesophagus remains in many versions of the modified Sugiura operation. Ginsberg and coworkers (1982) proposed that esophagogastric devascularization be performed without dividing the main vagus trunks; only a proximal gastric vagotomy is done, thereby avoiding a pyloroplasty. Hidalgo Huerta and colleagues (1983) proposed using a Nissen fundoplication to allow wrapping of the transection line, which may prevent reflux possibly caused by extensive dissection of the cardia. Johnson and colleagues (2006) reported that devascularization without esophageal transection has similar safety and outcome as devascularization with esophageal transection to control variceal bleeding. In a prospective, controlled, randomized trial that included 55 patients, Orozco and colleagues (1998) reported that splenectomy may be unnecessary in the Sugiura procedure for control of variceal bleeding; they showed that the no-splenectomy group had fewer blood transfusions and less postoperative portal vein thrombosis, and no difference was reported in rebleeding and encephalopathy rates compared with the splenectomy group.

LAPAROSCOPIC DEVASCULARIZATION

With the development of laparoscopic instrumentation and advanced surgical techniques, the gastroesophageal devascularization procedure can now be performed laparoscopically.

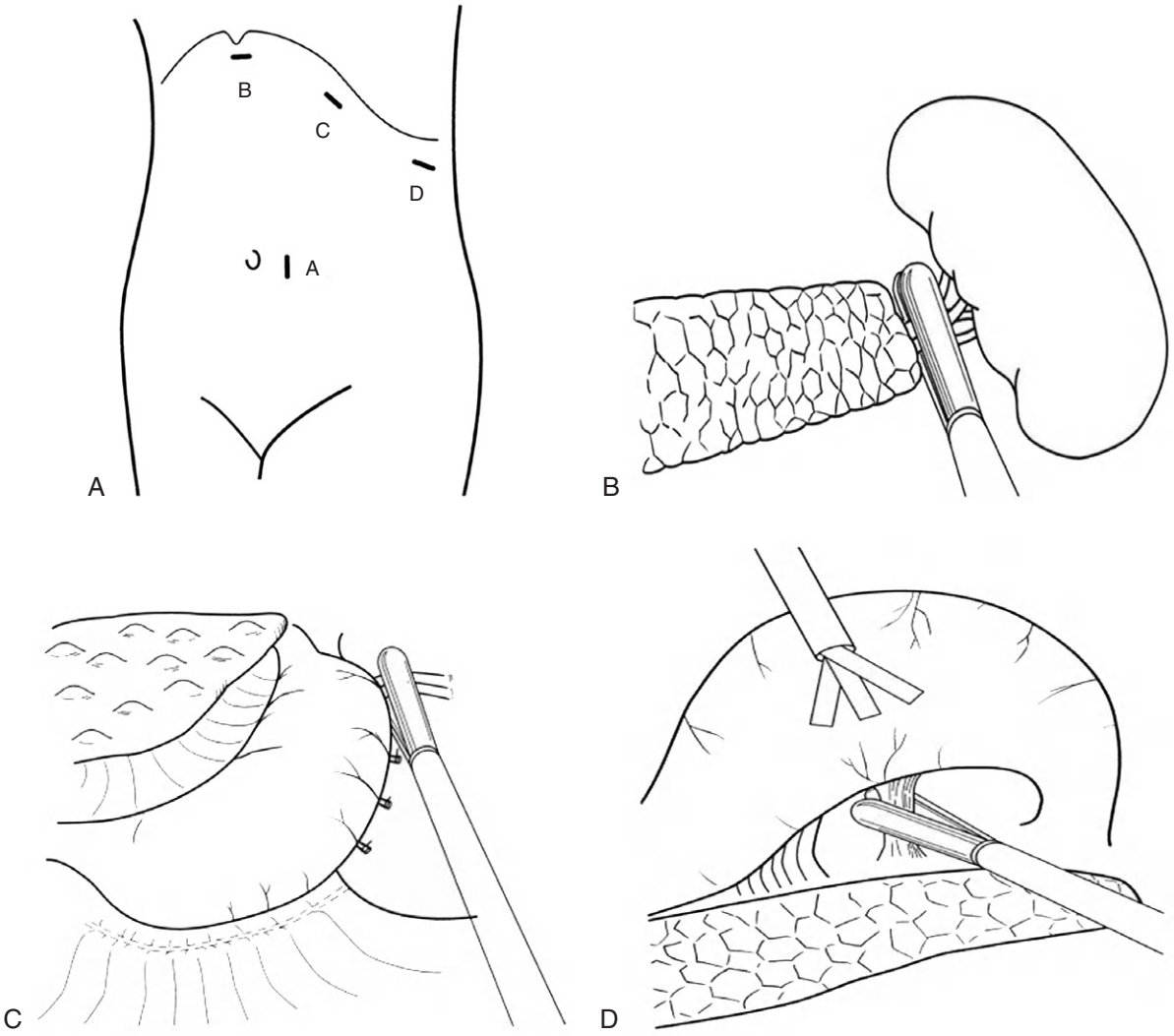


FIGURE 75C.5. Port sites. **A,** Close to the umbilicus, where a laparoscope is inserted (**B** to **D**), in the left upper abdomen along the subcostal line, is where 12-mm trocars are inserted. **B,** The splenectomy is completed with an autosuture device, and the splenic artery and vein are cut. **C,** Devascularization along the fundic area is done with the autosuture device after dissecting the posterior wall of the stomach. **D,** Devascularization along the lesser curvature, including the left gastric artery and vein, is done with the autosuture device, while the greater curvature of the stomach is lifted up. *(From Hashizume M, 1998: Laparoscopic gastric devascularization and splenectomy for sclerotherapy-resistant esophagogastric varices with hypersplenism. J Am Coll Surg 187:263-270.)*

The patient is placed in a right semidecubitus position; the trocar port sites are shown in Fig. 75C.5A. The laparoscope is introduced through the cannula close to the umbilicus, and three other 12-mm trocars are inserted into the left subcostal region. The splenocolic ligament is divided with the Harmonic Scalpel (Ethicon, Cincinnati, OH), and the spleen is mobilized from splenophrenic and splenorenal ligaments by both blunt dissection and coagulation. Exposure of the splenic hilum is completed by a division of the gastrosplenic ligament, and the short gastric vessels are divided with a Harmonic Scalpel or autosuture device (Linear Cutter; Ethicon); the autosuture device can also be useful for resecting the spleen at the splenic hilum (Fig. 75C.5B). A large, nylon surgical sack (Endo Catch II; U.S. Surgical, Norwalk, CT) is introduced into the abdominal cavity, and the spleen is maneuvered into the sack, where it is grasped by forceps and crushed with a Kelly clamp and removed.

Devascularization of the short gastric vessels is completed along the greater curvature of the upper stomach after splenectomy. First, the posterior wall of the fundus is dissected and devascularized with the autosuture device (Fig. 75C.5C). Next, the lesser omentum is opened with the Harmonic Scalpel, and the esophageal branches of the left gastric vessels are cut along the lower esophagus. The lesser curvature of the stomach is then dissected until the left gastric artery and vein are exposed, while the greater curvature is lifted up with a retractor (Fig. 75C.5D). Finally, the upper stomach is freed from its bed, and devascularization completed.

Kitano and associates (1994) first reported seven cirrhotic patients with bleeding esophagogastric varices treated by laparoscopic devascularization of the lower esophagus and upper stomach. Hashizume and colleagues (1998) successfully applied the laparoscopic Hassab procedure for sclerotherapy-resistant esophagogastric varices combined with hypersplenism. In

Table 75C.1

Interventions for Bleeding Esophagogastric Varices

Procedure	Rebleeding Rate (%)	Complication	References
Hassab	6.2-8.3	Gastric outlet obstruction	Hassab, 1998 Laosebikan et al, 2005
Sugiura	10-26	Esophageal leak, stenosis, portal vein thrombosis	Inokuchi, 1985 Orozco et al, 1992; Dagenais et al, 1994
Endoscopic sclerotherapy	20-53	Systemic embolization	Greig et al, 1990 Sarin, 1997 Ryan et al, 2004 Khan et al, 2006
TIPS	20-50	Stent stenosis, thrombosis, hepatic dysfunction	Casado, 1998 Rosemurgy et al, 2005 Khan et al, 2006
DSRS	0-11	Shunt occlusion, encephalopathy	D'Amico et al, 1995 Khan et al, 2006

TIPS, transjugular intrahepatic portosystemic shunt; DSRS, distal splenorenal shunt

subsequent years, other authors (Danis et al, 2004; Jiang et al, 2009; Wang et al, 2008; Yamamoto et al, 2006) reported their experience with laparoscopic devascularization with splenectomy and concluded that this is a feasible, relatively safe, and minimally invasive surgical procedure in selected patients.

RESULTS

A number of treatment options exist for bleeding esophagogastric varices, including surgical shunting, nonshunt operations, and endoscopy with sclerotherapy or variceal ligation (Table 75C.1). The two kinds of devascularization of gastroesophageal varices are the Hassab and Sugiura procedures, and the reported rebleeding rates, respectively, are 6.2% to 8.3% and 10% to 26%. A concerning complication of the Hassab operation is gastric outlet obstruction as a result of vagus trunk transection without pyloroplasty. The specific complications of the Sugiura operation are esophageal leak and stenosis from the esophageal transection procedure. Compared with the rebleeding rate of 20% to 50% in endoscopic sclerotheapy, devascularization operations seem to be better for rebleeding control. The distal splenorenal shunt has a superior rebleeding control rate, but shunt occlusion and encephalopathy have limited its clinical application in some centers. Although the devascularization operation is complex, it can achieve rebleeding control.

Operative Mortality

The overall operative mortality rate of the Hassab procedure in Egypt (Hassab, 1967) is 12.4%, and the overall operative mortality rate is 8.5% for the Sugiura operation in Japan (Inokuchi, 1985). The rates compare favorably with the operative mortality rates of various other abdominal operations performed in cirrhotic patients (Franzetta et al, 2003; Sirinek et al, 1987). When the devascularization operation is used as an emergency procedure, the operative mortality rate increases dramatically to 38.4% in the Hassab and 20.6% in the Sugiura procedure (Table 75C.2). The overall and emergency operative mortality rates with the modified Sugiura operation from Japanese reports (Inokuchi, 1985) are 7.1% and 31%, respectively. A laparoscopic Hassab operation was recently developed, but experience is still limited and it has only been performed in highly select patients. Other variations of the Sugiura procedure have been proposed outside Japan; however, given the limited case experience, it is not possible to gauge surgical mortality rates accurately with the modified procedures.

Table 75C.2

Operative Mortality Rates of Devascularization Procedures for Esophagogastric Varices

	NO. PATIENTS				OPERATIVE MORTALITY RATE (%)			
Procedure	Total	Elective	Emergency	CTP C*	Total	Elective	Emergency	References
Hassab	355	316	39	—	12.4	9.2	38.4	Hassab, 1967
Laparoscopic Hassab	36	—	—	4	0	0	0	Jiang et al, 2009; Hashizume et al, 1998
Sugiura	1300	1028	272	—	8.5	5.3	20.6	Inokuchi, 1985
Modified Sugiura	854	754	100	—	7.1	4	31	Inokuchi, 1985
Other modified Sugiura	20	16	4	4	20	0	100	Ginsberg et al, 1982
	38	25	13	4	10.5	0	10.5	Johnson et al, 2006
	22	22	—	—	5	5	—	Orozco et al, 1998

*Number of Child-Turcotte-Pugh (CTP) class C patients included.

Table 75C.3

Postoperative Complications and 5-Year Survival After Devascularization for Esophagogastric Varices

Procedure	Rebleeding Rate (%)	Chronic Encephalopathy	Esophageal Leakage	Esophageal Stricture	Portal Vein Thrombosis	5-Year Survival (%)	References
Hassab	6.2-12	0-4.2	—	—	—	73-85	Lu, 1990 Abu-Elmagd et al, 1993 Hassab, 1998
Sugiura	5-26	0-7	6-14	2-28	1-6	32-75	Peracchia et al, 1980 Suigura & Futagawa, 1984 Inokuchi, 1985 Dagenais et al, 1994 Mariette et al, 1994
Modified Sugiura	3.9-31	0-8	5-7.1	7.6-17	—	23-72	Inokuchi, 1985 Jin & Rikkers, 1996 Borgonovo et al, 1996 Selzner et al, 2001 Johnson et al, 2006

Operative Morbidity

The rates of complications and 5-year survival in various devascularization operations are different (Table 75C.3). The correlative factors should be related to the severity of the liver cirrhosis (e.g., Child-Turcotte-Pugh class C), etiology of the liver disease (schistosomal or cirrhotic portal hypertension), and the surgical methods used (with or without esophageal transection). The rebleeding rates are 6.2% to 12%, 5% to 26%, and 3.9% to 31% with the Hassab, Sugiura, and modified Sugiura procedures, respectively. The range of the rebleeding rates may be attributable to the complete or incomplete devascularization procedure (Hassab, 1998). Most devascularization procedures do not result in deterioration of liver function, and chronic encephalopathy is generally not exacerbated. Complications of esophageal leakage and stenosis are related to esophageal transection. The rate of esophageal leakage and stenosis with the Sugiura operation are 6% to 14% and 2% to 28%, respectively. The incidence rates for the modified Sugiura operation are similar, and the risk of portal vein thrombosis after the Sugiura procedure has been emphasized by Sugiura and Futagawa (1984). Portal vein thrombosis may be linked to thrombocythemia or to a decrease in portal blood flow after splenectomy (Takenaka et al, 1990) and affects 1% to 6% of patients. The 5-year survival rate with the Hassab operation is 73% to 85%, seemingly better than other devascularization procedures. However, these improved results may be attributable to the frequent use of schistosomal portal hypertension with preserved liver function. The 5-year survival rate of the Sugiura and modified Sugiura operations is approximately 70% and dramatically decreases to about 30% in the emergency setting.

ROLE OF SPLENECTOMY AND DEVASCULARIZATION IN LIVER TRANSPLANTATION

Shunt and nonshunt operations cannot improve liver function in cirrhotic patients in the long term; this can only be accomplished with liver transplantation. Some shunt operations impair liver function and result in worsening of hepatic encephalopathy (Henderson et al, 2006). Nonshunt operations, such as the Hassab and Sugiura procedures, seem to preserve liver function and increase hepatic artery flow in the short term (Zhang et al, 2009). Technique and experience accumulation has improved the success rate of endoscopic variceal ligation for variceal bleeding; however, endoscopic variceal ligation and devascularization with splenectomy can occlude collateral veins both inside and outside the esophageal wall (Liu et al, 2006). Laparoscopic devascularization with splenectomy combined with endoscopic variceal ligation may be an ideal procedure for consideration as a bridge to liver transplantation in cirrhotic patients with variceal bleeding. This approach not only controls variceal bleeding, but also may maintain liver function and may be associated with decreased surgical adhesions when compared with open devascularization procedures.

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CHAPTER 76B

Technique of portocaval shunting

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OVERVIEW

Surgical shunts for portal hypertension and variceal hemorrhage are rarely undertaken today, in large part as a result of the recent popularity gained by transjugular intrahepatic portosystemic shunting (TIPS) (see Chapter 76E), a general lack of interest by surgeons, and the rising number of liver transplant centers across the United States. As a result, the number of hepatobiliary surgeons who have expertise in surgical shunting is declining, which is not to imply that this is appropriate, but it is true. Although current data document that surgical shunting is superior to TIPS in regard to patency, survival, risk of rebleeding, and maintaining effective hepatic blood flow, TIPS now predominates current therapy for variceal bleeding, likely because of its less invasive nature. The scope of this chapter is to describe the technical aspects of performing a native side-to-side portacaval shunt and a small-diameter prosthetic H-graft portocaval shunt. Unlike an end-to-side portacaval shunt, these shunts potentially preserve effective hepatic blood flow and are not ascitogenic.

Variceal hemorrhage secondary to portal hypertension presents an enormous challenge and responsibility to surgeons. Varices that are actively bleeding should be treated pharmacologically and endoscopically, if possible, prior to surgical management (see Chapters 75A and 75B). In the opinion of most providers, it should be a priority to stabilize the patient with nonoperative measures rather than attempt an emergency surgical shunt. The primary goal of surgery is to control ongoing hemorrhage and to prevent future life-threatening hemorrhage without inducing hepatic dysfunction. Patients should not be candidates for imminent liver transplantation (i.e., within 6 months), and an optimal candidate should have a Model for End-Stage Liver Disease (MELD) score less than 14 or have a Child-Turcotte-Pugh (CTP) class of A or B. However, for patients with advanced liver disease without prospects for transplantation, shunting is advocated for resource conservation and control of hemorrhage, albeit with increased risk of hepatic decompensation. With a recent episode of hemorrhage, the total bilirubin may be elevated, which increases the MELD score at the time of hospitalization. In these circumstances, it is helpful to extrapolate the patient's MELD score or CTP class back to a time prior to the most recent hospitalization and/or hemorrhage.

A side-to-side portacaval shunt, as well as a small-diameter prosthetic H-graft portacaval shunt (HGPCS), is constructed for bleeding esophageal or gastric varices as a result of portal hypertension, most commonly caused by cirrhosis. Side-to-side portacaval shunts are placed electively or as an emergency in patients with a history of bleeding esophageal and/or gastric varices not amenable to or failing endoscopic therapy; prophylactic shunts are not recommended. In patients with acute bleeding, every effort is made to correct underlying coagulopathy and metabolic disorders, as well as to control active bleeding, using pharmacologic and endoscopic measures or balloon tamponade. An absolute contraindication to side-to-side portacaval shunt is the presence of portal vein (PV) thrombosis; therefore, PV patency is assessed preoperatively to document patency using color-flow Doppler ultrasound or other tests, such as magnetic resonance angiography (MRA) or computed tomography (CT). Side-to-side portacaval shunts are indicated for Budd-Chiari syndrome or other disorders that severely impair hepatic outflow. Contraindications to use include PV or inferior vena cava (IVC) thrombosis, multiple previous abdominal operations, morbid obesity, severe mitral regurgitation and/or aortic stenosis, and poor cardiopulmonary reserve. In contrast to large-diameter side-to-side portacaval shunts, a small-diameter (8 to 10 mm), calibrated, side-to-side portacaval shunt preferentially maintains hepatopetal flow and a normal (6 to 8 mm Hg) pressure gradient between the PV and IVC.

A focused preoperative investigation should include a determination of MELD score and CTP class; assessment of underlying cardiac dysfunction—such as mitral regurgitation or aortic stenosis—and cardiorespiratory reserve; evidence of current alcohol abuse; nutritional status; and presence of ascites and/or encephalopathy. If cardiac dysfunction is suspected, an echocardiogram should be obtained to avoid postoperative heart failure. A transabdominal color-flow Doppler ultrasound or other test is mandatory to assess portasplanchnic patency, directional flow, and patency of the vena cava.

SURGICAL SHUNTS IN THE AGE OF TIPS

TIPS is a "definitive" nonsurgical treatment option for portal hypertension, often coined a "bridge to transplantation," but with many critical issues. The most common causes of TIPS failure are shunt thrombosis and stenosis, both of which lead to variceal rehemorrhage. Numerous reports have shown that hepatic decompensation is unacceptably common after TIPS. In addition, the survival data after TIPS are not comparable to surgical shunts, most notably small-diameter prosthetic HGPCSs (Clark et al, 2010). Of concern is that TIPS excessively diverts nutrient effective hepatic blood flow (EHBF) from liver parenchyma that is already compromised by increased sinusoidal resistance to portal blood flow (Rosemurgy et al, 1995, 2003), thus potentially accelerating hepatic decompensation. Although TIPS does successfully partially decompress the PV and corrects the abnormal physiologic pressure gradient between the PV and IVC, its failures and shortcomings should be recognized, as this treatment option is undertaken frequently,

without thorough consideration of its consequences. Although TIPS is viable for portal pressure decompression and temporary relief from variceal bleeding, the "bridge" to transplantation built by this procedure is seldom crossed; less than 10% of patients who undergo TIPS undergo liver transplantation.

Both TIPS and surgical shunts decompress the portal system, but surgical shunts—notably small, calibrated, side-to-side portacaval shunts and HGPCSs—relatively preserve effective hepatic blood flow. With TIPS, a decompression of portal venous pressure, along with the ensuing decrease in sinusoidal pressure, results in a concomitant increase in arterialization of the liver. However, after TIPS, increases in arterial blood flow, or "arterialization of the liver," are not sufficient to compensate for relative excessive diversion of portal blood flow from the hepatocytes. Excessive decreases in total nutrient blood flow (EHBF) to hepatocytes result after TIPS relative to small-diameter calibrated and reinforced side-to-side portacaval shunts, such as an HGPCS (Rosemurgy et al, 2003). The critical, life-threatening issues of decreased EHBF and variceal rehemorrhage loom over an otherwise successful TIPS decompression.

Variceal hemorrhage after TIPS is relatively common and often results from shunt stenosis or thrombosis. Despite strict follow-up and assessment, TIPS patients experience more shunt occlusion and stenosis, although occlusion can usually be corrected by interventional radiology. The issue is that patients require multiple interventions to maintain shunt patency, whereas with an HGPCS, occlusion is less common. Vigilance with follow-up is necessary after TIPS; often the first sign of TIPS malfunction is variceal rehemorrhage (Rosemurgy et al, 2005).

The long-term complications of nonpatency, shunt stenosis, and thrombosis associated with TIPS are well documented. In 2005, a randomized controlled trial of 132 patients undergoing TIPS versus HGPCS was reported (Rosemurgy et al, 2005). The data demonstrated that stenosis and thrombosis after TIPS placement occurred in significantly more patients, and with greater frequency, compared with HGPCS. In the 32 patients who received TIPS, 66 interventions and/or revisions were required to maintain shunt patency during a 1-year follow-up period. In this study, only seven patients required intervention for patency after HGPCS, and five patients had irreversible TIPS occlusion. Most importantly, irreversible shunt occlusion often presented as major variceal hemorrhage. Of the 32 patients who underwent revisions for TIPS stenosis or thrombosis, 20 of these patients had major variceal rehemorrhage within 30 days, two patients rehemorrhaged after 30 days, and none of the patients had stenotic or thrombosed shunts following HGPCS (Rosemurgy et al, 2005). Also, TIPS has proven to be more expensive than pharmacologic, endoscopic, or surgical shunt treatments, owing to the number of interventions necessary to maintain patency (Kravetz, 2007). Indeed, the "Achilles heel" of TIPS is its lack of patency, and the success of TIPS as a portal decompression procedure is masked by continuing stenosis and thrombosis, requiring more cost for intervention and follow-up. Proponents of TIPS believe this has changed with the advent of covered stents.

A critical issue of TIPS is subsequent mortality. Median time to death after shunting was 29 months (41 ± 39.4 months) after TIPS compared with 56 months (53 ± 40.1 months) after H-graft shunts. Predicted survival was identical in both groups, and actual survival was significantly better for each shunt than predicted, using survival data at 3, 6, 12, and 24 months after shunting (Table 76B.1). However, actual survival with H-graft shunts was superior to survival after TIPS. Furthermore, the time to failure for patients undergoing TIPS or HGPCS was significantly different. For all patients of all CTP classes, TIPS had a median time to failure of 14 months (29 ± 33.2) compared with a median time to failure of HGPCS of 43 months (48 ± 41.9). In a patient with a severely impaired liver, a difference of nearly 30 months is critical, as that time could be utilized to undergo transplantation, if such were indicated and possible.

Table 76B.1

Predicted and Actual Survival for Patients Undergoing TIPS or Small-Diameter HGPCS

		3 mo (%)	6 mo (%)	12 mo (%)	24 mo (%)
TIPS	Predicted	67	59	52	41
	Actual*	77	71	64	53
HGPCS	Predicted	68	60	54	43
	Actual*†	79	79	74	68

Nearly identical predicted survival documents an unbiased randomization. Actual survival after each shunt was superior to predicted survival; differences in actual survival cannot be explained by poor outcomes after each shunt. Actual survival was superior after 8-mm prosthetic H-graft portacaval shunts.

*Better than predicted survival ($P < .001$, Mantel Henzel chi-squared test)

†Better than actual survivial after TIPS ($P < .001$, Mantel Henzel chi-squared test).

TIPS, transjugular intrahepatic portosystemic shunt; HGPCS, prosthetic H-graft portacaval shunts.

For patients with poor hepatic reserve, the implications of reduced EHBF to an already diseased liver parenchyma can be devastating. EHBF is nutrient-rich portal blood flow—carrying venous return from the spleen, small intestine, and colon—and oxygen- and nutrient-rich arterial blood flow. This venous inflow to the liver also carries protein products and toxins that need to be neutralized, reduced, detoxified, or broken down to some degree by the liver. Given the changes in portal blood flow associated with TIPS, hepatic "arterialization" after TIPS is inadequate to maintain EHBF (Rosemurgy et al, 2003), therefore hepatic decompensation is promoted after TIPS.

TECHNIQUE OF SIDE-TO-SIDE PORTACAVAL SHUNTS

For a side-to-side portacaval shunt, the patient is positioned in a 30-degree left lateral decubitus position with rolled sheets. A transverse incision is used to divide the right rectus abdominis muscle and a portion of the external oblique and transversus abdominis muscles. Variations in incisions have been described, but in any case, the midline usually does not need to be crossed. Well-padded self-retaining retractors are placed over the gallbladder and hepatic flexure to expose the hepatoduodenal ligament.

A limited Kocher maneuver is undertaken, utilizing electrocautery generously, beginning at the foramen of Winslow with division of the tissue caudally. The peritoneal membranes contain collateral vessels that can be controlled with cautery, and identification and ligation of lymphatics in this area seems unnecessary. The ventral surface of the vena cava is exposed, and dissection of the areolar tissue encasing the vena cava is carried out circumferentially to the level of the renal veins. Often small veins entering the cava must be ligated during the

course of the dissection. Once its mobilization is complete, a vessel loop or umbilical tape is placed around the vena cava, which should elevate toward the PV without difficulty.

The hepatoduodenal ligament is then incised posteriorly and laterally with electrocautery, and the PV is identified. If present, the common bile duct and replaced hepatic artery are retracted medially with a vein retractor. Whatever shunt is utilized, it is very important to identify and preserve an accessory or replaced right hepatic artery to avoid deficiencies in EHBF after shunting. The dissection is carried out along the axis of the PV in a cranial then caudal fashion. While grasping the vein with a Russian forceps, a Yankauer suction tip is utilized to gently lift the fibroareolar tissue away from the vein. A circumferential dissection ensues with placement of a vessel loop around the PV; the vessel loop is used to retract the vein laterally, as the PV is mobilized to its bifurcation distally and toward the pancreas proximally.

To determine whether the mobilizations of both vena cava and PV are adequate, the vena cava is raised ventrally, and the PV is retracted posterolaterally, each with their respective vessel loops. Although typically unnecessary, a small portion of pancreas may be divided to ensure an adequate length of PV; in addition, a portion of the caudate lobe may be resected to ensure adequate caval length and exposure. Prior to and upon completion of the shunt, venous pressures in the PV and IVC are measured with a 25-gauge needle and a pressure-transducing setup identical to that utilized with an arterial line.

A side-biting Satinsky clamp is placed over the ventral aspect of the vena cava, and two right-angled vascular clamps are placed approximately 5 cm apart on an overlying segment of PV. A 2.5-cm longitudinal strip of vena cava is excised following venotomy. Excision of this "window" is to ensure adequate outflow for the shunt. Similarly, a 2.5-cm strip of PV is excised along the posterolateral aspect of the vein. Heparinized saline is injected within the lumina of both vessels. Beginning in the middle of the left/back wall of the anastomosis, a 5-0 double-armed polypropylene is used in a running manner at the cephalad and caudal extents (Fig. 76B.1). The sutures are tied at each corner of the anastomosis, at the cephalad and caudad extents. The right side or front wall is completed with two 5-0 polypropylene sutures, beginning at each corner; these are tied to the free ends of the posterior layer, and the right side is run from each end toward the midportion of the anastomosis. Prior to tying the sutures together, the vascular clamps are partially released, beginning with the vena cava, to release thrombus that may have formed. Upon completion of the anastomosis, the clamps are sequentially released, beginning with the vena cava, followed by the distal PV clamp and finally the proximal vein clamp. Portal and caval pressures should be similar—that is, equal or near equal—following completion of the shunt. An elevated gradient above 4 to 5 mm Hg should alert the surgeon to a technical problem that must be addressed expediently to decrease the risk of PV or shunt thrombosis.

Postoperative care includes careful monitoring of vital signs and urine output as well as judicious usage of intravenous fluids. Central venous pressure measurement is useful as a guide to the end point of resuscitation. It is important to be attentive to mental status changes and development of ascites, as these may be signs of shunt dysfunction. If shunt failure is suspected, a transabdominal color-flow Doppler should be obtained for confirmation. The best way to study shunt function is through transfemoral cannulation of the shunt and portal system. Through this approach, the shunt can be imaged radiographically, pressures across the shunt can be measured (i.e., the PV-IVC pressure gradient), flow in the portal system can be graded, and large collaterals from the portal system to the gastroesophageal variceal complex can be embolized.

TECHNIQUE OF SMALL-DIAMETER (8 MM) H-GRAFT PORTACAVAL SHUNTS

For a small-diameter HGPCS, the patient is placed supine on the operating table and rolled into a 30-degree left lateral decubitus position by placing a rolled sheet beneath the patient's right side. A transverse incision is utilized from the midline, extending just beyond the lateral border of the rectus sheath. The incision is placed over the liver edge, if palpable. Because of collaterals that may be present, the falciform ligament is carefully divided if necessary. Our preference is to use the table-mounted Omni retractor in conjunction with wound protectors; once the wound is saturated with Clorpactin solution and well padded, a sternal blade is placed cranially (Rosemurgy, 2007).

A Kocher maneuver is initiated at the foramen of Winslow and carried caudad, using electrocautery liberally. The goal is to expose approximately 5 cm of IVC, including only about one half of the ventral circumference of the vessel, thus facilitating placement of a side-biting Satinsky vascular clamp (Fig. 76B.2). Because the patient is rotated to the left, a common error is to carry the dissection lateral to the vena cava into the renal hilum; this should be avoided.

Once the vena cava is adequately exposed, attention is then turned to the hepatoduodenal ligament. A splanchnic blade is placed over a well-padded gallbladder. This retraction should be toward the patient's left shoulder, effectively rotating the common bile duct and any replaced/accessory right hepatic artery ventrally and medially. The dissection is then carried parallel and dorsal to the common bile duct. Lymphatics are predominantly found in this area, overlying the PV, and these should be ligated to avoid postoperative ascites formation. Care should be taken to identify an accessory or replaced right hepatic artery and to avoid injuring it. A vein retractor is placed over the common bile duct, and it is retracted medially to facilitate exposure of the PV. As the PV becomes visible, a generous portion of the vein should be grasped with Russian forceps. The enveloping tissue of the posterior hepatoduodenal ligament may be similarly grasped, and the plane is developed with a Yankauer sucker. Gentle, small strokes will separate the enveloping tissue from the PV without injuring any small branches. The ventral and medial surface of the PV is exposed in a similar fashion, grasping the vein with Russian forceps, retracting laterally, and passing the Yankauer sucker along the ventral surface of the vein. A right-angle clamp is placed around the PV, followed by a vessel loop (Fig. 76B.3). The vessel loop may then be used to retract the vein laterally and expose a generous circumferential portion of the PV if necessary, although circumferential dissection of the PV is generally superfluous.

A segment of 8-mm externally reinforced polytetrafluoroethylene (PTFE) graft is used for the prosthetic small-diameter HGPCS. The graft is fashioned to measure 3 cm from toe to toe and 1.5 cm from heel to heel. Because the PV is naturally oriented approximately 60 degrees to the vena cava, the bevels of each end of the graft are at 90 degrees to each other. Once the graft is cut to size, it is placed in a syringe full of heparinized

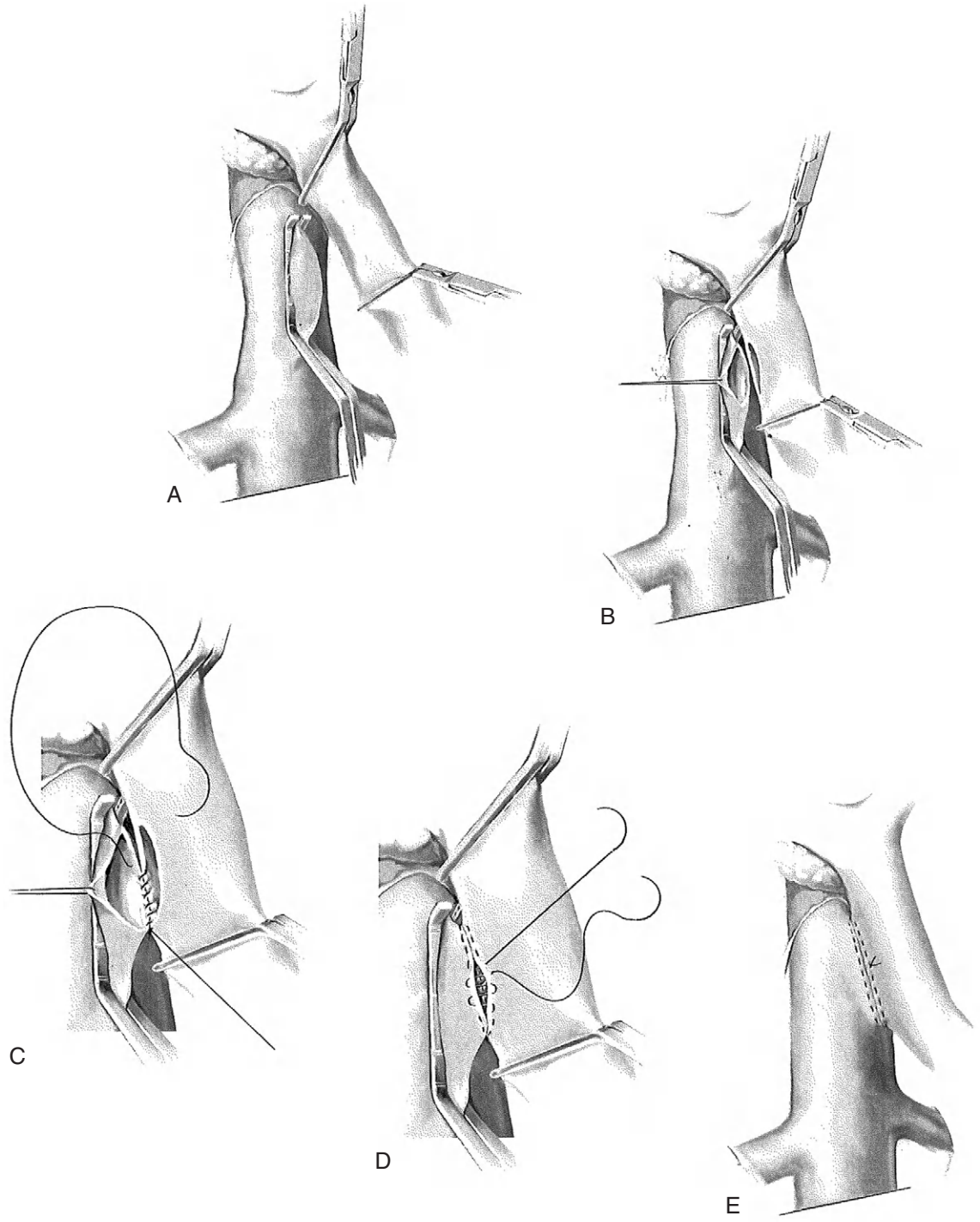


FIGURE 76B.1. Side-to-side portacaval anastomosis. *(From Orloff M, Orloff S, 2007: Portacaval shunts: side-to-side and end-to-side. In Clavian P, Sarr M, Fong Y [eds]: Atlas of Upper Gastrointestinal and Hepato-Pancreato-Biliary Surgery. New York, Springer, pp 687-702.)*

saline. With a finger over the tip of the syringe, suction is placed on the syringe. Dislodged air bubbles will emanate from the graft, and vigorous tapping on the side of the syringe will facilitate their dispersal. By removing air from the graft, heparin will completely bathe the prosthesis and facilitate Doppler ultrasound postoperatively, which may enhance patency.

A ringed forceps is used to grasp the anterior wall of the vena cava, retracting ventrally as a side-biting Satinsky clamp is placed upon the vein. The vascular clamp must be fully closed to prevent the wall of the IVC slipping from the clamp. A portion of the vena cava wall is then excised that should measure approximately 4 mm long and 2 mm wide ex vivo. The anastomosis to the vena cava is sewn with running 5-0 polypropylene suture, beginning at the cephalad apex of the anastomosis and progressing along the back, or left, medial wall (Fig. 76B.4). Begin by placing a horizontal mattress suture at the heel/

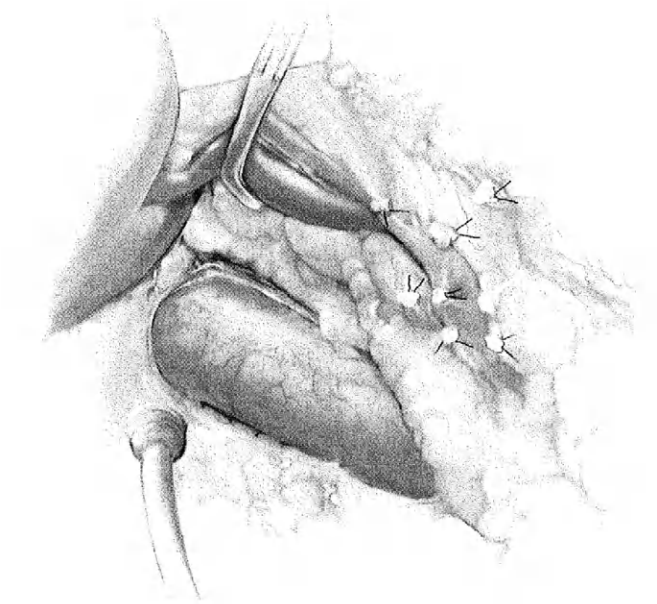


FIGURE 76B.2. Kocherization and preparation of the vena cava. *(From Rosemurgy A, et al, 2007: 8-mm Interposition Portacaval Shunt. In Clavian P, Sarr M, Fong Y [eds]: Atlas of Upper Gastrointestinal and Hepato-Pancreato-Biliary Surgery. New York, Springer, pp 675-685.)*

cephalad apex of the anastomosis, and run the suture in-to-out on the vein and out-to-in on the graft until beyond the toe of the graft. At that point, the other limb of the 5-0 polypropylene is utilized to complete the lateral front right wall of the anastomosis. The IVC-graft anastomosis can be assessed by occluding the graft with a right-angle clamp and releasing the occlusion of the Satinsky clamp (Fig. 76B.5). The Satinsky clamp is then replaced on the vena cava, and the graft is irrigated with heparinized saline to remove blood and clot.

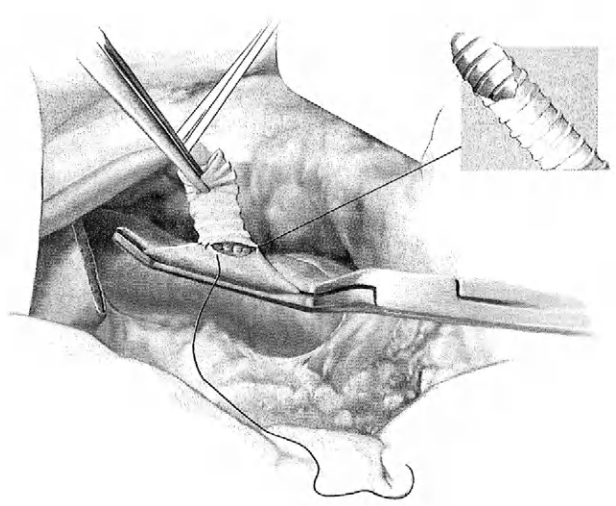


FIGURE 76B.4. Graft-caval anastomosis. *(From Rosemurgy A, et al, 2007: 8-mm Interposition Portacaval Shunt. In Clavian P, Sarr M, Fong Y [eds]: Atlas of Upper Gastrointestinal and Hepato-Pancreato-Biliary Surgery. New York, Springer, pp 675-685.)*

In constructing the PV-graft anastomosis, the posterolateral wall of the PV is grasped with a Russian forceps and retracted laterally. A right-angled side-biting clamp is then placed on the PV, although the PV need not be completely occluded to perform the anastomosis. An 11-blade scalpel is used to achieve a venotomy, which is then extended with Potts scissors. A retraction suture is placed in the mid-ventral venotomy to facilitate exposure (Fig. 76B.6). The anastomosis begins at the mid-dorsal/posterior aspect of the venotomy using a double-armed 5-0 polypropylene suture. Again, a horizontal mattress suture is placed, followed by a running suture (Fig. 76B.7), sewing in-to-out on the vein and out-to-in on the graft in a cephalad then caudal direction. Once the back row is complete, the suture is drawn tight with a nerve hook. The ventral layer is then sewn

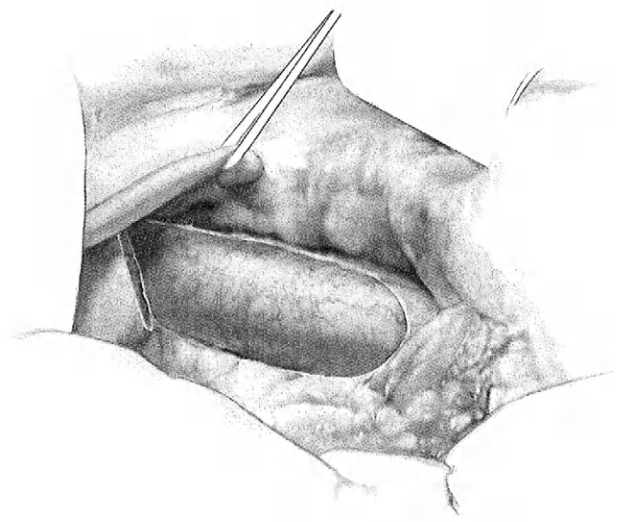


FIGURE 76B.3. Exposure of portal vein. *(From Rosemurgy A, et al, 2007: 8-mm Interposition Portacaval Shunt. In Clavian P, Sarr M, Fong Y [eds]: Atlas of Upper Gastrointestinal and Hepato-Pancreato-Biliary Surgery. New York, Springer, pp 675-685.)*

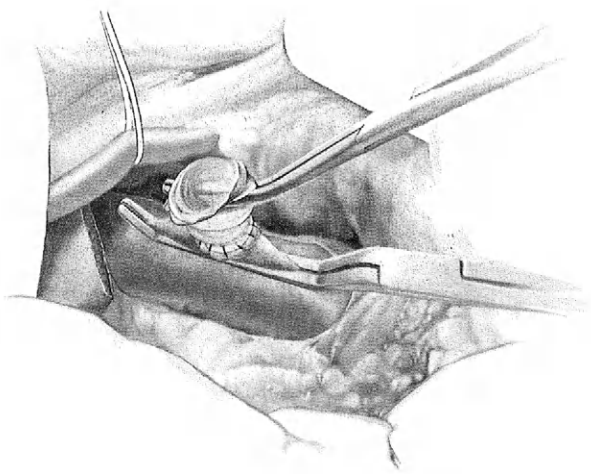


FIGURE 76B.5. Testing the graft-cava anastomosis. *(From Rosemurgy A, et al, 2007: 8-mm Interposition Portacaval Shunt. In Clavian P, Sarr M, Fong Y [eds]: Atlas of Upper Gastrointestinal and Hepato-Pancreato-Biliary Surgery. New York, Springer, pp 675-685.)*

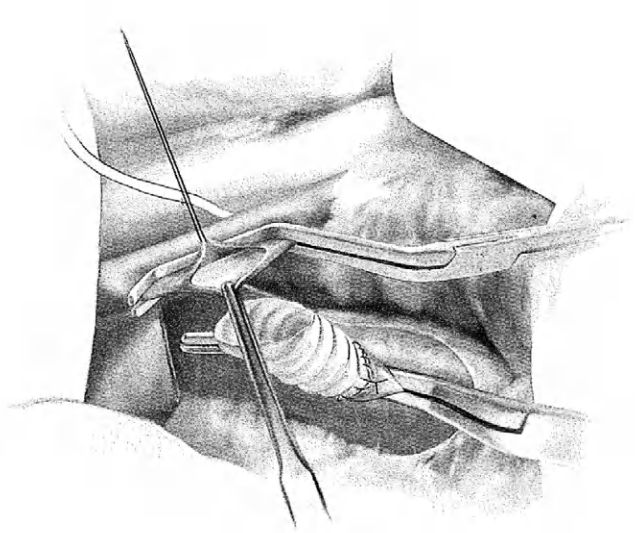


FIGURE 76B.6. Preparation of the portal vein–graft anastomosis. *(From Rosemurgy A, et al, 2007: 8-mm Interposition Portacaval Shunt. In Clavian P, Sarr M, Fong Y [eds]: Atlas of Upper Gastrointestinal and Hepato-Pancreato-Biliary Surgery. New York, Springer, pp 675-685.)*

with each free end of the double-armed suture, converging upon the midportion of the venotomy. Prior to closure, the PV clamp is partially released to blow clot and debris. Again, once the clamp is reapplied, vigorous irrigation of the graft and PV with heparinized saline is carried out.

Next, the sutures are tied along the anterior aspect of the anastomosis; this requires that arm of the suture be reversed to tie the sutures from opposing sides of the anastomosis (Fig. 76B.8). The clamp on the vena cava is removed prior to removing the clamp on the PV; a palpable thrill should be present in the vena cava cephalad to the anastomosis. Two metallic clips are preferentially placed cephalad and caudal to the caval

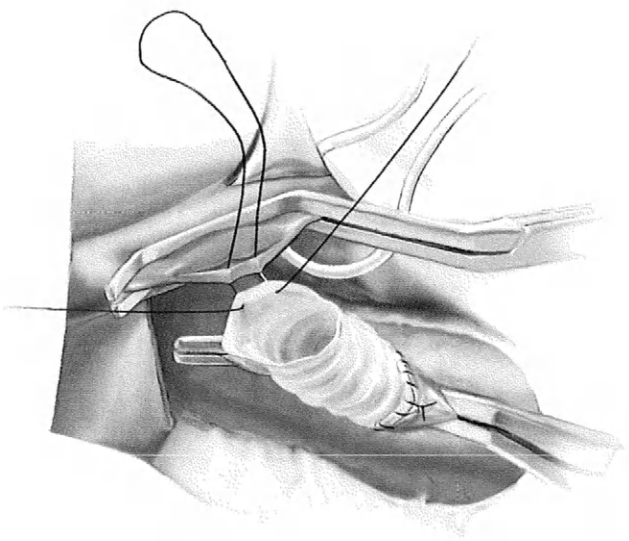


FIGURE 76B.7. Portal vein–graft anastomosis. *(From Rosemurgy A, et al, 2007: 8-mm Interposition Portacaval Shunt. In Clavian P, Sarr M, Fong Y [eds]: Atlas of Upper Gastrointestinal and Hepato-Pancreato-Biliary Surgery. New York, Springer, pp 675-685.)*

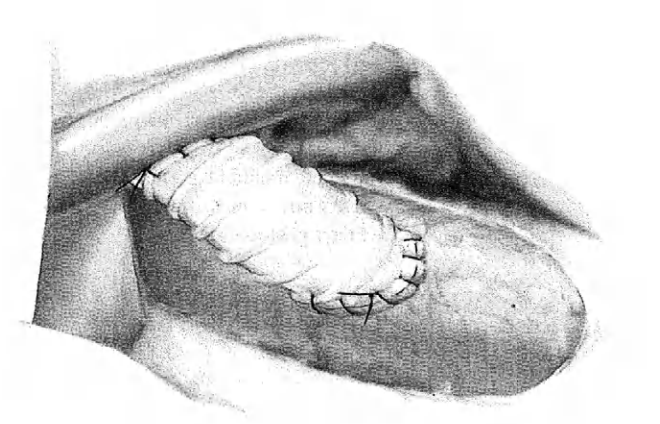


FIGURE 76B.8. The completed small-diameter prosthetic H-graft portacaval shunt. *(From Rosemurgy A, et al, 2007: 8-mm Interposition Portacaval Shunt. In Clavian P, Sarr M, Fong Y [eds]: Atlas of Upper Gastrointestinal and Hepato-Pancreato-Biliary Surgery. New York, Springer, pp 675-685.)*

anastomosis to allow radiologists to identify and cannulate the anastomosis (Fig. 76B.9).

Pressures within the PV and vena cava should be measured prior to beginning and immediately following attainment of the anastomosis. This may be accomplished using a 25-gauge needle and sterile pressure-transduction tubing identical to an arterial line. The tubing is connected to the needle and then passed to anesthesia to connect to the monitor. A near 20-mm Hg PV-IVC pressure gradient is generally observed prior to shunting, with an approximate pressure of 30 mm Hg present in the PV and a pressure of 10 mm Hg in the vena cava. Pressures are again measured after shunting, and we expect the gradient to fall by more than 10 mm Hg to less than 10 mm Hg; usually, a

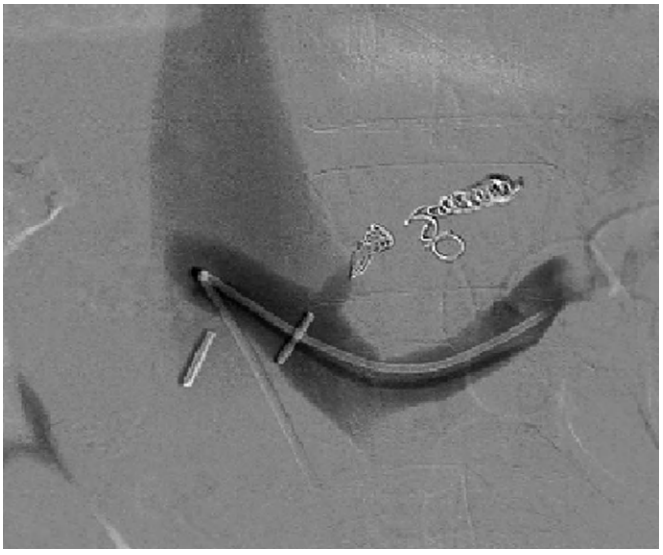


FIGURE 76B.9. Transfemoral portal venography after application of coils in the coronary vein following 8-mm H-graft portosystemic shunt. Note opacification of the inferior vena cava, documenting flow through the shunt. *(From Rosemurgy A, et al, 2007: 8-mm Interposition Portacaval Shunt. In Clavian P, Sarr M, Fong Y [eds]: Atlas of Upper Gastrointestinal and Hepato-Pancreato-Biliary Surgery. New York, Springer, pp 675-685.)*

6- to 8-mm Hg gradient is observed. As expected, the caval pressure rises, and the portal pressure decreases. If the portal pressure and the PV-IVC pressure gradient fall by 10 mm Hg or more, and the PV-IVC pressure gradient is less than 10 mm Hg in the presence of a thrill on the IVC, long-term patency should be expected.

Postoperatively, the patient is placed in a monitored unit. We are judicious in regard to intravenous (IV) resuscitation after surgery, not exceeding a rate equal to the patient's maintenance requirements. IV therapy is discontinued as early as postoperative day 1, and we allow the patient to begin a trial of liquids, progressing the diet as tolerated. On the third or fourth postoperative day, a transfemoral shunt study is carried out by interventional radiology. As previously mentioned, metallic clips were placed at the vena cava–graft anastomosis to facilitate this procedure. Documentation of patency with venography and acceptable pressure measurements are necessary prior to discharge. Again, a gradient near 6 to 8 mm Hg is sought. New-onset encephalopathy and/or ascites following surgery should raise concern for PV or graft thrombosis. With concerns, a repeat transfemoral shunt study will confirm patency, or an intervention can be undertaken.

CONCLUSION

Variceal hemorrhage secondary to portal hypertension is a life-threatening condition that is most effectively treated by surgical management. Unfortunately, in the United States, most portal decompression procedures are implemented by nonsurgeons in the form of TIPS. Pharmacologic and endoscopic therapy should be first employed to address acute hemorrhage followed by a surgical shunt on an elective basis if possible. Small-diameter (8 mm) prosthetic H-graft portosystemic shunts have been studied in a prospective randomized trial and are superior to TIPS in regard to patency and survival. Additionally, effective hepatic blood flow is maintained at an acceptable level with the small-diameter HGPCS, unlike TIPS or other surgical shunts that divert an excessive amount of portal blood flow away from the hepatic parenchyma. Experience with side-to-side portacaval shunts is also promising and supportive, especially when undertaken in an emergency. Technical aspects of portacaval shunts are reproducible and should be within the armamentarium of hepatobiliary surgeons.

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CHAPTER 76C

Distal splenorenal shunt

J. Michael Henderson

BACKGROUND

The distal splenorenal shunt (DSRS) was developed by Warren and colleagues in 1967 to achieve selective variceal decompression to prevent recurrent variceal bleeding. Selective variceal decompression combines the benefit of a decompressive shunt to control bleeding with maintenance of portal hypertension and portal flow to the cirrhotic liver to help maintain liver function. The original, classic article on selective variceal decompression described the animal work leading up to the initial clinical data on DSRS (Warren et al, 1967). Proof of concept was shown in the animal studies and in the results of the first six patients in whom DSRS was performed. The unique prior experiences of Warren and Zeppa led to the evolution of this concept: Warren had seen that total shunts control variceal bleeding, but at the cost of liver failure, whereas Zeppa had seen devascularization procedures maintain portal perfusion, but at a cost of significant risk of rebleeding.

Over the next 4 decades, DSRS became the most widely used operation to control variceal bleeding, with a worldwide following (Orozco et al, 2007). The technique continued to evolve, with greater degrees of portal azygos disconnection improving its effectiveness (Henderson et al, 1989). However, in the 1990s, the evolution of improved endoscopic therapy with banding (see Chapter 75B), introduction of transjugular intrahepatic portosystemic shunting (TIPS; see Chapter 76E), and coming of age of liver transplantation (see Chapter 97) left few indications for shunt surgery for variceal bleeding (see Chapter 76A).

INDICATIONS FOR DSRS

The indications for DSRS have markedly diminished in the last decade, as other options have improved, and the available expertise of surgeons facile at performing DSRS has diminished. That said, DSRS remains a good option for the following patients:

- Patients with variceal bleeding refractory to endoscopic and pharmacologic therapy who have well-preserved and stable liver function
- Patients with portal hypertension and normal livers, such as those with portal vein thrombosis, who have refractory bleeding and a patent splenic vein
- Patients in some geographic locations, where there is only one chance to control bleeding, and they cannot return for the multiple visits required for management with endoscopy or TIPS

PATIENT EVALUATION

Patients being considered for DSRS require full evaluation to define 1) gastroesophageal varices as the source of bleeding, 2) the cause of the portal hypertension, 3) status of liver function and damage, and 4) vascular anatomy. Evaluation for possible DSRS is only appropriate in patients on propranolol with documented recurrent variceal bleeding or persistent high-risk varices and who have had adequate endoscopic management. Accurate endoscopic evaluation is therefore the first step. In this context, these patients have had upper diagnostic and therapeutic endoscopy at the time of an acute variceal bleed, and follow-up endoscopy is aimed at therapeutic variceal obliteration. Prior to considering patients for DSRS, endoscopy should confirm persistent varices or portal hypertensive gastropathy.

The cause of portal hypertension for most patients in the United States and Europe with variceal bleeding is cirrhosis. In these patients, the first question to be addressed is whether the patient now or in the future is a candidate for liver transplantation. If the patient is likely to need a transplant in the next 1 to 2 years, surgical shunt is not indicated. If the patient has good liver function and is unlikely to need a transplant in the near future, DSRS may be a good option. Other etiologies of portal hypertension—portal vein thrombosis or noncirrhotic portal fibrosis, in which patients have normal liver function—need to be defined early in the evaluation, because the long-term prognosis depends on best prevention of variceal bleeding. Such patients may be candidates for DSRS earlier in their management.

Liver function is assessed from clinical findings and laboratory studies. Jaundice, ascites, and encephalopathy are the three clinical signs and symptoms of advanced liver disease and indicate that patients are not candidates for surgical decompression. Laboratory measurements of serum bilirubin, albumin, serum creatinine, and prothrombin time prolongation are the most useful studies to assess the status of cirrhosis. Combining the clinical and laboratory parameters to discern the Child-Turcotte-Pugh (CTP) class and/or Model for End-Stage Liver Disease (MELD) score gives an objective assessment of risk (Table 76C.1 and Box 76C.1).

Imaging for portal venous anatomy helps with diagnosis and treatment planning and should be performed as part of the evaluation of patients after their initial variceal hemorrhage. Doppler ultrasound can usually visualize the splenic, superior mesenteric, and portal veins as well as the hepatic veins for liver outflow. Early identification of thrombosis of the portal and/or splenic veins may alter the whole approach in the management of the patient. Ultrasound also should examine liver morphology, particularly for evidence of focal lesions suggestive of hepatocellular carcinoma. Computed tomography (CT) or magnetic resonance (MR) vascular imaging and morphologic assessment can augment ultrasound studies; usually these are sufficient to make clinical decisions.

Arteriography may sometimes be required for final definition of the veins before surgical intervention. The components of this evaluation can include the following:

Table 76C.1

Child-Turcotte-Pugh Classification

	NO. POINTS		
	1	2	2
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Increase in prothrombin time (sec)	1-3	4-6	>6
Ascites	None	Slight	Moderate
Encephalopathy	None	1-2	3-4

Grade A: 5-6 points
Grade B: 7-9 points
Grade C: 10-15 points

1. Hepatic venous pressure gradient (HVPG)
2. Left renal vein anatomy and drainage (this is abnormal in 20% of the population)
3. Superior mesenteric, portal, and splenic vein patency, flow direction, and venous anatomy on the venous phase of the arterial study
4. Major variceal inflow paths on the same study as in number 3 above

This combination of venous and arterial angiographic study can give information not available with ultrasound, CT, or magnetic resonance imaging (MRI).

Candidates for DSRS are CTP class A or B 7 or 8 patients (i.e., their CTP score is 7 or 8 points), usually without ascites, who are considered to have stable liver disease and are unlikely to need liver transplantation in the next 5 years.

TECHNIQUE FOR DISTAL SPLENORENAL SHUNT

Attention to detail in perioperative and postoperative monitoring and management of a patient undergoing DSRS improves outcome. Monitoring requires an arterial line, a central venous catheter, and a urinary catheter. Good venous access should be obtained in the event that rapid transfusion is required.

Blood and blood products should be available: packed red blood cells, fresh frozen plasma, and platelets may be required if there is major intraoperative blood loss or perioperative hemorrhage. A cell saver can be used in higher risk patients and may reduce blood bank requirements.

The patient is positioned on the operating table with the left arm at the side and the left side slightly elevated. Hyperextending the operating table to open the angle between the left lower ribs and iliac crest aids in exposure and access to the tail of the pancreas. The primary operating surgeon is on the patient's right. The operation is more easily completed when the first assistant (to the left of the table) also has experience with the procedure.

Box 76C.1

Model for End-Stage Liver Disease Score for Liver Disease Severity

Score = $0.957 \times \log_e$ creatinine (mg/dL) + $0.378 \times \log_e$ bilirubin (mg/dL) +1.120 $\log_e$ INR

INR, international normalized ratio

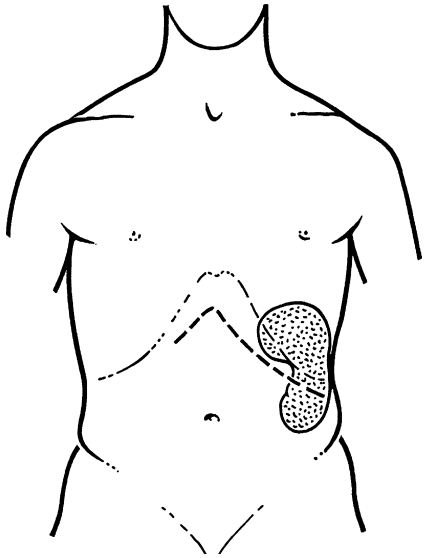


FIGURE 76C.1. The left subcostal incision extends across the midline and right rectus muscle.

The steps in DSRS are illustrated. The preferred incision is a long left subcostal incision, extended across the right rectus muscle (Fig. 76C.1). Coagulating diathermy should be used extensively in patients with portal hypertension to achieve hemostasis in dividing tissues. If present, ascites should be aspirated and cultured, and a liver biopsy specimen should be obtained to document the status of the liver at the time of the procedure.

Step 1: Exposure

The initial steps of this procedure provide access to the vessels. The pancreas is exposed by opening the lesser sac (Fig. 76C.2) and interrupting the gastroepiploic arcade from the pylorus to the first short gastric vessels. Exposure is greatly enhanced by taking down the splenic flexure of the colon from the lower pole of the spleen. This is done most easily by initially mobilizing the left side of the splenic flexure of the colon, then identifying the plane from there back into the lesser sac at the tail of the pancreas. The splenocolic ligament is divided, giving excellent exposure to the inferior margin of the pancreas from the mesenteric vessels to the splenic hilus. The pancreas is then fully mobilized along its inferior border over its entire length, so that it is turned completely on its side; this is achieved with a combination of Bovie coagulation and ligature of tissues (Fig. 76C.3). The inferior mesenteric vein is the first venous landmark identified: in 50% of patients, this vein enters the splenic vein; in the other 50%, it enters the superior mesenteric vein. The inferior mesenteric vein should be traced up to these vessels and then divided to aid further exposure.

Step 2: Isolation of the Splenic Vein

The superior mesenteric and splenic vein junction is identified, initially on its posterior surface; this is a safe plane for initial dissection. The splenic vein should be isolated along its inferior and posterior aspect with dissection occuring right on the vessel (Fig. 76C.4). At this point, the splenic, superior mesenteric, and posterior aspects of the portal vein all should be cleared (Fig. 76C.5).

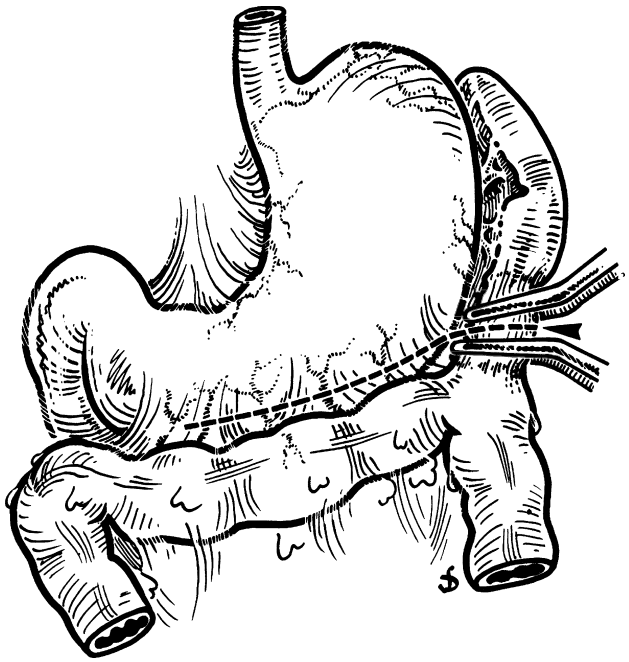


FIGURE 76C.2. Access to the pancreas is through the gastrocolic omentum. Dividing the splenocolic ligament improves exposure and divides collateral varices to the splenic hilus.

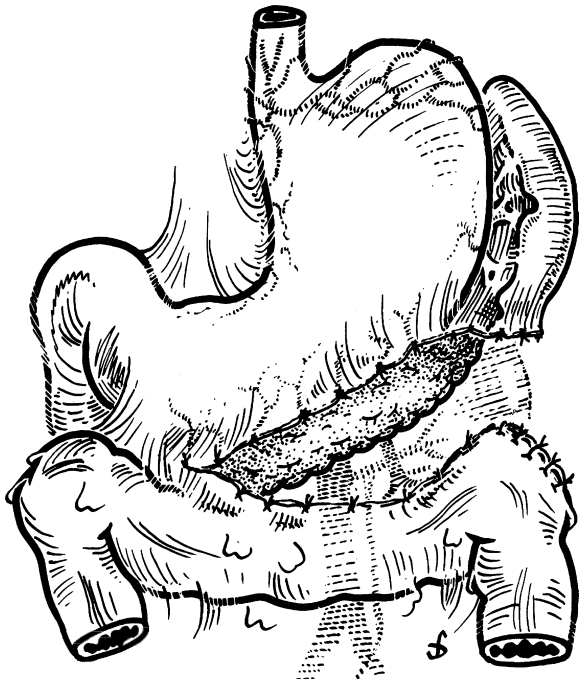


FIGURE 76C.3. The pancreas is mobilized from the superior mesenteric vein to the spleen by dividing the posterior parietal peritoneum along its inferior margin.

When the posterior plane is free, attention turns to the anterior and more difficult plane of dissection on the splenic vein. Tributaries rarely enter the anterior surface of the portal vein; so this plane between the neck of the pancreas and the portal vein should be opened first, then the pancreas should be cautiously separated and dissected from the anterior and superior surfaces of the splenic vein. The key is to dissect the pancreas

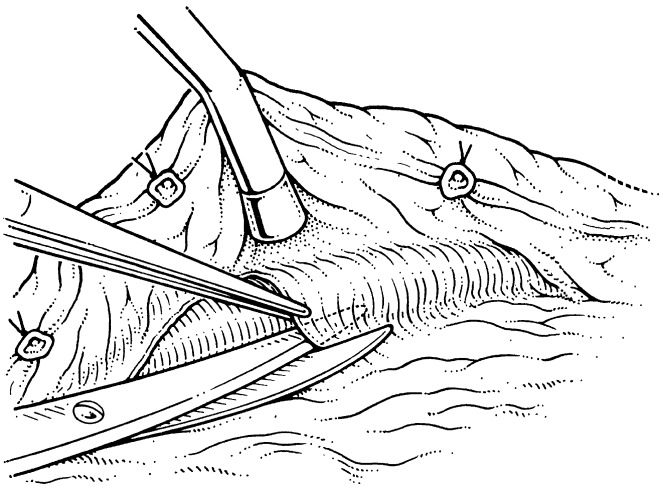


FIGURE 76C.4. The splenic vein is dissected initially along its inferior and posterior edge. This dissection must be directly on the vein.

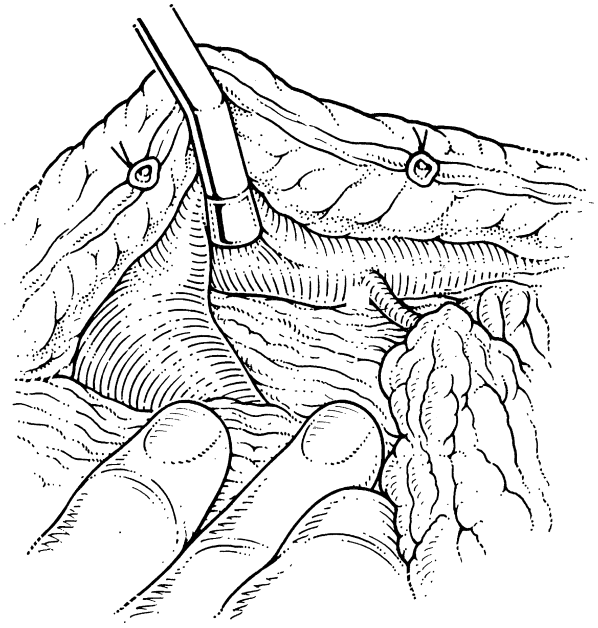


FIGURE 76C.5. The posterior plane behind the splenic vein should be developed first, and the plane behind the confluence of the splenic vein, superior mesenteric vein, and portal vein is opened.

off the splenic vein rather than the other way around. This requires a delicate touch and is best achieved by spreading the tissues gently in the line of the tributaries and at right angles to the splenic vein. This isolates the tributaries, and when identified, a fine right-angle clamp is passed around them, with a 3-0 tie on the vein side and a clip on the pancreatic side (Fig. 76C.6). As much of the splenic vein as possible should be dissected in this manner before dividing the splenic vein at the superior mesenteric vein junction.

Step 3: Isolation of the Left Renal Vein

The left renal vein is isolated and mobilized from the retroperitoneum; this is best done before dividing the splenic vein at the superior mesenteric junction. Preoperative renal venography

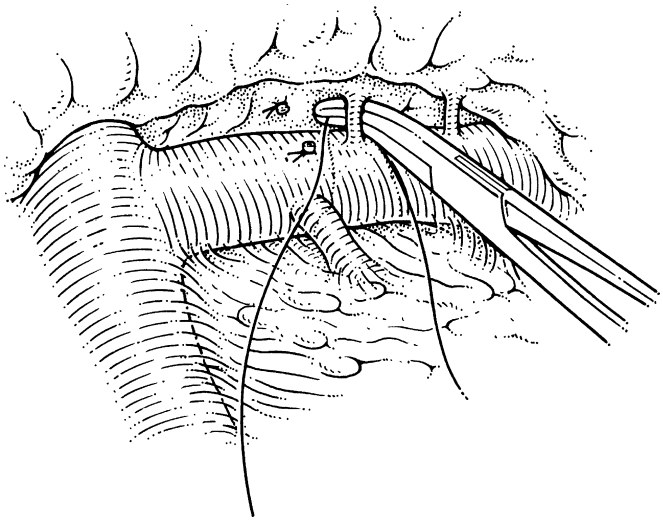


FIGURE 76C.6. Isolation of tributaries from the pancreas into the splenic vein requires their dissection at right angles to the splenic vein. These vessels have thin walls and require gentle dissection.

should have shown the anatomy and defined any abnormality: a circumaortic left renal vein is found in 16% of the population, and in 4%, the left renal vein is totally retroaortic; the latter may preclude performance of DSRS. In circumaortic anatomy, the anterior branch is usually larger and is adequate for outflow for DSRS.

The retroperitoneum is opened just to the left of the superior mesenteric artery and in front of the aorta; these landmarks are identified by palpation. The divided tissue in front of the left renal vein should be ligated, because there are many lymphatics in it, and ligation minimizes the risk of postoperative chylous ascites. Initial dissection should be minimal to identify the left renal vein, which should be mobilized over an adequate length to allow it to be brought up into a side-biting vascular clamp. The left adrenal vein should be divided, whereas the gonadal vessel is left intact, because it can serve as an outflow tract. The vein should be mobilized over approximately 3 cm, and as a guide, the anastomosis usually is made just anterior to the adrenal vein orifice.

Step 4: Division of the Splenic Vein

This is the step that lines up the splenic and left renal veins for anastomosis. The superior mesenteric end of the splenic vein is ligated with a 2-0 silk, and a large clip is placed flush with the vein behind that tie; this has led to the lowest incidence of thrombus within the portal vein at postoperative angiography. At this point the surgeon must judge whether enough splenic vein has been dissected free of the pancreas to allow it to come down to the left renal vein without kinking or tension. In the event that more dissection of the splenic vein is needed, this can now be performed more easily, because the vein can be manipulated downward, as shown in Figure 76C.7. The disadvantage of this maneuver is that the pressure in the splenic vein has increased with ligation, which leads to greater risk of tearing of the small tributaries.

In patients with alcoholic cirrhosis, data have shown that complete dissection of the splenic vein from the pancreas (*splenopancreatic disconnection*) is advantageous in leading to

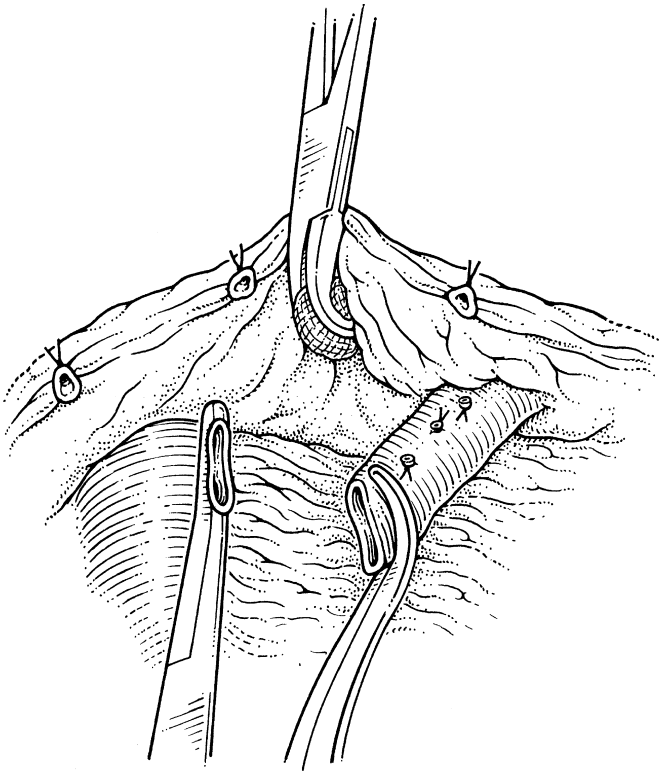


FIGURE 76C.7. Division of the splenic vein allows the angle between the pancreas and vein to be opened. This improves exposure for dissection of small tributaries to the splenic vein at the cost of increased pressure in the vein.

improved long-term maintenance of portal perfusion (Henderson et al, 1989). If this modification of DSRS is used, the complete dissection should be done at this time. Data do not support the need for entire splenopancreatic disconnection in patients with nonalcoholic liver disease.

Step 5: The Anastomosis

This is performed without tension, and usually the splenic vein needs to be trimmed so that when the clamps are removed, the vein is not redundant and lies without kinking. This alignment can be difficult to judge, particularly if the two veins are overlying each other. The position of the clamps and trimming of the splenic vein are shown in Figures 76C.8 and 76C.9. The left renal vein is opened over sufficient length without removing an ellipse. The posterior row of the anastomosis is completed with a running suture, with stay sutures placed at either end, and the suture is run on the inside; the anterior row is usually interrupted to avoid risk of a purse-string effect. The completed anastomosis is shown in Figure 76C.10.

Step 6: Portal Azygos Disconnection

The final step is interrupting the main paths by which the high-pressure portal vein attempts to connect to the now low-pressure splenic vein. These paths are by 1) transpancreatic collaterals, 2) collaterals along the mesocolon to the inferior ramus of the splenic vein, and 3) the left and right gastric venous systems (Henderson et al, 1985). The pancreatic siphon of large collaterals flowing through the pancreas can be prevented by

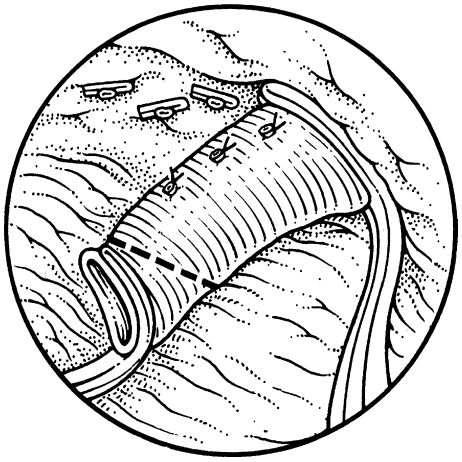


FIGURE 76C.8. Sufficient splenic vein must be dissected out of the pancreas for the vein to come down to the left renal vein without tension or kinking. An adequately dissected splenic vein usually needs to be trimmed.

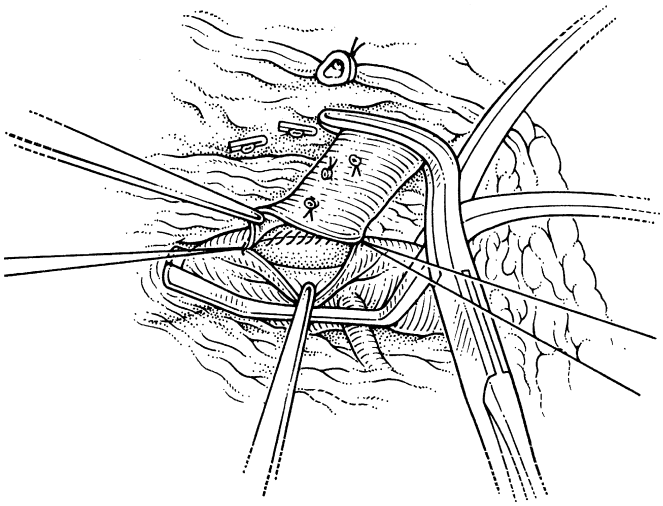


FIGURE 76C.9. The posterior anastomosis is made with a running suture. The clamps must be held for a tension-free anastomosis.

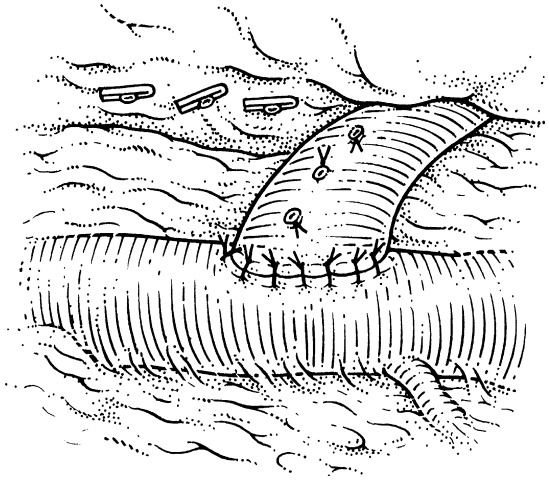


FIGURE 76C.10. The anterior row of the anastomosis is completed with interrupted sutures.

splenopancreatic disconnection as described earlier. The decision whether to do this is made on a benefit-risk basis, depending on the ease of full dissection. The collaterals that develop in the mesocolon have a final common pathway in the splenocolic ligament to the lower pole of the spleen and do not develop if the splenic flexure is taken down as described earlier. The transgastric collaterals are minimized by ligating the left and right gastric veins. The right gastric vein is usually small, but it should be interrupted just above the pylorus. The left gastric (coronary) vein may be very large, and it should be clipped or divided at its junction with the portal or splenic vein. It also should be isolated immediately above the pancreas and divided at this location.

Step 7: Closure

Abdominal closure should be in two layers with a running nonabsorbable suture. No drains are placed.

PATIENT MANAGEMENT

General Measures

Most patients who have a DSRS have cirrhosis. The perioperative risks are from liver failure, ascites, and infection, and these can be minimized by careful management. Risk factors should be defined before surgery, and patient selection is key to minimizing perioperative risk, as described in Patient Evaluation.

Ascites is the major risk factor postoperatively, but this risk can be reduced by careful fluid, diet, and diuretic management. Preoperatively, it is important that the patient maintain a low-sodium diet. If diuretics are necessary, adequate doses of an aldosterone antagonist diuretic to reduce renal sodium reabsorption are given. Perioperatively, the intravenous infusion of free sodium should be minimized, and if plasma volume expansion is required, 5% albumin or fresh frozen plasma should be used. Maintenance fluids should be 5% dextrose with half-normal saline. Postoperatively, when an oral diet has been started, the patient should be limited to 2 g of sodium per day, and dietary fat should be restricted to 30 g/day for the first month to reduce the risk of chylous ascites. In the early postoperative period, 100 mg/day spironolactone (Aldactone) should be given to minimize sodium retention and aid postoperative diuresis. Furosemide may be added to this regimen if significant postoperative ascites occurs. Rarely, paracentesis may be necessary. By following this management routine in CTP class A, B7, or B8 patients, the risk of ascites is minimized.

Infection is a further risk factor in patients with cirrhosis. Antibiotics should be given in the perioperative period. In the postoperative period, infection always should be considered as a possible explanation for patients who fail to progress.

Liver failure should not be a postoperative risk, if patients are appropriately selected for DSRS. CTP class A and B7 or B8 patients should not decompensate, unless they have an excessively difficult procedure with significant hypotension. Should liver decompensation develop, the only management is with liver transplantation.

Specific Measures

Before hospital discharge, the patient should have 1) stable liver function, 2) documented shunt patency, and 3) no increasing ascites. Shunt patency can be assessed indirectly with Doppler

ultrasound, but I advocate shunt catheterization at 1 week postoperatively to document patency and flow and to measure pressures. If the shunt is patent at this time, it is unlikely to undergo subsequent thrombosis or stenosis. The one exception is when DSRS is made with a recanalized splenic vein; this increases the risk of stenosis and requires further shunt catheterization at 3 to 6 weeks. Standard liver biochemistry should be measured on alternate days postoperatively. The bilirubin may increase by 1 to 2 points, but it rarely increases to greater than 5 mg/dL in appropriately selected patients. Fluid management was discussed earlier. Patients are usually ready for discharge from the hospital 6 to 8 days after surgery.

Follow-up

Patients undergoing DSRS should be maintained in long-term follow-up, primarily to follow the underlying liver disease. Cirrhosis is a chronic disease that tends to be progressive, and although data suggest DSRS does not accelerate the rate of progression of cirrhosis, patients may have to be considered for liver transplantation. Reevaluation every 6 to 12 months is recommended.

RESULTS

The goals of DSRS are to prevent recurrent variceal bleeding and, by maintaining portal perfusion, not to accelerate the course of the underlying liver disease. In the 1990s and 2000s, several series documented that these goals can be achieved. Most of these series are in good risk patients (CTP class A and B), and results have been excellent.

Bleeding control is equal to or greater than 90% (Henderson et al, 1992; Herman, 1995; Orozco et al, 1997; Rikkers, 1998; Livingstone et al, 2006; Elwood et al, 2006). The highest risk time for rebleeding after DSRS is in the first month (Richards et al, 1987). The technical failure rate should be less than 5%, and it should be defined before hospital discharge with direct shunt catheterization as described earlier. If a technical problem occurs with the anastomosis at that time, surgical reexploration should be undertaken; if it cannot be corrected, splenectomy and devascularization are indicated. Late thrombosis of DSRS is unusual, although patients with portal vein thrombosis undergoing DSRS have a higher rate of shunt stenosis requiring balloon dilation (Warren et al, 1988). Bleeding control is significantly better than that achieved with endoscopic therapy, which is approximately 25% to 30%.

Portal perfusion is maintained at late follow-up in 90% of patients with nonalcoholic liver disease. In patients with alcoholic cirrhosis, loss of portal perfusion occurs in 50% of patients (Henderson et al, 1985). Zeppa and colleagues (1978) documented poorer survival after DSRS in alcoholic patients than in nonalcoholic patients but never proved cause and effect. The mortality rate can be improved in the latter population by complete splenopancreatic disconnection (Henderson et al, 1989). In this modification, the entire splenic vein is dissected free of the pancreas before anastomosis. Splenopancreatic disconnection also has been documented to improve survival in nonalcoholic patients.

Hepatic function is maintained after DSRS in CTP class A and B patients as shown in the series in the 1990s. The rate of transplantation in these patients is currently less than 20%, but longer term follow-up may show an increase in this number at 10 to 20 years. Survival after DSRS is dictated by the severity of the underlying liver disease. The series from the 1990s and 2000s cited above documented 5-year survival of 80% to 90% for CTP class A and B patients.

Two major questions have arisen over the past 5 years: How often is variceal decompression needed, given improved pharmacologic and endoscopic treatment? (D'Amico et al, 2002) And is a surgical shunt ever needed in the era of TIPS? Current data show refractory bleeding through endoscopic and pharmacologic therapy in 15% to 20% of patients; most of these patients have poor liver function, and their only reasonable decompression option is liver transplantation.

The relative efficacy of surgical decompression versus TIPS has been studied in two randomized trials. One study assessed the 8-mm portacaval shunt versus TIPS, and although the surgical limb had better bleeding control, overall outcome was not significantly different (Rosemurgy et al, 2005). In a randomized trial (Henderson et al, 2006) of DSRS versus TIPS in CTP class A and B patients, the rebleeding rates were not significantly different, 6% and 11%, but 83% of TIPS patients required reintervention and dilation to achieve this outcome. Survival and encephalopathy rates were not significantly different in this study. Cost-effectiveness analysis showed a slight advantage to TIPS in this trial (Boyer et al, 2008), and it can be concluded that TIPS is equally effective as DSRS.

In summary, DSRS is an excellent operation for controlling refractory variceal bleeding in patients with portal hypertension and well-preserved liver function. Its current role is, however, minimal given the evolution of other therapeutic options, as succinctly summarized by Hector Orozco (Orozco et al, 2007): "What a pity. There have been many ideas to resolve a problem, many years of work, many patients treated, and one surgical solution that was approaching the ideal: low morbidity, low mortality, low recurrence of the hemorrhagic episodes, and long survival. Despite all of this, we threw it away because we did not know how, when, and to whom we might give it."

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CHAPTER 76D

Mesocaval shunt

Matthew P. Landman and C. Wright Pinson

HISTORY OF THE MESOCAVAL SHUNT

Eck first described decompression of the portal system via the portacaval shunt in 1877. The first mesocaval shunt was developed primarily for children with portal vein thrombosis by Marion in 1953 (Marion et al, 1965) and Clatworthy in 1955. In the Marion-Clatworthy J-shunt, the inferior vena cava (IVC) is divided just proximal to the confluence of the iliac veins, and the proximal end is anastomosed to the lateral aspect of the superior mesenteric vein (Clatworthy, 1955). In 1954, Valdoni also described this procedure in a discussion regarding treatment options for portal hypertension. Because of the complications of venous stasis, including intractable lower extremity edema, this shunt never gained popularity in adults.

In 1970, Read and colleagues described the use of homologous vein graft as a conduit for the mesocaval shunt. In 1972, Drapanas reported good success with prosthetic mesocaval shunts by showing efficacy in 25 patients with acute exsanguinating variceal hemorrhage and popularized the procedure. Throughout the 1970s, several authors reported success with autologous, homologous, heterologous, and synthetic mesocaval shunts for the treatment of bleeding varices.

INDICATIONS FOR MESOCAVAL SHUNTS

With remarkable advances in endoscopic therapy, interventional radiology, and liver transplantation, the role of surgical shunts in the treatment of complications related to portal hypertension has been revised (see Chapter 76A). Although alternatives exist, surgical shunts remain an important intervention in some patients. The use of transjugular intrahepatic portosystemic shunts (TIPS; see Chapter 76E) has decreased the need for surgical shunts dramatically. TIPS provides only short-term treatment, however; it requires constant monitoring and frequent intervention, and such shunts are appropriate only in patients with advanced liver disease, as a "bridge" to transplantation, or in severely ill patients with a short life expectancy. In contrast, surgical shunt are best performed in patients who have bleeding varices refractory to endoscopic intervention with good hepatic reserve (i.e., Child-Turcotte-Pugh [CTP] classes A and B). Indications for surgical shunt procedures include variceal hemorrhage with good hepatic reserve, failed TIPS, portal vein thrombosis, Budd-Chiari syndrome, refractory ascites, portal hypertensive biliopathy, and small-for-size syndrome in liver transplantation; although more recently, portal decompression has emerged for the treatment of small-for-size syndrome in liver transplantation.

The most common indication for surgical shunt is bleeding varices refractory to medical and endoscopic therapy in patients who have good hepatic reserve and do not need liver transplantation in the near future. Henderson and colleagues (2000) showed excellent outcomes in CTP class A and B cirrhotic patients with refractory bleeding who received surgical shunts. In their series, the overall survival and rebleeding rates were 86% and 6.3%, respectively, with a median follow-up of 36 months. The choice between TIPS and surgical shunts depends on the patient's hepatic reserve and timing to possible transplantation. If transplantation is expected within 1 to 2 years, TIPS is likely to bridge the patient to transplantation without the need for surgical intervention. However, if transplantation is unlikely to occur within 1 to 2 years, surgical shunting is warranted; more than 50% of TIPS patients require intervention within this time period.

Orloff and coworkers (2002) reported the use of portosystemic shunts in the treatment of 200 children and adults with extrahepatic portal hypertension secondary to portal vein thrombosis. In contrast to patients with intrahepatic portal hypertension secondary to cirrhosis, this patient population is often younger and healthier and often has preserved liver function, making them excellent surgical candidates. In this large series by Orloff and colleagues (2002), 100% of patients had normal liver biopsies with normal liver function, and 66 patients (33%) underwent Marion-Clatworthy–type cavomesenteric shunts with no immediate postoperative mortality. Of note, six adult patients experienced postoperative lower extremity edema. The 15-year actuarial survival was noted to be 95% for all shunt types, with shunt patency at 97.5%. Liver function remained normal for 99% of these patients at 5 years. The authors concluded that portosystemic shunting is the most effective treatment for these patients and that these procedures should be performed early in the course of variceal bleeding episodes.

Although Budd-Chiari syndrome (see Chapter 77) with obstruction of the hepatic venous outflow was traditionally treated with portosystemic shunt procedures, other treatment options—including hepatic vein angioplasty, catheter-directed thrombolysis, TIPS, and liver transplantation—have been successfully introduced. After reviewing 54 Budd-Chiari syndrome patients treated at Johns Hopkins Hospital over 20 years, Slakey and colleagues (2001) concluded that shunting and transplantation result in 5-year survival rates of at least 75% in these patients. Fisher and associates (1999) advocated the use of hepatic vein angioplasty for Budd-Chiari syndrome patients with short-length hepatic vein stenosis or occlusion and surgical shunting for patients with diffuse hepatic vein occlusion or failed angioplasty; others recommend TIPS. However, recanalization of the hepatic veins is not always successful and may require a shunt procedure.

A study using the porcine transplant model suggested that mesocaval shunts may provide protective effects for small-for-size liver grafts by protecting them from portal flow–related injuries (Smyrniotis et al, 2003). Case reports are emerging that demonstrate successful use of this technique to alleviate portal

hypertension associated with small-for-size syndrome after living-donor liver transplantation (Boillot et al, 2002; Kokai et al, 2008). A porcine model has demonstrated retention of liver regenerative capabilities despite reduction of venous inflow after left hepatectomy with mesocaval shunt (Pouyet et al, 2007). Given the critical organ shortage and increasing use of segmental grafts, this approach may prove clinically useful in the future.

Because subsequent transplantation often is anticipated in patients receiving portosystemic shunts, the shunt procedure should minimize as much as possible any potential compromise of the technical aspects of the transplant operation. In contrast to portacaval shunts, the distal splenorenal and mesocaval interposition shunts do not alter the porta hepatis anatomy. In a case control study comparing decompressive procedures involving the hepatic hilum with both TIPS and other surgical shunts, Dell'Era and colleagues (2005) noted significantly higher operative times, higher transfusion requirements, increased hospital and intensive care unit (ICU) stays, and higher perioperative mortality in patients with procedures that affected the hepatic hilum. These findings have been reproduced by other authors as well (Menegaux et al, 1994; Mazzaferro et al, 1990; Brems et al, 1989), however, other studies have not found this association (Gonzalez et al, 2005; Abou Jaoude & Almawi, 2001; Boillot et al, 1991). The mesocaval interposition shunt is technically less challenging than the distal splenorenal shunt and requires minimal retroperitoneal dissection. It effectively relieves portal hypertension, and in contrast to the distal splenorenal shunt, it also relieves or prevents secondary ascites.

SHUNT MATERIALS AND MESOCAVAL SHUNT SIZE

Multiple variations of the mesocaval shunt procedure have been described in the literature, and significant debate has ensued regarding the ideal graft material and diameter for the mesocaval shunt. In 1970, Read and colleagues presented a series of eight mesocaval shunts with homologous vena cava. Also in 1970, Lord and associates published a report on seven mesocaval H-grafts with polytetrafluoroethylene (PTFE) prostheses, of which six remained patent for 20 months. Despite Lord's early success, many clinicians remained fearful of using prosthetic grafts in the venous system because of experimental failures in long-term patency. In 1972, Drapanas published data on 25 more mesocaval shunt procedures that used 19- to 22-mm Dacron interposition grafts and showed excellent patency rates. Drapanas cited a superiority of Dacron over PTFE for better incorporation into host tissues and continued to use Dacron in his studies.

Throughout the 1970s, several other groups reported success with large-diameter prosthetic grafts. In 1977, Filtzer and coworkers reviewed their institution's experience with 20 patients who underwent mesocaval shunt procedures using 18- to 22-mm Dacron grafts for bleeding esophageal varices. The long-term patency rate approached 90%. In 1975, Drapanas and associates published a follow-up study on the hemodynamics of 80 mesocaval shunts using large-diameter (18 to 22 mm) Dacron grafts. In this series, a decrease in mean portacaval pressure by 50% was noted, and 44% maintained hepatopetal portal flow. Only three graft thromboses occurred, and overall patency rate was 95%. One patient developed graft infection, however, with subsequent sepsis and death.

Although recurrent esophageal varices and hemorrhage were rare after these procedures, the large-diameter portacaval and mesocaval grafts (16 to 22 mm) often resulted in total portal shunting and loss of prograde portal flow, which many investigators thought led to progressive liver dysfunction and high rates of encephalopathy. Sarfeh and colleagues (1986) investigated the importance of maintaining hepatic portal perfusion for prevention of encephalopathy by systemically reducing the portacaval H-graft diameters. After reviewing 88 patients treated with portacaval shunting for bleeding esophageal varices, they reported maintenance of hepatopetal flow in 82% of patients with 8-mm PTFE H-grafts, 46% with 10 mm PTFE H-grafts, and only 3% with 14- to 20-mm Dacron grafts. Preserved prograde portal flow correlated with decreased rates of encephalopathy, which was observed in only 9% of patients with 8-mm PTFE H-grafts compared with 39% of those with large-diameter Dacron grafts. Although early graft thrombosis was more common in the small-diameter grafts (16%), the cumulative shunt patency rate was 97% for those grafts. One patient experienced graft infection with subsequent sepsis and death. In another study, Isaksson and colleagues (2005) noted that patients with a 14-mm mesocaval shunt had a steady, worsening performance in postoperative follow-up on several psychometric tests, and the rate of hepatofugal portal flow was 90% at 12 months in these patients.

Throughout the 1980s, most reports of small-diameter grafts focused on their use in the portacaval position as opposed to a mesocaval shunt. All studies showed a slightly increased rate of perioperative shunt thrombosis over the large-diameter shunts; this was mostly managed via angiographic revision (Collins et al, 1994; Rypins et al, 1988), and all small-diameter portacaval shunt procedures were coupled with aggressive portal vein collateral ablation.

More recent studies have shown the efficacy of small-diameter mesocaval shunts. Mercado and associates (2000) reviewed a 10-year experience with 10-mm PTFE mesocaval shunts for the treatment of bleeding esophageal varices in mostly low-risk patients with preserved hepatic function. Thirty-three patients underwent the procedure; 81% maintained long-term patency evaluated by angiography, but 15% developed episodes of rebleeding. Only 11% had encephalopathy, and 12-month survival was 81%. Mercado and colleagues (1996) also compared the distal splenorenal shunt with the 10-mm PTFE mesocaval shunt and showed decreased encephalopathy, decreased shunt thrombosis, and fewer changes in portal flow with the distal splenorenal shunt but no differences in mortality or rebleeding rates. They concluded that the mesocaval shunt continues to have a role in the surgical treatment of portal hypertension, when a selective shunt cannot be performed.

Despite considerable debate in the literature since the early 1970s, no definitive answer exists to the question of which graft material works best for the mesocaval shunt procedure. The small-diameter shunts provide preserved prograde portal flow in the early postoperative period but may still be associated with encephalopathy and loss of hepatopetal flow over time. In addition, postoperative encephalopathy rates vary considerably in the literature, from less than 10% to greater than 50%. Although rare, graft infection in the prosthetic grafts was uniformly fatal in the literature.

Reynolds and Southwick in 1951 first described the use of autologous vein graft for interposition between the portal vein and vena cava. Stipa and colleagues (1978) compared their

experience with the side-to-side portacaval shunt versus autologous internal jugular vein interposition mesocaval shunt in 79 patients with variceal hemorrhage and portal hypertension. Although no differences in survival were reported between the two groups, encephalopathy was greater in the portacaval shunt patients (54%) compared with the mesocaval shunt patients (35%), and 95% of the patients with mesocaval shunts maintained hepatopetal portal flow. Gonzalez and associates (1977) also reported the use of autologous vein graft in 26 patients; no graft infections were reported for patients undergoing mesocaval shunts with either homologous or autologous vein graft. These shunts require more time to harvest vein, however, and they may not be appropriate in an emergency or urgent setting.

The literature also shows favorable patency rates with mesocaval shunting. Ilkgul and coworkers (2005) reported an 89% overall patency rate over a median follow-up of 42 months in patients with autologous internal jugular vein grafts. Sigalet and colleagues (2001) found a 100% shunt patency at 4.3 years in 20 pediatric patients using autologous vein graft. It is important to note that all of the mesocaval shunts discussed in this review provided adequate portal decompression with low perioperative mortality and infrequent recurrence of variceal hemorrhage.

PREOPERATIVE EVALUATION AND MANAGEMENT

The patient should undergo an evaluation for encephalopathy, and if encephalopathy is present, the patient is not a good candidate for the procedure. Preoperative mesenteric angiography with late-phase portography, magnetic resonance angiography (MRA), or computed tomography (CT) angiography must be performed in all patients before the procedure. Additionally, venacavography and wedged hepatic venous pressure gradients can provide important anatomic and physiologic data. It is necessary to confirm the presence of an adequate-diameter superior mesenteric vein (SMV) and to show the direction of portal flow through the collateral vessels.

Before the operation, if possible, the patient should undergo diuresis with spironolactone and furosemide to minimize postoperative ascites. The patient should also receive standard antibiotic prophylaxis in the holding area immediately before surgery, but a formal mechanical bowel preparation is unnecessary.

Technique

Exposure

A transverse mid-abominal, right low subcostal, or midline incision may be used (Fig. 76D.1). Because of portal hypertension, a few large collateral vessels may be encountered in the subcutaneous tissue; these should be doubly ligated and divided instead of divided with electrocautery. When the peritoneum is opened, ascites is removed, and the abdomen is explored; a mechanical retractor is placed to provide maximal exposure. A liver biopsy often is performed and always should be done for any areas suspicious for hepatoma.

Exposure of the Superior Mesenteric Vein

The transverse mesocolon is retracted cephalad, and the small intestine is retracted caudad and to the left to expose the root of the mesentery and the ligament of Treitz. A transverse incision is made in the posterior parietal peritoneum to initiate

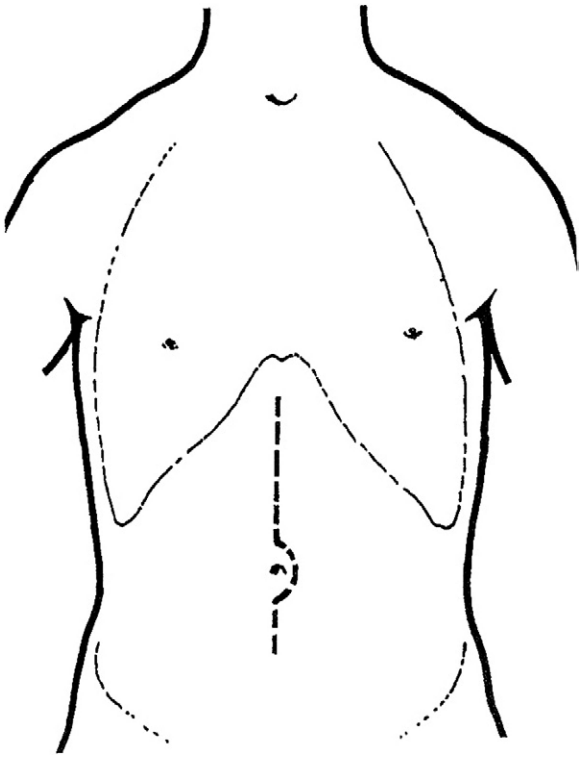


FIGURE 76D.1. The incision options for the mesocaval shunt procedure: transverse midabdominal, right low subcostal, or midline.

dissection of the SMV, which usually overlies the right lateral margin of the vertebral bodies. The superior mesenteric artery usually is located anterior and to the left of the SMV (Fig. 76D.2); however, these relationships are inconstant; Doppler may help identify the vascular structures.

During dissection of the SMV, multiple lymphatic channels and lymph nodes are encountered. Large, hypertrophied lymphatic channels should be ligated before division to prevent uncontrolled lymph flow during and after the procedure, which may contribute to postoperative ascites.

When the SMV is identified, it is mobilized and skeletonized from the inferior border of the pancreas to below the confluence of the ileocolic and jejunal veins, which form the SMV proper. Small branches are doubly ligated and divided, and large branches are controlled with vessel loops. The SMV is dissected bluntly on the anterior surface, and sharp dissection is limited, until the vein and all tributaries are identified. Usually, a large tributary vein enters the right posterior lateral border of the SMV between the ileocolic and middle colic veins, which should be controlled with a vessel loop. Occasionally, the inferior mesenteric vein, rather than the splenic vein, enters the side of the SMV directly. If so, the inferior mesenteric vein should also be controlled with a vessel loop before opening the SMV.

Ideally, a 6- to 7-cm length of large-diameter SMV should be exposed and mobilized to accommodate the graft. If necessary, the graft may extend onto the ileocolic vein. Alternatively, if the SMV is quite short, the ileocolic vein or middle colic vein or both may be sacrificed. In a patient with portal hypertension, the ileocolic vein may be quite large and could be mistaken for the SMV. A shunt between the ileocolic vein and cava is inadequate, however, for portal decompression.

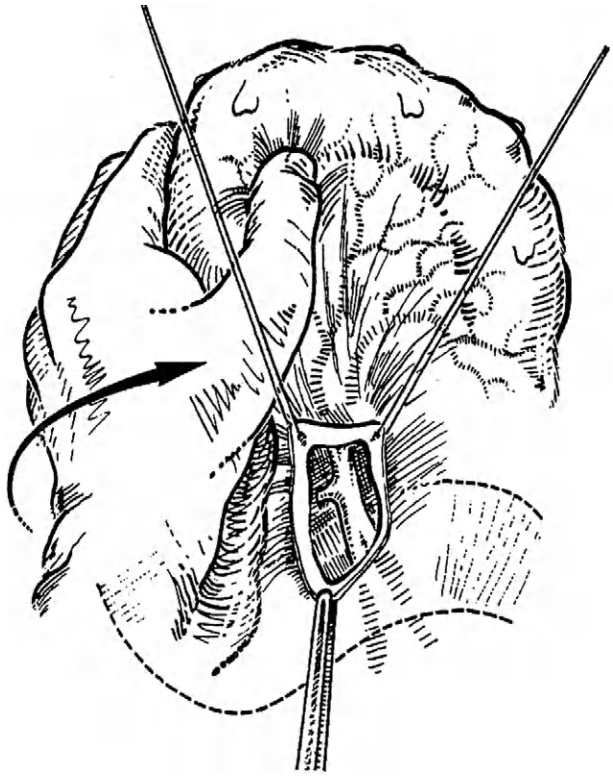


FIGURE 76D.2. Exposure of the superior mesenteric vein.

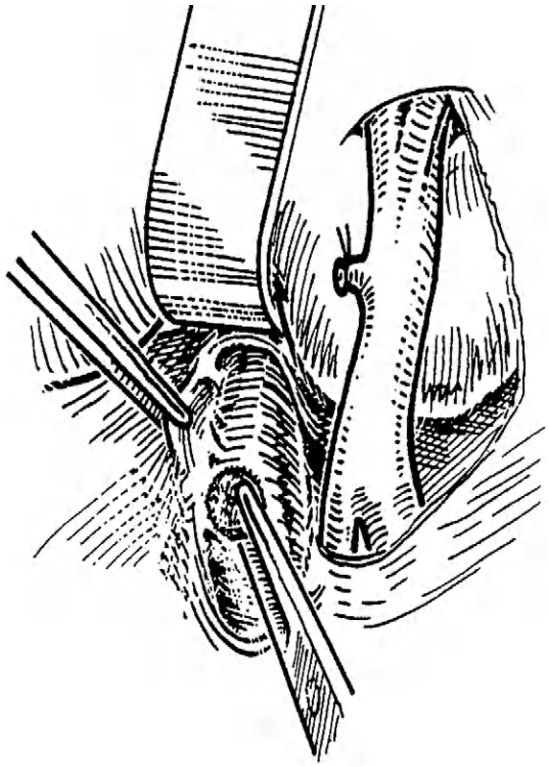


FIGURE 76D.3. Dissection of the anterior and lateral surfaces of the inferior vena cava and its relationship to the superior mesenteric vein.

Exposure of the Inferior Vena Cava

When an adequate length of the SMV is circumferentially mobilized, the IVC is identified by a direct approach through a window in the right colonic mesentery. Alternatively, the right colon and mesentery may be reflected to the midline, allowing access to the right retroperitoneum. The distal second portion and third portion of the duodenum are mobilized with a reverse Kocher maneuver. It is important to ligate and divide the large lymphatic channels in the retroperitoneum to avoid a significant lymphatic leak. A 6- to 7-cm length of IVC is dissected along the anterior and lateral borders (Fig. 76D.3). It is not necessary to mobilize the cava circumferentially but only enough to allow placement of a large Satinsky clamp for partial occlusion.

After mobilization of the SMV and IVC, soft tissue between these structures can be divided to allow graft to take the optimal route, but ligation of the large vessels should be avoided.

Preparation of the Vena Cava and Venotomy

The IVC-graft anastomosis is performed first, which eliminates the problems of diminished exposure for the caval anastomosis and prolonged SMV occlusion. A vascular suture can be placed in the anterior wall of the vena cava and used to tent it upward, while a large Satinsky clamp is placed to occlude the cava partially (Fig. 76D.4). It is important that the clamp occludes the superior and inferior ends of the vena cava segment to prevent bleeding during the anastomosis. The suture used to tent the cava is excised with an ellipse of anterior caval wall to form the venotomy (Fig. 76D.5). Using angled Pott scissors, the venotomy is enlarged to the same diameter, usually 8 to 12 mm, as the chosen ringed Gore-Tex or internal jugular vein graft. If the opening is too large, the graft does not assume a circular shape at the anastomosis.

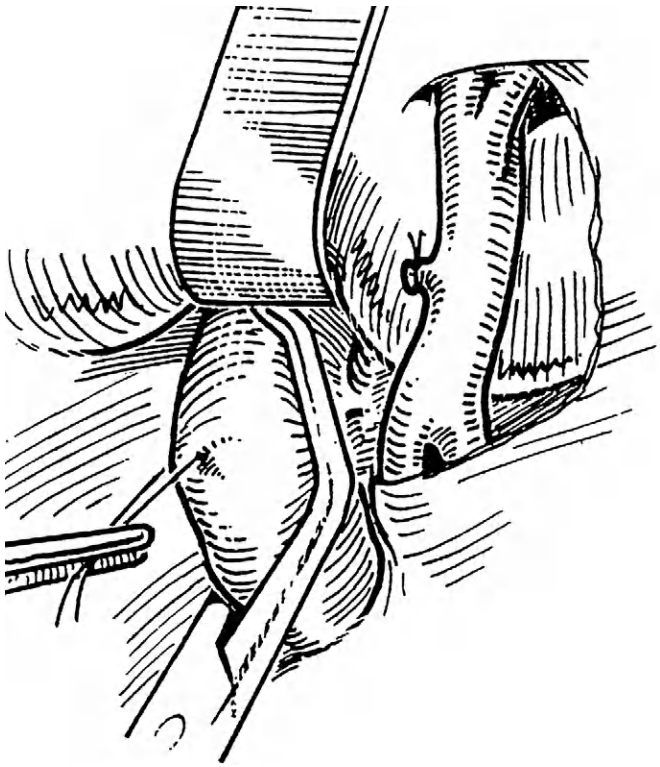


FIGURE 76D.4. Occlusion of the inferior vena cava with a Satinsky clamp and preparation of the vein for venotomy.

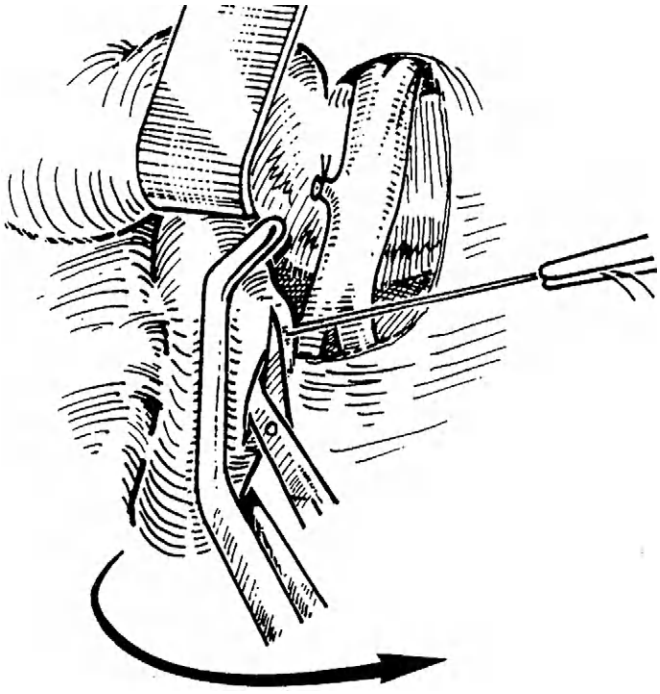


FIGURE 76D.5. Inferior vena cava venotomy.

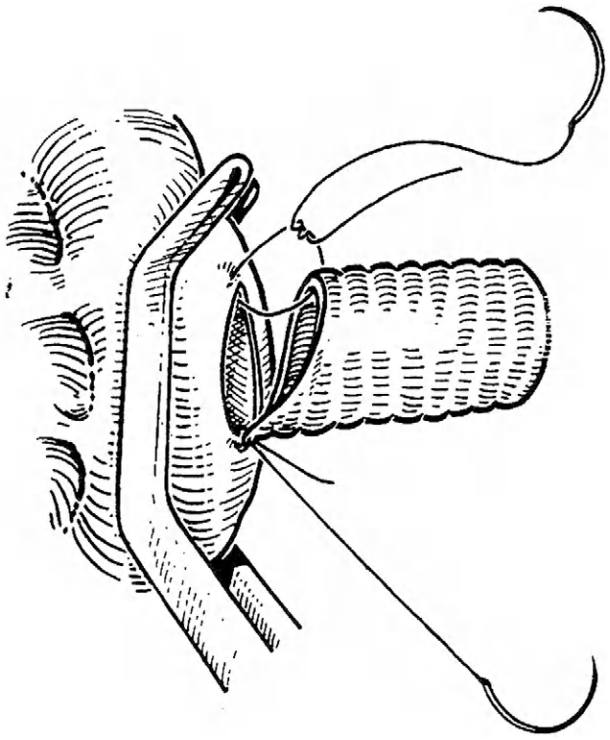


FIGURE 76D.6. Inferior vena cava–graft anastomosis.

Inferior Vena Cava–Graft Anastomosis

The caval anastomosis is located in the deepest and most dependent area of the wound, and good exposure is essential. The duodenum is retracted superiorly, and the rest of the viscera are retracted inferiorly. Two corner sutures are placed using 5-0 synthetic, nonabsorbable suture material at each end of the venotomy, and these are tied to position the graft over the venotomy (Fig. 76D.6). A stay suture also is placed midway along the medial caval venotomy lip for gentle traction to distract it away from the lateral suture line and to prevent incorporation into the opposite wall. The Satinsky clamp is rotated to the patient's left, and the right side of the anastomosis is completed first. It is started at the inferior margin using one end of the corner stitch and working upward, placing the continuous sutures outside-in on the graft and inside-out on the vein (Fig. 76D.7). At the superior margin, the suture is tied to one end of the superior corner stitch.

After completion of the right-side anastomosis, the Satinsky clamp is rotated to the patient's right, and the other end of the superior corner suture is run inferiorly to complete the left side of the anastomosis (Fig. 76D.8). Figure 76D.9 shows the completed anastomosis. A nerve hook may be used to ensure proper positioning of the cava or graft before each needle bite.

A vascular clamp is placed on the prosthesis, and the Satinsky clamp is released to ensure hemostasis of the anastomosis. Any anastomotic leaks are repaired, and the Satinsky clamp is reapplied to the vena cava. The vascular clamp is removed from the graft, and any remaining blood is suctioned from the graft lumen and irrigated with heparinized saline.

Superior Mesenteric Vein–Graft Anastomosis

In the SMV-graft anastomosis, the length of the graft is crucial. The graft assumes a C configuration as it passes inferiorly around the lower border of the third portion of the duodenum, then anterior to the third portion of the duodenum and uncinate process, before it is finally is anastomosed obliquely to the anterior-lateral surface of the SMV. If the graft is too short, undue tension is placed on the suture line, and the SMV is retracted and distorted. If the graft is too long, it becomes redundantly bowed and distorted when the clamps are removed.

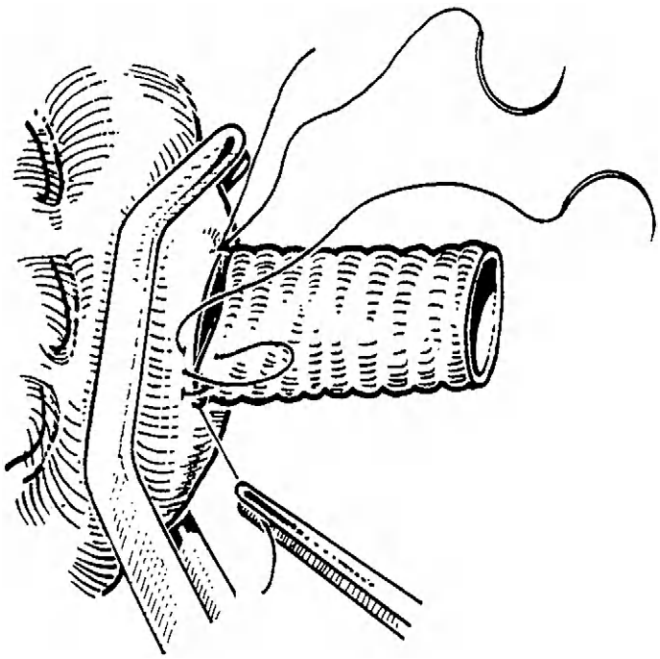


FIGURE 76D.7. The cava and graft are rotated medially, and the right lateral suture line is performed first.

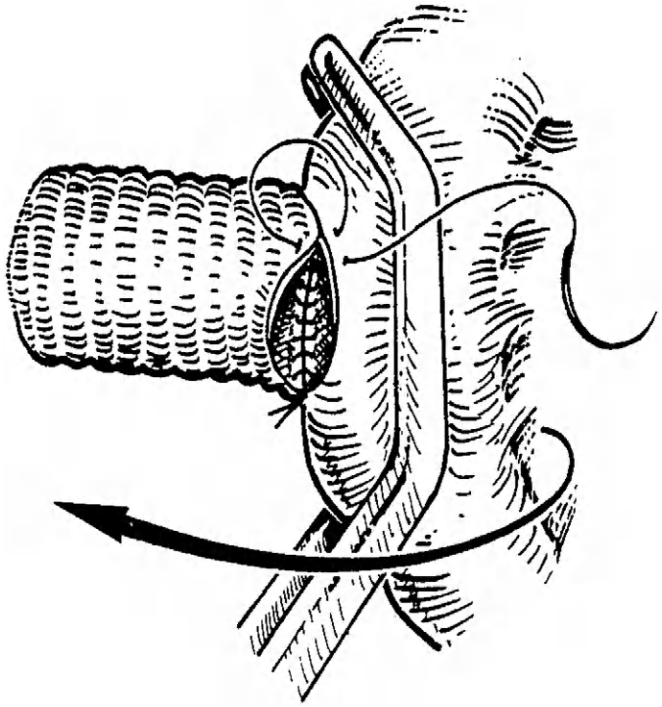


FIGURE 76D.8. The cava and graft are rotated laterally, and the left (medial) suture line is performed.

It also is helpful to mark the graft to maintain proper orientation. Alternatively, the graft may be short and relatively straight, assuming more of an H-graft appearance.

When the appropriate length is determined, the graft is cut obliquely to the angle at which it is to be anastomosed to the SMV. Two straight Cooley clamps are applied proximally and distally on the SMV, and the vein is partially rotated to allow the anastomosis to be performed on the anterior-lateral aspect of the vein. Retraction of the vessel loops placed on the tributaries provides adequate control of the tributaries during the anastomosis. Alternatively, vessel loops may be used to control all of the veins.

A small ellipse is excised from the anterior-lateral aspect of the SMV, and the venotomy is extended proximally and distally using angled Pott scissors to match the length of the obliquely cut graft. For H-shaped shunts, the venotomy is more right posterior-lateral on the vein. Sutures are placed at both ends of the venotomy and graft using 5-0 or 6-0 synthetic nonabsorbable suture material tied to approximate the vein and graft. The right lateral suture line is performed first in a continuous fashion from within the graft and vein, and is carried from the superior suture to the inferior suture (Fig. 76D.10). The left lateral suture line is created in a similar fashion by rotating the vein to the patient's right for better exposure (see Fig. 76D.10). The left lateral suture line also is started at the superior suture and carried down and tied to the inferior stay suture.

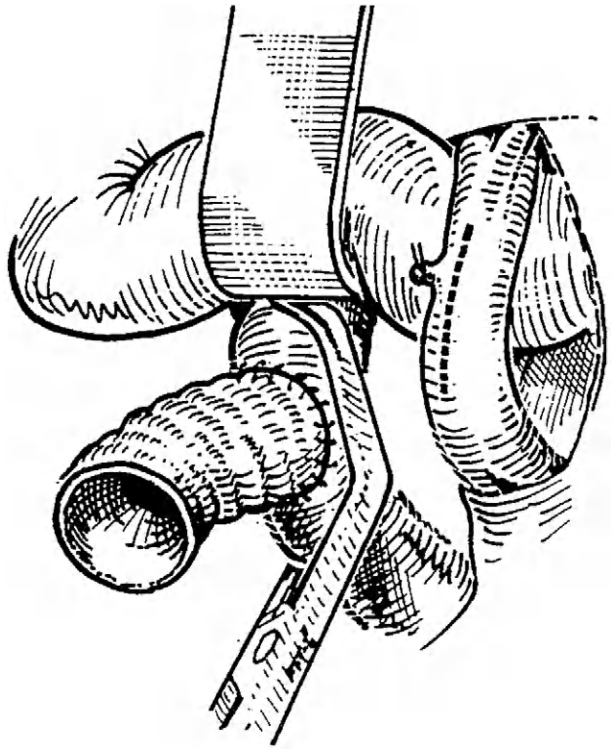


FIGURE 76D.9. The inferior vena cava–graft anastomosis is complete.

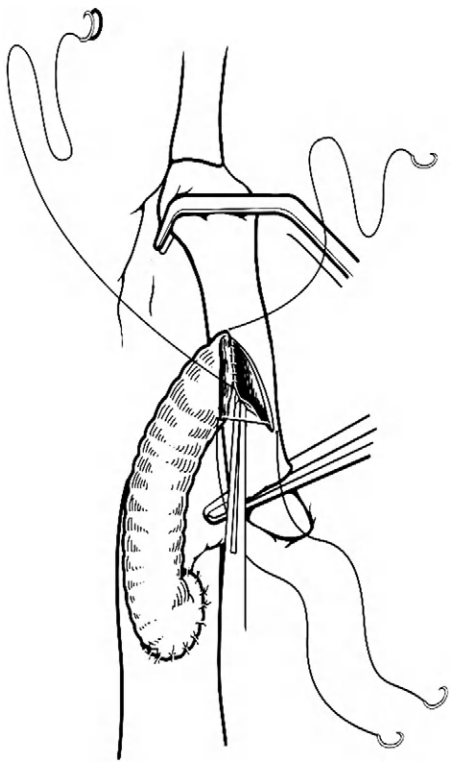


FIGURE 76D.10. After occlusion with vascular clamps, the superior mesenteric vein (SMV) venotomy is performed at the anterior-lateral aspect of the SMV, and the SMV-graft anastomosis is started. *(Illustration courtesy Dominic Doyle, Medical Arts Group, Vanderbilt University.)*

Evaluating the Anastomosis

The Satinsky clamp on the IVC is removed first, and all anastomotic leaks are repaired. The clamps are removed from the SMV, and flow is allowed through the shunt; gentle pressure may be applied to the anastomosis for hemostasis, and Doppler ultrasound may be used to interrogate the graft and anastomosis.

The pressures in the portal system are measured by positioning an 18 gauge needle connected to a water manometer into the SMV near the SMV-graft anastomosis (Fig. 76D.11). With the graft patent and mesenteric systemic flow intact, the pressure is measured as the decompressed portal pressure. The graft is clamped, and the pressure is rechecked to confirm that the system is indeed decompressed. A reduction in the pressure gradient by 12- to 18-cm H_2O should be expected. Also, a thrill may be palpated in the graft. When it is established that no technical problems exist with the graft, such as kinking or compression by surrounding tissues, the abdomen is irrigated, hemostasis is ensured, and the abdomen is closed.

Postoperative Evaluation and Management

Immediately after the procedure, shunt patency should be confirmed by duplex ultrasound, MRI, or CT angiography (Fig. 76D.12). If it is not possible to determine shunt patency via noninvasive techniques, an angiogram must be performed.

Postoperative care includes strict volume management. It is important to keep the central venous pressure as low as possible but to maintain appropriate cardiac output to preserve renal perfusion and function. Although most patients develop some postoperative ascites, it usually clears with a functioning shunt. Initially, patients should be cautious with their diet to minimize the risk of encephalopathy, but only rarely is it necessary to restrict patients to a meat-free diet and lactulose regimen.

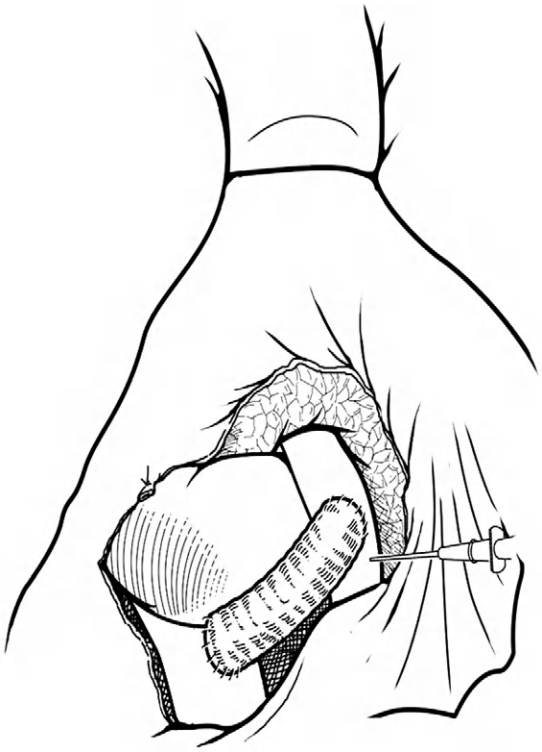


FIGURE 76D.11. After completion of the interposition mesocaval shunt, the portal system pressures are measured. *(Illustration courtesy Dominic Doyle, Medical Arts Group, Vanderbilt University.)*

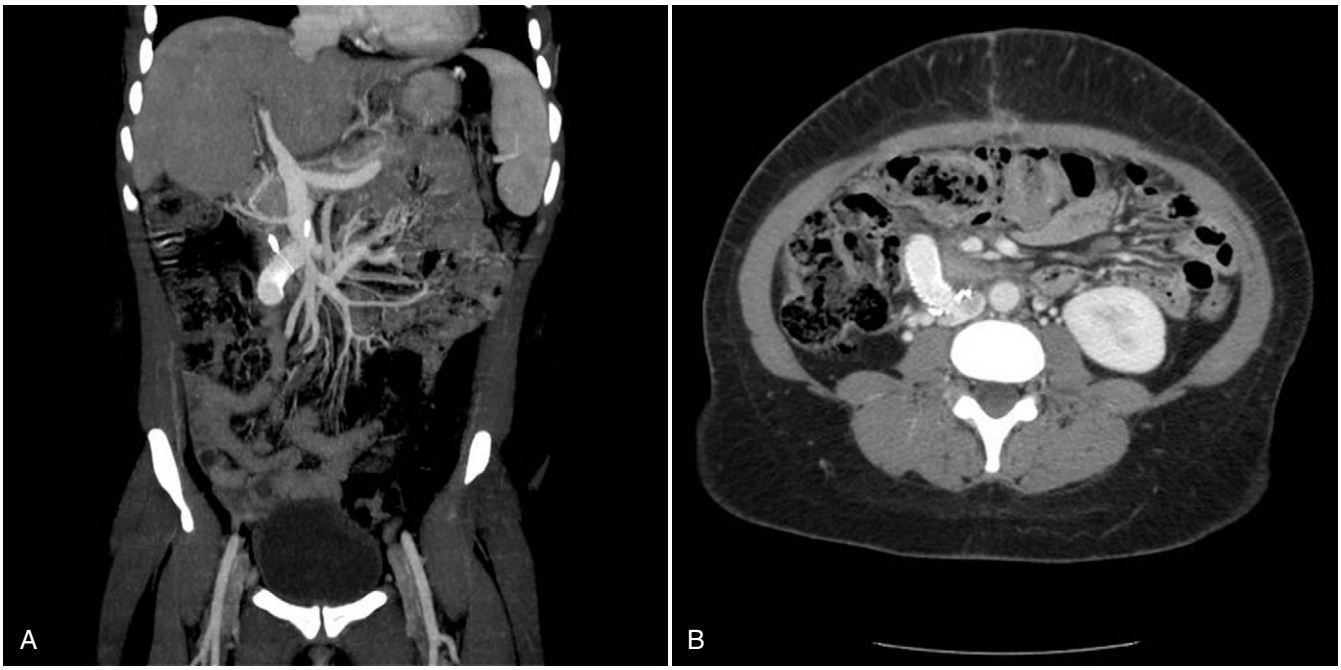


FIGURE 76D.12. Computed tomographic angiography of a patent interposition mesocaval shunt. **A,** Coronal image. **B,** Transverse image. *(Image courtesy Dr. Ravi Chari.)*

If gastrointestinal bleeding recurs, the patient should undergo shunt interrogation to determine shunt patency. Several studies also recommend routine shunt evaluation by either duplex ultrasound or angiography (Mercado et al, 1996; Orloff et al, 2002; Rypins et al, 1988). We perform follow-up duplex ultrasound every 3 to 6 months after the procedure for the lifetime of the shunt. Shunt stenosis is managed routinely with percutaneous transfemoral dilation and, rarely, stenting of the stenosis; operative revision is done only with failure of the less invasive interventional procedures. For early and late shunt thrombosis, most studies advocate shunt thrombectomy. After balloon catheter placement and dilation across any stenosis, an angiocatheter is placed at the SMV-graft anastomosis, and streptokinase is infused at a rate of 5000 U/hr for 24 hours (Rypins et al, 1988; Sarfeh et al, 1986).

SUMMARY

Despite advances in endoscopic therapy, interventional techniques, and liver transplantation, surgical shunts are important therapeutic tools in select patients. Because of its technical simplicity and low complication rate during subsequent liver transplantation, the mesocaval shunt is an ideal surgical shunt choice in some patients. It has been proven to effectively relieve portal hypertension and secondary ascites and to prevent recurrent variceal hemorrhage.

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CHAPTER 76E

Transjugular intrahepatic portosystemic shunting: indications and technique

Michael Darcy

OVERVIEW

In the 20 years since its introduction, transjugular intrahepatic portosystemic shunting (TIPS) has gone from being a procedure reserved for desperate circumstances to one that is now routinely used to manage some complications of portal hypertension. The broader utilization of TIPS has been accompanied by changes in the indications and techniques, influenced by greater experience and better knowledge of outcomes.

INDICATIONS

Variceal Bleeding

Bleeding gastroesophageal varices not controlled by medical or endoscopic means was the original indication for which TIPS was devised, and this is still the primary indication. TIPS can routinely decompress the portal system to drop the portosystemic gradient (PSG) and will lead to immediate cessation of bleeding in 95% of patients (Fig. 76E.1). A number of randomized trials have compared TIPS to best medical management (Cabrera et al, 1996; Cello et al, 1997; Garcia-Villarreal et al, 1999; Gulberg et al, 2002b; Jalan et al, 1997; Merli et al, 1998; Pomier-Layrargues et al, 2001; Rössle et al, 1997; Sanyal et al, 1997; Sauer et al, 1997). These have demonstrated that TIPS provides better long-term control of variceal bleeding. In these studies, recurrent bleeding occurred in 18% to 56% of patients in the sclerotherapy cohorts versus only 9% to 23% of patients in the TIPS arms. Not only were these differences statistically significant for the primary outcome, the crossover rate from endoscopy to TIPS was 5% to 28%, but only 0% to 7% of the TIPS patients crossed over to endoscopic treatment.

Despite the improved control of bleeding, TIPS did not yield a survival benefit in most of these studies. One possible explanation for this is that by shunting portal blood flow from the liver, some deterioration in liver function occurs, and this might offset the improved survival related to control of hemorrhage. Alternatively, it is possible that the studies simply did not follow patients long enough to demonstrate the survival benefit. In most of the randomized trials, the survival in the TIPS group was longer than the medical therapy group but not long enough to achieve statistical significance; perhaps longer follow-up might have yielded a significant difference.

Better stratification of patients might also have yielded different results, as evidenced by one randomized trial (Monescillo et al, 2004) that stratified patients according to early measurement of their hepatic venous pressure gradient (HVPG) and then randomized high-risk patients (HVPG >20 mm Hg) to medical management or early TIPS placement. Not only did the TIPS group have fewer episodes of recurrent bleeding, both the in-hospital and 1 year mortality rates (11% and 38%) were significantly lower than in the non-TIPS cohort (38% and 65%).

One caveat regarding many of the randomized trials is that most were done using bare metal stents to create the shunt. Thus, within 6 to 12 months, the majority of the shunts in the TIPS group had stenosed. The current standard of care is to use stent grafts (polytetrafluoroethylene-covered stents) for TIPS procedures. These newer stent grafts have much improved patency and yield even better control of variceal bleeding than the bare metal TIPS (Angeloni et al, 2004; Angermayr et al, 2003; Bureau et al, 2007; Tripathi et al, 2006). Although more studies need to be done with stent grafts, at least one randomized trial (Garcia-Pagan et al, 2010) showed significantly better 1-year survival for TIPS performed with these improved stents compared with medical management (86% vs. 60%, $P < .01$).

The main downfall to TIPS is the development of new hepatic encephalopathy or exacerbation of existing encephalopathy, which occurs in 20% to 31% of cases (Boyer & Haskal, 2010). It is for this reason that TIPS is still recommended only after failure of medical management and not as front-line therapy for variceal bleeding. Interestingly, despite improved patency, the stent-graft TIPS has actually been associated with a lower incidence of encephalopathy compared with bare-stent TIPS (Bureau et al, 2007; Tripathi et al, 2006). This is another reason why the randomized trials comparing TIPS to medical management need to be repeated with the newer stent grafts.

Gastric Varices and Gastropathy

Gastric varices are also frequently seen in patients with portal hypertension and are actually associated with a higher rate of hemorrhage-related mortality compared with bleeding from esophageal varices (Garcia-Tsao & Bosch, 2010). TIPS can also provide good control of bleeding related to this condition, although the efficacy compared to endoscopic management is less clear. One large retrospective study comparing TIPS to endoscopic cyanoacrylate injection failed to demonstrate a benefit for TIPS in either control of bleeding or survival (Procaccini et al, 2009). However, another trial (Lo et al, 2007) that randomized patients to either TIPS or variceal obliteration with endoscopic cyanoacrylate injection showed that rebleeding was significantly less frequent in the TIPS group (11% vs. 38%, $P = .014$).

TIPS has also been used to treat portal hypertensive gastropathy, but data are sparse, and no randomized trials have evaluated the use of TIPS for this condition. Some investigators believe that TIPS is less effective for this condition, and several

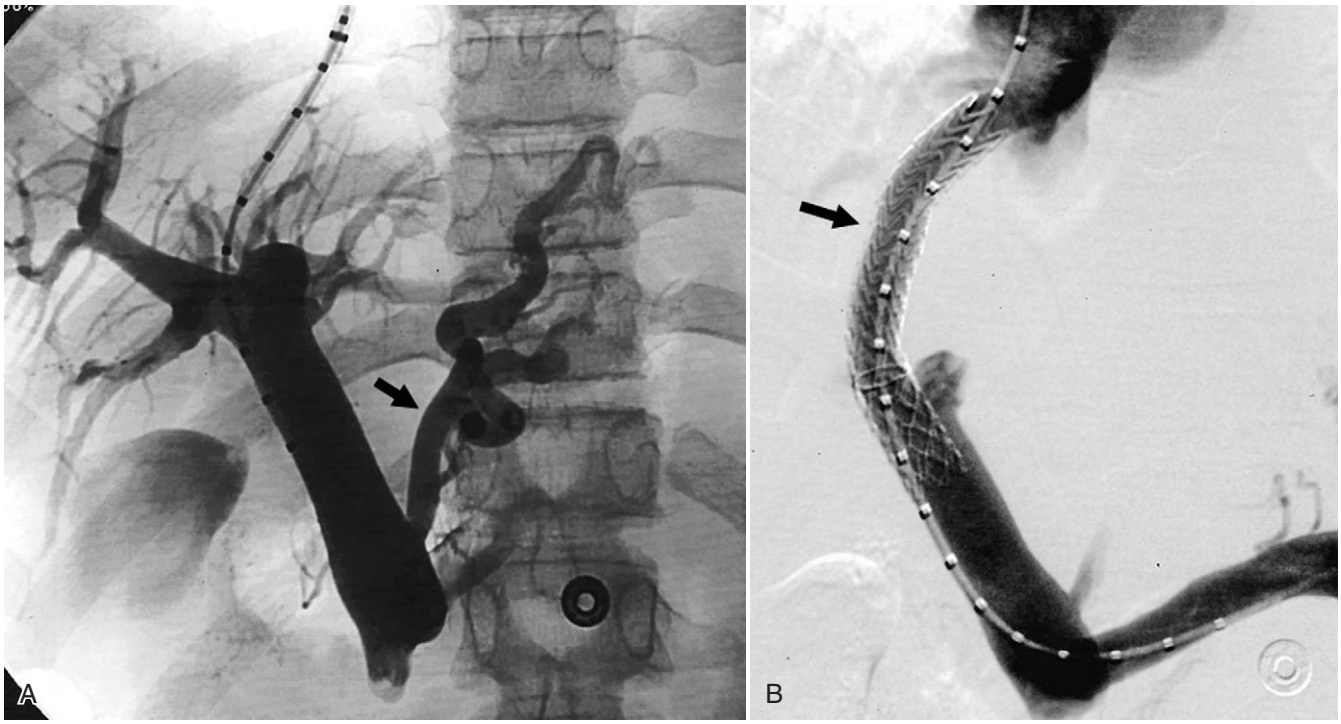


FIGURE 76E.1. A, Initial portal venogram shows a very large coronary vein (*arrow*) giving rise to gastroesophageal varices. **B,** Immediate post-TIPS portal venogram demonstrates good flow through the TIPS (*arrow*) and no further flow into the coronary vein.

studies have a shown a poor correlation between HVPG and the presence or severity of gastropathy (Bellis et al, 2007; Shimizu et al, 2002). Given that the function of TIPS is to reduce portal pressure, this lack of correlation between the severity of gastropathy and portal pressures may account for the more variable results seen with TIPS in this condition.

Ectopic Varices

The effective portal decompression achieved by TIPS has led to expansion of the indication to include bleeding from ectopic varices, which most often arise in enteric stomas and are caused by portal hypertension transmitted to the peripheral tributaries of the mesenteric veins. Several small series have described successful treatment of varices in these locations by decompression with TIPS (Spier et al, 2008; Kochar et al, 2008; Han et al, 2007; Vidal et al, 2006; Macedo et al, 2005; Alkari et al, 2005; Vangeli et al, 2004; Ryu et al, 2000). The rebleeding rate in this indication is higher than expected after decompression of the portal system, which has led several authors (Kochar et al, 2008; Vangeli et al, 2004) to suggest that the ectopic varices should also be embolized at the time of TIPS.

Ascites

Although TIPS was designed to treat variceal bleeding, early investigators recognized that the procedure also led to a reduction or resolution of ascites in many patients. A number of randomized controlled trials have compared TIPS to large-volume paracentesis (LVP) (Ginés et al, 2002; Lebrec et al, 1996; Rössle et al, 2000; Salerno et al, 2004; Sanyal et al, 2003). A meta-analysis of these trials (Deltenre et al, 2005) showed that at 4 and 12 months, ascites was controlled in 66% and 55% of the TIPS patients, respectively, compared with 24% and 19% for the LVP patients. Despite the improved control of ascites, survival was higher, but not statistically better, in the TIPS groups. Another meta-analysis of the data did show a slight survival benefit for the TIPS patients (Salerno et al, 2007). Again, these studies were all done with bare metallic stents, and because survival is better after TIPS with stent grafts, these studies bear repeating with the current technology. Data from trials of stent grafts show improved control of ascites compared to bare-stent TIPS. Jung and colleagues (2009) reported ascites control at 1 year in 64% of TIPS procedures performed with the Viatorr device (W.L. Gore, Flagstaff, AZ) versus only 33% in patients with bare metal stents.

Patients with intractable ascites tend to be a sicker population, and despite successful decompression of the portal system, survival in this cohort is likely to be lower compared with those who have had TIPS done for variceal hemorrhage (Wallace et al, 2004); however, TIPS can still lead to significant improvement in quality of life (Gulberg et al, 2002a). One caveat is that the physiologic effect is not always immediate, and some patients do not show resolution of ascites for 2 to 3 months after the TIPS; another is that the clinical response does not appear to be as good when TIPS is used to treat recurrent ascites in patients after liver transplantation. One small retrospective study (Saad et al, 2010) reported a clinical success rate of only 16% in patients after transplant.

Hepatic Hydrothorax

Based on the success with managing ascites, TIPS has also been applied to hepatic hydrothorax, which occurs in 5% to 10% of cirrhotic patients and can lead to significant shortness of breath and inability to perform normal daily activities. Similar

to ascites, TIPS is not used for primary therapy but instead is reserved for patients who are refractory to medical management. Patients requiring multiple thoracenteses or chest tubes can benefit from TIPS, with a beneficial response reported in 74% to 79% of patients undergoing the procedure (Dhanasekaran et al, 2010; Gordon et al, 1997; Spencer et al, 2002). Of those who respond, about two thirds have complete resolution of the hydrothorax, and the remainder experience partial resolution of the effusion but are symptomatically improved, with either decreased or resolved dyspnea. In our experience (Spencer et al, 2002), the patients who showed no clinical response to TIPS were all critically ill with elements of multiorgan failure, and 30-day mortality was 83%. Thus TIPS is unlikely to be helpful as a last-ditch effort to improve pulmonary function in severely ill patients on mechanical ventilation.

Budd-Chiari Syndrome

Since the early 1990s, TIPS has also been used to relieve the portal hypertension and hepatic congestion associated with Budd-Chiari syndrome (Ochs et al, 1993). The results obtained depend on the patient's physiologic status. Several studies (Khuroo et al, 2005; Blum et al, 1995) have shown that a more fulminant presentation correlates with decreased survival; however, patients with a more chronic form of Budd-Chiari syndrome have fairly good results with TIPS. The largest series of TIPS done for Budd-Chiari syndrome included 124 patients (Garcia-Pagan et al, 2008b). The 1- and 10-year transplant-free survival rates were 88% and 69%. This was significantly better than expected for this patient population and has led to a change in the guidelines so that TIPS is now a recommended treatment in patients who fail anticoagulation therapy (Boyer & Haskal, 2010). This study also demonstrated that patients with a greater degree of hepatic dysfunction did not benefit as much as those with better preserved hepatic function.

Portal Vein Occlusion

Portal vein (PV) occlusion is one indication for TIPS that sometimes arises even in patients without severe cirrhosis. The benefit of TIPS is that it provides a pathway into the portal system for introduction of mechanical thrombolytic devices (Fig. 76E.2) and also provides outflow to help maintain flow once portal patency is reestablished. TIPS has also been shown to be beneficial in treating portal hypertensive complications in patients with portal thrombosis who are awaiting liver transplantation (Bauer et al, 2006). The technical success rate for establishing a shunt and maintaining patency of the portal system is 70% to 100% (Bilbao et al, 2004; Radosevich et al, 1993), with the technical failures a result of the inability to traverse the portal occlusion. Clinical success—that is, termination of hemorrhage—was achieved in all patients in whom a TIPS was successfully created. This approach needs to be carefully considered in consult with a liver transplant surgeon and transplant hepatologist in transplant candidates, because TIPS placement in this setting can compromise access to the proximal PV, which has the potential to influence the outcome of liver replacement.

Preoperative Decompression

A relatively new application of TIPS has been for preoperative portal decompression in patients who need to undergo major intraabdominal, nonhepatic operations (see Chapter 70B; Azoulay et al, 2001; Gil et al, 2004; Schlenker et al, 2009). For patients with severe portal hypertension that requires colonic resection, the operative mortality can be quite high. Portal hypertension poses a risk in terms of dilated collateral veins, increased risk of operative bleeding, and the possibility of portal hypertension–related ascites, causing infectious complications or incisional ascites leakage postoperatively. In the reports of

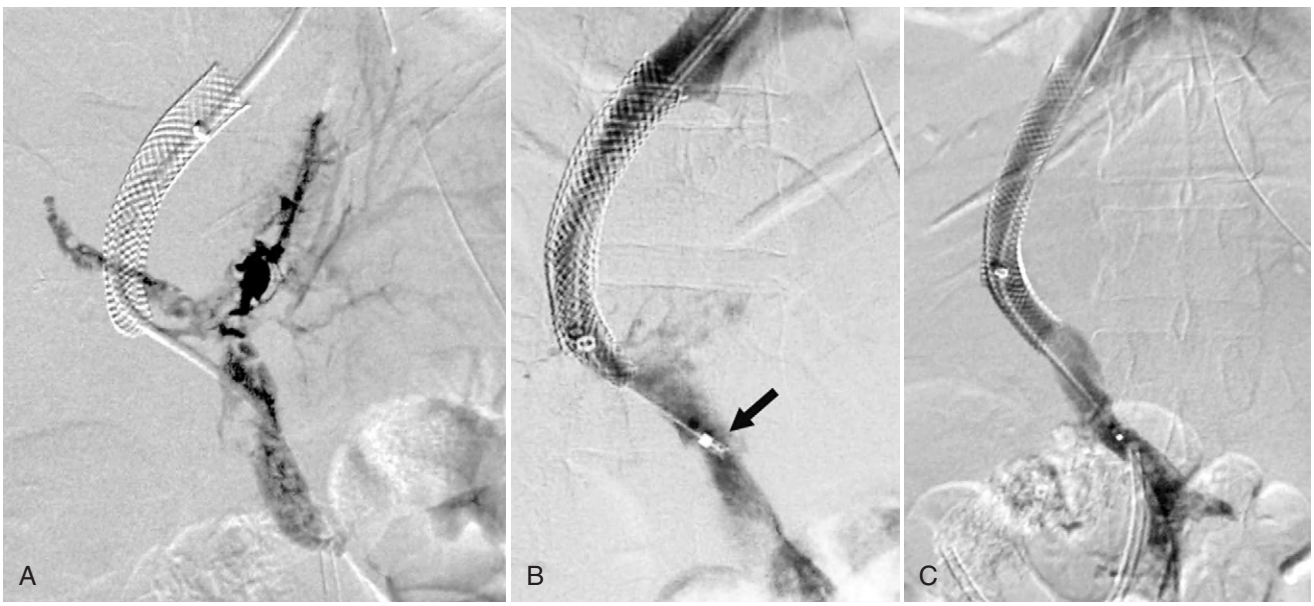


FIGURE 76E.2. A, Portal venogram after initial deployment of transjugular intrahepatic portosystemic shunting (TIPS) stent in a patient with preexisting portal thrombosis. Multiple filling defects are seen throughout the main portal vein and branches. **B,** Using a mechanical thrombectomy device (*arrow*) to lyse the portal thrombus. **C,** Final venogram with a patent portal vein and good flow through the TIPS.

TIPS for this indication, the operations were carried out without excessive bleeding or ascitic complications.

One unresolved question concerns how much time to allow between the TIPS and the operation to ensure optimal decompression of the dilated collateral veins. Although waiting a few weeks after portal decompression seems prudent, one group reported safely operating 2 days after TIPS (Theruvath & Adams, 2010). Given that TIPS can cause complications of its own, it should not be utilized casually for preoperative decompression.

CONTRAINDICATIONS

When medical and endoscopic methods have failed to control massive variceal hemorrhage, TIPS may be the only potentially lifesaving option. Thus most of the contraindications typically cited are only relative contraindications; however, if the indication for TIPS is nonemergent, these contraindications assume greater importance. Right heart failure is one of the most significant contraindications, because TIPS can precipitate acute death from total heart failure (Peron et al, 2000), but this complication has been reported so infrequently that it is impossible to define an absolute threshold for right heart pressures above which TIPS should not be performed.

Because TIPS diverts portal blood flow away from the liver, worsening of hepatic function can occur. This deterioration in hepatic function is often temporary, but if the patient already has preexisting hepatic dysfunction, TIPS may cause progression to more serious problems. The major problem is determining the threshold beyond which TIPS should not be performed. Multiple factors have been correlated with increased risk of post-TIPS liver failure, including less favorable Model for End-Stage Liver Disease (MELD) scores or Child-Turcotte-Pugh (CTP) class, increases in the serum bilirubin level, advanced age, a high serum creatinine level, the urgency for TIPS, and the presence of encephalopathy.

Various authors have proposed schemes to decide prospectively who should be treated with TIPS (Harrod-Kim et al, 2006; Malinchoc et al, 2000; Montgomery et al, 2005; Pan et al, 2008). Of these, the MELD score tends to correlate best with 1-year survival (Chalasani et al, 2000). Different MELD scores have been proposed as the cutoff above which patients should not undergo TIPS, but these figures must be weighed against the risk inherent in the patient's condition. In situations of life-threatening variceal hemorrhage, TIPS can often be life saving, even in a patient with a high MELD score.

Cavernous transformation is generally considered a contraindication, because it greatly increases the difficulty of gaining access to the portal system. Furthermore, even if a portal branch is accessed, it may be impossible to negotiate across the main PV occlusion to a portion of the portal system that is patent. Cases have been described in which a TIPS was created to a dilated periportal collateral with successful decompression of the portal hypertension (Brountzos et al, 2004; Wils, et al, 2009). Detailed preprocedure cross-sectional imaging can be useful to assess for the presence of a large, dominant collateral that can act as a target for the shunt.

Polycystic liver disease has been listed as an absolute contraindication because of potential intracystic hemorrhage, although successful TIPS in polycystic livers has been reported by us and others (Bahramipour et al, 2000; Shin & Darcy, 2001; Sze et al, 2006); some of these were even done with bare metallic stents without significant bleeding despite needle entry into the cyst cavity during creation of the parenchymal tract. The reason for the lack of intracystic hemorrhage would appear to be that the shunt provides a low-resistance pathway to the right atrium, and there is little reason for blood to flow into the contained space of a cyst. Although technically challenging, evidence is insufficient to suggest that polycystic liver disease should continue to be listed as a contraindication.

Active spontaneous bacterial peritonitis (SBP) is a potential risk for contamination of the stent graft being implanted. Thus if the indication for TIPS is nonemergent, the procedure is usually postponed until the SBP has cleared.

TECHNIQUE

TIPS can be performed with a high degree of technical success, usually over 95%. Despite this, the procedure remains technically challenging for many interventional radiologists, and careful attention to details is critical to ensure success.

Patient preparation is similar to other procedures that require heavy sedation or general anesthesia, and preprocedure imaging of the PV is helpful to ensure a patent PV. Although TIPS can be performed in the face of portal thrombosis that has not progressed to cavernous transformation, the procedure is more difficult in this setting and may require percutaneous transhepatic access. Puncture of the liver capsule can occur during TIPS, resulting in peritoneal hemorrhage; assessment and optimization of the patient's platelet count and coagulation parameters are therefore critical. Prophylactic antibiotics should be administered, because a permanent stent graft is being implanted, and cases of TIPS infection have been described (Mizrahi et al, 2009; Sanyal & Reddy, 1998; Suhocki et al, 2008). In patients with massive ascites, a peritoneal drain should be placed at the start of the case. As the ascites is drained, it helps with fluoroscopic visualization of the device being used, and it also gives the patient a head start at resolving the ascites. Additionally, drainage can be a useful intraprocedural way to monitor any intraperitoneal hemorrhage that may develop.

The procedure is started by accessing the jugular vein. The right internal jugular is the preferred access, because it provides a straight path into the inferior vena cava (Baijal et al, 1996) and hepatic veins. When the right internal jugular vein is occluded, the left internal jugular vein can be utilized. Despite the seemingly tortuous course from that access to the hepatic veins, use of stiff guidewires and long sheaths allows a high rate of technical success when starting from the left jugular (Hausegger et al, 1998). If both internal jugular veins are occluded, collateral veins or external jugular veins can sometimes be used for access. Alternatively, if the jugular vein is only partially thrombosed, the occlusion can be probed with a catheter and guidewire. If the obstruction can be traversed, a sheath may be placed to allow use of this access.

Next, a hepatic vein (HV) is catheterized, because this is the starting point for creating the transhepatic tract; typically the right HV is chosen because of its larger size. However, this is not always the best choice. If the patient has a small, shrunken liver and a large amount of ascites, the liver is often deviated in a cephalad direction. This causes an acute angulation of the right HV as it enters the inferior vena cava (IVC), which makes it very difficult to advance catheters and needles into the HV. In this setting, the middle HV is a better choice, because the pathway from the IVC into this vein is still relatively straight, even when ascites elevates the liver.

At this point, the angiographic catheter should be exchanged for a balloon occlusion catheter. Through this catheter, wedged venography can be done to localize the PV prior to making needle passes. Although a nonballoon endhole catheter can be used for wedged venography, all cases of hepatic capsular rupture during wedged venography have occurred with very peripherally positioned endhole catheters (Semba et al, 1996; Theuerkauf et al, 2001). A more centrally positioned balloon occlusion catheter allows the forceful injection to diffuse through a larger number of HV branches, thus decreasing the chance of rupture. Carbon dioxide (CO_2) gas is the preferred contrast agent for wedged venography. The lower viscosity compared with liquid iodinated contrast allows better flow through the sinusoids and better opacification of the PV (Krajina et al, 2002).

While the balloon catheter is in place, some recommend doing free and wedged HV pressures to determine the HVPG and confirm the presence of portal hypertension before creating the TIPS. Monescillo and colleagues (2004) have demonstrated that stratifying patients into low-risk (HVPG <20 mm Hg) and high-risk (>20 mm Hg) categories predicts the risk of recurrent bleeding and the chance of medical treatment failure. However, these pressures can be misleading; PV thrombosis may artifactually lower the wedged pressure, because it is a presinusoidal obstruction. Also, some patients who have gigantic varices decompressing the PV may actually have normal portal pressures (Fig. 76E.3) even when measured directly in the PV.

If the patient has a large umbilical vein collateral on the anterior abdominal wall, this can be punctured using ultrasound guidance and used as a pathway to feed a catheter into the portal system. Through this catheter, contrast can be injected to delineate the portal anatomy, plus the catheter can be positioned to act as a real-time target for the transhepatic needle passes (Fig. 76E.4). Unfortunately, such large umbilical collaterals are available in the minority of cases.

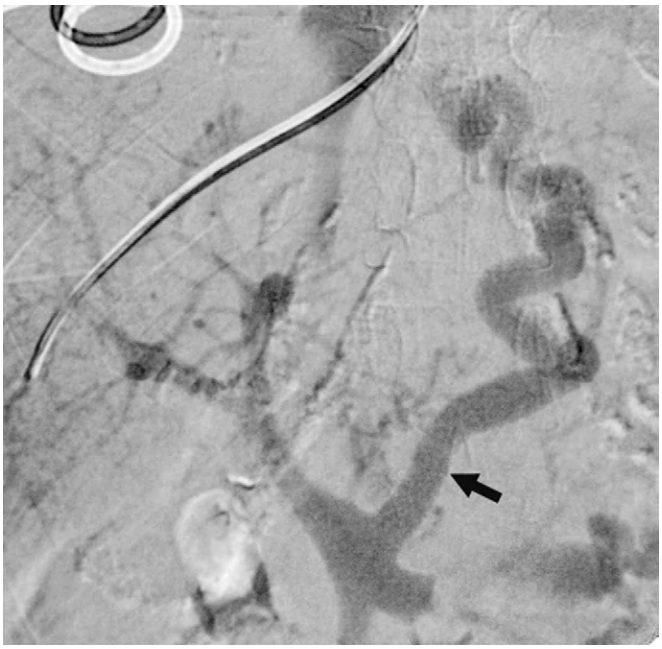


FIGURE 76E.3. Wedged hepatic venogram in a patient with long-standing portal hypertension who has a gigantic coronary vein (*arrow*), larger even than the main portal vein. In this patient, the coronary vein decompressed the portal system so well that the initial measured portal pressures were normal.

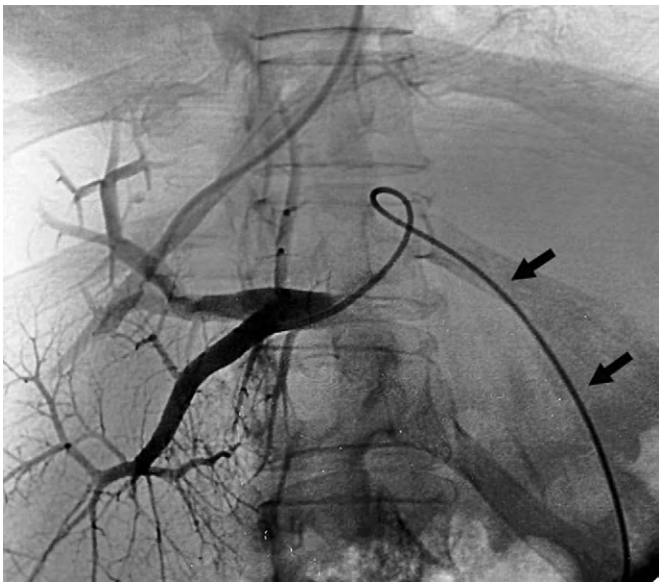


FIGURE 76E.4. A catheter has been introduced via the umbilical vein (*arrows*) through the left portal vein, and it is positioned in the right portal trunk, where contrast is injected to define the target for the transparenchymal puncture.

Next, a needle must be advanced into the portal system. Typically the preferred target is the trunk of the main right PV. Puncturing at the portal bifurcation is not recommended, because this is often extrahepatic, and access here increases the risk of intraabdominal hemorrhage. Access in more peripheral portal branches often leads to a tortuous tract that is more difficult to properly dilate and stent. Occasionally, the right portal trunk is a less optimal target than the left PV. This occurs when the right PV is thrombosed, or when the right lobe is shrunken and elevated, as can occur in patients with severe cirrhosis and massive ascites. In the later setting, the angle from the IVC to the right PV is often too acute to allow easy passage of the rigid transjugular needles. Middle HV to left PV tracts are often straighter and easier to create in this situation. A recent study (Chen et al, 2009) also found that TIPS created through the left PV were associated with a significantly lower rate of encephalopathy than right PV TIPS, but this has not been validated in larger studies.

An interesting variation on TIPS is the direct intrahepatic portosystemic shunt (DIPS) procedure (Hoppe et al, 2008). With this technique, intravascular ultrasound is used to guide a needle puncture directly from the IVC into the PV through the caudate lobe. The reported advantages of this are that the needle puncture is continuously monitored and guided into the IVC, in contrast to the relatively blind needle passes done during a TIPS procedure. In addition, the intrahepatic tract is relatively shorter than for a TIPS. This theoretically should lead to better patency, and in fact, primary patency at a mean of 256 days follow-up was 100% (Hoppe et al, 2008). Despite these potential advantages, DIPS has not been widely adopted.

Because accessing the PV is the most difficult part of a TIPS procedure, many investigators have tried to develop new

guidance mechanism that will aid this portion of the procedure. One promising approach is the use of magnetic resonance (MR) guidance (Arepally et al, 2006; Kee et al, 2005). Although MR guidance allowed the PV to be accessed with relatively few needle passes, it did seem to add to the complexity of the cases. In the study by Kee and colleagues (2005), the average procedure time was 2.5 hours, whereas in general practice, a TIPS can often be performed within 60 to 90 minutes.

Immediately after advancing a catheter into the PV, it is necessary to confirm its position with contrast venography. During the transhepatic puncture, it is possible to access a hepatic arterial branch instead of the PV. If this is not recognized, and the operator proceeds with the case, a hepatic artery to HV shunt may be created with disastrous results (Kerlan et al, 1994). Initial venography also serves to identify the point of entry into the portal system. This has implications for the safety of completing the procedure, because access into the main PV or the portal bifurcation is often an extrahepatic segment of the vein, and balloon dilating such a tract may lead to intraperitoneal hemorrhage (Kim et al, 2001).

Pressures should next be measured via the PV catheter and in the right atrium via the side arm of the access sheath. This is necessary to establish the baseline pressures and portosystemic gradient, not only to confirm portal hypertension but to provide a baseline value against which the TIPS results will be compared. However, as mentioned before, it is important to recognize that portal pressures may actually be normal in cases with clearly documented portal hypertension, if the varices or retroperitoneal collaterals are large enough to decompress the portal system completely. As long as the portal hypertensive complications are well documented—for example, endoscopic visualization of bleeding esophageal varices—TIPS is still indicated despite the low pressures, because this will redirect blood flow away from these large bleeding varices.

The next step is to measure the length of the tract to determine what size device to implant. This is done with a catheter with radiopaque markers on it. The tract is measured from the entry point in the PV back to the HV-IVC junction. It has been shown that patency is lower if the stent does not extend all the way to this point (Clark et al, 2004), because stenoses can form above a TIPS even in short segments of uncovered HV. Identification of the HV-IVC junction can be challenging, because the rapid inflow of unopacified IVC blood may hinder accurate localization of HV insertion. Positioning the sheath near the HV-IVC junction and injecting forcefully into the sheath to reflux contrast down the IVC is a useful maneuver to help define the HV-IVC junction (Fig. 76E.5).

The initial step for creating the shunt is to use a balloon catheter to dilate the parenchyma along the tract. This is typically done with an 8-mm low-profile balloon, because advancing larger, higher profile balloons into the PV can be very difficult initially. The dense periportal fibrosis can cause significant resistance to advancement of the catheter. A stiff guidewire, such as an Amplatz stiff wire (Cook, Bloomington, IN), is necessary to support the catheter.

Next, the tract has to be held open by deploying a stent. Although TIPS was first done with bare metal stents, restenosis became a significant problem. Primary patency decreased to 50% within 6 to 12 months, and many of the stenoses were due to pseudointimal hyperplasia in the shunt, as it coursed through the liver parenchyma (Saxon et al, 1998; Sterling & Darcy, 1997). Pathologic and histologic studies suggested that this

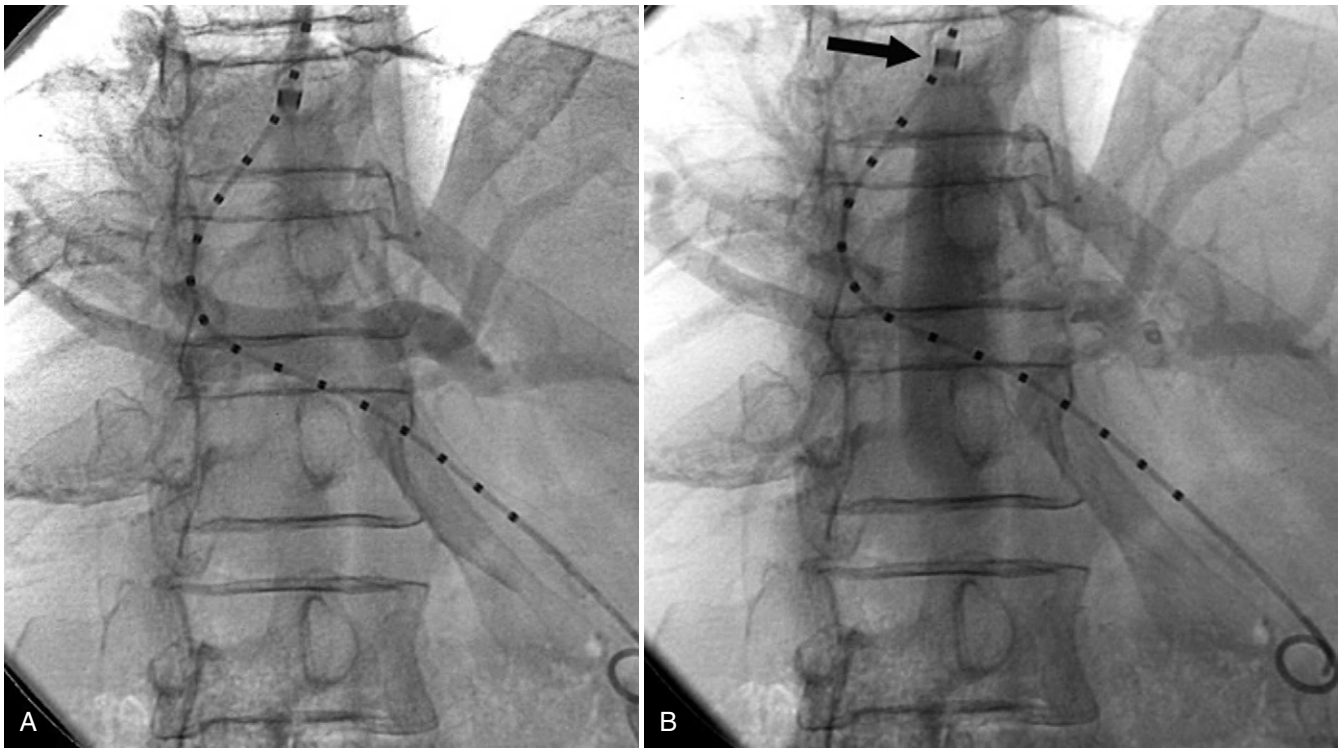


FIGURE 76E.5. A, Initial injection via the catheter in the portal vein does not define the hepatic vein–caval junction optimally. **B,** Injection via the sheath (*arrow*) positioned near the hepatic vein–caval junction better defines the location of the inferior vena cava.



FIGURE 76E.6. Transjugular intrahepatic portosystemic shunting created with a Viatorr device. The radiopaque band (*arrow*) defines the junction between the uncovered stent and the graft-covered portion, which lines the parenchymal tract.

pseudointimal hyperplasia was stimulated by communication with biliary epithelium, resulting from traumatic entry into the liver parenchyma during tract formation (LaBerge et al, 1993; Stout et al, 1995). To correct this problem, investigators started using stent grafts to exclude the liver parenchyma and bile from the shunt lumen.

One stent-graft device specifically designed for TIPS that has FDA approval for that application, the Viatorr device, has a 2-cm long, bare stent component that sits in the PV and a stent-graft segment—lengths vary from 4 to 8 cm—covering the parenchymal tract (Fig. 76E.6). Studies to date have shown significantly improved patency compared with stent grafts created with bare metal stents (Bureau et al, 2007; Tripathi et al, 2006; Vignali et al, 2005). An Italian multicenter study (Vignali et al, 2005) reported primary patency of TIPS created with Viatorr to be 76% at 2 years. Similarly, a randomized trial between Viatorr and bare-stent TIPS reported 2-year primary patency rates of 76% and 36% respectively (Bureau et al, 2007).

When stenoses do occur in patients with a Viatorr TIPS, they almost always develop in a short segment of uncovered HV above the shunt. For this reason, it is recommended to carry the stent graft right up to the HV-IVC junction. As radiologists gain more experience with proper placement of TIPS shunts, HV stenoses are likely to become even less of an issue. The improved patency of stent grafts now makes it feasible to use TIPS for long-term portal decompression rather than simply as a bridge to liver transplantation.

One concern that arose when stent grafts were first used was an increased potential for encephalopathy; however, for reasons that are not obvious, encephalopathy rates were actually lower with stent grafts than with bare metallic stents (Bureau et al, 2007; Tripathi et al, 2006). Along with the improved patency, a stent-graft TIPS provided better control of variceal hemorrhage in several studies (Angeloni et al, 2004; Bureau et al, 2007; Tripathi et al, 2006), although differences in survival did not reach statistical significance. Angermayr and colleagues (2003) did, however, show a significant improvement in survival: 76% at 3 years versus 62% for bare-stent TIPS.

Stent diameter is another variable that comes into play when choosing a device. Viatorr stents come in diameters of 8, 10, and 12 mm. Although 12 mm bare stents were often used, this was primarily to compensate for the pseudointimal hyperplasia that would develop. Because this is not really an issue with the Viatorr device, 12-mm diameter shunts are rarely utilized. The choice between an 8- and 10-mm Viatorr usually hinges on the patient's condition, although the 8 mm devices tend to be favored for patients with preexisting encephalopathy or borderline liver function to reduce the degree of diverted portal blood flow; however, this approach has not been validated.

In order to deploy a Viatorr, a delivery sheath must be advanced into the PV. This is because the bare portion of the stent, the caudal 2 cm of the Viatorr, is constrained only by the delivery sheath: as soon as it exits the sheath, that portion of the device expands. The need to have the sheath in the PV is occasionally a problem. If the tract is tightly curved, the sheath may kink once the inner dilator is removed. If the kink is significant, the sheath may not be able to pass across the Viatorr device. Switching to a self-constrained stent graft, such as the Fluency (Bard Peripheral Vascular, Tempe, AZ), allows passage of the device without needing to get the sheath through the tract into the PV (Fig. 76E.7). One theoretical disadvantage to this stent graft is the potential to occlude flow into the portal branches, because it is totally covered by PTFE, although this feature does not appear to increase the complication rate.

After stent-graft deployment, repeat portal venogram is performed, and pressure measurements are taken to confirm proper placement of the device, assess for complications related to stent placement, and ensure that the portal system has been adequately decompressed. The venogram should show good flow through the shunt and no further flow in varices or collateral pathways. Generally, the flow in the portal branches will also become hepatofugal toward the shunt, even if good hepatopetal flow was present prior to shunt creation. Pressure measurements should show a successful reduction in the portosystemic gradient. Typically, the target is to get the portosystemic gradient below 12 mm Hg, the commonly accepted threshold below which variceal bleeding is unlikely. Some speculate that resolution of ascites may require a slightly lower portosystemic gradient (PSG), down around 8 mm Hg (Boyer & Haskal, 2010). If the PSG is too high, careful venography and a pull-back pressure measurement are necessary to ensure that the tract is fully stented and that there are no kinks or thrombi that might be limiting flow through the shunt.

In some patients, the gastroesophageal varices may still fill on the post-TIPS venography despite adequate lowering of the PSG. This occurs in patients whose variceal channels are grossly enlarged. These pathways may be so large that the resistance to flow through them is the same or less than the resistance to flow through the TIPS; therefore embolization of these vessels may be needed to eliminate flow through them and redirect flow through the shunt.

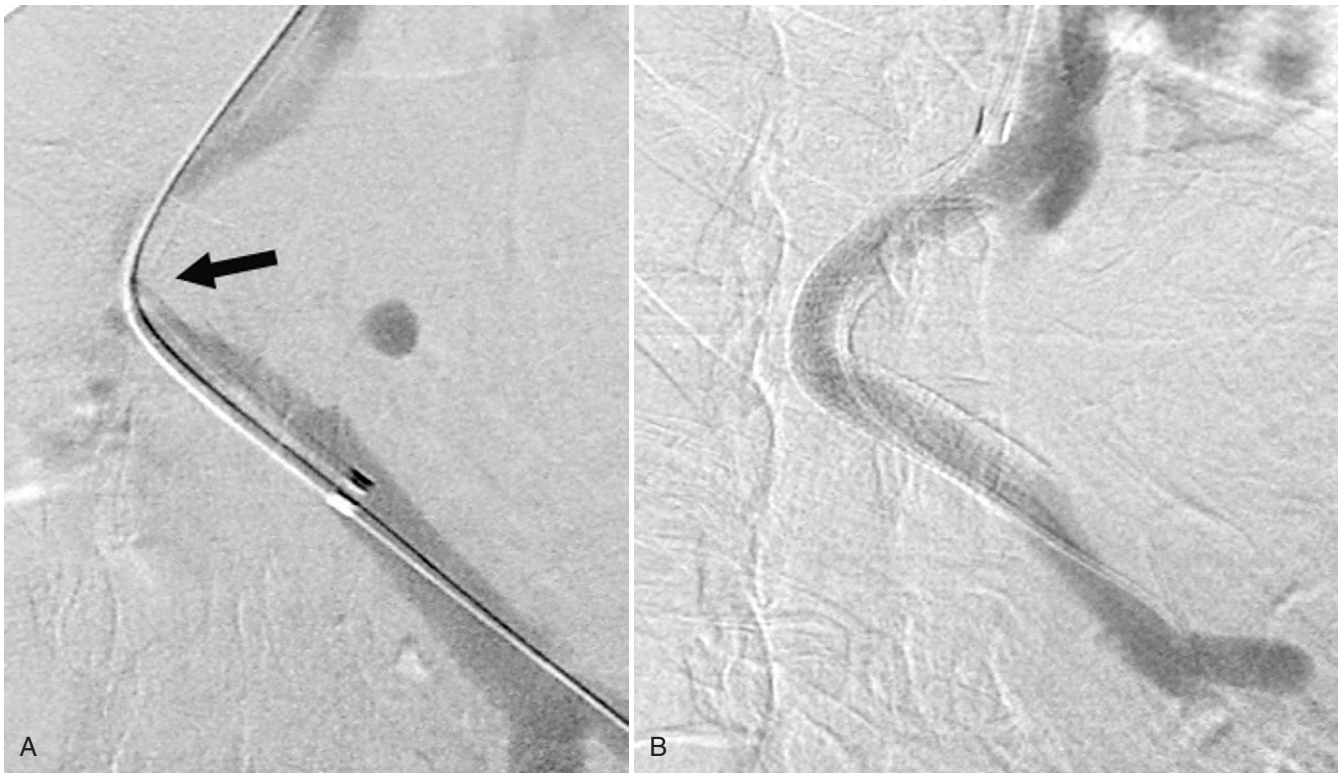


FIGURE 76E.7. A, Venogram done after advancing the sheath into the portal vein shows a kink (*arrow*) in the sheath; the Viatorr device could not be advanced past it. **B,** Final portal venogram after completing transjugular intrahepatic portosystemic shunting with a Bard Fluency stent graft.

SPECIAL TECHNICAL CONSIDERATIONS

Budd-Chiari Syndrome

When TIPS is being considered in patients with Budd-Chiari syndrome, the hepatic veins may be extensively thrombosed such that catheterization is not possible. In this situation, the needle that passes across the liver parenchyma may need to start from the HV stump, if it can be engaged, or directly from the IVC itself (Gasparini et al, 2002). The retrohepatic segment of the IVC is approximately 5 to 6 cm in length; to avoid creating a tract with a greater chance of hemorrhage, the needle passes should start from within this segment of the vein. Whereas a normal puncture from the right HV involves anterior and medial direction of the needle, a needle pass directly from the IVC must be directed more laterally. As with other indications, use of graft-covered stents improves outcomes. In a recent study looking specifically at Budd-Chiari patients (Murad et al, 2008), the 2-year primary patency was 12% for bare stents versus 56% for stent grafts.

Portal Thrombus

Performing TIPS in patients with portal thrombosis requires a moderate level of expertise. One of the major technical challenges is accessing the PV. Although this can often still be accomplished from a transjugular route, use of a percutaneous transhepatic tract is sometimes needed to initially recanalize the PV (Radosevich et al, 1993). Once access is established, it is usually beneficial to deploy the stents across the parenchymal tract even before attempting lysis of the portal thrombus. TIPS provides a great conduit for using mechanical thrombolytic devices in the PV. Often, the thrombus is more chronic in nature and does not easily lyse, thus extending stents down the main PV to a patent segment below the thrombus is frequently necessary to establish good flow through the shunt. Because these stents can complicate a subsequent liver transplant operation, it is important to discuss the likelihood and timing of transplantation prior to placing a stent in the main PV. When the patient is close to receiving a new liver, we have elected to not perform TIPS rather than risk increasing the complexity of the transplant operation.

Polycystic Liver

A polycystic liver presents additional challenges, both from the presence of the cysts and because of the liver's expanded size. Preprocedure CT scans can be used to analyze the distribution of cysts and their position relative to the right hepatic and PVs. The planned tract may be adjusted based on this analysis. If aspiration is done while passing the needle across the liver parenchyma, entry into a cyst is recognized by aspiration of clear fluid; the needle can then be redirected around the cyst. Because polycystic livers are usually expanded by the cysts, the parenchymal tract will tend to be longer than a TIPS in nonpolycystic livers. Thus multiple stents may be needed to fully cover the parenchymal tract.

References are available at expertconsult.com.

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CHAPTER 79B

Cystic hepatobiliary neoplasia

Olivier Farges and Valérie Paradis

OVERVIEW

The vast majority of nonparasitic cystic lesions of the liver are simple cysts. They are unilocular, do not communicate with the biliary tree, have a serous content, and although the epithelium does divide to account for volume expansion, they are not considered a tumor and have no malignant potential. Furthermore, they do not tend to recur following partial resection. These lesions are described in detail elsewhere in this textbook (see Chapter 69A). Although primary or secondary solid hepatic malignancies may become cystic as a result of tumor necrosis, it is extremely rare for them to be totally cystic, although this has been described in case reports for embryonic liver sarcoma, malignant fibrous histiocytoma, or metastases from a variety of primaries, most including neuroendocrine tumors or even colorectal primaries (Yang et al, 2009; Kim et al, 2009; Ding et al, 2006; Sugawara et al, 2000).

Primarily cystic hepatobiliary neoplasms that constitute another group of cystic tumors are extremely rare. They are of biliary origin and comprise both benign (with malignant potential) and malignant tumors that have initially been given the names of *cystadenoma* and *cystadenocarcinoma* (Ishak & Kamal, 1994); however, increasing evidence, in particular from Asian authors, suggests that biliary cystic neoplasia comprises a wider group of entities that resemble those described in the pancreas as being either mucinous cystic neoplasms (MCNs) or intraductal papillary mucinous neoplasm (IPMNs) (Zen et al, 2006a, 2006b). The main difference relates to the presence or absence of an ovarian stroma (OS) and whether a luminal communication exists between the tumor and the bile ducts.

No international consensus has been reached, and detailed characteristics of these tumors are not always described in the literature, casting some confusion on previous descriptions and reports of cystadenoma. Although the same confusion has been observed for cystic tumors of the pancreas, the clinical and pathologic differentiations of these two tumors are now accepted worldwide, now that a consensus on the definition of *pancreatic* MCNs has been reached (Kloppel et al, 2000; Suzuki et al, 2004). A second problem in analyzing the literature is that because of the rarity of the tumor, the number of large series is very limited, and most references are case reports.

DEFINITION

The initial definitions of cystadenoma by Edmondson in 1958 and by Wheeler and Edmondson in 1985 were strict and included three distinctive features: the lesion should be 1) multilocular (composed of multiloculated cysts) 2) lined by a columnar epithelium, and 3) accompanied by a densely cellular ovarian-like stroma.

This definition was revisited in 1994 by Devaney and colleagues following retrospective analysis of a larger series of 70 patients. Although most fulfilled the criteria set out by Edmondson and Wheeler, that definition was considered too restrictive, as the presence of an OS was inconsistently observed. Furthermore, not all cystadenoma-like lesions they saw were multilocular, and the epithelium lining was not exclusively of the columnar type; it was associated in one third with a cuboidal epithelium. This led the authors to suggest that lesions diagnosed as cystadenoma (or cystadenocarcinoma) should include cystic tumors both with and without OS as well as those having a unilocular gross appearance. More precisely, only 14% of the tumors they observed lacked OS, and only a single patient had a unilocular tumor, which actually was a cystadenocarcinoma.

Although being a landmark study by showing that cystadenoma-like lesions encompass different entities, those with OS exclusively observed in women and those without observed in both genders, with potentially different courses, which will be discussed below; this revision might have introduced some confusion, as detailed pathologic description of tumors subsequently reported as being cystadenoma (cystadenocarcinoma) has not always been provided, and some occasionally resemble atypical benign cysts or cystic forms of intrahepatic cholangiocarcinoma, rather than genuine cystadenoma (or cystadenocarcinoma), on the imaging or pathologic pictures illustrating these series and case reports.

Recently it has been suggested that by differentiating biliary cystic tumors based on their stroma and communication between the tumor and the bile duct, two groups of biliary tumors could be identified that are the counterparts of pancreatic cystic neoplasms. The first group has OS, typically does not communicate with the bile duct, and is the biliary counterpart of pancreatic mucinous cystadenoma. The second group lacks OS, communicates with the biliary ducts, and is sometimes referred to as *intraductal papillary mucinous neoplasm of the bile duct* (IPMN-B), similar to the intraductal papillary neoplasm of the pancreas. A consensus has not been reached yet on a naming convention, but in any case, most agree that only those tumors with OS should be termed *cystadenoma*.

HEPATOBILIARY CYSTADENOMA WITH OVARIAN STROMA

The most classic primary cystic tumors of the liver are hepatobiliary cystadenoma. Being of biliary origin, these tumors may occur anywhere along the biliary tree, including the common hepatic duct, cystic duct, or gallbladder; but the most frequent location, found in 83% to 94% of the patients, is the liver (Devaney et al, 1994; Buetow et al, 1995). These tumors are well known because of their inherent risk of malignant transformation, common to all adenomatous lesions, although this risk has not been precisely quantified.

Incidence

Cystadenomas are exceedingly rare. No accurate incidence estimates are available, but the largest series included 52 patients (Devaney et al, 1994), and most studies since then have comprised fewer than 10 patients; in the early 2000s, it was estimated that fewer than 200 patients had been reported (Duchini, 2001). It is frequently quoted that intrahepatic cystadenomas constitute fewer than 5% of cystic lesions of the liver based on an old report (Ishak et al, 1977), but this figure is likely overestimated; it has since become obvious that the prevalence of simple cysts of the liver in the adult population is higher than previously thought.

Pathology (See Chapter 78)

Cystadenomas are almost always solitary, and they may range in size from less than 1 to 40 cm; they are generally large, with a mean diameter of 15 cm (Buetow et al, 1995). Cystadenomas have been reported to develop equally in the right and left liver or to involve both lobes (approximately 33% each) (Devaney et al, 1994; Akwari et al, 1990); however, a striking feature in our experience, as well as in recent series, is the very high proportion of tumors occurring in the left paramedian section (segment IV) (Daniels et al, 2006; Lewin et al, 2006; Seo et al, 2010). Pictures of cystadenoma provided in the literature also show tumors in this location almost exclusively; an example is shown in Figure 79B.1.

Cystadenomas are grossly lobulated and multiloculated and usually contain clear to mucinous fluid (Buetow et al, 1995). Hemorrhagic fluid may be present (Lewin et al, 2006), but this is very rare and should raise the suspicion of malignancy (Buetow et al, 1995). A bilious content is similarly very unusual (Buetow et al, 1995), as lack of communication with the biliary tree is a distinctive feature; however, fistulization of cystadenoma in the biliary tree has been reported (Hanazaki, 1996; Yi et al, 2009), the same as for pancreatic mucinous cystadenoma, which may explain the bilious content.

The internal lining is generally smooth but may contain microscopic, or more rarely macroscopic, polypoid lesions projecting into the lumen (Fig. 79B.2). This internal lining has three distinct layers: 1) an epithelial layer, 2) a mesenchymal stroma, and 3) an outer layer of collagen connective tissue that separates it from the adjacent parenchyma (Fig. 79B.3).

The epithelial lining, as for pancreatic cystadenoma, consists of glandular, nonciliated cells arranged in a single, flat row with occasional papillary or polypoid projections, pseudostratifications, and cryptlike invaginations. In two thirds of the patients, the epithelium is columnar, but in one third, it consists of a combination of columnar and cuboidal epithelium. The epithelial lining may show denuded areas with chronic inflammation and hemorrhage. The columnar cells contain histologically benign appearing, basally located nuclei and intracellular mucin. The lining epithelium occasionally shows papillary infoldings, and mild epithelial atypia with a slight increase in the size of the basally located nuclei has been reported to be at least focally present in most patients. More severe dysplasia consisting of a multilayer appearance of hyperchromatic cells with loss of polarity appears much less frequently. Foci of intestinal metaplasia are also rare, seen in the form of numerous goblet cells. Atypia and metaplasia are suggestive of a high risk of malignant transformation (Devaney et al, 1994).

Phenotype has been further characterized in a limited number of patients. The epithelium shows strong and diffuse cytoplasmin staining with antibodies against CEA and CA19-9, whereas CA-125 staining is focal or absent (Subramony et al, 1993; Logroño et al, 2002). It also stains positive for CK-7, CK-19, CK-8, and CK-18 (Abdul Al et al, 2007), which supports a biliary origin, and it is negative for inhibin-α (Owono et al, 2001; Abdul Al et al, 2007), vimentin (Owono et al, 2001), and estrogen or progesterone receptors (Daniels, 2006), and CD56 is only expressed focally (Gütgemann et al, 2006).

The *stroma* consists of a compact arrangement of bland, spindle-shaped cells with round to oval nuclei. This appearance is reminiscent of OS, hence the name given to these tumors; but it has also been found to resemble the primitive mesenchymal elements associated with the developing biliary system in the fetus. This stroma may be abundant in some patients and focal in others, but mitotic activity is not prominent. It expresses estrogen and progesterone receptors, as does the stroma of pancreatic cystadenoma (Daniels et al, 2006; Weihing et al, 1997); α-inhibin, a gonadal protein that has a more limited expression

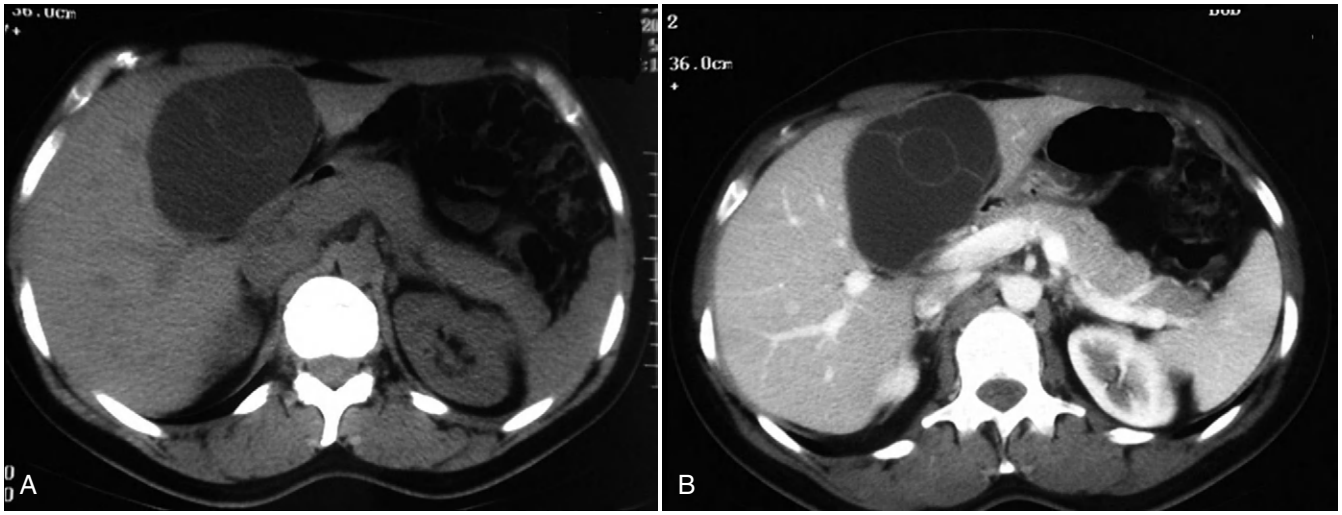


FIGURE 79B.1. Cystadenoma with ovarian-like stroma. The cyst has a thin wall and septa that enhance after injection of contrast agent (**B**). Note that the tumor is in segment IV, which occurs frequently.

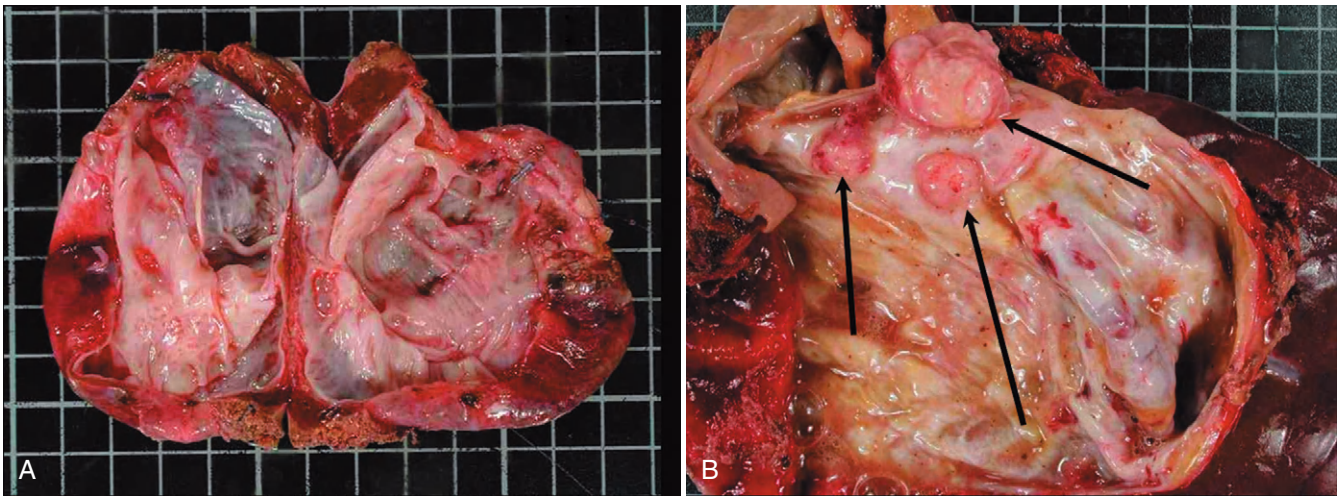


FIGURE 79B.2. Cystadenoma with ovarian-like stroma. The internal lining is smooth but may contain microscopic (**A**) or macroscopic (**B**) polypoid lesions.

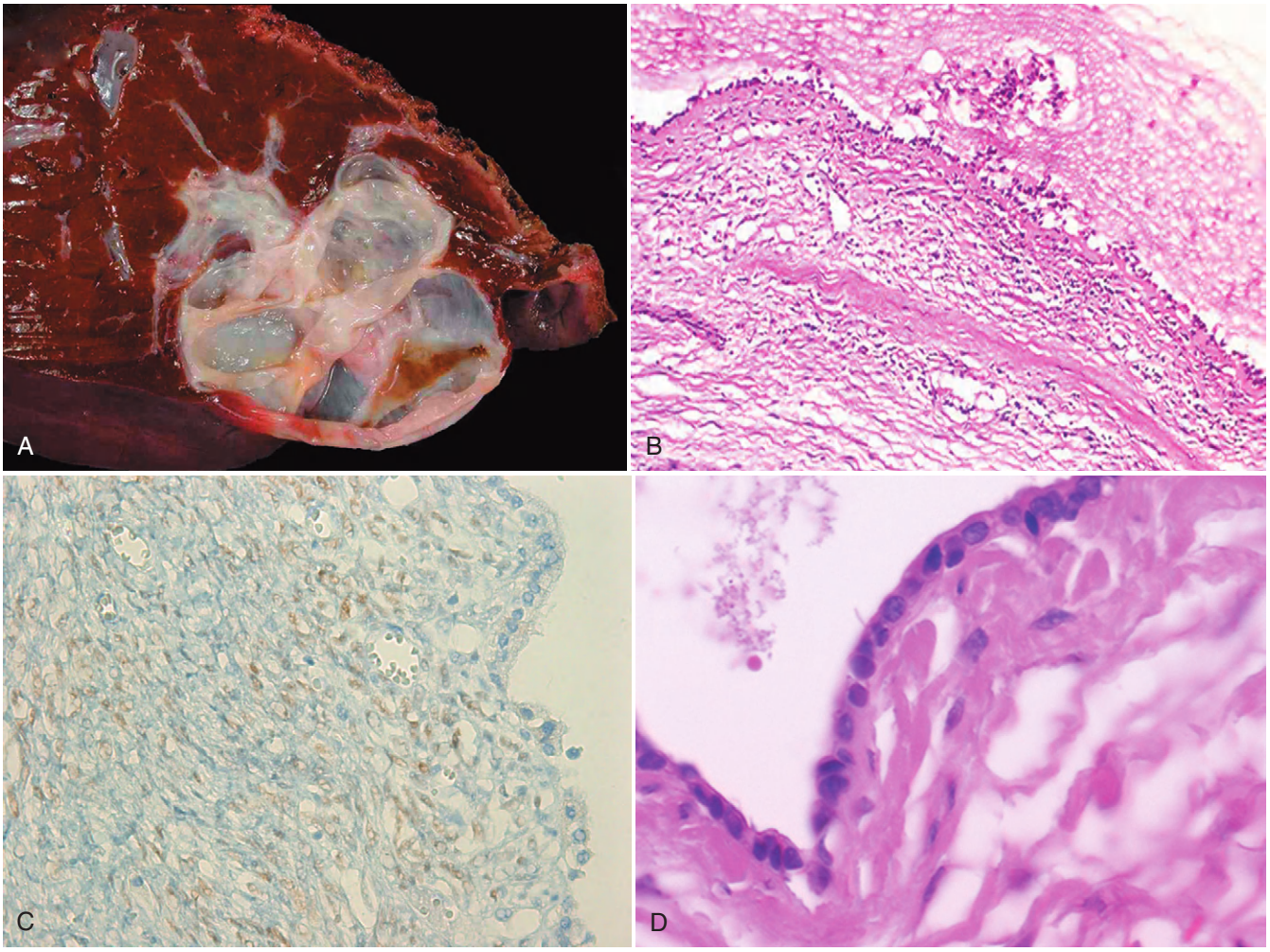


FIGURE 79B.3. Cystadenoma with ovarian-like stroma. **A,** Macroscopic view showing a multilocular cyst. **B,** Hematoxylin and eosin staining demonstrates a regular epithelial lining covering a densely packed, ovarian-like stroma and a hyalinized fibrous band that separates the cyst from the adjacent liver. **C,** Presence of progesterone-receptor–positive cells in the stroma. **D,** Histology of a simple biliary cyst composed of an unstratified epithelium of small cuboidal cells lining a fibrous wall is shown for comparison.

in the sex cord–stromal tissue, is also expressed in both hepatic and pancreatic mucinous cystadenoma (Ridder et al, 1998; Lam et al, 2008) and in sex cord–stromal tumors. They are immunoreactive with α–smooth muscle actin, vimentin, but also desmin. There is no immune reaction with CEA, CA19-9, or CA-125 (Devaney et al, 1994; Logroño et al, 2002).

A *densely hyalinized pseudocapsule* surrounds the tumor and separates it from the adjacent liver tissue, which explains how these tumors can be enucleated.

Despite the similarities between hepatic and pancreatic mucinous cystadenomas, few studies have compared the phenotypes of both lesions. One reported denser and more abundant stroma, more intense estrogen or progesterone receptors, and more α-inhibin in hepatic than in pancreatic cystadenomas, but the significance of this is unclear (Lam et al, 2008).

Risk Factors and Origin

There are no clearly identified risk factors apart from gender, as cystadenomas with OS are exclusively observed in women. However, a history of previous oral contraceptive use does not appear to be a distinctive feature (Devaney et al, 1994). Several hypotheses have been raised based on some pathologic features of the tumor, most notably the presence of an ovarian-like stroma or the occasional presence of eosinophilic or endocrine cells. It is still unclear whether cystadenomas are of congenital origin or are acquired neoplastic lesions.

The resemblance is striking among cystadenomas with OS located in the liver, pancreas, retroperitoneum, and ovary (Bakker et al, 2007; Nelson et al, 1988; Turbiner et al, 2007). The particular OS common to these locations contains estrogen and progesterone receptors and α-inhibin (Lam et al, 2008). These similarities suggest a common pathway of tumor development, although simultaneous occurrences of hepatic cystadenoma with pancreatic (Brachet et al, 2007) or ovarian cystadenoma (Skopelitou et al, 1996) are exceedingly rare.

One hypothesis is that during embryonic development, ectopic ovarian cells would have migrated to the liver or pancreas, released hormones and growth factors, and caused endodermally derived epithelium to proliferate and finally to form a tumor (Zamboni et al, 1999). The right and left primordial gonads are indeed located directly under the diaphragm prior to their descent, at the level of the dorsocranial side of the liver and the tail of the pancreas respectively. Furthermore, the cells covering the gonads show an activated morphology in contrast to the peritoneal epithelium elsewhere (Erdogan et al, 2006), which suggests that they have the ability to detach from the gonadal surface, cross the peritoneal cleft, and attach to the peritoneal surface of nearby organs. This hypothesis would explain the predominance of cystadenoma in the body or tail of the pancreas, rather than in the head, as well as the apparent predominance of liver cystadenoma in segment IV. Splenogonadal fusion has also been documented (Duncan & Barraza, 2005), and demonstration of endocrine cells in about 50% of cystadenomas is a distinctive feature (Terada et al, 1997) compatible with the hypothesis of these tumors developing from peribiliary glands.

The OS resembles the primitive embryonic mesenchyma of embryonic gallbladder and large bile ducts that contribute to the connective tissue surrounding the bile ducts (Subramony et al, 1993), and it has therefore also been suggested that these tumors could derive from ectopic embryonal tissue destined to form the gallbladder (Subramony et al, 1993) or from ectopic embryonic rests of primitive foregut sequestered within the liver (Wheeler & Edmondson, 1985).

Presentation

Intrahepatic biliary cystadenoma with an OS is exclusively observed in women. Age at diagnosis is highly variable, between 1 (Beasley et al, 1986) and 70 years, but it peaks in the fourth or early fifth decade. In most patients, the tumor is discovered during the workup of epigastric or right upper quadrant pain or vague abdominal complaints that include abdominal discomfort or swelling. Palpation of an abdominal mass that moves freely with respiration is also a classic circumstance of diagnosis. As the tumor may grow to a considerable size, a gradual increase in abdominal girth and/or compression of the stomach or duodenum may also occur; however, because of the slow progression of the neoplasm, the onset of symptoms tends to be insidious and to have evolved for a prolonged period of time before treatment (Akwari et al, 1990; Thomas et al, 2005). This may explain why most reported cystadenomas are large tumors. With the increasingly liberal use of imaging to investigate even the most minor symptoms, cystadenomas are often discovered incidentally, and it is possible that a significant proportion are not identified or are mistaken for simple cysts (Hara et al, 2001).

More acute episodes of pain have been reported in up to 35% of the patients, and most of these are related to biliary obstruction (Akwari et al, 1990; Erdogan et al, 2010). This is biologically witnessed by concomitant cytolysis or cholestasis. Jaundice or itching (Siriwardana & Pathirana, 2009) may also be present, whereas cholangitis is rare. Typically, such episodes are transient, and any jaundice tends to resolve spontaneously, which is compatible with the migration of mucous material or tumor embolus from the cyst into the bile duct (Fig. 79B.4). Such tumor protrusion in the bile duct lumen has been reported even for small cystadenomas less than 4 cm in diameter (Erdogan et al, 2006). An alternative mechanism of obstruction is simple compression of the biliary confluence by the cystadenoma. Other causes of acute presentation have included tumor rupture (Lempinen et al, 2005), superinfection, bleeding (Lewis et al, 1988), and caval compression (Catto et al, 1999), but these are rare.

Diagnosis

Differential Diagnosis

Apart from the other cystic tumors addressed in this chapter, most notably cystadenocarcinoma, the main differential diagnosis of cystadenoma is simple cysts that have become atypical on imaging studies as a result of intracystic bleeding (Kitajima et al, 2003) or previous sclerotherapy (Takayasu et al, 2003; see Chapter 69A). The risk of mistaking a cystadenoma for a benign cyst is that this lesion may be treated by simple unroofing, which is an inappropriate treatment associated with a high risk of recurrence (see Management below); to mistake a simple or atypical cyst for a cystadenoma is to perform an occasionally risky and unwarranted resection, because simple cysts do not require complete resection. Considering the very high incidence of simple cysts, the latter is probably much more common, and it has been shown that a cystadenoma-like lesion is almost as likely to be a simple cyst as to be a cystadenoma (Shimada et al, 1998; Teoh et al, 2006; Koea et al, 2008; Seo et al, 2010). Clinical history is totally unreliable in the diagnosis of hemorrhagic

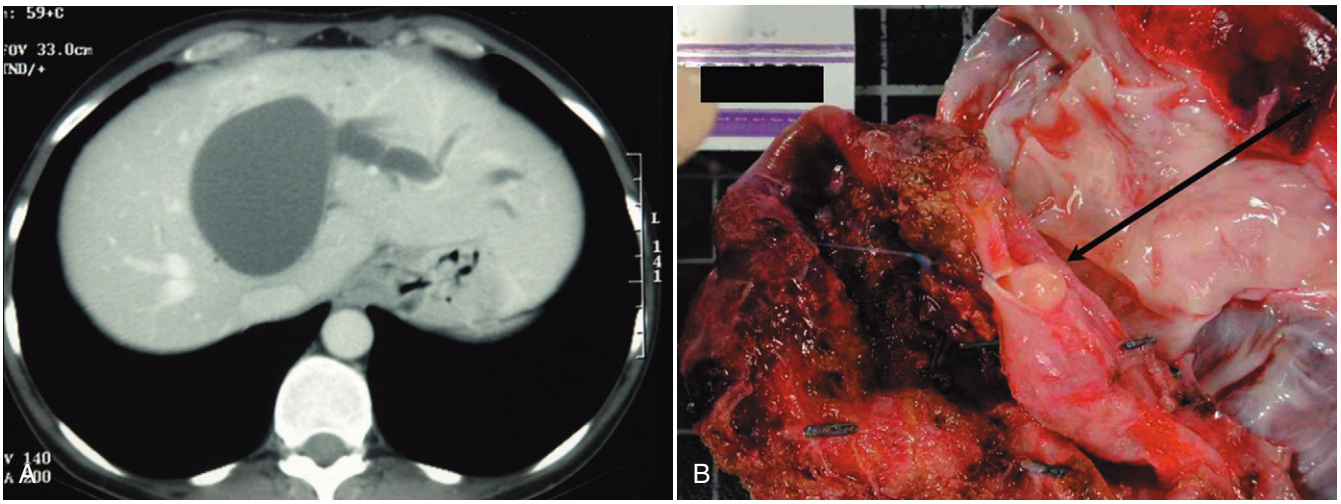


FIGURE 79B.4. Cystadenoma with ovarian-like stroma with tumor protrusion in the bile duct. **A,** Note the presence of dilated bile ducts upstream of the cyst located in segment IV. **B,** Tumor protruding into the left bile duct on the resected specimen.

cysts, as intracystic hemorrhage can occur in the absence of any symptoms (Kitajima et al, 2003), and the diagnosis mainly relies on imaging.

Alternative differential diagnosis must include nonsuppurative granulomatous infection of a simple cyst (Kawashita et al, 2006), hepatic abscess (Yamamoto et al, 2009), echinococcal cysts (Ramacciato et al, 2006), mesenchymal hamartoma (Mori et al, 2008), ciliated hepatic foregut cysts, intrahepatic lymphangioma, cystic hemangioma, cystic forms of hepatocellular carcinoma (HCC) or intrahepatic cholangiocarcinoma, mucin-producing metastases from thyroid or colon carcinoma and cystic metastases of the ovary, of melanoma, and of kidney and neuroendocrine tumors (Del Poggio & Buonocore, 2008). They have also been occasionally confused with pancreatic cysts (Logroño et al, 2002).

Imaging

The characteristic ultrasonographic (US) finding for biliary cystadenoma is an anechoic mass with echogenic internal septations (Fig. 79B.5). Papillary projections into the cystic space may also be seen. On CT scans, the lesions appear as multiloculated hypodense masses with a well-defined wall. The content demonstrates fluid attenuation because of the presence of mucin, blood, or bile. Fine septal calcifications may occasionally be seen, and both the wall and the septations enhance following administration of contrast material (see Fig. 79B.1).

With magnetic resonance imaging (MRI), cyastadenoma is typically seen as a fluid-containing multilocular cyst with homogeneous high signal intensity on T2-weighted images and homogeneous low or isosignal intensity on T1-weighted images (Lewin et al, 2006). These signals may vary depending on the content of the cystic fluid. Mucinous fluid will appear with an isosignal, serous fluid with a hyposignal, and hemorrhagic fluid with an hyperintense signal that can only be seen in the lower part of a fluid-fluid level. Thin internal septal structures separate fluid-filled spaces. These, along with the wall of the lesion, are contrast enhanced (Fig. 79B.6).

Contrast US is a promising exploration that allows analysis of the vascularization of the cyst wall and septa, but it has been used infrequently. An intracystic structure of complicated simple cysts corresponds to clots and is not enhanced (Akiyama et al, 2008). Although the periphery of the cyst may show enhancement, this corresponds to compressed adjacent liver, and this should be differentiated from enhancement of the cyst wall of cystadenoma (see Fig. 79B.5).

As for other cystic lesions, CT scan is less reliable and accurate than US or MRI. Cystadenoma in particular may wrongly appear unilocular on CT scan, whereas US (Korobkin et al, 1989) and MRI (Lewin et al, 2006; Williams et al, 2001) will visualize the internal septa. Two additional features besides multilocularity may help in the differential diagnosis of simple cysts: they are frequently multiple (Vuillemin-Bodaghi et al, 1997), whereas cystadenomas are single lesions; and although biliary dilation has been considered uncommon, a mild enlargement upstream of the tumor is probably more frequent than previously thought—using higher resolution imaging, enlargement was observed in one to two thirds of the patients in recent series (Lim et al, 2007; Seo et al, 2010). Along the same line, an increase in serum alkaline phosphatase levels has recently been shown to be a feature distinctive from simple cysts (Seo et al, 2010).

Cytology and Tumor Markers

CYTOLOGY. Aspiration cytology is either nonspecific or it shows chronic inflammatory exudates with large numbers of neutrophils, lymphocytes, and macrophages. A few groups of nonatypical bland cuboidal to columnar epithelial cells, occasionally arranged in papillary clusters, may be seen (Logroño et al, 2002).

TUMOR MARKERS. Unlike for the pancreas, measurement of tumor markers in hepatobiliary cystic lesions has been infrequently performed, and results are confusing. Early case reports have pointed to a link between cystadenoma and CA19-9 by showing its expression by epithelial lining and by revealing increased intracystic and serum concentrations (Thomas et al, 1992; Lee et al, 1996). However, CA19-9 is also expressed by normal biliary epithelial cells, and very high levels have occasionally been measured in the bile of patients with various nontumoral conditions (Horsmans et al, 1997; Shimada et al, 1998; Ker et al, 1991). It is also expressed by the epithelium lining

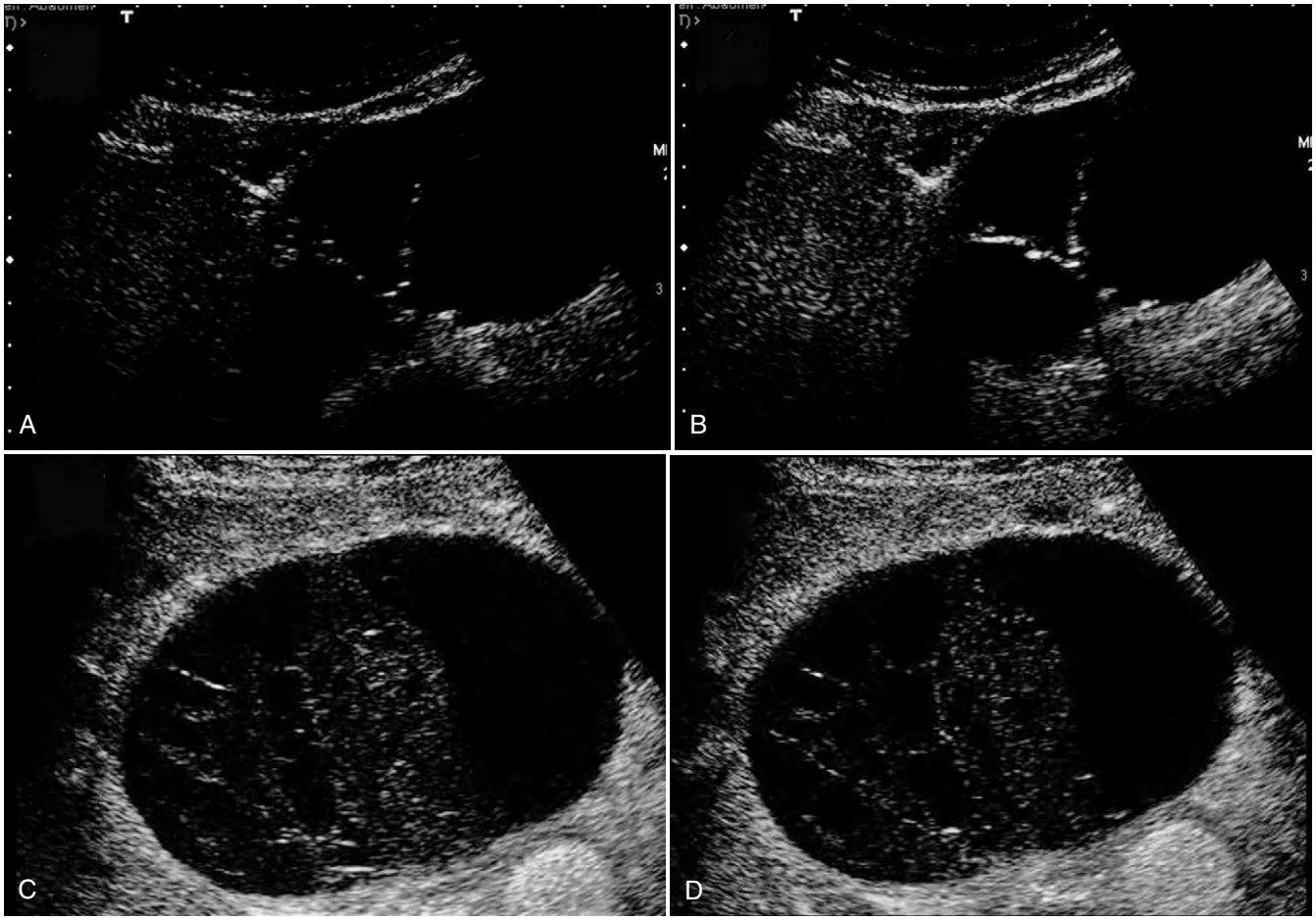


FIGURE 79B.5. Ultrasound (US) and contrast US of a cystadenoma with ovarian-like stroma (**A** and **B**) and of a hemorrhagic simple cyst (**C** and **D**). Normal US (**A** and **C**) and contrast US (**B** and **D**) are shown. The septa are enhanced in the cystadenoma, but in hemorrhagic cysts, the intracystic material corresponds to clots and does not enhance.

simple cysts of the liver (Park et al, 2006) and in the cystic fluid of simple cysts (Park et al, 2006; Choi et al, 2010). An increased serum concentration of CA19-9 in these patients has even been reported and can occasionally be very high, probably as a result of communication of the cyst with the circulation. Three studies have shown that cyst concentration (Choi et al, 2010; Seo et al, 2010) and serum concentration of CA19-9 (Park et al, 2006; Choi et al, 2010) are comparable in patients with cystadenoma and simple cysts. As will be discussed below, CA19-9 is also inaccurate in differentiating cystadenoma from cystadenocarcinoma (Horsmans et al, 1997).

It has also been suggested that a CEA concentration greater than 600 ng/mL in the supernatant of cystic liver lesions could accurately differentiate cystadenoma or cystadenocarcinoma from benign, nonmucinous cysts (Pinto & Kaye, 1989). The epithelial lining of cystadenoma indeed stains positive for CEA (Logroño et al, 2002); however, this has not been confirmed in subsequent studies, in which concentrations in cystadenoma and simple cysts were comparable (Shimada et al, 1998; Choi et al, 2010; Seo et al, 2010).

Complications

Cystadenoma with an OS is considered a precancerous lesion, as will be detailed below. Malignancy arises in most cases from the epithelium lining (cystadenocarcinoma), but sarcomatous transformation of the OS has also been reported (Akwari et al, 1990). No specific feature has been clearly linked to a higher risk of malignancy, apart from the presence of epithelial atypia (dysplasia) or intestinal metaplasia. The odds ratio for their association with malignancy has been calculated to be 8 (95% confidence interval [CI], 2.4 to 27.0) and 2.4 (95% CI, 1.2 to 3.5), respectively (Devaney et al, 1994).

Although cystadenoma with an OS by definition does not communicate with the biliary tree, fistulization in the bile duct may occur. Ensuing symptoms probably only occur in patients with a mucinous cystic content. Incidence of this complication is unknown, as it is only documented by endoscopic retrograde cholangiopancreatography (ERCP) and intraoperative cholangiography (IOC), which are not routinely performed. Other complications have included rupture in the peritoneal cavity, superinfection, bleeding, and caval compression, as previously mentioned.

Management

Cystadenomas require complete excision to prevent recurrence of symptoms and malignant transformation. Evidence that partial excision, aspiration, and external or internal drainage are ineffective is that recurrence has been noted very early on (Ishak et al, 1977; Wheeler & Edmondson, 1985; Lewis et al, 1988; Devaney et al, 1994) and that 40% to 50% of the patients

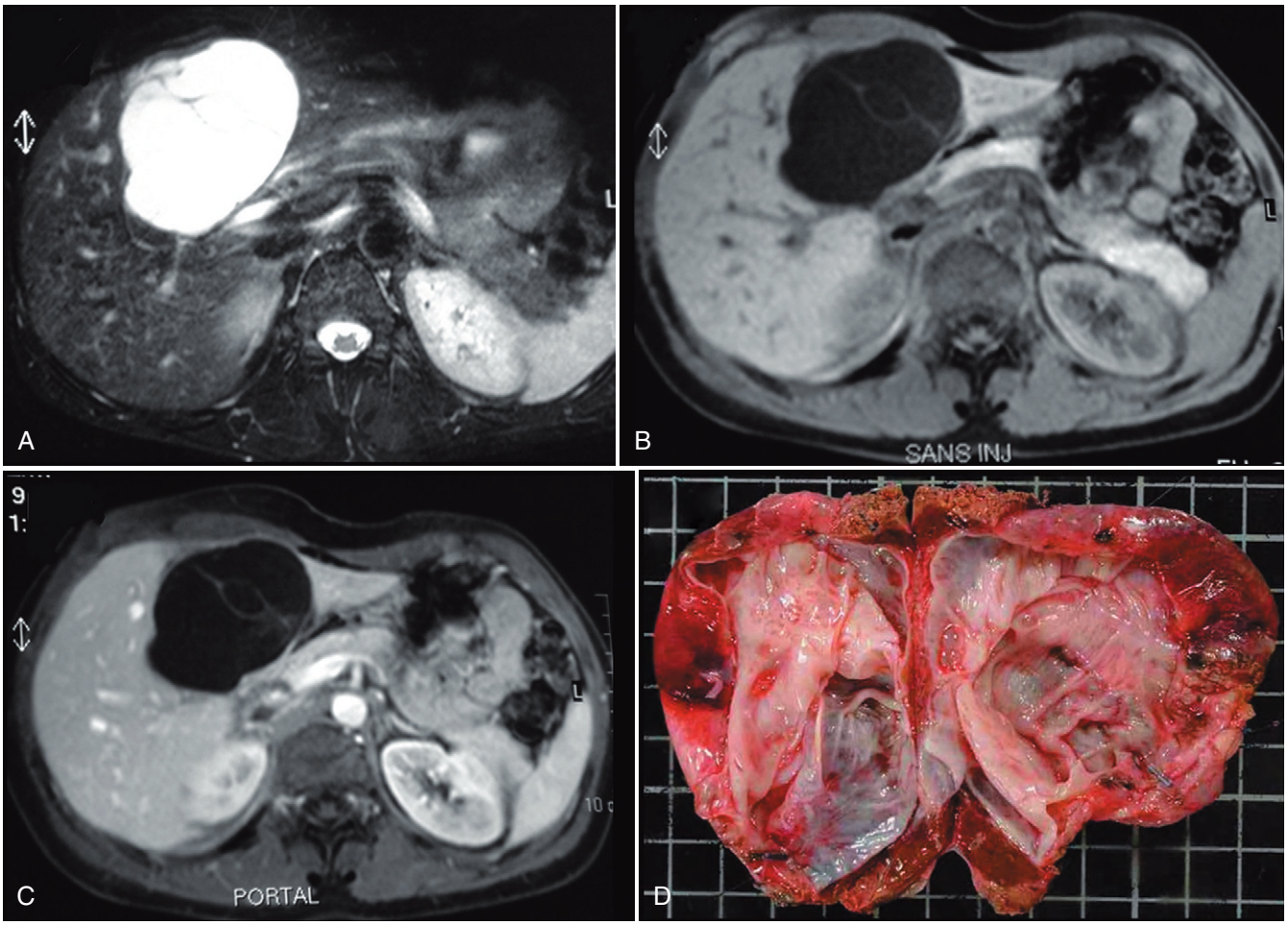


FIGURE 79B.6. Magnetic resonance imaging of a cystadenoma with ovarian-like stroma (**A**-**C**) and macroscopic view (**D**). Specimen is the same as in Figure 79B.1. **A,** The tumor is hyperintense on T2-weighted images. **B,** Septa are visible on T1-weighted images. **C,** Tumors enhance after injection of gadolinium.

culled by tertiary referral centers had undergone such previous treatments prior to referral (Hansman et al, 2001; Thomas et al, 2005; Vogt et al, 2005; Daniels et al, 2006; Delis et al, 2008). Updated evidence is shown in Table 79B.1. Recurrence occurs at a mean of 21 months but may be delayed up to 4 years (Vogt et al, 2005). This may explain why recurrence following incomplete resection has not been systematically observed, as most studies only have short-term follow-up (Barabino et al, 2004; Lewis et al, 1988; Manouras et al, 2008). Development of a cystadenoma following partial resection of a cystadenocarcinoma has also been documented (Woods, 1981; Devine et al, 1985; Lei & Howard, 1992; Akwari et al, 1990).

Fenestration of the cystadenoma with fulguration of the internal cystic lining has been attempted with occasionally adequate long-term success (Thomas et al, 2005), but experience is too limited to recommend this strategy. Although not documented, it is likely that some small cystadenomas mistaken for simple cysts have also been successfully treated with percutaneous ethanol injection. Ethanol is indeed effective in the management of simple cysts, hydatid disease, and hepatocellular carcinoma; however, this cannot be currently recommended, especially as most cystadenomas are large, and ethanol injection induces morphologic changes that prevent accurate follow-up of the cyst wall. In any case, the clinician should not rely on intraoperative frozen-section biopsies to differentiate simple cysts and cystadenoma, as these can be falsely negative even when repeated (Vogt et al, 2005; Manouras et al, 2008).

Surgery can consist of partial hepatectomy or enucleation, as there is a dissection plane between the cystadenoma and the adjacent parenchyma. Care should be taken when the cyst lies in segment IV so as not to injure the biliary bifurcation. IOC should be performed to document a potential biliary communication and exclude the presence of mucus or tumor material in the bile duct. Treatment of extrahepatic cystadenoma should include bile duct resection and bilioenteric reconstruction rather than simple enucleation from the bile duct wall. As for other tumors, laparoscopic resection can be an option for trained surgeons (Koffron et al, 2004; Veroux et al, 2005). A single case of recurrence following complete resection has been reported (Wheeler & Edmondson 1985).

HEPATOBILIARY CYSTADENOMA WITHOUT OVARIAN STROMA

Some cystadenomas have been reported that do not have OS. Before considering this diagnosis, several samples of the specimen should be analyzed, as in some patients, the OS may be only focally present (Devaney et al, 1994). Although cystadenoma with and without an OS have very similar clinical and morphologic features, a distinctive characteristic is that the

Table 79B.1

Outcome after Fenestration of Cystadenoma

Reference	Size (cm)	OS	Fenestration	Recurrence	Follow-up (mo)
Akwari et al, 1990	NA	+	Open	Yes, clinical	2
	8	+	Open	Yes, clinical	0.5
	11	+	Open	Yes, clinical	36
Gadzijev et al, 1996	NA	+	Open	Yes, clinical	24
Regev et al, 2001	NA	+	Laparoscopic	Yes, clinical	NA
	NA	+	Laparoscopic	Yes, clinical	NA
	NA	+	Laparoscopic	Yes, clinical	NA
Dixon et al, 2001	NA	+	Open	Yes, imaging	NA
Tan et al, 2002	NA	+	Laparoscopic	Yes, clinical	20
Koffron et al, 2004	NA	+	Laparoscopic	No	NA
Erdogan et al, 2006	NA	+	Open	Yes, clinical	72
Teoh et al, 2006	17	+	Laparoscopic	Yes, imaging	3
	17	+	Laparoscopic	Yes, imaging	3
	18	+	Open	No	6
Delis et al, 2008	NA	+	Laparoscopic	Yes, clinical	NA
	NA	+	Laparoscopic	Yes, clinical	NA
Korobkin et al, 1989	NA	NA	Open	Yes, clinical	60
	NA	NA	Open	Yes, clinical	360
Zacherl et al, 2000	NA	NA	Laparoscopic	Yes, imaging	3
Vogt et al, 2005	NA	NA	Laparoscopic	Yes, clinical	13
	NA	NA	Laparoscopic	Yes, clinical	120
	NA	NA	Laparoscopic	Yes, imaging	6
	NA	NA	Laparoscopic	Yes, clinical	3
	NA	NA	Laparoscopic	Yes	8
	NA	NA	Open	Yes	4
	NA	NA	Open	Yes	3
Thomas et al, 2005	NA	NA	Unstated	Yes	NA
	NA	NA	Unstated	Yes	NA
	NA	NA	Unstated	Yes	NA
	NA	NA	Unstated	Yes	NA
	NA	NA	Unstated	Yes	NA
	16	NA	Laparoscopic + fulguration	No	12
	16	NA	Laparoscopic + fulguration	No	72
Barabino et al, 2004	16	–	Laparoscopic	No	24
Fiamingo et al, 2004	10	–	Laparoscopic	No	24
Veroux et al, 2005	12	–	Laparoscopic	No	14
Manouras et al, 2008	16	–	Laparoscopic	No	6

OS, ovarian stroma; +, present; –, absent; NA, not available; Open, open surgery; follow-up, time to recurrence or duration of follow-up

former only develops in women, whereas the latter may develop in both genders. It is unclear, however, whether cystadenoma without an OS is a discrete entity, or whether it comprises a heterogeneous group of cystic tumors. For this reason, some pathologists would not retain the diagnosis of cystadenoma if the OS were lacking.

Incidence

The largest surgical series of cystadenoma, with or without an OS, published over the past 15 years have, as a rule, included a higher number of tumors with OS than without in a proportion of 5 to 10 to 1 (Table 79B.2; Buetow et al, 1995; Devaney et al, 1994; Erdogan et al, 2010; Regev et al, 2001); however, others have reported equal numbers (Owono et al, 2001; Vogt et al, 2005), and in one study, virtually all cystadenoma lacked OS (Koffron et al, 2004). This discordance is puzzling but probably speaks to the lack of strict pathologic definition of this entity. It is likely that a number of tumors previously diagnosed as cystadenoma without an OS were in fact simple cysts of the liver that had a multilocular appearance as a result of intracystic bleeding, or because several cysts were juxtaposed. They might also have included cystic forms of IPMN-B, which is addressed separately in this chapter.

Table 79B.2

Cystadenomas and Cystadenocarcinomas with and Without an Ovarian Stroma

Reference	OS	Cystadenoma (No. Patients)	Cystadenocarcinoma (No. Patients)
Ishak et al, 1977	+	8	6
Wheeler & Edmondson, 1985	+	13	4
Akwari et al, 1990	+	44	9
Devaney et al, 1994	+	44	6
	–	8	12
Buetow et al, 1995	+	22	4
	–	5	3
Tsiftsis et al, 1997	NA	2	1
Shimada et al, 1998	NA	1	1
Owono et al, 2001	+	2	0
	–	2	3
Hansman et al, 2001	NA	7	1
Regev et al, 2001	+	8	0
	–	0	1
Ammori et al, 2002	NA	6	2
Hai et al, 2003	+	0	1
	–	3	2
Koffron et al, 2004	+	6	1
	–	27	0
Vogt et al, 2005	+	10	1
	–	8	3
Thomas et al, 2005	+	18	1
Oh et al, 2006	+	5	2
	–	2	4
Daniels et al, 2006	+	12	0
Lewin et al, 2006	+	4	0
	–	2	1
Lim et al, 2007	+	14	3
Koea, 2008	NA	3	2
Pojchamarnwiputh et al, 2008	NA	5	7
Lee et al, 2009	NA	6	4
Seo et al, 2010	NA	13	7
Choi et al, 2010	NA	17	0
Erdogan et al, 2010	+	12	1
	–	1	1
Total	+	222	39 (15%)
	–	58	30 (34%)
	NA	58	24 (29%)

Percentage refers to the proportion of cystadenocarcinoma among cystadenomatous tumors.
+, present; –, absent; NA, not available

Pathology

Cystadenomas without OS are typically multilocular and have a mucinous content (Fig. 79B.7). The epithelium is phenotypically similar to the classic cystadenoma (see above). Devaney and colleagues (1994) did not observe areas of atypia or dysplasia in this variant, but others have (Owono et al, 2001). These tumors also tend to more frequently communicate with the biliary tree than cystadenoma with an OS. In particular, a higher proportion of patients are seen with bilious fluid within their cyst (Buetow et al, 1995); however, data are scarce, and ERCP and IOC have not been routinely performed. If confirmed this feature would strengthen the parallel between some, at least cystadenoma without an OS and IPMN-B.

The phenotype of the epithelium lining cystadenoma without an OS has been very inconsistently characterized but has been reported to stain positive for CK-7, CK-8, CK-18, CK-19, MUC1, MUC5, and MUC6 but not for CEA, CA 19-9, or MUC3 (Kazama et al, 2005; Qu et al, 2009). This phenotype is close to that of large bile ducts (see Chapter 78).

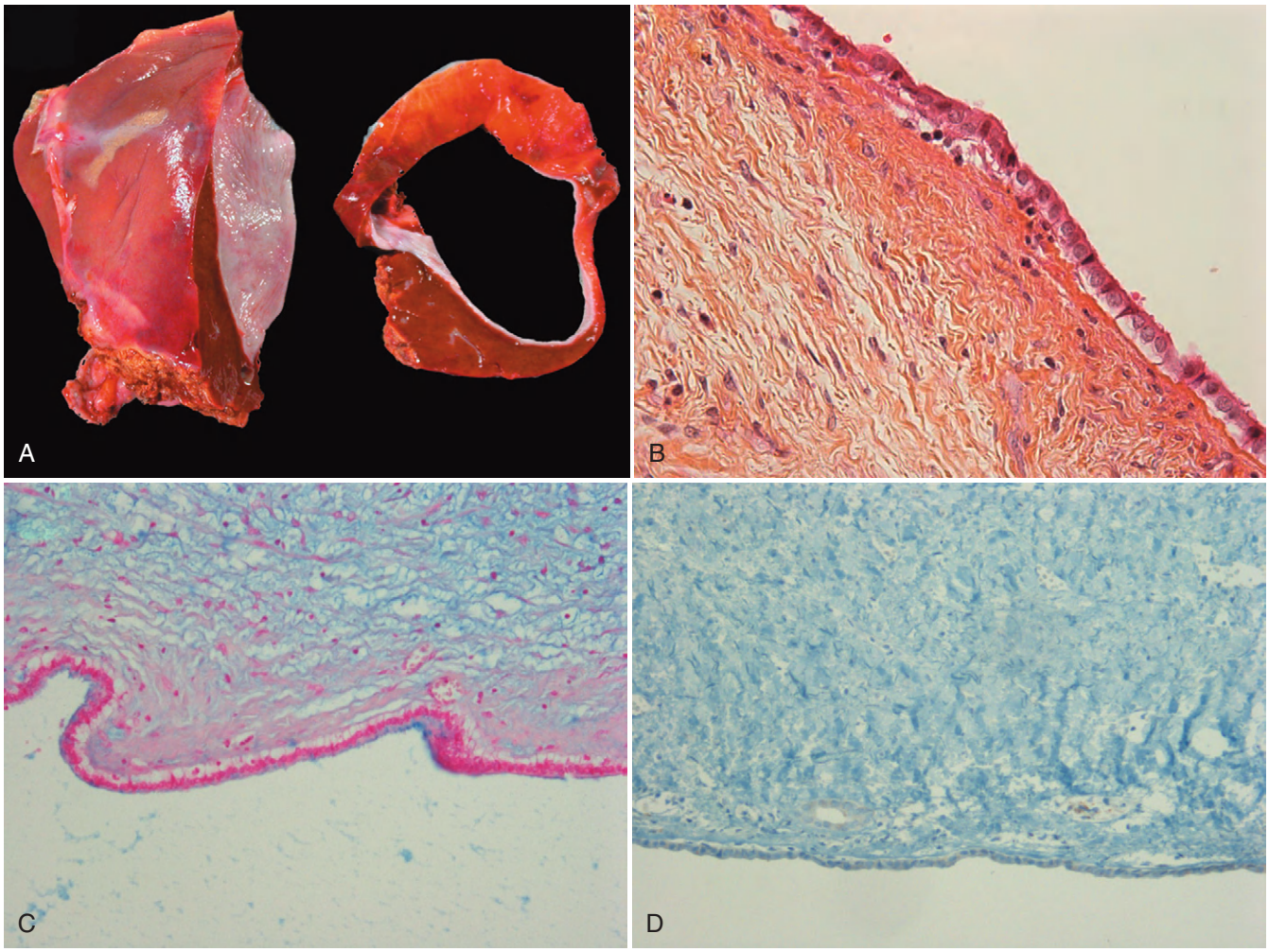


FIGURE 79B.7. Cystic mucinous tumor without ovarian-like stroma. **A,** Macroscopic view showing a unilocular cyst. **B,** Hematoxylin and eosin staining demonstrates cyst lining by an unstratified epithelium of regular cuboidal cells lying on a fibrous wall without ovarian-like stroma. **C,** Mucin production is observed in epithelial lining cells. **D,** No progesterone receptor immunostaining was observed in the fibrous wall.

Presentation and Diagnosis

Unlike those with OS, cystadenomas without OS have been described in both genders, and the sex ratio is actually close to 1 based on the rare available data (Owono et al, 2001; Buetow et al, 1995; Devaney et al, 1994). Otherwise, age (peaking between 40 and 60 years), symptoms, and size of the cyst are comparable (Buetow et al, 1995). Imaging studies have up to now been unable to differentiate between cystadenoma with and without an OS (Buetow et al, 1995; Owono et al, 2001; Lewin et al, 2006). In the cystic fluid, CA19-9 appears always increased, and CEA levels are also increased in most patients (Dixon et al, 2001; Koffron et al, 2004).

Natural History and Management

Very little data are available on the natural history of cystadenoma without an OS. Case reports suggest that it may undergo morphologic changes with a progressive increase in diameter, mural thickening, development of papillary nodules, and subsequent malignant transformation (Akiyoshi et al, 2003; Fukunaga et al, 2008). These changes have been observed over a prolonged period of time (10 years). Whether cystadenoma with and without an OS have the same malignant potential is unclear. It is accepted, however, that both require complete resection. IOC should be performed to document a potential biliary communication. If present, the diagnosis of IPMN-B should be considered and ruled out by frozen-section analysis.

CYSTADENOCARCINOMA

Definition and Incidence

Cystadenocarcinomas are very rare primary cystic tumors that do not primarily communicate with the biliary tree; they are lined by a tubulopapillary malignant epithelium (Fig. 79B.8). Single case reports exist in which malignancy was an adenosquamous carcinoma (Devaney et al, 1994) or it developed in the stroma (Akwari et al, 1990). Cystadenocarcinoma was first described in 1943 by Willis, but by 2000, only 100 had been reported in the literature (Lauffer et al, 1998; Bardin et al, 2004), and they were considered to account for only 0.4% of hepatic malignancies (Takayasu et al, 1988). Most have been

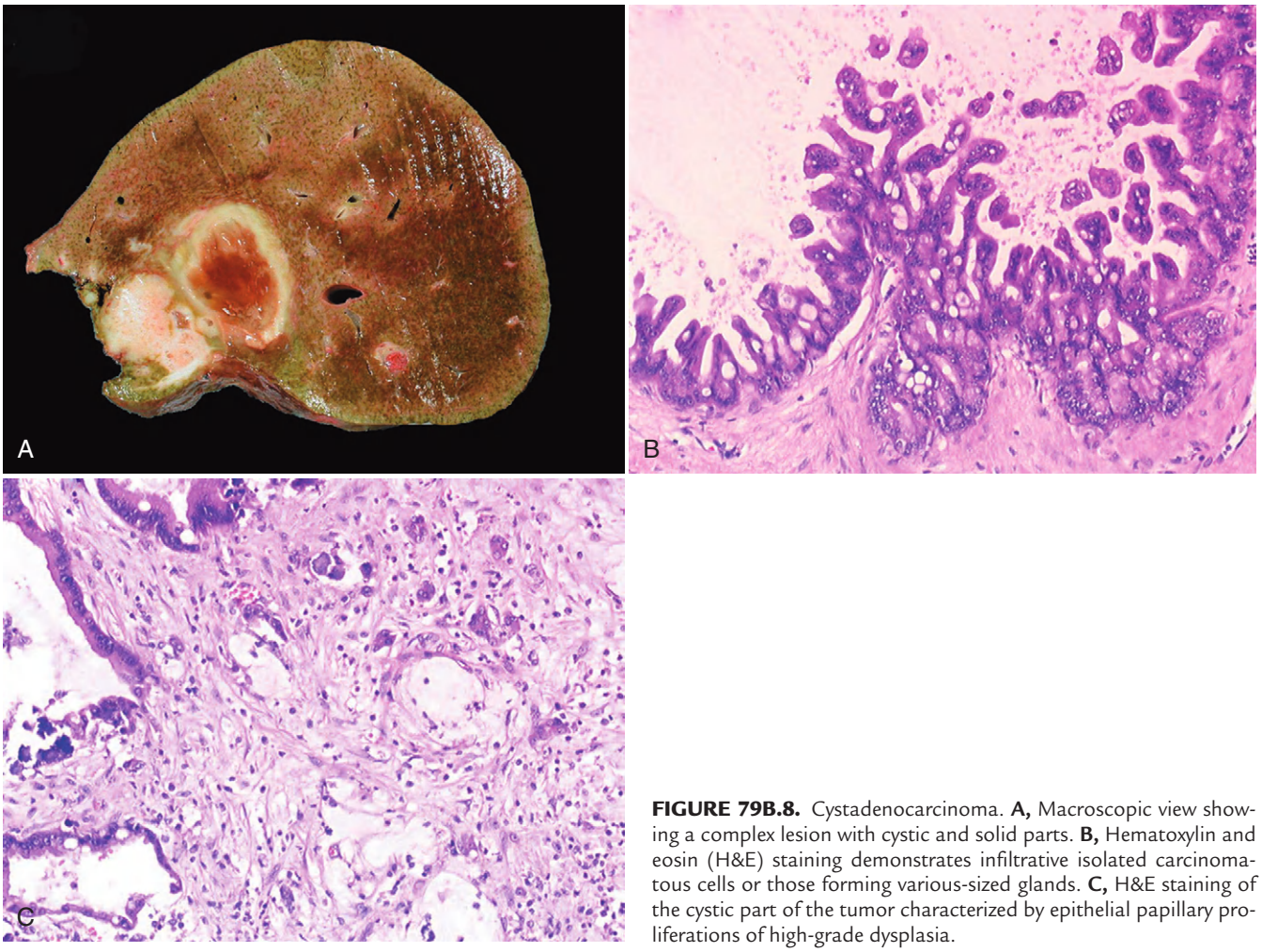


FIGURE 79B.8. Cystadenocarcinoma. **A,** Macroscopic view showing a complex lesion with cystic and solid parts. **B,** Hematoxylin and eosin (H&E) staining demonstrates infiltrative isolated carcinomatous cells or those forming various-sized glands. **C,** H&E staining of the cystic part of the tumor characterized by epithelial papillary proliferations of high-grade dysplasia.

found in the liver, with only anecdotal reports of locations in the extrahepatic bile duct and the gallbladder in particular (Waldmann et al, 2006). As for cystadenomas, these are usually stratified in two groups depending on the presence or absence of an OS (Ishak et al, 1977; Lee et al, 2009); however, some pathologists are reluctant to consider the diagnosis of cystadenocarcinoma when the OS is lacking, as these may correspond to cystic variants of mass-forming intrahepatic cholangiocarcinoma or to malignant IPMN-B (Zen et al, 2006). The distinction is not purely academic, as these tumors have distinct modes of spread and prognoses that could influence management. This should be taken into account when analyzing the literature, and even when reading this section.

Epidemiology and Presentation

Overall female to male ratio is 2:1, but cystadenocarcinomas with OS are exclusively observed in women, whereas those without OS are twice as frequent in men (Bardin et al, 2004). Although the age range is wide—from 18 to 88 years—it peaks in the late 50s and 60s (Lauffer et al, 1998; Seo et al, 2010), approximately 15 to 20 years later than cystadenomas. This difference is in especially obvious for those lesions with OS (Akwari et al, 1990; Buetow et al, 1995; Devaney et al, 1994; Wheeler & Edmondson, 1985).

Although usually nonspecific, symptoms are virtually always present and are initially rather indolent. They are common to cystadenoma and include abdominal swelling, discomfort, pain, or palpation of an abdominal mass. Biliary obstruction with jaundice is reported in 20% of the patients, related to biliary compression or migration of mucus or tumor material. Acute symptoms may otherwise occur as a result of intracystic hemorrhage or tumor rupture. As a rule, diagnosis is delayed, and the mean time interval between first symptoms and treatment is 29 months (Lauffer et al, 1998); one case was reported of a cystadenocarcinoma being discovered 1 year after bone metastasis (Berjian et al, 1981).

Origin and the Cystadenoma-Cystadenocarcinoma Sequence

Cystadenocarcinomas have no identified risk factors, and their origin is unknown, but it is usually assumed that they are the malignant counterpart of cystadenoma. The proliferating epithelial cells indeed resemble those observed in cystadenoma, both express a biliary-type phenotype, and typical areas of cystadenoma (benign columnar epithelium) coexist with malignant papillary epithelium in most patients (up to 90%; Lauffer et al, 1998). Longitudinal morphologic studies of single patients whose cystic lesions were followed for more than a decade

have also shown the progressive development of typical cystadenocarcinoma (Akiyoshi et al, 2003; Kubota et al, 2003). As a whole, cystadenocarcinomas also tend to be larger and to be discovered 5 to 10 years later than cystadenoma (Lauffer et al, 1998). The transition from one to the other is thought to occur through dysplasia or metaplasia that may be observed within cystadenoma (see Pathology above). This applies to both intrahepatic (Ishak et al, 1977; Akiyoshi et al, 2003) and extrahepatic cystadenoma (Davies et al, 1995; Coulter & Baxter, 1989) as well to cystadenomas both with and without OS (Ishibashi et al, 2007).

The risk of malignant transformation of cystadenoma into cystadenocarcinoma is unknown, as the tumor is rare, and limited data are available. A rough estimate can be made by comparing the relative proportion of "cystadenoma" and cystadenocarcinoma in published series (see Table 79B.2). Among resected patients, 15% of tumors with OS were malignant. Although biased, this estimate is consistent with that reported for choledochal cysts, also premalignant lesions. In contrast, the proportion of cystadenocarcinoma is apparently much higher among tumors without OS or an undefined stroma (see Table 79B.2). The reason for this discrepancy is unclear, which does not necessarily imply that cystadenomas without OS are at greater risk of malignant transformation. These could also include intrahepatic cholangiocarcinoma mistaken for cystadenocarcinoma or malignant IPMN-B (papillary cholangiocarcinoma; see Cystic Variants section below).

The time necessary for a cystadenoma, with or without OS, to undergo malignant change and subsequently become invasive in the cyst wall, the adjacent parenchyma, or neighboring organs is unknown. Case reports have shown that a lesion may remain morphologically unchanged for years, but that once mural nodules appear, these may progress within a few months (Akiyoshi et al, 2003). The propensity of, and time necessary for, the malignant epithelial proliferation to become invasive is also unknown. It has been reported that in approximately one third (Devaney et al, 1994) to one half (Lauffer et al, 1998; Nakajima et al, 1992) of the patients who had been operated, the tumor was confined to the cyst, which may explain the very high survival rates reported after complete resection. However, parenchymal extension appearing as satellite nodules or perineural and lymphatic invasion for tumors located close to a glissonian pedicle does exist, and distant metastases are present at the time of diagnosis in 20% of the patients (Lauffer et al, 1998).

Diagnosis

Cystadenocarcinoma could theoretically be mistaken for metastases from cystadenocarcinoma of the ovary or pancreas, but these are usually multiple, whereas cystadenocarcinomas are, as a rule, single lesions. The main difficulty lies in how best to differentiate them from cystadenoma on the one side and from cystic variants of mass-forming intrahepatic cholangiocarcinoma or malignant IPMN-B on the other side. It could be argued that these distinctions are of little practical importance, as all require resection; however, the extent of resection may differ.

Gross Morphology and Imaging

Cystadenocarcinoma shares most of the morphologic and radiologic features of cystadenoma. The lesions are solitary (Seo et al, 2010) and usually large, with an average diameter of 12 cm but growing up to 40 cm (Lauffer et al, 1998); they can also be small, and cystadenocarcinoma of less than 5 cm have been reported, including one of 2 cm (Lauffer et al, 1998; Williams et al, 2001; Lewin et al, 2006). Therefore a small tumor is not evidence that a lesion is benign. Macroscopically, they more frequently have a hemorrhagic or bilious content (Buetow et al, 1995), and hemorrhage or nodularity within the cyst wall is evident (Buetow et al, 1995; Lewin et al, 2006; Seo et al, 2010).

On imaging, cystadenocarcinomas are also more frequently associated with larger septa; intrahepatic cysts debris; bile duct dilation (Seo et al, 2010); enhancement of mural nodules on CT scan, MRI, or contrast US (Korobkin et al, 1989; Pojchamarnwiputh et al, 2008; Ren et al, 2010); and coarse calcifications along the wall or septa (Buetow et al, 1995; Korobkin et al, 1989; Fig. 79B.9). However, all of these features can also be observed in nonmalignant cystadenoma (Fukunaga et al, 2008; Choi et al, 2010), and differentiating both tumors on macroscopy or imaging alone has up to now proven very

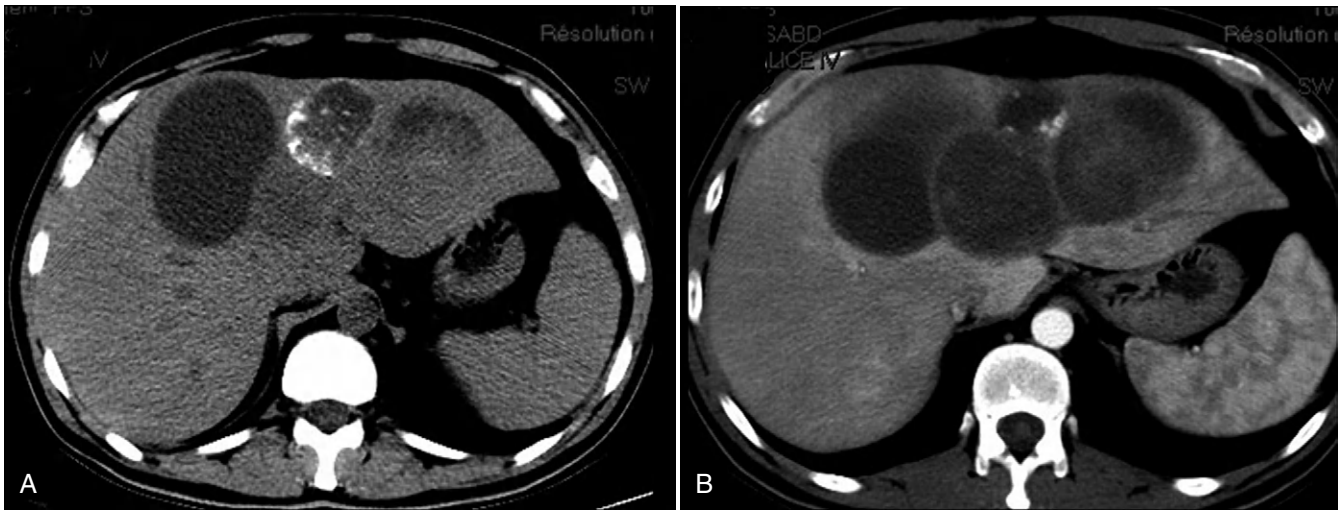


FIGURE 79B.9. Computed tomographic appearance of a cystadenocarcinoma. **A,** Gross calcifications are present along the cyst wall. **B,** Heterogeneous tissue material enhances within the cyst lumen after injection of contrast agent.

difficult (Buetow et al, 1995; Hai et al, 2003). Case reports exist of fluorodeoxyglucose positron emission tomography (FDG-PET) CT positivity (Takanami et al, 2009), but the accuracy of this exploration has not been evaluated.

Biology

An increase in serum tumor markers CEA and CA19-9 is very rare and, when present, is usually mild (Lauffer et al, 1998; Hai et al, 2003). This has also been described, in particular for CA19-9, in cystadenoma both with and without an OS (Hai et al, 2003; Horsmans et al, 1996; Kim et al, 1998; Thomas et al, 1992), and serum levels greater than 50,000 have been reported (Scoggins et al, 2004).

Cyst Content

Cystic fluid analysis does not provide discriminant information. The content is usually hemorrhagic, bilious, or mixed. Although in earlier case reports, fine needle aspiration cytology was found to be useful (Wee et al, 1993; Iemoto et al, 1983), more recent studies have shown that malignant or even atypical cells are very infrequently retrieved (Hai et al, 2003; Seo et al, 2010).

Although inconsistently measured, CA19-9 and CEA concentrations are usually increased in the cystic fluid; but this increase is comparable to that observed in cystadenomas, and CA19-9 is present at very high concentrations in most patients (Hai et al, 2003; Seo et al, 2010), although it has been reported to be normal in a patient whose cystadenocarcinoma did not stain positive for this tumor marker (Horsmans et al, 1997). Although some patients may have CEA levels higher than those observed in cystadenoma or simple cysts, most have normal or mildly elevated concentrations that are therefore not discriminant (Seo et al, 2010). This is consistent with the observation that the epithelium of both cystadenoma and cystadenocarcinoma stain positive for CEA (Tomioka et al, 1986).

Cyst sampling should in any case be performed with caution, as cystadenocarcinomas—and biliary tumors in general—have a high propensity for peritoneal seeding that has been observed following this procedure (Iemoto et al, 1981; Nakajima et al, 1992). Pleural effusion, presumed to be related to aspiration cytology, has also been reported (Hai et al, 2003).

Treatment

Surgery should consist of complete resection, and IOC should be considered, as some of these tumors may communicate with the biliary tree. As tumor extension cannot be reliably assessed on preoperative imaging, it is advisable to perform a formal resection with a wide margin rather than an enucleation. Resection of the biliary confluence followed by a hepaticojejunostomy may be required if the tumor lies close to the biliary confluence. Every effort should be made not to open the cyst, as peritoneal carcinomatosis has been observed after accidental cyst rupture despite negative cytology for tumor cells in cystic fluid (Kosuge et al, 1992). Partial resection of cystadenocarcinoma with an OS is associated with a dismal prognosis.

Following complete resection, the prognosis appears better overall than that of patients with hepatocellular carcinoma (see Chapter 80) or cholangiocarcinoma (see Chapter 50A). Cystadenocarcinomas associated with OS tend to have a more favorable course than those not associated with OS (Devaney et al, 1994; Asahara et al, 1999) with less frequent parenchymal, vascular, and lymphatic invasion (Hai et al, 2003). It is unclear, however, whether this relates directly to the presence of an OS; to gender (cystadenocarcinomas with an OS are exclusively observed in women), as shown for other malignancies; or to tumor invasiveness.

CYSTIC VARIANTS OF INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM OF THE BILE DUCT

IPMN-B is a relatively new, distinct pathology characterized by intraluminal papillary proliferation in the bile ducts that produce mucin (Nakanuma et al, 2002). They almost exclusively occur in the intrahepatic bile ducts or the left or right bile ducts, do not have an OS, and probably correspond to entities previously described using the terms *biliary papilloma, mucin-producing ICC, intraductal mucosal-spreading mucin-producing peripheral cholangiocarcinoma, intraductal growth-type peripheral cholangiocarcinoma,* and *intraductal variant of peripheral cholangiocarcinoma.* These tumors have striking clinical, histologic, and phenotypic similarities with IPMN of the pancreas (IPMN-P; Kim et al, 2000; Zen et al, 2006a; Fukushima & Mukia, 2000; Kloppel & Kosmahl, 2006), and both may occasionally coexist in the same patient (Ishida et al, 2002; Zalinski et al, 2007; see Chapters 56 and 57).

They may macroscopically be divided into two types: the *ductectatic type* evidences diffusely dilated bile ducts; the *cystic type* appears as a large cystic mass (Sakamoto et al, 1997). A parallel has therefore been drawn between branch duct cystic IPMN-P and cystic variants of IPMN-B that are thought to develop from small bile ducts. Because these variants of IPMN-B have both cystic (mucin) and solid (papillary projection) compartments, they may resemble cystadenoma or cystadenocarcinoma (Terada & Taniguchi, 2004; Aoki et al, 2005; Lim et al, 2007) and might have been mistaken for them in the past.

Definition and Etiology

IPMN-B, including its cystic variants, has mainly been described in the East, initially in patients with hepatolithiasis or *Clonorchiasis* infection (Chen et al, 2001). It develops in the bile duct lumen and is characterized by innumerable frondlike papillary infoldings, which consist of columnar epithelial cells surrounding slender fibrovascular stalks supported by connective tissue from the lamina propria. Further stratification is based on the presence and severity of atypia of the biliary epithelia: *type 1* is low-grade dysplasia, *type 2* is high-grade dysplasia, *type 3* is in situ and microinvasive adenocarcinoma, and *type 4* is invasive adenocarcinoma. Types 3 and 4 are associated with papillary tumor tissue and mucobilia in the large, dilated ducts containing stones; whereas this is frequently absent in type 1 lesions, intraductal spreading is virtually constant. This description was somewhat confusing, as these tumors had been observed in a specific context of chronic biliary inflammation; however, it has subsequently been described in the absence of such conditions (Shibahara et al, 2004; Zen et al, 2006a; Hayashi et al, 2008), although etiology remains unknown.

Pathology

Cystic IPMN-B morphologically is multilocular and frequently contains mucinous fluid (Fig. 79B.10). It may also occasionally

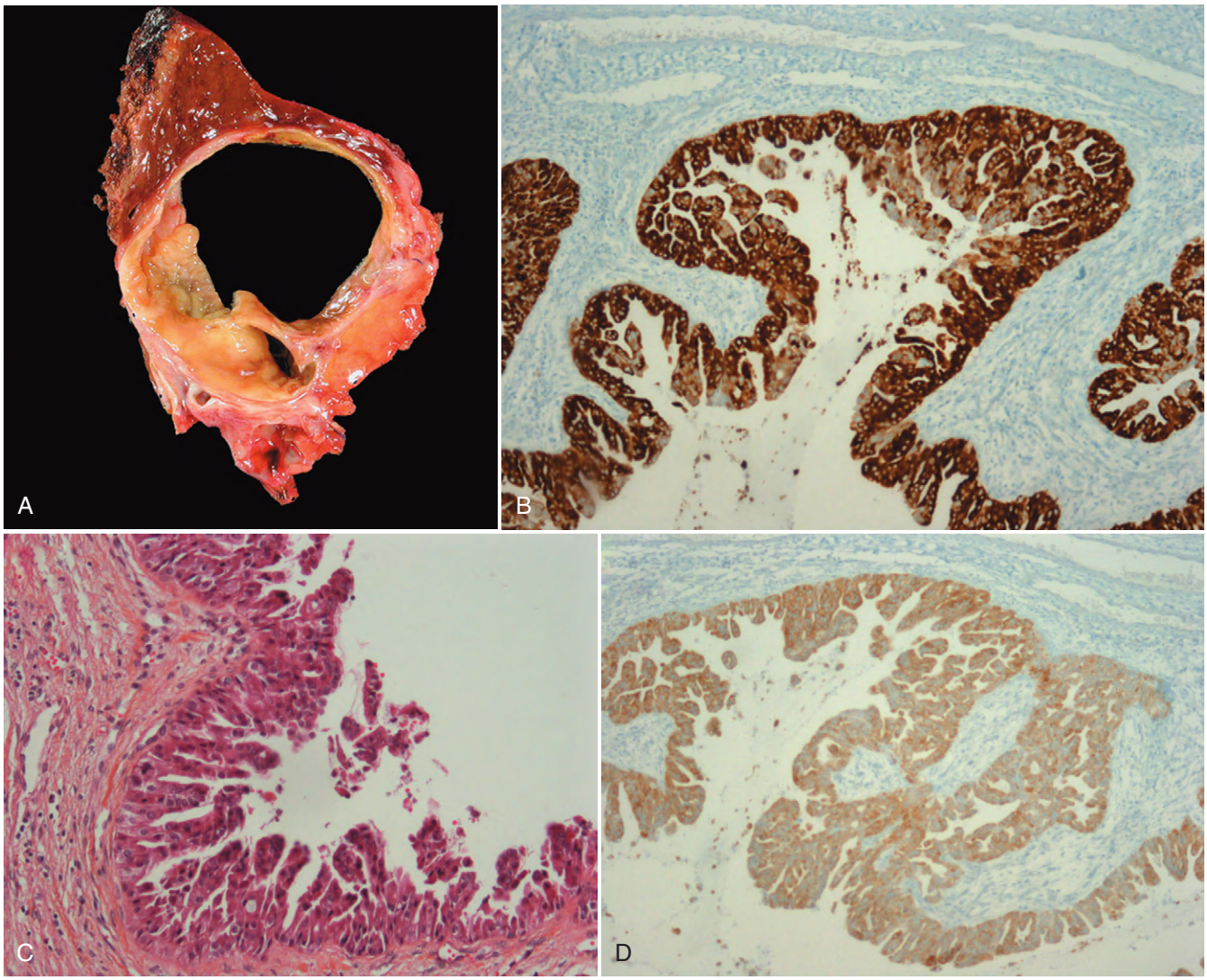


FIGURE 79B.10. Intraductal papillary mucinous neoplasia of the bile ducts (IPMN-B). **A,** Macroscopic view showing a multilocular cyst characterized by papillary mural nodules within a smooth wall. **B,** The lining epithelium is composed of papillary projections made of several layers of atypical cells. No features of mural invasion are present. **C,** Epithelial proliferation is strongly positive for MUC5. **D,** Cell proliferation displays slight MUC1 staining.

be hemorrhagic (Zen et al, 2006a). Papillary mural nodules within an otherwise smooth or finely granular wall are virtually constant except in totally benign lesions (Paik et al, 2008). In situ or invasive adenocarcinomas are particularly prevalent in IPMN-B and are present overall in up to 60% to 70% of the patients, and even higher rates have been found in the cystic variant (Yeh et al, 2006; Paik et al, 2008). This may either be a mucinous carcinoma, associated with profuse mucous secretion; a tubular adenocarcinoma, invading the bile duct wall with abundant fibrous stroma at the base of the papillary lesions and commonly associated with vascular, lymphatic, and perineural invasion; or a combination of these (Zen et al, 2006a, 2006b).

As for IPMN-P, the lining epithelia of IPMN-B has been classified into a *pancreatobiliary type*, *intestinal type*, *gastric type*, and *oncocytic type* (Zen et al, 2006b). More simply it can be categorized as a *columnar type*, which resembles the intestinal type of IPMN-P, and a *cuboidal type*, which resembles the pancreatobiliary type or oncocytic variant of IPMN-P (Shibahara et al, 2004). In one study, both were observed in the cystic form of IPMN-B, whereas only the columnar type was observed in the ductectatic form (see Chapter 78).

A parallel has been established between the cell type and the incidence of malignant changes. Cuboidal pancreatobiliary oncocytic-type epithelium is more frequently—actually, almost always—associated with the presence of carcinoma than the columnar type, but this is more frequently a superficial (in situ) tumor than an invasive one (Shibahara et al, 2004; Zen et al, 2006a).

The epithelium stains positive for CK-7 (biliary phenotype) and occasionally and inconsistently for CK-20 (intestinal phenotype). CA19-9 is observed diffusely, and CEA is restricted to areas of high-grade dysplasia and sometimes carcinoma (Zen et al, 2006a, 2006b).

Although MUC5AC is expressed in virtually all patients (gastric phenotype), MUC2 (intestinal phenotype) is more frequent in the columnar type, and MUC6 is more often seen in the cuboidal type (Shibahara et al, 2004; Zen et al, 2006a, 2006b). MUC1 is in contrast not expressed except in some invasive areas of tubular cholangiocarcinomas, in which MUC2 expression may disappear (Shibahara et al, 2004; Zen et al, 2006a, 2006b).

Diagnosis

Cystic variants of IPMN-B develop almost equally in both genders and peak in the sixth decade, which is 10 to 20 years older than for cystadenoma with an OS (Shibahara et al, 2004; Zen et al, 2006a). Many patients are asymptomatic, with their tumor discovered during a general health examination, but epigastralgia, jaundice, and cholangitis may occur. Cystic variants cannot be differentiated from cystadenoma or cystadenocarcinoma by their diameter, which may range between 2 and 17 cm (Lim et al, 2007; Yamashita et al, 2007), nor can it be discerned by thickness of septa or presence of calcifications (Lim et al, 2007); however, cystic variants are more frequently associated with prominent or large (>1 cm) mural nodules and bile duct dilation distal to the tumor. The latter is due to the issue of mucus from the cyst in the bile ducts. Communication with the biliary lumen is indeed a key feature (Kazama et al, 2005), but CT and MRI are insufficient to show the luminal communication (Lim et al, 2007; Yamashita et al, 2007), probably because it is too narrow. Preoperative ERCP or IOC is more reliable; in contrast, macroscopic examination of the specimen is inaccurate (Zen et al, 2006a).

Complications

The two main complications of cystic variants of IPMN-B relate to the migration of mucus or tumor material in the bile ducts and to malignant transformation. Mucobilia may result in transient symptoms of biliary obstruction, and biliary obstruction by mucus has occasionally resulted in bile duct rupture (Lim et al, 2004). Malignant transformation is particularly frequent, although the stage of malignancy is less advanced than for other biliary tumors (Zen et al, 2006b). As most of these tumors show malignant changes at the time of diagnosis, they are likely slow growing.

Management and Prognosis

Cystic IPMN-B requires resection, and an IOC should be performed to document the biliary communication and rule out the presence of mucus in the bile duct. As IPMN-B may spread superficially along the lumen of the bile ducts or be present in adjacent ducts, simple enucleation of the cyst may be insufficient. Formal hepatectomy should be performed, occasionally with extrahepatic bile duct resection and lymph node sampling. Even in patients with associated carcinoma, the prognosis is better than after resection of intrahepatic or hilar cholangiocarcinoma (Shibahara et al, 2004; Zen et al, 2006a, 2006b; Paik et al, 2008). Five-year survival is 61% and may be as high as 80% for those patients with the cuboidal cell type. Survival following resection of malignant IPMN-B is adversely impacted by the presence of the columnar cell type (Shibahara et al, 2004) and MUC1 expression (Higashi et al, 1999; Shibahara et al, 2004).

CONCLUSION

Cystic tumors of the liver are rare and comprise different entities that should be stratified with regard to content (mucinous or nonmucinous), tumor stroma (presence or absence of an OS), and relation to the bile ducts (communicating with the lumen or not). Cystic tumors with an OS (cystadenoma) occur in women, do not typically communicate with the bile duct, and in most cases are adenomas, although no reliable criterion differentiates them from cystadenocarcinoma. Malignant transformation may occur in up to 15%. IPMN-B may have a cystic appearance, occurs in both genders, and communicates with the biliary lumen, although this may be difficult to document; it may spread beyond the cystic mass in the adjacent bile ducts and frequently harbors severe dysplasia or malignancy, which may be either invasive or superficial. These lesions share several features and are currently considered to be the counterparts of the same lesions occurring in the pancreas; in any event, they require complete resection. Cystadenoma without an OS is an ill-defined entity that is not accepted by all pathologists worldwide, as they may include some IPMN-B or atypical cysts.

References are available at expertconsult.com.

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CHAPTER 81B

Metastatic malignant liver tumors: neuroendocrine

Saboor Khan, David M. Nagorney, and Florencia G. Que

OVERVIEW

The liver is second only to regional lymph nodes as the dominant site of metastases from all gastrointestinal (GI) tract malignancies. Because progression of hepatic metastases is the predominant cause of death in patients with GI cancers, hepatic metastases have been the focus of a multimodal treatment approach. Importantly, the accumulated experience documenting the survival potential of hepatic resection for selected patients with colorectal metastases (see Chapter 81A) has prompted evaluation of this approach for other malignancies metastatic to the liver. Whether similar approaches will prove effective for neuroendocrine metastases remains unclear.

Evidence supporting hepatic resection for metastatic GI neuroendocrine tumors (NETs) continues to emerge. Hepatic resection of metastatic NET to the liver is appealing because gastrointestinal NET has a similar route of metastatic dispersal through the portal venous system, as do colorectal cancers. Moreover, their natural history is typically prolonged compared with other GI tract cancers and, in fact, with other solid tumors. Initial experience with hepatic resection for metastatic NET (Foster & Berman, 1977) suggested that patients might benefit in terms of survival and symptom relief from clinical endocrinopathies when antihormonal and antineoplastic therapies were ineffective. Consequently, interest in hepatic resection for metastatic NET has grown. In addition to the prolonged natural history of NET and the clinically significant endocrinopathies, several other observations have supported further assessment of hepatic resection: 1) the prolonged presence of intrahepatic disease before evidence of extrahepatic progression, 2) the impression that the severity of clinical endocrinopathy correlates with the intrahepatic volume of metastatic disease, 3) the resectability of the primary and regional NET despite metastatic disease, and 4) the presence of normal, nonmetastatic liver. This chapter details the clinical data supporting hepatic resection for metastatic NET; presents the current outcomes for hepatic resection, hepatic transplantation, and ablative therapy for metastatic NET; and presents an algorithm for long-term management of patients with metastatic NET in the liver.

CLASSIFICATION OF GASTROENTEROPANCREATIC NEUROENDOCRINE TUMORS

Most neuroendocrine metastases to the liver are of GI or pancreatic origin, so-called *gastroenteropancreatic* (GEP) tumors (Rindi et al, 1998). GEP neuroendocrine tumors have historically been divided into two broad types, *carcinoid* and *noncarcinoid,* either of which may or may not be associated with hormone production that causes a clinical endocrinopathy (functional or nonfunctional, respectively). Traditionally, GI carcinoids (GICs) have been classified by their site of origin—*foregut* (lung, thymus, stomach, duodenum, pancreas, bile duct, gallbladder, and liver), *midgut* (small intestine, appendix, and proximal colon), and *hindgut* (distal colon and rectum)—because biologic and biochemical features within these groups vary. In contrast, pancreatic neuroendocrine tumors have been classified simply by whether they are functional (see Chapter 61). Regardless of origin, neuroendocrine tumors are similar histopathologically. Many histologic and morphologic features are shared by both benign and malignant tumors. Importantly, only the confirmed presence of metastases confers an unequivocal diagnosis of malignancy.

Clinical behavior for NET has ranged from an indolent to an aggressive clinical course with rapid cancer progression and death. For GEP neuroendocrine tumors, two schemes have been employed (Capella et al, 1995; Solcia et al, 2000). Broadly these classifications stratify patients with malignant GEP into *low-grade* (well-differentiated) or *high-grade* (poorly differentiated) NET (World Health Organization [WHO] classification) and subtype each as either *functioning* or *nonfunctioning*. In general, only patients with liver metastases from well-differentiated (low-grade) but not poorly differentiated (high-grade) NET are approached surgically. The TNM (tumor-node-metastases) staging has also been proposed (Rindi et al, 2006, 2007) and correlated with survival (Fischer et al, 2008; Pape et al, 2008a, 2008b; Skov et al, 2008). Some classifications tend to limit patients based on the number and extent of hepatic metastases on the radiologic imaging: a single metastasis (type I), isolated metastatic bulk accompanied by smaller deposits (type II), and disseminated metastatic spread throughout the liver (type III). These three groups differed significantly in regard to tumor-related characteristics, but this classification correlated with therapeutic approach and long-term survival (Frilling et al, 2009). The recently published guidelines by the North American Neuroendocrine Tumors Society (NANETs) highlight the importance of a uniform approach to pathologic reporting. This is especially relevant regarding differentiation and grade of individual tumors, which have a major impact on prognostication and choice of therapy (Klimstra et al, 2010).

GIC cancers produce a variety of proteins and peptide hormones (Onaitis et al, 2000; Schnirer et al, 2003). Almost all NETs are positive for neuroendocrine markers chromogranin A and neuron-specific enolase, but serum levels have correlated poorly with prognosis (Tomassetti et al, 2001); however, they are useful for treatment follow-up (Jensen et al, 2007; Nikou et al, 2008). Pancreatic NETs produce a wide variety of one or more peptides: gastrin, insulin, glucagon, and vasoinhibitory

peptide, among others (Gumbs et al, 2002; Mansour & Chen, 2004). Nonfunctional pancreatic NET implies either the production of an inactive peptide, subclinical hormone production, or no peptide production. Reviews for the specific endocrinopathies from pancreatic neuroendocrine tumors are cited for reference to recognize their implications in clinical management (Gumbs et al, 2002; Mansour & Chen, 2004).

Epidemiology

A brief overview of the most commonly encountered primary GEP NETs is presented because combined resection of the primary and regional extent of disease and hepatic metastases is frequently undertaken. GICs comprise nearly 75% of all carcinoids with the remainder primarily of bronchopulmonary origin. The distribution of GIC is composed of the small intestine (35%), rectum (23%), appendix (19%), colon (12%), stomach (6%), duodenum (4%), and hepatobiliary-pancreatic region (2%) (Modlin et al, 2003). The relative incidence of gastric and rectal carcinoids has increased over the last 3 decades but has decreased in the appendix. GICs are frequently associated with noncarcinoid tumors in the small intestine (29%), stomach (21%), and appendix (18%). Overall, localized disease characterizes the presentation of rectal (80%) and gastric (70%) carcinoids, and nonlocalized disease is represented in colonic (80%) and small intestinal (67%) carcinoids. Although GICs are often considered to behave benignly, 13% of patients have metastatic disease at presentation, and overall 5-year survival for GIC is only 67% (Kulke & Mayer, 1999).

Nonfunctional NETs of the pancreas have an equal sex distribution (Hochwald et al, 2001). NET of the pancreas occurs in 0.5 to 1 person per 100,000 population. Nonfunctional NET accounts for more than 50% of pancreatic NET in most series, and wide variations in incidence between types of NET are likely related to the definition of "nonfunctional." Multicentricity is not infrequent (15%). The epidemiology of functional pancreatic neuroendocrine tumors varies widely, with or without the multiple endocrine neoplasia (MEN) 1 syndrome, and is beyond the scope of this chapter; however, references are provided.

Small Intestinal Carcinoids

Small intestinal carcinoids are the most common GIC (Kulke & Mayer, 1999; Modlin et al, 2003). Patients usually present with abdominal pain, diarrhea, GI obstruction, and bleeding. Small intestinal carcinoids account for 90% of patients with the carcinoid syndrome. Approximately 20% of patients with the syndrome will have clinically evident carcinoid heart disease, and an even larger proportion will have occult heart disease detectable by echocardiography (Bernheim et al, 2007). Small intestinal carcinoids are often associated with dense mesenteric fibrosis, intestinal obstruction, hemorrhage, and intestinal ischemia secondary to vessel compression by metastatic regional lymph nodes and local release of vasoactive hormones (mesenteric angiopathy) (Eckhauser et al, 1981). Nearly 20% to 30% of patients have multiple GI carcinoids, and more than a third of patients have concurrent noncarcinoid cancers. Besides regional lymph node metastases, these carcinoids frequently metastasize to the liver, peritoneum, retroperitoneal nodes, and ovaries.

Resection is the only potentially curative treatment for small intestinal carcinoids (Hellman et al, 2002a; Loftus & van Heerden, 1995; Soreide et al, 1992; Woodside et al, 2004). Because of the frequency of the associated syndrome, careful preoperative evaluation and preparation are necessary. When suspected clinically, baseline urinary 5-hydroxyindole acetic acid (5-HIAA) levels should be obtained. The extent and site of the primary small intestinal carcinoid can be defined by barium contrast GI series, enteric computed tomographic (CT) scan, enteric magnetic resonance imaging (MRI), or by small bowel enteroclysis. Further imaging of the abdomen and chest for metastatic disease is best defined by contrast-enhanced CT. Often CT will identify mesenteric adenopathy and stranding characteristic of regionally advanced small bowel carcinoids even without identification of the site of the primary carcinoid on small bowel contrast studies.

Assessment of the relationship of the regional lymphatic metastases to the vessels of the small bowel is important in planning resection of the primary and regional extent of disease (Mullen et al, 2005). Despite the typical desmoplastic reaction adjacent to the involved regional lymph nodes, resection is feasible, except with extensive invasion of the third portion of the duodenum and the uncinate process of the pancreas, circumferential arterial and venous encasement without patent proximal arterial collaterals, or distal mesenteric arteries not large enough for reconstruction (Ohrvall et al, 2000; Schindl et al, 2002).

Various imaging methods may be helpful. Although not anatomically useful in operative planning, somatostatin receptor scintigraphy and octreoscanning are useful is evaluating the overall disease extent and the site of the primary, when not recognized by other studies; these are also helpful in modifying treatment strategies (Slooter et al, 2001). The role of MRI is increasing, primarily in assessing the extent of hepatic metastases. MRI is particularly sensitive in detecting small metastases within the liver and often will detect disease not seen by other imaging techniques inclusive of CT; however, MRI has limited applicability for defining the site of the primary carcinoid.

The recognition of carcinoid heart disease demands a thorough cardiac evaluation (Fox & Khattar, 2004). The major implication of carcinoid heart disease is the presence of right heart failure and the consequently elevated systemic venous pressures that can cause a pulsatile liver (implying hepatic vein pressures >25 mm Hg), which precludes hepatic resection. The presence of clinical significant carcinoid heart disease dictates medical treatment, and occasionally even valve replacement, prior to resection of the primary small intestinal carcinoid and the hepatic metastases (Moller et al, 2005). Survival after surgical repair of carcinoid heart disease is improved compared with medical treatment, even without surgical treatment of hepatic metastases (Connolly et al, 1995). Some patients may be candidates for hepatic resection after repair of carcinoid heart disease, depending upon objective decreases in systemic venous hypertension and the degree of functional cardiac improvement (Connolly et al, 2002; McDonald et al, 1999). Conversely, hepatic resection has been shown to be associated with decreased cardiac progression of the carcinoid heart disease and improved prognosis (Bernheim et al, 2008).

Any patient with the carcinoid syndrome requires preoperative and intraoperative somatostatin analogue therapy to prevent a *carcinoid crisis* (Oberg et al, 2004), a clinical syndrome of life-threatening intraoperative hypotension or hypertension and severe flushing with or without concurrent bronchospasm or arrhythmias. To date, the frequency and factors predictive of this perianesthetic complication remain unknown. Prevention is essential, and appropriate treatment should be prescribed in all patients undergoing intervention for metastatic carcinoid tumors (Kinny et al, 2001). Short-acting analogues

are preferred, even if the patient has received the long-acting analogue within 30 days. Management should consist of subcutaneous short-acting somatostatin analogue on call to operation and intravenous infusion of the analogue throughout the operation and in recovery. Additional intraoperative increases in infusion rates are appropriate for unexplained intraoperative hemodynamic instability.

Resection of small intestinal carcinoids should encompass the primary tumor, any multicentric tumors, and the regional lymph nodes. When intestinal ischemia is present, resection of the thickened, chronically ischemic bowel is indicated; resection of the regional lymph nodes is often possible by keeping the dissection immediately adjacent to the nodes and retracting the visceral vessels away from the involved nodes (Hellman et al, 2002a). Preservation of the blood supply to the GI tract is essential to prevent short-bowel syndrome. As mentioned previously, preoperative CT with intravenous contrast will define those patients with resectable nodal disease, which is very difficult to assess intraoperatively. Resection of hepatic metastases is generally indicated only if complete resection of the primary and regional disease is feasible. Resection of hepatic metastases should be performed concurrently, if all gross metastases can be excised. If nearly all of the hepatic disease can be resected (or ablated), cytoreductive resection should be considered, because both survival and symptom-free quality of life may be improved (Knox et al, 2004; Sarmiento et al, 2003; Chambers et al, 2008). Staged resections can be performed with similar expectations in outcomes. Overall 5-year survival for small intestinal carcinoid ranges from 50% to 67%.

Pancreatic Neuroendocrine Tumors (See Chapter 61)

An aggressive operative approach generally is warranted for NET of the pancreas (Fendrich et al, 2006; Hochwald et al, 2001; Matthews et al, 2002; Phan et al, 1998; Schurr et al, 2007; Solorzano et al, 2001). Resection remains the treatment of choice for patients with localized NET of the pancreas and for selected patients with hepatic metastases (Oberg & Jelic, 2008). Resection of the primary NET and the regional lymph nodes is generally possible despite their often large size. The extent and type of pancreatectomy is dictated by the site of the primary NET; pancreatoduodenectomy is used for NET of the head of the pancreas, and distal pancreatectomy/splenectomy is best for body or tail NET (see Chapter 62). In some cases, enucleation may be an alternative approach. For patients with locally invasive NET of adjacent structures or the GI tract, resection should be en bloc. Laparoscopic pancreatectomy is currently applicable for resection of most pancreatic NET (Fernandez-Cruz et al, 2002, 2008). Whether concurrent laparoscopic resection of the primary pancreatic NET and hepatic metastases is feasible has not been proven. Concurrent resection of primary pancreatic NET and hepatic metastases can be performed safely, although staged resections may be preferable, particularly in patients with involvement of the head of the pancreas (Sarmiento et al, 2002). Overall actuarial 5-year survival rates for NET of the pancreas range from 45% to 63% with a median survival of about 4 years.

Natural History

Regardless of whether NETs are classified as carcinoid or noncarcinoid, the natural history of patients with unresected or unresectable hepatic metastases has been similar. Overall, patients with unresected hepatic metastases from NETs have a 5-year survival of approximately 30% (Proye, 2001) and a median survival of 17 months (House et al, 2006).

Several factors affect the natural history of both carcinoid and noncarcinoid cancers (Durante et al, 2009). Clearly, liver metastases are the most significant factor adversely affecting outcome (Moertel, 1987; Pape et al, 2008a). With or without liver metastases from NET, 5-year survival is approximately 30% to 40% and 90% to 100%, respectively. Poorly differentiated NET and progressive neuroendocrine metastases in the liver (>25% volume increase on two CT scans within 3 months) further adversely affects survival among patients with hepatic metastasis (Madeira et al, 1998). Progression in size or number of hepatic neuroendocrine metastases can be expected in 90% after a median follow-up of 11.5 months (Skinazi et al, 1996). Carcinoid heart disease occurs only in the presence of metastatic carcinoid tumor to the liver independently and predicts poor survival. The survival of patients with clinically severe carcinoid heart disease is approximately 1.6 years; the survival rate is only 31% at 3 years, unless cardiac surgery is undertaken successfully (Connolly et al, 1995; Fox & Khattar, 2004). Patients with carcinoid heart disease should be considered for hepatic surgery, as stated before, because cardiac disease progression is reduced, and prognosis is improved (Bernheim et al, 2008).

Although uncontrolled functioning endocrinopathies from metastatic neuroendocrine tumors can be life threatening—for example, severe hypoglycemia from insulinoma and GI perforation from gastrinoma—the impact of such events on the natural history of these patients is unknown. Conversely, it is likely that clinical control of endocrinopathies can affect natural history of NET; however, specific studies to document clinical control of endocrinopathies by antihormonal therapy with objective tumor responses have not been well documented, except for gastrinoma before and after the use of H_2 blockers or proton pump inhibitors (Norton et al, 2003a).

Similar to carcinoid tumors, the 5-year survival of patients with pancreatic NET ranges from 30% to 40% with a median survival of approximately 40 months (Chen et al, 1998; Thompson et al, 1985). Whether the presence or absence of clinical endocrinopathies affects the natural history of patients with metastatic pancreatic NET is unclear; however, the specific NET likely affects overall natural history. Up to 75% of patients who present with midgut or hindgut tumors are likely to have liver metastases, in particular the nonfunctioning group, and those with a pancreatic primary (likely to be high grade) have the highest rate of liver involvement (Steinmuller et al, 2008). In a series of 35 patients with hepatic metastases, 60% of which were from gastrinomas, the 5-year survival was approximately 70%. The prognosis also is affected by the extent of metastatic NET in the liver (Chamberlain et al, 2000; Phan et al, 1998); the 5-year survival was only 24% with more than 75% tumor replacement of the liver, whereas 5-year survival approached 80% for less than 50% tumor replacement.

SURGICAL AND ABLATIVE TREATMENT OF HEPATIC NEUROENDOCRINE METASTASES

Hepatic Resection for Neuroendocrine Metastases

The current mainstay of treatment for metastatic GI neuroendocrine tumors to the liver is resection (see Chapter 90E);

however, no randomized controlled data support improved survival from hepatic resection of metastatic NET. Although hepatic resection of malignancy is employed most often with curative intent, the tumor biology of these typically indolent and slow-growing cancers renders them less responsive to more commonly employed palliative therapies, such as chemotherapy and radiation; thus, resection with palliative intent (cytoreduction) may afford patients a real and significant advantage in palliation and may prolong survival. Importantly, the focus on palliation and extension of life, rather than on complete remission, is conceptually a paradigm shift, because most hepatic resections are undertaken for cure in patients with metastatic solid cancers.

The treatment of hepatic metastases from NET is aimed at reduction of the mass of malignant tissue (cytoreduction) chiefly for two reasons: first and foremost, metastatic gastrointestinal NET is usually indolent and slow growing, with a well-differentiated histopathologic grade (WHO classification) (Solcia et al, 2000); thus chemotherapy and radiotherapy regimens targeted toward rapidly dividing cells are relatively ineffective; second, symptoms secondary to expression and secretion of biologically active peptides by these tumors is directly related to overall mass of tumor, although production of peptides may be heterogeneous among individual metastases. Similarly, pain and decreased performance status may negatively impact on quality of life for patients with nonfunctional NET metastatic to the liver. In patients who do respond to medical treatment, debulking surgery—cytoreduction of more than 90% of the liver tumors—is a valid and direct method of providing relief from symptoms. These reasons, coupled with improved safety for hepatic resection, have prompted some to advocate hepatic resection as a primary therapeutic option for patients with both functional and nonfunctional metastatic NET (Chambers et al, 2008). Based on these premises, hepatic cytoreduction, whether by hepatic resection or transplantation, should address clinical endocrinopathies and improve survival; as a corollary, the duration of response should be in proportion to the extent of the debulking or cytoreduction of the metastatic NET and the growth rate of the residual NET (House et al, 2006).

Currently, hepatic resection of metastatic NET is recommended if the primary tumor and regional disease are resectable or resected, and a minimum of 90% of the volume of hepatic metastases is resectable or ablatable (Steinmuller et al, 2008). Our initial results showed that debulking hepatic resection could be performed safely, and overall survival was about 75% at 4 years (Que et al, 1995). No significant difference in survival was found between patients undergoing complete (R0) or incomplete (R1 to R2) resections. Mean duration of symptom response was nearly 2 years. Subsequently, our findings in 170 patients undergoing hepatic resections showed that symptoms resolve in 98% of patients. Median time to symptom recurrence was 45 months, and 59% of patients experienced recurrent symptoms at 5 years. Overall survival was 61% and 35% at 5 and 10 years, respectively, and perioperative mortality rate was 1.2%. Recurrence, however, was 84% at 5 years and 94% at 10 years (Fig. 81B.1; Sarmiento et al, 2003). Examples of results obtained from cytoreductive hepatic resection for neuroendocrine tumors are shown in Figure 81B.2.

A review of the current literature on hepatic resection for metastatic NET is summarized in Table 81B.1. The cumulative findings from these reports support an aggressive operative approach for metastatic NET. Overall 5-year survival has ranged from 41% to 82% with a median 5-year survival of up to 100%. Only four perioperative deaths have been reported among the tabulated patients (n = 556). When addressed, resolution of endocrine symptoms exceeded 90% in most series, although duration of response was not routinely reported.

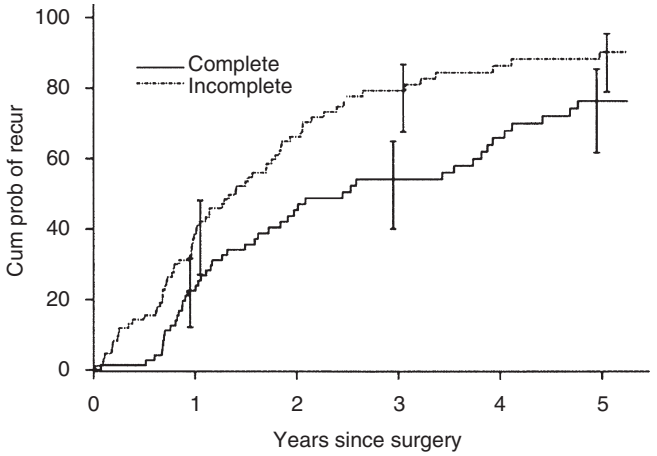


FIGURE 81B.1. Recurrence rate was lower for patients with complete resection of the tumor compared with incomplete resection. Cum Prob of Recur, cumulative probability of recurrence. *(From Sarmiento JM, et al, 2003: Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. J Am Coll Surg 197:29-37, with permission from the American College of Surgeons.)*

Although the majority of patients reported to date have had metastatic carcinoid cancer to the liver, survival has not differed appreciably among patients with carcinoid and noncarcinoid (primarily islet cell) cancers. Current data do not show that survival is affected by the presence or absence of clinical endocrinopathy. Interestingly, although complete macroscopic resection of hepatic metastases (R0/R1) has been undertaken more frequently, survival has not significantly differed among patients with complete or incomplete hepatic resection of metastatic NET, provided cytoreduction exceeds 90% of the estimated hepatic cancer volume (Que et al, 1995; Sartori et al, 2005). Significant improvement in quality of life with prolonged survival also has been confirmed for patients undergoing adequate (>90%) cytoreduction (Knox et al, 2004). These data suggest that hepatic resection of metastatic NET is safe and clinically effective, and overall operative survival is nearly double that of patients with unresected metastases. Few other factors related to the primary NET, metastatic disease, or patients appear to correlate with survival.

A major challenge is providing treatment for bilobar synchronous hepatic metastases, which are relatively common. Although one-step surgery may be feasible, it might require right portal vein embolization (see Chapter 93) to enhance the size of the future liver remnant. Compared with two-step surgical procedures that include resection of the primary and clearance of left liver, followed by right portal vein occlusion and a second step consisting of right or extended right hepatectomy, it seems that with or without preoperative portal vein embolization, one-step surgery is associated with a higher rate of R2 resection and more postoperative complications (Elias et al, 2003; Kianmanesh et al, 2008; Steinmuller et al, 2008). This

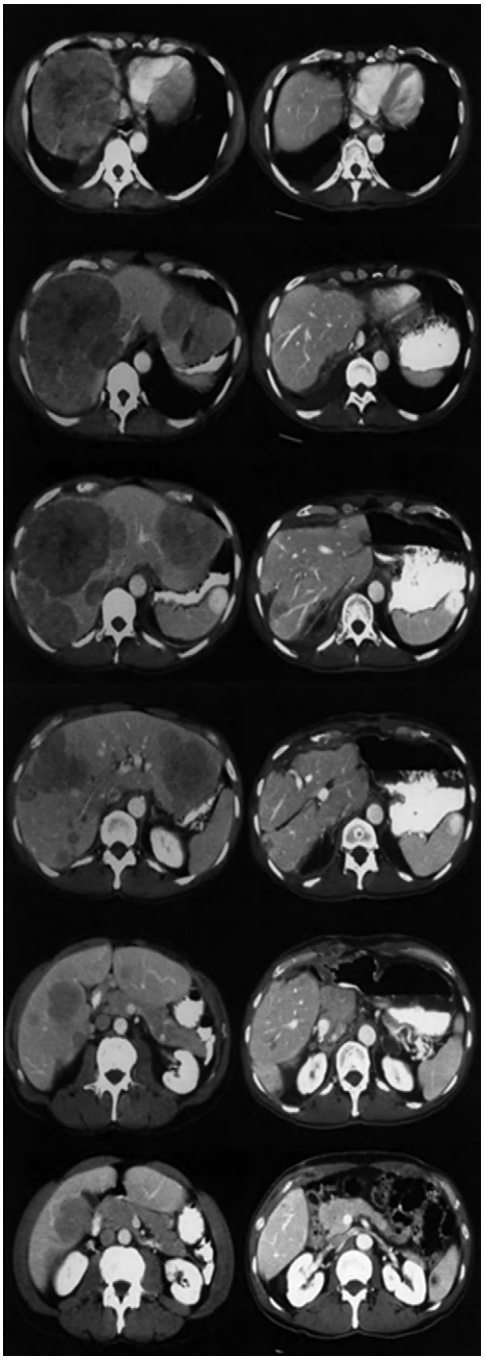


FIGURE 81B.2. Computed tomographic images for a patient with metastatic carcinoid tumor before (*left*) and 18 months after (*right*) cytoreductive hepatic resection. Intrahepatic recurrences were ablated by percutaneous radiofrequency ablation.

might in part be due to preoperative intensive selection of patients in two-step procedures and dissociation of major liver and abdominal surgery; however, compared with liver transplantation, the two-step procedures represent a valid alternative by pushing the limit of respectability in type III patients, especially those with bilobar, synchronous liver metastases (Kianmanesh et al, 2008; Steinmuller et al, 2008).

Complete resection remains the goal of cytoreductive hepatic resection, because both progression rate and median time to clinical recurrence are significantly reduced. The theoretic impact of minimizing residual metastatic NET in the liver on outcome is depicted in Figure 81B.3. Resection of more than 90% of the volume of hepatic metastases can result in significantly different residual cancer volumes based on variations of the incident metastatic volume. Figure 81B.3 shows the projected outcomes of three different residual tumor volumes on symptom recurrence and survival, assuming a greater than 90% resection and a cancer doubling time of 6 months. Both time to recurrence of symptoms and survival are related to residual metastatic cancer volume. The clinical impact of cytoreductive hepatic resection is not more than 90% resection of metastatic NET in the liver but the minimization of residual metastatic volume, that is, not resected volume but rather residual liver volume.

The overall frequency of recurrence or progression after hepatic resection is approximately 80% at 5 years. Intrahepatic progression of residual metastases after R1 or R2 resection or recurrence after R0 resection dictates subsequent liver-directed therapy, unless the risk of liver failure or extrahepatic disease spread override this issue. Although cure of patients with metastatic NET to the liver is infrequent, prolonged palliation is possible. Patterns of intrahepatic recurrence have not been well studied, but intrahepatic recurrence is typically multicentric in our experience. The extent and distribution of hepatic recurrence dictates the choice of therapy. For solitary recurrences, either resection or ablation is appropriate. Given that serial imaging usually identifies small recurrences after hepatic resection, percutaneous ablative approaches are preferable, because morbidity associated with percutaneous RFA is less than that after repeat resection, which is advised for lesions in sites that preclude safe RFA. Sequential ablation or resection is undertaken as recurrence is recognized, until precluded by extent of recurrence within the liver. Metastatic NET that precludes ablation or resection is treated by embolization or chemoembolization, with or without systemic chemotherapy in the absence of extrahepatic disease and with chemotherapy in the presence of extrahepatic disease. A schema for management of neuroendocrine metastases to the liver is outlined in Figure 81B.4.

Hepatic Transplantation for Neuroendocrine Metastases (See Chapters 97A and 97E)

Orthotopic liver transplantation (OLT) has been frequently employed for the treatment of metastatic NET (Table 81B.2). The rationale for OLT is similar to that for resection, with the caveat that adequate cytoreduction by resection is precluded by extensive intrahepatic disease and the absence of extrahepatic metastases. OLT during the time period of intrahepatic disease may be curative or at least significantly palliative. Unlike resection, OLT addresses all hepatic metastases and should provide similar, if not greater, duration of palliation of symptoms and survival. The attractiveness of R0 resection afforded by OLT and the high recurrence rate of NET associated with resection has fostered ongoing evaluation of OLT for metastatic NET (Mazzaferro et al, 2007).

As with resection, OLT was undertaken if the primary and regional NET had been resected, and distal metastases were excluded by octreotide scintigraphy and dynamic CT or MR imaging. Outcomes have been reported for 239 patients. Results and selection criteria have varied, and actual duration of follow-up has been limited, but 1-year survival has ranged from

Table 81B.1

Hepatic Resection for Metastatic Neuroendocrine Tumors

First Author, Year	No. Patients	Perioperative Deaths (N)	Postoperative Symptom Control (%)	Survival % (5 Year)
Chen, 1998	15	0	–	73 (5)
Chamberlain, 2000	34	2	90	76 (5)
Grazi, 2000	19	0	95	92 (4)
Nave, 2001	31	0	–	47 (5)
Yao, 2001	16	0	100	70 (5)
Jaeck, 2001	13	0	100	68 (6)
Ringe, 2001	31	0	–	47 (5)
El Rassi, 2002	11*	0	100	91 (5)
	15†	0	100	50 (5)
Norton, 2003b	16	0	100	82 (5)
Sarmiento, 2003	170	2	96	61 (5)
Knox, 2004	13	–	100	85 (5)
Hibi, 2007	21	0	98	41 (5)
Chambers, 2008†	30	0	75	74 (5)
Kianmanesh, 2008	41 (23*)	0	–	79 (5)
Eriksson, 2008†	42	0	70	80 (5)
Scigliano, 2009*	38	0	–	79 (5)
Frilling, 2009*	23	0	100	100 (5)
Mazzaferro, 2007	36	0	–	85 (5)
Gomez, 2007	18	5%	–	86 (5)
Landry, 2008	23	0	–	75 (5)

*Curative
†Cytoreductive

50% to 100% (mean, 82%), and 5-year survival from 36% to 89% (mean, 57%), with a mean overall follow-up of 36 months. Interestingly, only 23 patients have reportedly reached actual 5-year disease-free survival. Symptomatic relief from clinical endocrinopathies, when present, has been uniformly complete, but duration of symptom relief after OLT has not been clearly documented. Rates of recurrence are generally similar to those after resection, and criteria of patient selection for OLT likely account for this finding.

Several studies have attempted to correlate clinicopathologic factors to survival. Age, location of the primary NET, extent of the primary operation, extent of hepatic metastases, Ki67 index, E-cadherin expression, genetic instability (TP53), and histologic features have been assessed. Age less than 50 years, limited hepatic metastases, low Ki67 index, regular E-cadherin staining, and R0 resection of the primary NET with no evidence of locoregional progression for 1 or more years has correlated with prolonged survival (Fernandez et al, 2003). Current data preclude routine use of these factors as selection criteria for OLT until further confirmed.

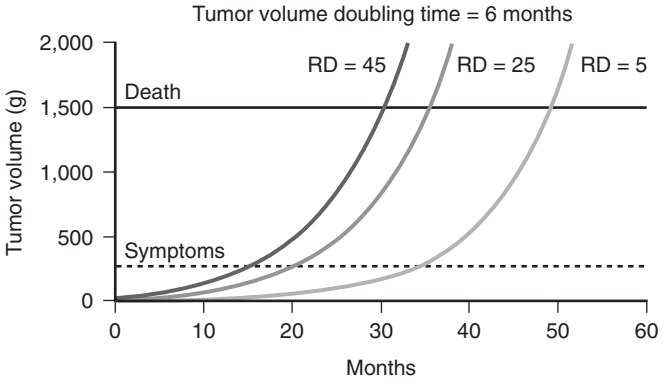


FIGURE 81B.3. Projected tumor doubling time as a function of residual tumor volume after cytoreductive resection and its impact on symptom recurrence and survival over time. RD, residual disease.

Current data do not support OLT as a primary treatment modality for metastatic NET (Clark et al, 2006; Fernandez et al, 2003; Mazzaferro et al, 2007; Steinmuller et al, 2008), but it should be considered an investigative treatment alternative in specialty centers. OLT should probably be considered only in patients with resected primary NET, after a period of disease stability, with exclusion of any extrahepatic disease, and only for selected NET. Whether other biologic or genetic markers will improve the reliability for selection remains unclear.

Radiofrequency Ablation of Neuroendocrine Hepatic Metastases

Multiple minimally invasive ablative modalities exist for the treatment of liver tumors, including cryotherapy, percutaneous ethanol injection (PEI), and thermal techniques such as radiofrequency ablation (RFA), microwave ablation, and interstitial laser thermotherapy (ILT) (see Chapters 83, 84, and 85). Currently, RFA is the most widely used ablative technique for hepatic tumors in general because of its versatility, ease of use, and relatively low risk of complications (Bleicher et al, 2003;

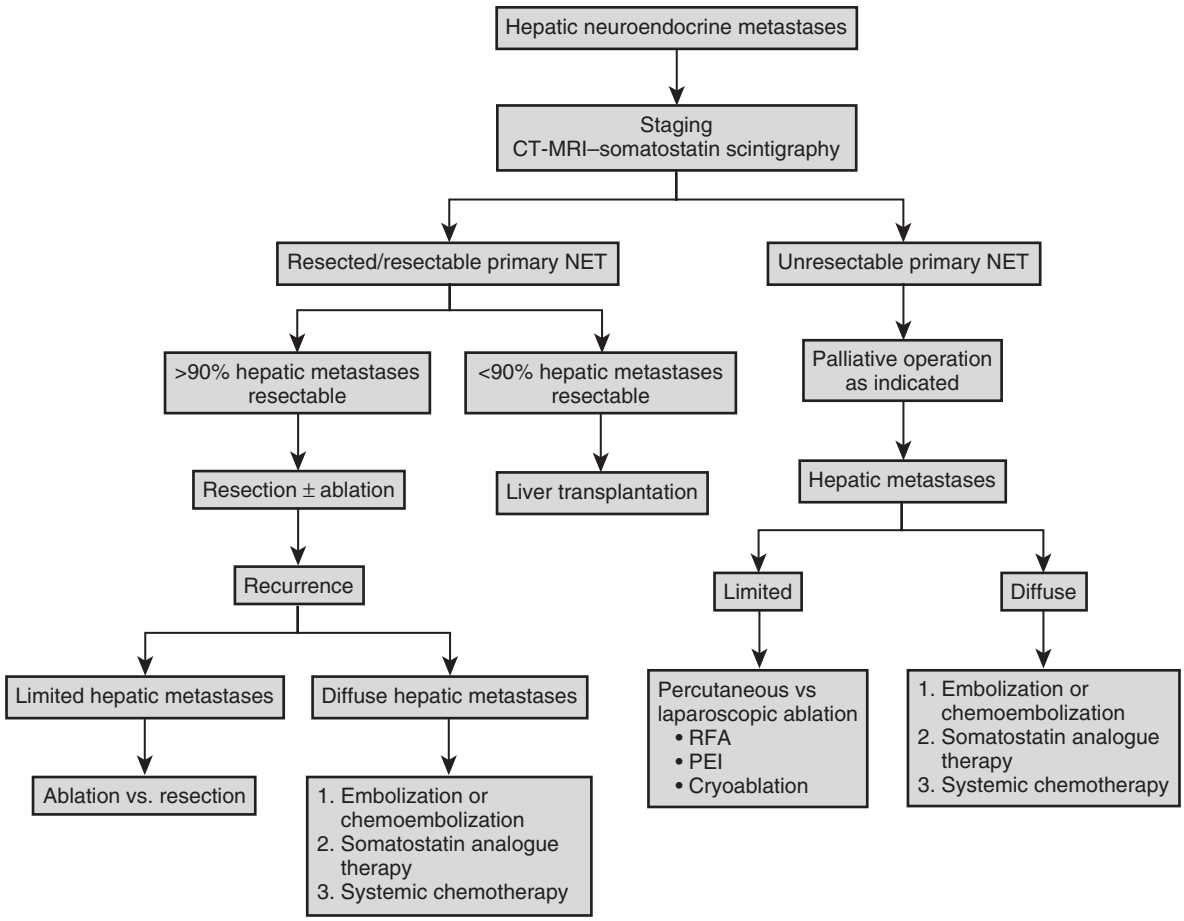


FIGURE 81B.4. Management algorithm for patients with neuroendocrine liver metastases. CT, computed tomography; MRI, magnetic resonance imaging; NET, neuroendocrine tumor; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation

Table 81B.2

Hepatic Transplantation for Metastatic Neuroendocrine Tumors

First Author, Year	No. Patients	Median Follow-up (mo)	1-Year Survival (%)	5-Year Survival (%)	5-Year Disease-Free Survival
Lehnert, 1998	103	—	70	47	7*
Pascher, 2000	4	42	100	50	1
Coppa, 2001	9	39	100	70	—
Ringe, 2001	9	24	67	—	0
Olausson, 2002	9	22	89	—	0
El Rassi, 2002	5	52	80	40	0
Cahlin, 2003	7	36	100	0	0
Rosenau, 2002	19	38	89	80	3
Florman, 2004	11	30	73	36	1
Fenwick, 2004	2	70	100	50	1
Van Vilsternen, 2006	19	18	87	—	—
Marin, 2007	10	34	86	57 (3 years)	—
Olausson, 2007	15	55	90	90	2
Frilling, 2006 & 2009 (4 perioperative deaths)	17	60	—	67	8
Le Treut, 2008	85	—	72	47	20*

*Multicenter collective review

Giovannini & Seitz, 1994; Livraghi et al, 2003; Pearson et al, 1999; Wong et al, 2001); however, its utility for NET metastases will be limited by disease extent in most patients.

The application of RFA for metastatic NET arose after its efficacy was established in the treatment of hepatocellular carcinoma and metastatic colorectal cancer (Curley et al, 1999; Pawlik et al, 2003; Solbiati et al, 2001a; Wood et al, 2000). Local tumor control was achieved in 82% to 98% of treated metastases, although duration of follow-up varied (Bleicher et al, 2003; Bowles et al, 2001; Curley et al, 2000; de Baere et al, 2000; Pawlik et al, 2003, Pearson et al, 1999; Rhim & Dodd, 1999; Solbiati et al, 2001a). Local recurrence rates were higher in patients with colorectal metastases and lower in those with neuroendocrine hepatic metastases (Bleicher et al, 2003; Solbiati et al, 2001b), which is likely related to differences in disease biology and length of follow-up. Successful ablation typically occurred in the treatment of metastases smaller than 3 cm (de Baere et al, 2000; Kettenbach et al, 2003; Solbiati et al, 2001b; Wood et al, 2000); only 50% of tumors greater than 5 cm were ablated completely, even with repeated ablation (Goldberg & Ahmed, 2002).

Published experience with RFA for neuroendocrine hepatic metastases has been limited. RFA has been employed both primarily and as an adjunct to resection. Objective tumor destruction has been well documented and has been shown highly effective in local tumor control, with local recurrence in 3% to 5% of treated metastases (Berber et al, 2002; Hellman et al, 2002b). Improved survival with RFA of metastatic NET has been suggested for selected patients (Elias et al, 2003, 2009).

Duration of follow-up is insufficient to determine actual durability of local control given the protracted natural history of neuroendocrine cancers. Progression of hepatic metastases occurs in about 30% of patients within 2 years (Berber et al, 2002; Hellman et al, 2002b). Specific factors of the hepatic metastases—such as site, degree of necrosis or fibrosis, and hormonal markers—have not yet been correlated to RFA response.

RFA effectively relieves clinical endocrinopathies related to neuroendocrine hepatic metastases; nearly 90% of patients report some degree of symptom relief following ablation (Berber et al, 2002; Hellman et al, 2002b; Henn et al, 2003; Siperstein et al, 1997; Siperstein & Berber, 2001), and duration of relief from symptoms usually is 10 months or longer (Berber et al, 2002; Henn et al, 2003). These findings approach those reported after hepatic resection of metastatic NET (Chamberlain et al, 2000; Sarmiento et al, 2003). For limited hepatic metastases, RFA can achieve similar results percutaneously; however, it must be emphasized that the proportion of patients with disease that is amenable to percutaneous ablation is small. In the setting of extrahepatic disease, isolated hepatic ablation will have a limited effect on symptoms (Henn et al, 2003); however, clinical efficacy will depend upon the volume and site of extrahepatic tumor and the specific hormone expression.

Serum and urine neuroendocrine tumor markers are generally proportional to tumor burden (Jensen et al, 2007; Moertel, 1987). The response of such markers to RFA has been variable. In a study of 34 patients treated with intraoperative RFA, only 65% had a decrease in serum tumor markers afterward (Berber et al, 2002). Persistently elevated tumor markers after RFA likely reflect patient selection, completeness of ablation, and occult or overt neuroendocrine cancer within the abdomen or elsewhere. A favorable response in reduction of serum tumor markers following ablation may predict the durability of symptomatic response and may be associated with improved survival and decreased incidence of disease progression (Berber et al, 2002).

Ethanol Ablation of Hepatic Neuroendocrine Metastases (See Chapter 85)

Ethanol ablation has also been incorporated into the treatment of primary and secondary hepatic neoplasms, including metastases from neuroendocrine malignancies in selected patients (Castells et al, 1993; Giovannini, 2002; Giovannini & Seitz, 1994; Lencioni et al, 1995; Livraghi et al, 1995, 1999; Shiina et al, 1993). Several studies have documented a complete intrahepatic response in patients with hepatic neuroendocrine metastases treated with percutaneous ethanol injection (PEI) (Livraghi et al, 1991), which permits ablation of metastases adjacent to structures at risk of damage by RFA.

Highly selective ethanol ablation can be performed on metastases adjacent to vital structures, such as the hepatic flexure of the colon; those adjacent to large vessels vulnerable to the heat-sink effect; and those adjacent to central bile ducts, where subsequent biliary stricture may occur (Fig. 81B.5). Moreover, metastases of very small size can also be ablated successfully with ethanol, with limited collateral injury to adjacent liver.

Cryoablation of Hepatic Neuroendocrine Metastases (See Chapter 85)

Intraoperative cryoablation is effective in the treatment of primary and secondary tumors of the liver (Finlay et al, 2000; Mahvi & Lee, 1999; Neeleman et al, 2001; Seifert et al, 1998b; Sheen et al, 2002; Zhou & Tang, 1998). Based on a collective review of 1990s literature, local recurrence develops in about 30% of cryoablated tumors (Seifert et al, 1998b). In a direct comparison of cryoablation and RFA in the treatment of both primary and secondary hepatic tumors, RFA was shown to be more effective in local control (2% vs. 14% local recurrence) with fewer complications (3% vs. 41% complication rate) (Chung et al, 2001; Pearson et al, 1999).

Current experience with cryoablation for hepatic neuroendocrine metastases reflects ablations performed intraoperatively (Bilchik et al, 1997; Cozzi et al, 1995; Goering et al, 2002; Seifert et al, 1998a). Most often, the intraoperative cryoablation is performed in conjunction with resection of the primary tumor and hepatic metastases (Cozzi et al, 1995; Seifert et al, 1998a). Local control of neuroendocrine hepatic metastases has occurred in 95% of treated tumors (Chung et al, 2001; Cozzi et al, 1995; Seifert et al, 1998a), which is similar to other ablative techniques. Some relief of symptoms has been shown in all patients, even with recognized subtotal ablative debulking (Bilchik et al, 1997; Cozzi et al, 1995; Seifert et al, 1998b), and postoperative ablative adjuvant therapy with a long-acting somatostatin analogue can prolong symptom-free survival (Chung et al, 2001).

Guidelines for Ablation

General guidelines for the ablation of liver metastases are analogous to the treatment of hepatocellular carcinoma and colorectal metastases. Recognizing the prolonged survival and clinical endocrinopathies associated with metastatic NET, broader application of ablation as a component of multimodal treatment

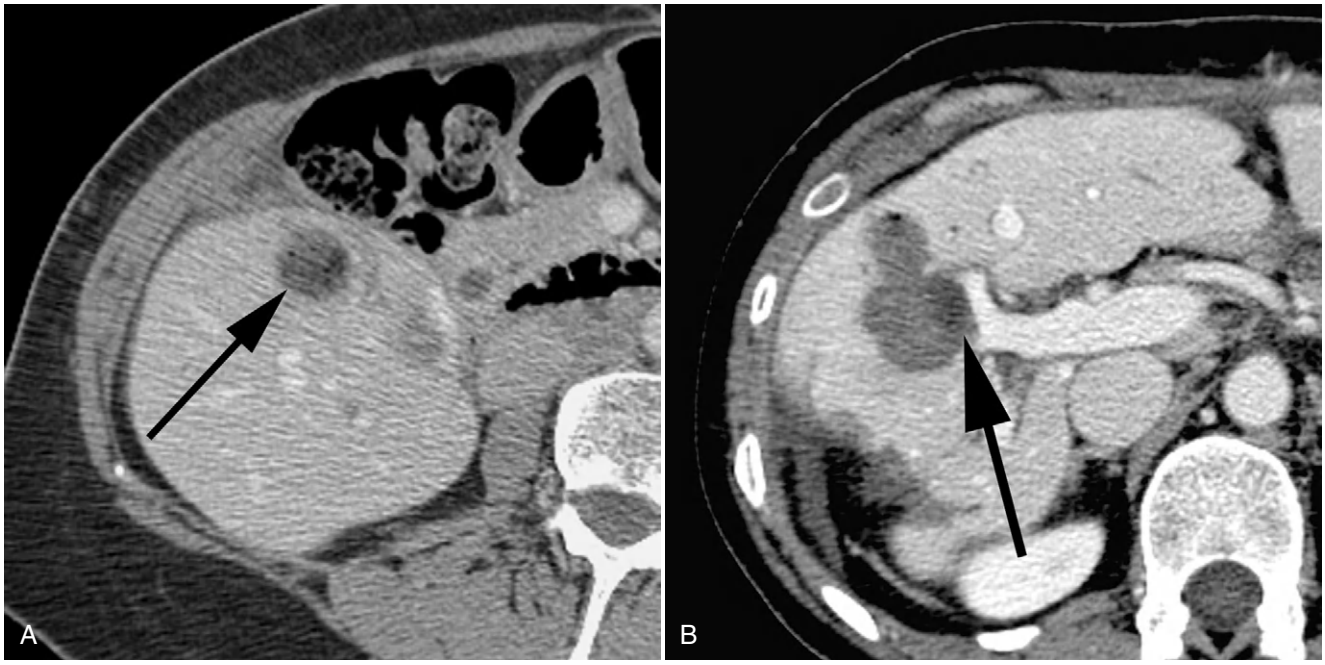


FIGURE 81B.5. Ethanol ablation of critically located neuroendocrine hepatic metastases. **A,** Computed tomography (CT) with intravenous contrast shows nonenhancing, low-density, post–ethanol ablation changes within treated 2 cm carcinoid hepatic metastasis (*arrow*), located near the hepatic flexure of the colon. Radiofrequency ablation (RFA) was deferred due to risk of thermal injury to the colon. **B,** CT with intravenous contrast shows combined RFA and ethanol ablation changes in a carcinoid metastasis located adjacent the right anterior portal vein. Subtle low-density ethanol changes medially in the treated tumor are noted by the *arrow*. Ethanol was selectively used because of the relative cooling of the ablation zone by adjacent blood flow, which could result in inadequate ablation ("heat-sink effect").

is warranted. Indeed, because reports of surgical experience have shown that cytoreduction of NET can considerably improve both patient symptoms and survival, the corollary of an aggressive ablation of progressive hepatic neuroendocrine metastases should provide similar patient benefit.

Three clinical scenarios exist for ablation of neuroendocrine hepatic metastases: 1) as an adjunct to concurrent surgical resection of hepatic metastases; 2) as treatment of limited hepatic metastases in patients unfit for operation; and 3) as the primary hepatic therapy when clinical expertise or intraoperative circumstances preclude safe resection. Palliation of symptoms is an inherent aim for all patients with functional neuroendocrine symptoms.

RFA complements intraoperative resection of hepatic neuroendocrine metastases. Given the extensive hepatic tumor burden typically encountered, ablation affords selective treatment of metastases located deep in the liver or in sites not further resectable after partial hepatectomy. Adjunctive RFA optimizes debulking of hepatic metastases, reduces the extent of resection, and increases overall candidacy for surgical treatment.

Resection is precluded in many patients with neuroendocrine metastases to the liver because of the extent of tumor burden, comorbid disease, or prior hepatic resection. In such patients, percutaneous ablation allows for less invasive tumor debulking and may have some advantage over chemotherapy alone, as shown by Ruers and colleagues (2007).

In contrast to nonneuroendocrine metastases, surgical experience justifies subtotal debulking of significant hepatic tumor by the ablation of multiple metastases (Fig. 81B.6). Generally speaking, if the metastasis is visible with imaging, it can usually be treated in some manner with percutaneous ablation, using either RFA or ethanol, provided sufficient liver parenchyma has been preserved to prevent hepatic decompensation.

This large-volume ablation contrasts with the ablation of limited disease. Such a patient might have one or two very small hepatic metastases such that surgical resection might be considered overly aggressive given the effectiveness of percutaneous RFA in treating such tumors (Fig. 81B.7). Percutaneous treatment is typically performed on an outpatient basis and obviates the longer hospitalization after resection. Moreover, given the invariable recurrence of metastases following surgical resection (Sarmiento et al, 2003), percutaneous ablation is well suited for the patient who has undergone prior liver surgery. Unlike surgical resection, ablation can easily be performed on multiple occasions based on occurrence of new metastases.

RFA of neuroendocrine hepatic metastases allows a relatively noninvasive mechanism to treat patient symptoms, similar to the role of hepatic resection. In our experience, less than 5% of patients are treated solely for tumor-related symptoms. The focus of such ablative treatment is usually twofold, with both debulking of the patient's hepatic tumor and secondary symptom management (Fig. 81B.8).

Microwave (MW) ablation therapy is a local treatment by which tumors are destroyed by coagulation from the passage of MWs into tissue. MW therapy is emerging as a reliable technique under a variety of clinical situations. Two main zones are described after ablative therapy: central and transitional. No viable cells were demonstrated in 93% of lesions after treatment, even up to 6 cm in diameter (Gravante et al, 2008).

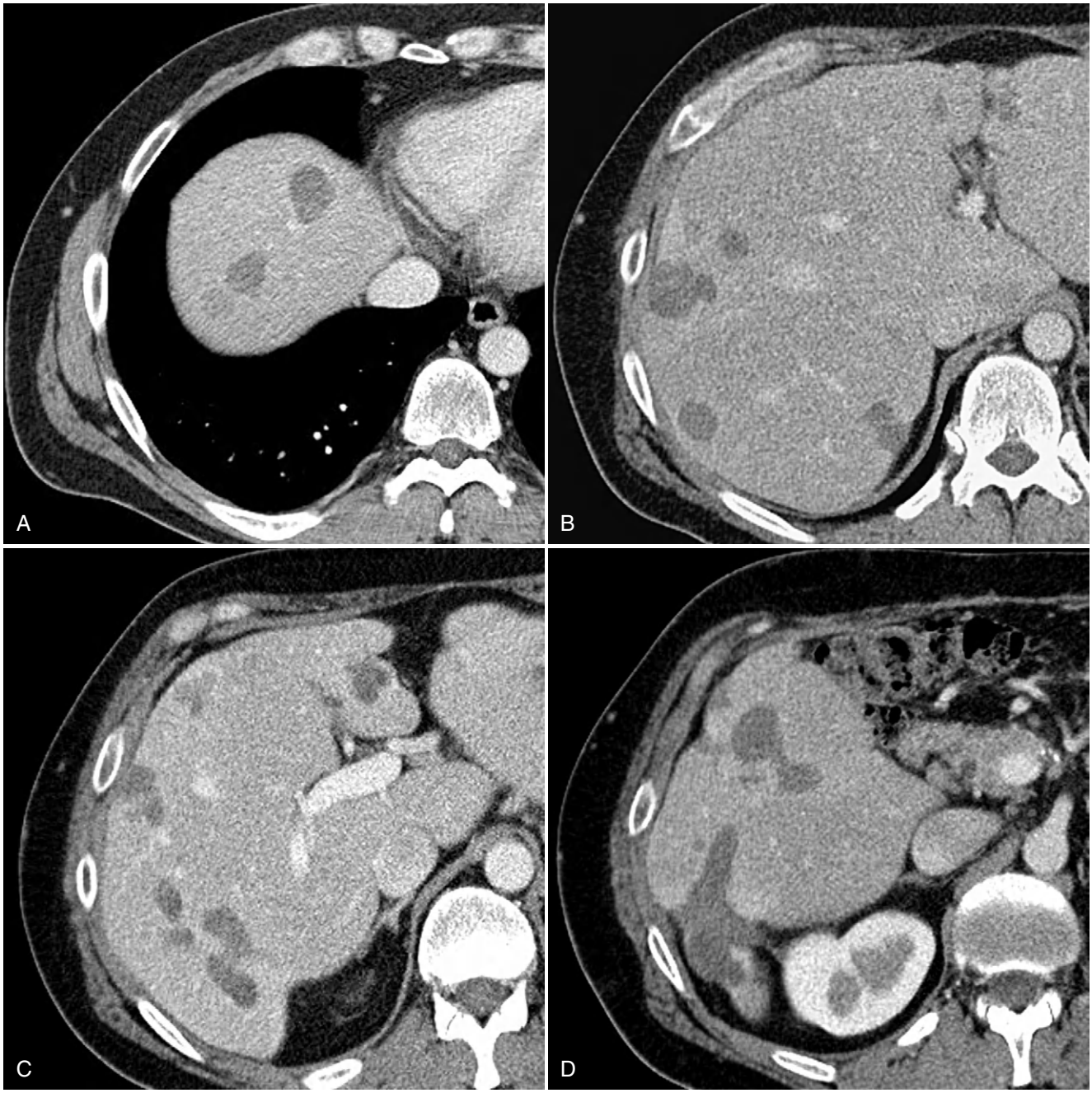


FIGURE 81B.6. Radiofrequency ablation (RFA) of multiple neuroendocrine hepatic metastases. Patient with metastatic islet cell carcinoma has undergone four RFA procedures with the treatment of 50 metastases, including the treatment of 19 metastases in a single percutaneous ablation session. **A** to **D,** CT images following intravenous contrast shows the extensive nonenhancing ablation defects throughout the liver.

Although data comparing RFA with MW are awaited, the results reported in observational studies indicate that MW may have a role when larger ablation zones are required (Boutros et al, 2010).

MEDICAL TREATMENT OF HEPATIC NEUROENDOCRINE METASTASES

The several approaches for the medical treatment of metastatic NET include somatostatin analogues, chemotherapy, immunotherapy, embolization or chemoembolization, and internal irradiation with iridium 131 conjugates (de Vries et al, 2002; Van Essen et al, 2009).

Somatostatin Analogues

Octreotide is a synthetic somatostatin analogue with a significantly longer half-life and duration of action than native somatostatin (Lamberts et al, 1996). It is primarily cytostatic but can also be cytotoxic. The effect of somatostatin analogues is mediated through type 2 and type 5 somatostatin receptors, inhibiting the cellular release of hormone. Response may correlate to

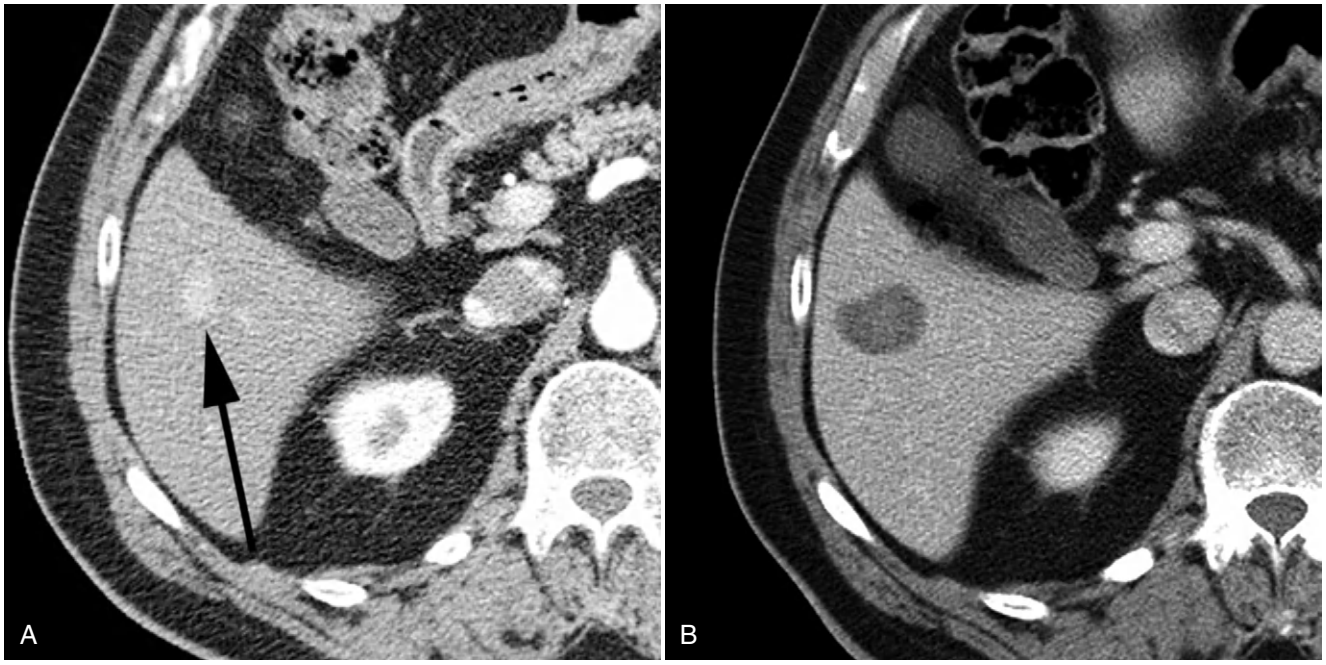


FIGURE 81B.7. Percutaneous radiofrequency ablation (RFA) of metastatic carcinoid in a nonsurgical patient. **A,** Computed tomography (CT) with intravenous contrast shows a subtle, hyperenhancing, solitary 2.3-cm metastasis in the right lobe of the liver (*arrow*). Given limited disease and surgical risk in this 115-kg patient, the metastasis was treated with RFA. **B,** CT obtained 3 months following ablation shows no recurrent tumor.

somatostatin receptor scintigraphy (Janson et al, 1994); the analogues also can affect cell-cycle arrest in G_1 phase, induce apoptosis, and inhibit angiogenesis. Lantreotide is currently the longest acting or slowest release analogue. Octreotide dose ranges from 100 to 500 μg three times daily, and lantreotide is given 60 to 120 mg every 4 weeks.

Somatostatin analogues have been associated with a biochemical response in about 70% of patients, and symptomatic relief is seen in 60% to 90% (Oberg et al, 2004). Objective reduction in tumor size, or more than 50% of the largest diameter, has occurred in less than 10% of patients. Stabilization of NET has been observed in 36% to 70% of patients for a median duration of 12 months (Oberg et al, 2004). As expected, symptomatic response has been correlated with improved quality of life, although response to somatostatin analogue therapy varies by type of NET. As noted previously, short-acting somatostatin analogue therapy is used to prevent or to treat the carcinoid crisis periprocedurally for any intervention such as resection, transplantation, ablation, or embolization. In general, somatostatin analogue treatment is well tolerated. Steatorrhea, diarrhea, abdominal discomfort, and biliary sludge or gallstones can develop but rarely preclude continued use (Kaltsas et al, 2004; Kvols et al, 1987; Trendle et al, 1997). More recently, the long-acting analogues of somatostatin, such as lanreotide and long-acting octreotide, have become available and are the mainstay of symptomatic treatment (Modlin et al, 2008).

Chemotherapy

Systemic chemotherapy is generally reserved for patients with advanced or progressive disease, where other treatment efforts have failed (Brentijens & Saltz, 2001; Kaltsas et al, 2001; Rivera & Ajani, 1998). Recent results of randomized trials have established the role of sunitinib in the management of pancreatic NETs. It has been shown to increase progression-free and overall survival (Raymond et al, 2011). Data from previous trials are also presented. Patients with pancreatic NET have been more responsive to chemotherapy than those with carcinoid tumors (Rivera & Ajani, 1998), and streptozocin-based combinations with 5-fluorouracil (5-FU) and doxorubicin have resulted in objective responses in 45% to 69% of patients (Oberg, 2001; Moertel et al, 1992); however, a more recent study reported disappointing results using a 5-FU and streptozocin combination (Maire et al, 2009). Median duration of response for high-grade NET is about 8 to 9 months. Carcinoid tumors may be less sensitive to cytotoxic agents because of the preponderance of low-grade malignant (well-differentiated) histology and low proliferation index (Bajetta et al, 2002). Dacarbazine, 5-FU, and epirubicin combination therapy has achieved objective tumor response in about 30% of patients with carcinoid tumors (Bajetta et al, 2002; Oberg et al, 2004), and median duration of response for carcinoid tumors is about 6 months. Some success has been achieved with hepatic artery infusional cisplatin in pancreatic NET metastases (Igarashi et al, 2007).

α-Interferon

Systemic α-interferon (α-IFN) may be used to treat advanced NET. The mechanism of α-IFN is mediated through direct inhibition of the cell cycle (G_1/S phase), protein and hormone production, and antiangiogenesis; it is mediated indirectly by increased immune stimulation (Oberg et al, 2004). Although an objective tumor response is seen in only 10% to 15%, both symptomatic and biochemical responses have been observed in about 40% to 60% of patients (Biesma et al, 1992; Fjällskog et al, 2002; Jacobsen et al, 1995; Moertel et al, 1989; Oberg et al, 1986, 2004). Disease stabilization has occurred in 40% to 60% of patients. Adverse reactions to α-IFN are common and may dictate its discontinuation; chronic fatigue and hematologic cytopenias are the most common side effects.

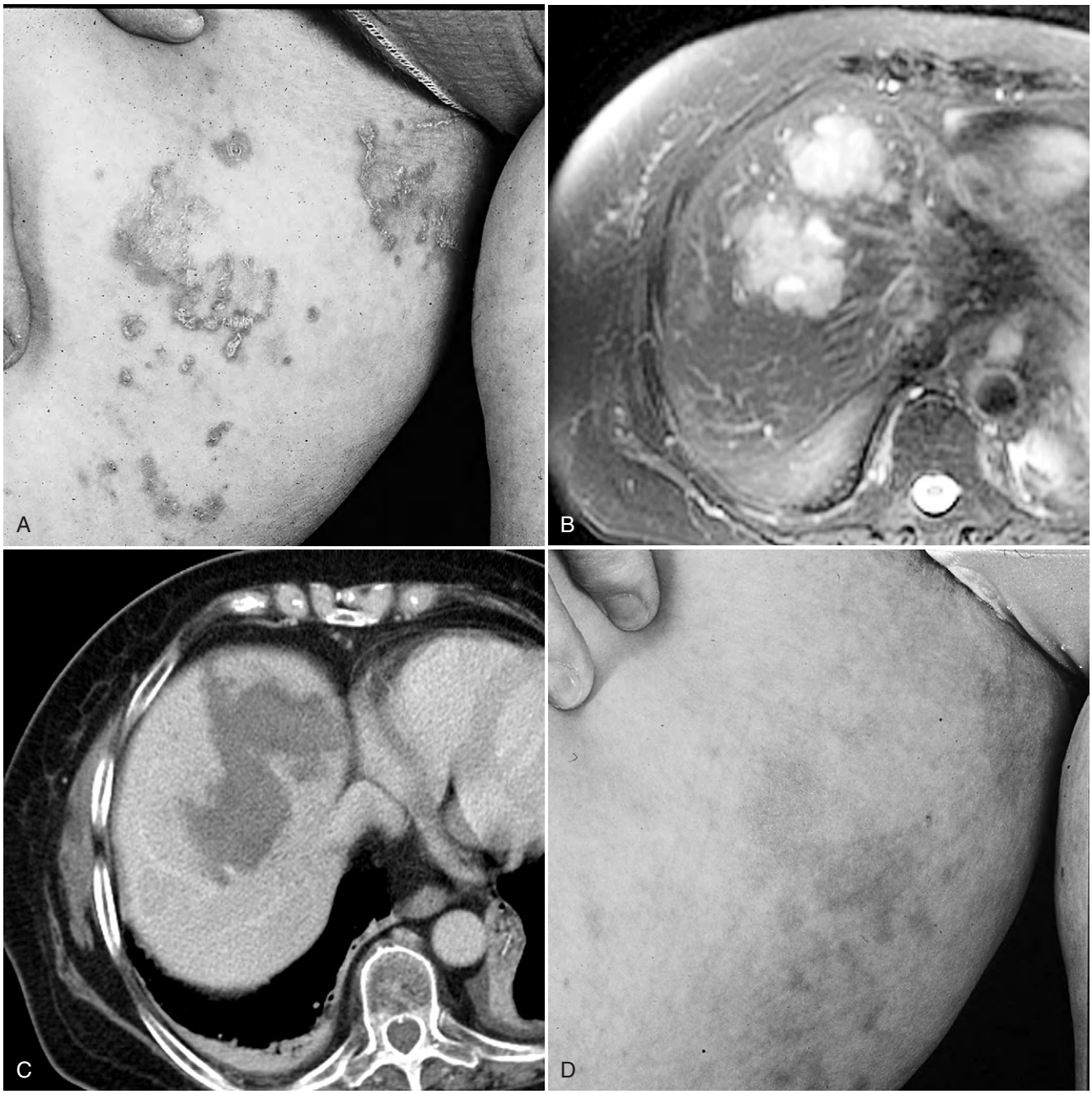


FIGURE 81B.8. Percutaneous radiofrequency ablation (RFA) for relief of symptoms from metastatic glucagonoma (serum glucagon, 16,000 pg/mL). **A,** Symptomatic necrolytic migratory erythema days before ablation session. **B,** Magnetic resonance imaging shows multiple hyperintense hepatic metastases. **C,** CT performed hours after the RFA shows large, corresponding nonenhancing ablation defect in the liver parenchyma. Patient's rash resolved within days of the RFA. **D,** At 2-month follow-up, patient was asymptomatic with healed rash, and serum glucagon was 3700 pg/mL. *(From Atwell TD, et al, 2005: Radiofrequency ablation of neuroendocrine metastases. In vanSonnenberg E, et al, [eds]: Tumor Ablation: Principles and Practice. New York, Springer Business + Science Media, pp 332-340.)*

Embolization or Chemoembolization of Hepatic Neuroendocrine Metastases (See Chapter 83)

Neuroendocrine metastases are intensely hypervascular. Embolization of the hepatic arteries results in ischemia of the metastases and causes variable degrees of tumor necrosis, which can alleviate symptoms or endocrinopathies (Perry et al, 1994). Embolization alone or in combination with intraarterial chemotherapy (chemoembolization) has been employed for relief of symptoms. Repeated embolization is possible depending upon the interventional vascular technique used, selective or nonselective. Objective tumor responses to embolization alone have ranged from 30% to 70% with similar symptomatic response rates (Brown et al, 1999; Oberg et al, 2004). Intermittent or temporary dearterialization with the use of an implantable hepatic artery occluder provides similar symptomatic relief for 6 to 12 months (Bengmark et al, 1982). Duration of response has ranged from 15 to 30 months, and chemotherapy following embolization has prolonged duration of response (Moertel et al, 1994). These findings, coupled with the theoretical advantages

of high intrahepatic concentration afforded by arterial infusion of chemotherapeutic agents, have prompted evaluation of chemoembolization. Although chemoembolization has been used for metastatic NET, range and duration of response has been similar to embolization alone (Fiorentini et al, 2004). To date, no randomized trial comparing embolization with and without chemotherapy have confirmed a significant difference in outcomes or response, and observational data have shown no statistical difference between the two groups (Pitt et al, 2008; Ruutiainen et al, 2007). A combination of chemoembolization with hepatic artery chemoinfusion for patients with unresectable hepatic disease has achieved better than 3-year survival for the majority of patients (Christante et al, 2008).

Complications are generally tolerable, although not insignificant. A postembolization syndrome consisting of nausea, right upper quadrant abdominal pain, fever, and elevation of serum transaminases usually lasting for 3 to 7 days is common. Parenteral analgesias, intravenous hydration, and antipyrexics are often necessary. Antibiotic prophylaxis is recommended for embolization. Other side effects include gallbladder necrosis, hepatic abscess, and renal failure. Patients with large (>5 to 10 cm) metastases and those with more than 50% to 70% hepatic replacement are at greater risk of complications. Sequential lobar embolization may reduce the severity of the postembolization syndrome and may lower the risk of complications. Mortality after embolization has ranged from 2% to 7%.

New Drugs and Targets

Recent randomized trials assessing the utility of sunitinib maleate notwithstanding (Raymond et al, 2011) the crucial issue with rigorous assessment of medical treatment is that most studies are retrospective, assess heterogeneous tumors, commonly lack standardized entry criteria, reflect single-center experience, and are underpowered. As previously discussed, the tyrosine kinase inhibitor sunitinib malate has shown proven efficacy in the management of metastatic pancreatic NETs (Raymond et al, 2011). It has recently been approved by the FDA and has been adopted by several European countries.

Traditional DNA-damaging cytotoxic drugs are of limited efficacy in GEP NETs for reasons outlined above. Several proangiogenic molecules are overexpressed in NETs, such as vascular endothelial growth factor (VEGF) and its receptors and related signaling-pathway components: epithelial growth factor receptor, insulin-like growth factor-1 receptor, phosphoinositide-3-kinase, RAC-α serine/threonine-protein kinase (AKT), and mammalian target of rapamycin (mTOR). New drugs that target some of these molecules are under assessment in early clinical trials, such as bevacizumab (monoclonal antibody against VEGF). Angiogenesis and mTOR inhibitors (temsirolimus, everolimus) may have potential, but less than 20% of patients show a radiologic response (Konings et al, 2009; Yao et al, 2008). Although strategies that use these biologic agents might advance the management of GEP NETs, they were first developed for other tumor types. The development of more effective drugs for GEP NETs will need improved understanding of GEP NET biology and perhaps the discovery of a molecular target specific to all or some subtypes of GEP NETs. Use of somatostatin receptors to target so-called *passenger drugs*—that is, active cytotoxic drugs that are physically linked to agents that bind to somatostatin receptors—might hold promise.

Recently, the combination of two oral cytotoxic agents, capecitabine and temozolomide, has been shown to have significant activity in patients with advanced pancreatic endocrine tumors. A response rate of 70%, combined with a progression-free survival of 18 months, was recently reported (Strosberg et al, 2010).

Peptide Receptor Radionuclide Therapy

GEP NETs overexpress peptide receptors, mainly subtype 2, which become internalized after ligand binding; therefore they are targets for cytotoxic drugs coupled to somatostatin, such as radiolabeled somatostatin analogues. Using indium 111 diagnostic scintigraphy for these receptors can identify tumors that express somatostatin receptors (Nasir et al, 2008; de Jong et al, 2009). This new treatment is proving to be safe and effective and might become an important treatment strategy for lesions that express adequate densities of somatostatin receptors (Kwekkeboom et al, 2008).

Primary Hepatic Neuroendocrine Tumors

Albeit rare, neuroendocrine tumors may arise primarily within the liver. Hepatobiliary neuroendocrine tumors accounted for only 2% of all GI carcinoids in the Surveillance Epidemiology and End Results (SEER) database over a 30-year period, and primary hepatic carcinoids accounted for less than half of these tumors (Modlin et al, 2003). Most reports of primary hepatic carcinoids are single-case experiences, and case series are usually limited to less than 6 patients (Knox et al, 2003). Primary hepatic carcinoids have similar histopathologic and immunohistochemical findings as extrahepatic carcinoids. Most primary hepatic carcinoids are nonfunctional and are rarely associated with the carcinoid syndrome; however, because they can be functional and may be associated with a specific endocrinopathy, and not limited only to the carcinoid syndrome, they should probably be termed *primary hepatic neuroendocrine tumors* and not *hepatic carcinoids.*

The diagnosis presumes a thorough search and exclusion of an extrahepatic neuroendocrine tumor. The cell of origin is unknown. Pancreatic heterotopia has been postulated as a source of these tumors. Some may arise from intrahepatic biliary tract radicles, because carcinoids of the extrahepatic biliary tract are more common. Moreover, most primary hepatic neuroendocrine tumors arise centrally or in the perihilar area within the liver (Hwang et al, 2008). Finally, some primary hepatic neuroendocrine tumors may in fact be metastases from an occult primary NET or a primary NET that had spontaneously regressed. A history of prior GEP resections warrants careful pathologic review of the resected specimen to exclude a missed primary NET. Conversely the absence of an identifiable extrahepatic site of NET after resection is posited as evidence supporting the liver as a primary site.

NET shows a female predominance (65%), and mean age at presentation is 50 years. Typical symptoms and signs at presentation include abdominal pain, jaundice, weight loss, and rarely a specific endocrinopathy. The imaging features are similar to other neuroendocrine tumors (Fig. 81B.9). The criteria for resectability of primary hepatic NET are similar for other hepatic malignancies. Because of the central location within the liver, extended lobar hepatic resections are frequently required for resection of these tumors. Hepatic transplantation has also been employed.

A review of the literature reveals an overall 5- and 10-year survival of 78% and 59%, respectively (Knox et al, 2003).

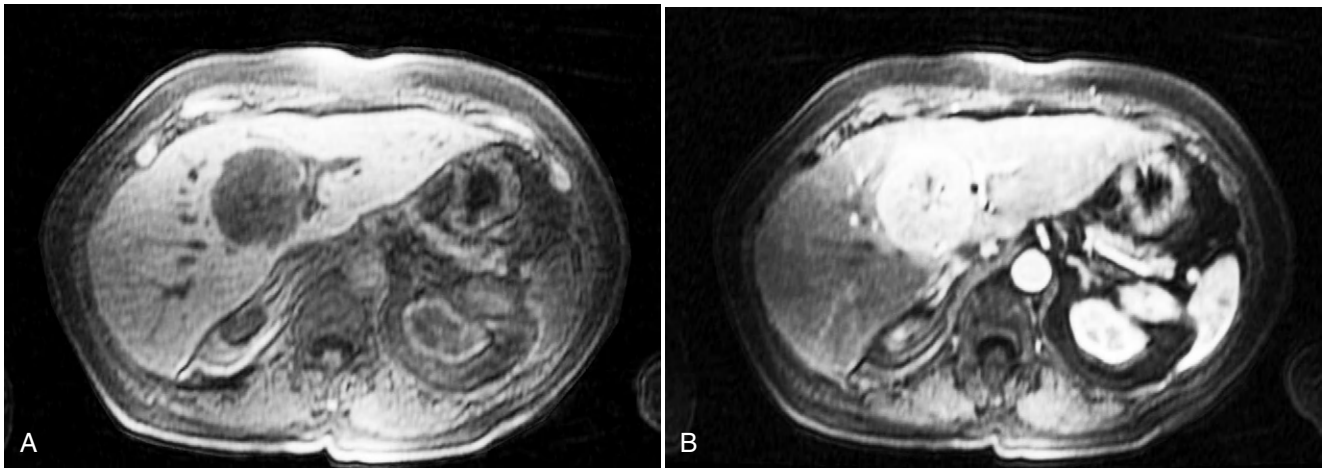


FIGURE 81B.9. T1-weighted **(A)** and T2-weighted **(B)** magnetic resonance images of a primary hepatic neuroendocrine tumor depicting the expected features of discrete hypervascular solitary mass residing centrally within the liver.

Among the 44 patients reported to have had hepatic resections for treatment, 5- and 10-year survival were 80% and 68% respectively (Knox et al, 2003). Predictors of long-term survival have been few, and analysis of such factors is limited by the low prevalence of primary hepatic NET. In fact, hepatic multicentricity and bilaterality, extrahepatic metastases at the time of resection, advanced age, and gender have not correlated adversely with survival. Recurrence within the liver has not been uncommon, and repeat resections have been reported and are associated with further prolongation of survival. Hepatic transplantation has also proven effective for primary hepatic NET deemed unresectable otherwise by standard techniques (Fenwick et al, 2004). The overall and disease-free survival after hepatic transplantation are similar to those of standard resection, albeit limited in duration of follow-up and number of patients reported. Current data preclude assessment of antihormonal therapy and chemotherapy, although anecdotal reports suggest responses are similar to those in patients with extrahepatic NET.

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CHAPTER 81C

Noncolorectal nonneuroendocrine metastases

Jürgen Weitz and Ronald P. DeMatteo

OVERVIEW

Hepatic resection is a well-established therapy for patients with liver metastases from colorectal or neuroendocrine carcinoma. Resection of liver metastases from colorectal cancer (CRC) results in a 3-year survival rate of 30% to 61% and a 5-year survival rate of 16% to 51%, depending on patient selection (Choti et al, 2002; Fong et al, 1997, 1999; Scheele et al, 1995; Schlag et al, 1990; Tomlinson et al, 2007; see Chapter 81A). In patients with hepatic neuroendocrine metastases, 5-year survival rates of 76% have been achieved with surgical resection, and some surgeons occasionally employ liver transplantation (Chamberlain et al, 2000; Lehnert, 1998; see Chapter 81B). In contrast, the role of hepatectomy in patients with liver metastases from noncolorectal, nonneuroendocrine (NCNN) tumors is not well defined, but the number of reports on this topic is increasing.

SERIES SUMMARIZING MULTIPLE PRIMARY TUMOR TYPES

Most current reports regarding hepatectomy for metastases of NCNN tumors combine multiple primary tumor types in order to have a sufficient number of patients to analyze. Despite this approach, most series are still limited by small numbers or inclusion of patients with neuroendocrine metastases (Benevento et al, 2000; Buell et al, 2000; Elias et al, 1998; Goering et al, 2002; Hamy et al, 2000; Hemming et al, 2000; Karavias et al, 2002; Laurent et al, 2001; Schwartz, 1995; Takada et al, 2001; van Ruth et al, 2001; Yamada et al, 2001).

Goering and colleagues (2002) reported the outcome of 48 patients who had undergone liver resection or ablation for liver metastases from noncolorectal tumors. With a median follow-up of 48 months, the 5-year survival rate was 39%, and the median overall survival was 45 months. No difference was found in survival between patients treated with liver resection versus those treated with cryotherapy. The 3-year survival for patients with primary neuroendocrine (n = 13), genitourinary (n = 16), and soft tissue tumors (n = 15) was 91%, 52%, and 34%, respectively ($P = .26$).

Elias and colleagues (1998) performed hepatectomy in 147 patients with liver metastases from a noncolorectal primary. Operative mortality was 2%. The overall 5-year survival rate was 36% with the following results for various primary tumors: breast cancer 20% (n = 35), neuroendocrine tumor 74% (n = 27), testicular cancer 46% (n = 20), sarcoma 18% (n = 13), and gastric cancer 20% (n = 11). The authors pointed out that the overall survival was similar to results they obtained in 270 patients who underwent liver resection for metastases of CRC.

Hemming and associates (2000) performed liver resections in 37 patients with NCNN primaries. After a median follow-up of 22 months, the overall 5-year survival rate was 45%. Curative resection and primary tumor type were independent prognostic markers of overall survival in this series. In the subgroup with nongastrointestinal primary tumors (n = 30), the overall 5-year survival rate was 60% compared with 0% for patients with gastrointestinal primary tumors (n = 7; $P = .01$).

Laurent and coworkers (2001) analyzed the outcome of 39 patients who underwent potentially curative resection of NCNN liver metastases. Patients had primary gastrointestinal (n = 15), genitourinary (n = 12), or miscellaneous (n = 12) tumors. The 5-year survival for the entire group was 35%. Notably, 5-year survival was 100% for patients with a disease-free interval that exceeded 24 months from removal of the primary versus 10% otherwise ($P = .01$). No other prognostic parameters were identified.

The Memorial Sloan-Kettering Cancer Center (MSKCC) experience of hepatic resection for metastases from NCNN carcinoma was analyzed by Weitz and associates (2004). The objectives of this study were to define perioperative and long-term outcome and to define prognostic factors for survival in 141 patients who underwent resection for liver metastases from NCNN carcinoma during the period from April 1981 through April 2002. Table 81C.1 depicts the primary tumor types. The median operative time was 238 minutes (interquartile range, 180 to 321 minutes), and the median blood loss was 600 mL (interquartile range, 250 to 1420 mL). The median length of hospital stay was 9 days (interquartile range, 7 to 12 days). Of 141 patients, 46 (33%) developed postoperative complications, but the 30-day mortality rate was 0%. The median follow-up was 26 months, with a median follow-up of 35 months. The 3-year relapse-free survival rate was 30% (median, 17 months), and the 3-year cancer-specific survival rate was 57% (median, 42 months). Primary tumor type and length of disease-free interval from the primary tumor were significant independent prognostic factors for relapse-free and cancer-specific survival (Figs. 81C.1 to 81C.3; Table 81C.2).

Margin status was significant for cancer-specific survival and showed a strong trend in relapse-free survival. Patients with a primary reproductive tract tumor who underwent R0 resection had the best outcome, with a 3-year cancer-specific survival of 78%. In the group of patients with primary non–reproductive tract tumors, survival after R0 resection was influenced largely by the length of the disease-free interval. Patients with a disease-free interval of 24 months or less achieved a 3-year survival of 36%, but only 5% were free of relapse after 3 years. Patients with a non–reproductive tract primary and a disease-free interval of more than 24 months had a 3-year cancer-specific

Table 81C.1

Primary Tumor Type of Patients Undergoing Liver Resection for Metastatic Noncolorectal, Nonneuroendocrine Tumors

Primary Tumor	No. (%)
Breast	29 (20)
Melanoma	17 (12)
Reproductive tract	39 (28)
Testicular	20 (14)
Gynecologic	19 (14)
Ovarian	12
Endometrial	4
Cervical	2
Fallopian tube	1
Adrenocortical	15 (11)
Renal	11 (8)
Gastrointestinal	12 (9)
Stomach	3
Duodenal	1
Pancreatic	5
Ampullary	2
Anal	1
Other	13 (9)
Lung	4
Salivary gland	3
Nasopharyngeal	2
Glottal	1
Tonsil	1
Thyroid	1
Sweat gland	1
Unknown	5 (3)

Data from Weitz J, et al, 2004: Partial hepatectomy for metastases from non-colorectal, nonneuroendocrine carcinoma. Ann Surg 241:269-276.

survival of 72% and a 3-year relapse-free survival of 30%, with 14 5-year survivors in this group.

Laparoscopy might be a reasonable staging tool for patients with NCNN liver metastases. D'Angelica and coworkers (2002) examined 30 patients with potentially resectable NCNN tumors based on preoperative imaging. Nine of these patients had unresectable disease, six of whom were identified by laparoscopy.

Adam and colleagues (2006) reported the results of 1452 patients undergoing hepatic resection for NCNN liver metastases. The primary tumors were most commonly located in the breast (32%) and the gastrointestinal (GI) tract (16%) or were urologic tumors (14%). Operative mortality rate was 2.3%, with a surgical morbidity of 21.5%. Overall 5- and 10-year survival rates were 36% and 23%, respectively. On multivariate analysis, patient age (>60 years), type of primary tumor (non-breast, melanoma, or squamous cell histology), extrahepatic disease, R2 resection, and major hepatectomy were independent adverse prognostic factors. Using these factors, patients could be classified into low risk (0 to 3 risk factors, 5-year survival: 46%), medium risk (4 to 6 risk factors, 5-year survival: 33%), and high risk (>6 risk factors, 5-year survival: <10%; $P = .0001$).

The retrospective nature of all of these studies and the consequent bias related to patient selection represent major limitations. Nevertheless, the general theme is one of potential benefit in selected patients with limited disease, specific primary tumor types, and a prolonged disease-free interval.

SERIES FOCUSED ON ONE PRIMARY TUMOR TYPE

Sarcoma

One of the largest surgical series of patients with sarcoma metastatic to the liver was composed of 56 patients who underwent liver resection (DeMatteo et al, 2001). These patients were selected from 331 patients with liver metastases from sarcomas who had been admitted to MSKCC during the years 1982

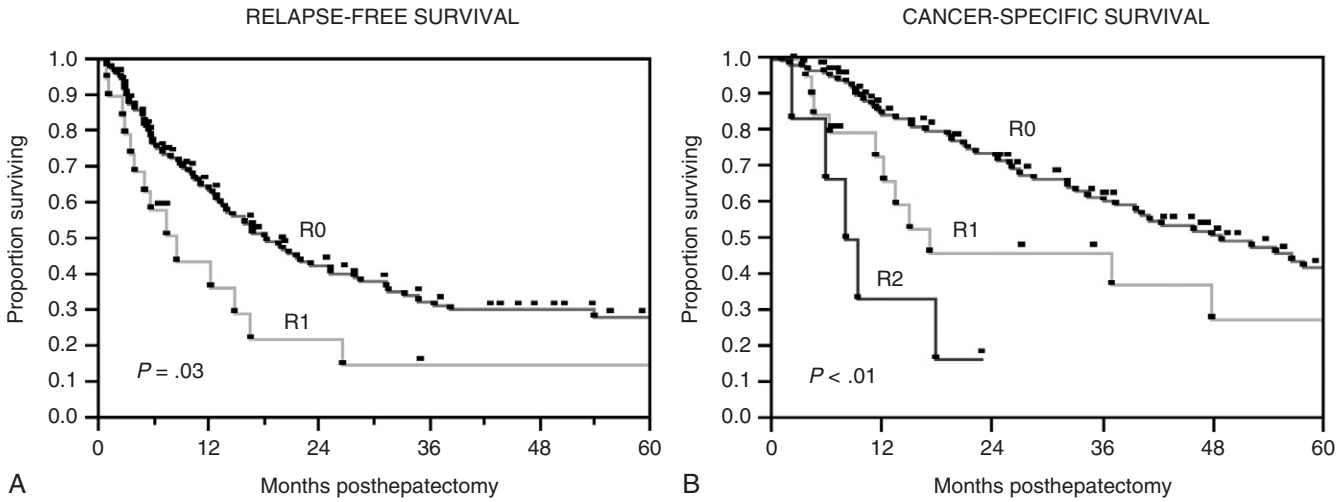


FIGURE 81C.1. Survival after resection of hepatic metastases stratified according to margin status (R0, n = 116; R1, n = 19; R2, n = 6). **A,** Relapse-free survival. **B,** Cancer-specific survival. *(From Weitz J, et al, 2004: Partial hepatectomy for metastases from non-colorectal, non-neuroendocrine carcinoma. Ann Surg 241:269-276.)*

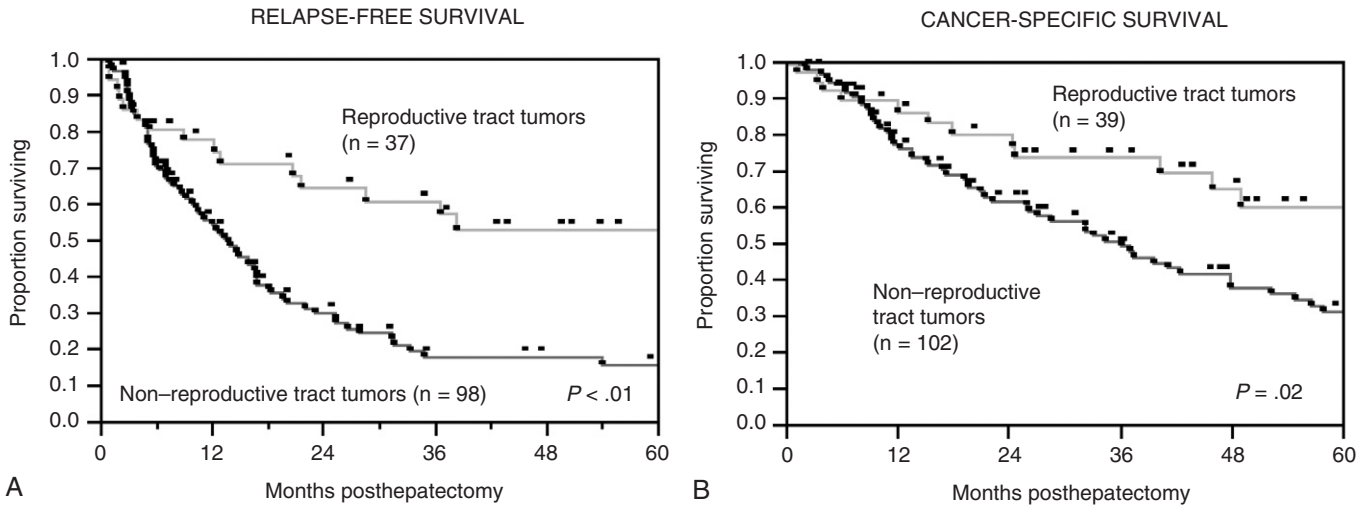


FIGURE 81C.2. Survival after resection of hepatic metastases stratified according to primary tumor type (reproductive tract versus nonreproductive tract tumors; patients with R2 resection were excluded for relapse-free survival). **A,** Relapse-free survival. **B,** Cancer-specific survival. *(From Weitz J, et al, 2004: Partial hepatectomy for metastases from non-colorectal, non-neuroendocrine carcinoma. Ann Surg 241:269-276.)*

through 2000. Gastrointestinal stromal tumors (GISTs; Fig. 81C.4) and leiomyosarcomas were the most common histology; no perioperative deaths were reported in patients undergoing complete resection of the tumor, and the 5-year overall survival rate was 30% with a median of 39 months in completely resected patients. Patients who did not undergo complete resection had a 5-year survival of only 4% (Fig. 81C.5). A disease-free interval of less than 24 months was a significant adverse prognostic parameter for survival on univariate and multivariate analysis (Fig. 81C.6).

In a report from Pawlik and colleagues (2006b), 66 patients undergoing liver resection and/or ablation were included; the 5-year disease-free and overall survival rates were 16.4% and 27.1%, respectively. Patients in whom RFA was part of the treatment and patients who did not receive chemotherapy, mostly imatinib mesylate for metastatic GISTs, showed a significantly reduced survival.

The treatment strategy for patients with liver metastases from GISTs has changed since the development of the targeted agent imatinib mesylate, which achieves dramatic tumor response rates (Corless et al, 2004; DeMatteo, 2002) such that imatinib is now the first-line treatment. Resection is considered for patients when they reach the maximal response to imatinib, if all gross tumor can be removed and for those who have immediate or limited acquired resistance to the drug (Antonescu et al, 2005). Patients with mulitfocal resistance to imatinib seem not to beneftit from surgical intervention (DeMatteo et al, 2007).

Breast Cancer

In a small proportion (4% to 5%) of patients with breast cancer, liver metastases are the only sign of disseminated disease (Fig. 81C.7; Elias et al, 2003). Although it has not been formally proven that liver resection prolongs survival for selected patients with liver metastases of breast cancer, 5-year survival was 33% to 61% in more recently published series (Caralt et al, 2008; Elias et al, 2003; Vlastos et al, 2004). Patients with liver

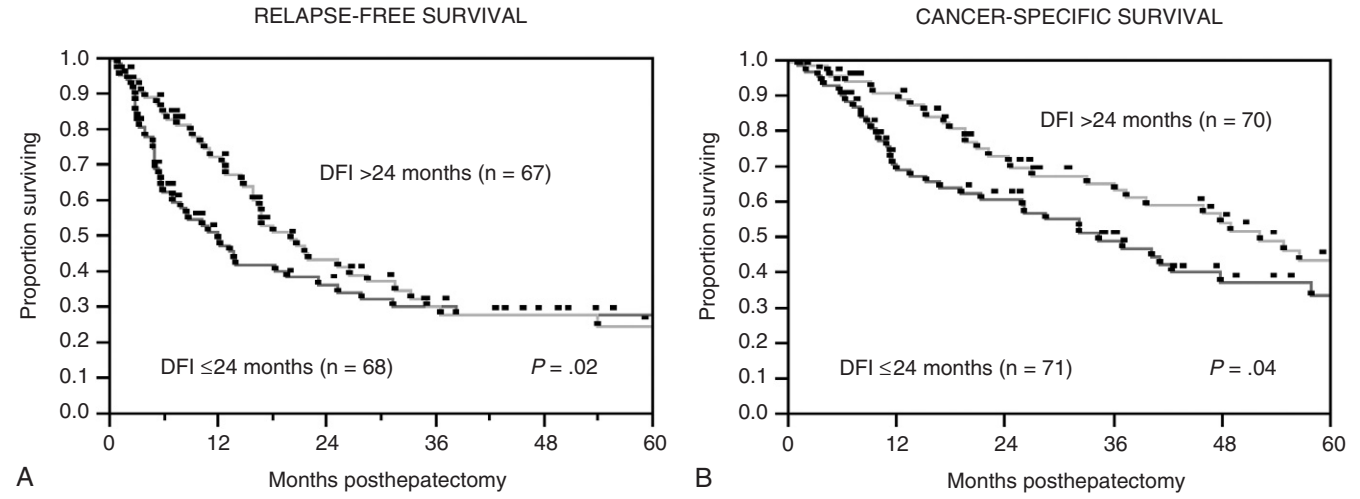


FIGURE 81C.3. Survival after resection of hepatic metastases stratified according to disease-free interval (*DFI*); patients with R2 resection were excluded for relapse-free survival. **A,** Relapse-free survival. **B,** Cancer-specific survival. *(From Weitz J, et al, 2004: Partial hepatectomy for metastases from non-colorectal, non-neuroendocrine carcinoma. Ann Surg 241:269-276.)*

Table 81C.2

Multivariate Analysis of Prognostic Factors of Patients Undergoing Liver Resection for Metastatic Noncolorectal, Nonneuroendocrine Carcinoma

	RELAPSE-FREE SURVIVAL*		CANCER-SPECIFIC SURVIVAL	
Factor	**Hazard Ratio (95% CI)**	***P* Value**	**Hazard Ratio (95% CI)**	***P* Value**
Disease-Free Interval				
≤24 mo	1.4 (1.1-1.8)	.02	1.4 (1.0-1.8)	.03
>24 mo	Reference		Reference	
Primary Tumor				
Adrenocortical	0.9 (0.5-1.6)	<.01	0.7 (0.4-1.3)	.02
Breast	0.9 (0.6-1.5)		1.0 (0.6-1.7)	
Gastrointestinal	0.6 (0.3-1.1)		0.8 (0.3-1.5)	
Reproductive tract	0.4 (0.2-0.6)		0.4 (0.2-0.7)	
Melanoma	1.0 (0.5-1.9)		1.5 (0.7-2.7)	
Renal	1.1 (0.5-2.2)		0.7 (0.3-1.3)	
Other	1.6 (0.8-2.9)		1.7 (0.3-1.3)	
Unknown	Reference		Reference	
Margin Status				
R0	Reference	.08	Reference	<.01
R1	1.8 (0.9-3.2)		2.1 (1.1-4.1)	
R2	ND*		2.7 (0.8-7.9)	

*Relapse-free survival patients with incomplete macroscopic resection (n = 6) were not included in the analysis.
CI, confidence interval; ND, not determined

Data from Weitz J, et al, 2004: Partial hepatectomy for metastases from non-colorectal, non-neuroendocrine carcinoma. Ann Surg 241:269-276.

metastases from breast cancer receiving chemotherapy only rarely, if ever, survive 5 years (Wyld et al, 2003). Even with aggressive systemic chemotherapy, the median survival for patients with isolated liver metastases of breast cancer was only 23 to 27 months, with time to progression of 8 to 10 months in two more recent trials (Atalay et al, 2003). Resection for liver metastases in this setting may prolong survival for a subset of highly selected patients (Singletary et al, 2003).

Table 81C.3 summarizes the published studies of liver resection for metastatic breast cancer. Meaningful comparisons between these studies cannot be made, because they are heterogeneous studies reporting small patient numbers with different inclusion criteria and treatment strategies. Valid criteria for selecting patients who might benefit from hepatic resection for metastases of breast cancer cannot be defined at this time.

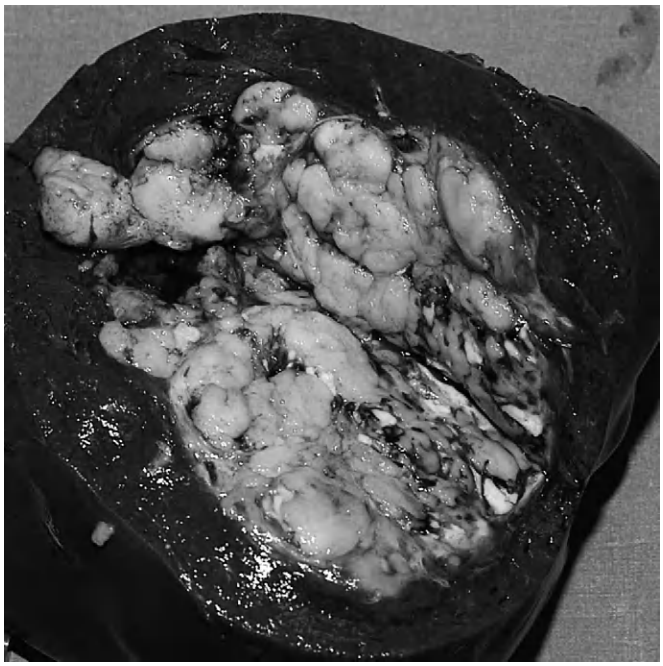


FIGURE 81C.4. Right hepatectomy for a liver metastasis from gastrointestinal stromal tumor.

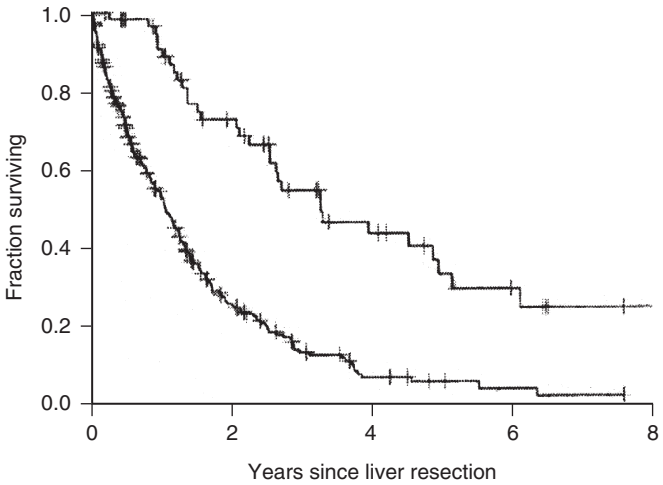


FIGURE 81C.5. Disease-specific survival of patients with liver metastases from sarcoma who underwent complete resection (*upper line,* n = 56) versus other treatment (*lower line,* n = 275; *P* = .0001). *(From DeMatteo RP, et al, 2001: Results of hepatic resection for sarcoma metastatic to the liver. Ann Surg 234:540-548.)*

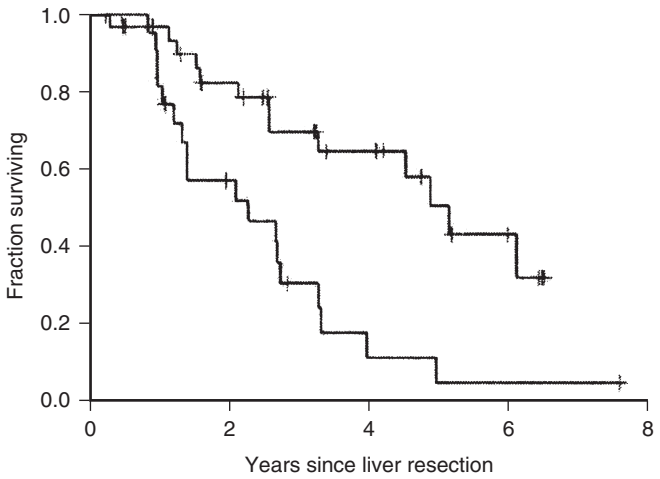


FIGURE 81C.6. Disease-specific survival of patients after complete resection of liver metastases from sarcoma with a disease-free interval of more than 2 years (*upper line,* n = 32) versus less than 2 years (*lower line,* n = 24; *P* = .002). *(From DeMatteo RP, et al, 2001: Results of hepatic resection for sarcoma metastatic to the liver. Ann Surg 234:540-548.)*

A common recommendation is that patients with extrahepatic disease should not undergo liver resection, even though some studies did not find a worse prognosis for such patients. Some authors also suggest that patients should first undergo systemic chemotherapy, and that only patients who do not progress should undergo liver resection. Formal randomized trials confirming this strategy have not been performed. Recently, a report regarding radiofrequency ablation (RFA) has been published; median survival for included patients was 30 months, but the follow-up time was only 19 months, and the local tumor progression rate was 25% (Meloni et al, 2009).

Melanoma

Melanoma recurs after potentially curative resection in approximately one third of patients, with almost every organ being at risk (Allen & Coit, 2002). Hepatic metastases are diagnosed in about 10% to 20% of patients with stage IV melanoma, even though it is well documented that most patients have liver metastases on postmortem examination. Patients with liver metastases as the initial site of metastatic disease have a very poor prognosis, with a median survival of 4.4 months (Rose et al, 2001). Most patients have unresectable disease, owing to extrahepatic disease or disseminated hepatic metastases. This point was shown by a study from the John Wayne Cancer Institute and the Sydney Melanoma Unit (Rose et al, 2001). During the years 1971 through 1999, 26,204 patients with melanoma were seen in these institutions, and 1750 patients (6.7%) had liver metastases. Only 34 patients underwent surgical exploration for attempted liver resection, and hepatectomy was performed in 24 patients. Of these 24 patients, 12 had synchronous extrahepatic disease, and 18 patients could be rendered disease free surgically. The 10 patients who underwent exploration only had a median survival of 4 months; the overall survival of all patients with liver metastases treated nonoperatively was 6 months. Overall survival in the patients who underwent complete resection was 28 months, with a median disease-free survival of 12 months. One patient achieved 10-year survival, and the 5-year overall survival was 29%. Complete gross resection and histologically negative margins were associated with an improved disease-free survival, and complete gross resection showed a trend for improved overall survival (*P* = .06).

From this experience, one might conclude that extrahepatic disease per se is not a contraindication for resection, as long as all disease is resectable. Selection of patients is crucial, which is well documented in this study. Only 1.4% of all patients with liver metastases underwent hepatic resection, and these patients had a median disease-free interval of 58 months before presenting with hepatic metastases. Several other small series in the literature mostly comprise fewer than 10 patients undergoing liver resection for metastatic melanoma, with median survival times of 10 to 51 months (Herman et al, 2007; Rose et al, 2001). Repeat hepatic resection might be beneficial for some patients who can be rendered disease-free surgically (Mondragon-Sanches et al, 1999).

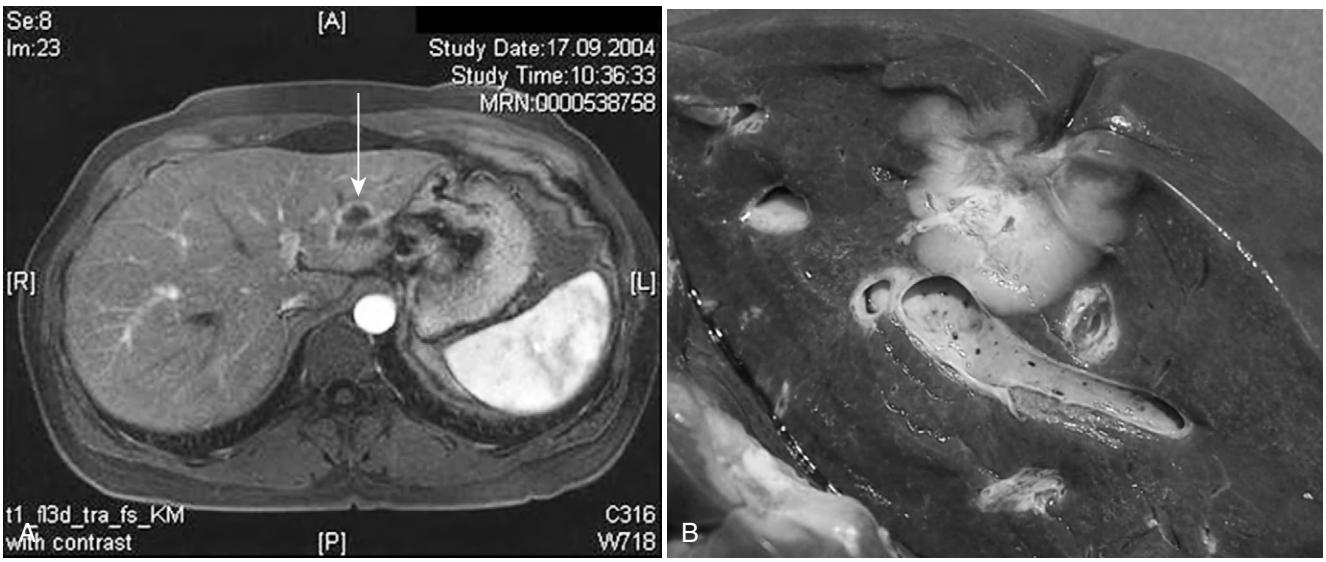


FIGURE 81C.7. Liver metastasis of breast cancer. **A,** Computed tomographic scan shows the lesion (*arrow*) to have early peripheral contrast enhancement. **B,** The patient underwent resection of segments II and III; a gross photograph of the sectioned specimen is shown.

Table 81C.3

Results of Liver Resection for Metastatic Breast Cancer*

Reference	No. Patients	Median Survival (mo)†	Adverse Prognostic Factors	Comments
Caralt et al, 2008	12	36	Disease-free interval <24 mo	Seven patients developed hepatic recurrence
Vlastos et al, 2004	31	63	None	Inclusion criteria: no extrahepatic disease
Elias et al, 2003	54	34	Negative receptor status (odds ratio, 3.5)	Inclusion criteria: no extrahepatic disease, no disease progression on chemotherapy
Carlini et al, 2002	17	53	None	Inclusion criteria: no extrahepatic disease
Pocard et al, 2000	49	42	Short disease-free interval; node-positive primary	Inclusion criteria: good performance status, objective response on chemotherapy, 1 to 3 liver metastases
Selzner et al, 2000	17	27	Short disease-free interval	6041 patients with breast cancer treated during study interval
Yoshimoto et al, 2000	25	34	None	67% of patients developed recurrence in the liver
Seifert et al, 1999	15	57	None	Inclusion criteria: no extrahepatic disease
Raab et al, 1998	34	41.5‡	R1 resection; local recurrence of primary tumor	59% of patients had isolated metastasis

*Only series including >10 patients are presented.
†Overall survival
‡For patients undergoing R0 resection

Uveal Melanoma

Uveal melanoma is a distinct entity that seems to have a different tumor biology, and it commonly spreads to the liver. About 50% to 80% of patients with uveal melanoma who develop distant metastases have liver involvement. Hsueh and colleagues (2004) reported 112 patients with metastatic uveal melanoma, and 78 patients had liver metastases. A total of 24 patients underwent surgical resection for metastatic disease, five with liver metastases. A multivariate analysis showed resection, but not site of metastasis, to be a significant predictor of survival. The median survival for patients undergoing resection was 38 months in this series, with a 5-year survival of 39%. Aoyama and colleagues (2000) presented a series of 12 patients with metastatic uveal melanoma, nine with liver metastases. Median recurrence-free survival after complete resection was 19 months, with a median overall survival exceeding 27 months, emphasizing that selected patients with metastatic melanoma may benefit from resection. In a report from Pawlik and colleagues (2006a), 16 patients with liver metastases from ocular melanoma underwent resection; the median time to recurrence was 8.8 months. Compared with patients undergoing liver resection for metastatic cutaneous melanoma, more patients developed recurrent disease in the liver (53% vs. 17%); however, the 5-year survival was significantly better for metastatic ocular melanoma (21% vs. 0%; $P = .015$). Despite these data, most patients with liver metastases from uveal melanoma are not candidates for a complete resection. For these patients, regional chemotherapy might offer increased response rates, and probably increased overall survival, compared with other treatment options (Feldman et al, 2004).

Gastric and Pancreatic Cancer

Most reports on liver resection for NCNN metastases of gastrointestinal origin are based on patients with gastric cancer. Patients undergoing hepatic resection for metastatic gastric cancer are highly selected, which is apparent in the report of Ochiai and colleagues (1994), who treated 6540 patients with gastric cancer. Liver resection for metastases was performed in only 30 of these patients (0.46%). Table 81C.4 summarizes more recently published data; there have been few long-term survivors.

Only a handful of long-term survivors have been reported after the resection of liver metastases from pancreatic ductal adenocarcinoma (Detry et al, 2003). In a report from Shrikhande and colleagues (2007), 11 patients underwent combined pancreatic and liver resection for metastatic pancreatic cancer, with a median survival of 11.4 months. A recent review on this topic summarized 103 patients who underwent liver resection for metastatic pancreatic cancer; median survival ranged from 5.8 to 11.3 months (Michalski et al, 2008). Consequently, surgery remains highly controversial and unlikely to benefit most of these patients. For other primary malignant tumors of the pancreas that show a less aggressive tumor biology, such as solid pseudopapillary tumor of the pancreas, resection of liver metastases might be justified (Martin et al, 2002).

Renal Carcinoma

About 10% of patients with renal tumors develop liver metastases, and they have a dismal prognosis: fewer than 10% survive beyond 1 year, and only about 2% to 4% develop hepatic disease that is amenable to complete resection. Several series in the literature report fewer than 10 patients undergoing liver resection for metastatic renal tumors, with survival exceeding 5 years in about 13% of patients (Alves et al, 2003). In one series, 14 patients with liver metastases from primary renal tumors underwent partial hepatectomy (Alves et al, 2003). Median survival was 26 months, with a 3-year survival of 26%. Patients with a disease-free interval less than 24 months and patients with a diameter of the metastases exceeding 5 cm showed a worse prognosis. In patients with recurrence after hepatic resection, survival was better for patients who could undergo a repeat hepatectomy. In a more recent report on 31 patients, 5-year overall survival was 39% for the whole patient group and 50% for margin-negative patients (Thelen et al, 2007). In patients with hepatic metastases from renal tumors who are candidates

Table 81C.4

Results of Liver Resection for Metastatic Gastric Cancer*

Reference	No. Patients	Median Survival†	Adverse Prognostic Factors	Comments
Sakamoto et al, 2003	22	21.4 months	>1 liver metastasis	Inclusion criteria: no extrahepatic disease
Shirabe et al, 2003	36	3-year survival, 26%	Lymphatic invasion‡; venous invasion‡; >3 liver metastases	Four 5-year survivors; 61% of patients developed liver recurrence
Okano et al, 2002	19	3-year survival, 34%	Synchronous metastases; >1 liver metastasis; no fibrous pseudocapsule	Four 5-year survivors; 63% of patients developed liver recurrence of metastasis
Ambiru et al, 2001	40	2-year survival, 27%	Synchronous metastases	Six 5-year survivors; 72% of patients developed liver recurrence
Fujii et al, 2001	12	16.3 months	Disease-free interval <12 months; metastases >5 cm	—

*Only series including >10 patients are presented.
†Overall survival
‡Primary tumor

for a complete resection, surgical exploration may be justified. Other therapies should also be considered, such as hepatic artery embolization and targeted molecular therapy, such as with sunitinib.

Reproductive Tract Tumors

Effective chemotherapeutic regimens are available for most reproductive tumors. Resection is only one component of a multimodal approach to the treatment of liver metastases from these tumors. The development of liver metastases is a well-defined adverse prognostic factor for patients with germ cell tumors (Gholam et al, 2003). Rivoire and associates (2001) attempted to define guidelines for the resection of liver metastases from germ cell tumors. These authors examined 37 patients who had undergone liver resection for metastatic germ cell tumors. All patients had received cisplatin-based chemotherapy before surgery. Median survival was 54 months with an overall 5-year survival rate of 62%. The authors defined three prognostic factors associated with a worse outcome: 1) pure embryonal carcinoma in the primary tumor, 2) liver metastasis greater than 3 cm, and 3) presence of viable residual disease after chemotherapy. Because no patient with liver tumors less than 1 cm had viable disease, the authors recommended a nonsurgical approach for these patients. Men with liver tumors greater than 3 cm in diameter represent a high-risk group that may not benefit from partial hepatectomy, but resection was recommended for the other subgroups.

Hahn and coworkers (1999) presented data regarding 57 patients undergoing liver resection for metastatic testicular cancer after systemic chemotherapy. In 48 patients, concomitant cytoreductive procedures for extrahepatic disease were performed. The overall 2-year survival rate was 97.1%. Pathologic analysis of resected specimens showed either a benign lesion or only necrotic tumor in 58% of specimens. Three of five patients with active disease and persistently elevated serum markers died during follow-up, underlining the importance of response to chemotherapy as a predictor of outcome.

Patients with metastatic ovarian or fallopian tube carcinoma usually do not present with isolated liver metastases, because the disease is generally diffuse within the abdomen and pelvis. Cytoreductive surgery that reduces disease to less than 1 cm when combined with chemotherapy is an accepted treatment approach. For these diseases, liver resection may be necessary because of true liver metastases or secondary liver involvement by peritoneal disease. A median overall survival of 62 months after hepatic resection has been described with this approach in 24 patients, with 18 patients having extrahepatic disease at the time of hepatectomy (Yoon et al, 2003). In this study, complete resection of all gross disease was possible in 21 patients, whereas in three patients, tumor debulking to less than 1 cm was performed. Merideth and colleagues (2003) reported 26 patients who underwent liver resection for metachronous metastases from ovarian carcinoma; cytoreduction was suboptimal (residual tumor = 1 cm) in five patients. Median disease-related survival was 26.3 months, and a disease-free interval exceeding 12 months and optimal cytoreduction were associated with improved outcome. Other reports also justify hepatic resection in metastatic ovarian carcinoma (Bristow et al, 1999; Chi et al, 1997; Lim et al, 2009). Unlike most other tumors, ovarian cancer is usually confined to the liver surface, and although extensive involvement can be seen, intraparenchymal hepatic metastases are uncommon (Fig. 81C.8).

Liver resection for metastases from cervical and endometrial cancer have been reported in the literature with an overall survival of 7 to 50 months (Kollmar et al, 2008; Tangjitgamol et al, 2004). Selected patients may benefit from hepatectomy; however, because of the small number of published cases, no general conclusions can be drawn from the available data.

Other Primary Tumors

Resection of liver metastases of lung cancer has been reported, and in selected patients, long-term survival has been achieved. Di Carlo and associates (2003) summarized the available data from the literature. Liver resection was performed in 14 patients with liver metastases from lung cancer, and two patients lived longer than 5 years.

A recent report summarized the results of hepatic resection for metastatic squamous cell carcinoma from various primary sites (anus, head/neck, lung, esophagus, and others) (Pawlik et al, 2007). The median overall survival was 22 months, with



FIGURE 81C.8. Axial computed tomographic image of a large ovarian metastasis to the left liver. Note that the tumor is extending into the liver from without, with no penetration is evident through the liver capsule.

synchronous disease, metastasis size greater than 5 cm, and positive surgical margins being adverse prognostic parameters.

Patients presenting with liver metastases from an unknown primary tumor are a challenge to manage, because median overall survival is approximately 5 months. Liver resection or ablative therapy might be appropriate for some patients, in whom all disease can be destroyed or removed, but a median disease-free survival of only 6.5 months has been reported (Hawksworth et al, 2004).

CRITICAL EVALUATION OF LIVER RESECTION FOR METASTATIC NONCOLORECTAL NONNEUROENDOCRINE TUMORS

Before discussing the rationale of liver resection for metastatic NCNN tumors, it is helpful to consider the reasons for the relative success of liver resection for metastatic CRC. As a result of the favorable long-term outcome after resection and the improved safety of liver resection, the treatment strategy for patients with liver metastases arising from primary CRCs has changed in the past 2 decades. Liver metastases from CRC are no longer viewed as indicators of untreatable, widespread, systemic disease, and cure is still possible with surgery in some patients.

Two different concepts explain the relatively favorable outcome of patients undergoing hepatectomy for liver metastases from CRC: First, the tumor biology of metastatic CRC may be different from that of other solid tumors. Tumor cell dissemination of CRC via the bloodstream may be inefficient and could lead to death of most of the tumor cells shed into the bloodstream before the development of clinically significant metastases. Implantation of circulating colorectal tumor cells in the liver may be particularly effective owing to the expression of particular adhesion molecules (Mizuno et al, 1998; Sugarbaker, 1993; Weiss, 1990). The second reason may be the venous drainage of the large intestine via the portal vein to the liver. Tumor cells that reach the liver through the portal vein may be effectively entrapped by the liver, preventing systemic spread. If this concept is correct, tumor cells must overcome hepatic filtration to reach the systemic circulation and cause distant metastases (Sugarbaker, 1993).

Both notions are substantiated by clinical and experimental findings. It could be shown that the liver is an effective filter for CRC cells, because these cells can be found more frequently in blood samples obtained from the portal vein compared with blood samples from the vena cava (Koch et al, 2001). Tumor biology is also important, however, because the most relevant prognostic factors after resection of colorectal liver metastases, such as length of disease-free interval and nodal status of primary tumor, are at least in part surrogates for tumor biology (Fong et al, 1999).

These concepts are crucial when trying to define the value of surgical resection of noncolorectal liver metastases. Except for gastrointestinal primaries, the liver is not the primary filter for venous blood from the organs being discussed in this chapter. Liver metastases from nongastrointestinal cancers indicate systemic tumor spread; this makes selection of patients with good tumor biology a crucial factor to offer hepatic resection to patients who may benefit the most. Tumor biology depends mainly on the primary tumor type, which is shown by the fact that relapse-free and cancer-specific survival for patients with reproductive tract primary tumors is significantly longer compared with that of patients with non–reproductive tract primary tumors in most studies.

When selecting patients for liver resection, it also is important to select patients with more favorable tumor biology within a particular histology. Disease-free interval, or the time between the treatment of the primary tumor and the development of liver metastasis, may be a valid surrogate marker in this respect, with a longer disease-free interval being associated with less aggressive tumor biology. Most studies support this concept, because patients with a longer disease-free interval show a longer relapse-free and cancer-specific survival after hepatectomy.

The biologic behavior of liver metastases also is most likely linked to the behavior of the primary tumor, because positive lymph node status or venous invasion of the primary tumor predicts worse outcome after hepatectomy for liver metastases in some studies. Tumor biology also appears to determine whether a patient would respond to systemic chemotherapy, which might be an important component when managing these patients, as has been shown for hepatic metastases of reproductive tract primary tumors.

Another important point that should be considered when contemplating hepatic resection for a patient with NCNN metastases is the likelihood of achieving a microscopically complete tumor resection. In most studies, long-term survival can be achieved only if the tumor can be removed completely, which depends on tumor-related factors and surgical expertise. When summarizing the published data, primary tumor type, length of disease-free interval, and pathologic features of the primary tumor may be valid criteria to assess the potential outcome after a planned hepatic resection for patients with metastatic NCNN tumors. By applying these criteria, long-term survival after potentially curative resection of liver metastases can be achieved. The use of systemic chemotherapy to assess the biologic behavior of the tumor also should be considered, although randomized trials validating this approach are lacking.

CONCLUSION

Hepatic resection for metastatic NCNN tumors is safe and is associated with a favorable outcome in highly selected patients. Primary tumor type and disease-free interval seem to be valid selection parameters. Because hepatic resection is often the only modality offering a potential cure, it should be considered in some patients with metastases from NCNN tumors.

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CHAPTER 84B

External-beam radiotherapy for liver tumors

Alice Ho and Karyn A. Goodman

OVERVIEW

The advancement of radiation therapy (RT) for hepatobiliary tumors over the last decade has been a remarkable achievement that has improved delivery, outcomes, and quality of care for patients with primary liver and biliary tumors. Whereas RT for tumors in or near the liver has been limited by the tolerance doses for the liver, as well as for the surrounding normal organs, more conformal techniques and sophisticated treatment-planning software have made focal treatment fields possible. Accurate delivery of targeted treatment, which is hampered by the significant degree of organ motion in the abdomen, has historically been problematic for clinicians; however, the emergence of novel imaging and motion-management techniques are allowing for more targeted therapy of these tumors and new attempts to escalate the dose of RT. Classic approaches to portals and fractionation have been abandoned in favor of more focal techniques of irradiating liver tumors. These techniques typically consist of innovations designed to minimize normal hepatic irradiation and enhance target conformality, such as intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), and the use of motion management. The role of all of these new approaches in the radiotherapeutic management of primary liver and biliary tumors will be discussed. In addition, the role of new alternative fractionation protocols and the use of radioisotopes in the management of primary liver tumors will also be highlighted.

TECHNICAL INNOVATIONS

Intensity-Modulated Radiotherapy

Over the last decade, more sophisticated imaging and treatment-planning techniques have allowed for more focal delivery of RT. Now routine is computed tomography (CT)-assisted three-dimensional conformal radiation therapy (3D-CRT), which uses diagnostic CT or magnetic resonance imaging (MRI) to define normal and target structures. IMRT is a further technical innovation, now frequently used in hepatobiliary radiation. As opposed to conventional radiation that uses large, fixed radiation portals and field borders based on correlations between the bony anatomy and the soft-tissue target, IMRT uses CT-based planning, and the target volumes and normal structures are delineated individually on axial CT imaging. With conventional RT, normal tissues adjacent to target structures cannot be spared and receive the prescribed radiotherapy dose, limiting the radiation dose that can be delivered safely. When planning treatment using IMRT, the radiation dose is prescribed to the target volume, and strict dose constraints are placed on normal tissues. The IMRT plan is then developed using a computer-optimized algorithm to deliver radiation of varying intensity to the target volume via multiple beams to meet the requirements for the target volume coverage and normal tissue constraints. The overall result is a highly conformal dose distribution customized to the shape of the tumor (Fig. 84B.1). This minimizes exposure of surrounding normal tissues and organs to high-dose radiation.

Image-Guided Radiotherapy and Motion Management

The development of 3D-CRT and IMRT, which allow for delivery of more conformal radiotherapy to the tumor, has made more accurate localization of the tumor at the time of treatment necessary to avoid missing the target. The need to improve targeting in radiation treatment has led to the development of image-guided radiation therapy to reduce the uncertainties of tumor positioning. On-board 3D CT imaging, known as *cone-beam CT* (CBCT), has been developed to allow real-time assessment of tumor positioning on the linear accelerator, while the patient is on the table prior to treatment delivery; however, CBCT scans may not show the target lesion in the liver because of limitations in resolution and contrast (Fig. 84B.2). Because liver tumors are not well visualized on standard megavoltage portal images or even on CBCT, surrogates for tumor location have been used to help verify tumor positioning prior to treatment. Fiducial markers (see Fig. 84B.2) have been introduced to help identify the tumor and allow for better visualization and improved setup for both conventionally fractionated treatments and, more importantly, for focal RT. Gold fiducial markers can be percutaneously inserted in or around the liver tumor, or postoperative clips can be used to help evaluate the postoperative bed on kilovoltage images. These fiducial markers are essential to allow for both tumor localization and assessment of tumor motion during treatment, and they are used in conjunction with many of the motion-management techniques described below.

Although 3D-CRT and IMRT offer the ability to tighten the margin around the target volume, the motion of the liver is complex because of organ deformation and rotation with respiration. Some series have found that the liver moves from 1 to 8 cm in the superior-inferior direction with respiration, and smaller shifts are noted in the anterior-posterior and left-right directions with breathing (Shirato et al, 2004). Because of this significant displacement over time, standard treatment techniques require large margins on the gross tumor volume to ensure a full dose to the tumor throughout the respiratory cycle.

Novel methods of accounting for target motion have been developed to improve the accuracy of treatment delivery. Motion management is often combined with IGRT for targeted, focal liver irradiation, as the bony landmarks do not precisely represent tumor location as a result of organ motion. The

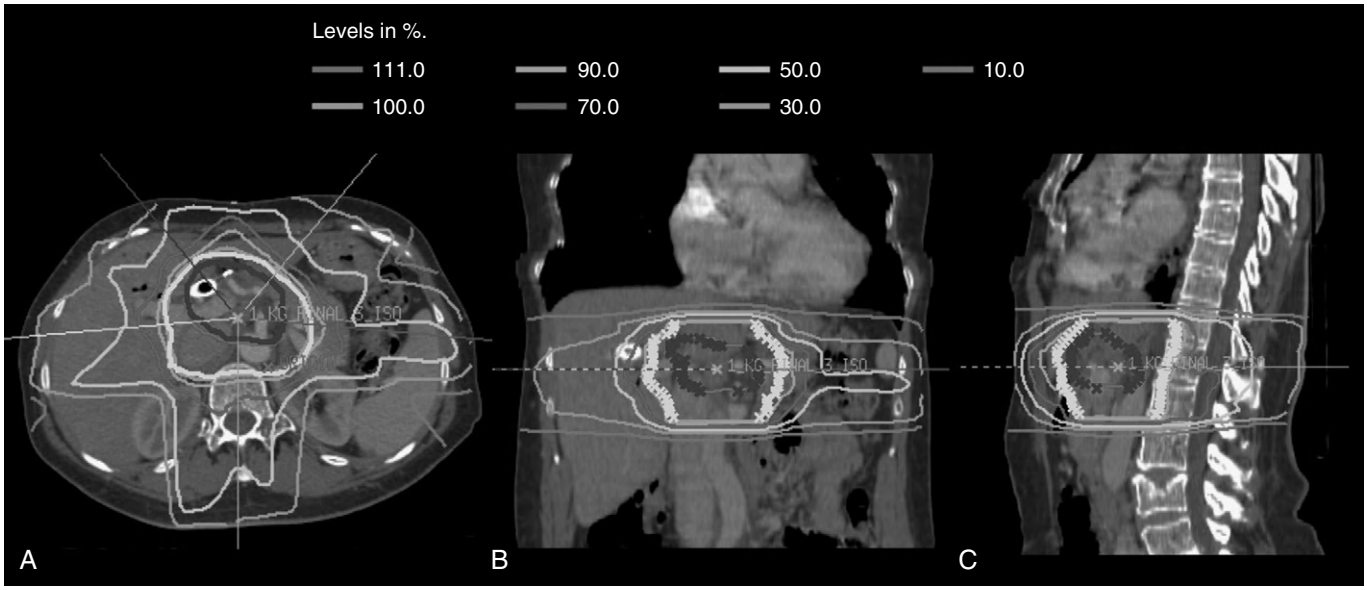


FIGURE 84B.1. Axial (**A**), coronal (**B**), and sagittal (**C**) views of an intensity-modulated radiotherapy plan for an unresectable hilar cholangiocarcinoma. *Hash marks* delineate the planning target volume, which encompasses the tumor and subclinical regions of spread (nodal regions). *Thick lines* delineate the gross tumor volume receiving a higher dose per day using a dose-painting technique. *Thin lines* represent the radiation isodose lines as described.

many approaches to motion management can be broadly categorized as *motion compensating*, such as respiratory gating and tumor tracking, or *motion restricting*, such as abdominal compression and active breathing control. *Respiratory gating* is a technique in which the radiation beam is turned on and off, depending on where the tumor is with respect to the respiratory cycle. The beam is generally turned on during expiration, when there is the least amount of motion. Respiratory gating is achieved using software to correlate the motion of the chest wall to the phase of respiration; however, the chest wall motion may not reflect the motion of the internal organs, thus this technique requires the ability to evaluate the motion of the tumor on a daily basis to evaluate the degree of respiratory motion of the tumor versus the chest wall motion. One option is to place high-density gold fiducial markers in or around the tumor to allow for radiographic tumor localization. With fluoroscopy, the radiopaque gold fiducial markers can be followed throughout the respiratory cycle to confirm that the treatment beam will be turned on at the appropriate time. For patients treated with the CyberKnife (Accuray, Sunnyvale, CA), the accompanying Synchrony tumor tracking system is used for real-time targeting of tumors. A series of light-emitting diodes (LEDs) are placed on the chest wall, and movement is detected by wall-mounted cameras in the treatment room. Using motion-tracking software, the Synchrony system (Colorado Cyberknife, Lafayette, CO) identifies, updates, and then correlates external body surface movement with movement of the internal tumor fiducials. Throughout the procedure, the Synchrony system monitors the target and modifies the correlation model as needed to follow changes in tumor motion. Abdominal compression uses a belt that is inflated to compress the abdominal cavity and limit the degree of respiratory excursion of the abdominal contents. Active breathing control is a method of breath holding that also limits the ventilatory motion while the beam is on.

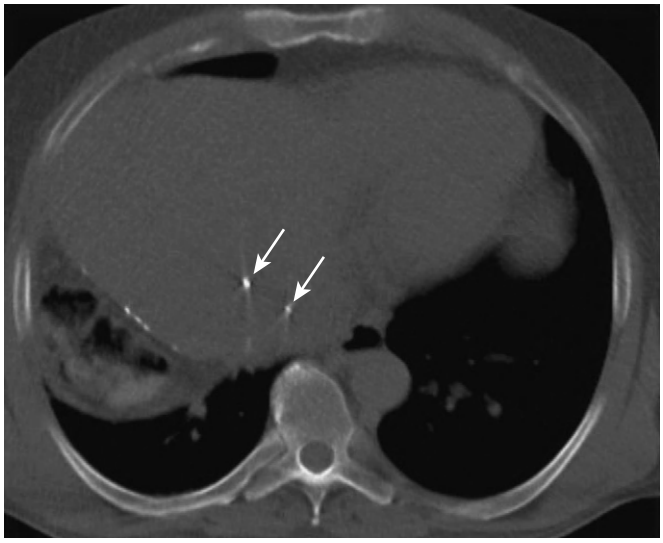


FIGURE 84B.2. Cone-beam computed tomographic image acquired on linear accelerator prior to treatment delivery. Low resolution limits identification of the tumor volume, but radiopaque gold fiducial markers (*arrows*) are visible and can be used for localization purposes.

HEPATOCELLULAR CARCINOMA

Early on, researchers determined that low doses of large-field hepatic irradiation were ineffective in controlling gross hepatocellular carcinoma (HCC) and that higher doses of whole-liver irradiation resulted in high rates of radiation hepatitis. Stevens (1994) states that 75% of patients treated with 40 Gy or greater radiation to the whole liver will develop liver dysfunction, and an early study of adjuvant liver irradiation for HCC (Fugitt et al, 1973) demonstrated that 4 of 52 patients treated with

more than 55 Gy had fatal hepatitis. These widely quoted early results have resulted in RT being placed on the list of potential palliative therapies for HCC.

With the development of 3D-CRT, high-dose, partial liver irradiation was also attempted for patients with unresectable liver tumors (Dawson et al, 2000; Lawrence et al, 1993; Robertson et al, 1997). Investigators at the University of Michigan have reported a Phase II study of 3D-CRT and concurrent intraarterial floxuridine chemotherapy for unresectable hepatobiliary disease. They treated 128 patients with unresectable HCC (n = 35), intrahepatic cholangiocarcinoma (n = 46), or colorectal hepatic metastases (n = 47). Doses ranged from 40 to 90 Gy (median, 60.75 Gy) and were based on the amount of normal liver tissue, evaluated by dose-volume histograms, that could be effectively excluded from the fields to a maximum risk of radiation-induced liver disease (RILD) of 10% to 15%. At a median follow-up time of 16 months (26 months in patients who were alive) the median survival was 15.8 months, and the 3-year survival was 17%; in addition, 38 patients (30%) developed grade 3 or greater toxicity, and 5 patients developed RILD, one of whom died.

More recently, studies of external-beam radiotherapy (EBRT) using IMRT have been reported. A dose-escalation trial of conformal radiotherapy using 3D-CRT (n = 24) or IMRT (n = 16) was performed at Fudan University in Shanghai (Ren et al, 2010). The median tumor dose was 51 Gy (range, 40 to 62 Gy), and the median dose to normal liver was 17 Gy (range, 9 to 22 Gy). None of the patients experienced grade 3 or greater toxicity. The acute hepatic toxicities were mainly elevated liver enzymes; in-field progression-free rates at 1 and 2 years were 100% and 93%, respectively; overall survival at 1 and 2 years was 72% and 62%, respectively.

Investigators from the University of Virginia reported their experience treating 20 patients with HCC using IMRT to deliver 50 Gy in 20 fractions with concurrent capecitabine (McIntosh et al, 2009). The median tumor size was 9 cm, and 45% of patients had Child-Turcotte-Pugh (CTP) class B cirrhosis. The average volume of liver that received greater than 30 Gy was 27%. None of the patients experienced grade 3 or greater acute or late toxicity, and no cases of RILD were reported. The median survival for patients who had class A and B disease was 22.5 months and 8 months, respectively. These numbers exceed those quoted for radiation or regional chemotherapy alone and match most surgical series, they should therefore serve as the basis for future studies using dose escalation and radiation sensitizers.

Alternative fractionation schemes have also been introduced in the treatment of HCC. Both hyperfractionation (lower dose per fraction, twice-daily treatments) and hypofractionation (high dose per fraction in fewer fractions) have been applied to improve response rates in liver malignancies. The rationale for hyperfractionation is the rapid doubling time of HCC tumors (estimated at 41 days) and the shortened treatment times. Hyperfractionation was used in the University of Michigan series (Ben-Josef et al, 2005; Dawson et al, 2000; Lawrence et al, 1993; Robertson et al, 1997). In a nonrandomized study by the Radiation Therapy Oncology Group (RTOG) (Stillwagon et al, 1989), 194 patients with advanced HCC—70% to 80% of whom had metastases or had failed prior treatment—received treatment to the whole liver. Conventional fractionation (3 Gy four times per week to 21 Gy) was used in 135 patients, whereas 59 received 24 Gy in 1.2 Gy fractions twice a day. Concurrent doxorubicin and fluorouracil were given intravenously every other day to both groups. The response rate for both was dismally low (approximately 20%) and unaffected by fractionation scheme. Both acute esophagitis and thrombocytopenia occurred significantly more often in the group that received twice-daily radiation.

With improved tumor localization techniques and motion-management modalities, hypofractionation using IGRT has been evaluated in the treatment of primary liver tumors. Focal, high-dose stereotactic body RT (SBRT) was evaluated in a Phase I study of 41 patients with primary liver tumors, the majority of which were HCC. Dawson and colleagues (2000) prescribed a variable dose of 24 to 54 Gy given over six fractions; the dose was dependent on the volume of liver irradiated and the estimated risk of liver toxicity using a normal tissue complication model. Grade 3 elevation of liver enzymes was seen in five patients (12%). No RILD or treatment-related grade 4 or 5 toxicity was seen within 3 months of SBRT, and overall clinical outcomes were better than expected for this high-risk population. This study was limited to patients with class A cirrhosis or better; however, the majority of patients with unresectable HCC have more advanced cirrhosis, and the underlying liver dysfunction must be considered when delivering any type of liver irradiation.

Emerging data show that dose-volume constraints may be used in cirrhotic patients receiving conformal RT for HCC (McGinn et al, 1998; Mornex et al, 2006). Such guidelines have been shown to allow safe delivery of relatively high doses of conformal RT for HCC (McGinn et al, 1998). These guidelines were used in a Phase II study that confirmed 3D-CRT could be used safely and effectively for patients with tumors less than 5 cm and class A or B cirrhosis (Mornex et al, 2006). SBRT appears to be a promising alternative for patients with unresectable primary liver tumors. This modality may prove to be an option not only for definitive treatment of primary liver tumors but also as a bridge to transplant for HCC patients.

Hypofractionated, focal RT using charged particles has also been studied, particularly in Asia. In small, nonrandomized studies, high-dose RT delivered with protons has been shown to result in acceptable local control and survival rates for unresectable primary liver tumors (Chiba et al, 2005; Fukumitsu et al, 2009; Matsuzaki et al, 1994). A recent prospective study evaluated 51 patients treated with proton RT to deliver 66 Gy equivalents in 10 fractions to those with one to three HCCs 10 cm or smaller (Fukumitsu et al, 2009); of these, 20% were CTP class B. The 5-year local control and survival were 88% and 39%, respectively, and 5-year survival was 46% among patients with solitary tumors and class A liver function. These results are similar to those obtained after surgery; liver function remained stable or improved in 84% of patients, and no RILD was observed. Investigators at Loma Linda Hospital reported the results of their Phase II study in which 34 HCC patients were treated with cobalt-60 Gy equivalents (CoGyEq) in 15 fractions using protons, resulting in a 2-year local control rate of 75% (Bush et al, 2004). Six patients underwent liver transplantation between 6 and 16 months after completion of RT, two of whom had no residual tumor. These newer modalities may be able to minimize normal tissue effects via precise dose localization and should be investigated further.

Selective internal RT (SIRT) or radioembolization using yttrium-90–labeled microspheres for the treatment of HCC has

gained interest in recent years (see Chapter 84A). The ^{90}Y microspheres have several advantages as a potential therapy for liver lesions, including the selective delivery of radiolabeled microspheres via the hepatic artery and the short-depth dose afforded by ^{90}Y, a β-emitter. A meta-analysis of SIRT using either resin or glass microspheres demonstrated that for HCC, a treatment response—complete response, partial response, and/or stable disease—was seen in 89% for resin microspheres and 78% for glass microspheres (Vente et al, 2009). In a large, multiinstitutional, retrospective review of 515 patients who received 680 treatments of SIRT, stable disease was seen in 76.8%, a partial response in 9.5%, a complete response in 4.5%, and progressive liver disease in 9% (Salem et al, 2010). The treatment was well tolerated, with an incidence of RILD of only 4% and nonliver grade 3 or greater toxicity in 6% (gastritis or gastric ulceration) (Kennedy et al, 2009). Salem and colleagues (2010) recently reported long-term outcomes for 291 HCC patients treated with intraarterial ^{90}Y microspheres. The median dose was 103 Gy per treatment, and the mean number of treatments per patient was 1.8. The overall time to progression was 7.9 months, and overall median survival was significantly longer among patients with class A disease (17.2 months) versus those with class B disease (7.7 months).

Recent data suggest that the use of combined RT and chemoembolization may give promising results. Seong and colleagues (2000) from South Korea evaluated 27 patients who had not responded to transarterial chemoembolization (TACE); failure was judged by incomplete tumor filling of Lipiodol adriamycin on angiogram/CT), and patients went on to receive RT (51.8 ± 7.9 Gy). They found objective responses in 67% of patients, a median survival of 14 months from the start of RT, and 1-year overall survival of 85% (Seong et al, 2000). In a separate review, Seong and colleagues (1999) evaluated 30 patients treated with TACE followed by planned RT and noted a 63% objective response rate and a median survival of 17 months. Cheng and colleagues (2000) reported similar results, with a median survival of 19.2 months in patients treated with combination radiation and TACE.

The role of radiotherapy for HCC tumor thrombosis has also been investigated. Vascular invasion is a relatively common and potentially lethal complication of advanced HCC, potentially leading to pulmonary metastases or infarction, Budd-Chiari syndrome, and cardiac and hepatic dysfunction. Portal vein or inferior vena cava (IVC) involvement by tumor thrombus is associated with an extremely poor prognosis and limits the ability to deliver therapy such as TACE. Radiotherapy has been used in many Asian centers to address portal vein or IVC thrombosis to reduce the thrombus size to minimize the risk of clot dissemination, alleviate portal hypertension, and allow for surgical resection or TACE (Koo et al, 2009; Zeng et al, 2005). Zeng and colleagues (2005) retrospectively reviewed the outcomes for 158 patients with HCC who had portal vein and/or IVC tumor thrombus diagnosed and treated at the Zhongshan hospital in Shanghai, China, from 1998 to 2003. Forty-four patients received EBRT (median dose of 50 Gy in 2-Gy fractions), and 144 did not receive EBRT. Approximately 80% in each group were also treated with TACE or resection. The 1-year survival was 0% for patients receiving no therapy, 10.7% for TACE alone, 27.8% for resection alone, and 34.8% for patients receiving any EBRT as part of their therapy. No deterioration of liver function was observed, and only seven patients developed additional elevations of alanine aminotransferase (ALT; less than twice upper limit of normal), and all returned to normal range within 1 month.

BILIARY TUMORS

Intrahepatic Cholangiocarcinoma (See Chapter 50A)

Complete resection remains the gold standard and best chance of cure for patients with intrahepatic cholangiocarcinoma (IHCC); however, even with a complete resection, the 5-year overall survival rates range from 21% to 63% (Carpizo & D'Angelica, 2009). Local recurrence is most common, thus adjuvant therapy has been investigated. A recent analysis of outcomes of patients with IHCC obtained from the Surveillance, Epidemiology, and End Results (SEER) database demonstrated an improvement in overall survival for patients undergoing adjuvant radiotherapy versus surgery alone (Shinohara et al, 2008). The median overall survival was 11 months for surgery and adjuvant RT versus 6 months for surgery alone.

Although patients with IHCC are somewhat less likely to have underlying liver disease than those with HCC, their tumors are often unresectable because of other limitations to curative surgical excision that include lymphadenopathy, vascular involvement, metastases, and multilobar or adjacent organ involvement (Chen et al, 1989).

EXTRAHEPATIC CHOLANGIOCARCINOMA (SEE CHAPTER 50B)

Historically, the use of EBRT for extrahepatic hepatocellular carcinoma (EHCC), including hilar and distal bile duct tumors, was largely limited to unresectable, recurrent, or gross residual disease treated in the pre-CT era, and this led to the conclusion that extrahepatic bile duct carcinomas were radioresistant; however, no evidence supports the idea that bile duct tumor cells have an inherent radioresistance, rather the doses of radiation generally administered have been limited by the surrounding structures. Indeed, some recent reports indicate that radiation limited to relatively small fields, but reaching higher dose levels, combined with more modern surgical approaches and techniques may have a positive effect on outcome (Cameron et al, 1990; Gonzalez Gonzalez et al, 1990; Schoenthaler et al, 1993). In general, this improvement has been found to be most marked in the setting of minimal residual disease (Schoenthaler et al, 1993), although occasionally an advantage is seen in unresectable patients treated with stents and radiation (Cameron et al, 1990).

The indications for postoperative RT are not yet clear. Patients with negative resection margins are rarely referred for consideration of RT, although the available data suggest isolated locoregional recurrence rates of up to 60% after curative resection. Investigators at the University of Michigan published their retrospective experience with adjuvant RT after a potentially curative resection in 81 patients with localized EHCC (Ben-David et al, 2006). With a median follow-up of 1.2 years, the median overall survival and progression-free survival were 14.7 and 11 months, respectively. Complete resection (R0) was the only predictive factor significantly associated with increases in both overall and progression-free survival, and no difference in outcomes was reported between R1 and R2 resections. The first site of failure was locoregional in over two thirds of patients.

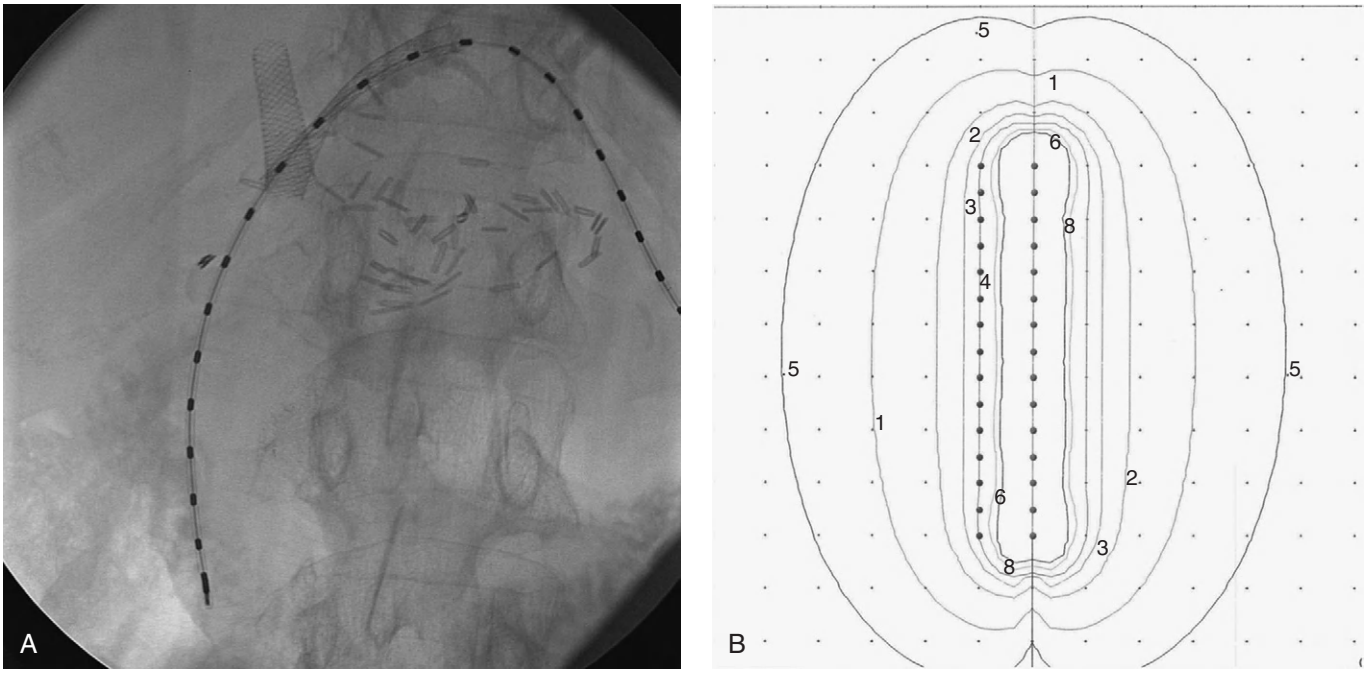


FIGURE 84B.3. Iridium-191 brachytherapy treatment for a hilar cholangiocarcinoma. **A,** Dummy wire in percutaneously placed catheter used to identify treatment area across the stent. **B,** Dose distribution to deliver 4 Gy to 1 cm from the source.

Clearly, local failure plays a significant role in many EHCC deaths, and this is a persistent problem after surgery with or without irradiation and after irradiation alone (Gonzalez Gonzalez et al, 1990; Schoenthaler et al, 1993).

Prognostic factors that may help determine which patients might benefit from adjuvant therapy include age younger than 65 years and small tumor size (Schoenthaler et al, 1994). The degree of differentiation, lymph node involvement, local invasiveness, and papillary characteristics may also serve as prognosticators. All of these factors must be weighed with the demands of upper quadrant irradiation, the patient's overall medical status, and the significant quality of life issues raised by this disease. As always, by far the most important prognosticator for survival is the extent of resection.

An ongoing intergroup study led by the Southwest Oncology Group (SWOG) is evaluating the use of adjuvant chemotherapy (gemcitabine and capecitabine) followed by chemoradiation (concurrent RT and capecitabine) for resected EHCC or gallbladder tumors. This Phase II study will help to establish the role of adjuvant therapy for EHCC.

Short-term morbidity associated with RT includes nausea, vomiting, malaise, fatigue, or weight loss, and many patients with indwelling catheters have intermittent fevers. Long-term post-RT complications, particularly duodenal, have been reported in the literature at rates that seem to vary with survival times; these are discussed in greater detail in later sections. Efforts to minimize the dose to nearby radiosensitive structures, and hence to minimize complications, may include brachytherapy in combination with EBRT, potentially using the new technology of high-dose-rate brachytherapy; intraoperative RT; higher linear energy transfer modalities; radioprotectors; and the increasing use of CT-based conformal planning systems.

Brachytherapy has been used at numerous institutions. Overall, a slight trend has been observed toward improved survival with its use as a boost (Jarnagin, 2000). The potential advantages are clear: the area is reasonably accessible via stents placed during surgery or by the interventional radiologist; a high dose can be limited to a few surrounding centimeters; and the risk of serious short-term toxicity is low, although most series report rates of cholangitis of 30% to 50%. Dose distributions can be quite satisfactory with the use of iridium-192 catheters. Ideally, an external-beam dose designed to eradicate microscopic disease (i.e., 45 to 50 Gy) is given first, followed by seed placement designed to give an additional high dose to the site of gross or highly suspect disease. Doses ranging from 15 to 100 Gy have been administered using ^{192}Ir, ^{131}I, and gold-198. Dose is usually prescribed at 0.5 to 1.0 cm from the radiation sources (Fig. 84B.3).

Long-term complications secondary to the high doses and use of stents are common and include stricture, bowel obstruction, and bleeding. In addition, the rapid dose falloff means that some of the high-risk area may well lie outside the high-dose area, so brachytherapy should only be used in conjunction with EBRT. No study has shown that brachytherapy alone has anything but the briefest of palliative effects, although reports of high-dose-rate brachytherapy are just beginning to appear in the literature (Kurisu et al, 1991).

Intraoperative RT has been used for EHCCs at several institutions. After promising preliminary work in Japan, an RTOG protocol (85-06) gave 14 to 22 Gy as intraoperative RT before 45 to 50 Gy external beam to eight evaluable patients with unresectable, unresected, or recurrent tumors. Two patients were alive, one with no evidence of disease, at the time of publication, with a median follow-up of 10.5 months (Wolkov et al, 1992), In their study of 15 patients, Busse and colleagues (1989) had a median survival of 14 months with a 50% local control rate using 5 to 20 Gy. In a study by Buskirk and colleagues (1992), the only long-term survivors had either

intraoperative RT or a brachytherapy boost. All of these reports involve the use of both intraoperative RT and EBRT, as the use of the intraoperative RT alone and brachytherapy alone have not been shown to have a durable impact. Intraoperative electron doses of 15 to 25 Gy have been given, again before external-beam treatments of approximately 45 to 50 Gy. Buskirk and colleagues (1992) leave transhepatic catheters in place after this procedure.

The role of liver transplantation for unresectable hilar cholangiocarcinoma is under active investigation (see Chapter 97E). Results from the Mayo Clinic are encouraging; they have been using 4500 cGy neoadjuvant chemoradiation, concurrent fluorouracil, and a brachytherapy boost, followed by liver transplantation (Rea et al, 2005). Of 71 patients enrolled, 38 underwent liver transplantation. The 3- and 5-year survival rates for this group were 82% and 82%. These results compared favorably with another group of patients who underwent resection, whose 3- and 5-year survival rates were 48% and 21%, respectively. It must be emphasized that transplantation is reserved for highly selected patients, and selection criteria are quite stringent, favoring those at earlier stages of disease compared with patients undergoing resection.

SUMMARY

Innovations in target delineation, liver imaging, focal radiation delivery, and motion management have led to a significantly more comprehensive understanding of the treatment of primary liver and biliary tumors with radiation therapy over the past decade. As radiation oncologists continue to explore new technologies that allow safe dose escalation to liver and biliary lesions, the outlook for improved outcomes for patients with hepatobiliary tumors appears promising.

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CHAPTER 85B

Cryoablation for liver tumors

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OVERVIEW

Hepatic resection is the standard of care for the majority of resectable primary and metastatic liver tumors confined to the liver (Cha et al, 2002; Fong et al, 1999; Scheele et al, 1995; Wei et al, 2006; see Chapters 80 and 81A). In patients with impaired liver function or small hepatocellular tumors, ablation is sometimes employed as first-line treatment (Chen et al, 2006; Livraghi et al, 2008); however, most patients with malignant liver tumors are not amenable to potentially curative resection because of anatomic, functional, or prognostic factors (see Chapter 2). Even when the malignancy is considered unresectable, local control of primary and isolated metastatic hepatic malignancy may change the natural history of these diseases. Several prospective and retrospective analyses have shown liver failure to be a common cause of death in patients with unresected liver tumors (Couto et al, 2007; Nagorney & Gigot, 1996). Ablative techniques can be combined with surgical resections to decrease hepatic tumor load and possibly eliminate it. They also expand the treatment options for disease recurrence in patients whose liver remnant is not optimized or amenable to surgical resection. With ablation, it is possible to prolong survival and increase the disease-free interval in patients. Cryotherapy was one of the original ablative techniques, but it has increasingly been replaced by radiofrequency ablation (RFA) and more recently microwave ablation (MWA) because of high complication rates and high local recurrence rates, somewhat cumbersome technology, and higher complication rates with cryoablation, although its use continues to be described for treating close or positive margins after resection.

PATIENT POPULATION

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world with more than 1 million cases occurring each year worldwide (see Chapter 80; Nordenstedt et al, 2010). It is well known that HCC is the most common malignancy in Southeast Asia and in sub-Saharan Africa owing to endemic viral hepatitis, especially hepatitis B. Since the 1990s the incidence of HCC has increased significantly in the United States and other Western countries as hepatitis C rates have risen. In the United States, the mortality rate for HCC has improved over the past 2 decades, as screening programs have identified patients with tumors at earlier stages. Of patients presenting with HCC, only 15% to 25% are operable, and less than 10% are resectable with curative intent (Bolondi et al, 2001; Farmer et al, 1994); however, most patients with unresectable disease have tumor confined to the liver. At a regional referral center for liver cancer, curative treatments can be applied to 30% to 40% of patients (Bruix & Llovet, 2002). More than half of patients presenting with primary liver cancer are potential candidates for hepatic regional therapy, of which a significant number may be amenable to ablative techniques.

Metastatic Disease

The liver is one of the most common sites of metastatic spread, particularly from gastrointestinal malignancies (see Chapter 81A). Most malignancies that recur in the liver do so in combination with extrahepatic metastases, making resection or ablative regional therapies unsuitable management strategies. In contrast, recurrences from colorectal primary tumors are localized to the liver in approximately one third of patients, allowing use of potentially curative regional interventions. Only a small proportion of patients with metastases confined to the liver are operable, and an even smaller fraction are resectable, owing to technical and prognostic factors. By evaluating all patients with hepatic colorectal metastases at a single center, Scheele and colleagues (1995) found 21% of patients with synchronous disease and 51% of patients with metachronous disease to be potentially resectable.

Most patients with metastatic disease confined to the liver are not candidates for resection therapies but are potentially eligible for regional ablative treatments. Systemic and regional chemotherapy for metastatic colorectal cancer has improved dramatically, with median survivals of greater than 20 months now commonly reported (see Chapters 86 and 87). Additionally, response rates for systemic chemotherapy are generally greater than 50%, and combined with regional chemotherapy, they approach 90%. Survival at 5 years for patients after resection of colorectal liver metastases in modern series ranges from 46% to 58% (Karanjia et al, 2009; Pawlik et al, 2005). Resectional and ablative therapies now must be interpreted in the context of effective chemotherapy, opening the door for downstaging of unresectable tumors and adjuvant therapy for borderline resectable tumors.

GENERAL INDICATIONS FOR NONRESECTIONAL THERAPY OF LIVER TUMORS

Numerous patient- and tumor-related factors conspire to make liver tumors "inoperable" or "unresectable." General and liver-related comorbidities are common contraindications to hepatic resection and are often independent of the extent of disease or proposed operation. Most patients with HCC have limited hepatic reserve secondary to cirrhosis or portal hypertension or both, which often precludes a safe liver resection (see Chapters 2 and 70A). Many technical factors make a hepatic malignancy

unresectable. Insufficient future liver remnant, involvement of all three hepatic veins, and involvement of portal inflow to both lobes of the liver are examples of such technical issues. Many techniques to deal with technically unresectable tumors have been developed, such as portal vein embolization, parenchymal-sparing segmental resections, and two-stage operations (see Chapters 92, 93A, and 93B); nonetheless, most liver tumors are still unresectable.

Cryotherapy has been used to treat many primary and metastatic liver tumors; however, extensive experience exists only for hepatic metastases from colorectal and neuroendocrine primary tumors and for primary liver cancer. Ablation should be considered a second-line alternative to liver resection in patients with resectable disease, except in patients with small HCCs, where the choice between resection and ablation is controversial; however, in the situations enumerated previously, in which resection is not possible or safe, ablation can provide a relatively effective alternative therapy with less morbidity than open hepatic resection. The most pronounced benefits of ablation in these situations are that it can be done laparoscopically, percutaneously, or with a small laparotomy; it can also preserve maximal parenchyma and minimize the overall surgical insult to the patient.

The choice of ablative device is surgeon dependent, and no absolute indications and contraindications apply to cryoablation specifically. Ablation often is employed in combination with resection to treat contralateral tumors in a small remnant.

PATHOPHYSIOLOGY OF CRYOABLATION

The methods by which subzero temperatures destroy tumors are not tissue specific, and both normal and neoplastic tissues are sensitive to extreme cold. Cryotherapy causes cell death by a variety of physical and chemical mechanisms that depend on the rate of cooling, absolute depth of hypothermia, rate of thawing, number of freeze-thaw cycles used, and delayed effects of ischemia after thawing. When a cryoprobe is inserted into the liver, three overlapping zones of injury develop within the ice ball. Rapid tissue freezing occurs closest to the cryoprobe, and the rate of freezing decreases in proportion to the distance from the probe, creating zones of intermediate and slow cooling. Similarly, a gradient of temperature develops in the ice ball, decreasing 3° C/mm to 10° C/mm from –170° C near the probe to just below 0° C at the periphery of the cryolesion. The dynamics of the freezing process cause different mechanisms of injury in these three idealized zones (Gage & Baust, 1998; Mascarenhas & Ravikumar, 1998).

Cooling Rate

The rate at which tissue cools affects the proportion of cells killed by a single freeze cycle. Maximal cell death is achieved at slow and rapid cooling rates, although from different mechanisms, whereas greatest cell survival is seen with intermediate cooling rates. Cellular dehydration causes lethal injury at slow cooling rates, whereas rapidly cooled cells are destroyed by the mechanical action of ice crystallization and expansion.

Slow Cooling Rates

Intracellular and extracellular fluids are complex solutions containing varying amounts of protein, macromolecules, and electrolytes. The presence of solutes in water depresses its freezing point and allows it to supercool, rather than crystallize, below 0° C. Because the composition of the intracellular and extracellular compartments differs markedly, the extracellular fluid freezes before the intracellular fluid. As ice forms in the extracellular space, solutes are excluded, making the remaining fluid hyperosmolar. Cellular dehydration occurs as the unfrozen intracellular water flows out of the cell along the osmotic gradient. At a critical level of dehydration, no further fluid can be extracted from the cell, because the intracellular macromolecules become concentrated enough to equalize the osmotic gradient across the cell membrane. The ion concentration across the membrane becomes deranged, however, allowing ions to flow into the cell from the hypertonic extracellular fluid to reestablish the Gibbs-Donnon equilibrium. As a consequence of cellular dehydration, the intracellular pH and ion concentrations are altered, proteins denature, and membranes and membrane-bound enzyme systems are disrupted. Some cells die as a direct result of dehydration, whereas others require the added insult provided during isotonic rehydration, which occurs during the thaw cycle. When the cryolesion thaws, the extracellular fluid melts first, briefly creating a relatively hypotonic environment. Water flows into the hyperosmolar and hypertonic cells causing them to swell, burst, or die. This type of injury predominates in the slowly cooled zone at the periphery of the cryolesion.

Intermediate Cooling Rates

With intermediate cooling rates (1° C to 10° C/min), the cells dehydrate as the extracellular fluid turns to ice; however, the temperature falls fast enough to freeze the intracellular water before cellular dehydration reaches the critical level to produce irreversible cell injury. Intracellular ice formation excludes solutes, increasing the intracellular osmotic concentrations, equalizing the osmotic gradient across the cell membrane, and stopping further cellular dehydration. As a result, the critical level of dehydration to allow influx of solutes is not reached, protecting the cell from the lethal injury caused by water influx secondary to isotonic rehydration during the thaw cycle. Cells in the zone of intermediate cooling do not suffer the consequences of the cellular dehydration, and their survival is improved.

Rapid Cooling Rates

Rapidly frozen tissue is destroyed by an altogether different mechanism. Cooling rates on the order of 50° C/min, found only in close proximity to the cryoprobe, cause intracellular fluid to freeze before cellular dehydration occurs. Intracellular ice is particularly lethal. Small ice crystals coalesce, causing a physical grinding action that disrupts organelles and cellular membranes leading to reproducible and certain cell death.

Depth of Hypothermia

Independent of the cooling rate, extensive tissue injury occurs at temperatures below –20° C, and temperatures below –40° C are lethal for almost all tumor cells. The mechanism of cell injury at these temperatures is the formation of intracellular ice. At higher temperatures, the rate of cooling influences the rate of ice formation and the mechanism of cell death; however, when the temperature is below –40° C, almost all of the water within the cell is frozen, ensuring complete tissue ablation. For cryotherapy to be reliable, all targeted tissue must reach these levels of hypothermia to achieve reproducible and certain cell death, the theoretic goal of cryotherapy. This level of hypothermia is

not consistently reached at the periphery of the ice ball, where temperatures may be 0° C.

The sensitivity of different tissues to hypothermia varies considerably. Most normal hepatocytes die at –15° C to –20° C, whereas at –10° C most hepatocytes survive. Bile ducts, connective tissue, and vascular structures tolerate slightly lower temperatures than hepatocytes. In contrast, liver tumors tend to require deeper hypothermia to –40° C for complete and reliable cell death. As a general rule, the –40° C isotherm is located approximately three quarters of the distance from the probe to the edge of the ice ball as seen at intraoperative sonography. To reach this level of hypothermia and obtain reliable ablation at the tumor margin, the ice ball is extended 1 cm beyond the peripheral edge of the tumor.

Thawing Process

Further damage to tissue occurs during the thawing process and varies according to the rate of the thaw. Rapid thawing of frozen tissue tends to increase cell survival, whereas slow thawing is more destructive than either rapid or slow cooling. In slowly thawed tissue, the extracellular ice melts before the intracellular ice, briefly making the extracellular fluid relatively hypoosmolar compared with the intracellular fluid. Free water flows down this osmotic gradient into the cells, causing them to swell and ultimately burst. Simultaneously, the ice within the cell undergoes recrystallization, especially in the temperature range of –20° C to –25° C. Recrystallization is a process by which ice crystals reform, coalesce, and enlarge, mechanically disrupting the cellular membranes. The effects of thawing are potentiated by allowing the entire lesion to reach ambient temperature slowly and passively.

Repeated Freeze-Thaw Cycles

Repeated freeze-thaw cycles in animal models have been shown to move the margin of reliable complete cell kill outward by producing larger ice balls more rapidly (Poppendiek, 1967). This movement is due to increased thermoconductivity of the previously frozen liver. Tissue near the cryoprobe is ablated adequately with one freeze-thaw cycle, because low enough temperatures are achieved to ensure complete cellular destruction. The added benefit of multiple cycles occurs in the periphery of the tumor, where the depth of hypothermia is unpredictable, and the cell kill is unreliable. Early histologic signs of cellular damage in lesions undergoing multiple freeze-thaw cycles are more dramatic, confirming the added benefit of such cycles.

Microvascular Effects

In addition to the acute physicochemical and structural damage to the cell and its environment, the lethal effects of cryoablation are potentiated by disruption of vascular structures, which causes delayed hypoxia and necrosis (Rubinsky et al, 1990). The vascular effects are acute and chronic. Freezing at slow cooling rates causes the radius of the sinusoids to increase by a factor of 2, which is equivalent to increasing the volume in the intravascular space by a factor of 4. The expansion of the vascular space tears the endothelium, exposing and disrupting the underlying basement membrane. Platelet thrombi develop, and permeability increases, leading to swelling and microcirculatory failure. The tissues supplied by these damaged vessels become ischemic and necrotic. This mechanism of injury is more important in the intermediate and slow cooling zones, where direct cellular injury by intracellular ice formation or dehydration is not reliable. For maximal benefit, cryosurgery should be performed so that there is rapid freeze, slow thaw, and repeated freeze-thaw cycles; however, experimental evidence has shown that high-flow venules at the periphery of an ice ball are crucial in shutting down the microcirculation of the tumor, and repeated cycles do not seem to improve this effect (Richter et al, 2005). It also has been shown in experimental models that the serine protease inhibitor aprotinin decreases platelet trapping and improves tissue destruction in cryolesions (Kollmar et al, 2004). The effects of cryosurgery on tissues are a result of direct cellular damage secondary to physicochemical effects and indirect cell damage secondary to loss of cellular integrity and destruction of vascular channels.

Morphologic and Histologic Changes After Cryotherapy

Immediately after thawing, the area of liver treated with cryoablative techniques appears dark red, swollen, and usually well demarcated. Histologic examination reveals congestion of the hepatic sinusoids associated with hemorrhage, decreased levels of cellular glycogen, and an absolute reduction in the number of mitochondria. With time, the lesion takes on a light gray color and slowly resorbs over the ensuing weeks. Microscopically, this period correlates with polymorphonuclear cell and macrophage infiltration of the tissue. The cryolesion is progressively replaced with fibrous tissue, usually with a persistent area of necrosis and fibrosis, but occasionally the lesion is completely resorbed.

Immunologic Effects of Cryoablation

In early studies of cryotherapy, anecdotal reports of regression of untreated tumor sites suggested a generalized, tumor-specific immunologic response to the cryoablated lesion (Faraci et al, 1975). These effects have not been substantiated in animal or human models, although it is unlikely that an antitumor immune response enhances the effect of cryotherapy.

OPERATIVE TECHNIQUE

Hepatic cryotherapy can be performed via a variety of approaches, including percutaneous, laparoscopic, and open methods, but the open approach allows the most flexibility and accuracy. Cryotherapy at laparotomy also is less anatomically limiting than minimally invasive approaches and permits treatment of lesions in areas difficult to access by other methods. The difficulty with the open approach is the morbidity that accompanies a major abdominal incision; however, minimally invasive cryotherapy techniques have been developed and are increasingly popular. The technology of laparoscopic instrumentation and percutaneous localization continues to improve for all types of ablation, and the role of these techniques continues to increase.

Preoperative Preparation

The extent, location, and proximity of the liver tumor to the hepatic vascular and biliary structures should be defined by careful review of preoperative imaging studies. Patients with more than 40% of the liver replaced with tumor are not

candidates for cryoablative techniques, because it is difficult to ablate this volume of tumor, and the perioperative morbidity is prohibitive. In general, the same preoperative preparations are required before cryosurgery as for liver resection, because a small percentage of patients may be converted to resection owing to unexpected resectability or intraoperative complications.

Two devastating complications associated with hepatic cryotherapy are the cryoshock syndrome, a complex of coagulopathy and renal and pulmonary failure, and intraoperative hypothermia (Seifert & Morris 1998); preoperative hydration is important to decrease the incidence of renal dysfunction (Bagia et al, 1998). Hypothermia is another significant complication that can be alleviated using heated fluid and airway circuits and a Bair Hugger (Arizant Healthcare, Eden Prairie, MN) warming system (Onik et al, 1993). Blood and blood products should be made available for the infrequent cases of intraoperative bleeding.

Cryotherapy at Laparotomy: Open Cryotherapy

The abdomen is approached through a right subcostal or bilateral subcostal incision with vertical extension in the midline. The peritoneal cavity is explored thoroughly to detect extrahepatic metastatic disease. Enlarged lymph nodes, particularly those in the porta hepatis, are evaluated by frozen section. The liver is mobilized from its ligamentous attachments and examined bimanually. Using a 5-mHz intraoperative ultrasound (US) transducer, each Couinaud segment of the liver is systematically scanned to determine the extent of disease and its relationship to the hepatic vascular and biliary structures. Suspicious lesions undergo US-directed core biopsies for histologic confirmation, but all lesions seen on preoperative studies should be confirmed by intraoperative US, biopsy, or both.

When an operative strategy is defined, the porta hepatis is encircled for the possibility of needing a Pringle maneuver during the procedure. The cryoprobe is introduced into the center of each lesion under US guidance. The placement is confirmed sonographically by viewing the probe in two or three perpendicular planes. In general, it is preferable to introduce the cryoprobe through the anterior surface of the liver, while monitoring the introduction of the probe and formation of the ice ball with the US transducer placed on the posterior side of the liver. Intraoperative US allows safe placement of the probe, avoiding injury to major intrahepatic vascular and biliary structures. To minimize tumor spillage and to avoid "cracking" the surface of the tumor, the cryoprobe is optimally inserted through normal liver before entering the tumor.

Depending on the depth of the lesion, direct introduction of the probe into the tumor or wire-guided, Seldinger-style localization may be used. The Seldinger technique is best used for deep intraparenchymal and nonpalpable tumors. First, the tumor is identified by intraoperative US. An echogenic needle is passed into the center of the lesion under US guidance and subsequently is exchanged for a J-wire (Fig. 85B.1A). When the J-wire is in place, the tract of the wire is dilated with a coaxial dilator and peel-away sheath. The dilator is withdrawn, and the cryoprobe is inserted through the sheath into the center of the tumor. The position of the cryoprobe is evaluated again using US in two or three different axes. The probe must be placed through the center of the tumor with the tip near the opposite margin to encompass the tumor completely within the cryolesion.

It is crucial to tailor the type of cryoprobe and freezing technique to the size and location of the tumor. The temperature gradient within the ice ball significantly affects the efficacy of the procedure. The temperature near the probe approximates that of liquid nitrogen, whereas at the periphery of the ice ball,

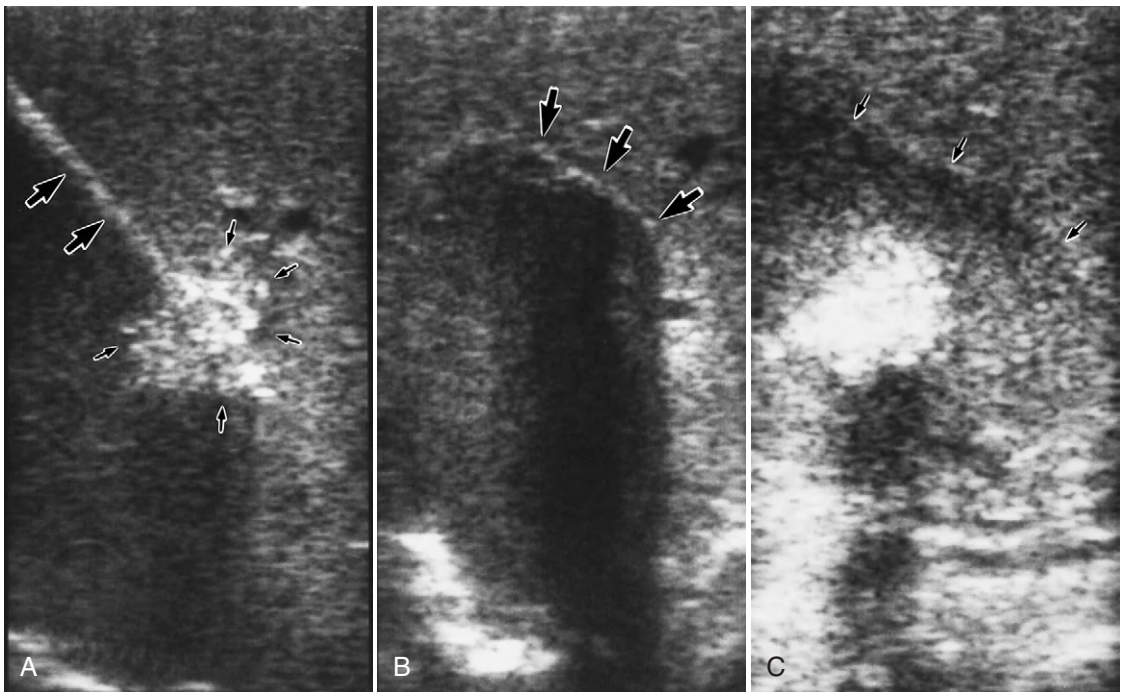


FIGURE 85B.1. A, Ultrasound (US) of an echogenic wire-guided localization of an intraparenchymal hepatic metastasis. *Large arrows* indicate the J-wire. *Small arrows* indicate the margins of the tumor. **B,** Intraoperative US of the ice ball. *Arrows* indicate the limits of the freeze front. **C,** US of the thawed ice ball showing the halo caused by edema around the ablated tumor. *Arrows* indicate margins of edema.

the tissue may be only a few degrees below 0° C. In addition, the rate of cooling is determined by the size of the probe, the flux of refrigerant, and the thermoconductivity of the uninsulated portion of the probe. To achieve maximum tumor ablation, the operator must understand the physical properties of the cryotherapy system. The system we use employs vacuum insulated probes and supercooled liquid nitrogen refrigerant. It permits the use of four simultaneous and completely independent probe placements. Two probes are available with this system, accommodating different size tumors. The 3-mm blunted probe creates a cryolesion 4 cm in diameter, whereas the 8-mm trocar point probe creates a 6-cm freeze zone. Two 8-mm probes, used in tandem, create a 10-cm cryolesion (Ravikumar et al, 1991b). Other systems have flat-faced probes that can be applied to a flat surface to create a hemispheric cryolesion of 3 to 4 cm, which can be helpful to treat close margins (Gruenberger et al, 2001).

When the trajectory is chosen, and appropriate placement of the probes is accomplished, the liver is insulated from surrounding tissues using laparotomy pads, towels, or rubber mats. After the probe is placed, and the surrounding tissue is protected, the freezing process is started. At −100° C, the probe sticks to the tissue, allowing placement of additional probes safely without dislodging the first probe; two or three probes can be placed in the liver at the same time, but we do not recommend treating more than three lesions simultaneously, because it is difficult to monitor concurrent cryoablations adequately, and the incidence of intraoperative hypothermia is higher.

Maximal cooling is started, and real-time US monitoring of the freezing process is carried out. The freeze front is seen as a hyperechoic rim with posterior acoustic shadowing (Fig. 85B.1B). Cooling continues until the freeze front extends 1 cm beyond the US margin of the tumor. Typically, the freezing process takes 8 to 15 minutes to complete, depending on the efficiency of the cryotherapy system and the size of the tumor. The freeze zone shown by intraoperative US closely approximates the pathologic and histologic volume of cryonecrosis.

After completion of the first freeze cycle, the tissue is allowed to thaw passively. Active rewarming is unnecessary and may adversely influence results. Complete thawing of the tumor may take 20 to 30 minutes, extending the overall operative time. Because cryotherapy failure usually occurs at the periphery of the ice ball, it is necessary only to thaw the most peripheral centimeter of the ice ball before initiating the second freeze cycle; this reduces operative time without compromising clinical efficacy. The second freeze-thaw cycle is accomplished in a similar fashion.

After completion of the second freeze-thaw cycle, the probe is actively rewarmed, allowing it to disengage before the tumor completely thaws. The probe tract is packed with absorbable knitted fabric, such as Surgicel or another hemostatic material, and gentle pressure is applied to the liver, preventing delayed hemorrhage from the probe tract. Rough handling of the thawing ice ball may cause a cleavage plane to develop at the interface of the ice ball and the normal liver parenchyma, which can cause massive bleeding. Generally, the probe insertion tract stops bleeding promptly, as the coagulation cascade activates at body temperature. After the two freeze-thaw cycles, the treated volume usually remains hyperechoic on US, whereas the surrounding normal liver becomes hypoechoic owing to edema; this gives the treated tumor a "halo" appearance on imaging studies (Fig. 85B.1C).

POSTOPERATIVE CARE

Drains are not used, and the abdomen is closed in the routine fashion. Postoperative care is usually unremarkable. Fluid shifts tend to be minimal, and patients usually can be fed on postoperative day 2. A transient elevation of the liver enzymes is usually seen, along with leukocytosis, a decrease in platelet count, and fairly high fevers in the early postoperative period. The increase in the liver transaminases is related directly to the volume of liver treated and usually resolves within 1 week. The platelet count falls for the first few days, then it stabilizes, only to return to normal or supranormal levels in 7 to 10 days. Less commonly, the coagulation profile deteriorates with increased partial thromboplastin and prothrombin times and elevation of serum levels of fibrin split products and D-dimers. Clinically significant disseminated intravascular coagulopathy (DIC) is rare, but pleural effusions are common as a result of liver mobilization and treatment of areas adjacent to the diaphragm. Most of the early consequences of the surgery resolve spontaneously, and the hospital stay is generally less than 6 days.

LAPAROSCOPIC CRYOTHERAPY

The introduction of videolaparoscopy and refinement of cryoprobe and US technology have allowed the development of laparoscopic cryoablative therapy. The laparoscopic cryoprobes are 40 cm long and can pass through a 5-mm port. Because the probes are not malleable, expertise in laparoscopic hepatic US and accurate placement of the working trocars are essential. Patients with lesions in segments VI and VII can be placed in the right side up position to maximize exposure. The wire-guided Seldinger technique described earlier has been adapted to facilitate accurate placement of the laparoscopic cryoprobe, and the dilators have been modified to make them stiffer than the dilators used in the open procedure. The probe is passed into the sheath, and the sheath is retracted to the liver edge during the freeze-thaw cycles. The cryoablation is completed under laparoscopic vision and US monitoring. A split-screen image allows simultaneous viewing of the probe and the US image of the developing ice ball.

The reported experience with laparoscopic cryotherapy is scant, and the patients are highly selected. With the expansion of RFA and its laparoscopic application, laparoscopic cryoablation has become less popular, and further publications have not been forthcoming. Reports have been limited to small case series, generally fewer than 10 patients, but the technique seems to be safe and effective in these highly selected patients (Seifert & Junginger, 2004). Despite current technologic limitations, the laparoscopic approach offers several advantages: it is minimally invasive, it eliminates the morbidity associated with a laparotomy incision, and it decreases the length of hospitalization and overall recovery.

PERCUTANEOUS CRYOTHERAPY APPROACHES

Percutaneous approaches for cryotherapy are established, although they have been relatively slow to develop; this is likely related to the explosion in popularity of percutaneous RFA. This approach originally was limited by the large diameter of current cryoprobes, location of the tumors, and accurate radiologic localization. Despite these problems, several moderate-sized

series have been published, which confirm the feasibility and safety of this approach. Guidance most typically was performed with CT or with US, but more recently, techniques using magnetic resonance imaging (MRI) have been developed (Wu et al, 2010).

FOLLOW-UP OF PATIENTS TREATED BY CRYOTHERAPY

Although cryotherapy is an accepted procedure for HCC and liver metastases, prospective and comparative data supporting its efficacy are limited. It is important for a reasonably standardized follow-up to be collected on all patients that includes careful documentation of recurrence patterns and disease-specific outcome. Follow-up of patients after cryotherapy comprises history and physical examination, contrast-enhanced CT scans, and tumor marker determinations. The patient should undergo clinical evaluation, serial liver tests, and tumor marker determinations every 3 to 4 months for 2 years and then every 6 months. carcinoembryonic antigen (CEA) and α-fetoprotein (AFP) levels usually reach their nadir at 4 to 8 weeks after ablation (Steele et al, 1990).

CT scans of the liver should be obtained at 4- to 6-month intervals for the first 2 years. It is important to obtain an early CT scan within a few weeks after treatment to be used as a baseline. Successfully treated tumors initially appear larger than the original lesion because of swelling and because of the margin of normal tissue also treated (Fig. 85B.2). Subsequently, the lesion decreases in size and may disappear completely. Gas bubbles may be seen within the necrotic tumor and may be a result of the packed probe tract. These bubbles rarely indicate hepatic abscess and should not be acted on unless other signs of sepsis are evident. In 3 to 6 months, the lesions shrink and leave behind a persistent area of fibrosis and architectural distortion.

TECHNICAL CONSIDERATIONS

Inflow Occlusion

The flow of warm blood through vessels adjacent to the tumor may act as a heat sink that changes the conformation of the ice ball and alter tumor ablation near the vessel. Some groups have used inflow occlusion with a Pringle maneuver to diminish these effects. Experimental studies have not confirmed these assertions in the porcine model, in which clamping the hepatoduodenal ligament did not alter the size of the ice ball that formed, the amount of liver necrosis, or the incidence of large vessel infarction (Kahlenberg et al, 1998). The relative contraindication to cryoablation near vessels may be only theoretic, and further evaluation of this problem is necessary.

Monitoring the Ice Ball

Most investigators use US to monitor the ice ball, because the pathologic size of liver necrosis closely correlates with the US size of the ice ball. Others have used thermocouples to monitor the temperature at the margin of the ice ball; however, this is an unnecessarily invasive procedure that provides no important additional information. Electrical impedance through the cryolesion is not as accurate as US in defining adequate ablation; but MRI is a promising technology, because it can accurately evaluate temperature gradients within the ice ball in real time. Spectroscopic information obtained by MRI also may provide accurate information on cellular necrosis. MRI is generally unavailable in most operating and interventional radiology suites and remains an investigational tool.

Bile Duct Warming

To protect the major bile ducts from the adverse effects of cryotherapy, some surgeons cannulate the bile ducts to circulate warmed fluids during the cryoablation. At present, there is not enough evidence of benefit to support this invasive procedure.

COMPLICATIONS OF CRYOTHERAPY

The complications of hepatic cryotherapy can be broadly classified into three types of problems: 1) operative, 2) technical, and 3) late onset. The operative complications include complications that are not specific to cryotherapy, whereas the technical and late-onset complications are directly related to the procedure (Table 85B.1). The overall morbidity rate ranges from

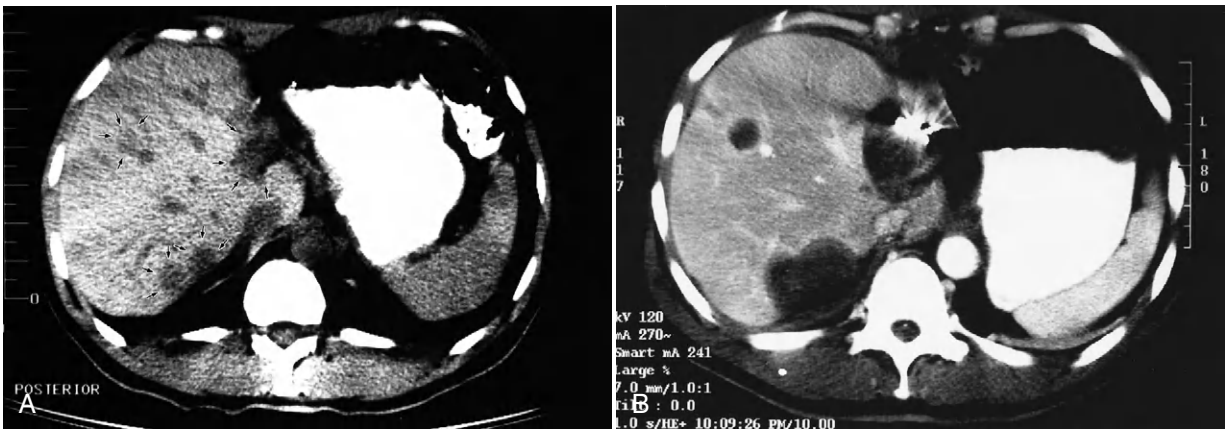


FIGURE 85B.2. A, Pretreatment computed tomographic (CT) scan shows multiple liver metastases (*arrows*) in a patient who had previously undergone resection of segments II and III for metastatic disease. **B,** CT scan 7 days after cryotherapy of five metastatic tumors. The area of necrosis is larger than the original lesions.

Table 85B.1

Complications After Hepatic Cryotherapy: Summary of 869 Patients in 20 Series

Complication	Incidence (%)	Range (%)
Cracking of ice ball	19*	1-25
Hemorrhage	3.7	0-13
Coagulopathy	3.8	0-8
Acute renal failure	1.4	0-17
Bile fistula/biloma	2.9	0-10
Intraabdominal abscess	1.7	0-9
Pleural effusion	6.3	4-18
Death	1.6	0-8

*Reported in only 5 of 20 studies

Modified from Seifert JK, et al, 1998: A collective review of the world literature on hepatic cryotherapy. J R Coll Surg Edinb 43:141-154.

10% to 40%, and the mortality rate ranges from 0% to 5% (Seifert & Junginger, 2004).

Generalized Hypothermia

Generalized hypothermia, a potentially serious adverse event, is generally rare, but it depends on the number of lesions treated and their proximity to blood vessels, especially the vena cava and hepatic veins. The consequences of intraoperative hypothermia are multiple and include cardiac depression, arrhythmias, and coagulopathy. These effects can be ameliorated by warming parenteral fluids and using closed-circulation body warmers and heating blankets. Perhaps most importantly, treatment of multiple large lesions simultaneously should be avoided.

Hemorrhage

After removal of the cryoprobe, hemorrhage through the probe tract is common. The blood does not clot, because the activity of the enzymes that activate the coagulation factors is depressed by the localized hypothermia. Pressure and hemostatic materials usually control the probe tract bleeding. More significantly, the tumor can crack at the interface with the normal uncryoablated tissue, and massive hemorrhage can ensue that requires transfusion, packing, or even conversion to resection. Careful handling of the frozen tissue and gentle extraction of the cryoprobe can minimize this complication, which has been reported in 0% to 25% of treated patients. Diligent use of intraoperative US to avoid moderate-sized vessels during probe placement minimizes this problem.

Bile Fistula and Bile Collections

Bile collections are reported after cryotherapy, affecting approximately 3% of patients in collected series (Seifert & Morris, 1998). Bile collections and fistulae are most common when superficial lesions are treated. Late strictures of the major bile ducts owing to injury during the freezing process may occur and predispose patients to cholangitis. The risk is increased for cryoablated tumors located near the hepatic hilum or the bifurcation of the major biliary ducts, although no long-term studies have confirmed this risk of bile duct injury and late stricture (see Chapters 42A and 42B).

Cryoshock

Cryoshock is a complex of multisystem organ failure, renal failure, and DIC after cryotherapy, and it is potentially lethal. The cause of this symptom complex is unknown, but it is responsible for 18% of deaths after hepatic cryotherapy. In a survey of all groups using cryotherapy, cryoshock was reported in only 21 of 2173 patients undergoing hepatic cryotherapy for tumor (Seifert & Morris, 1998). The cause of this phenomenon is likely related to systemic release of proinflammatory cytokines, such as tumor necrosis factor, interleukin (IL)-1, IL-2, and IL-6. Experimental studies have correlated the risk of this syndrome with larger ablations and with higher systemic levels of these cytokines (Ng et al, 2004; Seifert et al, 2002).

Mortality

The overall early mortality rate for cryotherapy is low at 1.5% (range, 0% to 8%) (Seifert & Junginger, 2004). In expert hands, the operative mortality for major hepatic resection is similar. The most common causes of death after hepatic cryotherapy are not specific to the cryotherapy but rather to cardiac and pulmonary comorbidities. The more common treatment-specific causes of death include cryoshock, liver failure, and hemorrhage.

LONG-TERM RESULTS OF CRYOABLATION

Cryoablation of Hepatocellular Carcinoma

Cryoablation of primary liver cancer has been reported in more than 200 patients. The outcome of these reported series is difficult to interpret, however, because many patients were treated with cryotherapy in combination with resection, chemotherapy, or hepatic artery ligation. There is about a 60% reduction (range, 40% to 82%) in AFP levels after cryotherapy in patients in whom AFP was elevated preoperatively. Reduction of AFP serum levels after cryotherapy does not clearly translate into a survival benefit.

For primary liver cancer patients treated with cryotherapy alone, the 5-year survival is approximately 30%. As expected, survival correlates well with the biologic characteristics of the tumor, of which size seems to be the most important factor. Zhou and colleagues (1996) showed that 5-year survival was 48% for tumors less than 5 cm, whereas it was only 25% for larger tumors (Zhou et al, 1996). The pattern of recurrence is predominantly in the liver after cryotherapy, but the reports typically do not describe whether the cryotherapy was complete, or what the intended margin was. In addition, it is often not reported whether the tumor recurred in the treated area, or whether these recurrences were a separate, intrahepatic, distant tumor resulting from intrahepatic metastases or new primaries. Few studies contain longitudinal survival information, and these results must be corroborated by larger multicenter studies controlling for tumor size, number of lesions treated, and adequacy of treatment.

It is difficult to compare the results of resection with cryotherapy, because the reported series generally are not comparable in terms of tumor characteristics. The operative mortality

for resection of HCC historically has been 6% to 8% in most series, but now with better selection criteria and improved techniques, mortality is generally less than 5%. The median survival is approximately 30 months, with 5-year survivals of 30% to 40%. Similar survivals are reported in selected patients who undergo percutaneous ethanol injection (PEI); however, these are performed in highly selected patients (see Chapter 85A). Livraghi and colleagues (1995) reported a multicenter trial of PEI for HCC that included 746 patients (Livraghi et al, 1995). Survival was related to the size of the lesion, number of tumors, and Child-Turcotte-Pugh (CTP) class of the associated cirrhosis. For unifocal tumors less than 5 cm, the 5-year survival rates were 47%, 29%, and 0% for class A, B, and C cirrhosis, respectively. Even in the presence of multifocal disease, 36% of patients with class A cirrhosis survived 5 years after PEI. Similar results have been reported by Castells and associates (1993) in a comparative study of resection and PEI for HCC less than 4 cm. At 4 years, survival was equivalent for the two modalities.

Hepatic artery infusion chemotherapy, hepatic artery ligation, and systemic chemotherapy all have 25% response rates for HCC. These responses have not led to improved survival, however, and these approaches remain investigational.

Because of patient selection and the combination of therapies used with cryotherapy, for the most part, comparisons with other modalities are meaningless. The development of RFA has generally replaced cryotherapy in the treatment of HCC. Future directions may include hepatic artery infusional chemotherapy after ablative therapies for unresectable tumors.

Cryoablation of Liver Metastases

Liver metastases arising from colorectal, lung, pancreas, and stomach primary tumors constitute the most common malignant tumors of the liver (see Chapter 81A). Most cancers that metastasize to the liver do so in combination with extrahepatic dissemination. The natural history and pattern of recurrence for colorectal cancer is different. Of the approximately 160,000 new cases each year, half develop liver metastases within 5 years of diagnosis. Approximately 20% of these patients (16,000) develop metastatic disease confined to the liver. Only a quarter (4000 to 5000 patients) are amenable to hepatic resection with curative intent; the remaining 12,000 patients with liver-only colorectal metastases are candidates for regional therapies to the liver. The number of patients being considered for liver resection is now increasing because of improved resection techniques and dramatic improvements in adjuvant chemotherapy.

The ultimate goal of regional treatment of liver metastases is increased survival, but long-term follow-up of patients after cryotherapy for liver metastases is inadequate. Most published studies do not have follow-up exceeding 2 years, and few groups have treated enough patients to draw valid conclusions regarding the efficacy of cryotherapy in this setting. Series with adequate follow-up reporting 3- and 5-year survival have been published, albeit with relatively small numbers. In addition, cryotherapy has been used primarily as a salvage procedure or in combination with other treatment modalities, including resection or hepatic artery ligation or infusion, which obscures the results for cryotherapy alone. Ravikumar and associates (1991a) reported overall and disease-free survivals of 78% and 39% at 5 years for 18 patients undergoing complete cryoablation of liver metastases. These encouraging results have not been duplicated in more recent studies, probably because of less stringent selection criteria. Most series (Table 85B.2) report median overall survival of about 2 years after cryoablation of liver metastases. In 24 patients treated with cryotherapy, regardless of whether the ablation was complete or not, Ravikumar and associates (1991b) reported disease-free and overall survival rates of 24% and 63%, respectively. Similarly, Weaver and colleagues (1995) found that 11% of patients were disease-free at a mean follow-up of 30 months, and 62% of treated patients were alive 24 months after cryoablation. Seifert and Morris (1998), in a series of 116 patients with colorectal metastases, showed a median survival of 26 months, and 13% of patients were alive at 5 years. More recent publications have reported 4- and 5-year actuarial survival ranging from 22% to 36% (Kerkar et al, 2004; Rivoire et al, 2002; Seifert & Junginger, 2004). Despite the wide variation in outcome with cryotherapy, some patients in each of the series achieved durable survival with this treatment. Actual follow-up is greater than 5 years for individual patients, suggesting that cryotherapy can be curative in some cases. Based on the worldwide data, it seems that durable local control is achieved in about 20% of patients treated with cryotherapy.

Because the series reporting survival are generally small and include patients treated with cryotherapy, in combination with resection for control of inadequate margins, and patients receiving hepatic artery infusion chemotherapy (see Chapter 86), the results cannot be combined for a proper meta-analysis. Because there are no randomized trials of cryotherapy, Tandan and coworkers (1997) undertook a critical comparative review of resection and cryoablation of colorectal liver metastases. This analysis reviewed 178 studies published from 1973 to 1995. Only studies with survival data exceeding 2 years and data for liver resection if the series included more than 60 patients were included; four cryotherapy and nine resection studies met these minimum inclusion criteria. The median follow-up times for the two procedures were 12 to 28.8 months for cryotherapy and 21 to 69 months for liver resection. The data on liver resection were found to be more valid and consistent, but this review supported a role for cryotherapy in the management of liver metastases. Based on this evaluation, the authors concluded that cryosurgery offers potential advantages in the treatment of liver metastases, it should not be used in cases of resectable disease outside of a clinical trial, and randomized trials comparing the two modalities are needed. Survival seems to be related to the size of the lesions, the volume of liver replaced by tumor, a low pretreatment serum CEA level, absence of extrahepatic metastases, and whether the lesion underwent complete ablation. Normalization of an elevated precryotherapy CEA has been a favorable prognostic factor. Failure to achieve this normalization of CEA probably results from residual unrecognized micrometastatic disease.

Complete response at the treated site ranges from 60% to 90%, and most recurrences are at sites away from the cryolesion. The pattern of recurrence in these patients is primarily in the liver, with or without synchronous extrahepatic disease. This finding underscores the need for additional therapy to further reduce the incidence of hepatic recurrence. With the improvements in regional and systemic chemotherapy, the utility of cryotherapy combined with chemotherapy has been shown even in grossly unresectable patients (Kemeny et al, 2001). An additional use for cryoablation is in the treatment of close or inadequate margins. Edge cryotherapy in these

Table 85B.2

Survival After Cryotherapy: Review of Published Series

First Author, Year	Type of Tumor	No. Patients	Type of Treatment	Median Survival (mo)	Median Disease-Free Survival	Overall Survival
Zhou, 1996	HCC	167	C, C+H, C+R	–	–	32% (5 yr)
Haddad, 1998	CRM, PLC, other	31	C, C+R	18	7	–
Seifert, 1998	CRM	116	C, C+R, C+H	26	–	13% (5 yr)
Yeh, 1997	CRM	24	C, C+R	31	20	85% (3 yr)
Adam, 1997	HCC, CRM	34	C, C+R	NR at 16	–	52% (2 yr)
Korpan, 1997	CRM	63	C, C+R	–	–	44% (5 yr)
Shafir, 1996	CRM, HCC, other	39	C	NR at 14	–	65% (3 yr)
Crews, 1997	CRM, HCC, other	40	C	–	–	30% (5 yr)
Weaver, 1995	CRM, other	140	C, C+R	22	11% at 30	62% (2 yr)
Wrens, 1997	HCC	12	C	19	–	–
Ravikumar, 1991b	CRM, HCC	32	C, C+R	–	24%	63%
Onik, 1991	CRM	18	C, C+R	33% at 29	–	–
Lam, 1998	HCC	4	C, C+R	1 NED, 3 AWD at 12 to 23	–	–
Lezoche, 1998	CRM, other	18	C	78% NED at 11	–	–
McKinnon, 1996	CRM, PLC	11	C, C+R	73% at 18	–	–
Heniford, 1998	CRM, other	12	C	83% at 11	–	–
Dale, 1998	CRM	6	C, C+R	100% at 17	–	–
Sheen, 2002	CRM, other	57	C, C+R	22	12	–
Rivoire, 2002	CRM	57	C, C+R	–	–	36% (4 yr)
Seifert, 2004	CRM	55	C, C+R	–	–	26% (5 yr)
Kerkar, 2004	HCC, CRM, other	98	C	33	–	22% (5 yr)

CRM, colorectal metastases; HCC, hepatocellular carcinoma; C, cryoablation; R, resection; H, hepatic artery ligation; NR, not reported; NED, no evidence of disease; AWD, alive with disease; PLC, primary liver cancer

situations has resulted in good local tumor control (Gruenberger et al, 2001; Hou et al, 2007; Yan et al, 2006). Survival after hepatic resection of liver metastases is substantially better (20% to 58%) than after cryotherapy, but the patient populations are not comparable. Cryotherapy generally has been reserved for patients who are unable to undergo resection and who might have a poorer prognosis.

COMPARISON WITH RADIOFREQUENCY ABLATION

Over the past 10 years, RFA has replaced cryotherapy in many centers (see Chapter 85C). Pearson and colleagues (1999) prospectively studied the complication rates and early local recurrence rates in patients with primary or metastatic liver tumors who were treated with cryotherapy or RFA. With a total of 54 patients treated with cryotherapy and 92 patients treated with RFA, a 41% complication rate was reported in the cryotherapy group compared with a 3% complication rate in the RFA group ($P < .001$). The majority of complications in the cryotherapy group were symptomatic pleural effusions and intrahepatic abscesses. Recurrence rates with a median follow-up of 15 months also favored RFA, with a 2% recurrence rate compared to 14% in the cryoablation group ($P < .01$). Percutaneous cryotherapy and RFA were compared in a retrospective study by Adam and colleagues (2002) with a group of 64 patients. They reported complication rates of 29% for cryotherapy patients and 24% for those who underwent RFA ($P = .66$), but local recurrence rates were 53% in the cryotherapy group, compared with 18% in the RFA group ($P = .003$).

SUMMARY

Because most patients who present with hepatic tumors are unresectable, ablation has a role in the treatment of primary and metastatic liver tumors. With improving chemotherapy for metastases, ablative techniques may play a larger role in the management of bilobar tumors and technically unresectable tumors. The availability of ablative treatment options expands the possible treatments for unresectable disease and allows resection in combination with ablation for more marginal candidates. Ablations can be performed safely in patients with significant comorbidity. Given high recurrence rates in many series that have examined results after ablation of primary or metastatic liver tumors, innovative approaches combining systemic or regional chemotherapy or both are needed to control micrometastatic disease. For now, ablation expands the possible treatments of these diseases and may alter the natural history of the tumor recurrence while also having an impact on survival. Due to higher complication rates and higher local recurrence rates in several series, cryotherapy has been replaced by radiofrequency ablation in most centers. It is relevant in centers where it is the only available ablative modality and for a historic understanding of the development of ablative techniques.

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CHAPTER 85C

Radiofrequency ablation for liver tumors

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OVERVIEW

Hepatic resection and transplantation are the only curative options for patients with liver metastases or primary liver tumors (see Chapters 80, 81, and 97). Unfortunately, resection is possible in only about 20% of patients; most hepatic malignancies are surgically inaccessible or are associated with a large tumor burden or inadequate hepatic reserve. Liver transplantation for hepatocellular carcinoma (HCC) is limited by a shortage of donor organs (see Chapter 97D). Patients with unresectable disease may be candidates for systemic therapy (see Chapter 88), local ablative techniques (percutaneous ethanol injection, microwave tumor coagulation, interstitial laser photocoagulation, cryosurgical ablation, or radiofrequency ablation [RFA]; see Chapter 85), or hepatic-directed therapy (hepatic artery ligation, chemoembolization, hepatic artery perfusion; see Chapters 83, 86, and 89).

Over the past decade, multiple clinical trials have evaluated RFA for the treatment of primary liver tumors and liver metastases. Animal experiments in the early 1990s determined the size and shape of ablations that could be achieved in the liver (Rossi et al, 1990). Rossi and colleagues (1996) then demonstrated the effectiveness of RFA for the treatment of HCC in humans. The Food and Drug Administration (FDA) approved RFA for generic tissue ablation in 1996 and for ablation of unresectable hepatic metastases in 2000. Since then, randomized trials have been performed in early HCC that demonstrate equivalent survival to resection (Lu et al, 2006), but prospective data in colorectal liver metastases are limited.

RFA destroys tumor by generating heat within a lesion. During RFA, a high-frequency alternating current changes the direction of ions around an alternating electrode charge. This creates frictional energy and heat conduction. As tissue temperature increases above 45° C, loss of cellular structure and protein denaturing result in tumor cell death. RFA can be performed in the operating room via celiotomy or laparoscopy, or it may be done in the radiology suite by a percutaneous approach. It can be used with other modalities of liver-directed therapy, such as resection and hepatic artery perfusion, and it can be used in conjunction with systemic therapy for other sites of metastatic disease. RFA continues to evolve with the introduction of new technology that increases the field of ablation and simplifies the technique. Long-term survival data have been reported in both HCC and colorectal hepatic metastases (Table 85C.1). A recently published position statement by the Society of Interventional Radiology (Gervais et al, 2009) describes four categories of patients that are preferred candidates for RFA: those with 1) inadequate liver function, 2) comorbid conditions, 3) anatomic distribution, and 4) for local tumor control as a bridge to transplantation.

RADIOFREQUENCY ABLATION TECHNOLOGY

RFA destroys tissue by generating enough heat to denature cell protein and cause cell death (Fig. 85C.1), which can occur instantaneously at 60° C, a temperature achieved by all RFA devices. During RFA an electrical generator produces a current that alternates directions rapidly. Charged molecules in the tissue follow the direction of the changing current: this results in friction, which produces heat. The current around the ablation electrode creates a relatively uniform zone of conductive heat that radiates out from the electrode. If tissue impedance is low, an expanding spherical zone of ablated tissue is created. As the temperature rises, tissue charring and desiccation occur. Also, nitrogen gas forms that can be seen on ultrasound (US) as air bubbles in the tissue. Both of these events raise tissue impedance and inhibit heat conduction, thereby inhibiting further tissue ablation. The spherical size of the ablated tissue is proportional to the square of the RF current (RF power density). It is also dependent on the size of the electrode and the duration of the applied energy. The RF power density decreases in proportion to the square of the distance from the electrode, resulting in a rapid decrease in tissue temperature with increasing distance from the electrode (Strasberg & Linehan, 2003). Changing technology strives to improve ablation zones by limiting impedance and increasing the RF power density.

Early RFA electrodes were unipolar. Because they produced a 1.5- to 2.0-cm cylindrical zone of ablated tissue, only tumors less than 2 cm in diameter could be ablated. These electrodes were eventually replaced by single electrodes that deployed multiarray tines (multiarray electrodes) to create a larger, more spherical zone of ablation. The current multiarray electrodes described below can ablate fields of 4 to 5 cm in diameter. Technologic developments to reduce tissue impedance and increase the zone of ablation will allow progressively larger tumors to be treated with single ablations.

Three different RF electrodes and generators are commercially available. The Radiofrequency Interstitial Tissue Ablation (RITA; AngioDynamics, Latham, NY) and RadioTherapeutics (Boston Scientific, Natick, MA) systems use multiarray electrodes (Fig. 85C.2). The RITA system has a single electrode through which multiple tines are deployed. The ablation is performed at sequential steps of electrode deployment. Thermoprobes measure temperature in the ablation zone, and an automated adjustment is then made to maintain a steady temperature during the ablation. The electrode/generator system measures temperature and time as end points of ablation. This system was recently modified by the addition of saline perfusion to reduce impedance and increase the diameter of the ablation field to 7 cm. The RadioTherapeutics system automatically

Table 85C.1

Survival Data for Radiofrequency Ablation of Various Tumor Types

First Author, Year	Mean Follow-up (mo)	Tumor Type (No. Patients)	RFA Approach	SURVIVAL (%)				
				1 Year	2 Years	3 Years	4 Years	5 Years
Rossi, 1996	22.6	HCC (39)	Percutaneous	94	86	68	40	–
Solbiati, 2001	6 to 52	Metastases from CRC (117)	Percutaneous	93	69	46	–	–
Llovet, 2001	10	HCC (32)	Percutaneous	85	–	–	–	–
Elias, 2002	14.4	HCC (5) Metastases (42)	Percutaneous	88	55	–	–	–
Abdalla, 2004	21	Metastases from CRC (57)	Open	–	–	37	22	–
Vivarelli, 2004	15.6	HCC (79)	Percutaneous	78	–	33	–	–
Poon, 2004a	13	HCC (80)	Percutaneous Laparoscopic, Open	84	–	–	–	–
Jakobs, 2006	21	CRC (68)	Percutaneous	–	–	68	–	–
Abitabile, 2007	21	CRC (47)	Percutaneous	–	–	–	–	21
Siperstein, 2007	24	CRC (234)	Laparascopic	–	–	–	–	18.4
Sorenson, 2007	23	CRC (100)	Percutaneous, Open	–	–	–	26	44
Veltri, 2008	24	CRC (122)	Percutaneous, Open	–	–	–	–	22
Gillems, 2008	38	CRC (40)	Percutaneous	–	–	–	–	40

CRC, colorectal carcinoma; HCC, hepatocellular carcinoma; RFA, radiofrequency ablation

adjusts current according to tissue impedance; temperature is not measured. The multiarray umbrella-shaped electrode can ablate fields of about 4 cm. The Cool Tip Cluster Electrode, a single or three-pronged electrode, is manufactured by Covidien (Mansfield, MA); each electrode is internally perfused with cold saline, the current is sent in pulses, and the system measures impedance and temperature. Ablation zones can reach 5 cm in diameter with the three-pronged device.

Technical Aspects of Radiofrequency Ablation

Patients who come to medical attention with liver tumors should be evaluated for curative resection or transplantation for HCC. Those whose performance status or disease location or distribution prohibits resection may be candidates for RFA. Prior to RFA, all patients should undergo computed tomography (CT), magnetic resonance imaging (MRI), and/or fluorodeoxyglucose (FDG) positron-emission tomography (PET). If these whole-body imaging techniques reveal extrahepatic sites of metastatic disease, systemic therapy may be a preferred option instead of resection or RFA. Patients with physiologically active neuroendocrine tumors are an exception in that debulking may reduce debilitating symptoms. Baseline hepatic function should be assessed through laboratory indicators of synthetic function and Child-Turcotte-Pugh (CTP) classification of liver dysfunction. A thorough history and physical examination are essential to determine patient performance and prior treatment history.

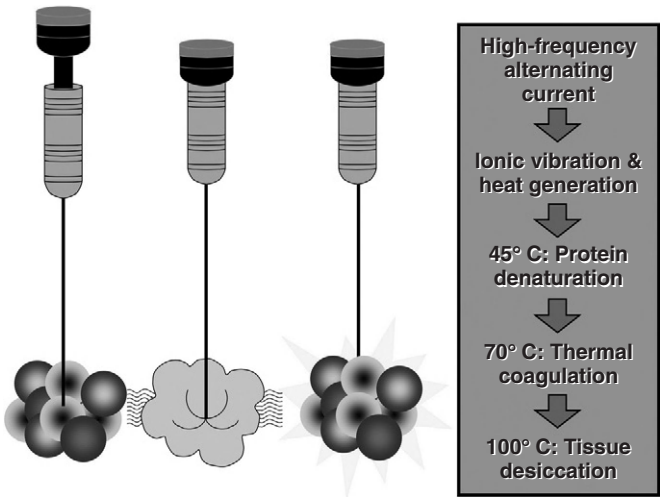


FIGURE 85C.1. Schematic of radiofrequency ablation.

If a surgical approach is undertaken, laparoscopy can reveal extrahepatic disease, and intraoperative US can identify intrahepatic disease not detected by preoperative imaging. A 30-degree angled laparoscope can be used to examine all parietal and visceral peritoneal surfaces, the lesser sac, omentum, and viscera. If extrahepatic disease is found, RFA should not be done, and systemic treatment should be considered. A flexible 7.5-MHz ultrasonic probe is used to evaluate the liver and determine the proximity of liver lesions to major vascular and biliary structures. The exact location of hepatic metastases will affect the technical approach for RFA.

If extrahepatic and/or extensive intrahepatic disease has been detected, ablation is unlikely to be of any benefit. US during surgical or percutaneous RFA or CT during percutaneous RFA is used to guide the probe into the lesion, and the ablation is monitored by real-time US imaging of an expanding hyperechogenic zone (Fig. 85C.3). Depending on the maximal ablation size achievable by the probe, multiple overlapping ablations may be needed to destroy a tumor and produce a surrounding rim of necrosis (Fig. 85C.4). This can be technically challenging. US cannot reliably distinguish between ablated and normal tissue, so ablation should begin at the most posterior portion of the tumor. The probe then can be withdrawn in approximately 2-cm increments to create sequential overlapping zones of ablated tissue. If target temperatures are not reached, as may be the case for lesions near major vascular

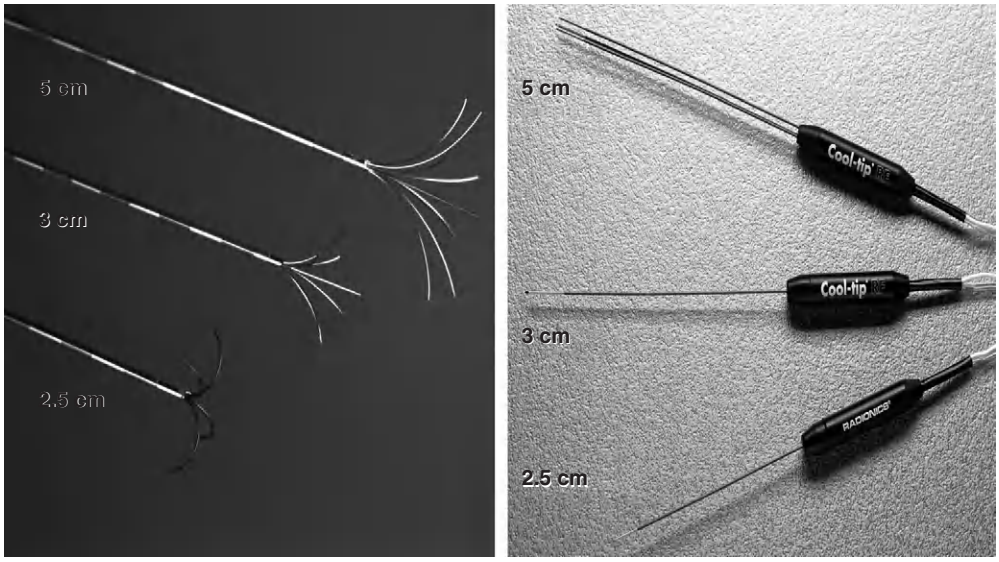


FIGURE 85C.2. RITA (*left*) and Radionics (*right*) probes used for radiofrequency ablation.

structures because of a heat-sink effect, the tines are withdrawn slightly or rotated approximately 45 degrees to increase the temperature in the region of ablation. Each ablation should create a 1-cm margin of treated normal parenchyma to ensure complete tumor destruction and reduce the risk of local recurrence. After ablation, as the RFA needle is withdrawn, the probe tract is cauterized to prevent hemorrhage and tumor seeding of the needle tract.

RFA can be performed by celiotomy (open), laparoscopy, or a percutaneous approach. The choice of technique depends on the patient's condition, the number and location of liver tumors, and the skill of the physician performing the ablation. Each approach offers certain advantages and disadvantages that must be weighed to determine the best approach for the individual patient.

Percutaneous Radiofrequency Ablation

A skilled interventional radiologist typically performs percutaneous RFA as an inpatient or outpatient procedure under US, CT, or combined guidance. The patient is sedated and/or given a local anesthetic. CT guidance provides several advantages: it allows precise placement of the electrode despite the generation of gas within the ablation, and it is possible to assess the adequacy of the ablation during the procedure by performing a contrast-enhanced scan. If areas of inadequate ablation are identified, additional targeted ablations can be performed during the initial procedure.

The percutaneous approach is somewhat limited, as some liver lesions can only be accessed by a surgical approach. Tumors near the periphery of the liver may be problematic because of the risk of thermal injury to other visceral structures such as the small bowel, stomach, or transverse colon; with an open technique, these structures can be retracted away from the liver. Other lesions can be approached percutaneously but raise technical challenges. For example, ablation of lesions at the dome of the liver might result in thermal injury to the diaphragm. Introduction of an air pocket can be used to separate the diaphragm and liver to avoid diaphragmatic thermal injury (Raman et al, 2004); this requires skill and may result in complications such as diaphragmatic injury or pneumothorax. Injection of saline or use of a balloon catheter has also been reported to separate structures from the liver to avoid thermal

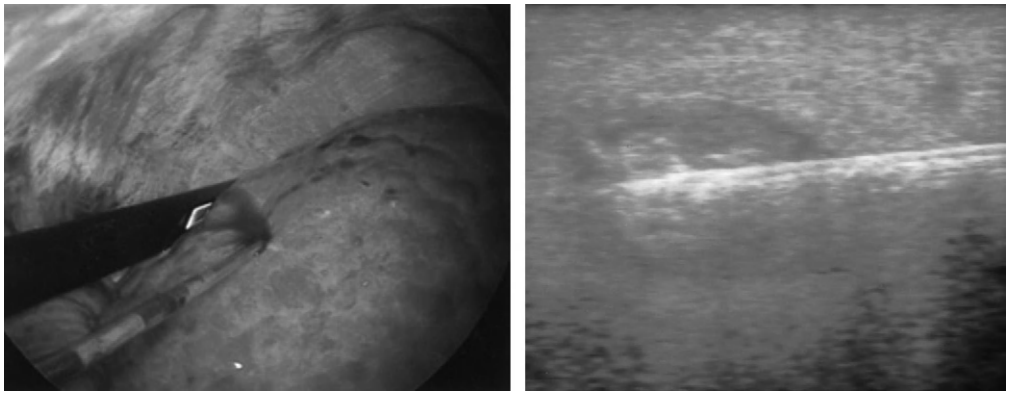


FIGURE 85C.3. Ultrasound-guided radiofrequency ablation.

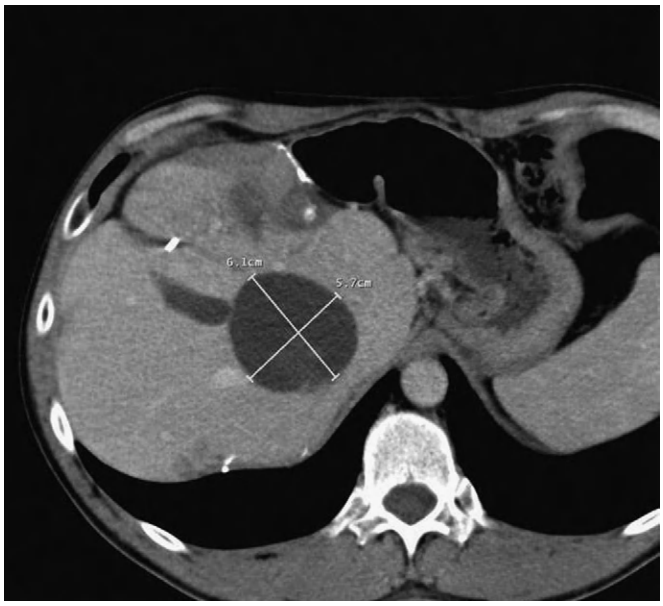


FIGURE 85C.4. Computed tomographic scan demonstrating large-volume ablation achieved with multiple overlapping ablation technique.

injury; however, clinically relevant diaphragmatic injuries are rare in our experience (Fig. 85C.5). Because a percutaneous approach is less invasive than a surgical approach, it may also be preferable in patients with comorbid conditions or poor medical status.

Open or Laparoscopic Radiofrequency Ablation

RFA via celiotomy or laparoscopy is performed in the operating room by a surgeon, while the patient is under general anesthesia. Unlike the percutaneous approach, a surgical approach allows visual inspection of the intraabdominal cavity for extrahepatic disease. Intraoperative US is used to evaluate the liver for intrahepatic lesions not seen on preoperative imaging. In a study of 308 patients undergoing laparoscopic RFA with intraoperative hepatic US, preoperative imaging failed to identify extrahepatic disease in 12% of patients and additional hepatic lesions in 33% of patients (Bilchik et al, 2000). Similarly, Siperstein and colleagues (2000) found that 30% of patients who underwent laparoscopic US of the liver prior to RFA had additional metastatic nodules not apparent on the preoperative CT scan. Larger liver lesions (>5 cm) are more easily treated with an operative approach than percutaneously. These lesions may require multiple overlapping ablations. Intraoperative occlusion of the portal triad can increase the ablation zone by decreasing the heat-sink effect created by nearby vessels. Furthermore, a surgical approach is sometimes necessary when other treatments are used in combination with RFA. For example, a surgical approach is ideal for patients who have bilobar liver metastases, who may benefit from concomitant liver resection. Larger liver lesions may be resected, and smaller lesions in the opposite lobe may be treated by RFA.

Laparoscopy is less invasive than celiotomy, and patients often require slightly shorter hospital stays. In some cases, a celiotomy is needed because of decreased access to the liver and limited position of the US and RFA probe under laparoscopy; However, in the presence of multiple adhesions in the abdomen from prior operations, or if the tumor cannot be approached safely, laparoscopy may not be possible. In this case, a celiotomy is warranted.

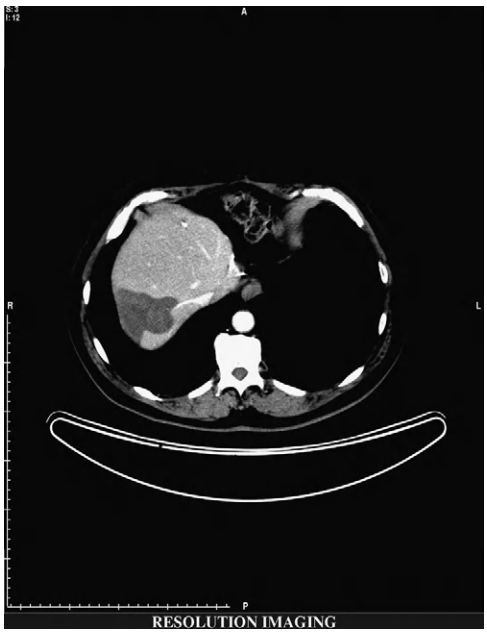


FIGURE 85C.5. Percutaneous ablation performed adjacent to the diaphragm.

Monitoring and Follow-up

After laparoscopic or percutaneous RFA, patients are usually admitted to the hospital for 23 hours or are discharged home the same day; after open RFA (celiotomy), patients are usually hospitalized for 3 to 5 days. In all cases, red blood cell and leukocyte counts, liver function tests, and temperature are closely monitored. RFA typically causes a mild transient elevation of liver function tests, core temperature, and leukocyte count. These should normalize within about 3 days. Continued elevation, especially 5 or more days after RFA, may be an indicator of a potential complication and should prompt further clinical investigation. Tumor markers such as carcinoembryonic antigen (CEA) for colorectal cancer metastasis and α-fetoprotein (AFP) for HCC can also be used to monitor patients as appropriate.

Contrast-enhanced CT scans obtained within a month and then at 3-month intervals after RFA should be compared with preprocedure CT scans. Liver necrosis from RFA can be seen as a nonenhancing hypodense region. When complete necrosis of the tumor is achieved, the resulting necrotic zone exceeds the original tumor size. Postprocedure CT scans are important to determine the success of RFA and to monitor the liver for evidence of recurrence. PET scans may also be particularly sensitive in the assessment of the adequacy of ablation and presence of marginal recurrence (Fig. 85C.6) or to distinguish viable tumor from areas of previous surgical or ablative therapy (Fig. 85C.7).

Current Practice

RFA has mainly been used for unresectable HCC or metastatic disease confined to the liver (see Chapters 80, 81A, and 81B).

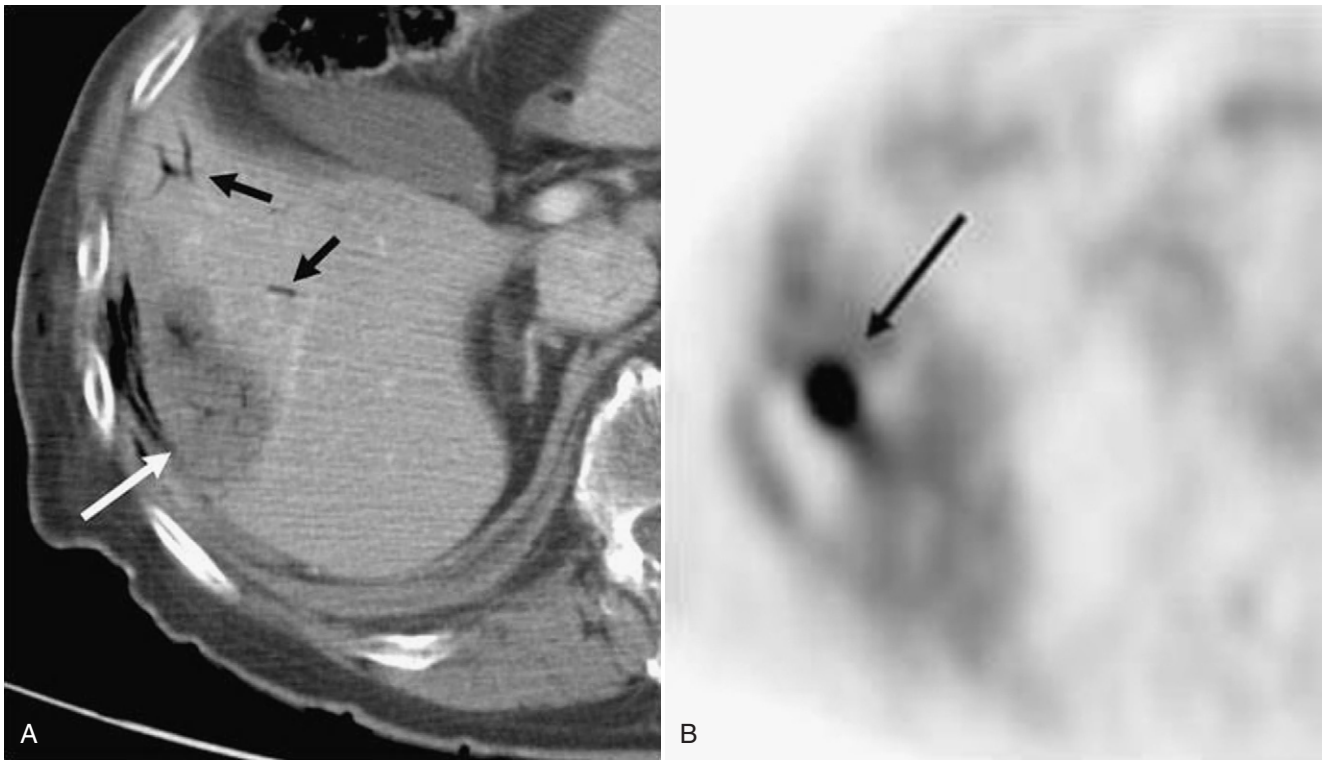


FIGURE 85C.6. A, Marginal recurrence not clearly visualized by computed tomography. **B,** Recurrence is clearly identified by positron emission tomographic scan.

Tumors may be deemed unresectable based on size, number, location, or doubling time. Therefore, selection of patients is based initially on a thorough preoperative workup that includes imaging to evaluate for other sites of disease, prior response to systemic therapy, and the biology of the disease. If systemic therapy eliminates extrahepatic metastases, and if its effects prove durable over several months, RFA of hepatic metastases may be considered; however, this applies to a small subset of unique patients. Some patients will have resectable disease but limited hepatic reserve. For example, a patient with cirrhosis and HCC might not have enough hepatic reserve for tumor resection but would be able to tolerate RFA. In other patients, resection of larger lesions and RFA of smaller lesions can completely eradicate tumor while maintaining hepatic reserve. Finally, patients who have multiple comorbid factors may not be good candidates for an operation and may be best treated by a less invasive approach such as percutaneous RFA.

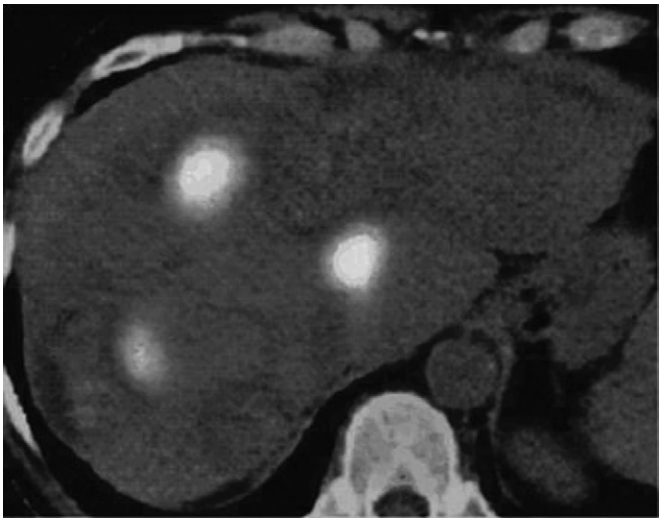


FIGURE 85C.7. Positron emission tomography scan demonstrating areas of viable tumor distinguished from areas of successful ablation.

Radiofrequency Ablation of Colorectal Hepatic Metastases (See Chapter 81A)

Resection offers the only curative option in patients with colorectal hepatic metastases, with 5-year survival approaching 60% (Ahmad et al, 2007; Pawlik et al, 2008; Tomlinson et al, 2007). The improvement in survival is attributed to more effective systemic therapy and expanded criteria for defining resectability. Despite these, many patients are poor candidates for resection, and RFA provides a locoregional alternative. In a recent review of 21 studies (Stang et al, 2009), the median progression-free survival after RFA ranged between 6 and 13 months; the median and 5-year survival ranged between 24 and 59 months and 18% to 40%, respectively.

No randomized trials have compared RFA to resection in patients with colorectal hepatic metastases. One retrospective study of 358 patients compared resection, RFA plus resection, RFA alone, and laparotomy with biopsy (Abdalla et al, 2004); RFA was used for cure when complete resection was not possible. All patient-related and tumor-related factors known to influence outcome were similar among the groups. The rate of recurrence was 84% after RFA alone, 63% after RFA plus resection, and 52% after resection alone. Local recurrence in the area treated was more common after RFA plus resection (9%) than after RFA alone (5%) or resection alone (2%). The

Table 85C.2

Radiofrequency Ablation vs. Resection for Hepatic Colorectal Metastases (Nonrandomized)

First Author, Year	No. Patients	Follow-up Median (mo)	Local Recurrence (%)	Overall Survival (%)
Oshow, 2003	20 resection	18	0	3 years (55)
	25 RFA		12	3 years (53)
Aloia, 2006	150 resection	31	5	5 years (71)
	30 RFA		37	5 years (27)
White, 2007	30 resection	68	0	5 years (65)
	22 RFA	17	36	3 years (28)
Park, 2008	59 resection	49	1.7	5 years (48)
	30 RFA		23	5 years (19)
Hur, 2009	42 resection	42	9.5	5 years (50)
	25 RFA		28	5 years (25)

RFA, radiofrequency ablation

3-year rate of overall survival was 73% after resection, 43% after RFA plus resection, and 37% after RFA alone. Patients who underwent RFA had a survival advantage over patients who underwent biopsy with or without chemotherapy. Four recent nonrandomized retrospective studies (Aloia et al, 2006; Hur et al, 2009; Park et al, 2008; White et al, 2007) demonstrated a survival benefit in patients undergoing resection versus RFA; the 5-year survival was between 48% and 71% for resection and between 19% and 27% for RFA (Table 85C.2). The survival analyses in these studies are limited by differences in patient selection, follow-up time, tumor type, and RFA approach, which make them difficult to compare.

Radiofrequency Ablation of Hepatocellular Carcinoma (See Chapter 80)

Locoregional methods for ablation of HCC include percutaneous ethanol ablation (PEI), chemoembolization, cryosurgery, and RFA, although RFA offers many advantages over PEI and cryoablation. In general, PEI requires multiple treatments and needle insertions to treat a single lesion, whereas RFA can treat the entire tumor with one or two probe insertions. Two randomized trials (Lencioni et al, 2003; Lin et al, 2005) have demonstrated superiority over PEI. The 2-year disease-free survival (DFS) was 96% in patients treated with RFA compared with 62% in patients treated with PEI (Lencioni et al, 2003). Similarly, Lin and colleagues (2005) demonstrated that in patients with HCC less than 3 cm in size, the 3-year DFS was superior in those treated with RFA. When compared with cryoablation, RFA is associated with less blood loss, less thrombocytopenia, and a shorter hospital stay (Bilchik et al, 2000). Cryoablation also carries the risk of a systemic inflammatory response, which can result in renal insufficiency, coagulopathy, hypotension, and death. This type of systemic response has not been reported with RFA.

Clinical trials of RFA for HCC have shown promising results (see Table 85C.1). Livraghi and colleagues (2008) demonstrated a local recurrence rate of only 2.8% at a median follow-up of 31 months for tumors smaller than 2 cm. Poon and colleagues (2004a) achieved a complete response rate of 91% for RFA of large (>3 cm) HCC and rates of local recurrence, distant intrahepatic recurrence, and extrahepatic metastasis were independent of tumor size.

Radiofrequency Ablation Versus Resection for Hepatocellular Carcinoma

Only two prospective randomized controlled trials have been done of RFA versus resection for the treatment of primary liver carcinoma (see Chapter 80). Chen and colleagues (2006) randomized 180 patients with a solitary HCC smaller than 5 cm to either resection or percutaneous RFA. The 4-year overall survival was 68% in the RFA group and 64% in the resection group. Local recurrence rates were also similar, with less morbidity in the RFA group. Lu and colleagues (2006) randomized 105 patients with either a solitary HCC tumor smaller than 5 cm or fewer than three tumors less than 3 cm in size to either a partial hepatectomy or percutaneous RFA and found that 3-year survival rates were similar in both groups (Table 85C.3),

Table 85C.3

Radiofrequency Ablation vs. Resection for Hepatocellular Carcinoma

Study	Patients	Morbidity (%)	Disease-Free Survival (%)	Overall Survival (%)
Chen et al, 2006*†	RFA: 71	4.2	46.4	67.9
	Resection: 90	55.6	51.6	64.0
Lu et al, 2006*‡	RFA: 51	8	51.3	87.1
	Resection: 54	11	82.3	86.4
Hong et al, 2005‡	RFA: 55	NR	40.2	72.7
	Resection: 93	NR	54.7	83.9
Lupo et al, 2007§	RFA: 60	10	0	32
	Resection: 42	16.7	14	43
Guglielmi et al, 2008§	RFA: 109	10	22	20
	Resection: 91	36	27	48

*Prospective randomized trials
†4-Year survival rates
‡3-Year survival rates
§5-Year survival rates
RFA, radiofrequency ablation; NR, not reported

but hospital stay and blood transfusions were significantly reduced in the RFA group.

Conflicting result have been reported in several nonrandomized studies (Hong et al, 2005; Lupo et al, 2007; Montorsi et al, 2005) that demonstrate therapeutic equivalence; others report a higher local recurrence rate and reduced survival in the RFA group (Vivarelli et al, 2004). This study was performed at two different centers; RFA was performed at one center and resection at the other. Overall and disease-free survivals were significantly better after resection; however, patients treated with RFA had more liver lesions and a higher CTP classification, both of which may have influenced outcome.

Guglielmi and colleagues (2008) also demonstrated that in HCC larger than 3 cm, significant improvement in survival was seen in patients undergoing surgical resection, but this did not translate to tumors smaller than 3 cm, nor did it apply to patients with multiple tumors.

Radiofrequency Ablation for Recurrent Hepatocellular Carcinoma

After resection or ablative therapies, most patients with HCC will succumb to progressive or recurrent liver disease. Hepatic resection is rarely feasible because of inadequate hepatic reserve, making RFA an effective therapeutic alternative. Taura and colleagues (2006) compared 610 patients who underwent a liver resection before and after 1990. The improved 5-year survival in the latter group (22% vs. 12%) was attributed to percutaneous RFA for intrahepatic recurrence. Similarly, Yang and colleagues (2006) demonstrated a survival benefit in 41 patients with recurrent HCC treated with percutaneous RFA. These studies suggest that RFA is effective in the management of recurrent HCC after resection, and RFA may be the treatment of choice for carefully selected patients with recurrent hepatic disease (Fig. 85C.8).

Radiofrequency Ablation as a Bridge to Transplantation (See Chapter 97D)

Many patients with HCC will succumb to liver failure because of a shortage of donors or will be removed from the transplant waiting list because of tumor progression; indeed, the dropout rate within a year has been reported as high as 38% (Yao et al, 2004). RFA has effectively been used as a bridge to transplantation. At a mean follow-up of 12.7 months, Lu and colleagues (2005) reported a dropout rate of only 5.8 months and 14% at a follow-up of 11.9 months (Brillet et al, 2006).

These encouraging data suggest that RFA is one modality that may be considered for prolonged waiting times. The impact on overall survival is less clear; however, one prospective study of patients with HCC awaiting transplantation undergoing RFA showed no survival benefit compared with the observation group (Porrett et al, 2006).

Tumor Response and Recurrence

CT or MRI is typically used to evaluate response rates (see Chapters 16 and 17); US does not accurately predict the extent of necrosis following RFA and should not be used to determine response. CT with contrast enhancement reveals a hypovascular ablated field with a rim of hypervascular inflammatory tissue; the rim enhancement area should disappear over several months time as inflammation resolves, and the treatment area should encompass the tumor and at least a 1-cm rim of normal tissue. Comparing preoperative imaging to postoperative imaging is important to determine that the tumor was adequately treated. Patients should receive serial CT scans after RFA to identify recurrences, which appear as irregular, nonenhancing areas on contrast CT.

Complete and Incomplete Response to Radiofrequency Ablation

Response rates vary from 48% to 98% across studies, in part because of differences in the size of treated lesions. Livraghi and colleagues (1999, 2000) evaluated percutaneous RFA in patients with HCC. The rate of complete response was 48% for tumors larger than 3 cm (2000), but it jumped to 90% for smaller tumors (1999), and the success rate was lower for infiltrating versus noninfiltrating HCCs. Similarly, Lencioni and colleagues (1998) found a statistically significant difference in response rates to percutaneous RFA for metastatic liver lesions larger than 3 cm (53%) versus those smaller than 3 cm (87%). Larger lesions typically require overlapping ablations, and areas of treated tumor may obscure US imaging of untreated tumor and result in higher treatment failures and recurrences.

The approach to RFA will also influence response rates (see Table 85C.1). Curley and colleagues (2000) reported that 6 of 76 patients who underwent percutaneous RFA had an incomplete response, whereas all 34 patients who underwent laparoscopic or open RFA had a complete response. This difference might be explained by better hepatic imaging with intraoperative US during laparoscopy or celiotomy than with transabdominal US during percutaneous RFA. Another possibility is that intraoperative probe positioning may be more accurate than percutaneous placement of the probe.

Tumor location adjacent to large vessels also influences response rates. Blood flow from large vessels will create a heat-sink effect that cools surrounding tissue and increases the temperature necessary for complete ablation. Large vessels are resistant to high temperatures that can damage surrounding tissue. Lu and colleagues (2002) found that porcine vessels smaller than 3 mm thrombosed or necrosed during RFA, but those larger than 5 mm were not affected. In another porcine model, vascular occlusion during RFA increased the volume of necrosis and prolonged the exposure of tissue to high temperatures (Chinn et al, 2001). De Baere and colleagues (2002) evaluated vascular inflow occlusion in patients undergoing RFA of tumors that were large (>35 mm) or near large blood vessels and found that balloon inflow occlusion significantly increased the area of ablation. These studies support the use of a Pringle maneuver to more effectively ablate tumors near major blood vessels and improve response rates. The use of RFA combined with hepatic artery embolization or chemoembolization is discussed in Chapter 83.

Rates of Recurrence at the Ablation Site

Recurrence rates are difficult to interpret across studies (Table 85C.4). Some authors report recurrences after complete ablation as determined by early postoperative CT or MRI, whereas others do not confirm complete response by postoperative imaging and report recurrences based on follow-up imaging. Investigators may report recurrence rates within the whole liver, rather than recurrence rates at the site of ablation, and the length of follow-up also impacts the recurrence rate. Bowles and colleagues (2001) evaluated 76 patients undergoing RFA of 328 tumors. Sixteen patients underwent repeated ablation for

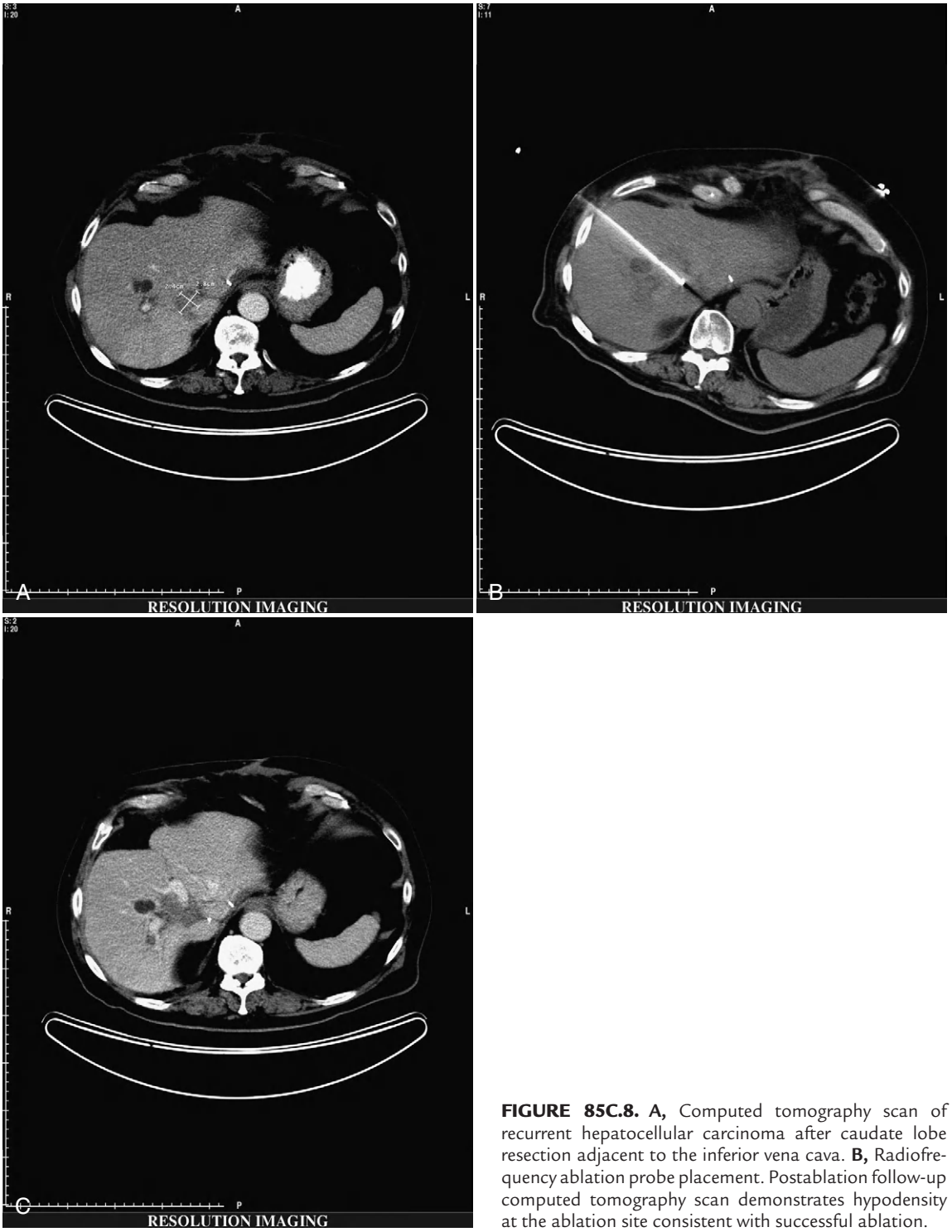


FIGURE 85C.8. A, Computed tomography scan of recurrent hepatocellular carcinoma after caudate lobe resection adjacent to the inferior vena cava. **B,** Radiofrequency ablation probe placement. Postablation follow-up computed tomography scan demonstrates hypodensity at the ablation site consistent with successful ablation.

recurrences or new lesions, and 30 recurrences were reported at the site of a prior ablation. Patients with large tumors, tumor vascular invasion, and hepatic dysfunction had a statistically higher recurrence rate. Solbiati et al (2001) evaluated 117 patients undergoing percutaneous RFA of colorectal metastases; time to local recurrence and frequency of recurrences were influenced by lesion size. Similarly, we found that tumor size significantly influenced local recurrence of metastatic disease, independent of RFA technique (Wood et al, 2000; Bleicher et al, 2003). No study has shown that differences in technique influence the rate of recurrence after a complete response.

Complications of Radiofrequency Ablation

Reported morbidity and mortality rates associated with RFA (Table 85C.5) can be difficult to interpret, in part because

Table 85C.4

Local Recurrence After Radiofrequency Ablation of Hepatic Tumors

First Author, Year	Mean Follow-up (mo)	Tumor Type (No. Patients)	RFA Approach	Tumors, n (%)
Rossi, 1996	22.6	Hepatocellular carcinoma	Percutaneous	54 (4)
Solbiati, 1997	18.1	Metastases	Percutaneous	27 (33)
Rossi, 1998	10	Hepatocellular carcinoma	Percutaneous	24 (4)
	12	Metastases	Percutaneous	16 (6)
Lencioni, 1998	6.5	Metastases	Percutaneous	41 (12)
Bilchik, 1999	6	Hepatocellular carcinoma (7) metastases (43)	Percutaneous, laparoscopic, open	132 (2)
Curley, 1999	15	Hepatocellular carcinoma (11) metastases (75)	Percutaneous, open	169 (1.8)
Siperstein, 2000	13.9	Hepatocellular carcinoma (11) metastases (170)	Laparoscopic	181 (12)
Curley, 2000	19	Hepatocellular carcinoma	Percutaneous, laparoscopic, open	149 (2.7)
De Baere, 2000	13.7	Metastases	Percutaneous, open	100 (9)
Llovet, 2001	10	Hepatocellular carcinoma ≤5 cm	Percutaneous	32 (6)
Livraghi, 2001	19	Metastases from breast cancer	Percutaneous	64 (8)
Bowles, 2001	15	Hepatocellular carcinoma metastases	Percutaneous, laparoscopic, open	328 (9)
Solbiati, 2001	6 to 52	Metastases from colorectal cancer	Percutaneous	179 (39)
Berber, 2002	1.6	Metastases from neuroendocrine tumors	Laparoscopic	227 (3)
Bleicher, 2003	11	Metastases	Percutaneous, laparoscopic, open	447 (12)
Jakobs, 2006	21	Colorectal	Percutaneous	183 (18)
Abitabile, 2007	21	Colorectal	Percutaneous	174 (9)
Siperstein, 2007	24	Colorectal	Laparascopic	665 (NR)
Sorensen, 2007	23	Colorectal	Percutaneous, open	332 (11)
Veltri, 2008	19	Colorectal	Percutaneous, open	199 (26)
Gillams, 2008	38	Colorectal	Percutaneous	40 (42)

technical approaches vary. Some investigators combine RFA with other treatments, such as liver resection, but addition of a second procedure may inflate the complication rate. Ablation of multiple tumors also increases the risk of complications such as bleeding or bile leak. Early studies often used multiple sequential RFAs for treatment of a single hepatic tumor, because the monopolar electrode gave a smaller thermal ablation field than the current cluster electrodes. The multiple ablations required to destroy larger tumors increased the potential for complications.

Unfortunately, the reporting of morbidities is not standardized. Some authors regard low-grade fevers, transient liver function test elevations, small pleural effusions, and right upper quadrant pain as minor complications, whereas others believe these are expected events that should not be reported. As expected, studies undertaken at institutions with skilled interventionalists or surgeons report fewer complications. Variations in patient selection and disease type also confound interpretation of results: for example, patients with HCC have different comorbid factors than those with colorectal metastases, and a patient's preprocedural state may influence the outcome of RFA.

Direct complications of RFA include biloma, biliary fistula, ascites, hepatic insufficiency, arteriovenous fistula, symptomatic pleural effusion, abscess, pain, hemorrhage, hydropneumothorax, pneumothorax, and thermal injury to surrounding structures. Burns related to grounding pads have also been reported, but these can be avoided by proper positioning of the pads, by using more pads for longer ablations, and by carefully following the manufacturer's directions. Other potential complications are those related to an operative procedure, such as myocardial infarction, cardiac arrhythmias, and pneumonia.

As illustrated by the following two cases, RFA should be undertaken only by skilled physicians able to identify and manage its complications and only at centers equipped with appropriate staff and equipment for acute care. Figure 85C.9 shows a bile duct injury caused by RFA of a colorectal cancer metastasis near the porta hepatis. The injury was treated with endoscopic retrograde cholangiopancreatography (ERCP) and biliary stenting. Figure 85C.10 shows a hepatic artery pseudoaneurysm attributed to RFA of liver metastases. This was successfully treated with embolization by a skilled interventionalist.

The best way to avoid potential complications of percutaneous RFA is to understand its technical limitations. A large multicenter study reported morbidity and mortality rates of 0.3% and 2.2%, respectively (Livraghi, 2003b). In this study, about 33% of all deaths and 10% of morbidities were associated with gastrointestinal thermal injury and perforation. Patients with prior abdominal surgeries resulting in adhesions and those with peripheral liver tumors had an increased risk for gastrointestinal injury during percutaneous ablation. The authors recommended consideration of open or laparoscopic RFA, instead of percutaneous RFA, for tumors within 1 cm of the liver edge adjacent to bowel.

Table 85C.5

Morbidity and Mortality Rates of Radiofrequency Ablation

Study	Tumor Type (No. Patients)	Approach (No. Patients)	Morbidity, n (%)	Mortality, n (%)
Rossi et al, 1996	HCC (39) metastases (11)	Percutaneous	0/48 (0)	0/48 (0)
Solbiati et al, 1997	Metastases	Percutaneous	1/16 (6)	0/16 (0)
Rossi et al, 1998	HCC (23) metastases (14)	Percutaneous	0/37 (0)	0/37 (0)
Lencioni et al, 1998	Metastases	Percutaneous	0/29 (0)	0/29 (0)
Curley et al, 1999	HCC (11) metastases (75)	Percutaneous, open	3/123 (2)	0/123 (0)
Livraghi et al, 1999	HCC ≤3 cm	Percutaneous	5/42 (12)	0/42 (0)
Bilchik et al, 1999	HCC (7) metastases (43)	Percutaneous Laparoscopic, open	0/50 (0)	2/50 (4)
Curley et al, 2000	HCC	Percutaneous laparoscopic, open	14/110 (13)	0/110 (0)
De Baere et al, 2000	Metastases	Percutaneous, open	5/54 (9)	0/54 (0)
Livraghi et al, 2000	HCC > 3 cm	Percutaneous	7/114 (6)	1/114 (0.9)
Wood et al, 2000	Metastases	Percutaneous Laparoscopic, open	7/84 (8)	3/84 (4)
Livraghi et al, 2001	Metastases from breast cancer	Percutaneous	2/24 (8)	0/24 (0)
Llovet et al, 2001	HCC ≤5 cm	Percutaneous	8/32 (25)	0/32 (0)
Wong et al, 2001	HCC metastases	Open Percutaneous (1)	8/40 (20)	0/40 (0)
Bowles et al, 2001	HCC metastases	Percutaneous Laparoscopic, open	7/76 (9) major 17/76 (22) minor	1/76 (1)
Solbiati et al, 2001	Metastases from CRC	Percutaneous	2/117 (2)	0/117 (0)
Zagoria et al, 2002	Metastases	Percutaneous, open	5/38 (13)	1/38 (3)
Berber et al, 2002	Metastases from neuroendocrine cancer	Laparoscopic	2/34 (6)	0/34 (0)
De Baere et al, 2003	HCC metastases	Percutaneous, open	NR per patient	5/312 (2)
Livraghi et al, 2003a	Metastases from CRC	Percutaneous	3/88 (3)	0/88 (0)
Bleicher et al, 2003	Metastases	Percutaneous Laparoscopic, open	3/153 (2)	18/153 (12)
Livraghi et al, 2003b	HCC metastases	Percutaneous	50/2320 (2)	6/2320 (0.3)
Curley et al, 2004	HCC metastases	Percutaneous laparoscopic	58/608 (11)	3/608 (0.5)
TOTAL			183/4161 (4)	28/4549 (0.6)

HCC, hepatocellular carcinoma; CRC, colorectal carcinoma; NR, not reported

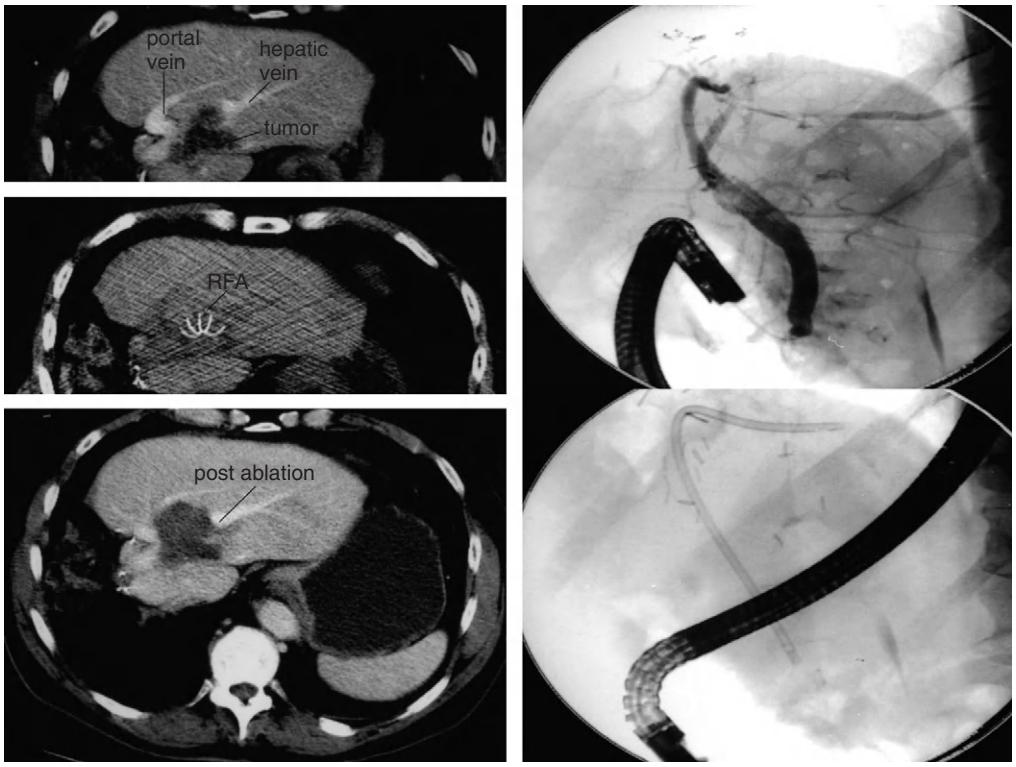


FIGURE 85C.9. Biliary injury following radiofrequency ablation treated with stent placement. RFA, radiofrequency ablation.

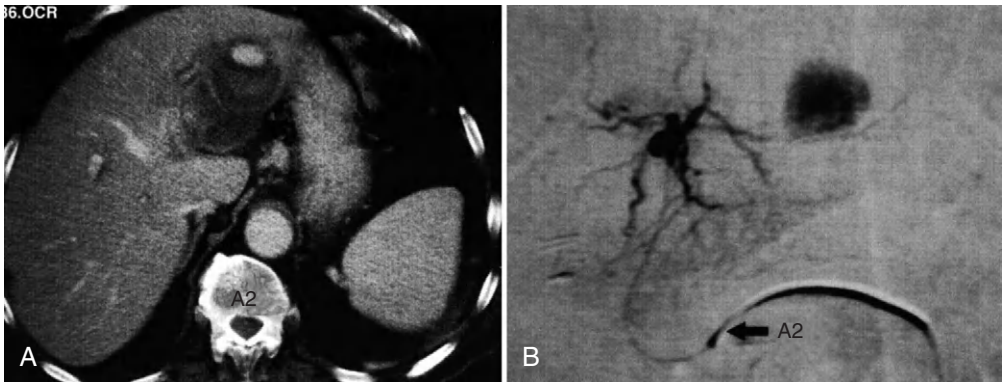


FIGURE 85C.10. Hepatic artery pseudoaneurysm following radiofrequency ablation.

Injury to the diaphragm is also a potential complication during percutaneous RFA, especially when tumors at the dome of the liver are treated. In an animal model, carbon monoxide was introduced into the peritoneal cavity to separate the diaphragm and the liver; although this reduced severe diaphragmatic injury during superficial hepatic RFA (Raman et al, 2004), the technique needs further clinical testing.

Abscess, one of the most frequent complications of RFA, typically occurs 1 week after ablation and requires percutaneous or surgical drainage (de Baere et al, 2003; Wood et al, 2000). Patients with bilioenteric anastomosis or biliary stenting appear to have a higher rate of abscess formation. All patients undergoing RFA should receive periprocedural antibiotics that cover coliforms as well as skin flora, and temperature and leukocyte counts should be followed after the procedure. Normally, low-grade fever and fatigue may occur immediately after RFA for up to 7 to 10 days, a so-called *postablation syndrome*; however, any persistent significant fever or elevation of white blood cell count should prompt CT imaging for possible hepatic abscess.

Reports of tumor seeding vary from 0.5% to 12% (de Baere et al, 2003; de Sio et al, 2001; Llovet et al, 2001), possibly reflecting differences in follow-up. Llovet and colleagues (2001) found that tumor seeding during RFA was related to subcapsular tumor location and poor tumor differentiation. Recent tumor biopsy, multiple needle insertions, and tumor hemorrhage during treatment may also increase the risk of needle-tract seeding. This complication can be avoided by limiting the number of needle insertions, angling the needle to traverse normal hepatic parenchyma prior to entering the tumor, and cauterizing the tract upon withdrawal of the needle. Nicoli and colleagues (2004) reported rapid diffusion of neoplastic cells after the creation of an arteriovenous fistula following RFA. The authors attributed seeding of tumor cells to the pressure gradient between the high-pressure tumor arteries and the low-pressure portal system; however, this is the only report of this complication in several thousand RFAs to date.

Injury to bile ducts during RFA can result in stenosis and proximal biliary dilation (see Chapter 42). Most physicians agree that tumors within 15 to 20 mm of a major bile duct should not be treated by RFA (Mulier et al, 2002); however, Elias and colleagues (2001) introduced intraductal cooling to prevent RFA-associated biliary stenosis. They infused cooled (4° C) Ringer's lactate through a catheter after choledochotomy. Intraductal cooling was undertaken in 13 patients undergoing RFA of tumors within 6 mm of a central bile duct; one patient had a local recurrence, and one developed biliary stenosis (Elias et al, 2004). Biliary stenting also can prevent biliary injury during ablation of tumors near the bile ducts (Wood et al, 2000).

SUMMARY

RFA can treat primary or metastatic liver tumors with success rates of 90% and little morbidity or mortality. It can be applied via an operative or percutaneous approach. An operative approach allows accurate assessment for the presence of extrahepatic disease and a better evaluation of intrahepatic disease. An operative approach also can isolate the liver from adjacent organs that could be injured during ablation, and it allows placement of the RFA probe in lesions that could not be reached by a percutaneous approach. A percutaneous approach allows the use of CT guidance, contrast-enhanced CT assessment of the ablation, shorter hospital stay, and it can also be performed as an outpatient procedure. Although the proximity of a tumor to certain structures may limit feasibility of percutaneous ablation, several techniques are available to separate adjacent structures from the ablation site. Percutaneous ablation may also be preferred in high-risk patients, those with limited hepatic reserve, or those with recurrent disease.

Two recent randomized trials demonstrate therapeutic equivalence compared with resection in small HCC tumors, but until more prospective studies have been performed, resection remains the initial choice for patients whose disease is confined to the liver. RFA may be an alternative for those unable to undergo resection because of limited hepatic reserve, bilobar disease, or poor medical status; in these cases, RFA can be very successful, and its results may be durable. Although RFA provides local control of metastatic colorectal liver metastases, its impact on survival is unclear. Systemic therapy should be used to treat or prevent other sites of metastatic disease.

As the field of RFA continues to evolve, further improvements in probe technology will allow larger zones of ablation and higher rates of complete response. Newer probes are now able to treat larger lesions with a single ablation, and this new technology will reduce limitations of tumor size on adequate response and recurrence rates. A multidisciplinary team is essential in the selection of appropriate patients for treatment.

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CHAPTER 85D

Microwave ablation and emerging technologies for liver tumors

Kwan N. Lau and David A. Iannitti

OVERVIEW

Hepatic malignancies are common, with more than 1 million diagnosed each year worldwide. Tumors can be primary, as with hepatocellular carcinoma (HCC) or intrahepatic cholangiocarcinoma (IHC), or they can be secondary, as with colorectal liver metastases (CLM), neuroendocrine malignancy, or metastases from other primary cancers, such as those of the breast or lung. Many patients come to medical attention with advanced disease that is not amenable to surgical therapy. Unresectable disease carries a poor prognosis, because systemic chemotherapeutic agents and radiation therapy have limited efficacy in treating many of these diseases. As a result of the limited treatment options in this particular patient population, liver-directed regional therapies have evolved that include selective internal radiation therapy (Cianni et al, 2009), transarterial chemoembolization (TACE) (Rathore et al, 2010), portal vein embolization (PVE) (Manizate et al, 2010), and ablative technologies.

Ablation is not a new concept; it has been used in medicine for more than 100 years, initially as a therapy designed for patients with unresectable lesions (Halsted, 1894); however, advancements in medicine have transformed ablation into an effective locoregional therapy with an improved perioperative profile for morbidity and mortality and options of performing the procedure using an open, laparoscopic, or percutaneous approach. It has evolved from injecting ethanol (Uflacker et al, 1986) to employing different energy sources, such as cryoablation (Iannitti et al, 1998), radiofrequency ablation (RFA) (Iannitti et al, 2002), and microwave ablation (MWA) (Simon et al, 2006) to achieve tumor destruction (see Chapters 85A through 85C). Current ablation therapies also provide the flexibility to perform procedures in an ambulatory setting to allow treatment of patients whose disease is not amenable to resection. The application of ablative technology does not necessarily preclude patients from future operations, nor does it compromise their chance for transplantation (Casaccia et al, 2009); however, complications resulting from ill-advised ablative procedures may complicate subsequent attempts at resection.

The most common thermoablative technologies used clinically are RFA and MWA. Both modalities produce tissue destruction, but the physical properties of the energy sources are different. MWA is a relatively new modality compared with RFA, and it provides important physical advantages over RFA.

Thermoablation is an effective modality, because irreversible thermal destruction of tissue occurs when temperatures above 50° C are maintained for an interval of 4 to 6 minutes (Larson et al, 1996). Vaporization and carbonization occur when tissue temperature is raised rapidly to over 100° C. Effective ablation relies on an adequate margin around the lesion, ideally 1 cm, to ensure complete eradication of microscopic foci. Large ablation volume may require multiple applications of thermal energy.

PHYSICS OF MICROWAVE ENERGY

MWA that achieves heat destruction of tissue involves both active and passive heating. The active heating process of microwave energy requires the presence of dielectric molecules, such as water, to function. MWA is an excellent option for thermal ablation of solid organs, such as the liver (Brace, 2009a, 2009b). Clinical microwave energy operates at a frequency of 900 MHz to 10 GHz (Fig. 85D.1), which is much higher than radiofrequency (460 to 480 kHz). As a dipole molecule, water is affected by the applied electromagnetic field broadcasted by the microwave antenna. This property is called *dielectric permittivity* (ε). Water molecules orient themselves to the rapidly changing polarity of the electromagnetic field, and vibratory energy generates heat production. This process is called *dielectric hysteresis*. Microwaves emit nonionizing radiation for heating, and this produces homogeneous heating within the field regardless of the tissue types; this distinguishes MWA from monopolar RFA in terms of mechanism of heating and makes it a clinically superior method for ablation. The passive phase of microwave heating is by conduction of heat beyond the active heating zone and is susceptible to local tissue factors, such as heat and current sinking, which will be discussed later in this chapter.

The MWA systems used in the United States today are 915 MHz, 2.45 GHz, and 9.2 GHz; however, only the 915-MHz and 2.45-GHz systems are commercially available for tumor ablation. The 915-MHz and 2.45-GHz systems are more effective for large tissue destruction than monopolar RFA, and the 915-GHz system is currently under investigation for ablating lesions in the breast. Microwave energy can be generated through a magnetron or solid-state amplifier (Brace, 2009a, 2009b), and the antenna broadcasts the electromagnetic energy to the target tissue. The coaxial cable consists of an inner and outer conductor, and dielectric material is placed between the two layers. At its tip, the outer conductor is stopped to expose the inner conductor for broadcasting the microwave energy (Fig. 85D.2). This inner conductor is covered in a ceramic pointed tip for insertion into the tissue, and microwave energy can pass freely through the ceramic. The power loss is influenced by power output, cable diameter, and antenna design. Given its broadcasting characteristic, the microwave system does not require a grounding pad.

Large ablative volume can be created by increasing the power and duration of the application. Several factors influence the final ablative size, including water content of the tissue, power output at the generator, power loss at the cable, antenna

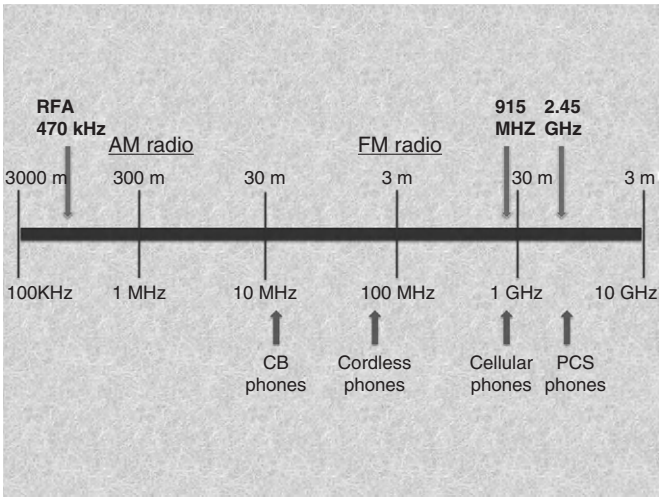


FIGURE 85D.1. Electromagnetic spectrum.

design, formation of clustered antennae, and the number of applications. Various tissue types exhibit different responses to microwave energy, and liver tissue usually exhibits a noticeable response to MWA (Hines-Peralta et al, 2006). Surgeons must understand the relationship between the different properties of tissue and the energy modality used to achieve successful ablation.

LOCAL TISSUE FACTORS THAT AFFECT THERMOABLATION

Local tissue factors play an important role in the final ablation volume and shape. The tissue's electric conductivity (σ) and dielectric permittivity (ε) influence the deposition of energy for radiofrequency and microwave, respectively, which explains why MWA is more effective than RFA in depositing energy across vessels and liver parenchyma.

Modalities using radiofrequency rely heavily on the tissue's electric conductivity, and heat is generated from ionic agitation of the molecules in the tissue. The tip of the monopolar RFA probe and the grounding pad forms a closed circuit, and alternate current passes between them. The current density is higher in the tip, compared with that of the grounding pad, because of the difference in surface area. The transfer of heat to the surrounding tissue is through conduction and is proportional to the amount of current deposited; however, the rate of perfusion to the target tissue could significantly affect the final heat transfer.

Coagulation necrosis of tissue is proportional to energy deposition minus heat loss (Goldberg et al, 2000). Hence, local tissue factors such as blood flow and tissue temperature affect energy deposition. Close proximity to blood vessels causes diversion of the current and decreases the amount of energy generated from the current; this is termed *current sinking*. The final ablative size is affected, because radiofrequency relies on heat transfer from the tip of the applicator, and the cooling from the vessel shunts the heat energy away; this phenomenon is termed *heat sinking*. Microwave technology also encounters such limitations but to a much lesser extent (Stauffer et al, 2003), because the propagation of microwave energy relies on the dielectric permittivity of the tissue, and it stays fairly constant along the broadcasted electromagnetic field (Table 85D.1). It can overcome the effect of current and heat sinking within its field and result in deeper heat penetration and more uniform ablative size. Outside the active heating zone, heat is propagated by conduction and is therefore susceptible to local factors such as heat sinking.

Another consideration is tissue desiccation and charring by the applicator during the heating process. Both conditions can significantly decrease the final ablative volume for RFA, because it requires a complete electric circuit to function. Acting as electric insulators, the resultant increase of impedance decreases the amount of current deposition and thereby decreases heat

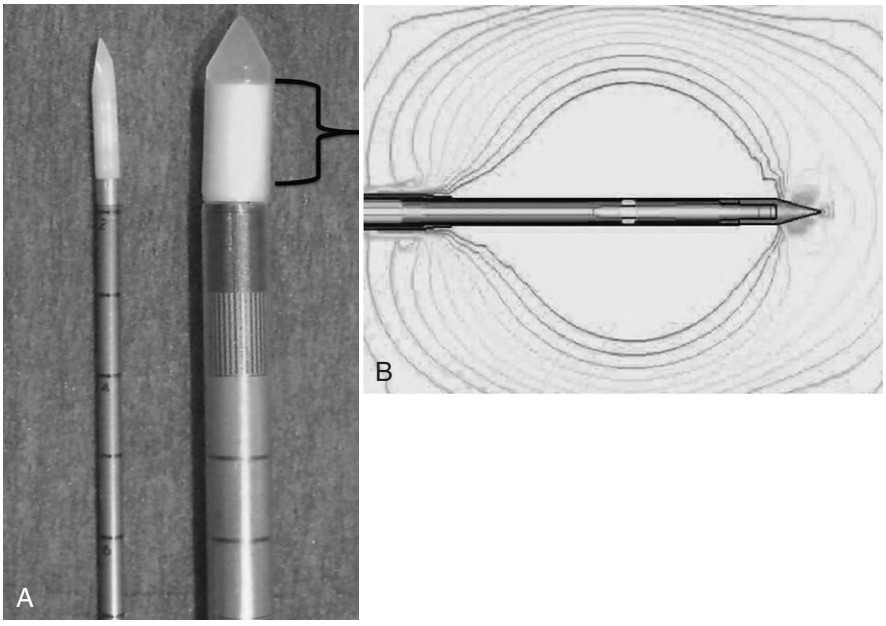


FIGURE 85D.2. A, *Left*, Microwave antenna as shown; *the bracket* points to the area from which microwave energy is broadcasted at the ceramic shield just beyond the termination of the outer conductor. **B,** Computer illustration of the projected microwave field from the microwave antenna.

Table 85D.1

Conductivity and Permittivity Among Various Tissues Compared with Liver Tissue

	Conductivity 470 KHz	Permittivity at 915 MHz	Permittivity at 2.45 GHz
Air	NA	0.02	0.02
Blood	5.14	1.79	1.51
Gallbladder	6.22	1.46	1.22
Bile	9.67	2.14	1.66
Liver	1	1	1

NA, not applicable

production. Moreover, if the target temperature is reached rapidly, above 100° C, the intracellular content vaporizes and carbonizes. The gas formation acts as an electric insulator that increases the impedance and hinders the heat diffusion (Dadd et al, 1996); both decrease the amount of current deposition and result in a less uniform ablative zone. Unlike radiofrequency, microwaves broadcast energy throughout the electromagnetic field and can achieve high power density uniformly, which results in deeper heat penetration and a more consistent ablative size.

915 MHz Versus 2.45 GHz

MWA, like RFA, can be carried out via three approaches: 1) open, 2) laparoscopic, and 3) percutaneous. The first clinical microwave system, Microtaze (Heiwa Electronics Industry, Tokyo), was developed in the 1990s. Clinical use was limited because of its 1.5-cm ablation zone (Saitsu et al, 1991, 1993), but 915-MHz and 2.45-GHz systems are currently available (Fig. 85D.3). Both systems were introduced to the United States market in 2008: the Viva Wave system (Valleylab, Boulder, CO) and the MTA microwave system (Microsulis Medical, Denmead, UK). Advancements in microwave technology and better antenna design have significantly improved ablative capabilities, and large-volume ablation can be reliably achieved.

The Viva Wave system uses a 915-MHz generator, and its power output can reach up to 45 W. It carries two different sized antennae for open and laparoscopic/percutaneous use and usually employs a three-antennae cluster design for achieving a 5-cm zone of ablation; it requires three generators firing in a nonsynchronized fashion. A saline-infused cool-shaft antenna is also available to reduce the incidence of skin burn during transcutaneous antenna placement. Another system was approved by the Food and Drug Administration (FDA) in 2008, the Micro-Therm X-100 (BSD Medical, Salt Lake City, UT). This is the only system with synchronized power output that uses multiple antennae.

The Acculis MTA (Microsulis Medical) is a 2.45-GHz system that uses a 5-mm antenna for its open application. It produces a 5-cm ablation zone reliably in 4 minutes and up to 8 cm in 8 minutes, with one application by a single antenna at 100 W. Currently under consideration by the FDA for approval is a 1.8-mm cool-shaft antenna for the laparoscopic/percutaneous approach.

The 2.45-GHz system is used more often in Europe and Asia, whereas the 915-mHz system is used in the United States; both are capable of producing an adequate ablation volume. The 2.45-GHz system uses a single antenna, and the 915-mHz employs a multiantenna array powered by separate generators. An advantage of using multiple antennae in different formations is to achieve various shapes and sizes of ablations (Simon et al, 2006). The microwave antenna is not composed of alloy but is coated with polytetrafluoroethylene (PTFE). It is not as rigid as the RFA metal applicator, and care should be taken during manipulation of the microwave antenna to prevent breakage at the tip of the antenna.



FIGURE 85D.3. Commercially available ablation systems. **A,** Viva Wave system (Valleylab, Boulder, CO). **B,** Acculis MTA microwave system. *(**B** Courtesy Microsulis Medical Ltd, Denmead, UK.)*

TECHNICAL CONSIDERATION FOR PERFORMING MICROWAVE ABLATION

Three approaches can be used for MWA: 1) open, 2) laparoscopic, and 3) percutaneous. The underlying principles to achieve successful ablation are the same. Each patient represents a unique circumstance, and the chosen approach should be tailored to the patient's need and the skill level of the practitioner. Lesions that are located anteriorly and not adjacent to a major pedicle can be ablated percutaneously using ultrasound (US), magnetic resonance imaging (MRI), or computed tomographic (CT) guidance. If the lesion is located deep in the liver, at the dome, next to a major pedicle, or adjacent to other structures such as the diaphragm and colon, ablation of these lesions should be performed surgically. The choice of an open or laparoscopic MWA is determined by the patient's history of celiotomy and the surgeon's level of advanced laparoscopic skill. If an open approach is used, it is best done through a subcostal or midline laparotomy.

Regardless of the approach, the patient is usually positioned supine on the table. The key of a successful ablative session is adequate exposure of the liver by taking down the suspensory attachments and performing a methodic evaluation of the liver by intraoperative US. All eight segments of the liver must be evaluated to ensure no lesions are missed, and it is helpful to review the preoperative imaging and formulate a table with information regarding the location and size of each lesion.

Once all lesions are identified, the plane of the needle tract should be evaluated to ensure that it does not cross a portal or major hepatic vein pedicle. The antenna is then deployed to treat the lesion. Close attention is paid to ensure no other structure is in the vicinity of the microwave field. Usually, the power and duration of each application is based on the size of the lesion and its proximity to major vessels, and 915 MHz can reliably reproduce a 5-cm ablative zone at 45 W for 10 minutes, and 2.45 GHz can achieve the same result with one antenna at 100 W for 5 minutes. The deepest lesion is usually treated first; in a staged procedure, the most difficult lesion is treated first.

Another consideration for ablating large lesions is how to overlap the zone of ablation. This is clinically challenging, given that the final ablative area is three-dimensional (3D), and the intraoperative US provides two-dimensional (2D) information in real time. Hence, a disciplined approach is needed to achieve adequate overlapping. Usually, the ablation is started at the most central medial portion of the lesion and progresses with the repeat ablations in an upward and outward fashion.

CLINICAL RESULTS OF MICROWAVE ABLATION FOR HEPATOCELLULAR CARCINOMA (SEE CHAPTER 80)

The first open microwave application for tumor destruction was reported in the early 1990s in Japan, when Seki and colleagues (1994) reported a series of 24 patients with HCC with a 92% survival at 3 years. The application of microwave technology has since expanded to treat colorectal liver metastases and metastases from other primary tumors; this will be discussed later in this chapter.

Clinical trials have evaluated the efficacy of MWA for treating HCC. In a Phase I trial that evaluated the safety of MWA, 11 patients underwent hepatoma ablation followed by resection (Simon et al, 2006). The complete destruction of viable tumor cells was confirmed by immunohistochemistry in the ablation zone. The average volume of ablation was 5.5 cm in diameter using three clustered antennae at 45 W for 10 minutes. The Phase II trial enrolled 87 patients for whom MWA was the primary treatment (Iannitti et al, 2007). In 94 ablation sessions, 224 lesions with a mean diameter of 3.6 cm were treated (Fig. 85D.4). The local recurrence rate was 2.7%, and regional recurrence was 43% during 19 months of follow-up; overall mortality rate was 2.3% with no procedure-related deaths. Major complications included two patients with postoperative fluid collections that required a drainage procedure and five patients with minor skin burn at the needle tract. This clinical trial proved that using MWA for hepatic tumors is a safe, effective treatment option with a low complication rate. Multiple series were subsequently published reaffirming the role of MWA in treating liver lesions (Table 85D.2; Kawamoto et al, 2005; Martin et al, 2009).

Clinical Results of Colorectal Liver Metastases (See Chapter 81A)

The most common hepatic lesions result from metastatic colorectal cancer (CRC). More than 50,000 patients die from diseases related to CRC yearly, and up to 60% of patients with CRC have metastasis to other organs. Despite advances in neoadjuvant therapy, roughly 60% of the patients are not candidates for hepatic resection, which remains the single most effective therapy. The 3-year survival rate is 30% for patients undergoing open resection, and the recurrence rate at 3 years is 54% (Wagner et al, 1984; Scheele et al, 1990). The low survival rate and high recurrence rate are due to the multicentricity of the disease and the presence of systemic microscopic foci.

The clinical results of MWA for colorectal liver metastasis are encouraging. The 3-year survival and local recurrence rate from multiple clinical series are comparable with published data from open resection (Liang et al, 2006; Shibata et al, 2000; Simon et al, 2006). In a small randomized controlled trial (RCT) with 30 patients, the overall survival was similar between the hepatectomy and MWA arms (Shibata et al, 2000). The lack of a large RCT makes a direct comparison of open resection with MWA difficult, and it may be difficult to obtain institutional review board approval for such a study in the United States on ethnical grounds.

The availability of MWA for patients with metastatic CRC and improvements in chemotherapy may improve overall survival. Patient management should involve a multidisciplinary team to determine the best treatment plan.

Clinical Results for Neuroendocrine Tumors and Metastasis from Other Primary Tumors (See Chapter 81B)

Lesions arising from neuroendocrine or other primary tumors should be evaluated for resection when clinically appropriate; however, curative resection is not possible in about 90% of the cases (Knigge et al, 2008). The focus of treatment should be palliative, and symptom relief can usually be achieved. Cytoreduction of the tumor can improve survival, with 5-year survival ranging from 40% to 60%. Most patients can be symptom free for 2 years (Weitz et al, 2005). Careful selection of therapeutic options combining different liver-directed modalities such as

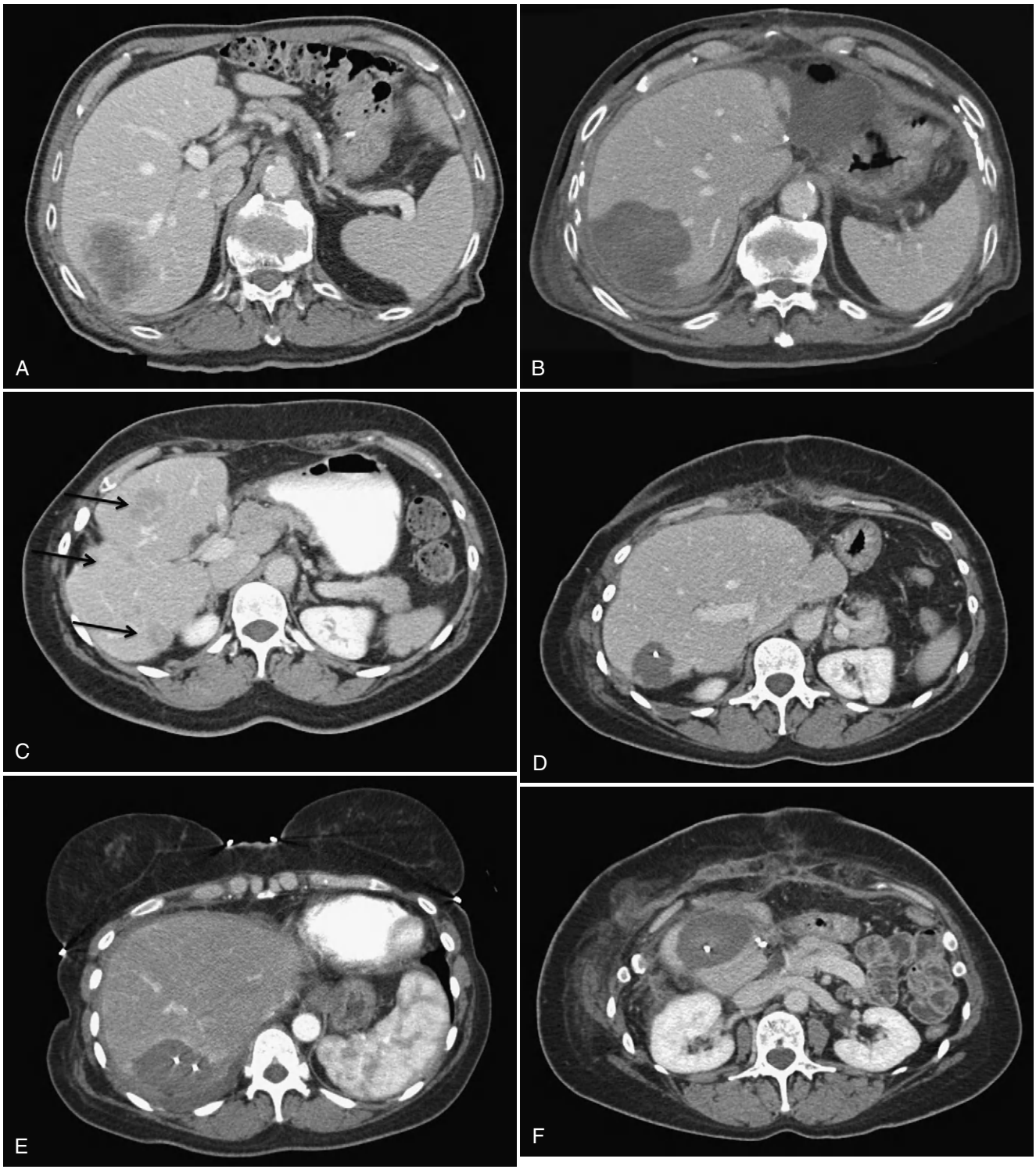


FIGURE 85D.4. Computer tomography (CT) images of for a large segment VII liver lesion. **A,** Preablation. **B,** Postablation. CT images of multiple neuroendocrine lesions in the liver. **C,** Preablation. *Arrows* indicate liver lesions. Postablation scans show successful ablation at segment VI (**D**), segment VII (**E**), and segment VIII (**F**).

Table 85D.2

Published Series Reporting Microwave Ablation Outcomes

First Author	Year	No. Patients	Frequency	Type of Study	Morbidity (%)	Mortality (%)	Local Recurrence (%)	Follow-up (mo)
Martin	2010	n = 100 HCC = 17 CLM = 50 Other = 33	915 MHz	Nonrandomized control trial	29	0	2	36
Liang	2009	n = 1136 HCC = 854 CLM = 86 Other = 196	2.45 GHz	Clinical case series	2.6	0.2	NA	NA
Iannitti	2007	n = 87 HCC = 23 CLM = 33 Other = 31	915 MHz	Nonrandomized control trial	16	2.3	2.7	19
Kawamoto	2005	n = 69 HCC = 69	2.45 GHz	Nonrandomized control trial	2.8	0	17.4	54

HCC, hepatocellular carcinoma; CLM, colorectal liver metastases; NA, not applicable

ablation, chemoembolization, selective internal radiation therapy (SIRT), and embolization may reduce the tumor burden and improve overall survival.

MICROWAVE ABLATION: SPECIFIC COMPLICATIONS AND FUTURE APPLICATIONS

MWA heats the entire electromagnetic field, and several potential complications may arise from this modality. Technical advances have made ablation near large vessels possible, which increases the potential for thrombus in the hepatic vein. The true incidence of hepatic vein thrombus (HVT) related to MWA is unknown. We identified three such cases in 122 MWA applications, all without symptoms, and the thrombus resolved after anticoagulation. We have used a porcine model to reproduce HVT, and it appears that puncturing the hepatic vein during MWA is a risk factor (Sindram, 2011). Surprisingly, the proximity of MWA to the hepatic vein is only associated with minimal endothelial damage.

Skin burn at the needle tract during laparoscopic/percutaneous application is an MWA-specific injury that has been reported in the literature (Iannitti et al, 2007). It can occur when the power output is increased, and the outer conductor does not sufficiently shield the microwave energy (Liang et al, 2009). The risk of skin burn can be minimized by reducing the inward angulation of clustered antennae, spacing antennae 1.5 cm apart, and applying an internal cooling tip with running saline to reduce the temperature (Sindram, 2011).

All structures within the microwave field are heated, so it is essential to be aware of critical structures within the field, such as the diaphragm and heart. Further research is ongoing for development of a microwave shield to potentially decrease risks to vital organs.

Another logical extension of microwave technology, similar to radiofrequency, is using the microwave energy to coagulate liver parenchyma before resection. Radiofrequency devices are commercially available for this purpose but require a longer application time.

Microwave technology offers superior physical properties compared with radiofrequency, and it makes ablating larger lesions in the liver possible. One series reported that large-volume ablation can be effectively and safely done with a recurrence rate of 22% for HCC lesions in sizes ranging from 3 to 7 cm (Yin et al, 2009).

EMERGING TECHNOLOGIES

The ideal ablation system should be safe, cost effective, and have reproducible ablation results and a tissue-specific applicator design with real-time feedback for dedicated algorithms to achieve optimal ablation size. Although no current system fits these criteria perfectly, new technologies that show great promise are on the horizon.

Evaluation of Surgical Device Innovation

Surgical innovation is rapid, and new technologies are developed so quickly that clinical validation is sparse. Traditionally, many surgical procedures were developed on a trial and error basis, which raised concern for patient safety during product development (Ergina et al, 2009). A framework to evaluate the safety of new devices is necessary to protect patients, but the framework must be flexible, so that regulatory bodies do not obstruct innovation. Surgeons involved in product development must have a thorough understanding of how the device works to minimize patient risk. The rapid emergence of different ablation modalities has made comparison among various technologies challenging. The introduction of a new device is usually based on case series to establish safety, followed by an RCT to prove its efficacy, before it is eventually approved by the FDA.

To critically evaluate ablation, a standardized evaluation of patient demographics that include preoperative chemotherapy, TACE, or other therapy should be recorded for a matched comparison (Barkun et al, 2009). The outcomes of ablation should be defined (local and regional recurrence, etc.) and the follow-up protocol outlined so results of different trials can be compared. Moreover, the complication profile should be uniform and based on a system similar to the Clavien-Dindo

classification for surgical complications (Clavien et al, 2009). An online database should be created with dedicated personnel to report data. These measures would facilitate collaboration of different institutions and provide more reliable data for patient safety and product development.

Real-Time Three-Dimensional Virtual Reality–Guided Targeting

The advancement in ablation technology has proved that large-volume ablation is a reality, but this capacity is useless if the targeting of a lesion is inaccurate. The complete destruction of a lesion requires an adequate margin, and achievement of this margin often requires multiple applications for adequate overlap of the ablation zone. The use of 2D ultrasound has greatly enhanced the ability to identify a target lesion, but deploying the microwave requires complex coordination between interpreting the information on the monitor and positioning the applicator to track the course from the parenchyma into the tumors. This complicated process has a learning curve, and even in the hands of an expert, improper applicator position can occur. So achieving an adequate 3D overlap of the ablative zone is challenging, especially when only 2D information is available. To aid the surgeon in this process, a real-time 3D system was developed by InnerOptic (Hillsborough, NC). Using either an electromagnetic field generator with sensors or stereoscopic infrared cameras with reflectors, real-time 3D information is generated into virtual reality images and projected on a true 3D stereoscopic screen (Fig. 85D.5). This provides valuable information for targeting lesions, especially from an angle that is out of the plane of the US probe. The safety and accuracy of various procedures such as biopsy, venous catheter placement, and percutaneous ablation might be improved once this system is available commercially.

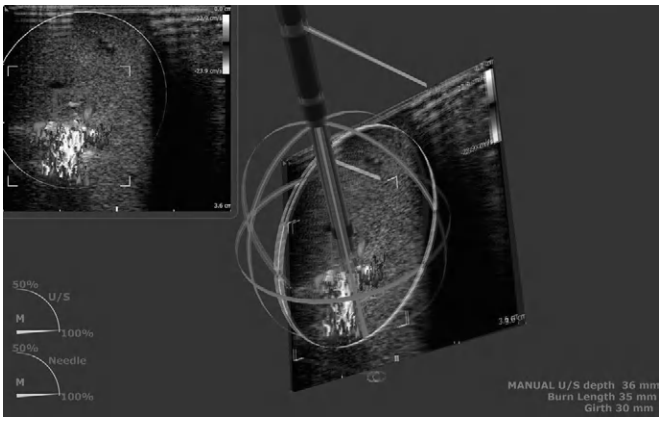


FIGURE 85D.5. Three-dimensional virtual reality image guidance system. Note the computer-generated ablation zone at the tip of the needle.

Other Ablation Modalities

Other modalities are currently under development to provide options for tumor ablation. The use of lasers, US, and pulsed electromagnetic waves are in various stages of development. We will briefly discuss laser interstitial thermotherapy (LITT), high-frequency focused US (HIFU), and irreversible electroporation here.

Laser Interstitial Thermotherapy

The application of lasers as a source of heat is not a new concept. Unlike laser therapy used in other industries, LITT uses a slow heating source, the neodymium:yttrium aluminum garnet (Nd:YAG) diode laser. It induces thermal coagulation by emitting laser light at a wavelength of 1064 nm from a low energy source of 3 to 20 W. After insertion of the laser fiber, LITT uses a slow heating process to prevent tissue coagulation, which reduces the penetration of the laser and limits the size of the ablation. LITT requires the photon of the laser to interact with the chromophores in the tissue to generate heat; hence conditions such as carbonization and vaporization, which decrease optimum penetration, significantly decrease the size of the ablation zone (Izzo, 2003; Sturesson, 1998).

Despite changes in the technology, LITT usually produces a relatively small lesion of 1 to 1.5 cm. Alterations of tip design have included using sapphire-tipped laser fibers, cool-tip applicators, and applications of different quartz diffusers; however, no significant improvement in ablative volume was observed with any of these (Castren-Persons et al, 1992; Heisterkamp et al, 1997). To overcome this deficit, a multifiber system was developed that is capable of producing lesions as large as 7 cm (Izzo, 2003); however, clinical use of this system is not widespread. Case series have reported favorable survival rates of 74% and 30% at 2 and 5 years, respectively (Mack et al, 2001), but no randomized trial has compared LITT with other ablative modalities, and further investigation is needed.

High-Intensity Focused Ultrasound

The application of US for diagnostic purposes is common, and regular transducers usually deliver time-averaged intensities of 0.1 to 100 W/cm^2 with compression and rarefaction pressure of 0.001 to 0.003 MPa, depending on the imaging mode used. US is a noninvasive modality, which makes it an attractive option for thermal ablation. In HIFU, the US beam can be focused to increase its intensity to 100 to 10,000 W/cm^2 to a focal region, with peak compression and rarefaction pressures up to 30 MPa and 10 MPa, respectively. Coagulation necrosis results in a few seconds with focal application of acoustic energy, which is converted to heat energy and is confined to a small volume of only 1 mm in diameter. The advantage of such a focused area is to decrease the undesired effect of thermal spread to adjacent tissue.

HIFU was first used to treat the eye, prostate, and kidney, but further investigation in ablating liver lesions has shown some promising results. A randomized trial compared TACE with HIFU, and a combination HIFU/TACE group showed a survival benefit of 6 months over a TACE-alone group (Wu et al, 2005). Research is ongoing for the treatment of liver lesions using HIFU, and clinical series have shown HIFU to be safe and effective, even near large blood vessels (Li et al, 2007; Zhang et al, 2009).

Irreversible Electroporation

A change in cell permeability caused by pulsed electrical energy, a phenomenon called *electroporation*, has been known for centuries and has been studied extensively in gene therapy and electrochemotherapy. Initially regarded as an undesired side effect, irreversible electroporation (IRE) is now under active

investigation for hepatic tumor ablation (Miller, 2005). IRE works by inducing cell necrosis after application of 1000 to 3000 V for a duration of milliseconds to microseconds (Padma et al, 2009). IRE is in its own class, because it does not involve thermal ablation; hence, local tissue factors such as heat or current sinking do not apply. Currently, no data for human use are available (Lencioni et al, 2010). An IRE system is commercially available now, and clinical investigation is ongoing to evaluate its safety and efficiency.

FUTURE DIRECTIONS

The future of ablation is exciting, and MWA will likely play a more prominent role in thermoablation. The theoretic advantages of its physical properties make it a reliable choice for ablation of liver lesions, especially for lesions larger than 3 cm or those near blood vessels. The addition of other modalities, such as high-intensity focused US and irreversible electroporation, complements MWA and allows practitioners more treatment choices for liver lesions. The emerging technologies, such as a real-time lesion-guidance systems, will increase the accuracy of ablation and may help define niche applications for various ablative modalities.

The continuing evolution of technologies for tumor destruction and the addition of accurate targeting systems will doubtless allow more surgeons to treat unresectable liver cancers with low morbidity and mortality. It is imperative to create a curriculum for upcoming hepatopancreatobiliary surgeons that will help them master ablative therapy and incorporate similar new technologies into practice.

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CHAPTER 90B

Hepatic resection for benign disease and for liver and biliary tumors

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OVERVIEW

Hepatic resection for removal of lesions of the liver may be necessary for a wide variety of conditions (Box 90B.1). Indications for partial hepatectomy include the treatment of primary benign or malignant growths of the liver and biliary tract or metastatic tumors, with the latter being the most common. Hepatic resection also may be necessary in the management of complex or symptomatic cystic disease involving the liver (see Chapters 68 and 69) and to allow access for repair of selected benign biliary strictures (see Chapter 42). Liver resection occasionally is necessary in the management of hepatic trauma. More recently, liver resection in living donors has been used in liver transplantation (see Chapter 98B).

The principles of segmental and subsegmental resection are not new (Nagasue et al, 1985), and they have been developed and refined through the years. Utilization of intraoperative ultrasound (IOUS) (Bismuth & Castaing, 1984; Castaing et al, 1985; Scheele, 1989) to identify intrahepatic structures (see Chapter 21) and a mastery of intrahepatic anatomy are paramount to performing safe resections. This chapter focuses on major resections, including right hepatectomy, left hepatectomy, and extended right (including segment IV) and left hepatectomy (including the right anterior sector). Commonly performed segmental resections, including caudate lobe resection, are briefly described. A more detailed description of segment-oriented resection of the liver is provided in Chapter 92.

Hepatic resection in patients with cirrhosis is further complicated by the presence of portal hypertension and a concomitant functional deficit of the future liver remnant (FLR) (see Chapter 90F). Liver resection for the removal of gallbladder carcinoma and cholangiocarcinoma at the confluence of the bile ducts can be especially troublesome in the postoperative period, because resection is frequently performed in the presence of biliary obstruction, bacterial contamination, and infection.

GENERAL PRINCIPLES

Benign Disease

Partial hepatectomy for the removal of benign tumors or cysts of the liver generally should be performed only for symptomatic patients, in the presence of doubt as to the diagnosis, or for tumors with known malignant potential (see Chapter 79). Removal of normal liver tissue should be kept to a minimum, thus when intervening for benign lesions, use of techniques for enucleation should be considered. Such enucleative methods may be utilized in the management of hemangioma, adenoma, and fibronodular hyperplasia. Enucleation also may be appropriate for tumor debulking of metastatic neuroendocrine tumors. The technique and principles of enucleation are described in the operation of pericystectomy for the removal of hydatid cysts of the liver (see Chapter 68).

Liver resection may be necessary in the management of some complex benign biliary strictures, especially when associated with ipsilateral liver atrophy (see Chapter 42). Some benign biliary conditions that sometimes necessitate resection include intrahepatic stones associated with recurrent pyogenic cholangitis (see Chapter 44) and Caroli disease, a congenital cystic disease of the liver (see Chapters 46 and 69). In these situations, the amount of normal hepatic parenchyma removed should be kept to a minimum in accomplishing the goal of the resection. Liver resection for hydatid disease is discussed in Chapter 68, and resection for hepatic trauma is discussed in Chapter 102.

Malignant Disease

When performing partial hepatectomy for malignant tumors, the guiding principle is to obtain negative margins of resection while maintaining patient safety. Ideally, the closest margin distance from the tumor edge should be approximately 1 cm (Are et al, 2007); however, the margin distance must often be sacrificed, both for patient safety and for preservation of major vascular structures in close proximity to the tumor that are required to sustain the future liver remnant. That said, complete resection with a close margin is still associated with improved survival, and thus the inability to obtain a wide margin based on preoperative imaging should not necessarily be a deterrent to resection (Pawlik et al, 2005; Poultsides et al, 2010). Furthermore, an effort should always be made to perform parenchyma-sparing resections without sacrificing oncologic efficacy.

The difficulty of achieving an adequate margin of clearance when performing wedge resections for peripherally situated tumors should not be underestimated. The deep margin is the most difficult to judge for adequate tumor clearance. Consequently, it has been shown that wedge resections can carry an unacceptable local recurrence rate (DeMatteo et al, 2000; Gall & Scheele, 1986), although this has not been universally observed (Zorzi et al, 2006). Another factor that may compromise wedge resections is the fact that the liver has a tendency to fracture at the interface between tumor and normal parenchyma. This is particularly a problem for hard tumors in a soft liver, as is often the case with metastatic colorectal carcinoma; thus the surgeon must maintain extreme caution during parenchymal transection for wedge resections to avoid a close margin, a problem best averted by transecting along anatomic planes defined by inflow and outflow structures.

Box 90B.1

Most Common Conditions for Which Liver Resection May Be Used

Benign Liver Tumors

Hemangioma
Adenoma
Focal nodular hyperplasia
Cystadenoma

Malignant Liver Tumors

Primary

Hepatocellular carcinoma
Cholangiocarcinoma

Metastatic, arising from

Colorectal cancer
Noncolorectal cancers and neuroendocrine tumors
Tumors directly invading the liver
- Adrenal tumors
- Renal carcinoma
- Gastric cancer
- Colonic cancer
- Retroperitoneal and inferior vena cava sarcoma

Gallbladder Cancer

Hilar Cholangiocarcinoma

Benign Conditions

Intrahepatic biliary strictures/fistulae
Intrahepatic biliary stones
Recurrent pyogenic cholangitis
Caroli disease
Liver cysts/polycystic liver disease
Parasitic cysts

Liver Trauma

Liver Resection in Liver Donors for Transplantation

Patients undergoing palliative resections for metastatic neuroendocrine tumors that are not amenable to complete resection may be good candidates for enucleation, as is often done for benign lesions (see Chapter 81B). Gallbladder carcinoma and cholangiocarcinoma situated at the confluence of the hepatic bile ducts frequently occlude biliary flow, and resection may be compromised not only by the adverse pathophysiology of obstructive jaundice, but also by infection that may have been introduced before operation as a result of either percutaneous or endoscopic stent placement. In addition, perioperative outcome is complicated by the concomitant partial hepatectomy and resection of the extrahepatic biliary apparatus and subsequent biliary reconstruction (see Chapter 50B).

The presence of cirrhosis also introduces unique challenges for performing liver resection. Preoperatively, appropriate patient selection is paramount to ensure that the FLR is adequate and that the patient will be able to tolerate the procedure. Intraoperatively, a firm, nodular, and enlarged liver poses technical difficulties in mobilization and parenchymal transection that may also contribute to increased blood loss secondary to portal hypertension. Postoperatively, the increased risk of liver insufficiency, hepatic failure, and increased susceptibility to infection are major concerns. Thus, resection should be reserved for patients with cirrhosis who have relatively preserved liver function, and the principles of parenchyma-sparing resection should be strictly followed (see Chapter 90F).

Principal Hazards

The main hazards of hepatic resection are biliary leakage and bleeding (see Chapter 25). Biliary leakage is a particular problem in patients in whom biliary reconstruction is necessary, for example, as in the removal of a hilar cholangiocarcinoma. Bleeding from the hepatic veins and the inferior vena cava (IVC) during parenchymal transection is a major concern. Bleeding is more likely to occur during major resection of superiorly and posteriorly placed tumors, where clearance is minimal between the tumor margin and the passage of the hepatic veins into the vena cava, or when tumors are closely adherent or adjacent to the IVC (Fig. 90B.1).

Future Liver Remnant

A healthy, noncirrhotic liver may tolerate a resection of up to 80% of its volume because the liver's enormous regenerative capacity enables functional compensation within a few weeks (see Chapter 5; Blumgart et al, 1971); however, such a favorable response cannot be taken for granted for extended hepatic resections. Only if reduction of the functional liver parenchyma is less than 50% can the risk of clinically significant liver insufficiency be virtually disregarded. Postoperative hepatic reserve is of particular concern after an extended left hepatectomy and when all of the parenchyma to the right of the falciform ligament is removed (extended right hepatectomy, which will be discussed later). Minimal to no risk of postoperative liver failure is present if most of the specimen volume has been replaced by an extensive tumor mass. In such patients, compensatory hypertrophy of the unaffected residual liver already has occurred preoperatively, and the loss of functional parenchyma is limited; however, a comparable volume of resection performed for multiple or unfavorably located smaller lesions carries a much greater risk of postoperative liver failure. Small tumors located adjacent to the inflow or outflow vessels of multiple segments may mandate removal of large amounts of functioning parenchyma.

Recently, some have advocated the liberal use of portal vein embolization (PVE) in this situation (see Chapter 93; Abdalla et al, 2002; Makuuchi et al, 1990; Palavecino et al, 2009); however, evidence is insufficient to suggest that PVE is associated with improved postoperative results in patients with normal parenchyma (Farges et al, 2003). In a series of 1800 liver resections performed at Memorial Sloan-Kettering Cancer Center (MSKCC), significant postoperative liver dysfunction and associated death occurred in only six patients (Jarnagin et al, 2002). In this series, PVE was utilized sparingly, and preoperative measures of liver function were not used routinely, such as the indocyanine green retention test; however, in patients with a damaged or steatotic liver—more common in obese patients, those with diabetes, and patients who have received substantial chemotherapy—the risk of postoperative liver insufficiency and failure is increased (Behrns et al, 1998; Kooby et al, 2003a). PVE may prove to be justified in this group of patients undergoing major resections. Biliary obstruction with jaundice is common in patients with hilar cholangiocarcinoma, who also are at increased risk. PVE in these patients also may be justified in select cases (see Chapters 50B and 93; Seyama et al, 2003).

In the cirrhotic liver, liver regeneration is much less effective; impairment of liver function after resection is greater, may last longer, and may result in terminal liver failure. Liver failure is

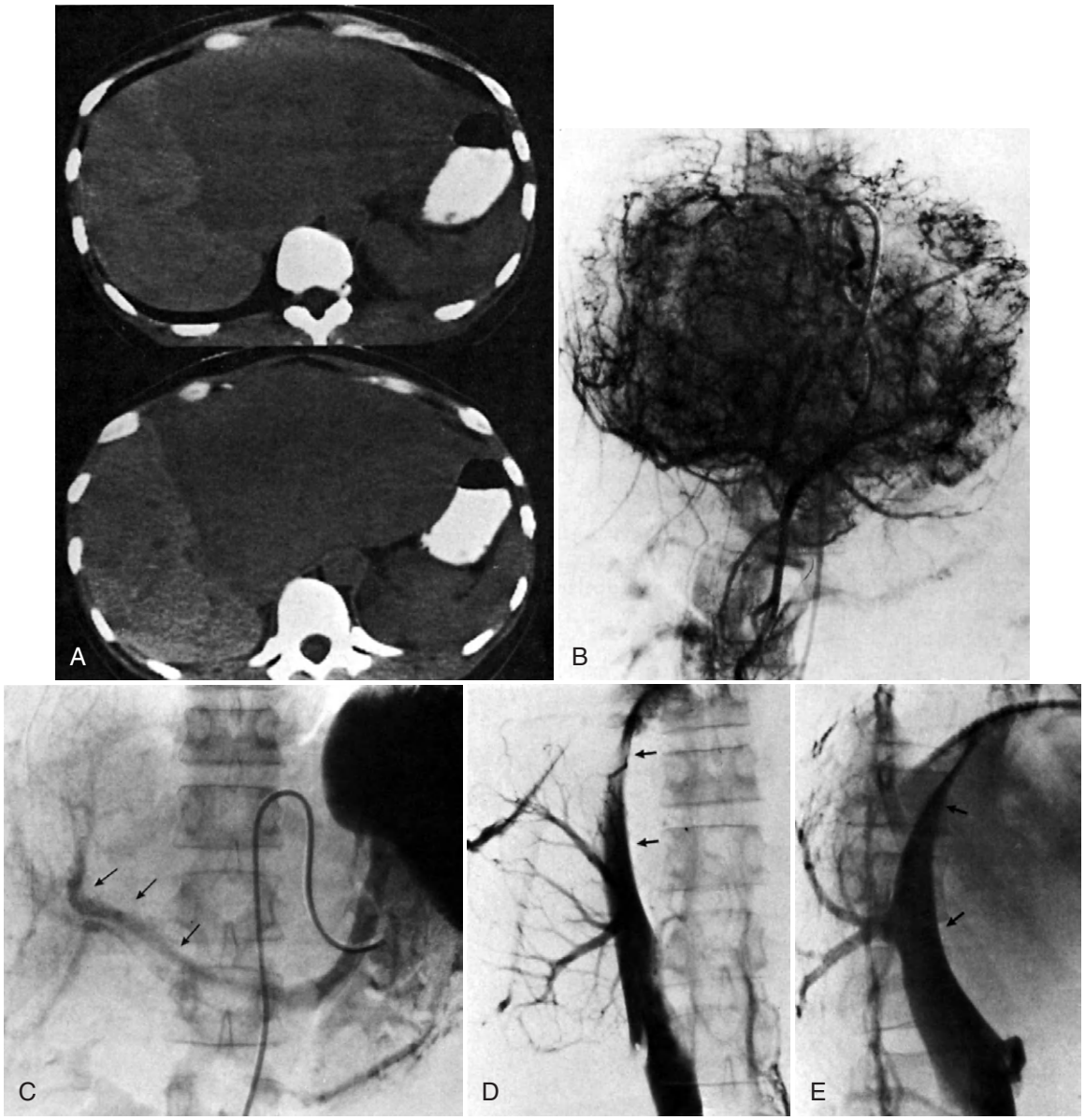


FIGURE 90B.1. **A,** Computed tomographic scan shows an enormous tumor occupying the left liver and extending beyond the principal plane into the right liver. Involvement of the vena cava and of the hilar structures is apparent. **B,** Selective hepatic artery angiogram reveals the gross size of the tumor within the left liver. **C,** Late-phase portogram shows gross displacement of the main trunk of the portal vein and its right branch (*arrows*). There is no filling of the left branch of the portal vein. Anteroposterior (**D**) and lateral (**E**) views of the inferior vena cava reveal severe compression but no tumor invasion; however, a collateral circulation has developed. The tumor proved to be a fibrolamellar hepatocellular carcinoma; it was treated by extended left hepatectomy. *Note:* Direct angiographic techniques have been supplanted by dynamic computed tomography and magnetic resonance imaging.

the most common cause of postoperative death after liver resection in patients with cirrhosis. Postoperative liver failure and postoperative mortality are related to the degree of preoperative liver decompensation and to the extent of nontumorous liver parenchyma removed. Liver failure may be precipitated by intraoperative bleeding, and a significant relationship has been found to exist between intraoperative blood loss, postoperative increase in serum bilirubin, and postoperative mortality. The occurrence of other postoperative surgical complications, such as abdominal infection, may also trigger postoperative liver failure. In addition, cirrhosis predisposes to multiorgan failure after hepatectomy. Although evidence supports the safety of major hepatic resection in cirrhotic patients with Child-Turcotte-Pugh (CTP) class A liver function (Fong et al, 1999a; Franco et al, 1990), it also suggests that PVE may improve perioperative outcomes by optimizing the FLR (Palavecino et al, 2009).

Portal Hypertension and Ascites

Liver resection leads to only a small increase in portal pressure in patients with a normal liver, but in patients with cirrhosis, a further augmentation of portal hypertension occurs, related to the amount of parenchyma removed and to an incapacity of the remaining liver to drain the splanchnic vascular bed. This increase in portal pressures may be the inciting factor that leads

to an increased risk of variceal bleeding after liver resection, observed more often in patients with cirrhosis.

The formation of ascites is one of the most frequent complications seen after liver resection in cirrhotic patients, occurring in 80% of patients. The etiology is likely twofold, the result of an increase in portal hypertension and of the ligation and division of lymphatics in the hepatic pedicle and liver ligaments. Postoperative ascites is a serious complication. Gross abdominal distension can interfere with ventilatory function and may result in leakage and disruption of the abdominal incision. Leakage of large-volume ascites may also lead to major fluid, protein, and electrolyte losses. In addition, ascitic fluid may become infected, and this may be an irreversible complication that leads to patient demise. Incidentally, ascites formation can also occur after liver resection and after fenestration in patients with polycystic liver disease (see Chapter 69B).

Infection

Despite the nearly universal formation of fluid collections after liver resections, particularly in the resection bed, infection of this fluid is relatively infrequent in most patients; however, a serious risk of infection follows liver resection in patients with biliary obstruction, especially in the presence of preoperative radiologic or endoscopic manipulation, and in cirrhotic patients. Alterations of humoral and cellular immunity are thought to predispose to infection after abdominal surgery in patients with cirrhosis. This risk is particularly high in patients with ascites or jaundice (Rimola et al, 1986). We also have empirically observed a slightly increased rate of infected fluid collections in patients undergoing simultaneous resections of a colorectal primary along with the liver metastases. In these combined resections, we now often leave an intraabdominal drain near the liver resection bed.

Selection of Patients for Liver Resection

When selecting patients for liver resection, the oncologic appropriateness of the resection must be considered first and foremost, followed closely thereafter by the general condition of the patient. Once resection is determined to be reasonable, and the patient appears to be a candidate from a general health perspective, the technical aspects of the resection must then be considered, including the extent of resection and the quantity and quality of the FLR. If the tumor can be completely resected without compromising hepatic arterial and portal venous inflow, biliary drainage, and venous outflow of the remnant, and if the FLR is of sufficient size in a well-functioning liver, nearly all patients are candidates for hepatic resection. Careful consideration must be taken when deciding to perform a major resection to remove multiple or centrally situated small lesions in patients in whom compensatory hypertrophy of the residual liver has not yet occurred. The selection of patients with a benign biliary stricture for hepatic resection is described in Chapter 42A, and the role of liver resection in specific situations, such as for hilar cholangiocarcinoma and hemangioma, are described below.

When considering patients with compromised liver function or cirrhosis for hepatic resection, it is important to understand that, in addition to the disease extent and the general condition of the patient, the degree of hepatic dysfunction is a major prognostic factor. The CTP classification system (Child & Turcotte, 1964; Pugh et al, 1973) is a simple means of assessing liver function preoperatively. Although more sophisticated tests can be used (see Chapter 2), the CTP classification is sufficient for most situations. Also, a low preoperative platelet count is a good surrogate marker for portal hypertension and underlying liver disease that otherwise may not be detectable (Bruix et al, 1996; Maithel et al, 2010). Operative mortality is much higher in CTP class B or C patients compared with those with class A liver function. Liver resection is particularly hazardous in a patient with a Pugh score greater than 8 (CTP class B). Serum bilirubin concentration is also an important prognostic factor, as liver resection is ill advised in patients with a serum bilirubin greater than 2 mg/dL or in the presence of clinically detectable ascites.

The extent of hepatectomy is guided by tumor size and location, but in general, the ideal is to remove as little parenchyma as possible. Small tumors located deep in the right liver are challenging, as it is preferable to avoid performing a right hepatectomy in such cases. If right hepatectomy is necessary, preoperative PVE of the affected lobe may allow hypertrophy of the contralateral side (see Chapter 93); however, the utilization of alternative methods for liver-directed therapy to obtain tumor control in a cirrhotic patient should be considered, especially in patients with multifocal disease. Alcohol injection, transarterial chemoembolization—bland, conventional, and using drug-eluting beads—cryoablation, radiofrequency ablation, microwave ablation, yttrium-90 therapy, and liver transplantation for managing tumors of the liver are discussed in detail in Chapters 84 through 86 and in Chapter 98.

ANATOMY AND CLASSIFICATION

Precise knowledge and mastery of the surgical anatomy of the liver, blood vessels, and biliary channels is essential for performing partial hepatectomy; this is described in detail in Chapter 1B. The liver is divided into sectors that comprise liver segments, each supplied by branches of the portal triads and drained by hepatic veins. Partial hepatectomy involves removal of one or more segments by isolation of the relevant portal pedicle, severance of the relevant hepatic veins and biliary drainage channels, and removal of the associated liver tissue.

The anatomic division between the right and left liver is not at the falciform ligament, but rather follows a line projected through a plane—the principal plane or Cantlie's line—running from the medial margin of the gallbladder bed to the left of the IVC posteriorly (Fig. 90B.2; Couinaud, 1954, 1957; Goldsmith & Woodburne, 1957; Healey & Schroy, 1953; McIndoe & Counseller, 1927). Each of these major right and left portions of the liver is divided into sectors and segments.

The Brisbane terminology dictates that the hepatic veins form the boundaries between the various sectors of the liver (Strasberg et al, 2000). Specifically, the medial margin of the right posterior sector is the right hepatic vein and comprises segments VI and VII. The right anterior sector is bordered by the right hepatic vein and middle hepatic vein, coursing along the principal plane, and it comprises segments V and VIII. Based on the Brisbane terminology, the area of liver that comprises segments IVa, IVb, and III forms the left medial sector; segment II forms the left lateral sector, because the left hepatic vein actually divides segment II from III. From a clinical perspective, resections of segments III, IVa, and IVb are rarely performed; furthermore, segment IVa/b is often referred to as the *left medial sector,* or the *left medial section* in Brisbane

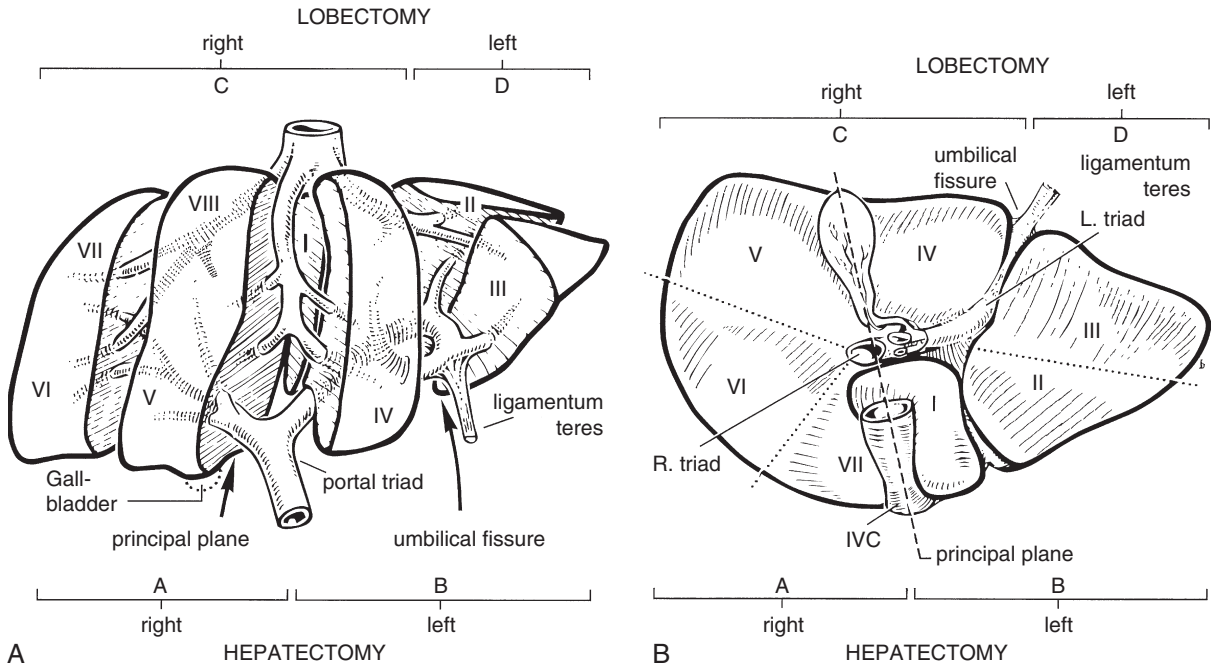


FIGURE 90B.2. **A,** Enlarged view to show the sectors (separated by the major hepatic veins) and the segmental structure of the liver. Each segment is supplied by a portal triad; the left portal pedicle traverses beneath segment IV to the umbilical fissure; the umbilical portion of the pedicle curves ventrally and caudally in the umbilical fissure. The blood supply to segment IV is recurrent as feedback vessels. **B,** Inferior surface of the liver; segment VIII is not seen because it lies superiorly. The anatomic division into right and left lobes by the umbilical fissure and into a right and left liver in the principal plane, along the principal scissura, is evident. IVC, inferior vena cava.

terminology, and it is bordered by the middle hepatic vein and umbilical fissure. The left lateral sector, or section, is comprised of segments II and III and represents the portion of liver to the left of the ligamentum teres and falciform ligament; thus in essence, the left liver is divided into a medial and lateral sector along the line of insertion of the ligamentum teres and the falciform ligament. This is the terminology that will be utilized for the remainder of this chapter. The portal venous and hepatic arterial branches conform to the segmental organization and run within the segments, and the draining hepatic veins converge posteriorly toward the inferior vena cava and mark the main scissurae of the liver (see Fig. 90B.2), within which they run (Couinaud, 1954, 1957).

Practically speaking, five types of major anatomic resections are practiced (Fig. 90B.3; see also Fig. 90B.2). The nomenclature of these operations is based on the anatomic descriptions of Couinaud (1954, 1957) and of Bismuth (1982; Table 90B.1). This classification emphasizes the importance of the scissurae of the liver and the umbilical fissure. The alternative, more commonly used terminology of Goldsmith and Woodburne (1957) is also listed in Table 90B.1. A newer terminology proposed by the International Hepato-Pancreatico-Biliary Association in Brisbane (Strasberg et al, 2000) is also referred to in Chapter 1 and is discussed above. The five different resections depicted in Figure 90B.3 can also be referred to as 1) right hepatectomy, 2) left hepatectomy, 3) extended right hepatectomy, 4) left lateral sectorectomy, and 5) extended left hepatectomy.

The portal vein and hepatic artery divide into major right and left branches outside the liver substance below the hilus (see Fig. 90B.2A). Here, when the overlying peritoneum is incised, it is possible to dissect each major branch beyond its bifurcation. The confluence of the right and left hepatic ducts

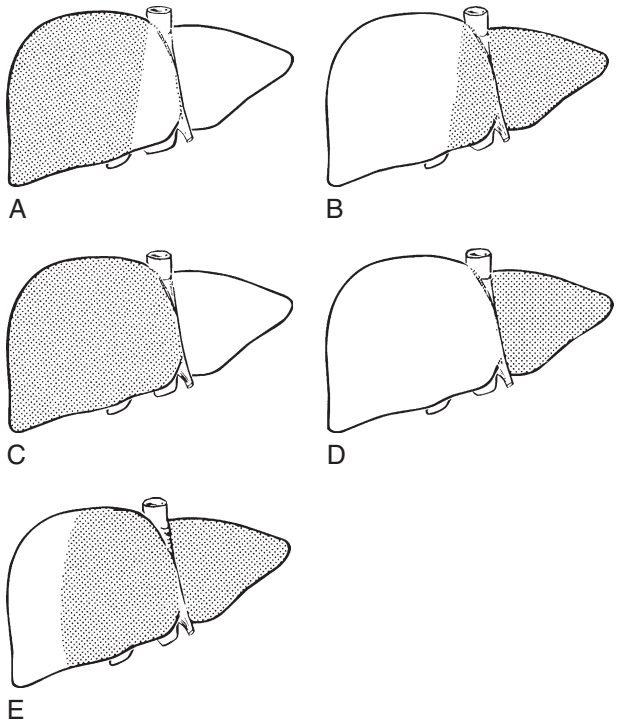


FIGURE 90B.3. Commonly performed major hepatic resections are indicated by shaded areas. **A,** Right hepatectomy. **B,** Left hepatectomy. **C,** Right lobectomy. **D,** Left lobectomy. **E,** Extended left hepatectomy. For the nomenclature of Goldsmith and Woodburne (1957), see Table 90B-1.

Table 90B.1

Nomenclature of Hepatic Resection

Couinaud (1957)	Goldsmith & Woodburne (1957)
Right hepatectomy (segments V, VI, VII, VIII; see Fig. 90B.3A)	Right hepatic lobectomy
Left hepatectomy (segments II, III, IV; see Fig. 90B.3B)	Left hepatic lobectomy
Right lobectomy (segments IV, V, VI, VII, VIII; sometimes includes segment I; see Fig. 90B.3C)	Extended right hepatic lobectomy*
Left lobectomy (segments II and III; see Fig. 90B.3D)	Left lateral segmentectomy
Extended left hepatectomy (segments II, III, IV, V, VIII; sometimes also segment I†; see Fig. 90B.3E)	Extended left lobectomy†

*Right lobectomy (extended right hepatic lobectomy) represents right hepatectomy extended to segment IV and has been referred to by Starzl and colleagues (1975, 1980) as *right trisegmentectomy;* this term is commonly found in the literature.
†Also referred to as *left trisegmentectomy* (Starzl et al, 1982).

also occurs outside the liver. At the hilum of the portal vein, the right branch is short, and its first branch often arises posteroinferiorly, close to the bifurcation, where it is easily damaged during dissection. By contrast, the left branch of the portal vein and the left hepatic duct pursue a longer, more horizontal extrahepatic course beneath segment IV and are more easily dissected free along their length.

The ligamentum teres (round ligament) runs sharply into the umbilical fissure of the liver, at the base of which the main vascular and biliary pedicle branches to the segments of the left liver (II, III, IVa, IVb). After entering the umbilical fissure, the left branch of the portal vein curves caudally and gives branches not only to the left lateral sector, segments II and III, but together with branches of the left hepatic artery, it gives rise to feedback vessels to the left medial sector—segment IVa and IVb of the left liver, also known as the *quadrate lobe* (see Fig. 90B.2A; Goldsmith & Woodburne, 1957; Starzl et al, 1975).

Outside of the liver substance, there is not a distinct sheath around the portal triad structures, and they must be dissected independently. The structures of the portal triad—the portal vein, hepatic artery, and bile duct—are covered with the Glisson capsule as they enter the liver parenchyma such that within the liver, they are contained in well-formed branching fibrous sheaths often referred to as *pedicles*. Thus, dissection outside of the liver substance mandates individual isolation of each portal triad structure, where there is considerable variation in anatomy. Pedicles are strong structures that contain the constituents of the portal triad, and intrahepatic dissection of these pedicles enables isolation and control of vascular and biliary elements without the need to individually expose each structure (Launois & Jamieson, 1992b).

The liver straddles the IVC immediately below the diaphragm, and the hepatic veins have a short extrahepatic course to empty into the vena cava (see Fig. 90B.2). This superior portion of the vena cava with the draining hepatic veins is masked behind a fold of peritoneum that extends from the cephalad aspect of the falciform ligament to the right and left triangular ligaments. The right hepatic vein emerges from the right scissura and usually enters the vena cava separately. By contrast, the left hepatic vein, which runs in the left scissura between segments II and III, is often joined by the middle hepatic vein, which occupies the principal scissura, before entering the vena cava. Several smaller veins from the posterior surface of the liver and the caudate lobe drain directly into the IVC.

An additional but important hepatic vein, the umbilical vein, runs beneath the falciform ligament and empties into the left hepatic vein. This vein is important in resections that remove segment IVa, because it provides drainage of segment IVb in the presence of ligation of the middle hepatic vein (see Chapter 92).

PREOPERATIVE CONSIDERATIONS

Preoperative Investigations

Preoperative investigations should seek to determine the nature of the lesion and give an index of resectability and the ideal surgical approach. Preoperative transcutaneous needle biopsy of liver tumor masses is not routinely necessary and is not always advisable (see Chapter 20). Preoperative biopsy should be pursued only if the information gained will alter the treatment plan. In the presence of a strong presumptive and clinical diagnosis of a potentially resectable liver tumor, we prefer to avoid the possibility of tumor dissemination, rupture, or hemorrhage, which may occur using percutaneous methods (Thompson et al, 1985). Laparoscopic exploration and visualization, particularly when used in combination with laparoscopic US, may provide valuable information regarding the presence of additional lesions not appreciated on preoperative imaging, and it may also reveal the presence of extrahepatic disease. By minimizing unnecessary laparotomy, this approach has been shown to increase the resectability rate of patients submitted to laparotomy (Jarnagin et al, 2000; John et al, 1994; Li Destri et al, 2008).

There are three major risks of hepatic resection: 1) hemorrhage, which may arise at the porta hepatis from branches of the hepatic artery or portal vein or posteriorly from hepatic venous radicles or the IVC; 2) biliary fistula or stricture as a result of damage to the biliary apparatus; and 3) postoperative liver insufficiency or failure. Intraoperative bleeding complications are most likely to occur when resecting tumors or other lesions that are large and in close proximity to the IVC and/or major hepatic veins (Hawkins et al, 2005). Similarly, tumors near the hilus at the confluence of the hepatic ducts and division of major vessels as they enter the liver substance can be challenging to remove. Given the numerous anatomic variations in the vascular and biliary anatomy of the liver, preoperative cross-sectional imaging should be routinely obtained and evaluated for important spatial relationships between tumor and these structures.

One such modality that provides valuable information in this regard is computed tomography (CT) (see Chapter 16). Peripherally placed lesions, unless substantially large, rarely involve the hilar structures or vena cava; however, more centrally situated lesions may involve major vessels close to the hilus, and appropriate CT scanning (see Chapter 16) can be most helpful in creating an image of the extent of disease and degree of vascular compromise by the tumor (Fig. 90B.4). Liver tumors can sometimes respect intersegmental planes and push structures away rather than invade them directly. This can be demonstrated not only by CT scan (Figs. 90B.5 and 90B.6), but also

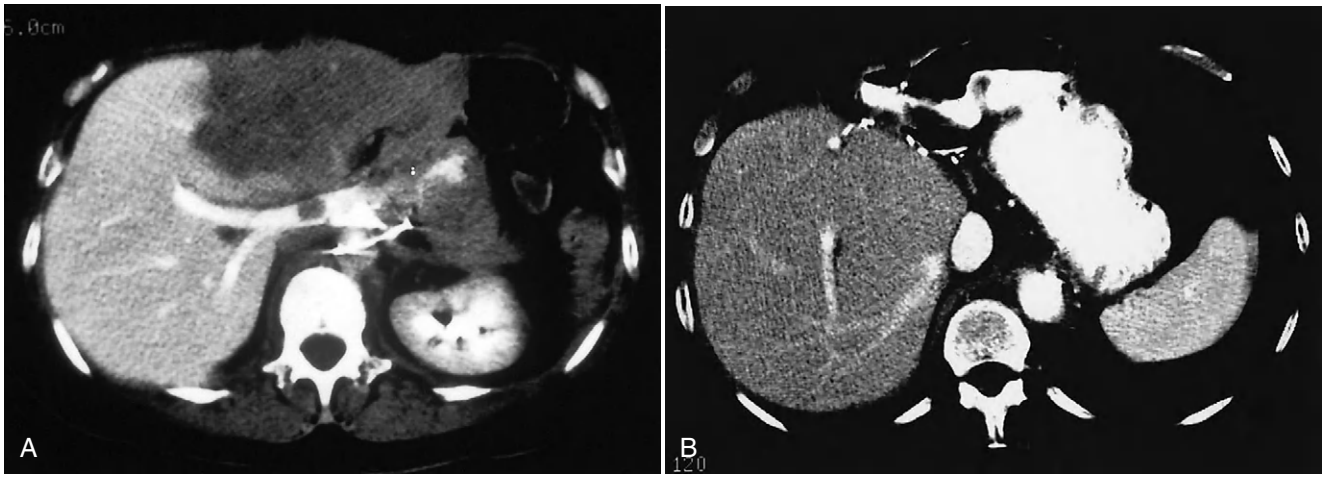


FIGURE 90B.4. Computed tomographic portography illustrates metastatic melanoma to the liver. **A,** A large metastatic deposit of melanoma occupies segments II, III, and IV and extends into segments V and VIII. The left portal vein contains an extension of tumor that protrudes into the main portal venous trunk. **B,** Extended left hepatectomy was performed together with resection of the affected portion of the portal vein and subsequent portal vein reconstruction. Recurrent tumor in the right buttock was excised 1 year after hepatectomy. The patient was alive and well without evidence of further recurrence in the liver 10 years postoperatively.

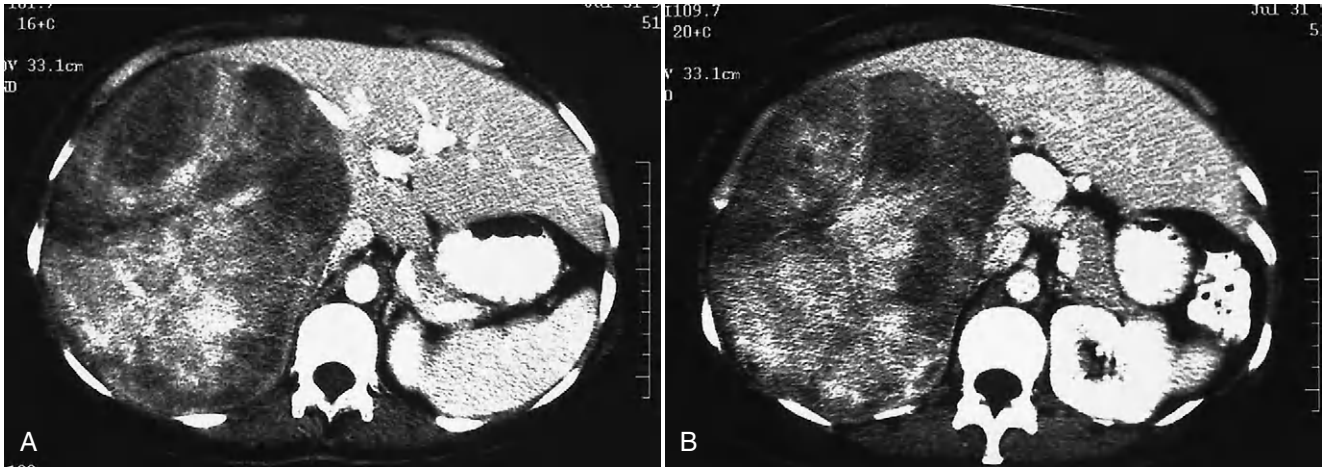


FIGURE 90B.5. A large, well-circumscribed tumor in the right liver has expanded and is adjacent to the inferior vena cava. **A,** Tumor has pushed the middle hepatic vein medially. **B,** Tumor protrudes by pressure effect into segment IV. Final histology revealed that this lesion was a benign fibrous tumor of the liver. Extended right hepatic lobectomy (right lobectomy) was performed without incident.



FIGURE 90B.6. Computed tomographic scan shows a large metastatic deposit from a hypernephroma occupying segments II, III, IV, V, and VIII of the liver. The tumor is pushing the posterior sectoral triad posteriorly. A thin rim of liver tissue separates the tumor from the vessels. In this instance, the plane of transection is dictated by the tumor. Hepatic resection by extended left hepatectomy was successfully carried out, and the patient was alive and well for more than 7 years.

can be confirmed by angiographic methods (see Fig. 90B.1) or by duplex ultrasound (US). However, with the advancement in technology and the high-quality images obtained with cross-sectional imaging, direct angiography is rarely necessary. Other tumors may hang from the liver in a pedunculated fashion (Baer et al, 1989), and they may be attached to the liver by a relatively small base, even when very large. Such "hanging" tumors are readily depicted on CT scan (Fig. 90B.7). Tumor involvement of the diaphragm also may be suggested by CT, but likewise, this should not deter the surgeon from attempted resection, because such apparent diaphragmatic involvement from metastatic tumors is frequently secondary to an adhesion to a site of previous necrosis of the tumor and not actually from direct tumor invasion (Weinbren & Blumgart, 1986). Primary tumors may still be approached for resection as well, even if they involve the diaphragm (Foster & Berman, 1977).

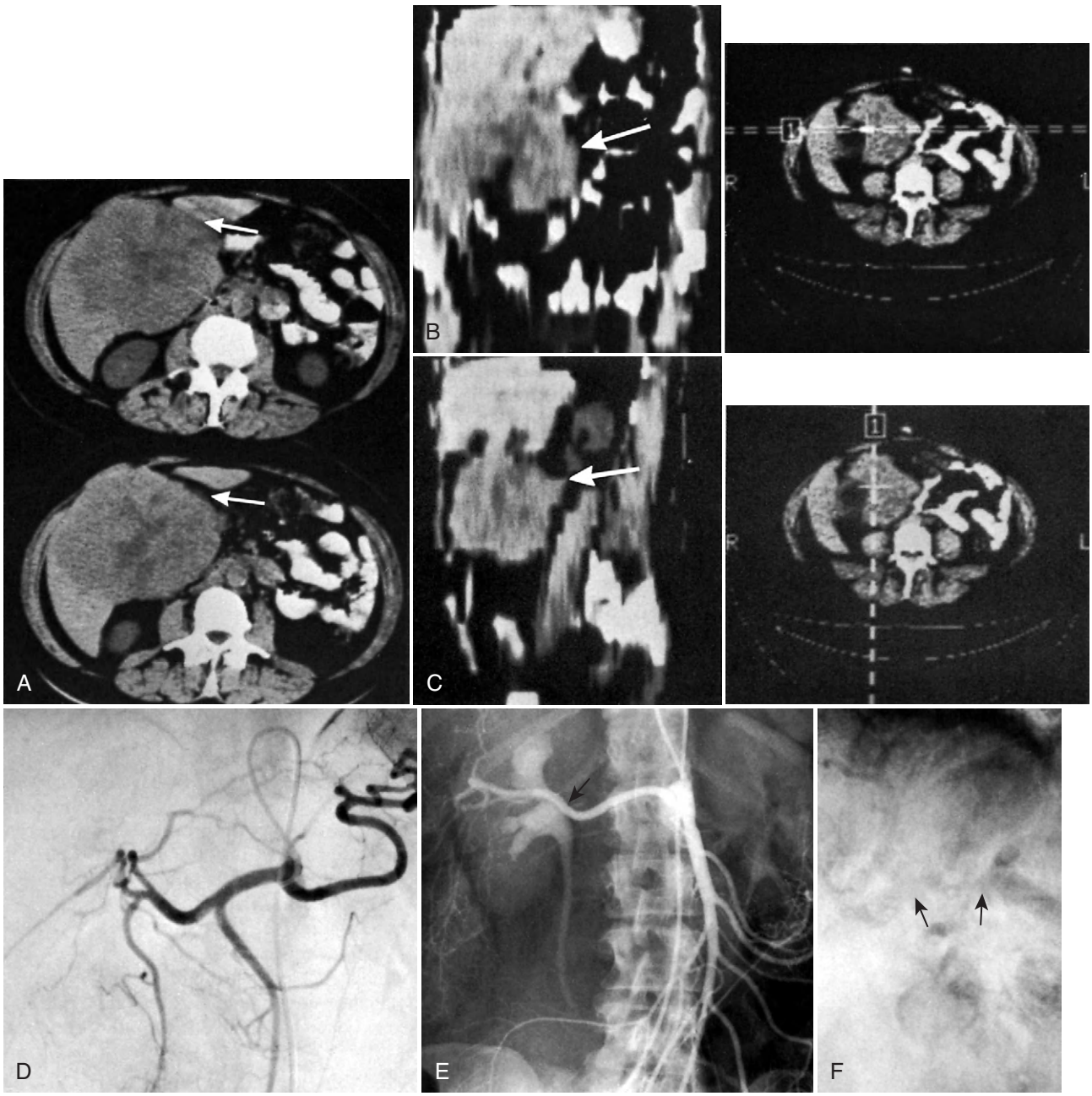


FIGURE 90B.7. **A,** Computed tomographic scan shows a large tumor apparent in the right liver and extending well into the left (*top arrow*). A gap between the tumor and segments II and III (*bottom arrow*) is apparent on the lower cut. **B,** Coronal reconstruction shows that the tumor (*arrow*) is pedunculated. **C,** Sagittal reconstruction shows the pedunculated (hanging) nature of the tumor (*arrow*), which originates from segments IV and V. **D,** Celiac axis angiogram shows the arterial supply to the tumor arising from the left hepatic artery. **E,** An accessory right hepatic artery is revealed to arise from the superior mesenteric trunk (*arrow*). **F,** Late-phase portogram obtained from selective splenic artery catheterization shows tumor involvement of the right branch of the portal vein extending to the portal venous bifurcation (*arrows*). The tumor proved to be a primary hepatocellular carcinoma, and treatment was by right lobectomy (extended right hepatectomy). *Note:* Angiographic techniques are now rarely used in diagnosis, but the images are retained for illustrative purposes.

Magnetic resonance imaging (MRI; see Chapter 17) has become increasingly valuable in the imaging of the liver before resection. Masses are well characterized, as are the presence of additional lesions sometimes not visualized on CT scan. MRI depicts major blood vessels accurately and is particularly valuable in the demonstration of the major hepatic veins and vena cava and their relationship to tumor masses (Fig. 90B.8). Compared to CT, MRI also may be more accurate in differentiating primary and secondary malignancies of the liver from benign lesions such as adenoma, focal nodular hyperplasia (FNH), or cysts.

US performed by an experienced operator is also of value in the preoperative assessment of multiple tumors, as it gives information regarding the size of the tumor and extent of liver involvement. US also may help distinguish cysts from solid tumors, and duplex US demonstrates tumor location with respect to important vascular structures, including the hepatic veins and vena cava (Gibson et al, 1986), and it is a valuable technique to further define blood vessels after initial CT scanning (Fig. 90B.9; Hann et al, 1998). US can be of particular importance in the preoperative evaluation of hilar cholangiocarcinoma by defining the extent of involvement of the portal vein and hepatic artery (Fig. 90B.10; Hann et al, 1997); however, as MRI and CT scan continue to produce higher quality images, the need for preoperative US evaluation has declined.

Hepatic angiography and inferior venacavography (see Chapter 19) usually are not necessary and should not be used except perhaps in the instance of large hemangiomata, for which precise information as to the arterial supply of the lesion

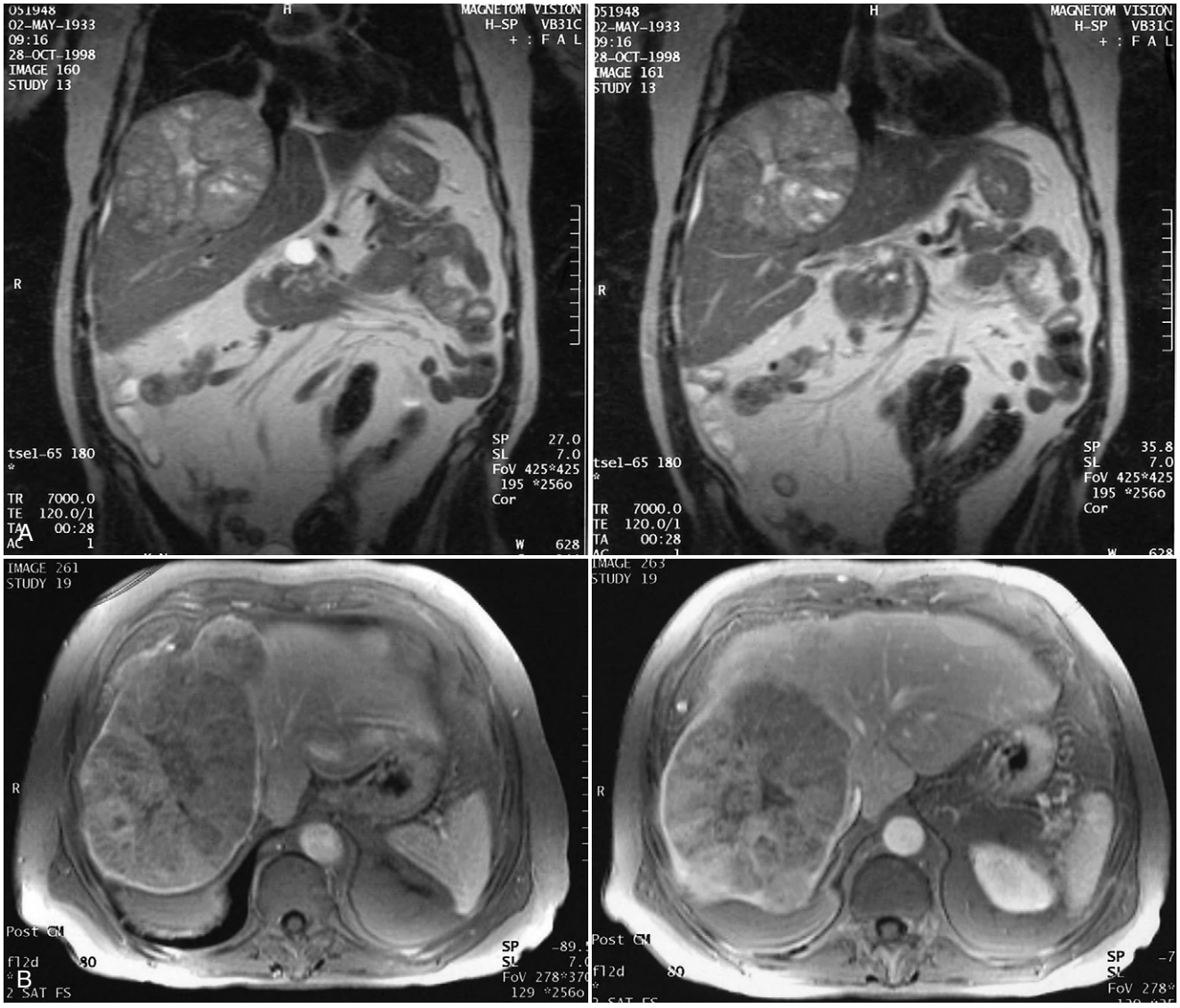


FIGURE 90B.8. Magnetic resonance imaging shows an extremely large but well-demarcated hepatocellular carcinoma occupying the right liver and extending into segment IV. **A,** Coronal views show that the tumor is seriously compromising and compressing the inferior vena cava (IVC); it extends upward and involves the right hepatic vein at its point of junction with the vena cava, distorting and compressing the suprahepatic IVC. At operation, the tumor—causing a pressure effect without direct invasion of the diaphragm—was found to lie just adjacent to the IVC–right atrium junction. **B,** Transverse scans illustrate the extent of the tumor and the severe compression of the IVC. Extended right hepatic lobectomy (right lobectomy) was done, and tumor clearance was obtained; hepatic vascular isolation was not used. The patient was alive and well 9 months after operation.

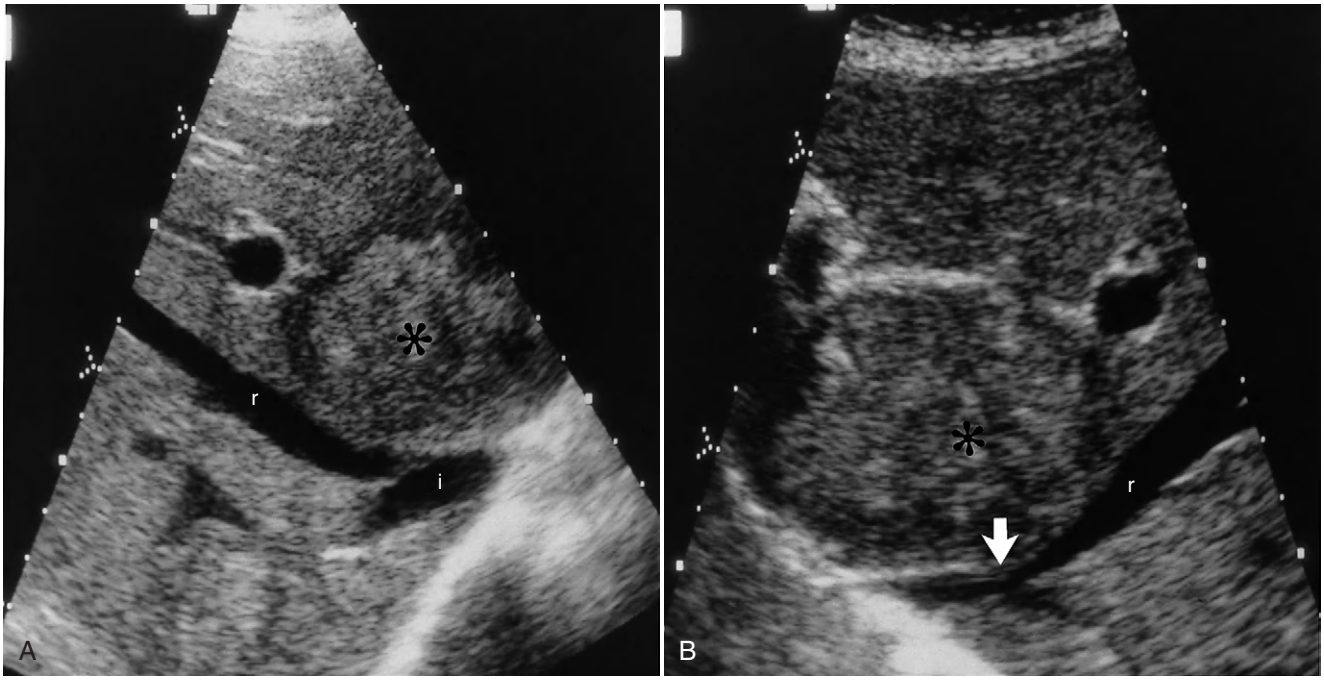


FIGURE 90B.9. Ultrasound defines the relationship between a colorectal metastasis and the veins at the hepatic vein confluence. **A,** Transverse ultrasound shows the metastasis (*asterisk*) making contact with the inferior vena cava (*i*) and right hepatic vein (*r*). **B,** Oblique intercostal projection confirms that the right hepatic vein is compressed (*arrow*) but not invaded by tumor (*asterisk*).

may assist at surgery, although modern advances in MRI and duplex US have all but rendered these studies obsolete. In the event that adequate US or MRI is unavailable, angiography still has a role in imaging (Blumgart, 1982; Voyles et al, 1983). Some figures of angiographic techniques are provided for illustrative purposes (Fig. 90B.11; see also Figs. 90B.1 and 90B.7), but it should be emphasized that they are unnecessary in most patients. In our practice, hepatic angiography is rarely obtained for the preoperative demonstration of extrahepatic arterial anatomy in patients being considered for placement of a hepatic arterial infusion (HAI) pump for postoperative adjunctive chemotherapy (see Chapter 86).

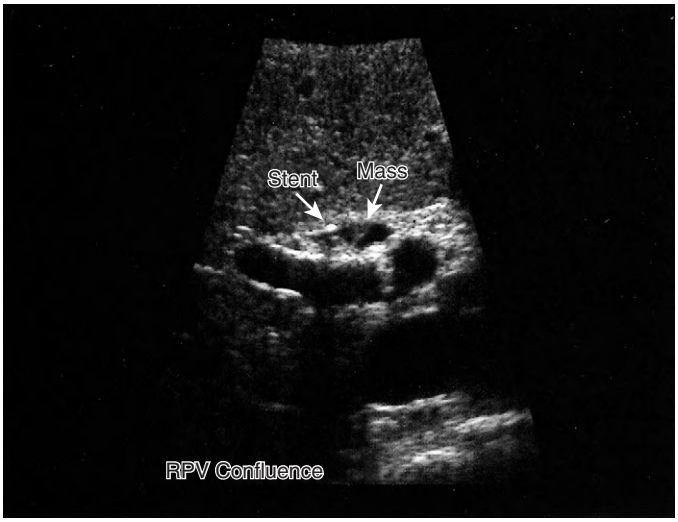


FIGURE 90B.10. Transverse ultrasound shows hilar cholangiocarcinoma at the confluence of the hepatic ducts. An endoscopically introduced stent is visible. The portal vein confluence immediately below the tumor is unaffected, and the portal vein is free. The tumor extended into the right hepatic duct, therefore an extended right hepatic lobectomy was necessary. The patient was alive, well, and tumor free 8 months after operation. RPV, right portal vein.

Other Investigations

To determine the oncologic appropriateness of hepatic resection, a thorough evaluation for the presence of extrahepatic disease should be performed by means of chest radiography, CT, or MRI before major hepatic resection is undertaken. When evaluating the chest, subcentimeter pulmonary nodules are frequently encountered that should not necessarily preclude hepatic resection, particularly for colorectal cancer liver metastases (Maithel et al, 2010). Positron-emission tomography (PET) scan may also be an important tool in the evaluation of the extent of spread of malignant disease (see Chapter 15; Beets et al, 1994; Fong et al, 1999a; Lai et al, 1996; Schüssler-Fiorenza et al, 2004).

If jaundice is present, and biliary involvement by the tumor is suspected, direct cholangiography may be carried out, either by endoscopic retrograde cholangiography (ERCP) or by percutaneous transhepatic cholangiography, to delineate the biliary anatomy (see Chapter 18); however, US and MRI cholangiography are noninvasive studies in many ways superior to direct cholangiography, and they have all but replaced preoperative invasive cholangiography for assessing tumor involvement of the bile ducts, such as in hilar cholangiocarcinoma (see Fig. 90B.10; see also Chapter 52). Of course, if preoperative biliary drainage is necessary, direct cholangiography, either endoscopic or percutaneous, will be required.

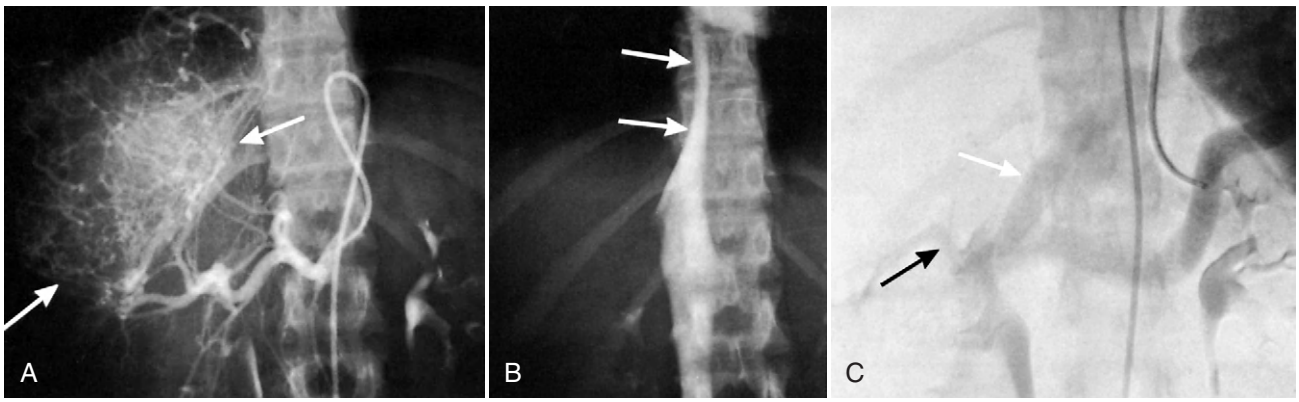


FIGURE 90B.11. A, Selective hepatic arteriogram shows a large primary hepatocellular carcinoma (*arrows*). **B,** Inferior venacavogram shows severe compression of the inferior vena cava (IVC) (*arrows*). Such severe compromise of the IVC demands vena caval control and precise dissection of the right hepatic vein. **C,** Selective splenic artery catheterization and late-phase splenoportogram show severe compromise of the right branch of the portal vein (*black arrow*). The left branch of the portal vein is intact (*white arrow*). Treatment was by right hepatic lobectomy. Angiographic techniques are now rarely performed.

Staging Laparoscopy

Staging laparoscopy and laparoscopic US are widely used to prevent unnecessary laparotomy in patients with hepatobiliary malignancy. Staging laparoscopy can significantly improve resectability rates at laparotomy, and laparoscopic evaluation has its greatest yield in detecting peritoneal metastases not detectable on cross-sectional imaging rather than identifying additional hepatic lesions. Furthermore, because of their location, laparoscopic evaluation often fails to identify lymph node metastases (Jarnagin et al, 2000; John et al, 1994; Lo et al, 1998). In one study at MSKCC (Jarnagin et al, 2000), 83% of patients subjected to laparotomy after laparoscopy underwent potentially curative resection, compared with only 66% of patients not staged laparoscopically (see Chapter 21).

Assessment of Resectability

Resectability is defined not only by what can be removed but, more importantly, by what can be left behind. Specifically, the liver remnant should be of sufficient quantity and quality with adequate inflow, outflow, and biliary drainage to sustain the patient's life in the postoperative period and for the duration of hepatic regeneration. In many instances, little difficulty is associated with assessing tumor resectability on preoperative imaging. This is particularly true for lesions situated in the periphery, at some distance from the major vascular structures, and with no radiologic evidence of additional tumors; however, at operation some patients may be found to have unexpected lymph node involvement or additional liver lesions visualized during laparoscopy or open exploration. This situation often relates to the oncologic appropriateness of resection, which should remain distinct from technical resectability. Given the advances and improved clarity of preoperative images, an unexpected finding at operation occurs in the minority of patients.

Major difficulties with accurate preoperative assessment of resectability can arise in two situations: First, tumors situated near the major hilar structures (see Fig. 90B.7) or those markedly compressing (see Fig. 90B.11) or involving the vena cava can be difficult to assess preoperatively. Involvement of major structures, such as invasion of bile ducts or portal venous branches, or apparent involvement of the IVC does not necessarily preclude resection (see Fig. 90B.1; Soreide et al, 1985). Second, very large tumors, which push structures aside and have been slowly growing over a long time, are difficult to define precisely, because pressure changes may mimic invasion on radiologic images. Thus, considerable caution must be exercised before declaring such cases unresectable. In patients with tumors of this nature, it is often difficult at initial exploration to be certain of resectability, and considerable dissection and mobilization is necessary before a clear-cut decision can be made. The morphologic configuration of tumors on imaging studies has been shown to have a clear relationship to subsequent resectability. Tumors that expand and compress surrounding tissues (*pushing tumors*) and tumors that are pedunculated and attached to the liver by a base of narrow width (*hanging tumors*) are nearly always resectable, and they can be distinguished from tumors that are irregular at the margins and clearly invasive (Baer et al, 1989).

In the early years of hepatic resection, the editor emeritus (Leslie H. Blumgart) adopted and promoted a deliberate policy of full investigation at laparotomy to assess resectability in all patients with solitary large liver tumors, provided no positive evidence of extrahepatic spread was apparent, patients were otherwise fit for major surgery, and the residual liver would be adequate. Of 22 patients with primary liver cancer evaluated in an early study, 13 patients were explored, and resection was carried out in all 13. Only three (23%) of the 13 underwent either a right or left hepatectomy or lesser procedure; the rest were submitted to extensive resections crossing the principal scissura (Cantlie's line) and necessitated extended resection (see Fig. 90B.11). Two of these 13 patients had tumor embolization before surgery to reduce vascularity and tumor size. Eight of these tumors were found to involve the right and left liver on CT scan; involvement of the main portal vein by tumor extension was found in two patients, one patient had involvement of the right branch of the portal vein, and six patients had severe compression or involvement of the IVC (see Fig. 90B.11). Although extrahepatic involvement was suspected in 3 patients, the resections carried out were potentially curative in 12 of the 13 patients with macroscopic clearance of all tumor; but in 1 patient with fibrolamellar hepatocellular carcinoma (HCC), a

deliberate extended resection was performed in the presence of regional lymph node metastases. No intraoperative or in-hospital (30-day) deaths were reported (Soreide et al, 1985). This early experience has been replicated in subsequent studies (Vauthey et al, 1993) and in studies by many other investigators.

The resectability rate within a specialized hepatobiliary surgery unit does not necessarily indicate the overall resectability rate for a particular tumor, because the patient population is highly selected; however, it does seem that an aggressive surgical policy is justified, even in patients with large solitary tumors. In particular, the size of the tumor alone is not a contraindication to resection, although for HCC, large tumor size is associated with earlier recurrence and reduced survival (Pawlik et al, 2005; Nathan et al, 2009). Other authors agree with this view and advocate an aggressive approach to resection (Adson & Weiland, 1981; Balasegaram & Joishy, 1981; Okamoto et al, 1984; Starzl et al, 1982; Steele et al, 1984).

As discussed earlier, radiologic demonstration of apparent involvement of major inflow and outflow vessels does not constitute an absolute contraindication to exploration for resection. Intraoperative techniques are now available to deal with portal vein and IVC involvement. This is particularly applicable to the fibrolamellar variant of HCC (Berman et al, 1980; Craig et al, 1980; Hemming et al, 1997; Nagorney et al, 1985; Soreide et al, 1986), as it tends to be less invasive to surrounding structures and is thus more readily removable. Furthermore, it may have a more favorable prognosis than standard HCC, and its presence should be suspected in patients who have a nonelevated α-fetoprotein with a large tumor in the background of a normal liver; other markers—particularly plasma neurotensin levels (Collier et al, 1984), vitamin B_{12} binding capacity (Paradinas et al, 1982), or both are increased with this tumor.

Some patients with primary HCC present with biliary tract obstruction secondary to tumor emboli within the bile ducts. These emboli may be shown by direct cholangiography, MRI cholangiography, or US. This presentation should not necessarily preclude an attempt at resection (Blumgart, 1978, 1980).

It has been stated that young patients with large, unresectable HCC are suitable candidates for transplantation, and many physicians and surgeons see liver transplantation as the only therapeutic alternative in such cases. This view seemed to be supported earlier by the National Institutes of Health (NIH) Consensus Development Conference Statement on Liver Transplantation (NIH, 1983); however, subsequent experience did not support this broad approach, and controversy emerged regarding the place of liver transplantation for the management of liver tumors. More recently, transplantation has emerged as an effective and viable treatment option in patients with cirrhosis and limited neoplastic disease, with the Milan criteria now firmly established for guiding patient selection (Mazzaferro et al, 1996). This issue is discussed further in Chapter 97D.

Finally, portal venous involvement in cholangiocarcinoma affecting the confluence of the bile ducts does not always preclude resection (Blumgart et al, 1984; Burke et al, 1998). This topic is fully discussed in this chapter and also in Chapter 50.

Preoperative Preparation

Preoperative preparation involves appropriate antibiotic prophylaxis and correction of anemia and coagulopathy. Patients with a significant history of active cardiopulmonary disease should undergo any indicated investigations and optimization prior to undergoing resection. All patients with chronic liver disease or cirrhosis are assessed carefully as to the possibility of present or past infection with hepatitis B or C virus, for a history of alcohol abuse, and for the magnitude of liver dysfunction as assessed by the CTP criteria and preoperative platelet count.

ANESTHETIC CONSIDERATIONS (SEE CHAPTER 22)

Intraoperative venous access should be appropriate to prepare for the possibility of major intraoperative bleeding. Adequate hemodynamic monitoring and facilities for rapid transfusion should be available, and the anesthesia team should be prepared for the possibility of a thoracoabdominal incision. Bleeding during hepatic resection usually occurs during parenchymal transection and arises from the hepatic veins or vena cava, thus we routinely perform a deliberate retrohepatic dissection of the minor and major hepatic veins before beginning parenchymal transection, unless the tumor location and size prohibit this approach and mandate an anterior approach.

To minimize bleeding during parenchymal transection, the anesthesiologist must maintain a low and controlled central venous pressure (CVP) below 5 mm Hg. For patients with relatively good health status, central venous access is not mandatory, as long as large-bore peripheral intravenous access is obtained, and the patient is not given much fluid until parenchymal transection is complete. To prevent air embolism, the dissection can be performed with the patient in a 15-degree Trendelenburg position. Low CVP is maintained at the desired level using a combination of minimal fluid resuscitation and agents that promote venodilation. A minimal intraoperative urine output (20 to 25 mL/h) is tolerated until parenchymal transection is complete (see Chapter 22; Cunningham et al, 1994; Melendez et al, 1998). Once the specimen is removed, hemostasis is achieved, and the patient is resuscitated.

Every effort should be made to avoid perioperative blood transfusion, as allogeneic red blood cell transfusion has been associated with worse perioperative outcome and possibly earlier cancer recurrence and shortened survival, although the latter remains controversial (Amato & Pescatori, 1994, 1998, 2006; Kooby et al, 2003b). The previous dictum of maintaining the hemoglobin at 10 gm/dL or hematocrit at 30% is no longer standard practice (Hebert et al, 1999). Allogeneic blood transfusion should be reserved for excessive blood loss and hemodynamic instability. A technique of acute normovolemic hemodilution, in which the patient's blood is removed intraoperatively and replaced with a combination of crystalloid and colloid fluids, can also reduce the need for allogeneic blood transfusion (Matot et al, 2002; Jarnagin et al, 2008; Maithel & Jarnagin, 2009); the blood that is lost is hemodiluted and contains less red blood cell mass. Once the dissection is complete, the blood removed from the patient earlier is reinfused, which minimizes the need for allogeneic transfusion. The body temperature should be carefully monitored, and normothermia is maintained with warmed fluids and external warming devices.

Should vascular isolation of the liver be necessary, the anesthetic management is slightly altered, because it requires the maintenance of cardiac output during cross clamping of the vena cava. We rarely use vascular isolation of the liver, even during the removal of large tumors close to or involving the hepatic veins and/or the IVC. Even tumors directly involving the vena cava may be removed without vascular isolation.

Nevertheless, some authors (Bismuth et al, 1989; Huguet & Gavelli, 1994; Huguet et al, 1978, 1992a, 1992b) have advocated vascular isolation techniques during hepatic resection, especially for large tumors. Other authors use this method for even limited resections (Kelly et al, 1996), but it is often unnecessary. Techniques for vascular isolation are discussed fully in Chapter 91A.

Postoperative analgesia can be delivered in the form of intravenous or epidural analgesia. The ability to metabolize narcotics after major liver resections may be reduced, thus patients must be monitored carefully for oversedation and respiratory depression. Our preference is to avoid using epidurals for major liver resections because of the potential for hemodynamic compromise, from the reduction in sympathetic tone and the rise in international normalized ratio (INR) that prevents epidural removal, and its association with increased risk of blood transfusion (Page et al, 2008).

OPERATIVE PROCEDURES

Patient Positioning

The patient should be positioned supine with the right arm extended at a right angle to the body. It is unnecessary to place the patient in a lateral decubitus position, as tilting the operating table allows for adequate exposure during operation. Electrocardiogram (ECG) leads should be kept clear of the right chest wall and the presternal area, and draping should expose the lower chest up to the nipple line and the entire upper abdomen to below the umbilicus (Fig. 90B.12). This exposure is adequate for most hepatic resections. If preliminary laparoscopy is to be performed, it is done at this stage.

For large, posteriorly lying tumors, a thoracoabdominal incision may be necessary, but this can usually be avoided with right lateral extension of the incision with good costal margin retraction. The abdomen should be widely exposed from midaxillary line to midaxillary line to allow adequate space for a transverse incision. A cross bar or similar device should be fitted to the table to hold a self-retaining retractor later to elevate the costal margin (see Fig. 90B.12). In patients in whom extracorporeal venovenous bypass is to be performed in conjunction with complete vascular isolation of the liver, or in those whose back-table resection is to be done in association with autotransplantation, or for cases of regional hepatic perfusion (see Chapter 89), the right and left groins, left axilla, and/or left neck should be prepared to allow access to the femoral vein, axillary vein, or internal jugular vein respectively.



FIGURE 90B.12. Position of the patient on the operating table. Note the wide exposure of the abdomen and chest. The cross bar later holds a large retractor, used to elevate the costal margin (see also Fig. 90B.14).

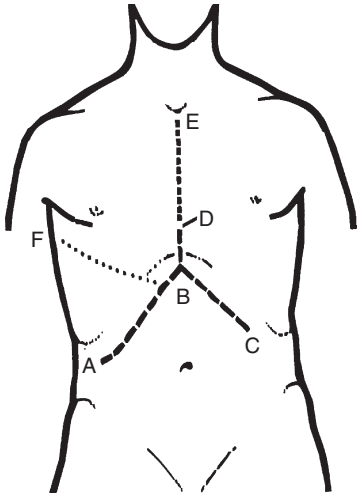


FIGURE 90B.13. Incisions used for partial hepatectomy. *ABC,* Rooftop incision with vertical extension. *DE,* Median sternotomy. *F,* Right thoracic extension. Most often an extended right subcostal incision (*ABD*) is adequate.

Incisions

The incision depends on circumstances (Fig. 90B.13), and the surgeon should not hesitate to extend or enlarge the wound to gain adequate access. For most hepatic resections, the initial incision should be an extended right subcostal incision (*ABD* in Fig. 90B.13) or a bilateral subcostal incision with a vertical extension. A slight variation of this incision that affords excellent exposure for most resections is an upper midline incision from the xiphoid process to approximately 2 to 3 cm above the umbilicus with right lateral extension toward a point midway between the inferior costal margin and anterior superior iliac spine. A limited upper midline incision may be made first to allow preliminary manual and visual exploration to exclude obviously unresectable disease or the presence of extrahepatic spread. In some situations, particularly for left-sided resections in thin patients, a midline incision is adequate. Large tumors of the right side of the liver, especially those lying posteriorly and involving the IVC, may require a right thoracoabdominal approach, but this is rarely necessary. Our experience in more than 2000 cases of liver resection necessitated a thoracoabdominal incision in only 3%. A median sternotomy gives good access, is rapid, and spares disruption of either pleural cavity, but it is also seldom required. If a median sternotomy is used, the diaphragm may be split through the central tendon to allow excellent exposure of the suprahepatic IVC and the major hepatic veins, and the open pericardium can be used to allow direct access to the intrapericardial IVC.

Exposure, Mobilization, and Assessment

When the abdomen is opened, the entire peritoneal cavity should be explored. In particular, the structures occupying the free edge of the lesser omentum, lymph nodes related to the hepatic artery and the celiac axis, and supraduodenal nodes should be assessed. Exploration of the lower abdomen through an upper abdominal incision may be difficult in patients who have had previous pelvic surgery, such as a sigmoid colectomy for primary colorectal cancer. When direct access is limited, palpation in conjunction with preoperative cross-sectional imaging (CT or MRI) and PET scans is sufficient.

Prior to exploration of the liver, the ligamentum teres is divided, and the falciform ligament is incised and separated from the anterior abdominal wall (Fig. 90B.14A). The falciform ligament is divided as far cephalad as the subdiaphragmatic IVC (see Fig. 90B.14, B and C). Vessels running within the falciform ligament are usually controlled with bovie electrocautery. A long suture should be left on the ligamentum teres to act as a retractor during subsequent exploration and dissection for manipulating the liver.

Visual and manual exploration of the liver should follow division of the ligamentum teres and falciform ligament. Elevation of the ligamentum teres helps expose the undersurface of the liver and the area of the hilus and umbilical fissure. Both hands should be utilized to enable bimanual palpation. Unless bimanual palpation is carried out, large lesions located deep within the parenchyma may be missed or underestimated with simple surface examination. The transparent tissue of the lesser omentum should be incised to facilitate manual palpation of the

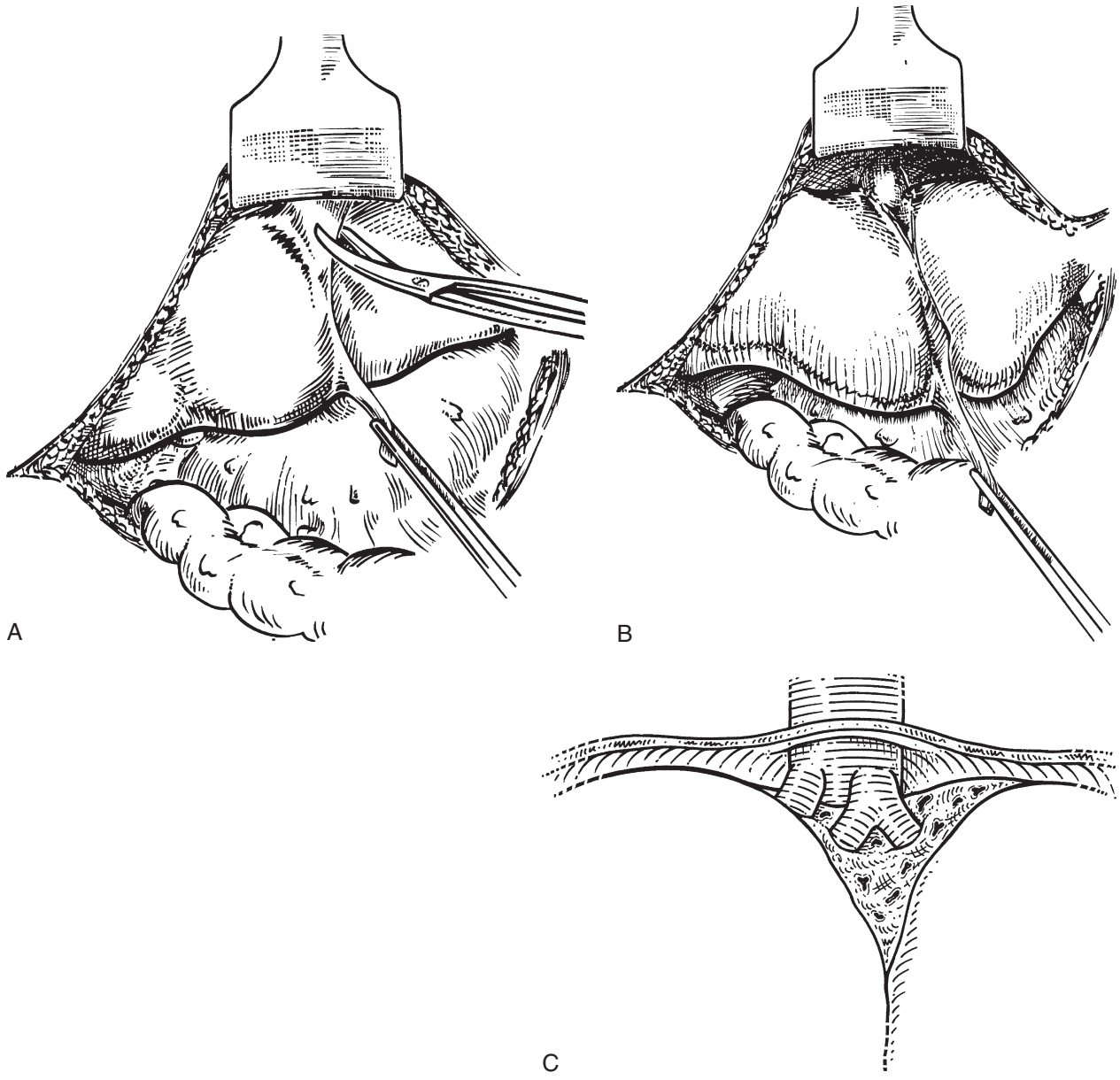


FIGURE 90B.14. **A,** The ligamentum teres is secured, and division of the falciform ligament is begun. **B,** The falciform ligament is divided backward to expose the suprahepatic inferior vena cava (IVC). **C,** Suprahepatic exposure of the major hepatic veins and IVC after division of the upper falciform ligament.

caudate lobe (segment I) and the celiac lymph node basin. If the lesser omentum needs to be further divided to facilitate an adequate evaluation, attention should be directed to the possible presence of an accessory or replaced left hepatic artery. Complete assessment and palpation of the right lobe requires mobilization of the right liver from the diaphragm and retroperitoneum. This maneuver may be delayed until US examination of the liver, in conjunction with initial palpation, indicates that the lesions are resectable.

Mobilization of the right liver begins with complete division of the falciform ligament and identification of the right hepatic vein. As the falciform ligament fibers begin to splay at the back, the surgeon must exercise caution, as the hepatic veins are in close proximity. Early identification of the right hepatic vein prevents subsequent injury during the lateral and posterior mobilization. Once the right vein is visualized, the peritoneal reflection at the edge of the right triangular ligament is incised laterally, and the incision is developed medially between the diaphragm and the liver, until the entire bare area of the liver on the right is exposed (Fig. 90B.15); this allows the liver to be turned to the left. During this dissection, the table is rotated a little to the left, so it is helpful for the surgeon to be standing to the patient's right.

Next, the short retrohepatic veins draining directly from the caudate lobe to the IVC are serially divided, progressing from the inferior aspect toward the hepatic veins. Complete exposure

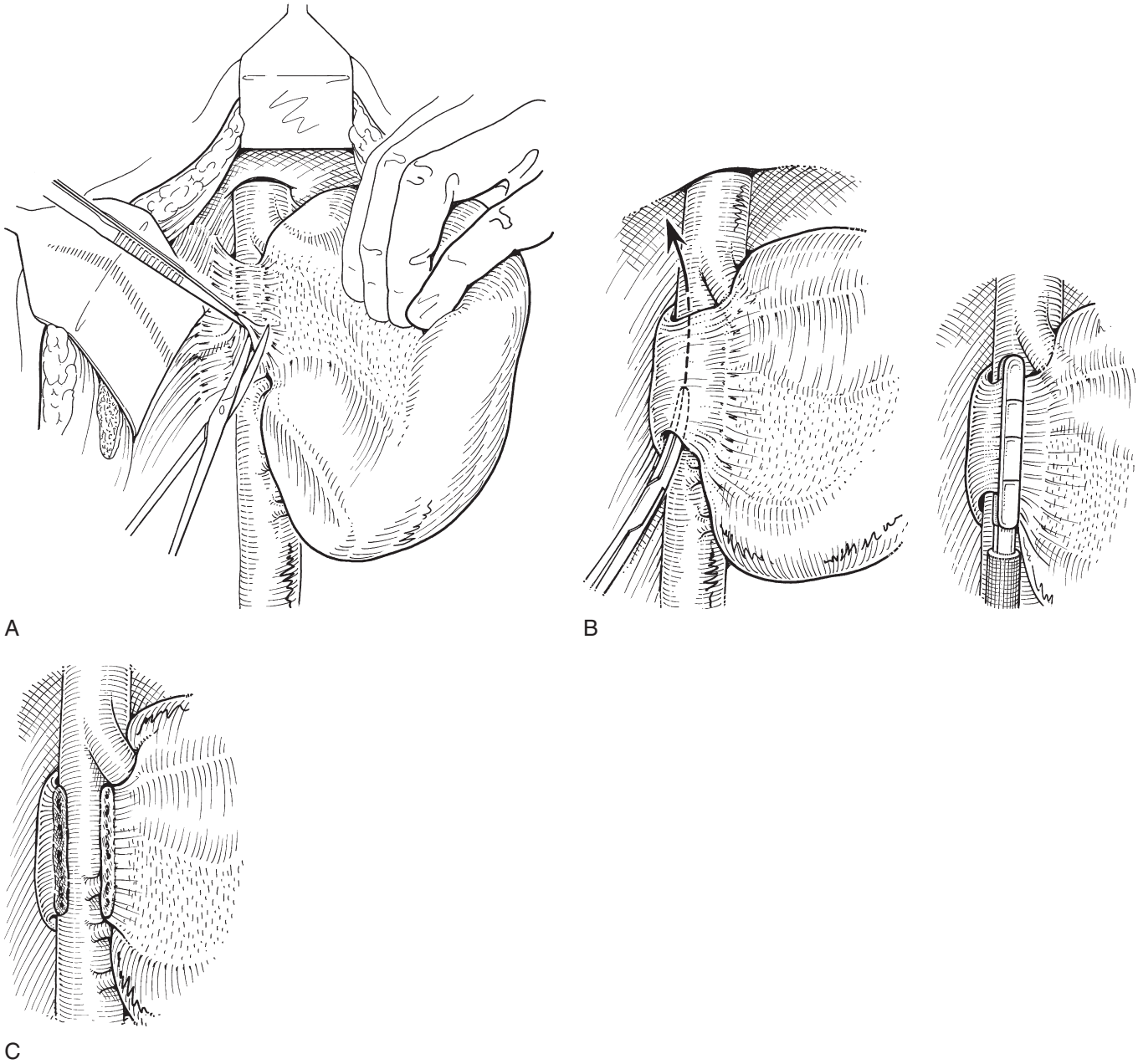


FIGURE 90B.15. A, Incision of the peritoneal reflection of the right triangular ligament allows mobilization of the right liver. The exposure is deepened to display the right lateral margin of the inferior vena cava (IVC). *Note:* If the right hepatic vein is to be exposed, the IVC ligament must be divided with scissors as illustrated. **B,** The ligament also may be mobilized, and a clamp is passed beneath it (*left*). It is divided with the Endo GIA (Covidien) vascular stapler (*right*). **C,** The retrohepatic IVC is fully exposed.

of the IVC and right hepatic vein requires division of the fibrous tissue, the vena caval ligament, which usually obscures the right side or the upper part of the retrohepatic vena cava (see Fig. 90B.15A). This division can be done with scissors (see Fig. 90B.15A), or an endoscopic gastrointestinal anastomosis vascular stapler (Endo GIA; US Surgical, Norwalk, CT) can be used (see Fig. 90B.15B) to expose the vena cava completely (see Fig. 90B.15C). The vena caval ligament also extends behind the vena cava posteriorly, embracing it and joining a similar fibrous extension from the caudate lobe on the left (see Chapter 1B). Rarely, this posterior part of the ligament is replaced by a thin rim of liver tissue, so that at this point, the vena cava runs through a tunnel of liver parenchyma. This can be a source of difficulty, but this thin plate of liver tissue can similarly be divided to expose the IVC completely. The vena caval dissection is particularly facilitated with low CVP anesthesia.

If the tumor is found attached to the diaphragm during mobilization of the right liver, this is usually only across a limited distance, and the affected area of diaphragm is separated, or a segment of the diaphragm is excised and subsequently repaired. An anterior approach with initial transection of the parenchyma without preliminary mobilization of the right liver is necessary and valuable in some cases (Lai et al, 1996b); this will be discussed later.

On the left side, the left lateral sector is mobilized by division of the apex of the left triangular ligament. The table is rotated a little to the right to allow good visualization. Care must be taken not to damage the stomach and spleen at the far left of the triangular ligament, and placing a laparotomy pad under the ligament helps to protect these structures while incising the ligament. The ligament is opened, and between its anterior and posterior leaves, the upper part of the IVC and the left hepatic vein become visible (Fig. 90B.16).

Intraoperative Ultrasound

We use IOUS to complete the assessment of the number and location of tumors along with their exact anatomic relationship with the major vascular and biliary structures within the liver parenchyma. US guidance is also utilized to perform a needle biopsy of small, deeply placed lesions and for ablative procedures, should such be necessary. Transhepatic cannulation of biliary or vascular elements to perform contrast studies (Hasegawa et al, 1991b) is rarely used; a detailed description of the use of IOUS in liver resection is provided in Chapter 21. Essentially, examination is carried out with a B-mode, real-time system. The probes utilized for IOUS are waterproof and sterile; a T-shaped probe or a finger probe is used that enables direct application of the probe to the liver surface, and the moisture of the liver allows good contact. Examination should be carried out in a systematic fashion, starting in the umbilical fissure, progressing to examination of the hilar structures, followed by a careful examination of the hepatic veins and finally of the hepatic parenchyma. In case of doubt, further examination may be done after mobilization of the right or left liver, particularly for posteriorly located tumors. The probe also may be used from the inferior surface of the liver.

The information obtained at IOUS is frequently valuable in assessing the liver and in planning resection. We have found that with modern high-quality preoperative imaging studies, more frequently than not, IOUS plays a confirmatory role in diagnosis rather than revealing features not suspected before laparotomy (Jarnagin et al, 2001b). This is particularly true in the noncirrhotic liver. High-quality laparoscopy and laparoscopic US are now available, and studies at MSKCC show that the findings at IOUS changed the operative plan in only a few patients; however, IOUS can help guide large segmental resections traversing narrow planes between the tumor edge and major vascular structures. Thus it is paramount that the surgeon have the ability to interpret IOUS in order to safely maneuver inside the liver.

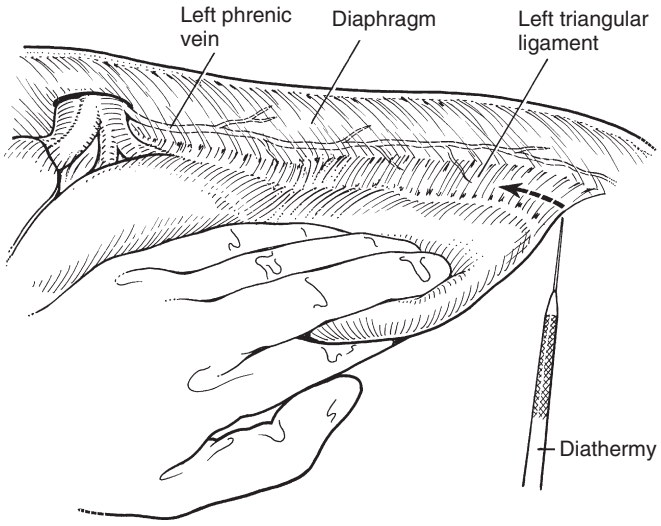


FIGURE 90B.16. The left triangular ligament is exposed and divided with cautery. Care should be taken not to injure the left phrenic vein.

MAJOR ANATOMIC HEPATIC RESECTIONS

All major hepatic resections mandate control of the inflow vasculature to the portion of liver to be resected, with preservation of adequate hepatic arterial and portal venous blood supply to the remnant. This may be done by dissection of the relevant portal pedicle at the hilus and outside the liver substance (Blumgart, 1982). Alternatively, the major branches may be secured within the liver by division of the liver tissue by finger fracture (Foster & Berman, 1977; Ton That Tung & Quang, 1963) or by crushing the liver substance with a Kelly clamp, as described by Ton That Tung (1979). More recently, Launois and Jamieson (1992a, 1992b) have advocated control of the intrahepatic pedicles if oncologically feasible; this is detailed in this chapter. In practice, most surgeons use a combination of techniques in hepatic resection (Fig. 90B.17). Biliary drainage from the remnant must be preserved without biliary leakage and without damage to the biliary tract. The hepatic venous outflow should be controlled after inflow division, and the liver parenchyma must be transected to provide tumor clearance in cases of malignancy.

Inflow Control and Preservation of the Integrity of the Biliary Tree

Control of the hepatic arterial and portal venous blood supply to the portion of liver to be removed can be obtained by extrahepatic dissection or alternatively by transecting the relevant

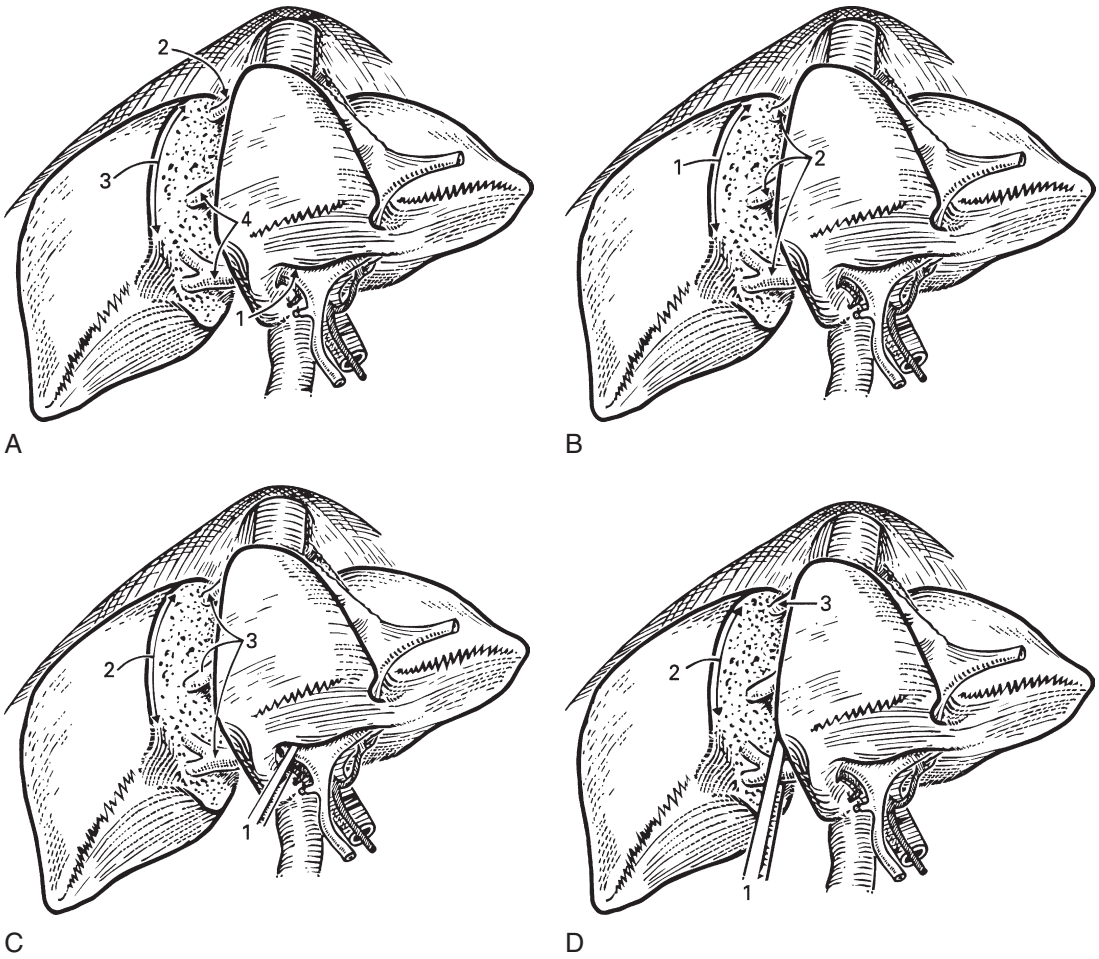


FIGURE 90B.17. Alternative steps in the performance of right hepatectomy. **A,** Initial division of the right portal triad (*1*) and of the right hepatic vein (*2*) and subsequent transection of the liver substance (*3*) with intrahepatic isolation of vessels (*4*). **B,** Initial parenchymal dissection (*1*) with intrahepatic control of the vessels (*2*). **C,** Initial dissection of the portal triad and clamp (*1*) followed by parenchymal transection (*2*) with intrahepatic control of the vessels (*3*). **D,** Intrahepatic control of the portal pedicles (*1*) followed by parenchymal transection (*2*) with subsequent intrahepatic control of the hepatic veins (*3*).

pedicles within the liver substance. Extrahepatic vascular dissection may be accompanied by extrahepatic dissection and control of the relevant biliary radicles, but this is associated with a higher risk of biliary injury, especially during dissection on the right side, where anatomic variations of the major right sectoral ducts at their junction with the main biliary channel are frequent (see Chapter 1). Thus, when performing extrahepatic dissection for vascular control of right-sided lesions, we typically divide the right hepatic artery and the right portal vein but leave the biliary structures for division within the pedicles at the time of parenchymal transection; however, extrahepatic biliary dissection must be performed for tumors that are close to the hilar structures, making an intrahepatic approach to the portal pedicles impossible without compromising tumor clearance. Extrahepatic dissection of the biliary system is, of course, mandatory in cases of hilar cholangiocarcinoma. For left-sided resections, although a pedicle approach is possible, we usually pursue dissection within or at the base of the umbilical fissure and well to the left of the hilar bifurcation. Since the work of Launois and Jamieson (1992b, 1993), we have used pedicular control.

Outflow Control

The major danger in controlling hepatic venous outflow is the risk of hemorrhage. Some authors prefer total vascular isolation techniques to overcome this problem, especially for large tumors abutting or involving the vena cava or major hepatic venous structures (Delva et al, 1989; Emond et al, 1995; Emre et al, 1993; Hannoun et al, 1993), but this is often unnecessary; for example, at MSKCC, total vascular isolation was not used in more than 1800 consecutive liver resections (Jarnagin et al, 2002).

Intrahepatic control of the hepatic veins, carried out during parenchymal transection, is feasible and acceptable for tumors that allow clearance superiorly with adequate tumor margins and with safe intrahepatic access to these vessels. Extrahepatic dissection and control of the major hepatic veins is possible in nearly all cases, and for the difficult tumor lying high and posteriorly, it enables adequate clearance together with reliable control of hemorrhage during right or left hepatectomy. Because the middle hepatic vein usually merges with the left hepatic vein prior to draining to the IVC, the middle and left hepatic veins

Table 90B.2

Comparison of Operative Indexes Between HVI and LCVP–Aided Hepatectomy

Reference	Technique	Total Patients	Major Resections*	Mean Blood Loss (mL)†	Median Blood Loss (mL)	Transfusion (U or mL)†
Delva et al, 1989	HVI	35	35	—	—	8 ± 8.3
Emre et al, 1993	HVI	16	13	18,660 ± 1683	1325	—
Hannoun et al, 1993	HVI	15	15	—	—	5.8 ± 4.7
Habib et al, 1994	HVI	56	33	1651 ± 1748	1200	930 ± 750
Cunningham et al, 1994	LCVP	100	69	1021 ± 964	1000	1.4 ± 2.1
Emond et al, 1995	HVI	48	44	1255 ± 1291	—	1.9 ± 2.6
Belghiti et al, 1996	HVI	24	24	1195 ± 1105	—	2.5 ± 3.4
Melendez et al, 1998‡	LCVP	496	357	849 ± 972	618	0.9 ± 1.8
Jarnagin et al, 2002	LCVP	1803	1027	—	600	4 ± 0.3§

*Major resections include all lobectomies and extended lobectomies.
†Values are reported as mean ± standard deviation.
‡Series included cirrhotic patients.
§Total transfusion of all blood products during hospital stay.
HVI, hepatic vascular isolation; LCVP, low central venous pressure

are often controlled as a single unit. If isolated left hepatic vein control is desired, a small hepatotomy is usually needed to dissect the plane between the two veins. Extrahepatic venous control necessitates two essential requisites that are applicable for all hepatic resections: 1) maintainence of CVP below 5 mm Hg (see earlier and in Chapter 22) and 2) precise extrahepatic dissection of the major hepatic veins. Dissection is performed with the patient in a 15-degree Trendelenburg position to minimize the risk of air embolism. Using this technique, no case of clinically significant air embolism has been encountered in 496 resected cases (Melendez et al, 1998). The techniques of vascular control described above are associated with an acceptable blood loss and a blood transfusion rate comparable with any series reported using total vascular isolation (Table 90B.2; Cunningham et al, 1994; Jones et al, 1998; Melendez et al, 1998). Furthermore, it avoids the need for fluid loading and for the use of pressor agents during periods of vascular isolation, and it prevents the adverse biochemical and hemodynamic effects that ensue when the clamps maintaining the vascular isolation are released.

Parenchymal Transection

Many surgeons place excessive importance on the technique of parenchymal transection, when in fact this aspect is not nearly as critical as proper exposure and vascular control, as outlined above. A number of methods may be used to transect the liver parenchyma. Our preference has been to use a simple crushing technique: the Glisson capsule is scored with diathermy along the line of proposed transection, and a Kelly clamp is used to crush the liver tissue and expose small vessels, biliary channels, and larger pedicles; once exposed, these structures can be secured and divided using a variety of techniques. The most simple and economic method is to use clips and suture ligation; however, a variety of devices can be used that include 1) computer-controlled bipolar cautery (LigaSure; Valleylab, Boulder, CO); 2) a saline-linked radiofrequency ablation monopolar device (TissueLink; TissueLink Medical, Dover, NH), or a bipolar variation (Aquamantys, TissueLink Medical); 3) a Harmonic Scalpel (SonoSurg; Olympus Key Med, New York, NY). All of these devices have been used with success by a variety of investigators (Clavien et al, 2004; Sakamoto et al, 2004; Strasberg et al, 2002). They also have been used successfully in the performance of laparoscopic partial hepatectomy, which will be discussed later. Larger structures can be controlled with sutures or vascular staplers (Fong & Blumgart, 1997).

The technique of using a Kelly clamp to crush the tissue is rapid and efficient, although the surgeon may choose to apply intermittent inflow occlusion (Pringle, 1908) to control blood flow to the remnant, usually maintaining inflow occlusion for periods of 15 minutes, interspersed by 5-minute periods of relief to allow perfusion of the remnant and decompression of the bowel. We rarely use prolonged periods of inflow occlusion, although this may done safely (Berney et al, 1998; Hannoun et al, 1993; Huguet et al, 1978, 1992a, 1992b), and we especially avoid prolonged occlusion during hepatic resection in patients with jaundice or cirrhosis. Prolonged portal inflow occlusion is unnecessary, and for major hepatic resections, complete parenchymal transection is usually accomplished in 20 to 30 minutes. During the short breaks between applications of the Pringle maneuver, the argon beam coagulator (Force GCU System; Valleylab) can be used to control small vessel oozing on the side of the remnant. Avitene (Davol, Warwick, RI), Surgicel (Ethicon, Somerville, NJ), or fibrin sealants also may be applied to the cut surface of the liver to achieve final hemostasis after transection is complete.

As a surrogate for the Kelly clamp to expose the intrahepatic vascular and biliary anatomy, an ultrasonic dissector may be used (Hodgson & DelGuercio, 1984) or a water-jet dissector (Baer et al, 1992b). The ultrasonic dissector (Hanna et al, 1996) has become popular and has some advantages in displaying vessels, particularly in the performance of segmental and subsegmental resections, and especially in the cirrhotic liver; but it is tedious and offers no apparent advantage in the performance of major resections. No published data are available to

indicate that the technique is associated with improved control of blood loss. The ultrasonic machine is expensive, and reliance on its use can leave the operator insecure when the instrument is not available. The new version of the water-jet dissector (Helix Hydro-Jet ERBE; USA Inc., Marietta, GA) is much more efficient than the original version, and it may be of considerable value in the exposure of major pedicles.

Some surgeons have described the use of coagulation devices, an example of which is the Habib 4X (AngioDynamics, Latham, NY). It uses radiofrequency energy to coagulate liver parenchyma indiscriminantly along the planned transection plane with or without with the use of vascular staplers; this is the primary mode of hepatic parenchymal transection, but it does not clearly expose the internal structures. We do not advocate such an approach and strongly believe that parenchymal transection should be a controlled dissection to avoid serious damage to the liver remnant.

Drainage of the Abdominal Cavity

Franco and colleagues (1989) suggested early on that hepatic resection should be performed without drainage. After performing a controlled clinical trial (Fong et al, 1996), the authors no longer use drainage routinely after major hepatic resection, unless there is ongoing biliary leakage from the cut liver surface that cannot be controlled with sutures. The placement of drains is associated with a prolonged hospital stay, an increased possibility of infection, and in our experience no decrease in the need for postoperative drainage catheters placed using interventional radiology; however, exceptions do exist, and sometimes a postoperative drain may need to be utilized. In our experience with simultaneous liver and colorectal resections, we have empirically noticed an increased incidence of infected fluid collections in the liver resection bed colonized with colonic flora. Thus for simultaneous resections, we now tend to leave a drain near the liver resection bed. In patients with cirrhosis who undergo resection, placement of a drain must be considered carefully, given the risk of significant ascites formation. Although a drain may protect the incision by preventing an ascitic leak and allowing the fascial closure to heal, the drain may become the source of protracted fluid loss with no clear end point of removal. Finally, we advocate drainage in patients undergoing resection, accompanied by biliary reconstruction. When drainage catheters are utilized, we maintain them on gravity-bag dependent drainage, as the amount of negative pressure generated by closed-suction drains is grossly underestimated (Fig. 90B.18; Grobmyer et al, 2002). For patients who undergo biliary reconstruction, the drain is removed usually within 4 to 5 days provided no bile leakage is evident.

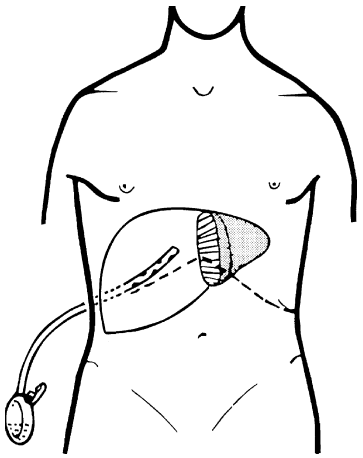


FIGURE 90B.18. Drainage of the right subdiaphragmatic space with simple large-bore drains connected to a closed system or to a suction apparatus. Our preference is abdominal closure without routine drainage.

Right Hepatectomy

Inflow and Biliary Control

The liver is elevated to display its inferior surface and the portal structures. We generally lower the hilar plate to expose the left hepatic duct and the confluence of the bile ducts (see Chapter 1B). Division of the peritoneal reflection along the free edge of the lesser omentum exposes the lateral side of the portal vein and the common bile duct. The peritoneum overlying the common bile duct is incised on the free edge of the lesser omentum and extending up into Calot's triangle, and the cystic duct and the cystic artery are exposed, ligated, and divided (Fig. 90B.19). The gallbladder can also be dissected in the anterograde fundus-down technique to expose the cystic duct and artery (see Chapter 33). The cystic duct is affixed with a suture ligature before being divided, and a tie is left on the cystic duct for later retraction.

Some surgeons now proceed to extrahepatic dissection of the right hepatic duct. We do not advocate this approach unless it is mandated for tumor clearance. Instead, we proceed to dissection of the right hepatic artery and portal vein and usually leave division of the right hepatic duct until later in the operation, during parenchymal transection.

The right hepatic artery is dissected, ligated, and divided (Fig. 90B.20). It originates from the main hepatic arterial trunk and passes posterior to the common bile duct in approximately 80% of patients (see Chapter 1B). It is usually ligated to the right of the common hepatic duct to protect the left hepatic artery from inadvertent ligation or injury and to facilitate access to the underlying portal vein. It is important to be certain that the left hepatic artery is preserved by palpation at the umbilical fissure after temporary occlusion of the right hepatic artery. Although the right hepatic artery can be ligated medial to the bile duct, we prefer to ligate it to the right of the common hepatic duct. We deliberately double-suture–ligate the proximal end and hold this after division for light traction to the left, which together with traction of the cystic duct stump is of considerable benefit in exposing the right portal vein.

The portal vein is approached laterally and posteriorly and is best exposed by dividing its peritoneal covering. The main portal trunk is exposed and dissected superiorly, until the left branch is revealed and preserved. Sometimes, the right anterior and posterior sectoral branches of the portal vein arise individually, and these origins may be separated by 2 cm (see Fig. 90B.20E). It is important not to misidentify these branches during dissection. The right branch of the portal vein may be delivered from the hilus by dividing the surrounding areolar tissue, and a good length amenable for division can usually be obtained. A renal pedicle clamp is passed gently around the right portal vein under direct vision, with special care taken not to damage the first posterior branch of the right portal vein,

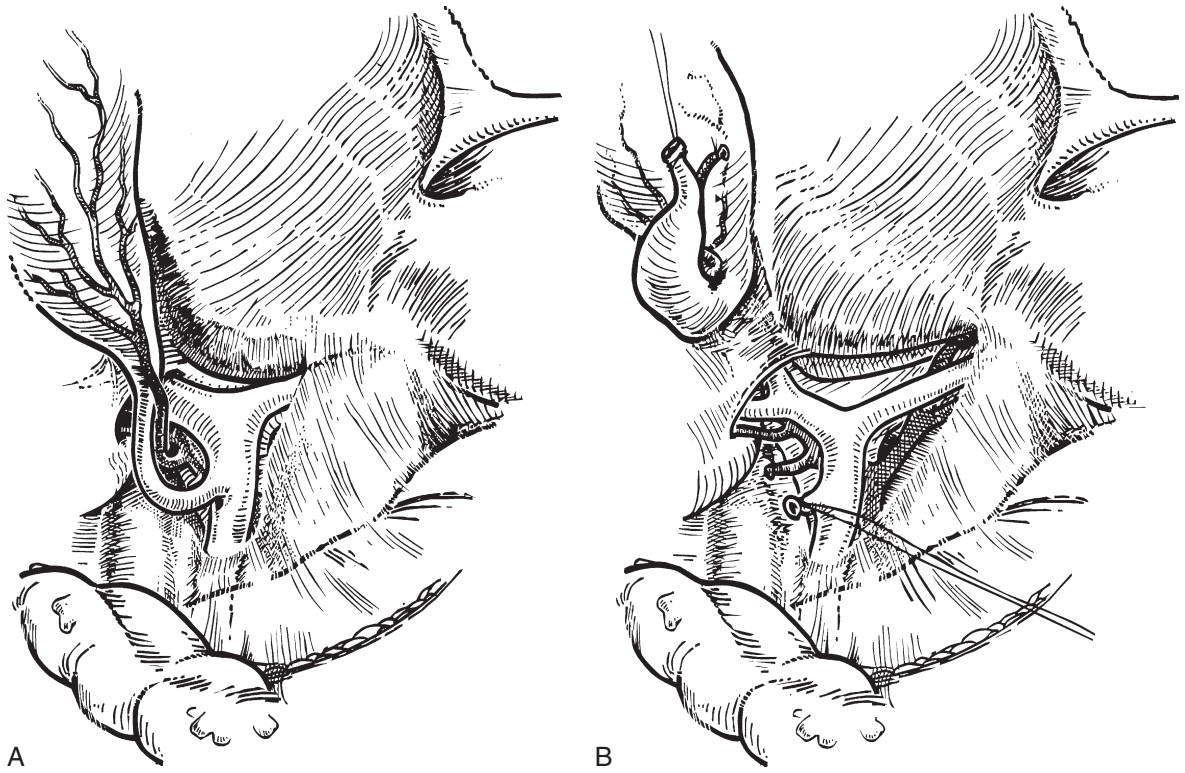


FIGURE 90B.19. A, The peritoneum overlying the common bile duct is incised on the free edge of the lesser omentum and extending up into Calot's triangle, and the common bile duct, common hepatic duct, and Calot's triangle are exposed. **B,** The cystic duct and cystic artery are secured, and a tie is left on the cystic duct for later retraction (see also Fig. 90B.20). The hilar plate is lowered to expose the left hepatic duct and the confluence of the bile ducts, and the right hepatic duct is dissected.

which comes off early and posteroinferiorly to supply the right portion of the caudate lobe. This branch should be deliberately identified to prevent inadvertent avulsion. If any difficulty is encountered in encircling the right portal vein, this branch should be individually ligated and divided before any instrument is passed around the right portal trunk.

Application of a straight-bladed vascular clamp is a safe method of transecting the right portal vein (see Fig. 90B.20). It is good practice to place two retaining prolene sutures to secure the vein before dividing it to prevent retraction. These sutures should be left with the needle in place and are used to oversew the stump after the vein has been divided (see Fig. 90B.20). If the vein is short, it is inadvisable to simply suture ligate the right portal vein and transect it, because the ligatures have a tendency to slip unless secured. The proximal stump should be doubly ligated. Another option to divide the portal vein, used with increasing frequency, is an Endo GIA (Covidien, Mansfield, MA) gastrointestinal anastamosis endovascular stapler (Fong & Blumgart, 1997). If the right anterior and posterior sectoral branches arise independently (see Fig. 90B.20E), they require individual control. If stapler transection of the right portal vein trunk or the anterior and posterior sectoral branches is contemplated, it is imperative to avoid compromise of the flow through the left vein.

If extrahepatic control of the right hepatic duct is necessary, the duct is now dissected. The confluence of the bile ducts and the origin of the extrahepatic course of the left hepatic duct should be seen clearly after lowering the hilar plate (see Fig. 90B.19B). Occasionally, and particularly if segment IV is large, it may help to divide the liver tissue that occupies the lower limits of the umbilical fissure and bridges the gap between the quadrate lobe (segment IV) and segment III of the left liver. This maneuver opens the umbilical fissure and allows better exposure of the subhepatic space.

When the right hepatic duct is dissected, it should be affixed, ligated, and divided (see Fig. 90B.20). Absorbable suture material should be used to prevent permanent suture acting as a nidus for future stone formation or infection. It may be that difficulty is encountered in passing a ligature around the right hepatic duct, in which case it may be divided under direct vision and subsequently oversewn with a 4-0 absorbable suture (e.g., polydioxanone suture [PDS]) on an atraumatic needle. Alternatively, an Endo GIA stapler can be used to divide and ligate the bile duct.

In many instances, the ducts draining the right anterior and posterior sectors are found entering the confluence separately, or the posterior sectoral duct may join the left hepatic duct (see Chapter 1B). In such cases, both of these major sectoral ducts should be individually identified and secured. It may be difficult to obtain a clear view of the right hepatic duct for dissection and ligation, in which case these structures are best left intact and divided intrahepatically. The duct or its major sectoral tributaries may be secured in the pedicles further laterally at the time of parenchymal dissection. We usually use this approach, because it is safe and obviates precise dissection of the ducts extrahepatically. Deliberate dissection of the hepatic duct must be carried out for tumors that approach the hilus of the liver and engulf the pedicles down to the point of entry of the portal triads into the liver substance.

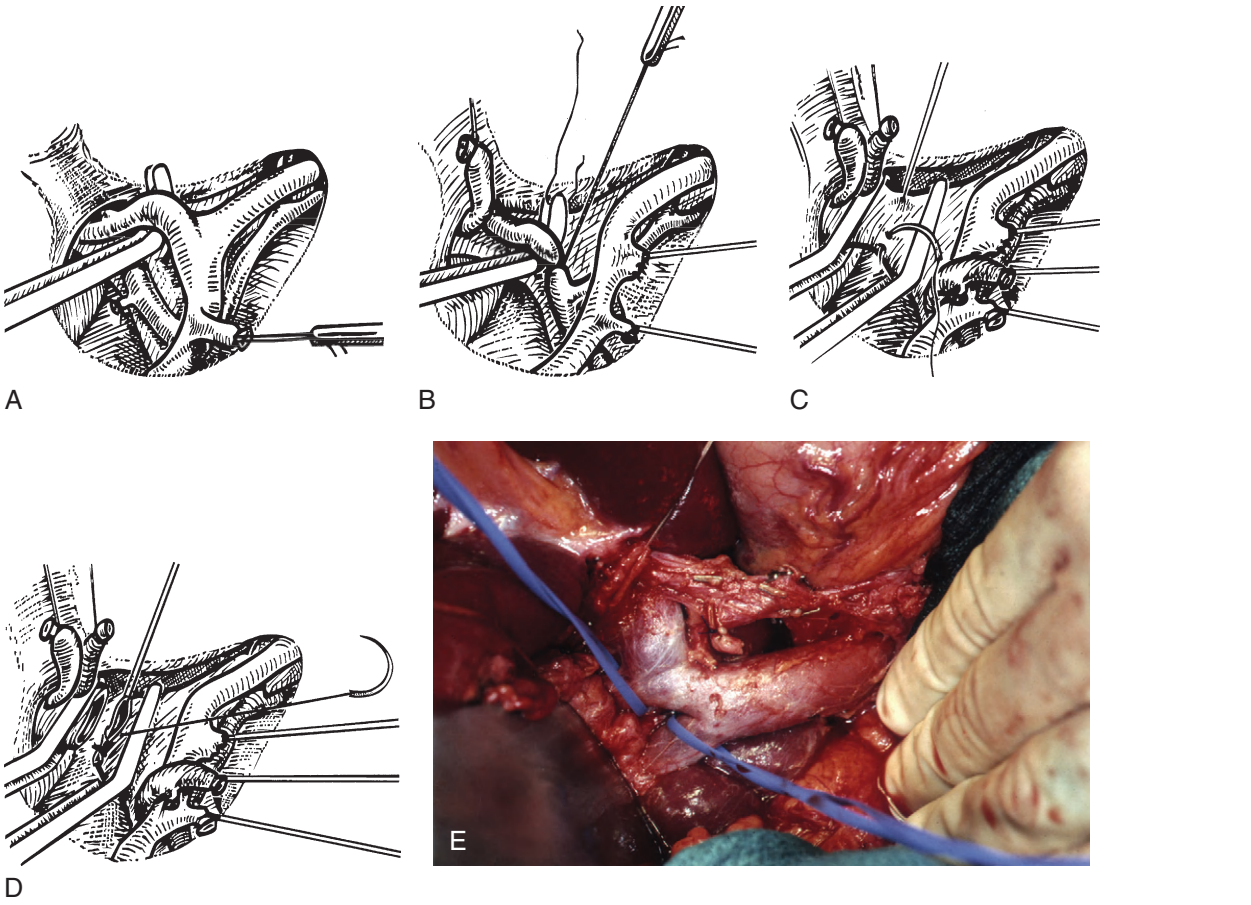


FIGURE 90B.20. **A,** The right hepatic duct is dissected (now, more often than not, we leave the right hepatic duct for intrahepatic control during parenchymal transection). The confluence of the hepatic ducts and the origin of the left hepatic duct are shown. **B,** The right hepatic duct has been affixed with absorbable suture material, divided, and ligated or oversewn. Alternatively, it may simply be divided under direct vision and then oversewn. In any event, the suture is held and retracted toward the left. Traction on the sutures attached to the cystic duct and the right hepatic duct stump allows retraction of the common hepatic duct and common bile duct to the left and assists display of the vessels beneath. The right hepatic artery is dissected, ligated, and divided, usually to the right (*as shown*) but sometimes to the left of the common hepatic duct. **C,** The right portal vein (PV) is dissected, and forceps are gently passed beneath it. Special care is taken not to damage the first branch of the right PV, which comes off early and posteroinferiorly. This branch is sought initially and ligated and divided or avoided. Straight-bladed vascular clamps are applied to the right PV. Note the retaining sutures that secure the vein before division. **D,** The vein is divided, and its proximal stump is oversewn using a vascular suture. The distal stump is affixed with 3-0 polyglactin 910 (Vicryl) suture and ligated. Light traction on the cystic duct, right hepatic duct stump, and right hepatic artery assists display. **E,** Photograph illustrates dissection of the PV and its branches, seen from the patient's right. The main PV gives rise to the anterior and posterior sectoral branches independently; both of these are surrounded by blue vessel loops. The left PV and the anterior right sectoral vein arise at the same point. It is important to recognize this variant anatomy and to identify all branches during dissection.

Pedicle Ligation

An important alternative to extrahepatic dissection of the hilar structures is the pedicle ligation technique that uses the intrahepatic approach first described in Japan by Takasaki and colleagues (1986a, 1986b) and then in the West by Launois (1994) and Launois and Jamieson (1992b, 1993). This approach is most useful for right-sided tumors located peripherally away from the hilus, which allows its use without compromising tumor clearance. This technique allows the surgeon to dissect and clamp the required sheaths early in the operation to better define the segment or segments to be removed.

Essentially, the method relies on intrahepatic definition and control of the portal triads to the segments to be removed. The structures of the portal triad carry the Glisson capsule with them, as they penetrate the liver and are contained in a well-formed sheath within the parenchyma (Fig. 90B.21). The

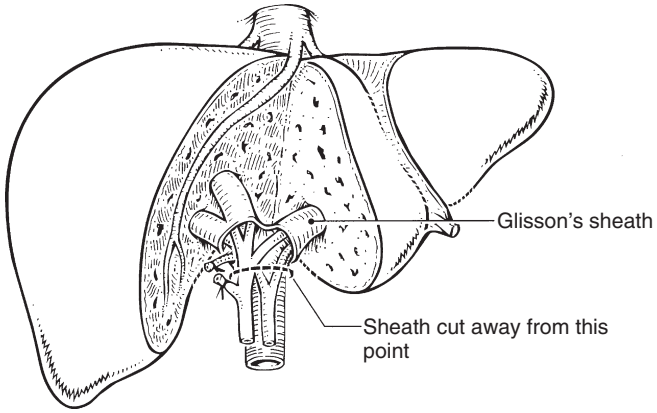


FIGURE 90B.21. Detailed view of the anatomy of the left and right portal pedicles at the hilus.

pedicular sheaths can be exposed after appropriate hepatotomies (Fig. 90B.22) and are tough enough to be encircled (Fig. 90B.23), dissected, and clamped. By eliminating the hilar dissection, pedicle ligation saves time and prevents potential injury to the contralateral vessels and bile ducts.

We have found it important first to ligate the most caudal retrohepatic veins draining from the caudate process and inferior part of the liver to the vena cava (see Fig. 90B.22A). Failure to do this has resulted in hemorrhage during passage of a finger or dissector (Fig. 90B.24) around the right portal pedicle, and this preliminary move is essential prior to using the right pedicle approach. Other than this cautionary note, the technique is almost identical to that described by Launois (described later). Care must be taken to respect the anatomy of the pedicles, in particular the pedicle to the right posterior sector (see Figs. 90B.23 and 90B.24). When the right pedicle has been exposed (see Fig. 90B.22B and E), and a trial of clamping reveals the demarcation line along the principal plane, the pedicle can be divided. A second confirmatory test prior to dividing the pedicle can be rapidly performed with real-time US to demonstrate flow with color Doppler in the left portal vein. We usually use a vascular stapling device to divide the pedicle (see Fig. 90B.22D and F; Fong & Blumgart, 1997). This method also can be used to control the left sheath, but we prefer to dissect the structures within the umbilical fissure, which will be discussed later.

Exposure and Control of the Right Hepatic Vein

The right hepatic vein may be controlled from within the liver during hepatic parenchymal transection, or it may alternatively be isolated and divided extrahepatically before proceeding with division of the liver tissue. Extrahepatic control of the right hepatic vein is important for large tumors lying posteriorly in segments VII and VIII adjacent to the vena cava, because it is difficult to obtain adequate tumor clearance during parenchymal dissection while avoiding potential major hemorrhage arising from accidental laceration to the vein.

To control the right hepatic vein, the liver is turned to the left, and the retrohepatic veins draining directly into the IVC are ligated. Some surgeons pass umbilical tapes around the vena cava above and below the liver, but this is not mandatory, and we usually omit this step in routine cases. If the surgeon chooses to do so, an umbilical tape can be passed rather easily below the liver, between the inferior surface of the liver and the right renal vein. To control the suprahepatic cava, the left triangular and coronary ligaments must be divided, and subdiaphragmatic dissection of the IVC enables passage of an umbilical tape. If difficulty is encountered in gaining control of the suprahepatic IVC below the diaphragm, as is sometimes the case with large tumors, the surgeon should not hesitate to extend the incision to the right chest or vertically, as a sternotomy. The need for such a maneuver should be anticipated based on preoperative imaging. It is dangerous to persist through an abdominal incision in an attempt to mobilize a rigid right lobe of a liver containing a large tumor, because the right hepatic vein may tear posteriorly. When the chest is open, the vena cava may be approached more easily. Through a median sternotomy, the pericardium can be opened, and the IVC can be controlled within the pericardial sac; however, this incision is usually unnecessary, and in most cases, the IVC and the right hepatic vein can be dissected through an abdominal incision alone. Mobilization and control of the right hepatic vein is often performed prior to inflow occlusion. Then, once the right portal vein and artery are ligated, the right hepatic vein can be divided as well. It is ill advised to divide the right hepatic vein prior to inflow occlusion, as this may result in venous congestion.

When dissecting the vena cava and the hepatic veins, it is important to maintain the CVP below 5 mm Hg to avoid inadvertent injury and substantial hemorrhage. To prevent air embolism, the patient can be placed in a 15-degree Trendelenburg position (Cunningham et al, 1994). The right hepatic vein is approached starting from the inferior aspect of the liver and working upward from the point where the caudate process crosses the IVC. The retrohepatic veins are sequentially dissected, controlled, and divided. This may be done with fine ligatures passed around the vessels with an aneurysm needle (Fig. 90B.25), but this can be tedious; for smaller vessels, we apply two clips on the vena cava side and one on the liver side of each vessel. These small veins can sometimes also be controlled with a coagulating device, such as a Harmonic Scalpel or the LigaSure device (Valleylab) when appropriate. Larger veins, and especially an inferior right hepatic vein, can be controlled by formal division between clamps or with an Endo GIA vascular stapler.

Complete posterolateral exposure of the right hepatic vein requires division of the IVC ligament, which obscures to a variable extent the right side of the upper part of the retrohepatic vena cava. This dissection may have been done at an earlier stage in the operation, but if not, it should be completed at this stage by the techniques described previously (see Fig. 90B.15). We often divide this caval ligament with an Endo GIA vascular stapler. It is important to perform an extensive retrohepatic dissection and to secure all the short hepatic veins draining from the posterior aspect of the liver; this dissection should be carried well over to the left of the IVC, because this is the only way sufficient access is obtained to visualize and dissect the main right hepatic vein safely.

Before any attempt is made to pass an instrument around the right hepatic vein, full exposure of the vein should be obtained superiorly. This exposure is achieved by dissecting the filamentous fibrous tissue above the liver and anterior to the suprahepatic IVC. This dissection may also have been done as a preliminary procedure during exposure and mobilization of the liver at an early stage (see Fig. 90B.14). In fact, it is advised to have the right hepatic vein in view prior to dividing the lateral attachments to the liver in order to prevent injury to the vein during lateral mobilization. The right phrenic vein emptying into the right hepatic vein provides a nice landmark for its location. This dissection must be performed right against the exposed liver substance, as it is ineffective and dangerous to wander away from the liver surface.

After the right hepatic vein is exposed and encircled, several methods may be used to safely divide it. Traditionally, a vascular clamp is applied on the caval side, usually with space for the application of a second clamp on the caval side and a third on the hepatic side, although this may not always be possible (Fig. 90B.26A). If it is not possible to place a clamp on the hepatic side, division of the vessel does not result in great hemorrhage, provided inflow control has been obtained previously. In any event, the vessel is now divided with a scalpel (see Fig. 90B.26B). One clamp is removed, and the exposed stump is closed with an over-and-over 3-0 polypropylene vascular suture (see Fig. 90B.26C). The proximal (hepatic) side of the right hepatic vein is now closed with a 3-0 polypropylene suture. Alternatively, in well over 1000 cases, we have used the Endo GIA vascular

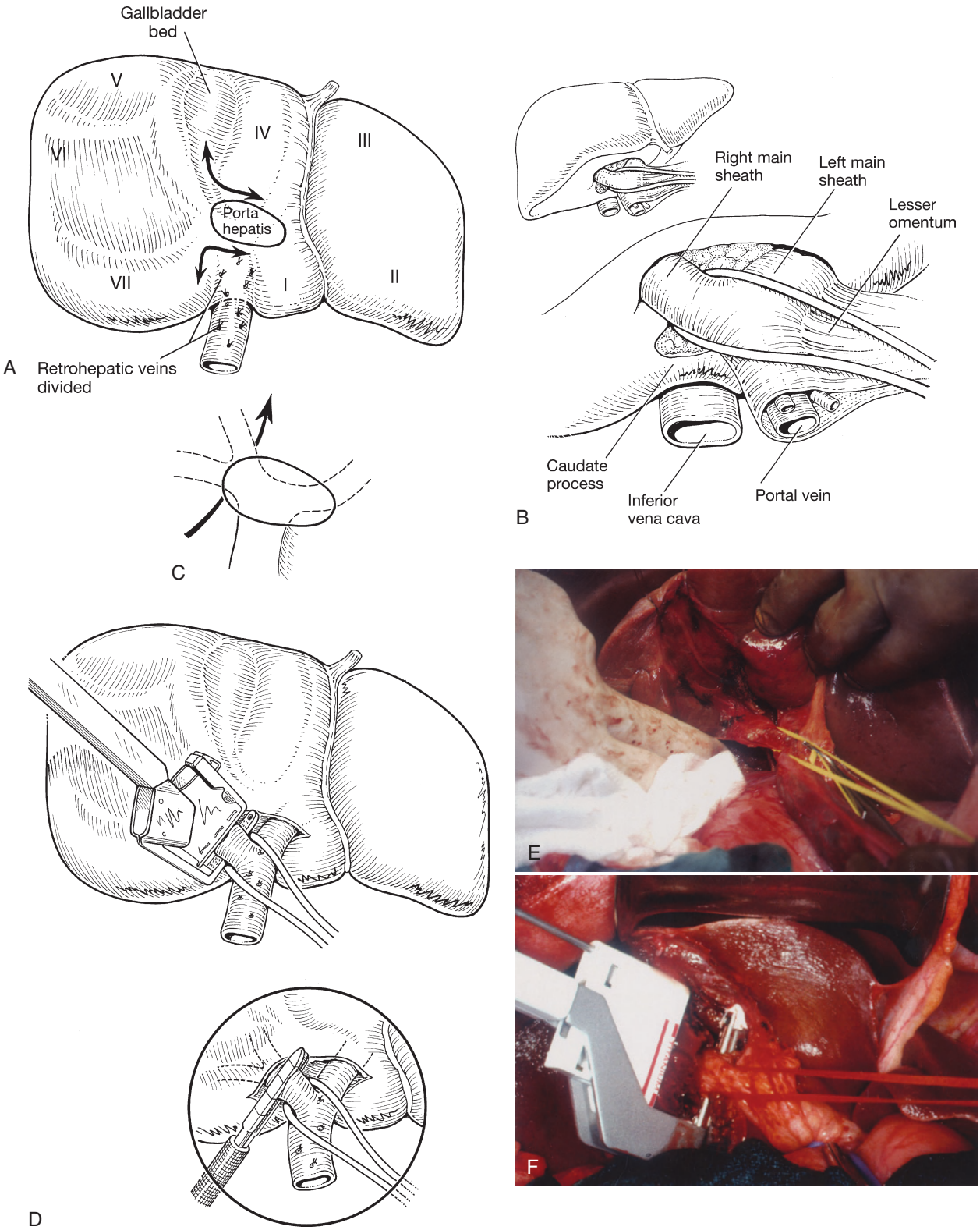
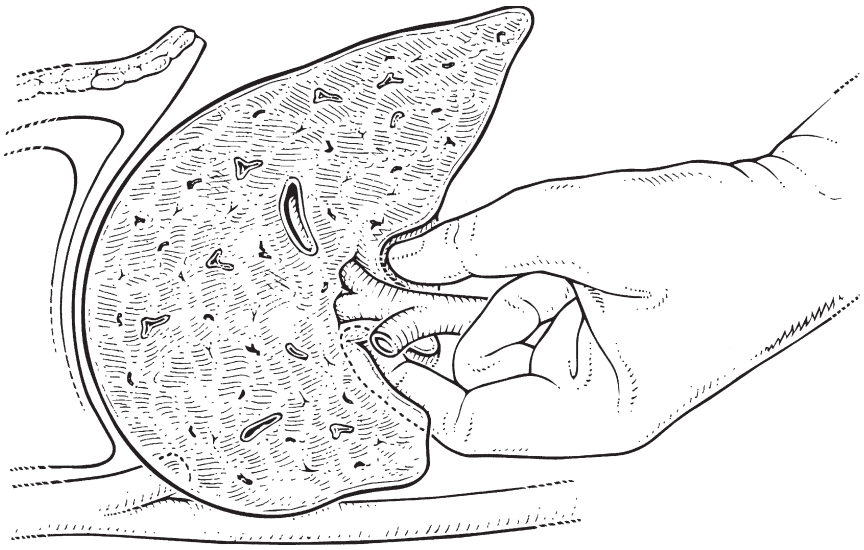
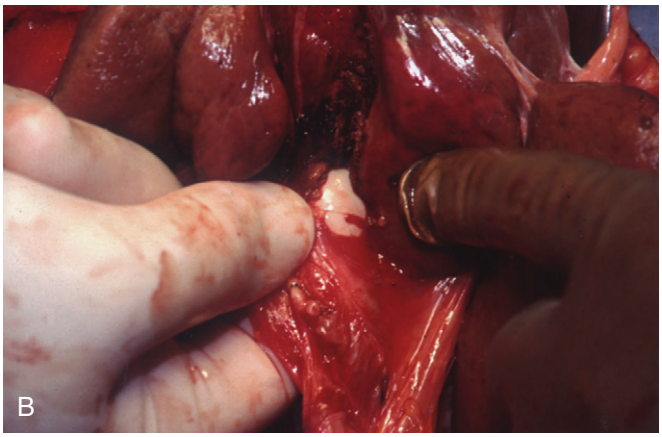


FIGURE 90B.22. **A,** Approach to the right portal pedicle. The liver has been mobilized from the inferior vena cava by division of the retrohepatic veins lying behind the caudate process. Hepatotomies have been made in the region of the gallbladder fossa and the caudate process. The curved double-headed arrows indicate the sites of the hepatotomies above and below the porta hepatis. The approach in the caudate process is essentially a posterior approach. **B,** A vessel loop is drawn about the right pedicle and pulled to the left to protect the left pedicular structures during control and transection of the right main sheath. **C,** The *curved arrow* indicates the path of the finger (see also Fig. 90B.23) or instrument during dissection of the right pedicle, allowing its isolation. **D,** The right portal pedicle is controlled and subsequently divided with a vascular stapler, such as the Endo GIA (*inset*). **E,** Intraoperative photograph shows the right portal pedicle exposed by finger dissection and surrounded by a yellow vessel loop, which is drawn to the patient's left (see also **B** above). The vessel loop is drawn firmly to the left, and the pedicle is divided using the stapler, as shown in **D. F,** Operative photograph shows division of the right portal vein pedicle, which is encircled by a red vessel loop pulled to the left. The vascular stapler is being used to divide the pedicle as illustrated in **D.**



A



B

FIGURE 90B.23. A, Illustration shows digital isolation of the right pedicle. **B,** Photograph illustrates insertion of the index finger through a hepatotomy in the caudate lobe, where it merges with the base of the gallbladder fossa to isolate the right portal pedicle. A vessel loop is drawn about the pedicle as shown in Figure 90B.22F.

stapler to divide the right hepatic vein and have rarely encountered any problems (Fig. 90B.27). The major concern is for misfiring of the stapler, which can result in a tear of the vein; however, this is an extremely uncommon event. The stapled approach is quick, effective, and safe (Fong & Blumgart, 1997), and we now use it routinely, except for large tumors located where the right hepatic vein drains into the IVC; by their size and rigidity, such tumors often limit the entry of the stapler into the tunnel to the left of the right hepatic vein and anterior to the IVC. Extrahepatic control of the middle hepatic vein is unnecessary during right hepatectomy. An important alternative approach to the right hepatic vein involves exposure by

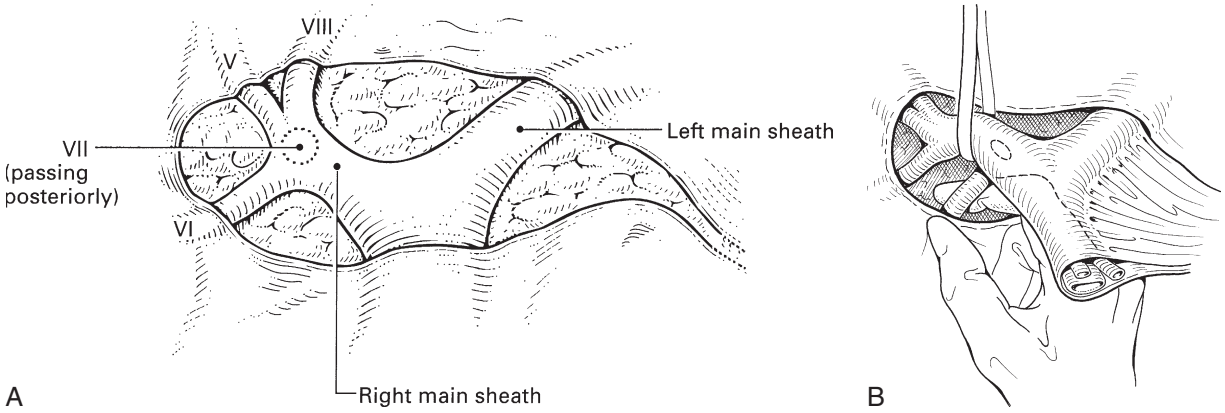


FIGURE 90B.24. A, Anatomy of the pedicles. The anterior sectoral pedicles to segments V and VIII pass upward. The posterior sectoral pedicles to segments VI and VII run posterolaterally. **B,** This illustration shows the approach to the right posterior pedicle (right lateral pedicle).

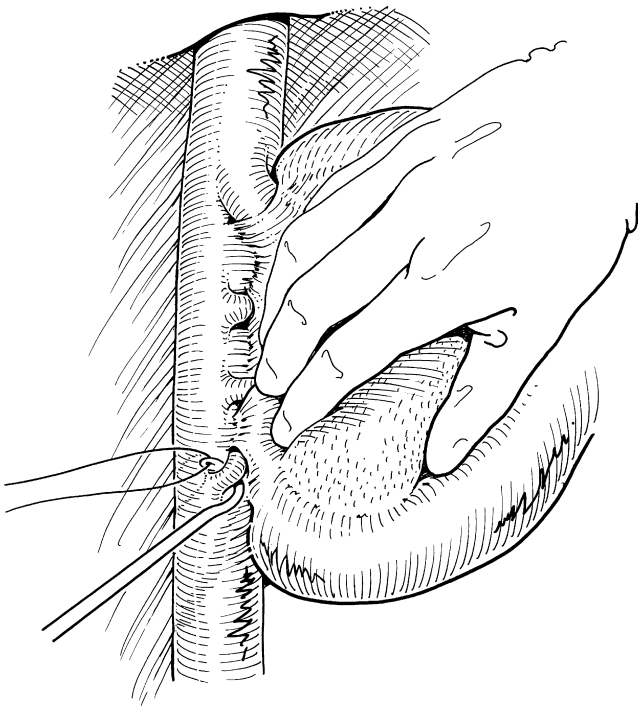


FIGURE 90B.25. Short hepatic veins issuing from the caudate lobe and the right liver are secured individually using aneurysm needles to pass fine sutures about the vessels, which are tied and cut. Alternatively, these vessels are clipped and divided. This procedure is carried upward beneath the liver until the right lobe is mobilized, and the vena cava is displayed up to the right hepatic vein. This is necessary for subsequent safe dissection of the right hepatic vein.

preliminary transection of the parenchyma down to the anterior surface of the IVC (Lai EC et al, 1996b). This so-called anterior approach is described later in this chapter.

Parenchymal Transection

Liver tissue is divided by a tissue-fracture technique, as described earlier. A Pringle maneuver is performed as needed, and the liver tissue is crushed in the line of transection, using a Kelly clamp or similar instrument (Fig. 90B.28) and leaving the vessels intact. During this process, inflow occlusion can be obtained by encircling and compressing the hilar structures in a vessel loop or umbilical tape. It may be helpful for the first assistant to compress the left liver with the hand and to pull it downward gently. Traction can also be applied by placing chromic sutures through the edge of the liver parenchyma on each side of the transection plane. Suction is applied at the blunt end of the sucker, which is used to tease the tissues away from the vessels (see Fig. 90B.28).

Large vessels may be isolated easily by crushing the tissue between the finger and thumb. When visualized, smaller vessels and bile ducts are ligated with metal clips, ties, or a coagulation energy device and divided. Large vessels may be suture ligated or controlled with an Endo GIA vascular stapler. As the tissue is divided, the fissure that is developed in the liver is opened by the operator, whose nondominant hand holds the right liver. With fingers located posteriorly in the region of the vena cava, that hand elevates the right lobe, opening the wound in the liver to expose its depth. As dissection proceeds, the middle hepatic vein is displaced to the left, and the dissection proceeds along its right margin. The branches from segments V and VIII are

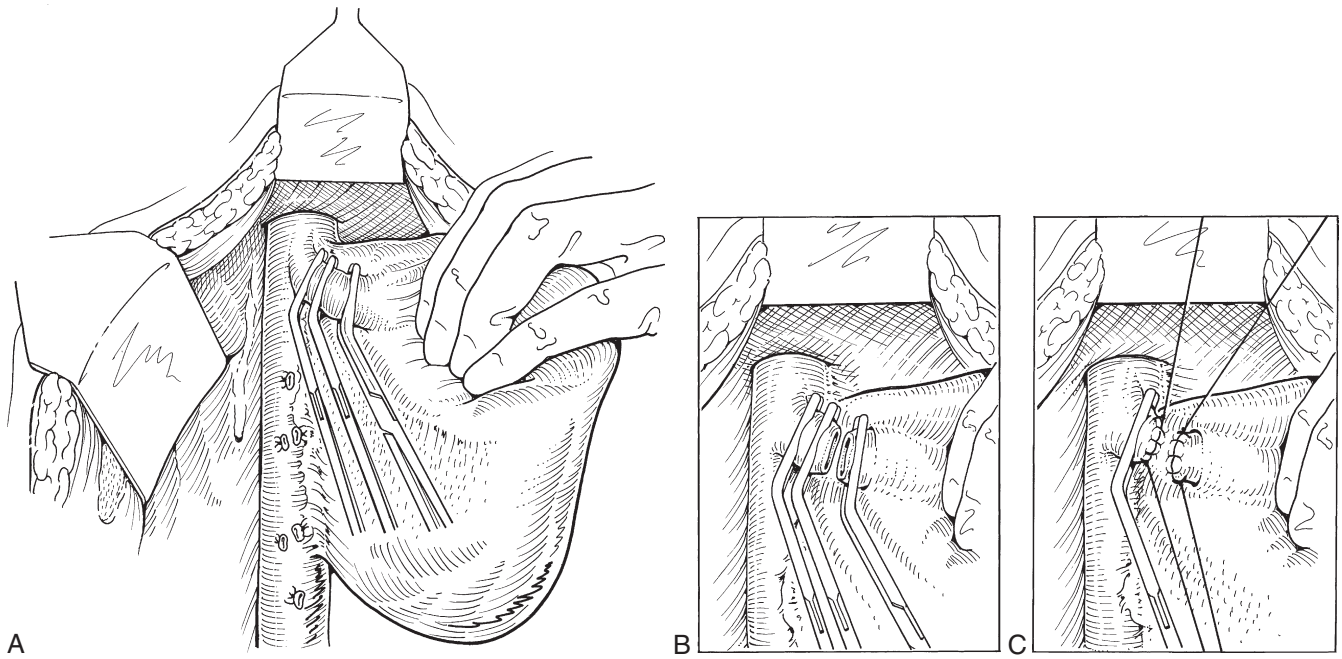


FIGURE 90B.26. A, Approach to the right hepatic vein. The right liver has been extensively mobilized, and the inferior vena cava is exposed up to the right hepatic vein. The right hepatic vein is dissected, and a vascular clamp is applied on the caval side. Another clamp is placed on the hepatic side, although this is not essential, because if the vein is divided after the portal triad at the hilus, bleeding from the exposed venous orifice can be readily controlled with a suture after division of the vein. A second clamp should be applied on the caval side before division of the vein, but if there is no space for this, a second clamp is applied immediately after the vein is divided. **B,** The right hepatic vein has been divided. **C,** The stump is closed with an over-and-over 3-0 vascular suture.

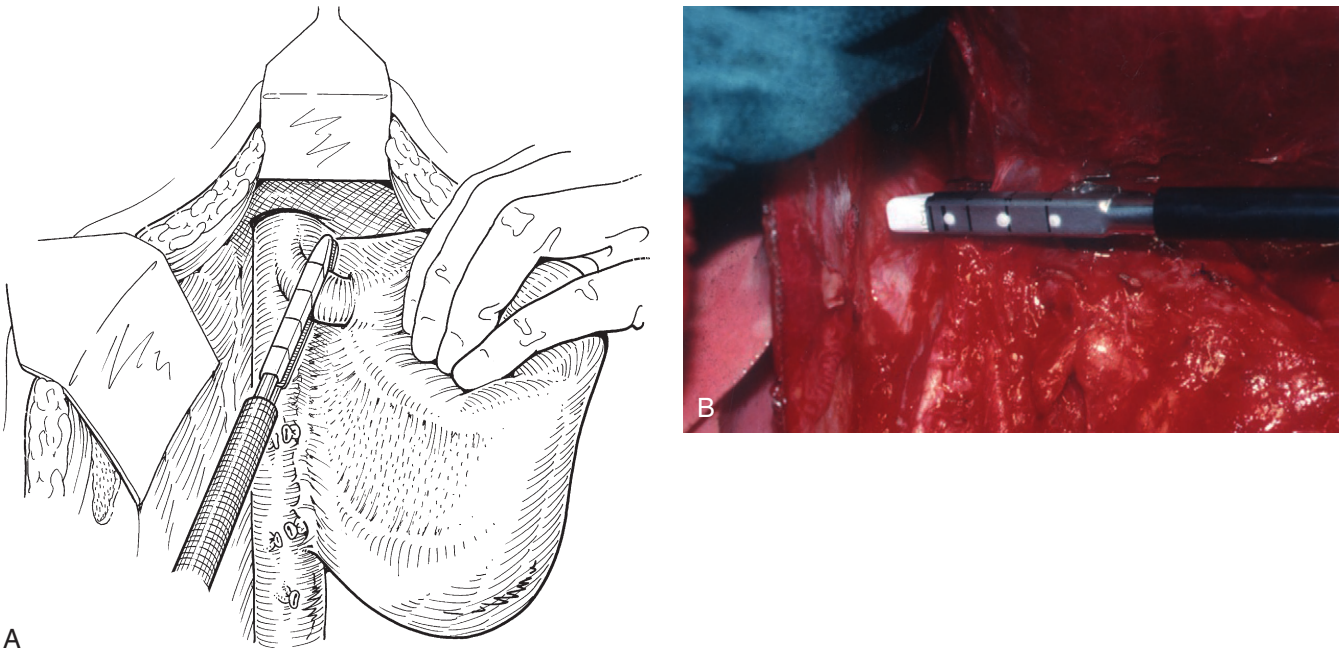


FIGURE 90B.27. A, The right hepatic vein also can be divided using the Endo GIA vascular stapler. This method is rapid and safe. **B,** Intraoperative image shows division of the right hepatic vein with the Endo GIA.

controlled. If the right sectoral bile ducts have not previously been divided extrahepatically, they are now controlled during division of the portal triads, whereupon the right portal triad is encountered and divided close to the hilus. If the right hepatic vein has not been secured behind the liver, it is now isolated and ligated or divided with the stapler within the liver (Fig. 90B.29).

Once the specimen is removed, final hemostasis is obtained by a variety of techniques. Suturing of large vessels is most appropriate; fibrinogen sealants (Guthy, 1986; Scheele, 1989) may be used for small vessels, but the argon beam coagulator is effective and is associated with very little tissue necrosis (Postema et al, 1993). In a few cases, if oozing should continue, and particularly if it seems to be coming from divided veins, the passage of large sutures (chromic catgut or vicryl) anteroposteriorly in a mattress fashion secures hemostasis. These sutures should not be so tight or so numerous as to cause tissue ischemia (Fig. 90B.30). It should be noted that the majority of bleeding at this stage of the operation is low-pressure venous oozing, which can often be controlled with manual pressure and time. Any bleeding from the exposed undersurface of the diaphragm must be carefully controlled; in this respect, the argon beam coagulator can be of great value.

Wound Closure and Drainage

If a diaphragmatic incision has been made, it is closed, and if any defects have been created in the diaphragm, these are similarly sutured. An attempt should be made to remove the pleural air via negative suction applied from the abdomen to obviate

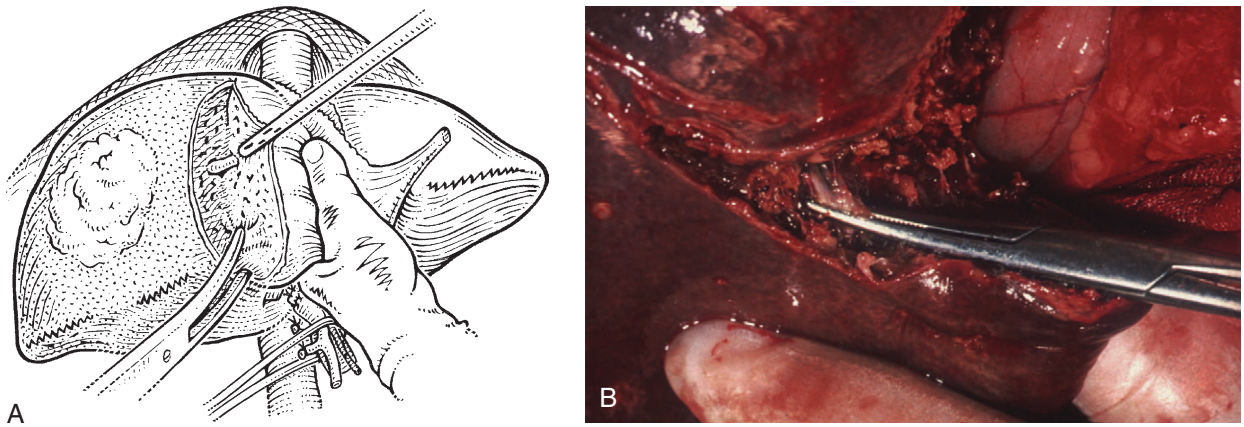


FIGURE 90B.28. A, Parenchymatous transection of liver tissue by a fracture or crushing technique using a clamp. The portal triad to the right liver has been divided, and a line of demarcation has developed. The liver tissue is opened in this line. The assistant's nondominant hand compresses the left liver close to the transection line. The operator opens the liver tissue, and a combination of crushing the liver between clamps, finger fracture, and strong suction exposes the vessels for ligation. The parenchymal transection is done with a vessel loop occluding the hilar vessels (Pringle maneuver). **B,** Intraoperative photograph shows the crushing of the parenchyma with exposure of vessels using a Kelly clamp.

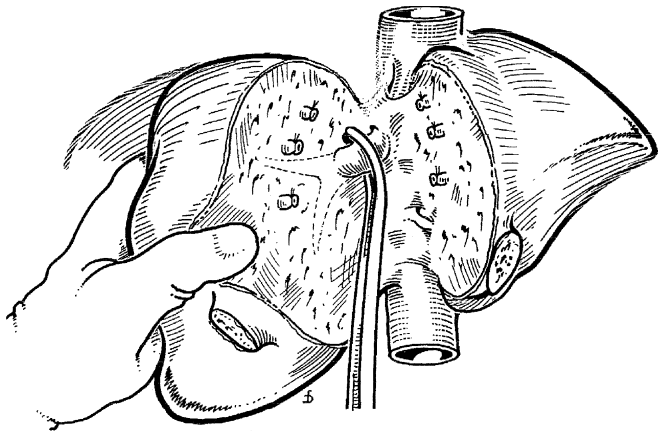


FIGURE 90B.29. Division of the liver tissue has progressed. The fingers of the operator's nondominant hand are located posteriorly, elevating the right lobe and opening the wound in the liver. At this stage, major hepatic veins are identified and secured within the liver substance. This is an alternative to extrahepatic isolation of the right hepatic vein.

the need for a chest tube. There is no need to attempt to close the exposed raw area of the liver with peritoneal flaps, because these could cause compression of liver tissue and distortion of hilar vessels. The ligamentum teres should not be used for this purpose, and similarly, omental grafts are usually unnecessary, although any convenient omentum may be laid against the raw surface. We do not drain the subdiaphragmatic space after routine liver resection, as discussed earlier; however, drainage of the subdiaphragmatic space is carried out with one or two drains if needed (see Fig. 90B.18). A chest drain may be needed in cases of diaphragm resection.

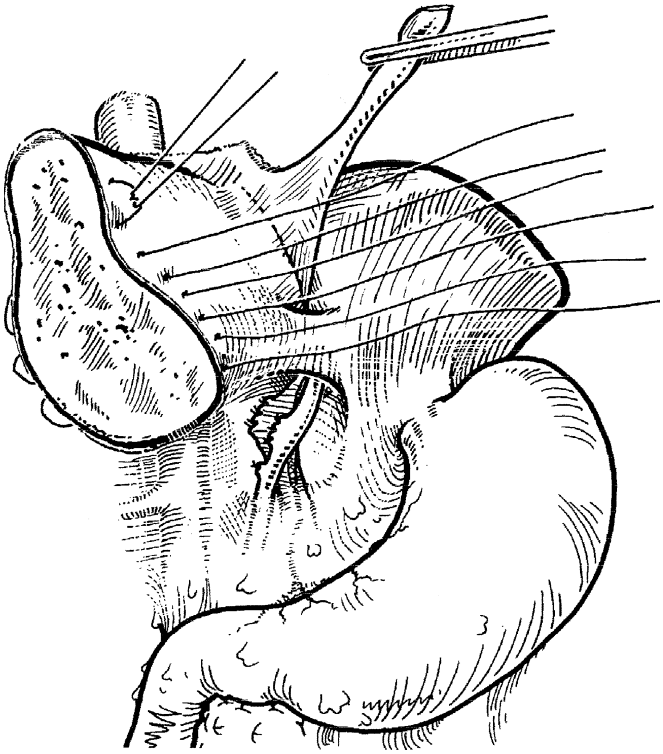


FIGURE 90B.30. Method of suture of the cut surface of the liver to achieve hemostasis. This technique is seldom necessary.

Anterior Approach to Right Hepatectomy

Hanging Maneuver

When performing a right hepatectomy, complete mobilization of the liver before parenchymal transection is considered a basic maneuver for conducting a safe procedure. When a large tumor invades the diaphragm or is attached to the lateral side of the vena cava at a higher level, mobilization may be difficult. In such cases, Lai and colleagues (1996b) reported an anterior approach with initial parenchymal transection from the anterior surface down to the IVC; this will be discussed later. Such an approach may also be useful for resecting large HCCs or adenomas that are soft and may fracture and bleed during the mobilization. Because it may be difficult to control bleeding in the deeper parenchymal plane, Belghiti and colleagues described a new technique of hanging the liver after lifting it with a tape passed between the anterior surface of the IVC and the liver parenchyma (Belghiti et al, 2001; Trotovsek et al, 2005).

The most important step in this maneuver is the definition of the anterior plane of the IVC. Initially, IOUS is performed to confirm the absence of tumor in contact with the anterior surface of the IVC. The upper surface of the liver is exposed up to the anterior surface of the suprahepatic IVC (see Fig. 90B.14). The space between the right and the middle hepatic veins is dissected approximately 2 cm downward; we find it convenient to do this using a right angle or a renal pedicle clamp. The anterior surface of the infraheptic IVC is exposed. The inferior-most veins draining between the caudate process and the vena cava are ligated and divided.

The most important step is the dissection of the plane anterior to the vena cava. A long Kelly clamp is passed gently upward, posterior to the caudate lobe. If a right inferior hepatic vein is present, it is dissected but not ligated, and the clamp is passed to its right side. With great care, the clamp is worked along the middle plane of the IVC, toward the space between the right and middle hepatic veins previously dissected. The tunnel beneath the liver measures about 4 to 6 cm of blind dissection, and the clamp appears between the right and middle hepatic veins. A tape is seized in the clamp and is pulled down behind the liver parenchyma; the tape then can be used to elevate the liver away from the anterior surface of the IVC.

Before parenchymal transection, the right pedicle is divided, devascularizing the right liver. The parenchymal transection is conducted from the anterior surface down to the posterior plane in front of the IVC. During the parenchymal transection, upward traction of the tape helps define the plane of transection and facilitates exposure of the deeper parenchymal plane in front of the IVC. After completing the exposure of the anterior surface of the IVC, the right side of the IVC is dissected with division and ligation of the inferior hepatic veins and IVC ligament. Finally, the trunk of the right hepatic vein is stapled with a vascular stapler or divided between clamps and oversewn. The coronary and right triangular ligaments are transected, and the specimen is removed. This technique can be applied routinely for right hepatectomy and does not necessarily need to be reserved only for large tumors abutting the right hepatic vein and IVC. One of the authors (J.B.) has considerable experience with this technique and has reported an experience of 200 cases performed safely (Ogata et al, 2007).

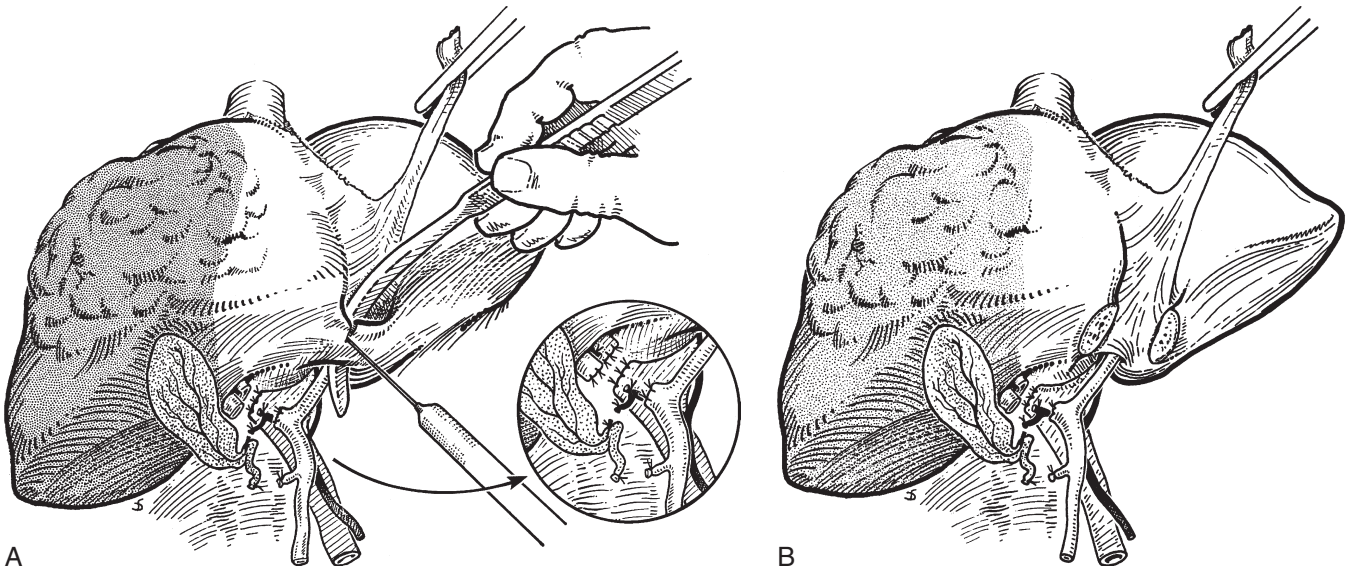


FIGURE 90B.31. A, Exposure of the umbilical fissure and division of the bridge of liver tissue at the base of the fissure. A director usually can be passed beneath the liver tissue, which is divided using diathermy. Note the vessels to the right liver already have been divided (*inset*). **B,** The bridge of liver tissue has been divided.

Anterior Approach

In some patients with very large right-sided hepatic tumors, an alternative is an anterior approach that involves initial parenchymal transection before the right hepatic lobe is mobilized. If this approach is adopted, the hilar inflow vessels are first controlled as described earlier, and the liver parenchyma is transected from the anterior surface of the liver working posteriorly. This parenchymal transection is pursued until the anterior surface of the right hepatic vein and IVC is encountered; the hanging maneuver described earlier can offer useful definition in this approach. Venous tributaries, including the right hepatic vein, are controlled from the front (Lai et al, 1996). The editor emeritus (Leslie H. Blumgart) has used this approach in selected patients and has found it possible even in the presence of diaphragmatic invasion.

Extended Right Hepatectomy

An extended right hepatectomy involves removal of segments IV, V, VI, VII, and VIII; this is in effect a right hepatectomy extended to segment IV. In the nomenclature of Goldsmith and Woodburne (1957), it is referred to as an *extended right hepatic lobectomy.* Starzl and coworkers (1975, 1980) referred to this procedure as a *right trisegmentectomy,* and this term is in common use in the United States.

The initial steps in the procedure are the same as described earlier for right hepatectomy, but the operation involves further dissection and mobilization before parenchymal transection. First, the quadrate lobe, segment IV of the liver, is devascularized; next, the middle hepatic vein must be divided. Occasionally, the caudate lobe (segment I) is removed together with segments IV through VIII as part of the procedure.

After inflow control to segments V, VI, VII, and VIII by extrahepatic dissection or pedicle control, as described for right hepatectomy, the next essential step is to display precisely the umbilical fissure of the liver (Starzl et al, 1975). A strong suture tied to the ligamentum teres is elevated. In many cases, the lower part of the umbilical fissure is concealed by a bridge of liver tissue fusing segment III of the left liver to the quadrate lobe (segment IV) (see Chapter 1B). This tissue is divided easily by passing a curved dissector beneath it (Fig. 90B.31). No large vessels traverse here, and hemostasis is readily secured by diathermy or with the argon beam coagulator.

After opening the umbilical fissure, the ligamentum teres can be visualized, running down to join the termination of the left portal vein within the umbilical fissure (see Fig. 90B.31B). The triad of the left portal vein, left hepatic artery, and left bile duct enters at the base of the umbilical fissure. Their anatomy is shown, with branching of the pedicles to supply segments II, III, and IV (Fig. 90B.32).

It is important for the safe performance of an extended right hepatectomy that the hilar plate be lowered (Fig. 90B.33; see Chapter 29), separating the main left bile duct from the undersurface of segment IV. Whether arising from the common hepatic artery or from the left gastric artery, the left hepatic artery always enters the base of the umbilical fissure and is not endangered during this operation. The middle hepatic artery supplying segment IV is sometimes identified separately, traveling to the right of the left hepatic artery and entering the umbilical fissure at its base and on its right (see Chapter 1B).

Close to the base of the umbilical fissure, a major branch—often two branches—of the left portal vein passes posterolaterally to the caudate lobe (see Fig. 90B.32). Division of these branches interrupts the portal flow to the caudate lobe, but this needs to be carried out only if the caudate lobe is to be removed together with the rest of the specimen. The vital step in the performance of an extended right hepatectomy is the division of inflow vessels that originate from the umbilical fissure of the liver from the left portal triads and feed back from the main left trunk to segments IVa and IVb, the medial sector of the left liver (see Fig. 90B.32). It is not important to attempt to divide these structures within the umbilical fissure, if no tumor is immediately adjacent to the fissure. It is easier and safer to secure them

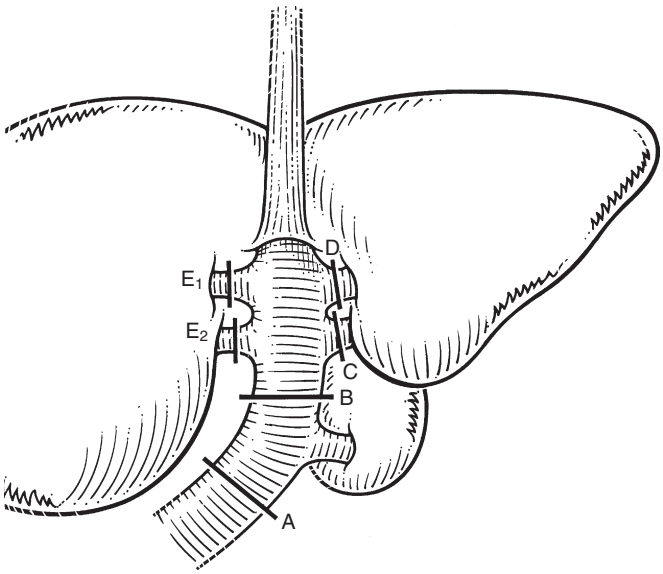


FIGURE 90B.32. Distribution and points of division of pedicles at the base of the left liver. **A,** Pedicle to left liver including segment I. **B,** Pedicle to left liver, sparing segment I. **C,** Pedicle to segment II. **D,** Pedicle to segment III. **E1,** Pedicle to segment IVb. **E2,** Pedicle to segment IVa.

within the liver substance during parenchymal dissection, just to the right of the umbilical fissure, because there is no chance of damage to the blood supply to or biliary drainage from the left lateral sector; however, when a tumor lies close to the umbilical fissure, it is necessary to control the feedback vessels at the right margin of the umbilical fissure. This control can be obtained by passing a suture around these vessels and ligating them in continuity (Fig. 90B.34). Alternatively, the vessels are dissected and individually ligated and divided.

The parenchymal dissection is begun anteriorly and proceeds down to the base of the umbilical fissure (Fig. 90B.35A). When the feedback vessels are divided, segment IV is devascularized. Division of the liver substance is developed toward the vena cava just to the right of the falciform ligament

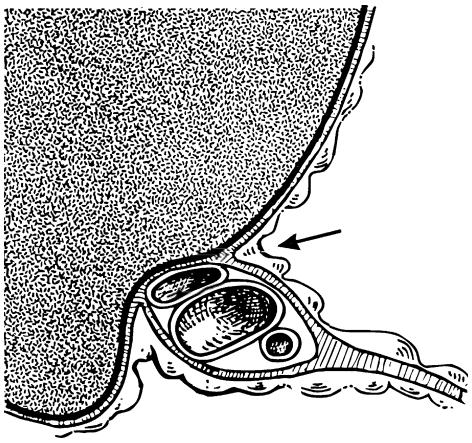


FIGURE 90B.33. Lowering of the hilar plate. The Glisson capsule is incised at the base of the quadrate lobe (segment IV), and the structures of the left portal triad are lowered from beneath the overhanging quadrate to expose the left hepatic duct. This step may be carried out before opening of the umbilical fissure.

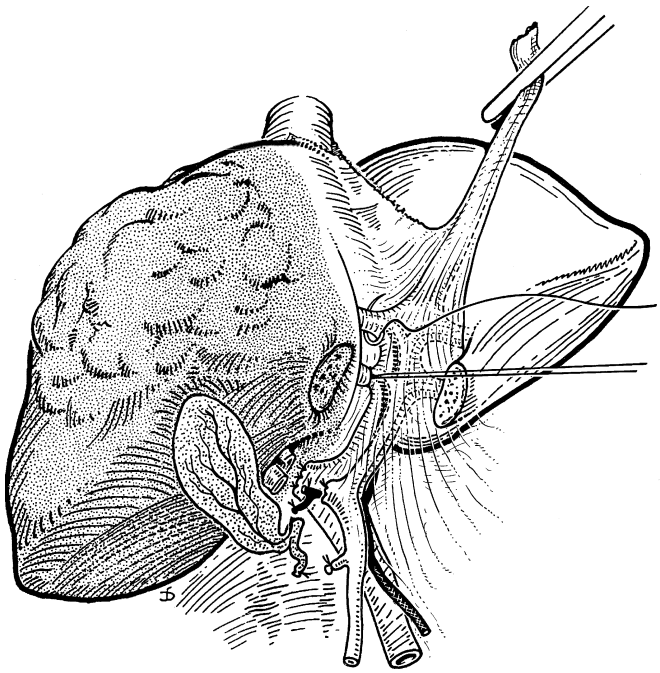


FIGURE 90B.34. Feedback vessels from the left portal triad may be secured in the parenchyma just a little to the right of the falciform ligament (see Fig. 90B.35). This dissection must be within the umbilical fissure in the event of adjacent tumor in segment IV, but this is more safely carried out within the liver tissue just to the right of the falciform ligament (see Fig. 90B.32). Preliminary suture ligation within the umbilical fissure may be performed as illustrated. This procedure deprives segment IV of its blood supply.

(Fig. 90B.35B). The middle hepatic vein is encountered as the dissection is deepened and projected toward the right. When it is identified, it is easily controlled by ligation or division with the Endo GIA stapler. If it is necessary to pursue the middle hepatic vein intrahepatically, toward the vena cava, to obtain tumor clearance, the index finger of the surgeon's nondominant hand can be slid gently along the upper surface of the vein (Fig. 90B.36). Any minor branches avulsed during this maneuver are controlled by finger pressure, and the vein is ligated distal to the finger (see Fig. 90B.36B). Alternatively, the tissue surrounding the vein can be crushed under direct vision, and the small tributaries that are exposed can be ligated. If the right hepatic vein has not previously been divided extrahepatically, it is now approached from within the liver substance, as described earlier, and appropriately controlled.

One particular difficulty may arise when a large tumor occupies segment IV and displaces the left bile duct at the base of that segment and as it traverses into the umbilical fissure (Fig. 90B.37). In such cases, mobilization of the left bile duct in the hilar area and at the base of the umbilical fissure is difficult, perhaps impossible, without deliberate excision of a portion of the left hepatic duct. In such cases, there should be no hesitation in sacrificing any necessary length of the left bile duct to obtain tumor clearance. After removal of the specimen, biliary repair may be carried out by anastomosing the stump of the left hepatic duct to the upper end of the common hepatic duct. Alternatively, biliary-enteric continuity may be restored by creation of a Roux-en-Y hepaticojejunostomy to the left bile duct, which is the preferred method (Fig. 90B.38).

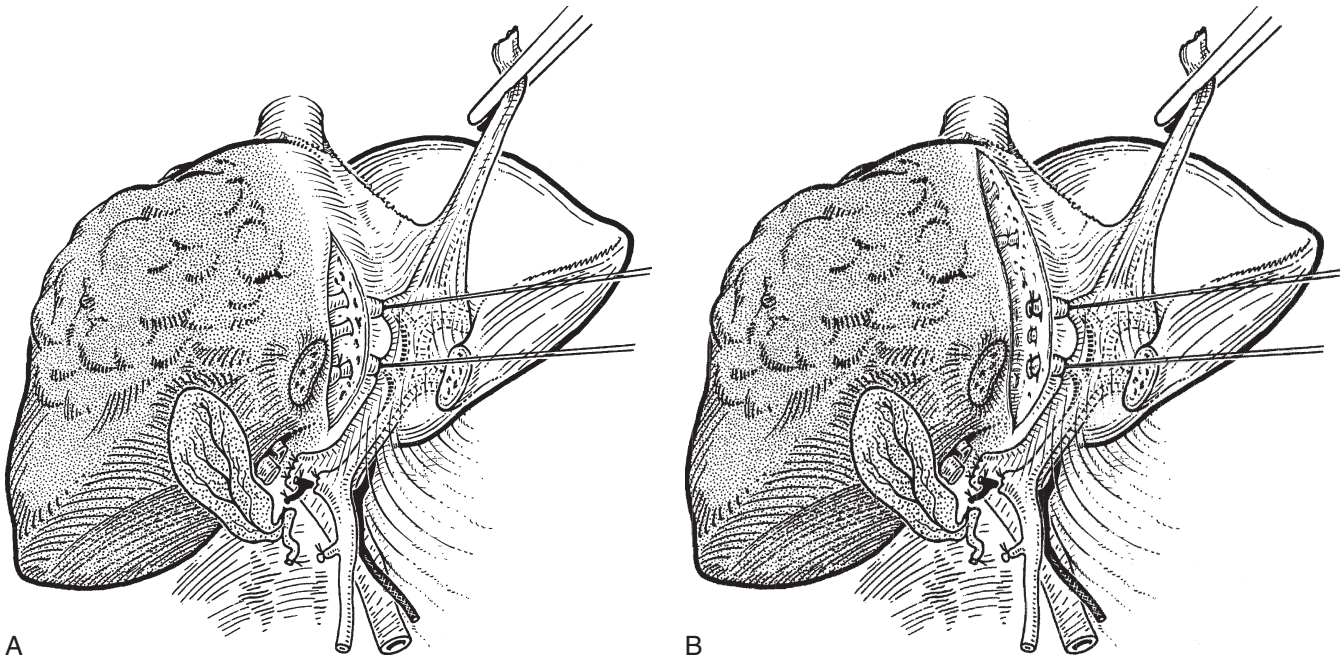


FIGURE 90B.35. A, Feedback vessels are secured within the parenchyma. **B,** Division of the liver substance is developed backward toward the vena cava just to the right of the falciform ligament.

Left Hepatectomy

Left hepatectomy can be a difficult procedure, particularly in the presence of a large, posteriorly situated tumor close to the junction of the middle and left hepatic veins with the vena cava.

Inflow Control

Inflow control to the left liver is obtained by dissection at the base of the umbilical fissure. The ligamentum teres is elevated, and the hilar plate is lowered as described earlier (see Fig. 90B.33). The left hepatic artery is easily identified by opening the peritoneum covering the left portion of the immediate subhilar area at the base of the umbilical fissure. It is double ligated and divided. The gastrohepatic ligament is inspected, and any accessory or replaced hepatic artery arising from the left gastric artery is similarly ligated.

Dissection at the base of the umbilical fissure exposes the left portal vein, as it traverses into the umbilical fissure; it should be controlled at this point and not at its origin from the main portal venous trunk. This dissection allows identification of the branches to the caudate lobe, which arise just before the left portal vein enters the umbilical fissure. If the caudate lobe is to

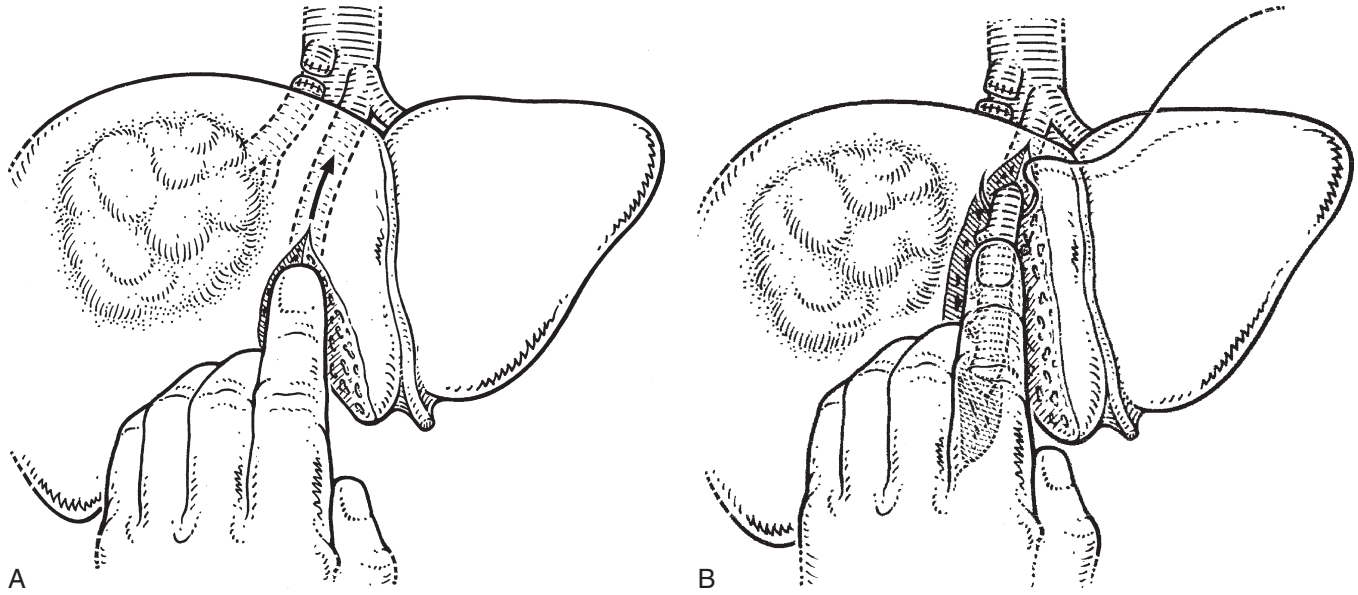


FIGURE 90B.36. A, The middle hepatic vein is exposed, and the index finger slid up its anterior surface shows its length. **B,** The middle hepatic vein is suture ligated.

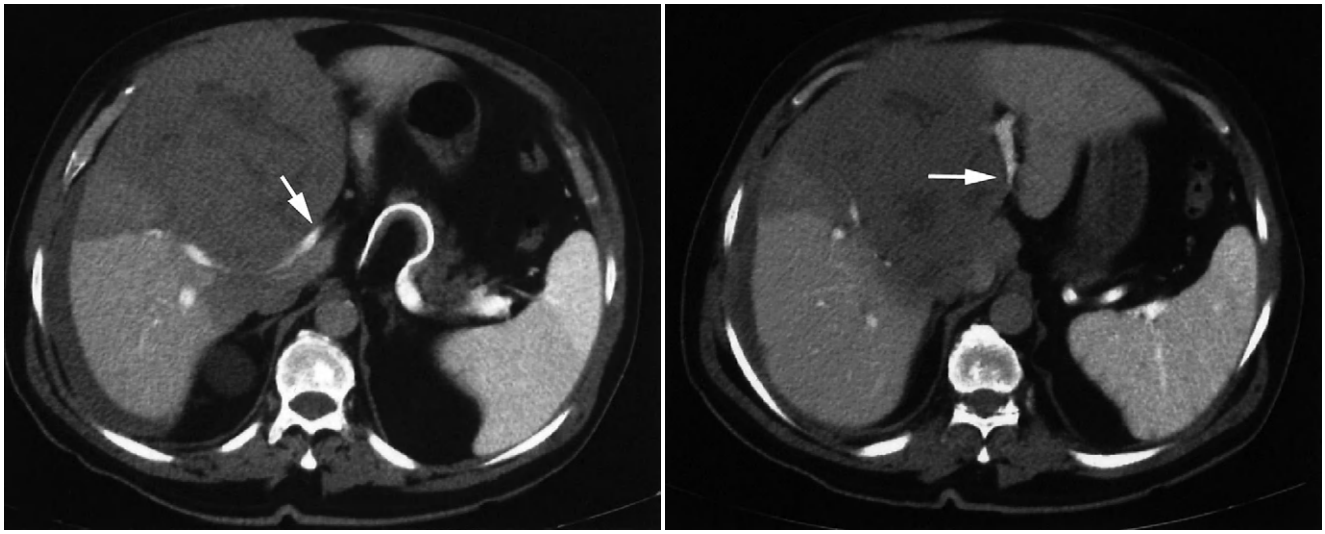


FIGURE 90B.37. Large metastatic carcinoma within segment IV threatens the integrity of the left hepatic duct (*arrows*). At operation, right lobectomy was performed, and a length of the left hepatic duct was excised and repaired as illustrated in Figure 90B.38.

be removed together with the left lobe, the vein is secured below the takeoff of the caudate branches (see Fig. 90B.32A). If the caudate lobe is to be preserved, which is usually the case, the vein is divided distal to the takeoff of the caudate branches (see Fig. 90B.32B). The left hepatic bile duct is easily identified just above the left portal vein, and it can be encircled with a suture and divided as it curves into the umbilical fissure; these steps are illustrated in Fig. 90B.39. A line of demarcation in the Glissonian plane, extending from the gallbladder fossa to the left of the vena cava, is now clearly visible on the liver surface (Fig. 90B.40) and is marked with a diathermy.

Outflow Control

The left lateral sector of the liver, segments II and III, is now mobilized from the diaphragm by division of the left triangular ligament from its tip up to the lateral margin of the suprahepatic IVC, taking care to avoid injury to the underlying spleen and stomach. As the dissection approaches medially, the surgeon must be careful not to injure the left hepatic vein. The upper surfaces of the left and middle hepatic veins and of the suprahepatic IVC are displayed (Fig. 90B.41; Czerniak et al, 1993). The main trunk of the middle hepatic vein usually joins the left

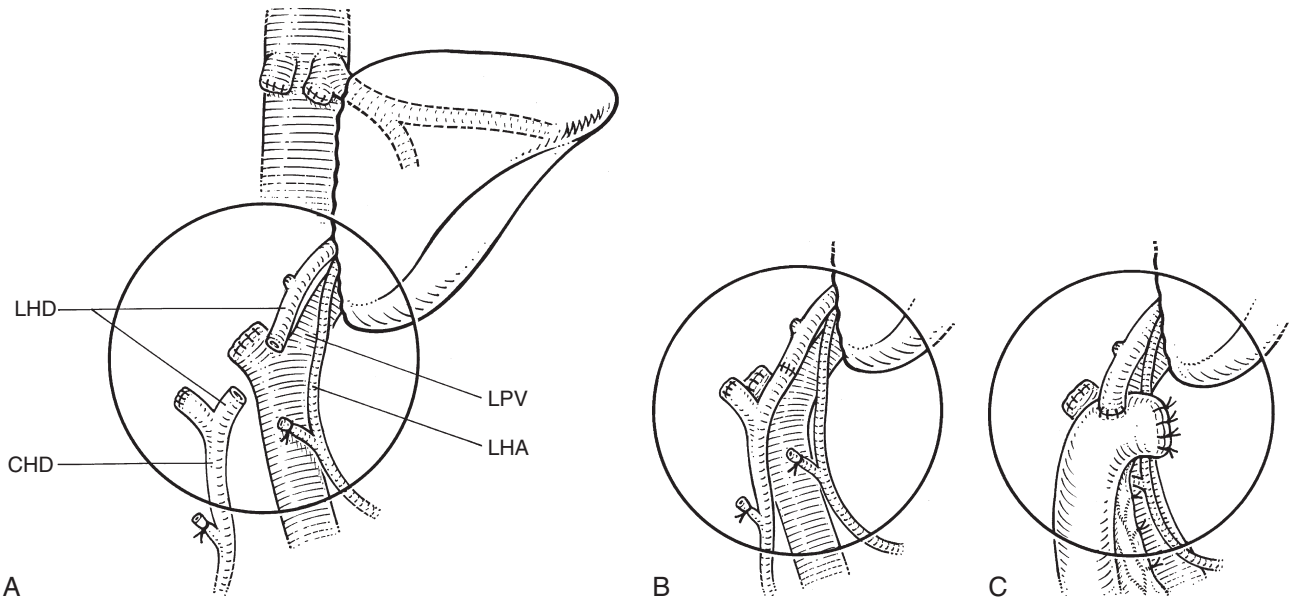


FIGURE 90B.38. The left hepatic duct may be compromised during right lobectomy for tumor extending into the base of segment IV and pushing into the umbilical fissure (see Fig. 90B.37). **A,** After resection with excision of a portion of the left hepatic duct (*LHD*). **B,** Repair of the duct by direct end-to-end anastomosis. **C,** Repair by hepaticojejunostomy Roux-en-Y. CHD, common hepatic duct; LHA, left hepatic artery; LPV, left portal vein.

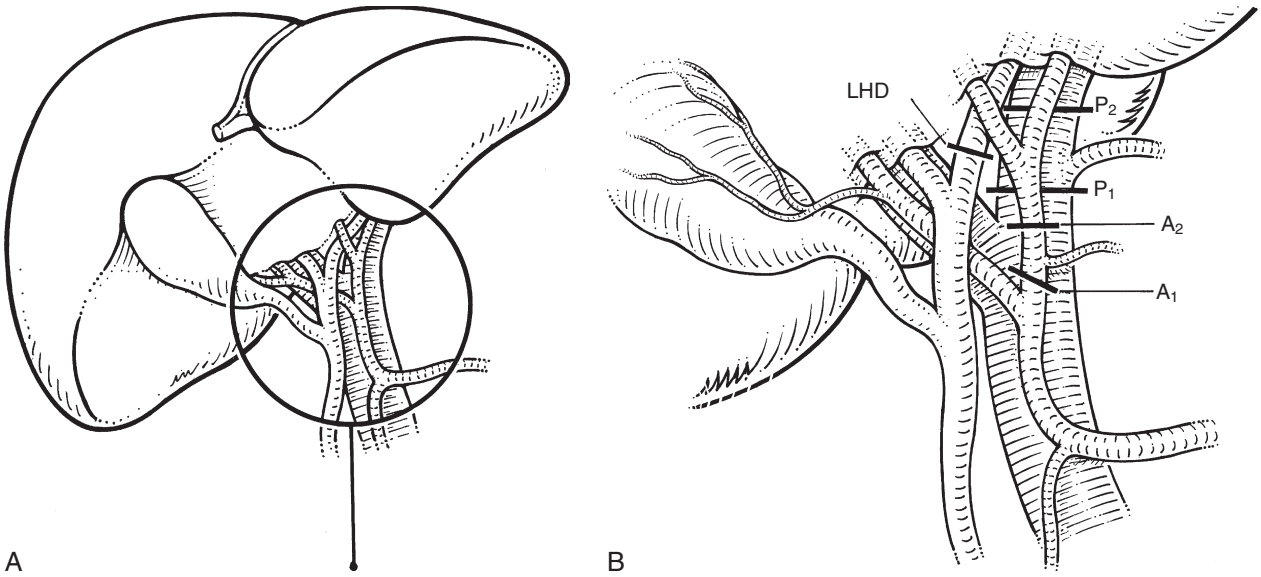


FIGURE 90B.39. A, Dissection for left hepatectomy at the base of the umbilical fissure. **B,** Left hepatic duct (*LHD*) is divided at the base of the umbilical fissure. A_1, point of division of left hepatic artery (LHA) for concomitant removal of caudate lobe; A_2, point of division of LHA for left hepatectomy; P_1, point of division of left portal vein (LPV) for left hepatectomy and caudate lobectomy; P_2, point of division of LPV for left hepatectomy alone.

hepatic vein but may enter the vena cava separately. In essence, the veins are cleared below the diaphragm, and their junction with the vena cava is displayed. The left lateral sector of the liver is turned to the right (see Fig. 90B.41), the gastrohepatic ligament is fully divided, and the ligamentum venosum is identified. We divide the ligamentum venosum close to its entry into the left hepatic vein. This division opens up a triangular tunnel, the sides of which are the left hepatic vein anteriorly, the anterior surface of the vena cava posteriorly, and the upper surface of segment II inferiorly. This tunnel is developed carefully, and an instrument is passed beneath the left and middle hepatic veins to emerge anterior to the vena cava, between the middle hepatic vein and the right hepatic vein (see Fig. 90B.41B), and the common trunk is controlled.

If the middle hepatic vein requires resection to obtain adequate tumor clearance, the common trunk can be divided at this time. It can be secured between vascular clamps, divided, and oversewn with a 3-0 polyproprylene suture. Alternatively, the Endo GIA vascular stapler may be used to divide the veins, which is our preferred method (Fig. 90B.42). If the middle hepatic vein can be preserved, the common trunk should not be divided. A small hepatotomy can be made in between the middle and left hepatic veins, which usually allows individual extrahepatic control of the left hepatic vein. Alternatively, the left hepatic vein can be divided intrahepatically during parenchymal dissection, if the tumor is located remotely. Controlling the major hepatic veins draining to the left liver is crucial in minimizing hemorrhage during the removal of large, left-sided tumors.

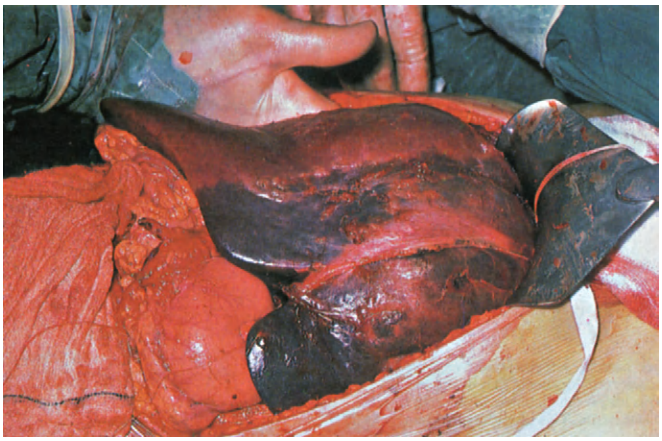


FIGURE 90B.40. The left liver has been devascularized before parenchymal transection for left hepatectomy.

Parenchymal Transection

A vessel loop or umbilical tape is now passed around the hilar structures to enable intermittent occlusion (Pringle maneuver) should it be necessary. The line of parenchymal transection follows the principal plane and can be either to the right or left of the middle hepatic vein, depending on what is necessary for tumor clearance. It is important that transection be carried out so that the parenchyma is divided posteriorly just anterior to the ligamentum venosum, separating the left liver from the anterior surface of the caudate lobe.

Extended Left Hepatectomy

In some instances, a large tumor occupying the left half of the liver encroaches across the principal scissura (Cantlie's line) into segments V and VIII, the anterior sector of the right liver (see Figs. 90B.1 and 90B.4). In other cases, multiple tumors occupy portions of the left liver and segments V and VIII. In such cases, left hepatectomy can be performed with extension of the procedure to also remove segments V and VIII.

The procedure is extensive, and although Couinaud (1957) described the anatomic basis for extension of a left hepatectomy to include removal of the anterior sector of the right liver, there

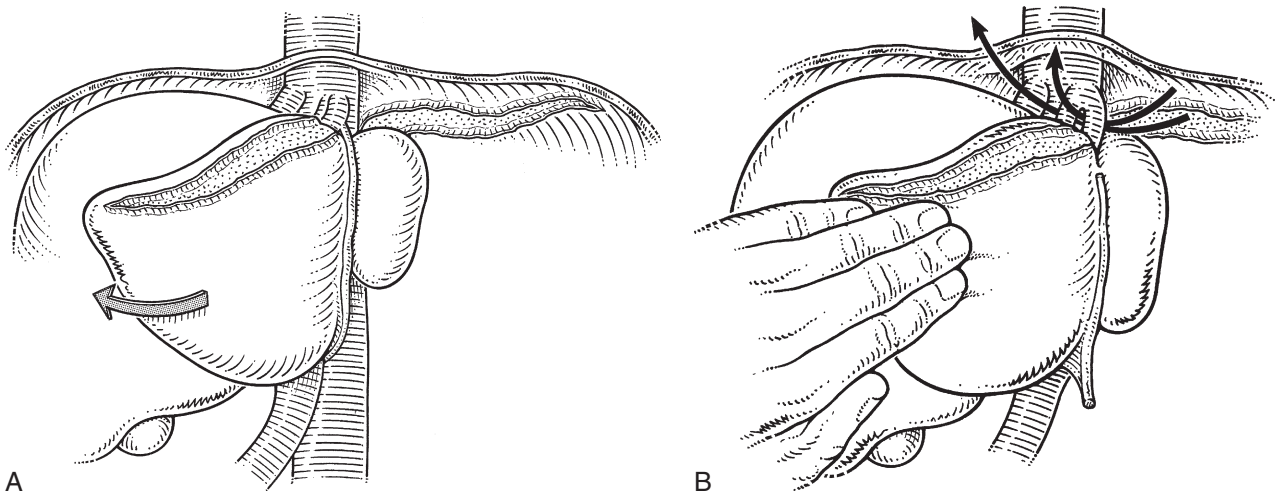


FIGURE 90B.41. Approach and dissection of the left and middle hepatic veins, applicable to left hepatectomy and extended left hepatectomy. **A,** The left lobe of the liver (segments II and III) is completely mobilized from the diaphragm and turned to the right. The gastrohepatic ligament is divided, and the line of the ligamentum venosum is exposed. **B,** The ligamentum venosum is divided. This maneuver allows the exposure of the window between the vena cava and the left hepatic vein. By dissection in this space, it is possible to dissect free the left and middle hepatic veins separately or together (*black curved arrows*). The left and middle hepatic veins are clamped, divided, and oversewn or divided with the Endo GIA vascular stapler.

were few reported series of successful operations. Joishy and Balasegaram (1980) reported extended left hepatectomy done in eight patients. The nature of these operations is described as indicating a line of transection to the right of the principal plane, but almost certainly not extending to the right scissura. An early description of this procedure was reported by Blumgart in 1978, but it was not until Starzl and colleagues (1982) reported four cases, which they referred to as *left hepatic trisegmentectomies,* that the necessary hilar dissection was described precisely. The difficulty in defining the plane of parenchymal transection on the right and in controlling hemorrhage and biliary complications was recognized. Subsequently, reports of small numbers of patients undergoing this procedure continued to populate the literature, but perioperative problems, and biliary complications in particular, were frequent (Al-Hadeedi et al, 1990; Hasegawa et al, 1989).

Preoperative Evaluation

Careful and detailed preoperative anatomic assessment is paramount, and patients should not be excluded from operation based on the size of the tumor alone. Even patients with very large tumors that displace blood vessels and compress bile ducts, so-called pushing tumors, may be selected for laparotomy (Baer et al, 1989). Quality cross-sectional imaging by either CT or MRI is important to delineate the expansile pushing form of a tumor (see Fig. 90B.6). US, including Doppler imaging of the portal and hepatic vessels, is also valuable in this regard. These studies also show impingement of large tumors on the vena cava. Arteriography and inferior venacavography are rarely if ever necessary.

Operative Technique

The operation involves removal of segments II, III, IV, V, and VIII (Blumgart et al, 1993). Segment I can be included in the resection if necessary for tumor clearance (Fig. 90B.43; see also Fig. 90B.32). An important aspect of the operative technique is the early and complete mobilization of the liver, not only by division of the left triangular ligament from its apex to the left of the IVC but also by complete division and mobilization of the ligament on the right. This mobilization not only allows palpation of segment VII for the presence of unsuspected additional tumor but also assists later in the identification of the correct plane of parenchymal dissection. IOUS is performed to confirm the previously defined anatomic configuration of the tumor and

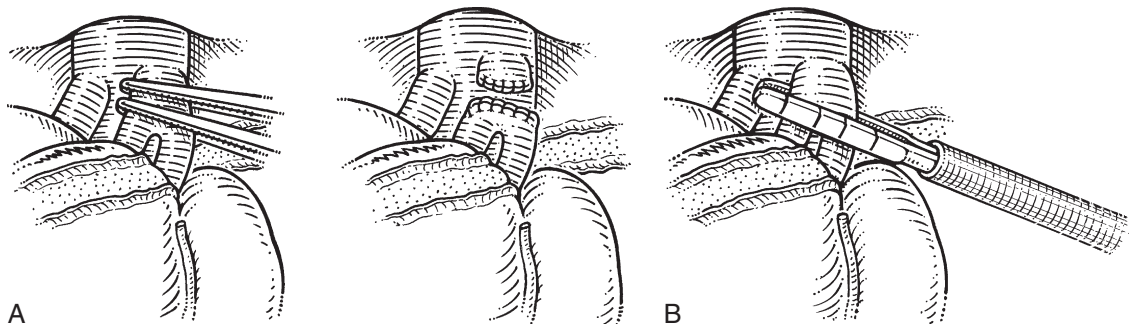


FIGURE 90B.42. A, The left and middle hepatic veins are clamped, divided, and oversewn. **B,** Alternatively, the veins may be divided with the Endo GIA stapler.

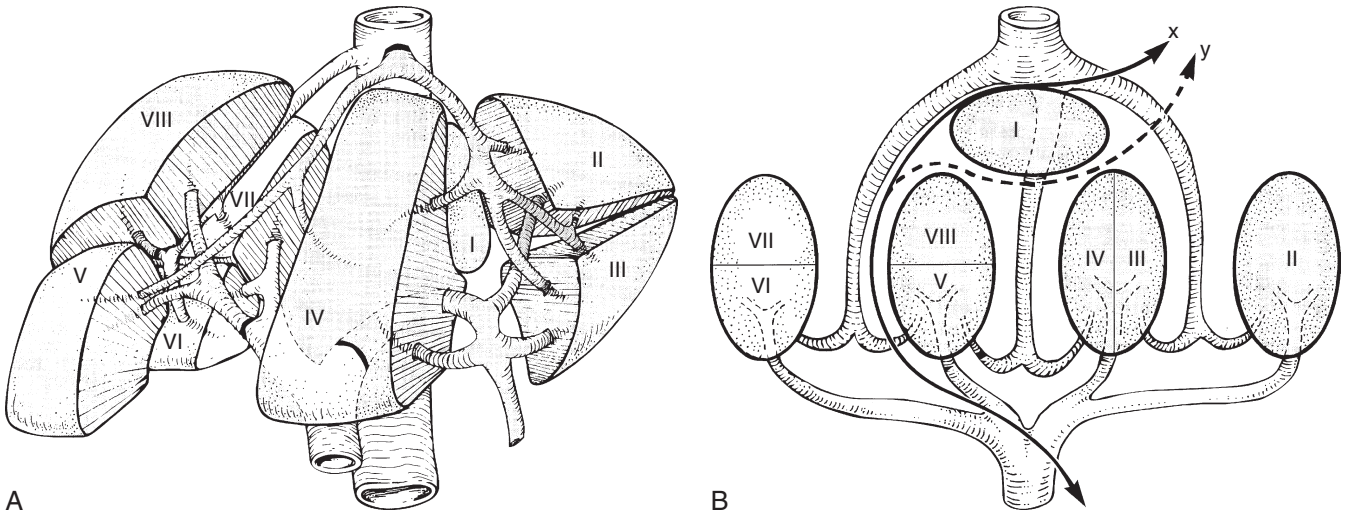


FIGURE 90B.43. A, Exploded view to show the sectors and segments of the liver. Extended left hepatectomy involves removal of segments II, III, IV, V, and VIII and sometimes segment I. The segments to be removed are shaded. The solid lines on the right anterior sectoral pedicle and the left portal triad illustrate the devascularization necessary. The solid line on the middle and left hepatic veins illustrates the point of hepatic venous transection. The right posterior sectoral triad supplying segments VI and VII is preserved, as is the right hepatic vein. **B,** Schematic representation of extended left hepatectomy. Note preservation of the posterior sectoral triad supplying segments VI and VII and of the right hepatic vein. The solid line *x* illustrates the line of transection for removal of the caudate lobe, and the dotted line *y* illustrates the line of transection if the caudate lobe is to be preserved.

major hepatic veins. In particular, an attempt is made to identify the presence of a large inferior right hepatic vein; its presence augments drainage of segments VI and VII and may allow the right main hepatic vein to be sacrificed during operation if required (Baer et al, 1991).

Initial dissection is identical to that for left hepatectomy. The suprahepatic bare area of the liver is fully exposed to display the suprahepatic IVC and the hepatic veins. The left liver is now turned to the right side, and the portal triad is approached from the left (Fig. 90B.44). The point of ligation of the portal vessels to the left liver is dictated by the involvement of the caudate lobe (segment I) by tumor. If segment I requires resection, the left hepatic artery, bile duct, and portal vein must be ligated close to the hilus to interrupt the blood supply to segment I and to the left liver (see Figs. 90B.32 and 90B.44). As described by Starzl and coworkers (1982) and Blumgart and colleagues (1993), however, when segment I is to be preserved, the structures of the left portal triad are secured at the base of the umbilical fissure to leave intact the biliary drainage and blood supply of segment I (see Fig. 90B.44).

After obtaining vascular control at the hilus, the middle and left hepatic veins and the left of the subdiaphragmatic IVC are dissected and exposed as described earlier for left hepatectomy (Czerniak et al, 1993). If the caudate lobe is to be removed en bloc, it is mobilized from the left side by dividing its direct venous tributaries to the IVC.

The difficult aspect of the operation is the definition of the line of transection of the parenchyma, which lies well to the right of the principal scissura. The plane is horizontal, lateral to the gallbladder fossa, and parallel and just anterior to the right scissura. In an attempt to define this plane, Starzl and coworkers (1982) described finger dissection, beginning from above and anterior to the main right hepatic venous entry into the vena cava. We have avoided this approach, which may be associated with considerable hemorrhage. It is important to define the plane of parenchymal dissection, however; it passes anterior to the right hepatic venous trunk and allows division of the anterior sectoral branch of the right portal triad, while preserving and avoiding damage to the posterior sectoral triad (Fig. 90B.45). Although there are no reliable surface markings, a plane passing from the anterior border of the right hepatic vein above and extending horizontally to emerge well to the right of the gallbladder fossa designates the approximate correct position within the parenchyma. This line can be accurately defined when it is possible to clamp the anterior sectoral pedicle to the right liver, and this is often possible using the pedicular glissonian approach. This approach should be possible in all cases in which the tumor does not extend so close to the right main pedicle as to make access impossible without compromising tumor clearance. The right anterior sectoral pedicle is isolated and clamped, and the right posterior pedicle is left intact; a line of demarcation extending along the right scissura develops rapidly (Fig. 90B.46).

The parenchymal transection phase is now carried out, opening the liver tissue from below, going upward, and keeping the plane of parenchymal dissection horizontal. Frequent use of IOUS facilitates continuing along the correct transection plane and spares injury to the right posterior pedicle and right hepatic vein. If significant bleeding occurs, it usually arises from branches of the right hepatic vein. Dissection carried out under low CVP (see Chapter 22) allows bleeding from the transected branches of the right vein to be visualized and controlled. When the right anterior sectoral pedicle has been identified, it should be test clamped prior to dividing it to ensure adequate perfusion to the posterior sector. The plane of transection is kept anterior to the right posterior pedicular structures. Unlike the hepatic veins, these structures are dense and white and should be readily appreciated.

Many large, expansile (pushing) tumors produce a narrow zone of compressed atrophic liver tissue just anterior to the

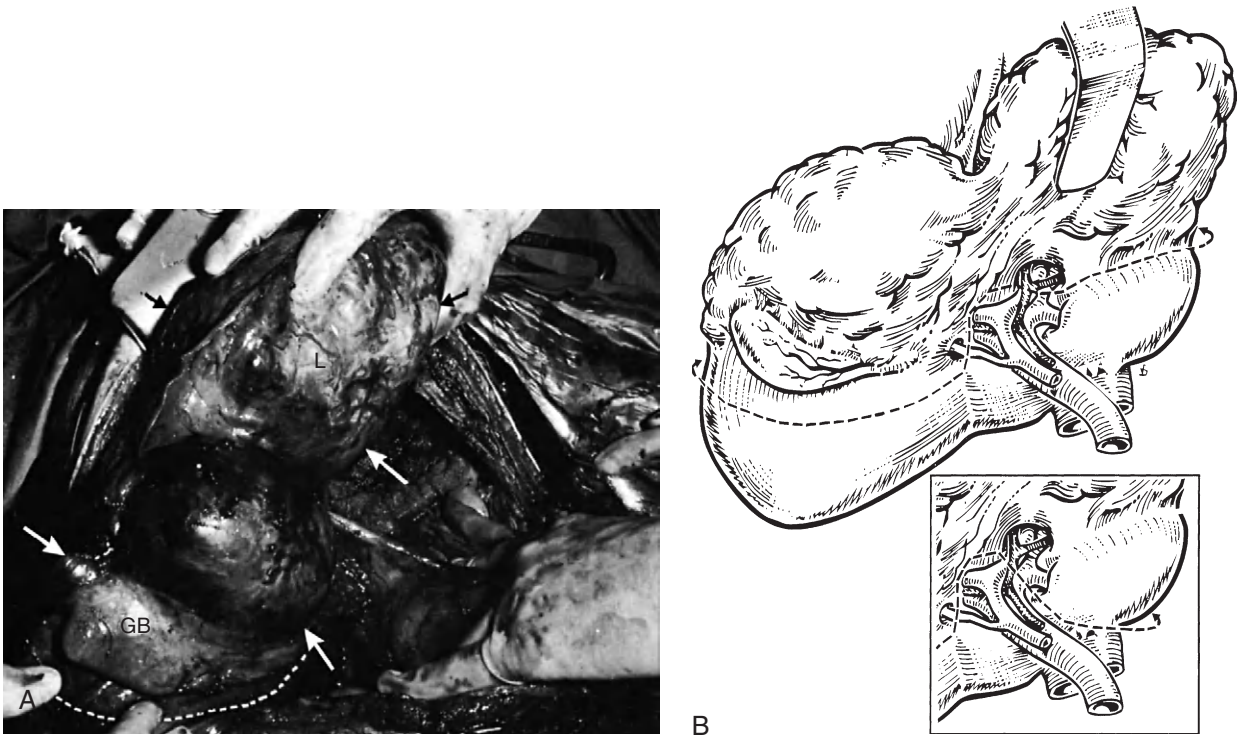


FIGURE 90B.44. A, Operative photograph of a large, left-sided primary hepatocellular carcinoma occupying the left lobe of the liver (segments II, III, and IV) and extending into segments V and VIII beneath the gallbladder (*GB*). The left lobe (*L*) has been mobilized and turned toward the right. The extent of the tumor is indicated by the *arrows*. The line of parenchymal incision in the right liver is indicated by the *dotted line*. **B,** Initial approach during extended left hepatectomy allows dissection of the portal triad structures from the left posterolateral aspect. The line of future transection is indicated. If the caudate lobe is to be preserved, the left portal vein is ligated beyond its caudate branch; but if the caudate is to be removed as well, the portal vein can be ligated more proximally (*inset*). The line of transection runs along the obliterated ligamentum venosum, then across the base of the quadrate lobe and hilus; it curves to the right, extending into the right scissura lateral to the gallbladder fossa. The dissection as illustrated in the main diagram would preserve the caudate lobe; in the inset, the caudate lobe also is removed (see also Fig. 90B.43).



FIGURE 90B.45. Extended left hepatic lobectomy. The liver tissue is entered for the parenchymatous transection just anterior to the estimated lower limit of the right scissura. This plane of dissection is followed, with the operator working toward the base of the gallbladder fossa and the point of entry of the right hepatic duct into the liver substance. The anterior sectoral vessel of supply and the bile ducts are identified in the liver substance (*arrow*) and can be ligated.

posterior pedicular triad. In such instances, although tumor clearance is narrow, it can be achieved by peeling the tumor away from the residual parenchyma in this atrophic plane. With large tumors, the plane of dissection is dictated by the tumor (see Fig. 90B.6). For smaller tumors, the plane of dissection can be anatomically defined.

If the middle and left hepatic veins have not been controlled and divided extrahepatically, they are ligated when encountered within the line of transection, and the parenchymal division is completed; however, it cannot be emphasized strongly enough that prior control of these veins is associated with substantially less venous bleeding during parenchymal transection.

After removal of the resected specimen, the remnant (segments VI and VII) presents an en face raw surface area (Fig. 90B.47). Any bleeding from small branches of the hepatic artery or portal vein is controlled, and any visible open bile ducts are closed with fine, resorbable sutures. Final hemostasis is achieved as described earlier, and the omentum may be laid over the cut surface. An increased risk for biliary complications attends this operation, and three of the four patients initially reported by Starzl and coworkers (1982) had biliary complications: two had fistulae, and one had bile duct stricture.

Experience: Extended Left Hepatectomy

Extended left hepatectomy has been described in some detail, because large tumors arising from the left liver and extending to the right, previously considered unresectable, can be removed successfully with complete tumor clearance and a chance of

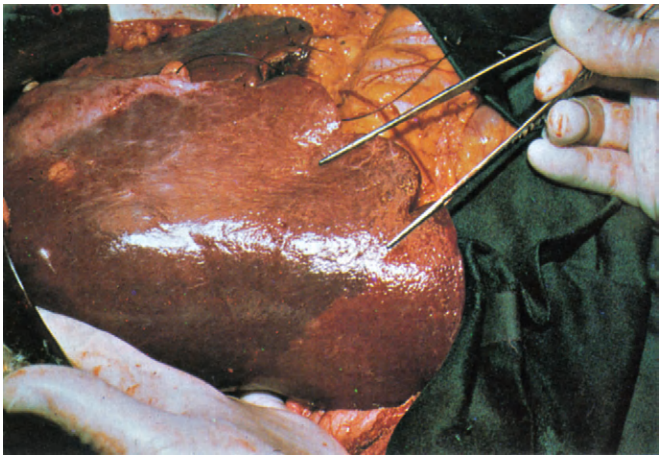


FIGURE 90B.46. Operative photograph taken during extended left hepatectomy for a large tumor occupying the left liver, which has already been devascularized; the anterior sector (segments V and VIII) is seen devascularized and demarcated from the posterior sector (segments VI and VII), which remains vascularized.

cure (Blumgart et al, 1993; Soreide et al, 1985). As stated earlier, prediction of resectability is sometimes difficult; but in large tumors with a clear-cut margin on cross-sectional imaging and evidence of displacement, rather than invasion, of right-sided posterior sectoral intrahepatic structures (see Fig. 90B.6), exploration for excision is worthwhile (Soreide et al, 1985). Although high perioperative morbidity and mortality and poor outcome have been reported with this operation (Hasegawa et al, 1989), many small series lend support to its utility (Al-Hadeedi et al, 1990; Bismuth et al, 1989, 1992; Blumgart et al, 1993; Elias et al, 1992; Houssin et al, 1993; Huguet et al, 1994; Iwatsuki & Starzl, 1988; Starzl et al, 1982; Tsuzuki et al, 1990).

In a series of 51 patients who underwent extended left hepatectomy at MSKCC from 1992 through 1998 (Povoski et al, 1999), no intraoperative deaths were reported, and postoperative morbidity was 53%; biliary leak and abdominal abscess were the most commonly encountered complications. Postoperative mortality rate was 8%. Compared with historic controls for hepatic resection at MSKCC from 1985 through 1994 (Fong et al, 1995), in which overall postoperative morbidity was 40% and postoperative mortality rate was 4%, morbidity and mortality rates were greater for extended left hepatectomy, although length of hospital stay was identical. In a more recent study, Cho and colleagues (2010) reported no operative deaths in 15 consecutive patients, emphasizing the importance of adequate venous drainage of the liver remnant. The morbidity in this study was high (40%), underscoring the point that extended left hepatectomy remains one of the most difficult procedures in hepatic resection surgery.

Factors that influence resectability and oncologic efficacy, especially with regard to such extensive anatomic dissections, have long been debated. In the series of patients from MSKCC, the finding of positive microscopic margins or of tumor within one high-power field (HPF) was associated with the largest hepatic lesions (Povoski et al, 1999).

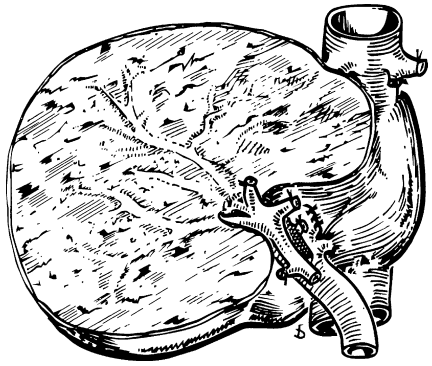


FIGURE 90B.47. The liver substance is removed anterior to the posterior sectoral ducts and vessels, and the upper part of this parenchymal dissection runs just anterior to the right hepatic vein and involves control of the middle and left hepatic vein. After resection, the right posterior sectoral portal triad can be seen branching on the surface of exposed liver tissue.

Left Lateral Sectorectomy (Left Lateral Segmentectomy)

The left lateral sector of the liver, which comprises segments II and III, is resected by approaching the portal triads to segments II and III in the umbilical fissure. Any bridge of tissue between segments III and IV is divided as described previously. The left lobe is mobilized, and dissection is carried out within the umbilical fissure to the left of the main triad; the pedicles to segments II and III usually can be dissected and controlled individually (see Fig. 90B.32). This approach is important in allowing tumor clearance for lesions close to the umbilical fissure. Alternatively, the liver may be split anteroposteriorly, just to the left of the ligamentum teres and the falciform ligament; as this is done, the vessels are encountered intrahepatically and divided serially. The latter approach is suitable only for more peripherally placed tumors.

As the liver tissue is divided, the left hepatic vein is encountered posteriorly and can be controlled within the liver substance. Division of the left hepatic vein usually completes the parenchymal transection. When a posteriorly situated tumor lies close to the junction of the left hepatic vein and the middle hepatic vein, it is best to approach the left hepatic vein extrahepatically, as described previously for left hepatectomy (see Figs. 90B.41 and 90B.42).

HEPATIC SEGMENTECTOMY

A detailed understanding of intrahepatic anatomy and advances in imaging technology have facilitated an approach to hepatic resection based on the removal of individual hepatic segments (Billingsley et al, 1998; DeMatteo et al, 2000; Franco et al, 1988; Gazelle & Haaga, 1992; Hemming et al, 1997; Takayama & Makuuchi, 1996). Hepatic segmentectomy is discussed in detail in Chapter 92 but is also briefly described here; however, resection of segment I, caudate lobectomy, is discussed in detail, because it is often done in combination with a major hepatectomy. The number of hepatic segments resected has been shown to be correlated with perioperative morbidity and mortality (Jarnagin et al, 2002).

Segmental resections offer a variety of advantages over classic major resections and nonanatomic wedge resections. Segmental resections conserve functional liver parenchyma and minimize the physiologic impact of liver resection. This is of

particular benefit in a patient with cirrhosis who has baseline impaired hepatocellular function. Nonanatomic wedge resection has been advocated as an alternative approach for parenchymal conservation (Brown et al, 1988); however, wedge resection can be hampered by excessive bleeding and unacceptable rates of margin positivity, as high as 35% in some series (Scheele et al, 1991, 1995). Uncontrolled intraoperative hemorrhage is usually avoidable with good parenchymal transection techniques and low CVP.

A segmentectomy may be regarded as a *unisegmentectomy,* when one segment is removed, or as a *plurisegmentectomy,* when two or more segments are excised (Castaing et al, 1985; Nagasue et al, 1985). More commonly performed segmental resections include resection of segment I, resection of segment IV, and segmentectomy to remove segments IV, V, and VI (Figs. 90B.48 and 90B.49). Central hepatectomy comprising resection of segments IV, V, and VIII is being increasingly performed, and this may be combined with resection of segment I, the latter operation being particularly indicated in some patients with hilar cholangiocarcinoma (Ogura et al, 1998). Resection of segments VI and VII is, in effect, a *right posterior sectorectomy,* and resection of segments V and VIII is a *right anterior sectorectomy.*

Although indicated for removal of some benign liver tumors and for biliary exposure in some cases of benign biliary stricture, isolated resection of segment IV is of value in the management of malignant lesions occupying only the quadrate lobe.

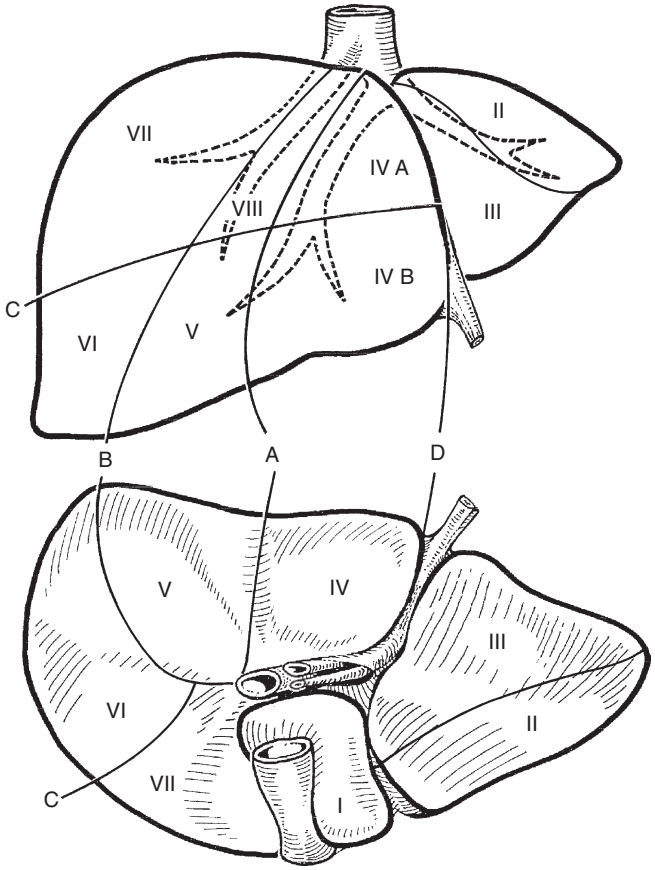


FIGURE 90B.48. Lines of resection for excision of various segments. Resection of segments VI and VII, right posterior sectorectomy. Resection of segments V and VIII, right anterior sectorectomy. Resection of segments IV, V, and VIII, central hepatectomy. Resection of segment IV follows *A-D*.

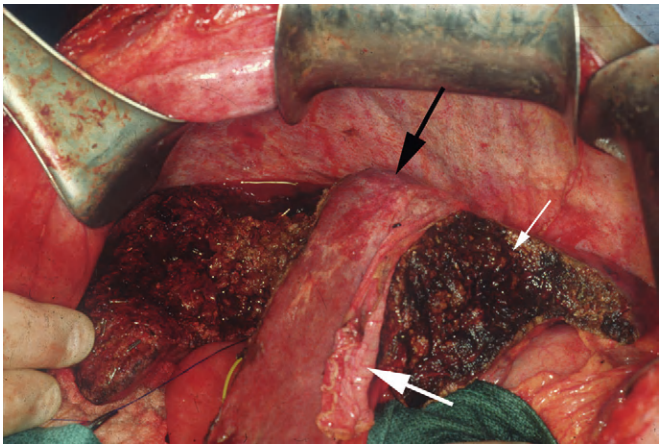


FIGURE 90B.49. Intraoperative photograph illustrates resection of segments III, V, and VIII. Segments II (*small white arrow*) and IV (*black arrow*) remain intact. The falciform ligament is evident (*large white arrow*).

Carcinoma of the gallbladder is a special case, because the organ lies between segments IV and V of the liver. Resection for gallbladder cancer should involve, at a minimum, removal of segments IVb and V (discussed later in this chapter and also in Chapter 49). A resection of segments II and III (Fig. 90B.50) may also be performed and is in effect a *left lateral sectorectomy.* Segment I may be removed on its own or in continuity with a right or left hepatectomy, central hepatectomy, or an extended right or left hepatectomy.

Segment I (Caudate Lobe) Resection

The caudate lobe of the liver is a frequent site of involvement in primary and secondary liver tumors. In addition, cholangiocarcinoma at the confluence of the hepatic ducts frequently involves caudate bile ducts and may extend to the caudate lobe. Resection of the caudate lobe of the liver is often necessary for complete tumor clearance. The procedure may be required as an isolated caudate resection, or it may be combined with a major hepatectomy. The anatomy of the caudate lobe and its

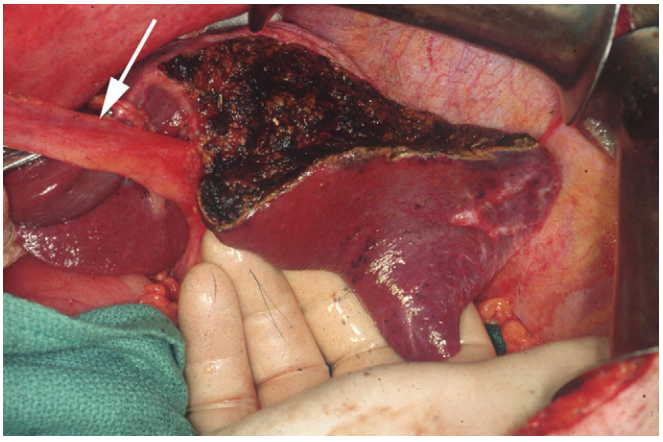


FIGURE 90B.50. Photograph illustrates resection of segment III. Segment II is turned forward by the operator's hand. The ligamentum teres is illustrated (*arrow*).

close proximity to major vascular structures make resection challenging.

Anatomy

The caudate lobe is the dorsal portion of the liver that embraces the retrohepatic IVC. The lobe lies between major vascular structures: at the inferior aspect of the liver, it is situated between the IVC posteriorly and the left portal triad anteriorly; at the superior aspect of the liver, it is bordered by the IVC posteriorly and the middle and left hepatic veins anteriorly (Figs. 90B.51 and 90B.52; see Chapter 1B). The main bulk of the lobe lies to the left of the vena cava, with the left and inferior margins being free in the lesser omental bursa. The gastrohepatic omentum separates the left portion of the caudate lobe from segments II and III of the left liver, as it passes between them and attaches to the ligamentum venosum. The left portion of the caudate lobe inferiorly traverses to the right side between the portal vein and IVC, where it is termed the *caudate process* as it fuses with the right lobe of the liver. Superiorly, the left portion of the caudate lobe is linked to the posterior margin of the hilum by a deep anterior portion, which passes embedded in the parenchyma immediately under the middle hepatic vein and fuses on the right side to segment VII, anterolateral to the IVC. The portion of the caudate lobe on the right varies but is usually quite small; it is often referred to as *segment IX*. The anterior surface of the caudate lobe within the parenchyma is covered by the posterior surface of segment IV, the limit being an oblique plane slanting from the left portal vein to the left hepatic vein. The caudate lobe has a constantly present left portion, and the right portion is of variable size (see Chapter 1B).

The inflow to the caudate lobe is supplied by branches from the right and left portal vein and the left hepatic artery close to the base of the umbilical fissure of the liver. The right portion of the caudate lobe, including the caudate process, receives predominantly portal venous blood from the right portal vein or the bifurcation of the main portal trunk; whereas on the left side, the major portal supply arises almost exclusively from the left branch of the portal vein. Similarly, the arterial supply and biliary drainage of the right portion is most commonly associated with the right posterior sectoral vessels or pedicle, and that of the left aspect is associated with the left main vessels (Mizumoto & Suzuki, 1988).

The hepatic venous drainage of the caudate lobe is unique in that it is the only hepatic segment that drains directly into the IVC. The number of hepatic veins varies (mean four, range one to nine; Heloury et al, 1988). In general, the veins are short and

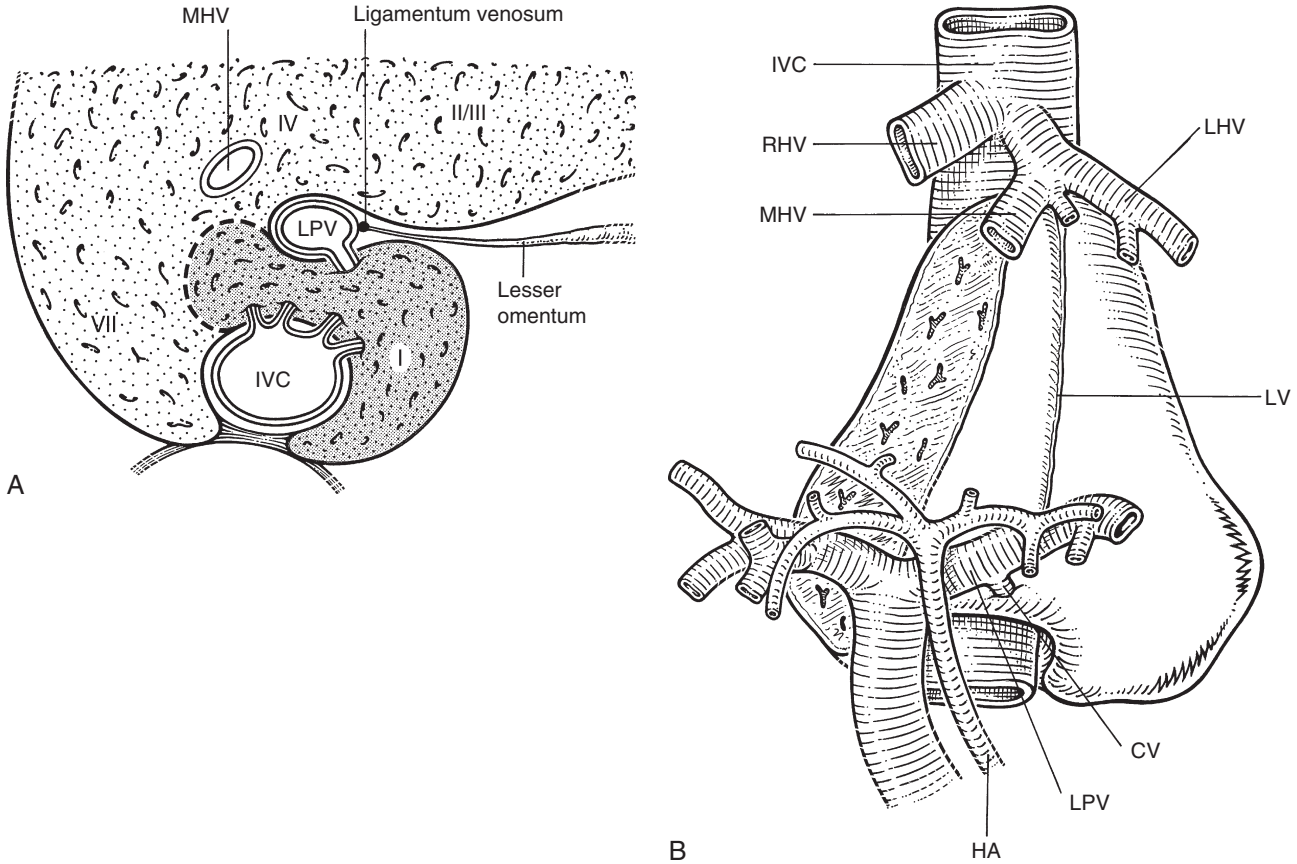


FIGURE 90B.51. A, Cross-sectional sketch shows caudate lobe anatomy at the level of the porta hepatis. Note the principal caudate branch of left portal vein (*LPV*). Note the position of 1) the lesser omentum and ligamentum venosum; 2) middle hepatic vein (*MHV*), which separates segments IV and V and is close to right portion of caudate lobe; and 3) the posterior ligamentous band joining segments I and VII. **B,** The relationships of the caudate lobe are illustrated. The caudate lies anterior to the inferior vena cava (*IVC*) but posterior to the portal venous structures; the caudate lobe has a right portion. Blood supply to the caudate lobe is mainly from the caudate branch (*CV*) of the LPV. This branch may arise from the main trunk of the portal vein in some cases. HA, hepatic artery; LHV, left hepatic vein; LV, ligamentum venosum; RHV, right hepatic vein.

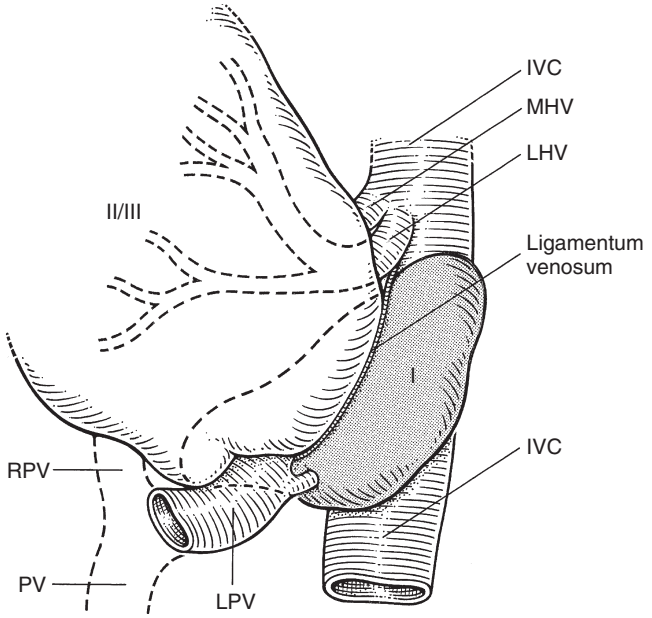


FIGURE 90B.52. Position of the caudate lobe relative to surrounding structures and particularly the vena cava. Segments II and III have been rotated to the right to expose the caudate lobe. The position of the ligamentum venosum is indicated. Note the extension of the caudate lobe between the vena cava and the portal vein (*PV*) anteriorly and between the vena cava and the middle and left hepatic veins (*LHVs*) superiorly. Caudate portal blood supply is via a branch of the left portal vein (*LPV*). IVC, inferior vena cava; MHV, middle hepatic vein; RPV, right portal vein (see also Fig. 90B.51).

drain from the caudate lobe directly into the anterior and left aspect of the vena cava (see Fig. 90B.51A and Chapter 1B); they may also drain into the posterior aspect of the vena cava, if a significant retrocaval caudate component is present, but this is rare.

The posterior edge of the caudate lobe, on the left, usually has a fibrous component that fans out to attach to the crus of the diaphragm; this extends posteriorly, behind the vena cava, and links with a similar component of fibrous tissue, protruding from the posterior surface of segment VII, and embraces the vena cava (see Fig. 90B.51A). In up to 50% of patients, this ligament is replaced, in whole or in part, by hepatic parenchymal tissue; thus the caudate may completely encircle the IVC and may contact segment VII on the right side. A significant retrocaval component may compromise a left-sided approach to controlling the caudate veins.

Resection

The major obstacles in caudate lobe resection are its mobilization, which mandates control of the retrohepatic caudate veins, and, in the presence of a large tumor, preventing and controlling bleeding from the posterior surface of the middle hepatic vein. Resection of the caudate lobe involves three major steps: 1) control of the inflow blood supply from the left portal vein and left hepatic artery, at the base of the umbilical fissure, and of other inflow vessels arising from the right portal vein; 2) dissection and ligation of the retrohepatic veins; and 3) division of the liver parenchyma between the right portion of the caudate process and the base of segments IV and the left side of segment VII to allow removal of the lobe (isolated caudate lobe resection).

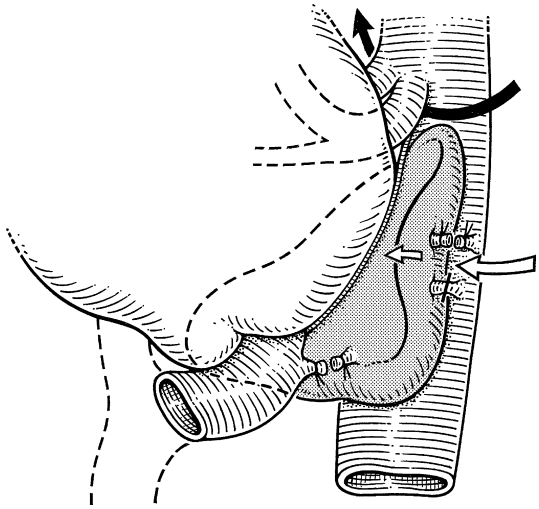


FIGURE 90B.53. Start of mobilization of the caudate lobe from the left. The caudate branch of the portal vein has been tied. The caudate lobe has been freed from the left side of the inferior vena cava (IVC) and turned medially (*small white arrow*). Dissection is proceeding between the vena cava and the caudate lobe (*large white arrow*). The retrocaudate hepatic veins are being tied. The *black arrow* indicates the tunnel between the middle and left hepatic veins and the IVC. Dissection of this tunnel allows placement of a clamp across the left and middle hepatic veins.

Dissection at the base of the umbilical fissure allows identification of the caudate vessels arising from the left side of the portal vein and the left hepatic artery, before these vascular structures enter the umbilical fissure (Figs. 90B.53 and 90B.54). The left lobe of the liver is mobilized and turned to the right. The left lateral margin of the caudate is freed by division of the fibrous extension of the tissue as it courses posteriorly to the IVC. This division allows access to the retrohepatic veins (see

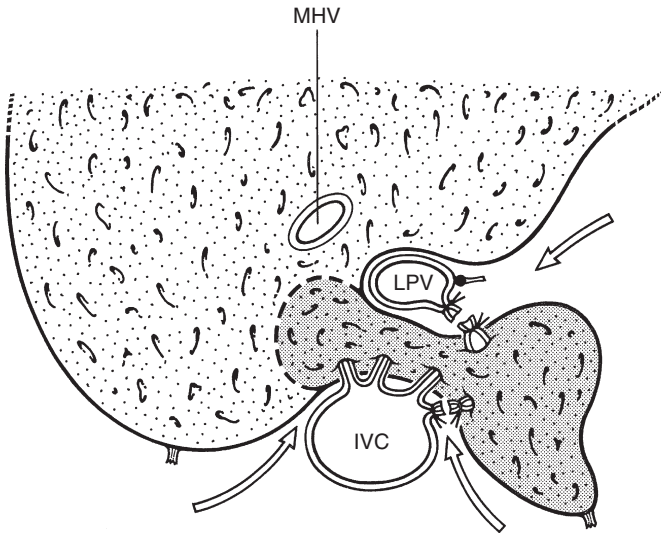


FIGURE 90B.54. Lines of approach (*arrows*) to free the caudate lobe. Compare with Figure 90B.51. The lesser omentum has been opened, and the caudate branch of the left portal vein has been tied. The ligamentous attachments of the caudate lobe posteriorly have been opened, and dissection of the retrohepatic caudate veins can be approached from the right or left side. IVC, inferior vena cava; MHV, middle hepatic vein; LPV, left portal vein.

Figs. 90B.51 and 90B.54). During this dissection, it becomes evident whether the caudate lobe is encircling the vena cava posteriorly, in which case no further attempt is made to free the lobe on the left side, but an approach should be made from the right (see Fig. 90B.54; Hasegawa et al, 1991a; Lerut et al, 1990).

After dividing the ligamentous attachments on the left side, the caudate can be elevated from the left, although providing adequate upward traction to expose the retrohepatic veins can be challenging, because there is often little parenchymal tissue to grasp. As the retrohepatic veins are encountered, they may be encircled and suture ligated or controlled with clips, working from the left side of the vena cava toward the right side; in this manner, complete mobilization can be performed (see Figs. 90B.51, 90B.53, and 90B.54). This technique is most suitable when the caudate lobe is not involved by a bulky tumor, such as in removal of the lobe in continuity to allow clearance in left hepatectomy for hilar cholangiocarcinoma. It is also valuable in extended left hepatectomy, during which it is our practice to attempt to use it as a matter of routine, because it allows less disturbance of the right liver.

A bulky tumor within the caudate lobe is often rigid, and upward mobilization of the caudate from the left is difficult and hazardous. In this case, the retrohepatic veins are best approached from the right side (see Fig. 90B.54; Lerut et al, 1990). Should right hepatectomy or extended right hepatectomy be necessary in continuity with caudate lobe resection, an approach from the right is easier and is a simple extension of the retrohepatic dissection. The right lobe is turned toward the left, and the retrohepatic veins are dissected serially, beginning from the inferior aspect of the caudate process and extending superiorly with division of all veins, until the major hepatic trunks are reached (Miyagawa et al, 1992). As this dissection is carried out, it is easy to extend it over the anterior surface of the IVC to the left side, until the caudate lobe is completely mobilized and freed from the vena cava (see Fig. 90B.54; Lerut et al, 1990).

For a right or left hepatic resection, which necessitates ligation of the middle hepatic vein, the caudate lobe is easily removed en bloc with the specimen without danger of tearing the posterior aspect of the middle hepatic vein, because it may be controlled extrahepatically for left-sided resections or intrahepatically for right-sided resections. In resection of the caudate lobe as an isolated procedure, and particularly if there is a bulky tumor within the caudate, it is important to recognize the risk of injuring the middle hepatic vein posteriorly during parenchymal dissection of the anterior aspect of the caudate lobe, which can result in substantial hemorrhage (Colonna et al, 1993). To prevent this, we have found it valuable to first isolate and control the left and middle hepatic veins extrahepatically, as described above (see Figs. 90B.41 and 90B.53). This maneuver provides temporary control during the parenchymal phase of dissection of the portion of the caudate lobe that lies anterior to the IVC, and it facilitates safe resection of large caudate tumors (Figs. 90B.55 and 90B.56). Some authors advocate splitting the liver anteriorly in the glissonian plane, thus separating the right and left liver and dividing the liver along the right margin of segment IV to approach the caudate lobe transhepatically (Yamamoto et al, 1992). A combination of these techniques allows preservation of middle hepatic venous flow and good control of bleeding. The resectional approach to performing a caudate lobectomy depends largely on the size and location of the lesion,

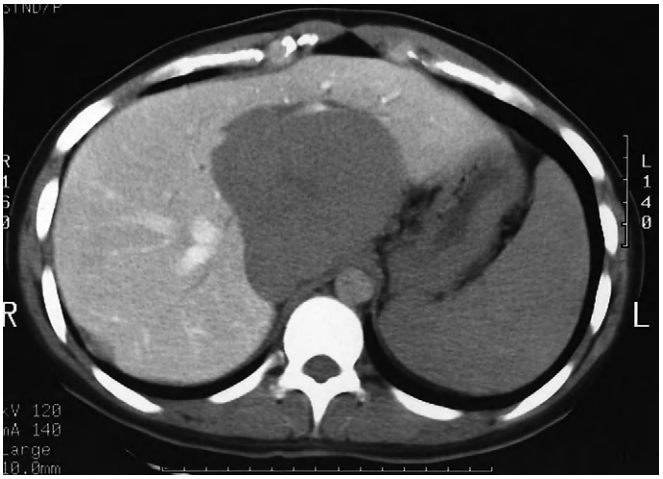


FIGURE 90B.55. Computed tomographic image of the liver of a 25-year-old woman with symptomatic focal nodular hyperplasia in the caudate lobe compressing the inferior vena cava and portal vein without invasion. Freeing of this tumor necessitated an approach to the retrohepatic veins from the right and left sides.

the type of associated resection, and the presence of scarring from any previous resection. In actuality, the liver frequently is rotated during the resection in order to approach it from both the left and right sides.

Preoperative imaging cannot accurately differentiate tumor invasion from compression of the IVC and of the portal vein, and thus most caudate lobe tumors warrant operative exploration to determine resectability. Many tumors that appear to invade the vena cava on preoperative imaging can be dissected

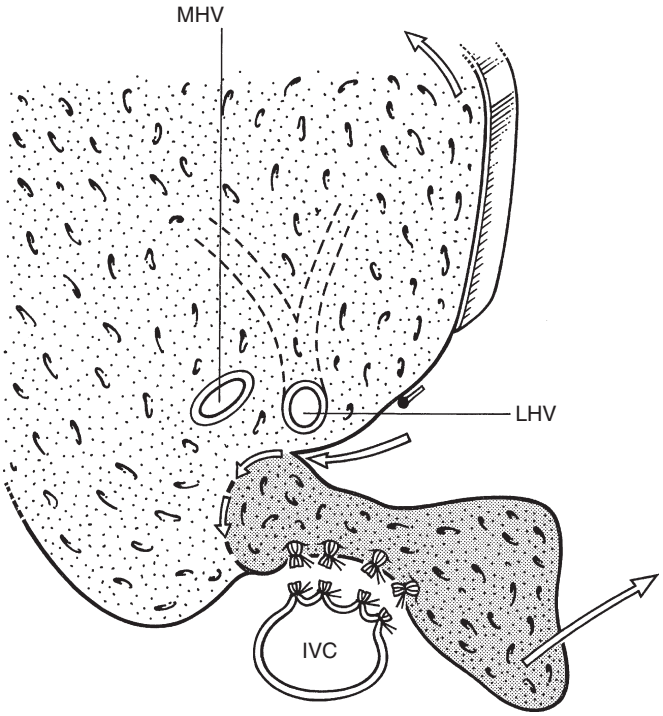


FIGURE 90B.56. Parenchymal phase of dissection (*arrows*). Note proximity of the left hepatic vein (*LHV*) and middle hepatic vein (*MHV*). The right portion of the caudate lobe lies just to the left of the MHV. IVC, inferior vena cava.

free of the cava in a tumor-free plane. In selected cases, the IVC can be resected in part or en bloc with the caudate lobe (Gardner et al, 1992; Takayama et al, 1991), but this is usually unnecessary. Short segments of the IVC can be repaired or reconstructed primarily or with autogenous grafts, whereas longer segments may require prosthetic grafts (Fig. 90B.57). A chronically occluded IVC can be resected without reconstruction, because abundant collateral vessels usually have developed (Takayama et al, 1991). Although techniques involving complete vascular isolation can be used for caudate lobe resection, this is usually not necessary.

Numerous series and case reports of caudate lobe resection are summarized in Tables 90B.3 and 90B.4. Nimura and associates (1990B) reported a large series of caudate resections for hilar cholangiocarcinoma. They described 45 complete caudate lobe resections for microscopic involvement of caudate bile ducts, including three isolated caudate lobectomies. The operative mortality rate was 7%. Elias and coworkers (1992) reported 20 resections involving the caudate lobe, only seven of which were complete caudate lobectomies. There were no operative deaths. Bartlett and colleagues (1996) reported a retrospective review of 21 consecutive complete caudate lobe resections over a 30-month period. Four of the 21 patients underwent complete isolated caudate lobectomy. The most common diagnosis was metastatic colorectal cancer in nine patients, and the most common procedure was an extended left hepatectomy with en

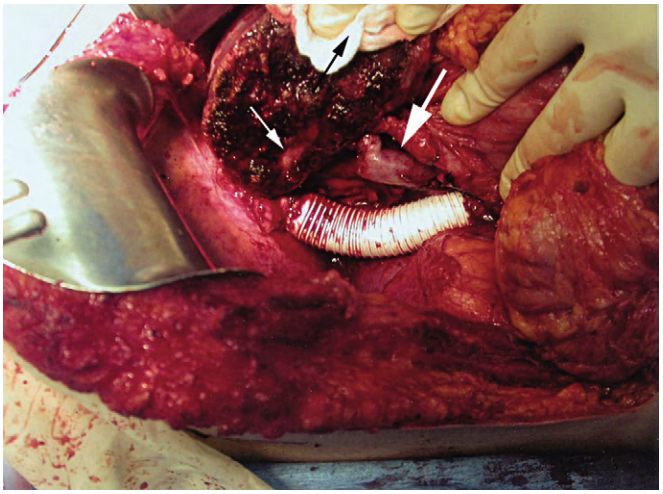


FIGURE 90B.57. Intraoperative photograph from the patient's right. Right lobectomy has been carried out together with excision of the caudate lobe and a portion of the inferior vena cava (IVC). Segments II and III are drawn upward and to the left by the operator's hand (*black arrow*). The middle hepatic vein coursing to join the upper IVC is seen (*large white arrow*); the IVC has been replaced by a Dacron graft. The main trunk of the portal vein and its left branch are illustrated (*small white arrow*). Tumor had occupied the dangerous portion of the caudate lobe, lying between the right branch of the portal vein, the middle hepatic vein, and the IVC.

Table 90B.3

Literature Review of Caudate Lobe Resections

Reference	No. Patients	Diagnosis	Procedure	Comments
Takayama et al, 1990	1	Hepatoblastoma	Left hepatectomy with complete lobectomy	Neoadjuvant therapy
Lerut et al, 1990	1	Benign adenoma	Isolated caudate lobectomy	Technique: right-sided retrohepatic approach to caudate veins
Moriura et al, 1990	3	Varied	Combined IVC resection	Technique: IVC reconstruction
Nimura et al, 1990b	45	Cholangiocarcinoma	Complete en bloc caudate lobectomy and IVC resection	Advocate routine complete caudate resection for cholangiocarcinoma
Takayama et al, 1991	1	Hepatoblastoma	Extended left hepatectomy with caudate lobectomy and IVC resection	No IVC reconstruction necessary after resection for chronic occlusion
Gardner et al, 1992	1	Metastatic colonic cancer	Caudate lobectomy with IVC resection	Technique: use of Gott shunt during IVC resection
Yamamoto et al, 1992	1	Hepatoma	Isolated caudate lobectomy	Technique: transhepatic approach
Elias et al, 1992	20	Varied	7 complete, 13 partial, 1 isolated caudate lobectomy	Emphasize varied approach to caudate; no deaths
Miyagawa et al, 1992	1	Benign adenoma	Isolated caudate lobectomy	Technique: vascular occlusion with temporary caval occlusion
Iyomasa et al, 1992	1	Cholangiocarcinoma	Isolated caudate lobectomy	Technique: isolated caudate lobectomy
Colonna et al, 1993	3	Focal nodular hyperplasia, metastatic colonic cancer	3 isolated caudate lobectomies	Technique: left approach to caudate veins
Shimada et al, 1994	9	Hepatocellular carcinoma	2 complete caudate lobectomies; 7 partial caudate lobectomies	High morbidity, high rate of early recurrence for HCC
Kosuge et al, 1994	1	Hepatoma	Isolated caudate lobectomy	Technique: counterstaining
Yanaga et al, 1994	2	Hepatoma	Isolated caudate lobectomy	Technique: vascular isolation by occlusion of hepatic veins
Bartlett et al, 1996	21	Varied	21 complete caudate lobectomies; 4 isolated caudate lobectomies	Technique: no vascular isolation
Hawkins et al, 2005	150	Varied (all malignant)	21 isolated caudate lobectomies	Technique: no vascular isolation

Reported from 1990 through 1996 and for 2004.
HCC, hepatocellular carcinoma; IVC, inferior vena cava

Modified from Bartlett D, et al, 1996: Complete resection of the caudate lobe of the liver: technique and results. Br J Surg 83:1076-1081.

Table 90B.4

Summary of Case Control Studies Comparing Laparoscopic with Open Partial Hepatectomy

Reference	No. Patients	Disease	Operative Time (min)	Blood Loss (mL)	Length of Stay (Days)	Morbidity (%)	Margin <1 cm (%)
Mala et al, 2002	15 vs. 14	Colorectal metastases	187 vs. 185	600 vs. 500	4 vs. 8.5*	13 vs. 29	29 vs. 37
Lesurtel et al, 2003	18 vs. 20	Mixed	202 vs. 145	236 vs. 429*	8 vs. 10	11 vs. 15	6 vs. 0
Morino et al, 2003	30 vs. 30	Mixed	150 vs. 140	320 vs. 479	6 vs. 8*	7 vs. 7	43 vs. 40
Farges et al, 2002	21 vs. 21	Benign	177 vs. 156	218 vs. 285	5 vs. 6.5*†	10 vs. 10	—
Shimada et al, 2001	17 vs. 28	HCC	325 vs. 280	400 vs. 800	12 vs. 25*†	6 vs. 11	41 vs. 50‡
Laurent et al, 2003	13 vs. 14	HCC	267 vs. 182*	620 vs. 720	8 vs. 12.5	No difference§	15 vs. 15‡

*$P < .05$
†Mean
‡<5 mm
§No significant difference was found among the specific complications analyzed.
HCC, hepatocellular carcinoma

bloc caudate lobectomy. In a more recent review from MSKCC (Hawkins et al, 2005), 150 patients underwent caudate lobectomy for cancer, including 21 isolated caudate resections (see Table 90B.3). The most common indications were metastatic colon cancer and hilar cholangiocarcinoma. Thirty patients required resection and reconstruction of the portal vein or vena cava (see Fig. 90B.57), nine patients (6%) died, and the death rate was significantly higher in patients who underwent major vascular reconstruction.

Resection of Segments II, III, IV, V, VI, VII, and VIII

Resection of isolated segments of the liver or combined resections of two or more segments necessitates control of the relevant pedicles (Fig. 90B.58). These resections are mentioned briefly here, but the technical details are described in Chapter 92.

Resection of Segment IV

Segment IV may be resected in its entirety (*quadrate lobe resection*), or a subsegmental resection of segment IVb can be done alone or in combination with an extended right hepatic resection. The procedure involves lowering the hilar plate to avoid injury to the left bile duct, exposure and control of vessels within the umbilical fissure, and parenchymal dissection to the right of the falciform ligament and along the principal scissura. Posteriorly, parenchymal transection separates segment IV from the upper surface of the right side of segment I. When combined with a right hepatectomy, a partial segment IV resection is feasible, because the inflow to segment IV comes from feedback vessels from the left, as they branch from the main left pedicle within the umbilical fissure. Thus, if a partial resection of segment IV is required to preserve parenchyma, the remnant of segment IV is well perfused.

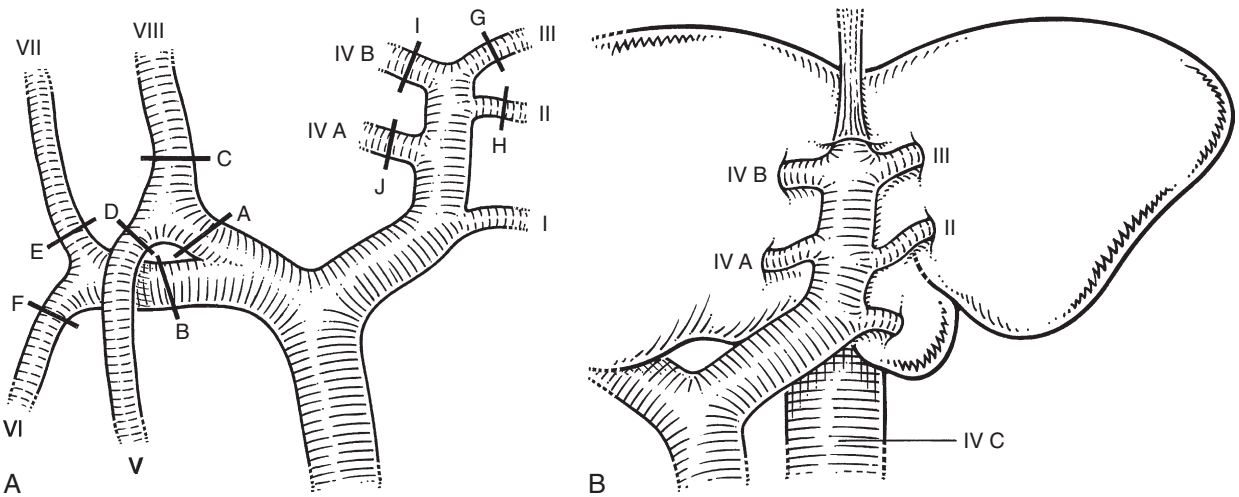


FIGURE 90B.58. A, Distribution of pedicles and points of control (*A* through *J*) for segmental resections. Note that control of the anterior (**A**) or posterior (**B**) sectoral pedicles allows anterior or posterior right sectorectomy. Control of pedicles at points *A, I,* and *J* allows central hepatectomy. **B,** Detailed diagram of the umbilical fissure of the liver (see also Fig. 90B.32). After the umbilical fissure is entirely exposed, the relevant portal triads to segments II, III, and IV are exposed. If the entire segment is to be removed, all portal pedicle branches from the umbilical portion to the right are divided. If segment IVb is to be resected only, its pedicle is divided. For left lobectomy, pedicles to both segments II and III are divided. For isolated segments II and III resection only, the relevant pedicle is controlled (see also Chapter 83 and Figs. 90B.49 and 90B.50).

Resection of Segments IV and V

The initial steps for removing segments IV and V are the same as those for an isolated segment IV resection. The liver parenchyma is split to the right of the falciform ligament, and the inflow vessels to segments IVa and IVb are divided. The liver tissue is then transected in an oblique line parallel to the right scissura to preserve segment VIII. This transection is then carried toward the right portal pedicle, and the middle hepatic vein is divided in the middle of the liver as the prinicipal plain is traversed. As the parenchyma is divided, the inflow pedicle to segment V is located, secured, and divided. This can be test clamped prior to division to ensure that the right anterior pedicle and inflow to segment VIII are preserved. The depth of parenchymal transection continues to include the gallbladder fossa and cystic plate, but to avoid injury, it must remain above the right and left hilar structures. The right and left parenchymal transection planes are then joined at this level to complete the resection (see Figs. 90B.48 and 90B.50). Resection of segments IVb and V, with preservation of segment IVa, is more commonly performed, often for gallbladder cancer, either en bloc with the gallbladder or after it has been removed in cases of incidental gallbladder carcinoma.

Resection of Segments V and VIII (Right Anterior Sectorectomy)

The primary indications for an isolated resection of segment VIII include small, solitary metastases and focal HCC in patients with cirrhosis. For resection of segments V and VIII (right anterior sector), the left plane of dissection is within the principal plane (Cantlie's line). The middle hepatic vein can be preserved or sacrificed, depending on the oncologic necessity. The lateral dissection is performed within the right portal scissura. The right hepatic vein must be preserved at its junction with the cava to allow adequate venous drainage of the right posterior sector, unless a large accessory right hepatic vein is present and can be preserved during right liver mobilization. The planes of parenchymal transection are as described by Makuuchi and colleagues (1993a). Inflow control is obtained by dividing the right anterior sectoral pedicle, and this should be test clamped prior to division to ensure that the posterior pedicle is intact.

Central Hepatic Resection

Central hepatic resection is a major procedure that involves en bloc resection of segments IV, V, and VIII. This procedure involves resection of liver parenchyma supplied by the right and left portal pedicles. This procedure is useful in preserving normal liver parenchyma for patients with central liver tumors and may include resection of segment I, particularly in selected patients with hilar cholangiocarcinoma (Ogura et al, 1998).

The approach involves a combination of the techniques described for resection of segment IV and resection of the right anterior sector. During the parenchymal transection phase, it is necessary to ligate the middle hepatic vein, because the dissection crosses the principal plane near the vena cava. Caution must be exercised to preserve the left hepatic vein, and the right hepatic vein must also be carefully identified and preserved (Kanematsu et al, 1984). For large centrally placed tumors that impinge on the area of the umbilical fissure, care must be taken not to damage the left hepatic duct at the base of the liver, within the hilar plate, or within the umbilical fissure. This is illustrated in Figure 90B.38.

Resections of Segments VI and VII (Right Posterior Sectorectomy)

For isolated resection of segments VI or VII, the major plane of dissection is usually just posterior to the right portal scissura. Inflow control is obtained by securing the segmental branches to segment VI or VII, the right posterior sectoral branches, within the liver (Reynaud et al, 1991). The right hepatic vein can be sacrificed for a segment VI resection. For an isolated segment VII resection, the right hepatic vein should be preserved to facilitate venous drainage of the remnant segment, VI unless an adequate accessory (inferior) right hepatic vein is present. Resection of segments VI and VII together (right posterior sector) can be done with or without sacrifice of the right hepatic vein, because venous drainage from segments V and VIII (right anterior sector) is carried by the middle hepatic vein.

Resection of Segment II or III

Isolated resection of segment II or III (see Fig. 90B.50) may be performed when it is necessary to preserve as much of the left lateral sector as possible. This is frequently the case when patients have undergone a prior liver resection or have underlying parenchymal disease. When isolated segmental resections in this area are performed, inflow control is achieved by isolation of the pedicles to segment II or III within the umbilical fissure, just left of the falciform ligament (Fig. 90B.59; see Fig. 90B.58). Ligation of the relevant pedicle provides demarcation of the parenchyma that guides resection. In these resections, the left hepatic vein must be identified and preserved to leave adequate venous drainage for the retained segment.

HEPATIC RESECTION FOR HILAR CHOLANGIOCARCINOMA

In the case of tumors close to the hilus of the liver or near the confluence of the hepatic ducts, a concurrent hepatic resection is usually necessary to obtain tumor clearance. Although the techniques described here are sometimes applicable for HCC involving hilar structures, the situation occurs more frequently when hilar cholangiocarcinoma extends into the adjacent liver or involves major vascular structures (Fig. 90B.60; see Chapter 50B). In this circumstance, the added complication of preoperative biliary tract obstruction is almost always present.

Some authors, particularly surgeons from Japan, routinely use preoperative biliary drainage and PVE for treating patients with hilar cholangiocarcinoma. We use these techniques selectively in deeply jaundiced patients or when the FLR is inadequate and PVE is required. In our experience, PVE is seldom needed (Kennedy et al, 2009; see Chapter 50B). In a series of 226 patients submitted to extended hepatic resection at MSKCC, the important preoperative variables associated with postoperative death were the presence of cholangitis, a preoperative creatinine value greater than 1.3 mg/dL, and a total bilirubin greater than 6 mg/dL. Five of 14 patients who died had biliary reconstruction procedures (Melendez et al, 2001). Most patients referred to MSKCC had already undergone biliary drainage procedures, sometimes inappropriately, via either percutaneous or endoscopic techniques. Many patients develop biliary infection secondary to drain placement, and we found that postoperative mortality is strongly related to presence of

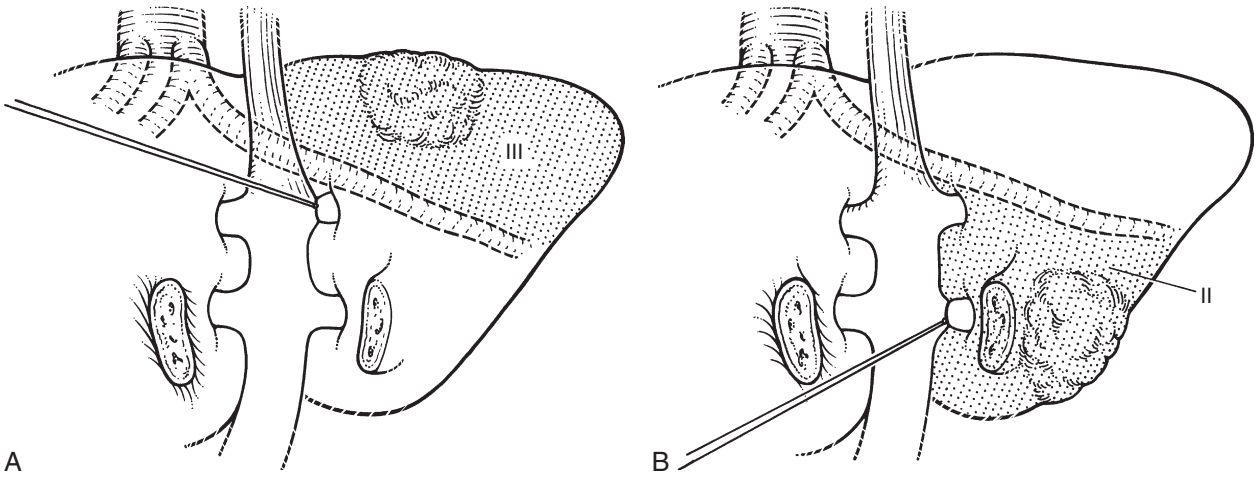


FIGURE 90B.59. **A** and **B,** Ligation of pedicles to segments II and III (see also Chapter 83 and Figs. 90B.48 and 90B.50).

infection. Similarly, in a study of 1803 consecutive liver resections performed from December 1991 through September 2001 at MSKCC, it was shown that patients with biliary malignancy had the highest morbidity and mortality of any patient group (Jarnagin et al, 2002). The indications for preoperative biliary drainage require further study, in particular, to define the criteria that necessitate such preoperative preparations. It should be noted that if preoperative PVE is needed, the FLR may require initial biliary decompression to facilitate an optimal hypertrophic response.

The major limiting factor for resection of hilar cholangiocarcinoma is related to involvement or compression of adjacent vessels and, in particular, main or branch portal vein involvement (Beazley et al, 1984; Blumgart et al, 1984; Voyles et al, 1983). The pattern of vascular involvement, taken in conjunction with ductal extension of tumor shown at cholangiography or on cross-sectional imaging (see Chapter 50B), gives valuable preoperative information to the surgeon with regard to the extent of operation and operative strategy (Burke et al, 1998; Jarnagin et al, 2002).

Local bile duct resection for small tumors not extending to the hilum or into the intrahepatic bile ducts or involving major vessels may be possible, but for more advanced lesions, liver resection is necessary to effect tumor clearance. Liver resection is mandatory when the lesion extends unilaterally into the right or left liver, and it is possible when the contralateral half of the liver is free of tumor and has an intact blood supply, making biliary reconstruction a viable option. More recent reports suggest that hepatic resection should be used in virtually all cases, because tumor clearance and long-term survival have been linked directly to hepatic resection (see Chapter 50B; Jarnagin et al, 2001a).

Hepatic resection in some instances may be limited to removal of the quadrate lobe (segment IV) or may include removal of segment I (caudate lobe); however, the procedures described subsequently relate to the more extensive resections,

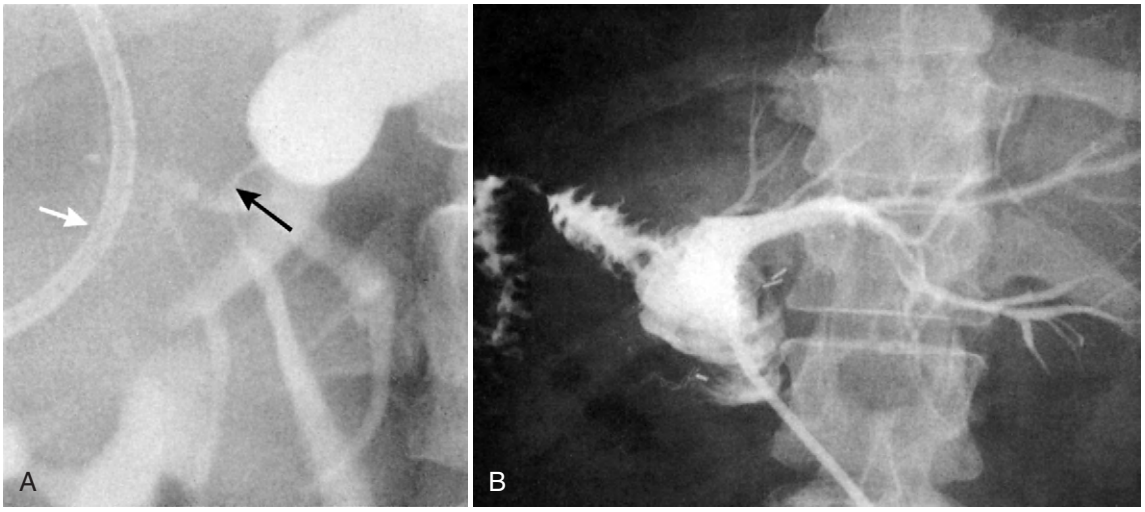


FIGURE 90B.60. **A,** Percutaneous transhepatic cholangiogram shows cholangiocarcinoma at the confluence of the bile ducts (*black arrow*). The left hepatic duct is involved only at its origin, but distally it is grossly dilated. A tube (*white arrow*) has been passed into the right hepatic ductal system using a percutaneous technique. There was involvement of the right branch of the portal vein by tumor, and the right hepatic artery was encased. Right hepatic lobectomy with tumor clearance was obtained. **B,** Tubogram in the postoperative period shows hepaticojejunostomy to the left hepatic duct at the level of the umbilical fissure. The patient was alive, well, and free of recurrence 3 years after operation.

right or left hepatectomy or extended right hepatectomy, which usually are necessary in these circumstances. The variations in technique compared with those described earlier relate to the dissection of the tumor at the hilus of the liver. A careful and detailed examination of the preoperative imaging is mandatory for these cases to assess for resectability and to plan the operation.

Preliminary laparoscopy before open exploration of the abdomen saves a proportion of patients with liver metastases or peritoneal seeding from a nontherapeutic laparotomy (Jarnagin et al, 2000). It is important to examine the liver for extension of the tumor and to obtain a biopsy any suspicious areas (Blumgart et al, 1984). Excisional biopsy with frozen section analysis of suspicious distant lymph nodes should be performed, as nodal involvement in distant lymph node basins—celiac, retropancreatic, and paraaortic—will negate any therapeutic benefit of resection. Should distant disease be present, a biliary bypass procedure can be performed if feasible, or, alternatively, patients are maintained postoperatively with either percutaneous or endoscopic stents.

To reach the confluence of the bile ducts and explore the related vessels, the operator must explore the area beneath the quadrate lobe. If no tumor invasion is evident at this point, the hilar plate is lowered according to the technique of Hepp and Couinaud (1957; Fig. 90B.61; see Chapter 29). If the left hepatic duct can be so lowered, the tumor is usually extending into the right hepatic duct, and a right hepatectomy is required. It is usually clear at this stage whether a sufficient length of the left bile duct can be preserved beyond the line of resection to allow tumor clearance and enable adequate reconstruction. In some cases, if the base of the quadrate lobe is involved over a limited area, the left duct may be identified further to the left, at the base of the umbilical fissure. Further exploration of the hilus can be facilitated by splitting the liver in the glissonian plane down to the hilus (Fig. 90B.62; Blumgart, 1980; Goff et al, 1967; Templeton & Dodd, 1963).

Before any form of resection is undertaken, involvement of the caudate lobe must be assessed. This is also assessed on preoperative imaging, specifically looking for bile duct dilatation in the caudate lobe, which is explored by exposing the IVC below the liver. The lowermost hepatic veins are divided to allow palpation of the caudate lobe from behind. Removal of the caudate lobe as an integral part of the operation is frequently necessary for left-sided tumors and is recommended as routine for all hilar tumors by some authors (Mizumoto et al, 1986; Nimura et al, 1990b). Central hepatic resection involving segments IV, V, and VIII together with the caudate is also possible (Ogura et al, 1998).

To allow for good exposure of the portal vessels and to facilitate a complete portal lymph node dissection, the common bile duct can be transected early in the operation, just above the duodenum (Figs. 90B.63 and 90B.64), and turned upward. Alternatively, if it is doubtful that resection is possible, the surgeon can attempt to do as much dissection as possible to expose the portal vein and hepatic artery without committing to bile duct transection. When the bile duct is to be transected, the duodenum is mobilized, and the bile duct is transected and ligated immediately above the duodenum. The duct is turned upward and forward, clearing the vessels of fascia and lymph nodes. As dissection proceeds, the gallbladder is also mobilized, so that the entire extrahepatic biliary apparatus is turned forward and upward (Fig. 90B.65). This allows a safe approach to the retroductal structures lying at the confluence behind the tumor.

The situation encountered next would be one of the following three scenarios: First, in patients whose tumor does not

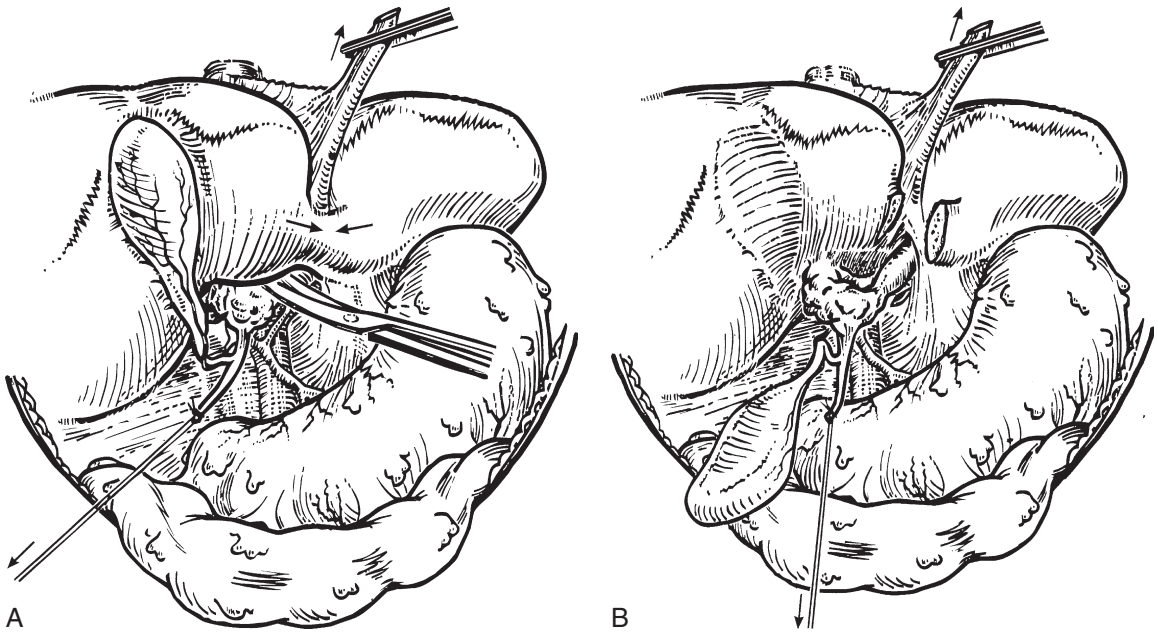


FIGURE 90B.61. A, Dissection to expose structures at the hilus of the liver. The ligamentum teres is strongly elevated, and the liver is turned upward. Dissection at the base of the quadrate lobe with scissors lowers the hilar plate. The bridge of liver tissue (*pair of arrows*) at the base of the umbilical fissure is still intact. The common bile duct is divided immediately above the duodenum, and its lower part is separated together with the associated connective tissue and lymph nodes. **B,** The biliary confluence has been delivered by lowering of the hilar plate, and the bridge of tissue at the base of the umbilical fissure has been divided.



FIGURE 90B.62. Hepatotomy in the glissonian plane. The left liver (*black arrow*) is separated from the right liver (*small white arrow*). The common bile duct has been transected and is elevated on a tie (*large white arrow*). A sling is passed about the left branch of the portal vein, which is involved by a cholangiocarcinoma just beyond this point, at the confluence of the bile ducts and extending into the left hepatic duct. The hepatic artery is dissected and shown to be free of tumor.

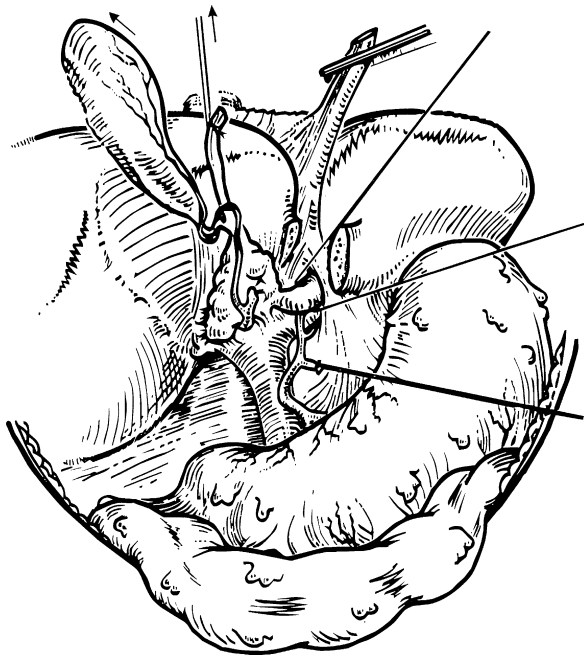


FIGURE 90B.63. The entire extrahepatic biliary apparatus has been elevated, together with the associated connective tissue and nodes, to allow dissection anterior to the bifurcation of the portal vein and elevation of the tumor, which is completely mobilized; the right hepatic artery has been tied and divided, and the portal vein has been skeletonized. The tumor extends into the right liver, and stay sutures are placed in the left hepatic duct.

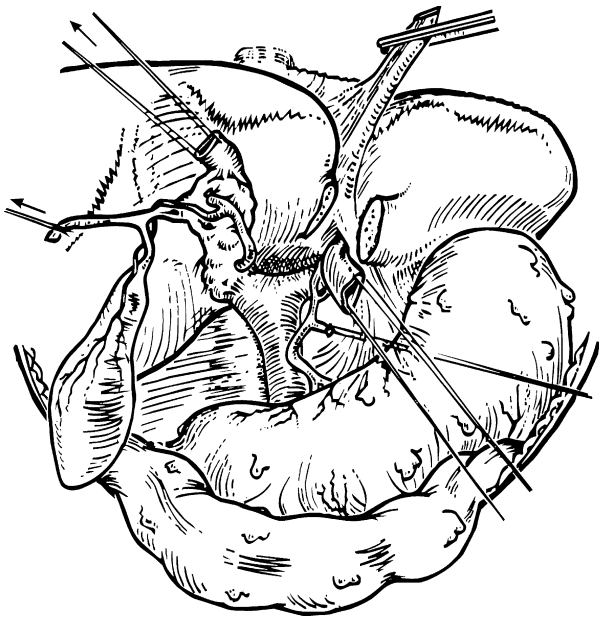


FIGURE 90B.64. The left hepatic duct has been divided, and the bifurcation of the portal vein has been cleared; however, the tumor is still attached to the right portal vein and extends into the right liver. An alternative method would leave the transection division of the bile duct until a later stage, during parenchymal transection.

involve the portal vein or hepatic artery, the lesion can be freed and turned forward. If the caudate lobe is involved, it should be mobilized as described earlier and freed for removal as an integral part of the resection. The left hepatic duct, having been previously mobilized, is now located, dissected, and secured with stay sutures. It is transected, and the specimen side is turned upward toward the right, which provides better exposure of the portal vein and hepatic artery (Fig. 90B.66). Alternatively, if the tumor extends into the left hepatic duct, it becomes necessary to transect the right duct initially and turn it to the left. It is also possible, and often practiced, to dissect the duct but delay transection until the time of parenchymal transection to maximize exposure and gain the most length for duct transection. In any event, when the ductal structures and the tumor are elevated, the relevant hepatic artery can be ligated, and the branch of the portal vein supplying the portion of the liver to be removed can be dealt with by clamping and oversewing in a standard fashion (see Fig. 90B.65A). An endovascular stapler can also be used to divide the portal vein. Hepatic resection proceeds as described previously for parenchymal transection, and the hepatic veins are controlled extrahepatically or within the liver substance (see Fig. 90B.65B).

The second situation is that the tumor may involve the right or left branch of the portal vein, with the area of bifurcation of the portal vein being entirely free. In this circumstance, the procedure is similar to that described earlier with the exception of the fact that transection of the affected portal branch may be difficult because of the proximity of the lesion. In this case, the portal vein transection can be postponed until after parenchymal division is complete to allow the best exposure for portal vein resection and, more importantly, for the reconstruction. If exposure is adequate, the portal vein can also be divided and reconstructed immediately, prior to parenchymal division.

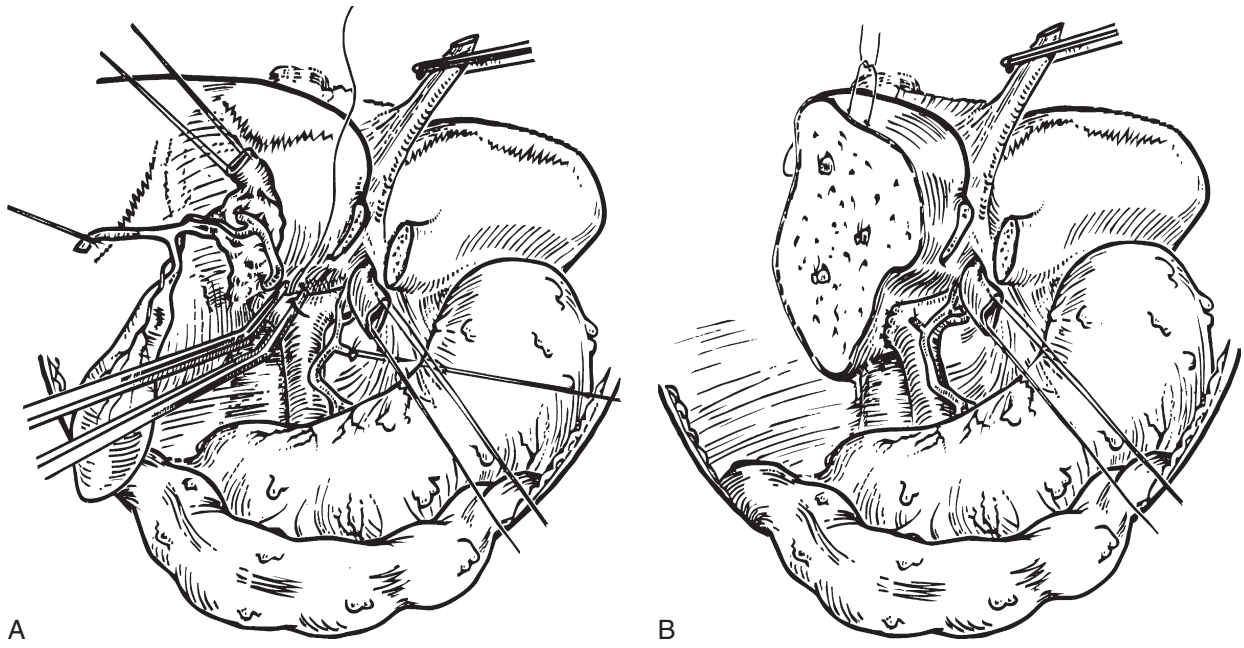


FIGURE 90B.65. **A,** Clamps are applied to the right branch of the portal vein, and a suture is passed through the vein between the clamps before the division of the vein and its subsequent suture. **B,** The right branch of the portal vein has been divided and oversewn using a 3-0 vascular suture. The right liver has been removed together with the attached biliary structures containing the tumor. The left hepatic duct is held on stay sutures, ready for subsequent anastomosis.

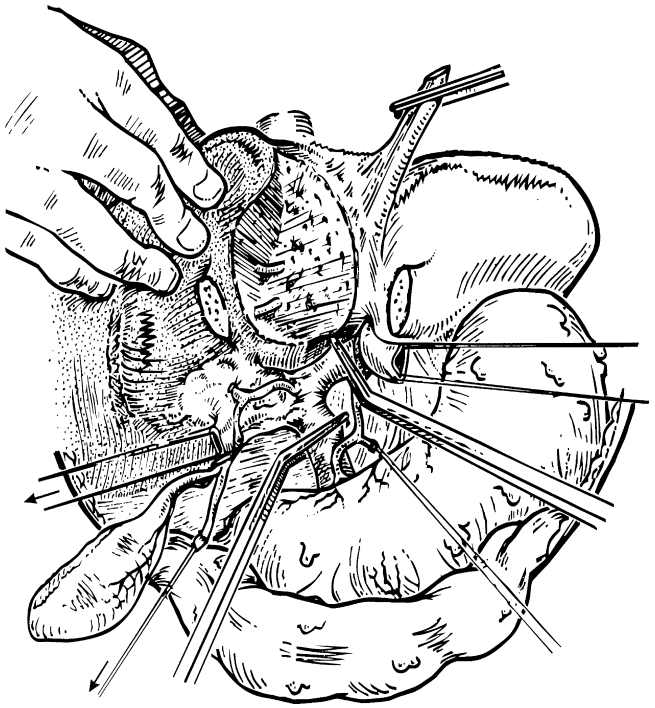


FIGURE 90B.66. Excision of hilar cholangiocarcinoma involving the bifurcation of the portal vein. The tumor is firmly attached to the portal vein. The initial steps are as described in Figures 90B.61, 90B.63, and 90B.64. The left hepatic duct has been identified and transected, and the right hepatic artery has been divided. The main trunk of the portal vein and its left branch have been dissected and are held in clamps; the tumor is firmly attached in the region of the bifurcation of the portal vein. Resection sometimes is facilitated by starting a split of the liver substance immediately to the right of the falciform ligament, dividing the feedback vessels that course to supply the quadrate lobe (segment IV).

In the third situation, the tumor may encroach on the portal vein bifurcation or involve the bifurcation directly. If this situation is encountered, a more extensive procedure is required. If the portal vein bifurcation is involved, and the tumor extends to involve the right ductal system, an extended right hepatectomy proceeds as follows: The common bile duct and gallbladder are mobilized and turned upward as described previously. Lowering of the hilar plate, as described earlier, is done if possible, and the left hepatic duct and the left portal vein are dissected. The right hepatic artery is ligated, but the left hepatic artery is preserved. Stay sutures are placed, and the left hepatic duct is transected. The left branch of the portal vein and its main trunk are cross-clamped (see Fig. 90B.66), and the affected segment of portal vein at the bifurcation is freed and turned to the right together with the medial part of the left hepatic duct (Fig. 90B.67). A direct anastomosis is performed between the main trunk of the portal vein and its own left branch (Fig. 90B.68). This anastomosis allows maintenance of an intact vascular supply to the left lobe.

The extended right hepatectomy proceeds along standard lines as described previously. As mentioned above, the portal vein resection can be postponed until the end of the procedure, after parenchymal transection is complete, to optimize exposure. If necessary, the caudate lobe is removed en bloc with the tumor. Biliary-enteric continuity is restored by fashioning a hepaticojejunostomy with a Roux-en-Y loop of jejunum to the left bile duct stump (see Fig. 90B.68).

Alternative methods for reconstruction of the portal vein using the splenic vein have been proposed (Longmire et al, 1973). An interposition of an autogenous venous graft may be necessary, if a long segment of portal vein is resected. If left hepatectomy is necessary, the principles of the procedure are as described earlier, but portal vein reconstruction may be more difficult.

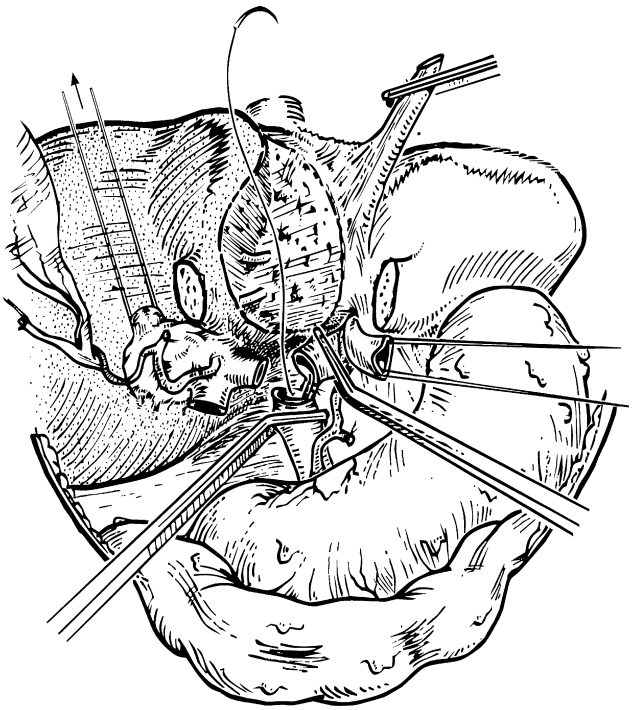


FIGURE 90B.67. The main trunk of the portal vein is divided, as is its left branch. The extrahepatic biliary apparatus, the confluence of the bile ducts, the tumor, and the bifurcation of the portal vein have been separated and are left attached to the right liver. The exposed ends of the main trunk of the portal vein and its left branch are approximated. End-to-end anastomosis is carried out using an over-and-over 4-0 vascular suture. When this anastomosis has been completed, the initial right hepatic lobectomy is completed, leaving a remnant of the liver comprising segments I, II, and III supplied by the left hepatic artery and the left branch of the portal vein and draining through the left hepatic duct. Individual caudate ducts exposed during the resection must be oversewn carefully or individually anastomosed. Alternatively, segment I, the caudate lobe, may be removed.

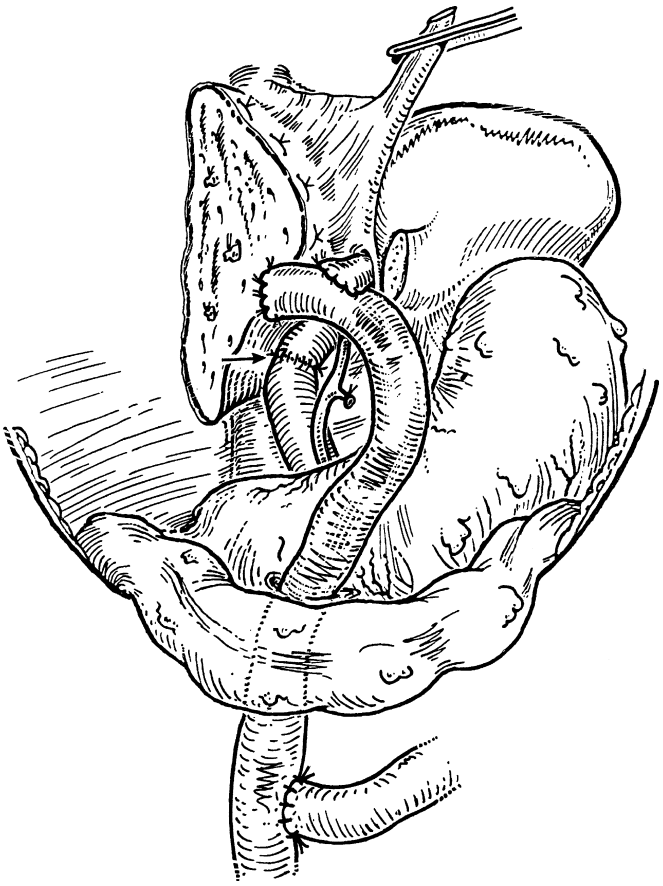


FIGURE 90B.68. The right hepatic lobectomy has been completed, with the line of resection running just to the right of the falciform ligament. The portal vein anastomosis is shown (*arrow*). A Roux-en-Y loop of jejunum is brought up in a retrocolic fashion and is anastomosed to the exposed left hepatic duct (see also Fig. 90B.60B).

In some cases, the division of the intrahepatic right or left hepatic ducts may be delayed until the final phase of parenchymal transection, and many surgeons prefer this approach. The selection of patients with hilar cholangiocarcinoma for liver resection and the results are discussed further in Chapter 50.

CRYOABLATION-ASSISTED HEPATIC RESECTION

Cryoablation, or the destruction of tissues by a freeze-and-thaw process, is a recognized approach to the treatment of malignant tumors (see Chapter 85B). The destruction of hepatic tumors using cryoablation is well described. Most studies (Atkinson et al, 1992; Charnley et al, 1989, 1991; Horton et al, 1991; Onik et al, 1991, 1993; Ravikumar & Steele, 1989; Ravikumar et al, 1987, 1991) report in situ freezing of hepatic tumors, and this is described in detail in Chapter 85B. The use of the cryoprobe as a device to assist during resection also has been suggested (Welling & Lamping, 1990) and developed (Polk et al, 1995).

Cryosurgery is used to assist resection in three particular situations. First, wedge resections, especially for lesions situated on the dome of the liver, are fraught with difficulty, not only regarding control of hemorrhage within the depths of the wedge but also in obtaining tumor-free margins. Wedge resections of the liver have been associated with an extremely high local recurrence rate. A major reason for the positive margin associated with wedge resections is the likelihood of fracturing the specimen along the interface of the hard tumor and soft liver. Freezing a rim of normal hepatic tissue around the tumor prevents fracture along this tumor-liver interface. Second, in many patients, major hepatic resection is required for removal of unilateral lesions, but accompanying minor lesions in the contralateral lobe could be resected if only a small amount of functional hepatic tissue were removed. Third, although cryosurgery has been used in the management of HCC (Zhou, 1992a, 1992b), it has been used in a cryoablative manner. The use of cryoablation-assisted resection in cases of HCC in the cirrhotic liver allows removal of tumors with adequate margins of clearance and maximum preservation of functional parenchyma.

Technique

The liver is examined by bimanual palpation and IOUS using a 7.5-mHz transducer, and lesions suitable for cryoablation-assisted resection are identified. The Glisson capsule is scored with diathermy at the point of insertion of the selected cryoprobe (Fig. 90B.69), which is gently inserted using direct vision

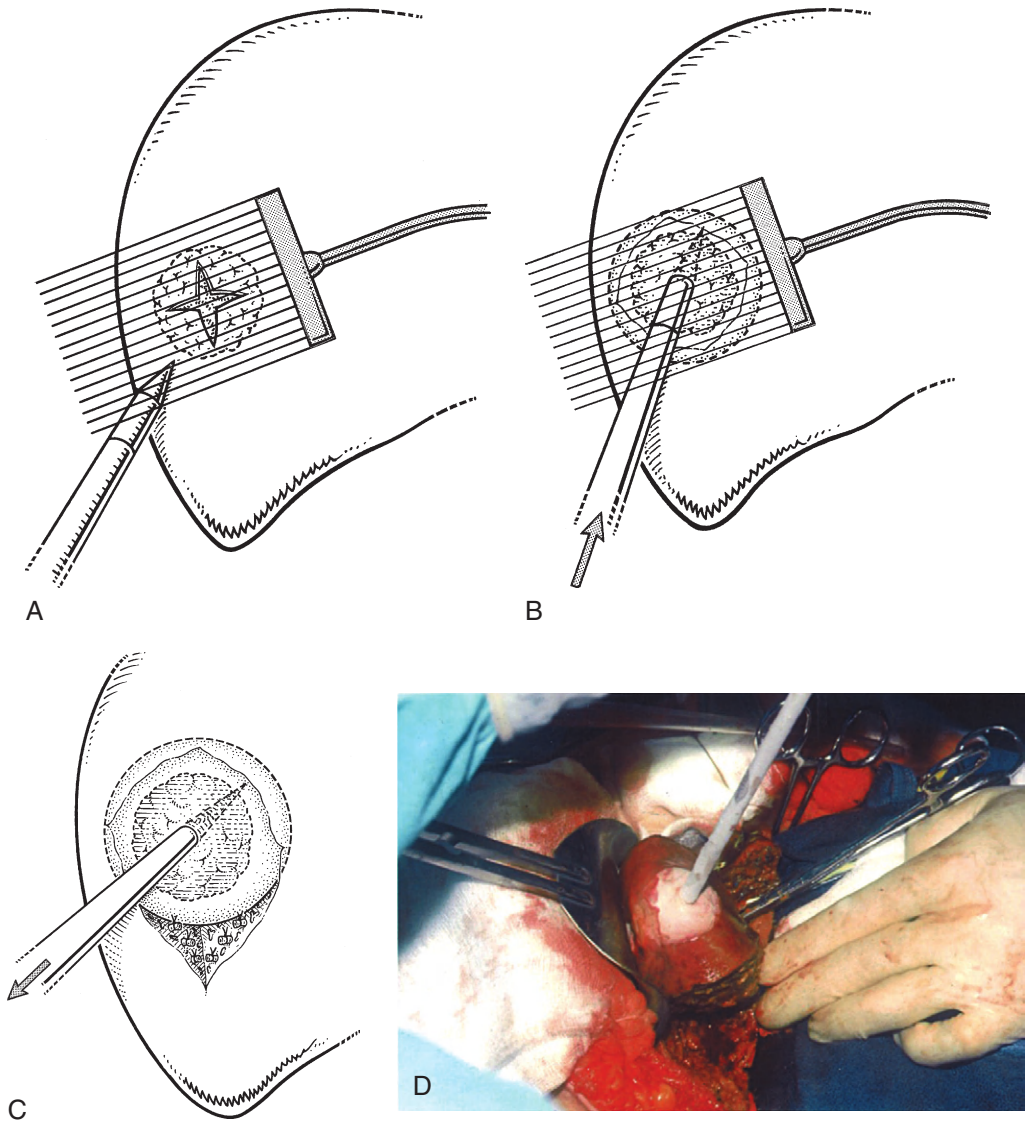


FIGURE 90B.69. **A,** Tumor is located using intraoperative ultrasound (US). The Glisson capsule is scored in cruciate fashion with the diathermy. **B,** The cryoprobe is introduced, and with its position controlled using US guidance, the tumor is frozen to approximately 1 cm of clearance. **C,** The cryoprobe is used as a handle to manipulate the tumor, which is excised at the ice ball's edge. **D,** Intraoperative photograph shows a cryoprobe inserted into a tumor in segment VI. The tumor is being removed using cryoablation-assisted technique.

and guided by US to the center of the lesion to be resected. Laparotomy pads are placed to protect adjacent structures. We occlude vascular inflow (Pringle maneuver) before starting the freeze cycle. Once the freeze cycle is initiated, US is used to monitor freezing. The freeze margin is easily seen as a hyperechoic rim with posterior acoustic shadowing that slowly develops from the center of the lesion. This margin is allowed to reach a distance of approximately 1 cm outside the periphery of the tumor (see Fig. 90B.69). At this point, hepatic vascular inflow occlusion is temporarily released. Two minutes are allowed for reperfusion of the liver after initial freezing, at which time the Pringle maneuver can be reinstituted for resection of the parenchyma. To maintain the ice ball at a constant size during resection, we allow freeze and thaw cycles of 1 minute each during the resection procedure; this cycling prevents extension of the ice ball or inadvertent removal of the probe, which can be used as a gentle handle to manipulate the lesion during resection. Dissection is performed directly on the ice ball or at a slight distance away from it (see Fig. 90B.69C). Traction on the cryoprobe and ice ball complex provides useful exposure to the line of parenchymal transection. Blood vessels are easily visualized, and they are individually controlled as they are encountered. In patients whose tumor approximates a major venous structure, such as the right hepatic vein, preliminary mobilization of the liver from the underlying vena cava and isolation of the right hepatic vein facilitate a safe resection.

The specimen is left attached to the cryoprobe (see Fig. 90B.69D) and is allowed to thaw, at which time it is removed and sectioned to ensure adequate resection margins. If there is doubt as to the adequacy of the margins, a flat cryoprobe may be inserted into the cavity, and further freezing of the relevant margin can be done.

ENUCLEATION OF GIANT HEMANGIOMATA AND OTHER BENIGN LIVER TUMORS (SEE CHAPTER 79A)

The surgical management of giant hemangioma was described in 1942 by Schumaker, and following the advent of noninvasive imaging techniques, interest in the subject has been renewed (Baer et al, 1987, 1992a; Iwatsuki & Starzl, 1988; Schwartz & Husser, 1987). Selective arteriography can give additional information by showing the characteristic patchy pooling of contrast material and by defining the intrahepatic and extrahepatic vascular anatomy, but it is rarely needed because of high-quality CT and MRI demonstrating a characteristic contrast-enhancement pattern.

A technique of enucleation (Alper et al, 1988; Baer et al, 1987, 1992a) is described below that can be applied to the elective management of a symptomatic giant cavernous hemangioma (Fig. 90B.70), ensuring minimal blood loss and the preservation of virtually all normal hepatic parenchyma. We also have used this technique to enucleate hepatic adenomas, fibronodular hyperplasia, and metastatic neuroendocrine tumors. Others (Lerner et al, 2004) have confirmed that this approach offers preservation of normal parenchyma and fewer complications than formal hepatectomy.

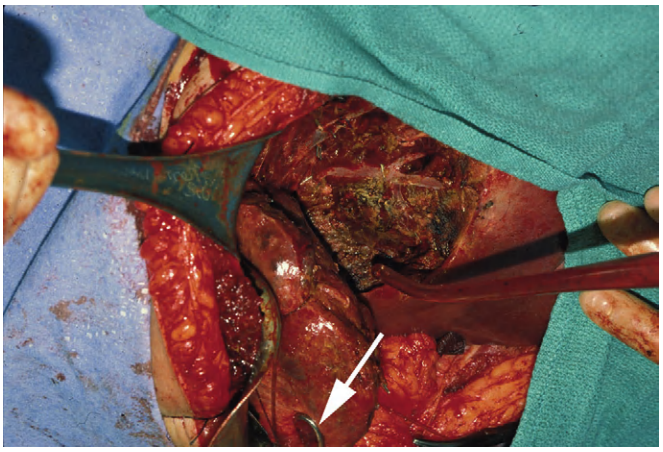


FIGURE 90B.70. Intraoperative photograph shows enucleation of a large hemangioma of the right lobe of the liver. The hemangioma has been compressed and can be manipulated with forceps (*arrow*). It is enucleated from the liver substance, and a major branch of the middle hepatic vein is seen exposed in the depths of the wound. Normal liver tissue is not sacrificed (see Fig. 90B.71).

Technique

The common hepatic artery is identified, and depending on the side of the lesion, the right or left hepatic artery is identified and controlled. Bleeding from the enucleation site is minimized by prior complete extrahepatic vascular control. Ligation of the right or left hepatic artery for a major lesion of the right or left liver is usually adequate; however, for lesions involving segment IV, a more selective dissection to control the relevant vessels within the umbilical fissure may be necessary. Once the arterial inflow is controlled, the lesion usually can be compressed and drained of its blood. As tension in the mass is relieved, it can be clamped to provide traction as the dissection proceeds, which is described later. Inclusion of only a few millimeters of liver tissue at the periphery of the hemangioma is usually the extent of parenchymal dissection required. At this point, a sheath of compressed liver tissue is encountered that defines the border between the cavernous tissue and the normal liver parenchyma. Dissection is now possible by gliding a finger along this plane, following the margin of the lesion and avoiding entry into the liver parenchyma or into the tumor itself; as blood vessels or bile ducts are encountered, they are controlled and divided. They can be controlled with suture ligatures, clips, or a coagulation device. Proceeding in this way, it is possible to shell out the hemangioma from the parenchyma without damage to major vessels or bile ducts (see Fig. 90B.70). The resulting hepatic defect after enucleation can be treated in a variety of ways. Generally, the bleeding from the bed of the hemangioma is minimal and can be controlled using compression and argon beam coagulation. The omentum also may be mobilized and placed over the raw surface as an omentoplasty.

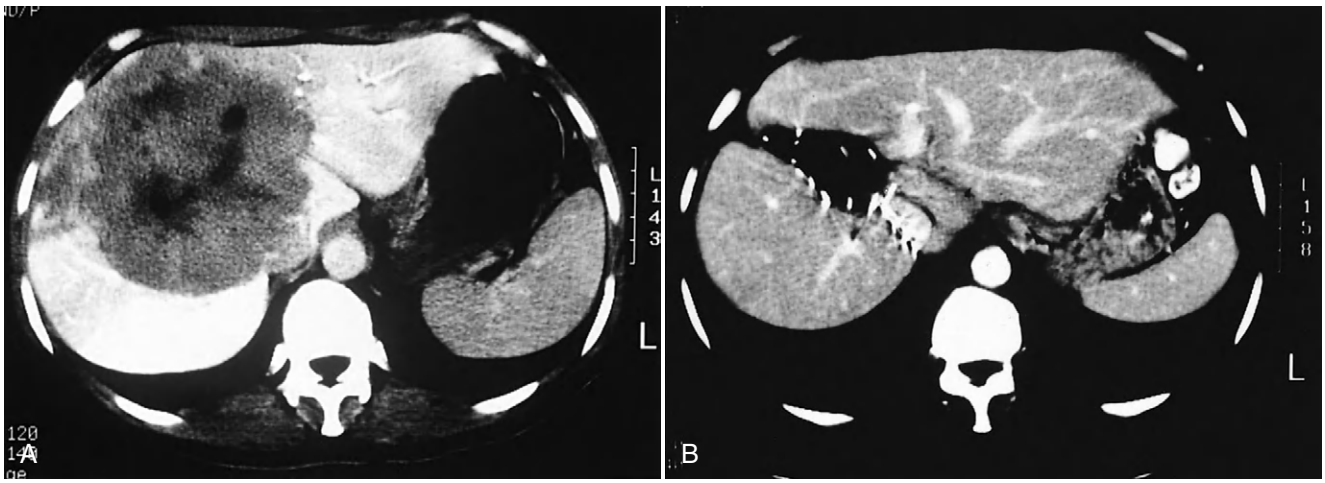


FIGURE 90B.71. A, Computed tomographic (CT) scan shows a large, symptomatic hemangioma within segments IV, V, VI, and VIII of the right liver. This hemangioma was enucleated without loss of any functional liver tissue. The large cavity was filled with an omentoplasty. **B,** CT scan after operation shows no loss of parenchyma.

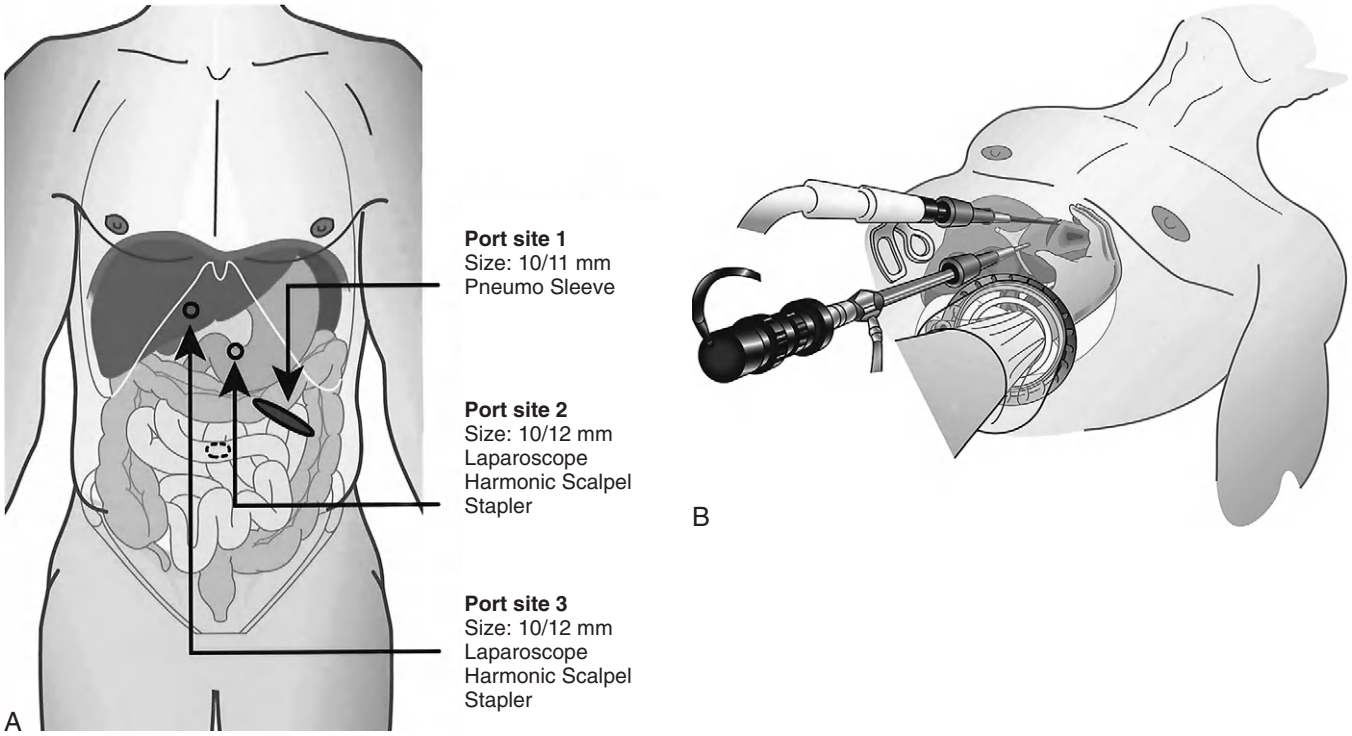


FIGURE 90B.72. **A,** Port placement for laparoscopic left lateral segmentectomy. These are the main ports; additional ports are placed as necessary. **B,** Laparoscopic left lateral segmentectomy. After complete mobilization of the left lateral segment by dividing the left triangular ligament, the liver parenchymal transection is performed using the Harmonic Scalpel (Olympus Key Med) and the vascular endoscopic stapler. The hand is used for retraction and to assess for tumor clearance. A bulldog clamp can be placed across the porta hepatis to provide for the Pringle maneuver.

The technique described allows large hemangiomata to be resected with a limited disruption of the surrounding liver tissue (Fig. 90B.71). The reason this technique of enucleation is possible is that these lesions are usually surrounded by a relatively avascular plane, which can be demonstrated on histology (Baer et al, 1992a). The few blood vessels that do transverse the capsule are controlled during the dissection, and the amount of normal functioning parenchyma removed is minimal. Even when the size of the tumor necessitates removal of most of the right or left liver, the disturbance in liver function is clinically insignificant. This enucleation technique also can be applied to pericystectomy in the operative management of echinococcal cysts, but great care must be taken not to disrupt the cyst contents (see Chapter 68; Fig. 90B.72).

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CHAPTER 90C

Extended hepatic resections for biliary tumors: an alternative approach

Tsuyoshi Sano and Yuji Nimura

OVERVIEW

Our recent approach to perihilar cholangiocarcinoma has gradually changed, from the very detailed preoperative percutaneous transhepatic biliary drainage (PTBD), cholangioscopy, and vascular imaging to multidetector-row computed tomography (MDCT) and three-dimensional CT angiography that facilitates sufficient assessment of tumor extension and staging to selective endoscopic nasobiliary drainage (ENBD), only for the future remnant liver. When cholangiography provides insufficient information of the tumor extent, or segmental cholangitis develops, additional PTBD should be applied to the undrained bile ducts. In this chapter we introduce a recently developed "Japanese" extended resection for difficult perihilar cholangiocarcinoma that might differ from the Western approach.

PREOPERATIVE DIAGNOSIS AND MANAGEMENT OF HILAR CHOLANGIOCARCINOMA

Accurate preoperative staging using extensive investigation is indispensable prior to radical resection for hilar cholangiocarcinoma (Nagino et al, 1998; Nimura, 1994, 1997; Nimura et al, 1990a, 1995b, 2000). Most cases of hilar cholangiocarcinoma are associated with jaundice as a result of obstruction of the proximal bile ducts, either within or outside of the liver. Obstruction usually involves multiple ducts as a result of proximal spread of carcinoma along the intrahepatic segmental bile ducts. Multiple applications of PTBD (Nagino et al 1992; Nimura et al 1995a; Takada et al 1976) to relieve the cholestasis and restore the functional reserve of the future remnant liver, we believe, is essential prior to operation involving extensive hepatic resection.

In the third edition of this text, we explained that the first step in the preoperative management of hilar cholangiocarcinoma was PTBD; however, MDCT is taken before biliary drainage to define which side of the liver should be resected, and PTBD applied by the direct anterior approach under fluoroscopic guidance (Takada et al, 1976) or ENBD for the future liver remnant (FLR) are selected to relieve cholestasis of the FLR. This offers both diagnostic and therapeutic advantage (Nagino et al, 1995a), and it minimizes PTBD sessions and the number of PTBD catheters. On the other hand, magnetic resonance cholangiopancreatography (MRCP) is occasionally insufficient to diagnose the difficult local anatomy of the separated intrahepatic segmental and/or sectoral ducts and to design an appropriate operative procedure, especially in patients with Bismuth type III or IV tumors (Bismuth & Corlette, 1975). In such cases, high-quality cholangiograms through the PTBD catheters, taken in various positions—supine, right and left anterior oblique, right and left lateral, and cephalad-anterior-oblique positions (Kamiya et al, 1994)—often clearly demonstrate the tumor location and provide the most reliable information on the proximal extension of hilar cholangiocarcinoma along the intrahepatic segmental bile ducts (Ebata et al, 2002; Sakamoto et al, 1998; Fig. 90C.1).

When cholangiography provides insufficient information on the tumor extent, additional PTBD is performed to the undrained bile ducts. After dilating the sinus tract of PTBD, percutaneous transhepatic cholangioscopy (PTCS) can also provide reliable information on anatomic variations of the biliary tree and mucosal extension of the cancer (Kamiya et al, 1994; Nimura, 1993; Nimura et al, 1989). Superficial mucosal extension of the carcinoma is often associated with polypoid and/or nodular tumors of a macroscopic type (Igami et al, 2009). Thus PTCS or per oral cholangioscopy with biopsy may be valuable in diagnosis of the extent of cancer (Itoi et al, 2000, 2007; Nimura et al, 1988; Sakamoto et al, 1997). On the other hand, coexistence of biliary tract infection negatively affects the functional reserve of the liver. When intrahepatic segmental cholangitis develops, even in patients with PTBD catheters during preoperative period, urgent additional selective PTBD to the affected segmental duct should be performed (Kanai et al, 1996; Fig. 90C.2).

Concomitant vascular resection and reconstruction is indicated in some advanced cases of hilar cholangiocarcinoma (Nimura et al, 1991). We previously performed visceral angiography, percutaneous transhepatic portography, and selective retrograde hepatic venography to assess the vascular invasion of the tumor (Nishio et al, 1999, 2003). Recently, three-dimensional images of MDCT using techniques of volume rendering, multiplanar reformation, and maximum intensity projection have taken over because of the high-quality images and reduced invasiveness (see Fig. 90C.13). We usually estimate the relationship between a tumor and the vascular system in the liver and hepatoduodenal ligament and diagnose the vascular involvement of the tumor on the multiplanar reformatted images; we plan the methods of resection and reconstruction—wedge or segmental resection, direct end-to-end anastomosis, or segmental auto vein grafting—by volume-rendered images and maximum-intensity projection images (Senda et al, 2009; Sugiura et al, 2008).

Postoperative morbidity and mortality rates remain considerable, particularly if extensive resection is necessary (Nagino et al, 2001). Postoperative liver failure sometimes occurs and

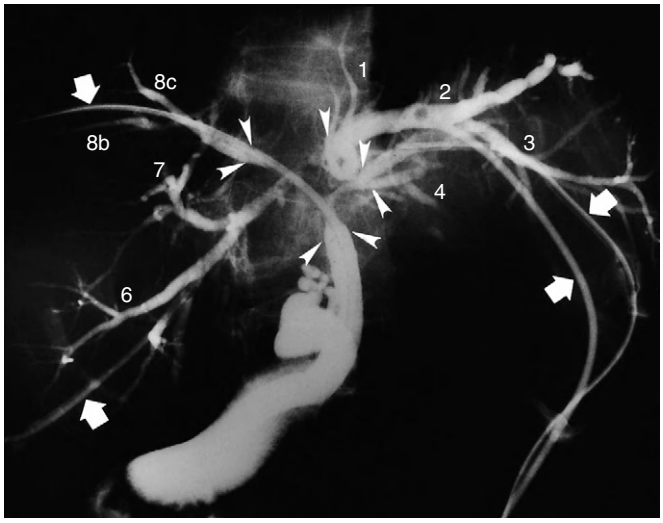


FIGURE 90C.1. A cholangiogram through four percutaneous transhepatic biliary drainage catheters (*arrows*) shows stricture at the hepatic hilum and suggests cancer extension along the intrahepatic segmental bile ducts (*arrowheads*). Numerals refer to the Couinaud's segments of the liver: *8b* is a lateral branch of the right anterior superior segmental bile duct, and *8c* is a dorsal branch of the right anterior superior segmental bile duct.

results in death. For this reason, liver resection is usually scheduled only after the liver has been decompressed and the serum total bilirubin concentration falls below 2 mg/dL. In addition, since 1989, we have routinely performed percutaneous transhepatic portal vein embolization (PVE) (Nagino et al, 1993, 1996, 2000, 2006a) as preoperative preparation for extensive liver resection. This is done to minimize the incidence of postoperative liver failure. After estimation of the resultant compensatory hypertrophy by volumetric CT scan (Nagino et al, 1995b, 1995c) and of the functional reserve of the liver as assessed by the indocyanine green clearance rate (Uesaka et al, 1996), hepatectomy is performed, usually 2 to 3 weeks after PVE. A Japanese series implemented a management strategy for patients with hilar cholangiocarcinoma that consisted of preoperative biliary drainage, PVE, and major hepatobiliary resection; it reported a 0% mortality rate in more than 100 consecutive cases (Sano et al, 2006).

Impaired intestinal barrier function does not recover with PTBD without bile replacement, which can restore the intestinal barrier function during external biliary drainage in patients with biliary obstruction, primarily as a result of repair of physical damage to the intestinal mucosa. Thus, in patients with hilar cholangiocarcinoma and external biliary drainage, we routinely replace bile prior to operation (Kamiya et al, 2004; Kanazawa et al, 2005). Also, perioperative administration of synbiotics can enhance immune responses, attenuate systemic postoperative inflammatory responses, and improve the intestinal microbial environment (Sugawara et al, 2006). These procedures may reduce postoperative infectious complications after major hepatobiliary resection in difficult patients with hilar cholangiocarcinoma.

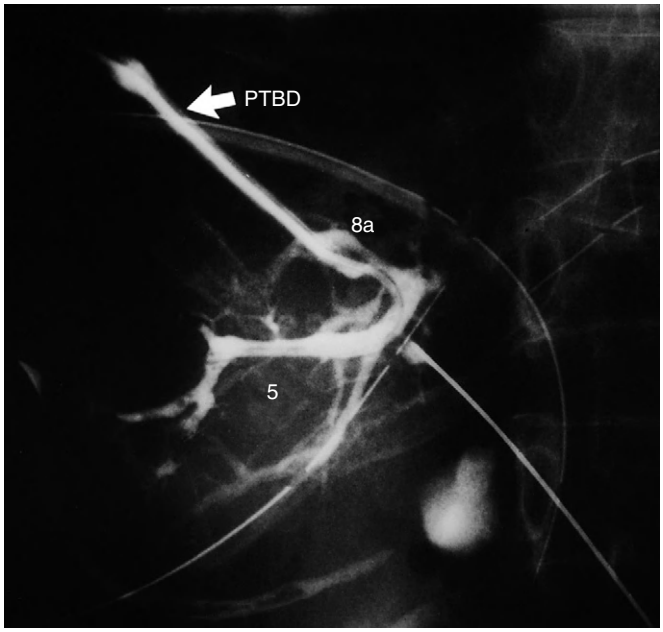


FIGURE 90C.2. Percutaneous transhepatic biliary drainage (*PTBD*), to the right anterior sectoral ducts performed for intrahepatic segmental cholangitis. *5,* A branch of the right anterior inferior segmental bile duct; *8a,* a ventral branch of the right anterior superior segmental bile duct.

RIGHT HEPATIC RESECTION WITH TOTAL CAUDATE LOBECTOMY, EXTRAHEPATIC BILE DUCT RESECTION, AND PORTAL VEIN RESECTION AND RECONSTRUCTION

Right hepatectomy with total caudate lobectomy is carried out for tumors involving the right anterior and posterior sectoral bile ducts, with sparing of the left medial segmental bile duct to segment IV, or when the right hepatic artery is also involved (see Chapters 50B and 90B). If the cancer involves the right hepatic duct and the left medial segmental duct, anatomic right hepatic trisectionectomy with caudate lobectomy is indicated (Nagino et al, 2006b).

At operation and after exploration of the peritoneal cavity, PTBD catheters are fixed at the liver surface to maintain intraoperative biliary drainage. The right lobe is often atrophic to some extent, and a faint demarcation between the right and left lobe is observed as a result of the preoperative PVE.

After retropancreatic lymph node dissection, the distal bile duct is divided above the pancreas with a histologic free margin; the hepatoduodenal ligament is dissected, and the vessels are skeletonized and removed (Bhuiya et al, 1992). The middle hepatic artery usually runs ventral to the left portal vein and enters the liver below the left medial segment branch of the portal vein; this artery is carefully preserved. The left hepatic artery enters the liver to the left of the umbilical portion of the portal vein (Figs. 90C.3 to 90C.5).

Following skeletonization of the hepatoduodenal ligament, preparation of the caudate lobe is carried out by isolation, ligation, and division of the arterial branches and portal branches of the caudate lobe. The details of the technique are described above (Figs. 90C.3 to 90C.7; see also Fig. 90C.12). Although the arterial branches directly arise from the left and right hepatic arteries, they cannot be accurately identified in some cases. Two to six branches of the portal vein arise from the left portal vein, two to three branches arise from the right portal vein, and one

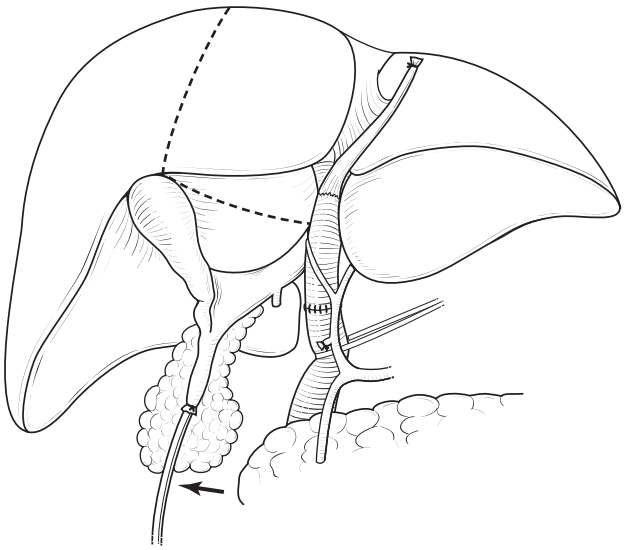


FIGURE 90C.3. A schematic illustration after skeletonization of the hepatoduodenal ligament is shown. A catheter is inserted from the distal stump of the common bile duct for intraoperative biliary drainage (*arrow*).

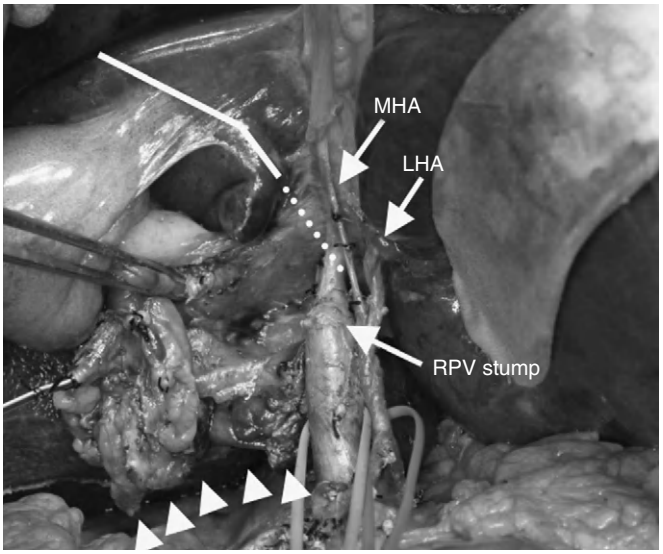


FIGURE 90C.5. Intraoperative image during a right hemihepatectomy with caudate lobe resection showing complete skeletonization of the hepatoduodenal ligament. Regional lymph nodes and connective tissues (*arrowheads*) are dissected en bloc. The transection line of the liver parenchyma (*solid line*) and the resection point of the left intrahepatic ducts (*dotted line*) are shown. The right portal vein (*RPV*) is transected at its origin with transverse suture closure. MHA, middle hepatic artery; LHA, left hepatic artery.

to two branches arise from the main trunk or the bifurcation of the portal vein.

The significance of total caudate lobectomy in cases of hilar cholangiocarcinoma is, of course, not resection of the parenchyma of the caudate lobe but clearance of the connective tissue of the hilar plate around the caudate bile duct branches, which are often involved by cancer (Nimura et al, 1990). After complete division of the caudate arteries and portal vein branches, the right hepatic lobe is mobilized, and short retrohepatic veins are ligated and divided. The caudate lobe is completely detached from the inferior vena cava (IVC) as described above, and the confluence of the right hepatic vein (RHV) with the IVC is carefully encircled, clamped, divided, and closed with a running suture or a vascular stapler.

In case of direct cancer invasion of the portal bifurcation, portal vein resection and reconstruction is performed prior to liver resection (Figs. 90C.8 to 90C.12). Direct end-to-end anastomosis of the main trunk of the portal vein and the left branch is carried out (Ebata et al, 2003; Nimura et al, 1991;

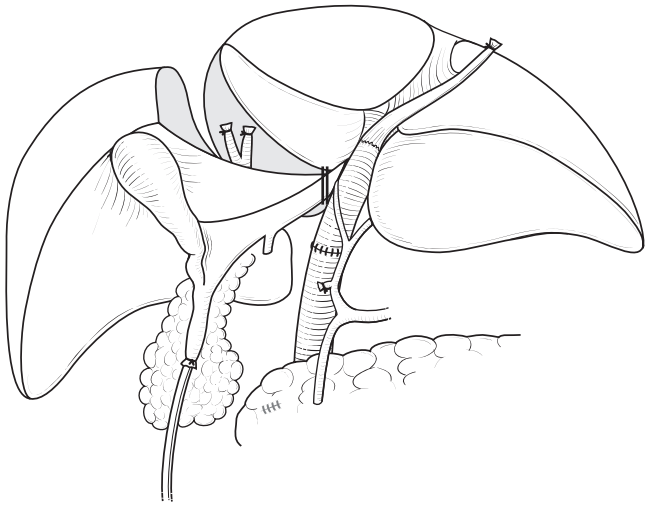


FIGURE 90C.4. A schematic illustration just prior to resection of the left intrahepatic sectoral ducts. The right liver and caudate lobe are extracted to the right side. The resection line is indicated by *double lines.*



FIGURE 90C.6. An intraoperative view of a right hemihepatectomy with caudate lobe resection depicts a view just prior to bile duct resection. The *dotted line* shows resection point of the left intrahepatic sectoral ducts.

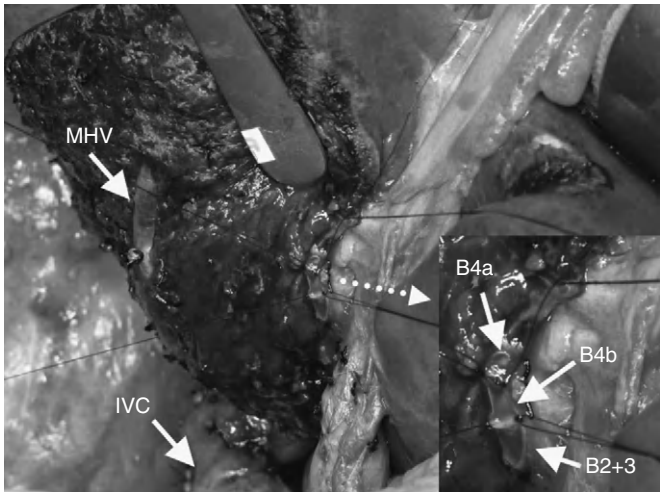


FIGURE 90C.7. Intraoperative view after right hepatectomy with total caudate lobectomy; extrahepatic bile duct resection is demonstrated. Hepaticoplasty is done for left hepatic segmental and/or subsegmental ducts. B4a, transected inferior branch of the left medial segmental bile duct; B4b, transected superior branch of the left medial segmental bile duct; B2+3, the left lateral sectoral bile duct; IVC, inferior vena cava; MHV, middle hepatic vein.

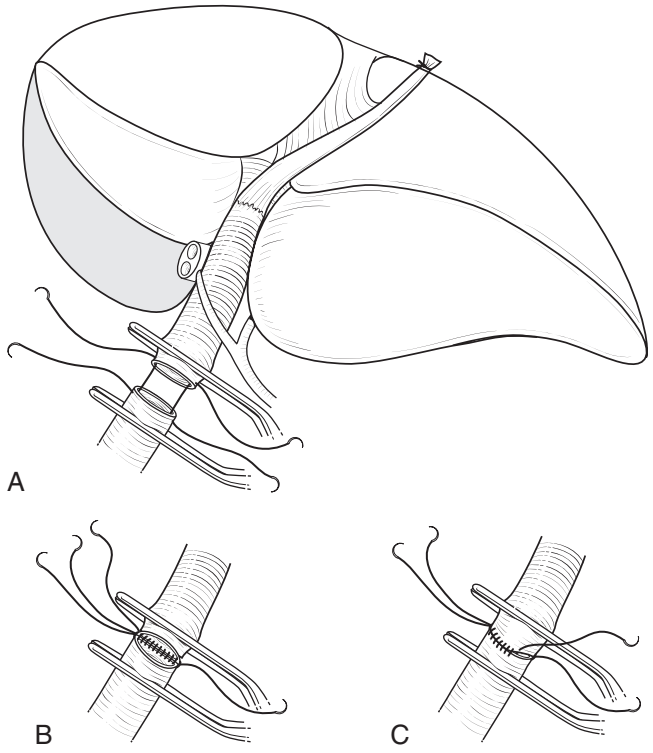


FIGURE 90C.8. Schematic illustration of portal vein resection and reconstruction by end-to-end anastomosis during right hepatectomy. After stay sutures are placed at both edges (**A**), the intraluminal technique is used for the posterior wall suture (**B**), and over-and-over sutures are placed for the anterior wall (**C**).

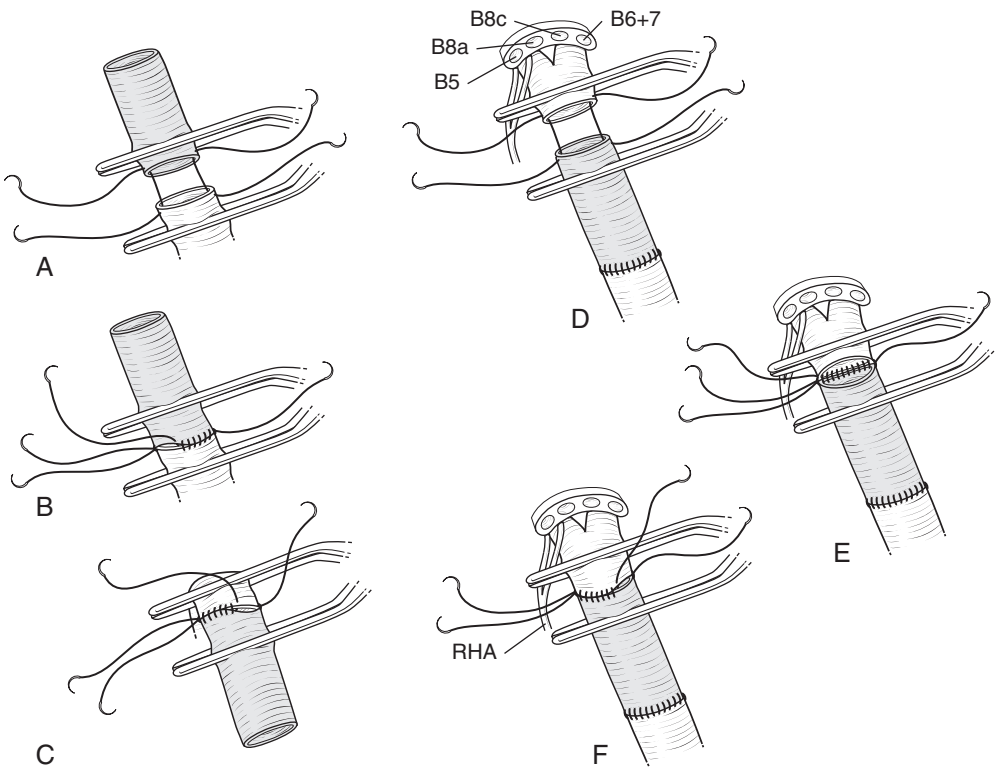


FIGURE 90C.9. Schematic illustration of portal vein resection and reconstruction using a right external iliac vein graft during left hepatic resection. First, the distal anastomosis between the right portal vein and the graft is performed using an over-and-over technique for both sides with 6-0 prolene. Next, stay sutures at both edges are placed, and the proximal side anastomosis between the vein graft and the main portal vein is performed with intraluminal technique for the posterior wall suture; an over-and-over technique is used for the anterior wall with 6-0 or 5-0 prolene. RHA, right hepatic artery.

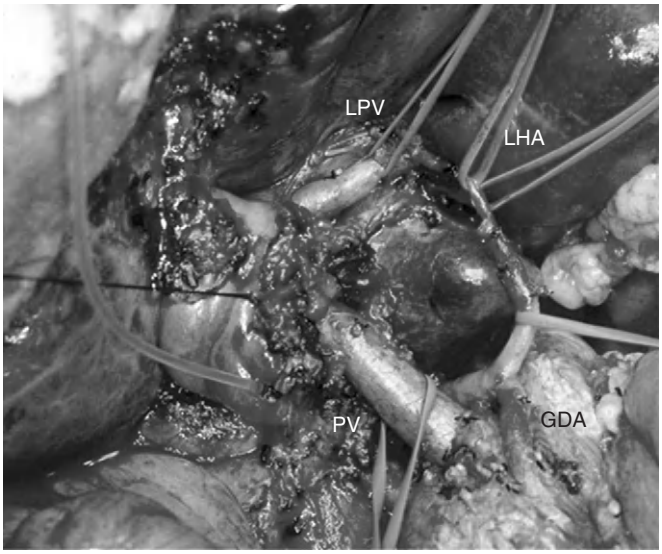


FIGURE 90C.10. An intraoperative image during a right hemihepatectomy shows tumor involvement of the portal vein. LPV, left portal vein; LHA, left hepatic artery; PV, main portal vein; GDA, gastroduodenal artery.

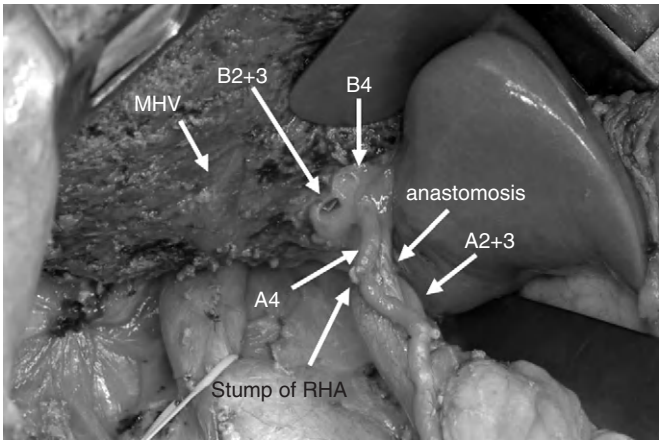


FIGURE 90C.12. Intraoperative image after a right hepatectomy with total caudate lobectomy, extrahepatic bile duct resection, and portal vein (PV) resection and reconstruction. The PV reconstruction is done by end-to-end anastomosis. The left medial hepatic artery (*A4*) originates from the right hepatic artery, which has been divided. B2+3, transected left lateral segmental bile duct; B4, transected left medial segmental bile duct; A2+3, left lateral sectoral hepatic artery; MHV, middle hepatic vein; RHA, right hepatic artery.

see Chapter 91B). Portal vein resection and reconstruction is carried out during the hilar dissection prior to hepatic parenchymal transection, because the portal flow to the FLR is easily impeded as a result of kinking during operative manipulations. Direct end-to-end anastomosis between the main portal trunk and the left portal vein is usually possible during right-sided resections (Kondo et al, 2003). On the other hand, interposition of an autogenous vein graft is often required during portal vein reconstruction, between the right portal vein and the main trunk during left-sided resections (Figs. 90C.9 to 90C.15). We usually harvest an external iliac vein for an autogenous vein graft by an extraperitoneal approach. The key to portal vein resection and reconstruction during right-sided hepatectomy is the feasibility of cross clamping the root of the umbilical portion of the left portal vein. In the case of left hepatectomy, isolation and clamping of the right posterior sectoral and/or the right anterior sectoral portal vein are key maneuvers.

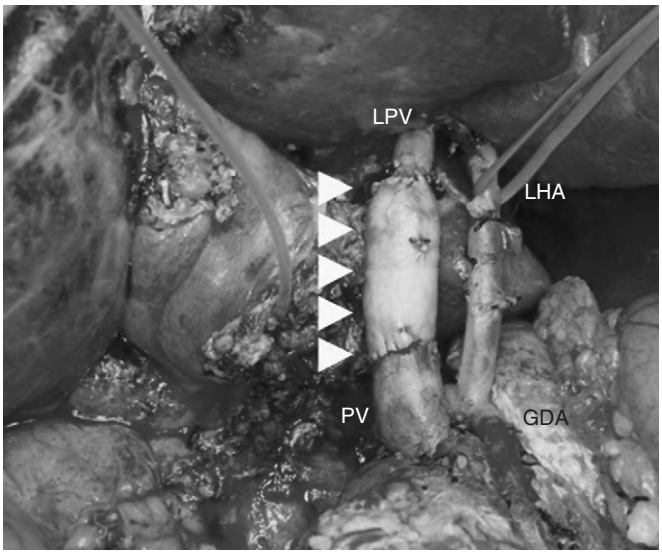


FIGURE 90C.11. Intraoperative view during a right hemihepatectomy shows portal vein resection and reconstruction with an external iliac vein (*arrowheads*). In many cases of right hepatobiliary resection, portal vein (*PV*) resection and reconstruction with or without an interposition graft is performed prior to liver parenchymal transaction. LPV, left portal vein; LHA, left hepatic artery; GDA, gastroduodenal artery.

After confirmation of the course of the middle hepatic vein (MHV) using intraoperative ultrasonography, liver transection is performed along the demarcation line that appears after ligation of the right hepatic artery. On the caudal aspect of segment IV, the liver transection line is horizontally advanced approximately 1 cm ventral to the hilar plate to achieve a free surgical margin. When the MHV is exposed, liver transection is reduced toward the left, lateral to the distal portion of the ligamentum venosum. When the caudodorsal aspect of the MHV is completely exposed, the confluence of the MHV and IVC is seen. At this point, the caudate lobe can be turned and pulled ventrally from behind the left lateral segment. Finally, the bile duct is transected after placing a stay suture, and the right hepatic lobe is resected en bloc with the entire caudate lobe, portal bifurcation, and extrahepatic bile duct. The transected bile duct stumps, left medial sectional branch (segment IV), left lateral anterior sectional branch (segment III), and left lateral posterior sectional branch (segment II) are noted just to the right of the umbilical portion of the left portal vein (see Fig. 90C.7).

Bilioenteric continuity is reestablished using a Roux-en-Y jejunal loop. In our fashion, the jejunal limb is brought to the transected hepatic ducts via the retrocolic-antegastric or the retrocolic-retrogastric route (Nagino et al, 2002). We perform hepaticojejunostomy in one layer using a 5-0 absorbable monofilament suture; a biliary drainage tube is placed across all anastomoses either through the jejunal loop and/or transhepatically (Nagino et al, 2007).

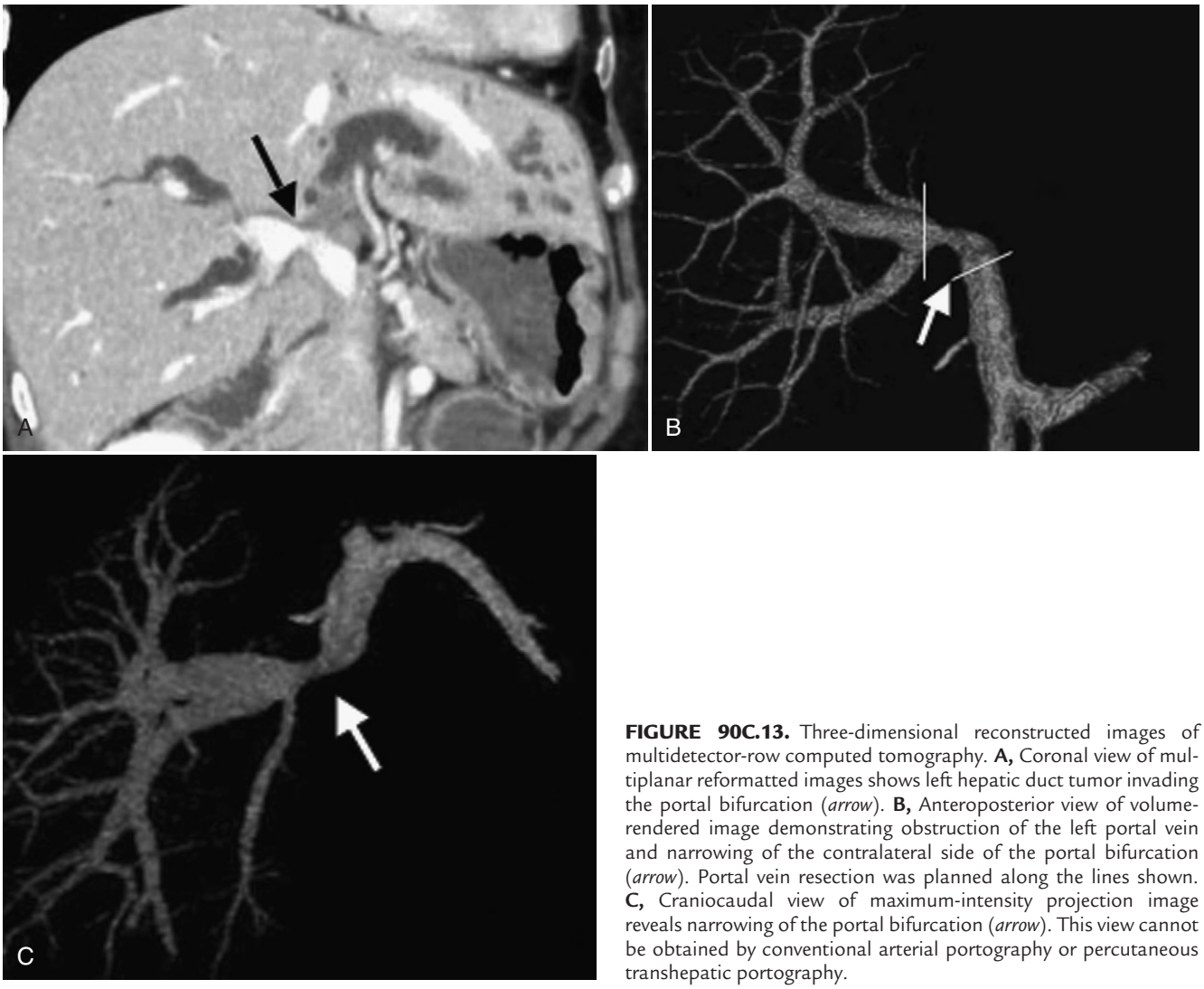


FIGURE 90C.13. Three-dimensional reconstructed images of multidetector-row computed tomography. **A,** Coronal view of multiplanar reformatted images shows left hepatic duct tumor invading the portal bifurcation (*arrow*). **B,** Anteroposterior view of volume-rendered image demonstrating obstruction of the left portal vein and narrowing of the contralateral side of the portal bifurcation (*arrow*). Portal vein resection was planned along the lines shown. **C,** Craniocaudal view of maximum-intensity projection image reveals narrowing of the portal bifurcation (*arrow*). This view cannot be obtained by conventional arterial portography or percutaneous transhepatic portography.

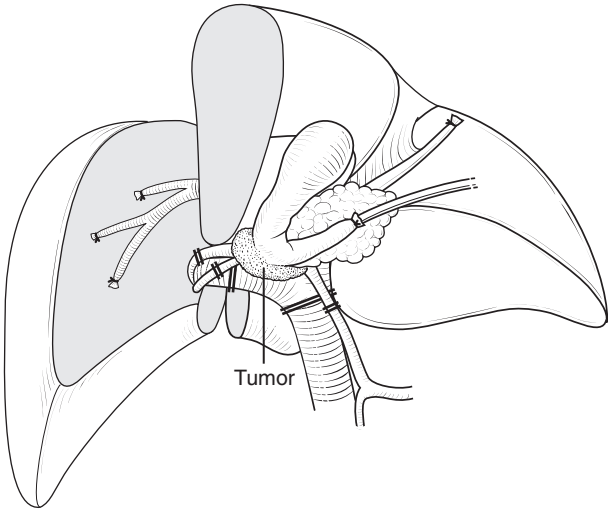


FIGURE 90C.14. Schematic illustration during an extended left hepatic resection, caudate lobectomy with simultaneous portal and hepatic arterial resection, and reconstruction. Resection lines for the hepatic artery, portal vein, and the left posterior sectional duct are shown by double lines.

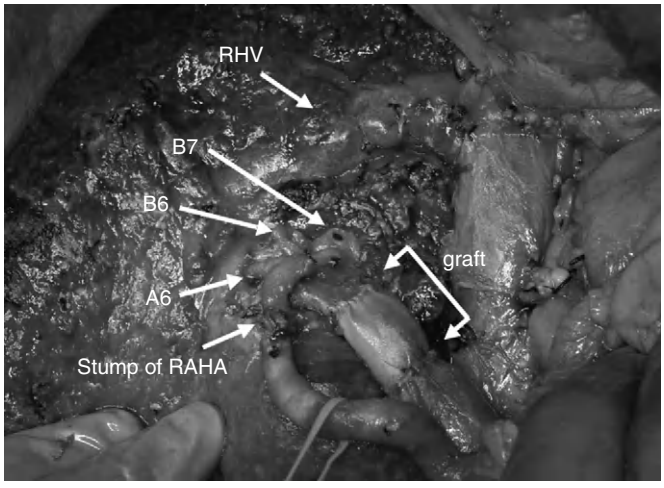


FIGURE 90C.15. Intraoperative view after an extended left hepatic resection with total caudate lobectomy, extrahepatic bile duct resection, and portal vein resection and reconstruction. The vessel loop is around the right posterior sectoral artery. An autologous graft using the right external iliac vein is demonstrated. The right posterior superior (*B7*) and the right posterior inferior (*B6*) segmental bile ducts are divided separately above the reconstructed portal vein. RHV, right hepatic vein; RAHA, right anterior hepatic artery; A6, right posterior inferior segmental hepatic artery.

EXTENDED LEFT HEPATIC RESECTION, CAUDATE LOBECTOMY, EXTRAHEPATIC BILE DUCT RESECTION, AND PORTAL VEIN RESECTION AND RECONSTRUCTION

Extended left hepatic resection with caudate lobectomy is used for hilar cholangiocarcinoma, which predominantly involves the left intrahepatic bile ducts in continuity with the duct to the right anterior section (see Chapters 50B and 90B). During the subhepatic dissection of the hepatoduodenal ligament, the left hepatic artery and middle hepatic artery, if present, are ligated and divided at their origins, and the right hepatic artery is carefully isolated up to its bifurcation into the anterior and posterior sectoral branches. Then the anterior sectoral branch and caudate lobe branches of the right hepatic artery are ligated and divided. Mobilization of the gallbladder provides a good operative view of the right posterior pedicle. The left portal vein is ligated and divided, followed by division of the right anterior branch of the right portal vein and caudate lobe branches arising from the main portal trunk and right portal vein. If cancer invasion of the portal bifurcation or the right portal vein is observed, combined portal vein resection and reconstruction is usually performed after liver transection for left hepatectomy or before liver transection in some cases of right hepatectomy. The caudate lobe and segment II and III are mobilized to the right, and the short retrohepatic caudate veins are ligated and divided, beginning on the left caudally and progressing cranially. When the confluence of the ligamentum venosum and the left hepatic vein (LHV) or IVC is displayed, the ligament is ligated and divided. The LHV and MHV are divided and closed with a running suture or a vascular stapler. The caudate lobe and the left lobe are then completely detached from the IVC.

Subsequently, the liver is transected along a demarcation line in the right portal scissura between the right anterior and right posterior sections. The course of the RHV is confirmed ultrasonographically. After parenchymal transection, the RHV should be exposed on the raw surface of the liver. The plane of the liver transection courses between the right posterior superior section (segment VII) and the right portion of the caudate lobe and begins from the sulcus on the right side of the caudate process and advances cranially along the right margin of the IVC. Finally, the right wall of the IVC is clearly exposed (Fig. 90C.16; see also Fig. 90C.15).

The right posterior sectoral bile duct is exposed cranially to the right portal vein and is divided so as to obtain histologically free margins. Finally, vascular clamps are placed distally and proximally to the involved portal bifurcation: the distal clamp is placed obliquely to adjust the caliber of the distal portal vein to the transversely transected main portal trunk, and the specimen is resected en bloc, including the entire caudate lobe, the involved segment of the portal vein, and the extrahepatic bile duct. The portal vein reconstruction between the main portal trunk and the right posterior sectoral portal branch is then performed (see Fig. 90C.16), and an interposition graft of autogenous vein is often necessary (see Fig. 90C.15).

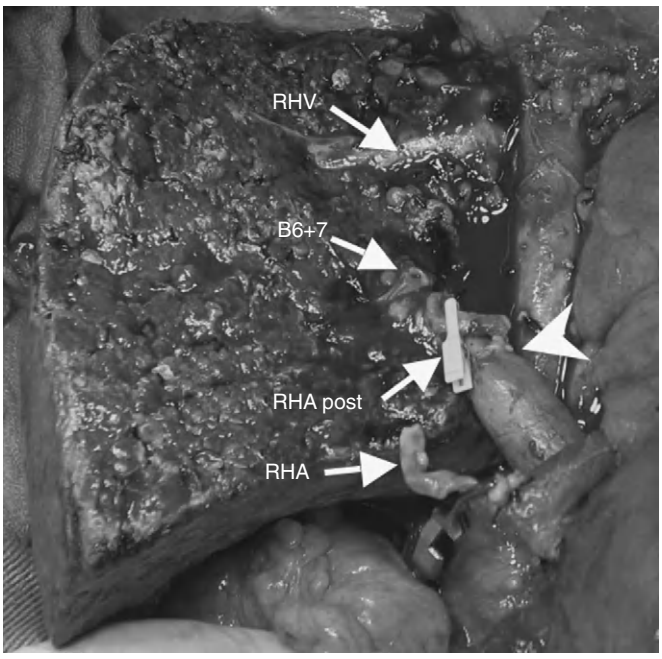


FIGURE 90C.16. Intraoperative image after extended left hepatic resection, caudate lobectomy, extrahepatic bile duct resection, and combined simultaneous resection of the right hepatic artery (*RHA*) and portal vein (PV). End-to-end anastomosis between the main PV and the right posterior sectional branch is accomplished (*arrowhead*). A posterior branch of the right hepatic artery (*RHA post*) and the proximal part of the RHA are cross-clamped with vascular clips. B6+7, stump of the right posterior sectoral bile duct; RHV, right hepatic vein.

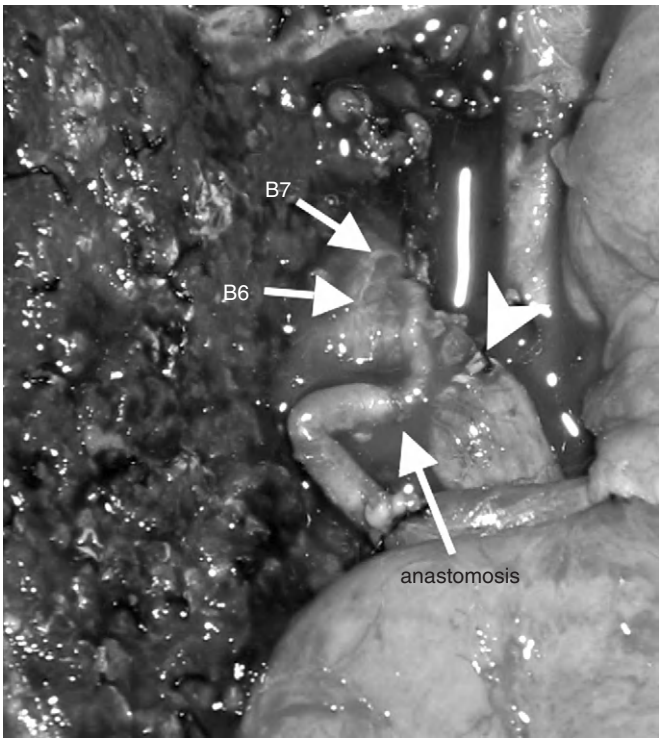


FIGURE 90C.17. Hepatic arterial reconstruction is through an end-to-end anastomosis between the proximal right hepatic artery and the posterior branch of the right hepatic artery with microscopic vascular techniques. The *arrowhead* shows the end-to-end anastomosis of the portal vein reconstruction. B6, stump of the right posterior inferior segmental bile duct; B7, stump of the right posterior superior segmental bile duct.

In some locally advanced cases, combined resection and reconstruction of the right hepatic artery with an end-to-end anastomosis is a requisite to achieve a negative margin (Fig. 90C.17; see also Fig. 90C.16). Microsurgical techniques are used for arterial reconstruction with or without using right gastroepiploic artery or radial artery as an interposition graft (Sakamoto et al, 2006). When arterial reconstruction is impossible, one potential countermeasure is creation of an arterioportal shunt to prevent possible leakage of the hepaticojejunostomy, liver abscess, and fatal liver failure (Kondo et al, 2004). Oblique-to-side anastomosis is performed between the common hepatic artery and the main portal vein. Three weeks after surgery, transcatheter arterial embolization of the common hepatic artery is carried out to prevent further portal hypertension. It must be remembered, however, that the development of liver failure or an abscess in the remnant liver are not eliminated by arterioportal shunting.

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CHAPTER 90D

Hepatic resection for living donor transplantation

See Ching Chan and Sheung Tat Fan

OVERVIEW

Donor hepatectomy is a major surgical operation performed on a healthy subject only for the benefit of a recipient, who requires liver transplantation (see Chapter 97A). In 1989, Strong (1999) performed donor left hepatectomy and removed segment IV of the liver on the back table prior to implantation of segments II and III into a pediatric recipient. In 1990, Tanaka and coworkers (Yamaoka et al, 1994) used a right liver graft to transplant a pediatric recipient. Living donor left liver transplantation (LDLT) for adults was first performed by Makuuchi in 1993 (Hashikura et al, 1994). The first case of right liver adult LDLT was performed by Fan in 1996 (Lo et al, 1997a). A priori, the right liver graft included the middle hepatic vein (MHV) to address the problems of small-for-size syndrome by providing good venous outflow of the right anterior sector. The first seven recipients who underwent right LDLT all had acute liver failure before the transplantation; one died from candidiasis and the other six survived (Lo et al, 1997b). Subsequently, semiurgent and elective cases were accepted.

DONOR WORKUP

Donor workup is started after indication for LDLT for the potential recipient is ascertained. The workup is to evaluate whether the donor will be psychologically and physically healthy in the long-term after recovery from the organ donation. In a stepwise fashion, expedience is achieved without omission (Chan et al, 2007a). Only healthy individuals who have reached the age of consent are accepted (Abecassis et al, 2000).

Step 1

A detailed medical history is taken to identify any comorbidities. A body mass index of 30 kg/m^2 or more (27 kg/m^2 for Asians; World Health Organization, 2004) raises the concern for fatty liver– and obesity-related comorbidites. Blood group compatibility is verified. Hepatitis B and C virus and HIV carrier status preclude liver donation, although hepatitis B core antibody positivity by itself does not preclude liver donation, it mandates lifelong prophylaxis with lamivudine in the recipient (Lo et al, 2003).

Step 2a

A psychologic assessment is performed to verify the potential donor's knowledge of the operation to be performed and coping skills. The donor should have adequate knowledge of donor and recipient morbidity, mortality, and survival and should be apprised of the urgency of the transplant.

Step 2b

Chest radiographs are taken, and an electrocardiogram is performed. Computed tomography (CT) of the liver under sodium bicarbonate cover (Merten et al, 2004) is also performed, and maximum-intensity projections of the portal veins and hepatic veins are produced. Volumetry of the donor liver by the Heymsfield method (Heymsfield et al, 1979) measures the volumes of the right liver and left liver (for pediatric recipients, segments II and III), using the MHV as a demarcation line on the plane between the right and left livers (Fig. 90D.1). Attenuation of the liver parenchyma in comparison with the spleen on the plain film is appraised for detection of fatty change. Hepatic vein anatomy is determined by the axial cuts in the venous phase and by maximum-intensity projections for easier appreciation. The presence of any inferior hepatic veins allows anticipation at the operation of either preservation or division. Attention to the presence of the segment IVb hepatic vein or segment III hepatic vein draining into the MHV calls for a more caudal division of the MHV to preserve adequate drainage of segment IV of the remnant left liver (Chan et al, 2004a). The right, left, and segment IV hepatic arteries are also illustrated by the three-dimensional (3D) reconstructions for the images obtained during the arterial phase.

Step 3

Liver biopsy is performed in selective donors and after genuineness and suitability of the potential donor is ascertained. Steatosis of up to 15% for right liver donors and 20% for left liver donors are acceptable.

Step 4

Informed consent is obtained from the donor and the donor's relative. Donor and recipient morbidity and mortality are stated explicitly.

SIDE AND SIZE OF GRAFT

The graft to standard liver volume ratio (Urata et al, 1995) is crucial in LDLT. A ratio of more than 35% is required for a predictable recipient success (Fan et al, 2003a). However, a 20% overestimation of the right liver graft size based on CT volumetry is commonly given a conversion factor of 1.19 g/mL

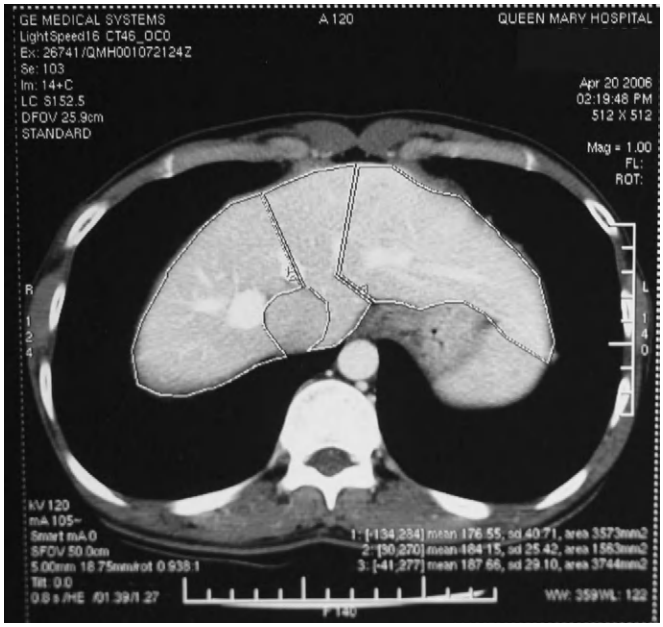


FIGURE 90D.1. Volumetric analysis of the donor liver on computed tomography.

(Chan et al, 2006a). Because the left liver is usually one third the size of the total liver, for a donor with a body size no larger than the recipient, the left liver is usually less than 35% of the recipient standard liver volume. For an individual with a larger left liver/right liver ratio, the left liver may be large enough. It is worth noting that in left LDLT, a gram-to-gram equivalence of graft is not applicable, and a left liver graft of the same size as the right is less efficacious (Chan et al, 2007b).

For right liver donation, the liver donor should have a remnant left liver of at least 30% of the total liver volume. For a pediatric recipient, a liver graft of 3% of the body weight is optimal; however, the graft size is lowered to 2% of the body weight for older children and teenagers because a graft of more than 5% of the body weight predisposes to hypoperfusion. In such cases, graft reduction to even a monosegment may be necessary.

DONOR RIGHT HEPATECTOMY (SEE CHAPTER 98B)

Exposure

The donor is placed supine on the operating table with care to avoid pressure sores over the occiput, heels, and sacrum. The position of the donor must be optimal for the surgeon and his first assistant to face the operative field directly, unhindered by the metal bars of the upper hand retractor or those used to set up a fence between the surgeon and anesthetist (Fan, 2007). Access is gained through a right subcostal incision with upper midline extension. The ligamentum teres is ligated and divided, and the falciform ligament is taken down. The two curved blades of the Bookwalter retractor (Codman and Shurtleff, Raynham, MA) pull the rib cage laterally and anteriorly to open up the aperture made by the costal margins. Excising the xiphoid process may improve access to the suprahepatic inferior vena cava (IVC) and the roots of the hepatic veins. Following careful laparotomy, intraoperative ultrasonography (IOUS) is performed to study the junction of the middle and left hepatic veins with the IVC. The relation of the segment IVb hepatic vein to the MHV, already known from CT, is ascertained by IOUS. This also registers the flow characteristics of the hepatic arteries, portal veins, and hepatic veins for reference throughout the operation.

Isolation of Major Vessels and Parenchymal Transection

The triangle of Calot is dissected, and the cystic artery is divided between ligatures. The gallbladder is dissected from its fossa, and the cystic duct is cannulated with a 3.5-Fr Argyle catheter (Tyco Healthcare, Mansfield, MA). The cystic duct is then severed at the site of insertion of the catheter for delivery of the gallbladder. Next, the peritoneum overlying the right hepatic duct (RHD) is divided for identification. A large metal LigaClip (Ethicon Endo-Surgery, Cincinnati, OH) is put on the liver capsule at the planned line of division of the RHD, 3 to 4 mm away from the duct confluence. The biliary anatomy is then demonstrated by operative cholangiogram with undiluted contrast under fluoroscopy with a C-arm. The image quality of the cholangiogram can be improved by temporary and gentle occlusion of the distal common bile duct with an atraumatic vascular clamp (Featherlight Bulldog Clamp; Geister, Tuttlingen, Germany) (Fig. 90D.2). To avoid devascularization of the donor distal common bile duct, care must be taken not to dissect more tissue than necessary for application of the clamp; the clamp must be removed once the cholangiogram is finished. The supine donor will have the right posterior sectoral duct demonstrated first, followed by the right anterior sectoral duct and then the left ducts (Fan et al, 2002). The parallax technique executed by rotation of the C-arm to the right clarifies the

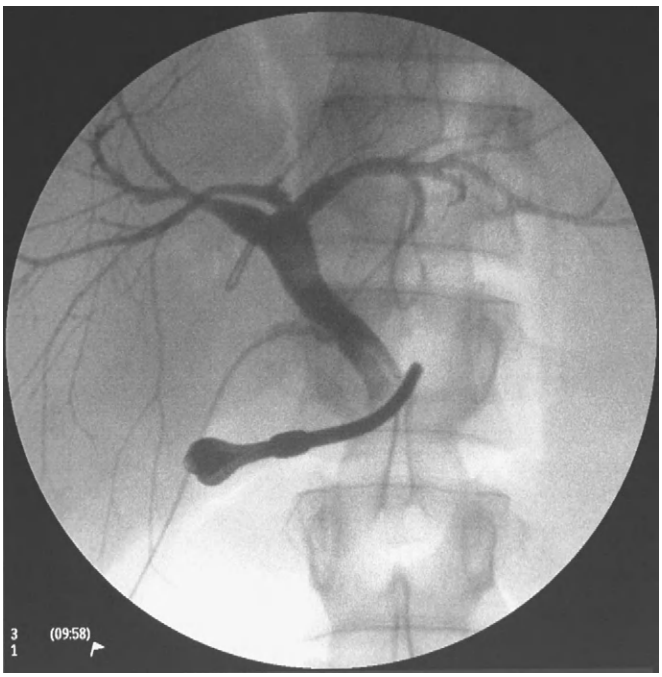


FIGURE 90D.2. Operative cholangiogram with metal clip marking the planned line of division of the right hepatic ducts.

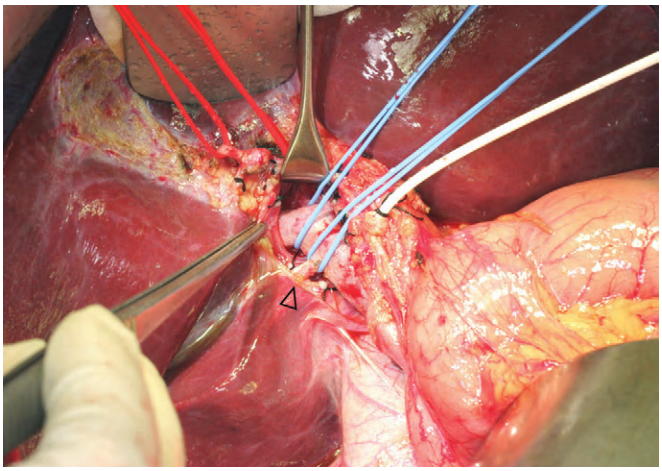


FIGURE 90D.3. Hilar dissection with isolation of the right hepatic artery and right portal vein. The branch of portal vein supplying segment VI was preserved (*arrowhead*).

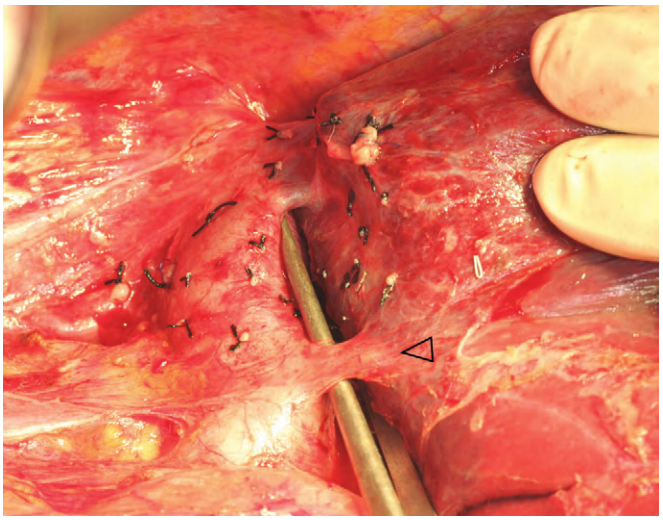


FIGURE 90D.5. The inferior right hepatic vein is isolated and preserved (*arrowhead*).

anteroposterior position of the right anterior and posterior sectoral ducts. This also provides the true anteroposterior view of the biliary system. A marking is made with reference to the LigaClip on the liver capsule with diathermy for the line of division of the RHD.

Hilar dissection is continued to isolate the right hepatic artery and right portal vein. The space between the right hepatic artery and right hepatic duct should not be disrupted in order to preserve the blood supply to the latter. To gain an entire length of the right portal vein, branches to the caudate lobe are ligated and then divided. It is important to note that a sizeable branch from the right portal vein may represent vessels supplying segment VI, which should be preserved (Fig. 90D.3). Temporary right liver inflow control is performed (Fig. 90D.4A) to mark the line of transection along Cantlie's line (Fig. 90D.4B) with electrocautery. The line on the inferior surface is just to the left of the gallbladder fossa, joining the planned line of division of the right hepatic duct marked earlier.

The right triangular ligament is then taken down, leaving the Gerota fascia intact. In a normal donor liver, the right adrenal gland can often be freed from the liver with careful dissection using electrocautery. Minor bleeding from the right adrenal gland is controlled by the argon beam coagulator, and more severe bleeding is addressed by plication with sutures. Short hepatic veins on the right side of the midline of the IVC are divided between ligatures and plicated as required. Inferior right hepatic veins (RHVs) larger than 5 mm are preserved for anastomosis with the IVC in the recipient (Fig. 90D.5).

In contrast to hepatectomy for neoplasm (see Chapter 90), continuous inflow control during liver transection is not practiced. Although the Pringle maneuver with intermittent reperfusion of the liver, which is adopted by some centers, has been shown to result in less blood loss in the donors, the difference did not reach statistical significance (Imamura et al, 2002). Possible explanations to this are that bleeding from the hepatic vein tributaries is not controlled by inflow control, and there is bleeding during the 5-minute reperfusion interval. Another potential advantage of the Pringle maneuver is downregulation of the apoptosis pathway by ischemic preconditioning for grafts with a long cold ischemic time (Clavien et al, 2000); however,

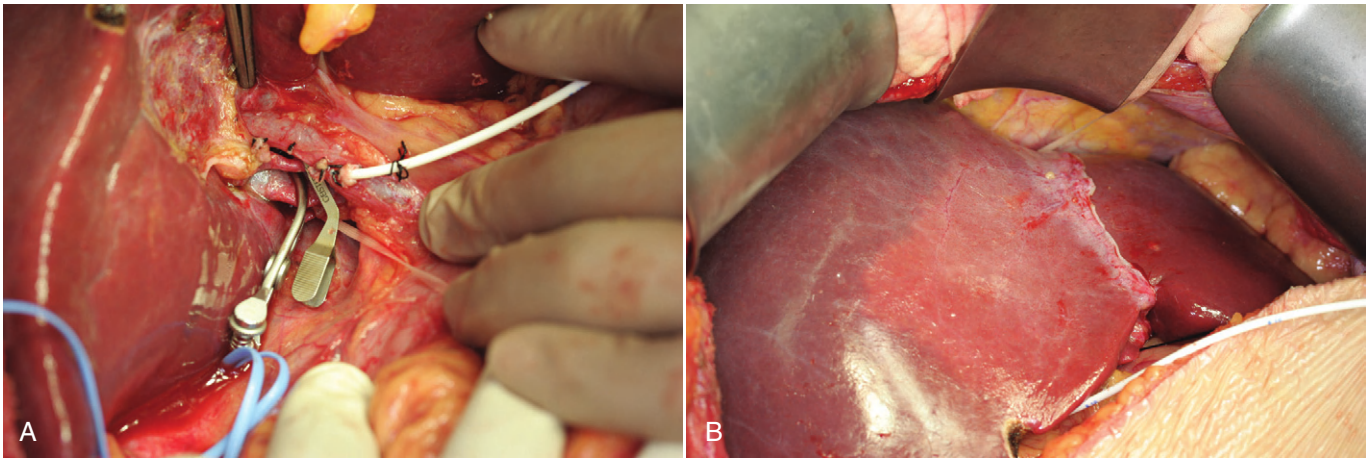


FIGURE 90D.4. **A,** Temporary hemiinflow control with vascular clamps applied to the right hepatic artery and right portal vein. **B,** Cantlie's line is revealed after temporary hemiinflow control.

this has been associated with poorer initial graft function by a prospective trial in deceased donor liver procurement (Azoulay et al, 2005). For adult LDLT, prolonged cold ischemia should not be an issue, because graft delivery matches the explantation of the native liver. In addition, a low central venous pressure (CVP) can be attained through good rapport with the anesthetist, and this lowered pressure has been proven effective in reducing blood loss (Jones et al, 1998). Elevating the head and the trunk by 10 to 15 degrees and complete muscle relaxation of the donor are also helpful.

After mobilization of the right liver from its posterior attachments, a full-thickness suture at the liver edge on both sides of this line helps open up the transection plane by the weight of hemostats. The placement of the laparotomy pad behind the right liver renders the transection plane more vertical, but not excessively so, to compromise retraction of the liver during transection. Liver parenchymal transection is started with electrocautery for the first 1 to 2 cm of parenchyma between segments V and IVb. The rest of the liver transection is done using the Cavitron Ultrasonic Surgical Aspirator (CUSA; Valleylab, Boulder, CO); it exposes the left side of the MHV, which lies two thirds of the depth from the superior surface of the liver (Fan et al, 2000). At a frequency of 23 kHz, the CUSA is set at an amplitude of 60% for the normal donor liver, and irrigation with normal saline continues at around 4 to 6 mL/min. The liver parenchyma is disrupted by cavitation of the aerosol. When the dissector is set at lower amplitudes, there is a tendency for the operator to bring the instrument into direct contact with the liver parenchyma, which will damage small and friable vessels. Suction is set to a moderately high level, just enough to provide a clear operative field. Electrocautery incorporated into the CUSA allows diathermy of vessels less than 1 mm in diameter. Should the segment IVb hepatic vein insert into the MHV, transection is stopped to preserve this vein for adequate drainage (Chan et al, 2004a).

At the liver hilum, the right portal pedicle containing the right hepatic duct is also dissected with minimal use of the CUSA. To denude the right hepatic duct from its blood supply, the dissection should not be overdone. The line of division already marked and verified by operative cholangiogram is followed, and any right hepatic ducts are severed with scissors tangential to the transection plane, which is often quite horizontal. The right hepatic duct stump is repaired by 6-0 polydioxanone continuous suture, and an operative cholangiogram is performed to confirm the patency of the left and main bile ducts (Fig. 90D.6). Liver parenchyma dorsal to the MHV and the caudate lobe are transected, until the IVC is exposed. Lifting up of the caudate lobe with a cotton-tape or a right-angled forceps facilitates the transection, and care must be taken to dissect in a definable plane between the liver capsule and the IVC.

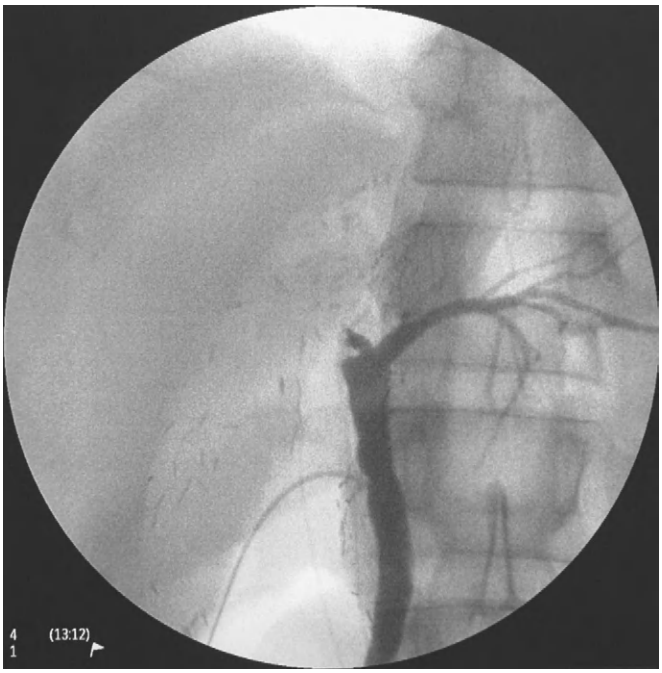


FIGURE 90D.6. Operative cholangiogram confirms patent left and main ducts.

Graft Delivery

To have short cold ischemic time, the graft is not delivered until the recipient is ready for explanting of the native liver. Graft delivery starts with application of a clamp onto the proximal right hepatic artery, distal to the segment IV hepatic artery. The right hepatic artery is then divided with scissors, and the right portal vein is divided between the vascular clamps, applied at a right angle to the course of the main portal vein. The MHV, RHV, and, if present, the inferior RHV are controlled with the vascular stapler (TA 30; Tyco Healthcare) prior to its division by scissors. To avoid stricture of the portal vein, the right portal vein stump is sutured in a transverse manner with 6-0 Prolene continuous back-and-forth sutures. Biliary leakage and patency of the remnant left hepatic duct are checked with intraoperative cholangiogram and dilute methylene blue instillation; the methylene blue in the bile ducts must be flushed away by normal saline. The cystic duct is ligated with 2-0 Vicryl, and the remnant left liver is maintained in the anatomic position by reconstitution of the falciform ligament with nonabsorbable sutures (Fig. 90D.7). Patency of the vessels is verified with IOUS. The hepatic flexure of the colon and the corresponding portion of the greater omentum are allowed to ascend into the right subphrenic space for prevention of adherence of the small bowel

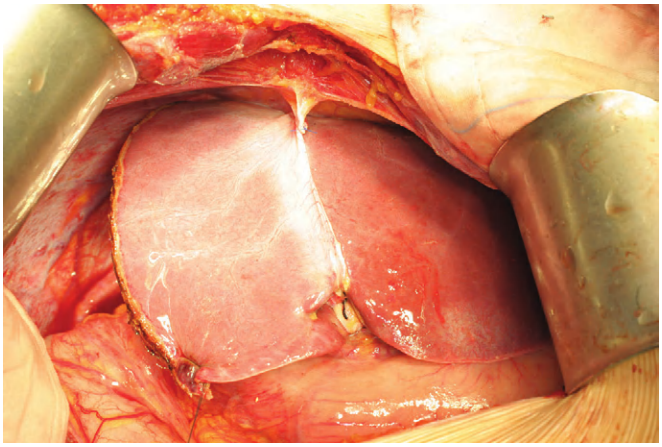


FIGURE 90D.7. Remnant left liver is prevented from dropping into the right subphrenic space by suturing the falciform ligament.

to the transection surface of the remnant left liver, and the abdomen is closed without drainage (Liu et al, 2005).

The outcomes of donor right hepatectomy including the MHV have improved with accumulation of experience. In our consecutive series of 200 donor right hepatectomies, all including the MHV, the operation time was shortened, and blood loss decreased with maturity of these techniques (Chan et al, 2007c).

INCLUDING THE MIDDLE HEPATIC VEIN

An area of ongoing controversy in right LDLT is whether or not to include the MHV. Deleterious effects of no drainage to segments V and VIII include severe venous congestion and necrosis of these segments (Lee et al, 2001). The decision to exclude the MHV requires demonstration of collaterals between segment V and VIII tributaries and the RHV (Cescon et al, 2002).

Researchers at Kyoto University devised an algorithm that includes the MHV when the graft is MHV dominant, or the graft to recipient weight is less than 1%, and in all cases, the remnant left liver is larger than 35% (Tanaka & Yamada, 2005). Chang Gung Memorial Hospital includes the MHV when the graft to estimated standard liver volume is 50% or less, or when the segment V and VIII hepatic veins are large, and the RHV is small (de Villa et al, 2003). Researchers at Tokyo University observed congestion of segments V and VIII of the graft after temporary clamping of the right hepatic artery before determining venous interpositional grafting (Sano et al, 2002).

We include the MHV in all right liver grafts for the simplicity and familiarity of the technique (Fan et al, 2003b). Irrespective of the venous drainage pattern of segment IV of the remnant left liver, the segment IVb hepatic vein is preserved. Utmost care is needed for its preservation, when it drains into the MHV (Chan et al, 2004a). On the back table, the outflow capacity is guaranteed by venoplasty of the MHV and RHV into a single cuff (Liu et al, 2003). The venoplasty is further marked by a more expedient hepatic vein to the IVC anastomosis and higher outflow capacity of the right liver graft (Liu et al, 2003).

In summary, adequate graft size and quality, excellent venous outflow, and moderate portal inflow are the keys to the success of LDLT.

DONOR LEFT HEPATECTOMY

For a donor with a low body mass index, an upper midline incision can provide adequate access for the procedure. The left coronary ligament is taken down, and adequate mobilization of the left liver requires division of the ligamentum venosum or Arantius ligament between ligatures. The left hepatic duct, which may have a short extrahepatic course, is marked by a large metal clip, and the planned line of division is verified by cholangiogram under fluoroscopic guidance. Special attention is given to identify an insertion of the right posterior sector duct into the left hepatic duct (Fig. 90D.8). In this situation, the left hepatic duct can only be divided to the left of the right posterior sectoral duct. The middle hepatic artery should be preserved, when it arises from the left hepatic artery. A middle hepatic artery that is not large and arises from the right hepatic artery can usually be sacrificed, and segment IV will be supplied adequately by collaterals from the left hepatic artery. A replaced left hepatic artery arising from the left gastric artery allows a good length of isolated artery (Fig. 90D.9). Temporary inflow control of the left hepatic artery and portal vein by the vascular clamp reveals the Cantlie line. Liver transection is to the right of the MHV by CUSA. A low insertion of the segment VIII hepatic vein into the MHV calls for caution in the final part of the liver transection; this segment VIII vein should be preserved for venous outflow of the right anterior sector of the remnant right liver, and inadvertent damage of the vein results in torrential bleeding. When compared with donor right hepatectomy also including the MHV, blood loss is more significant, and the operation time is longer; these are likely the results of a larger liver transection surface (Chan et al, 2007b).



FIGURE 90D.8. Operative cholangiogram with a large metal clip marking the planned line of division of the left hepatic duct.

SEGMENT II AND III DONOR HEPATECTOMY

By and large, exposure and hilar dissection are similar to donor left hepatectomy. Following isolation of the left hepatic artery and the left portal vein, an operative cholangiogram is performed with a large metal clip to mark the planned line of division of the left hepatic duct. Special attention still must be paid to the location of the right posterior sectoral duct, which may insert into the left hepatic duct. If the middle hepatic artery that supplies segment IV arises from the left hepatic artery, and enough length is distal to it, it can be preserved; otherwise, it is sacrificed, and the entire left hepatic artery is included in the graft. A middle hepatic artery that arises from the right hepatic artery is most favorable and need not be isolated. The liver transection line is about 1 cm to the right of the falciform ligament. The pedicles supplying segment IV are isolated, ligated, and plicated before division, whereas the caudate lobe is often not included into the graft, because the upper abdomen of the recipient often has limited space. The caudate vessels and bile ducts are ligated and divided and plicated if necessary.

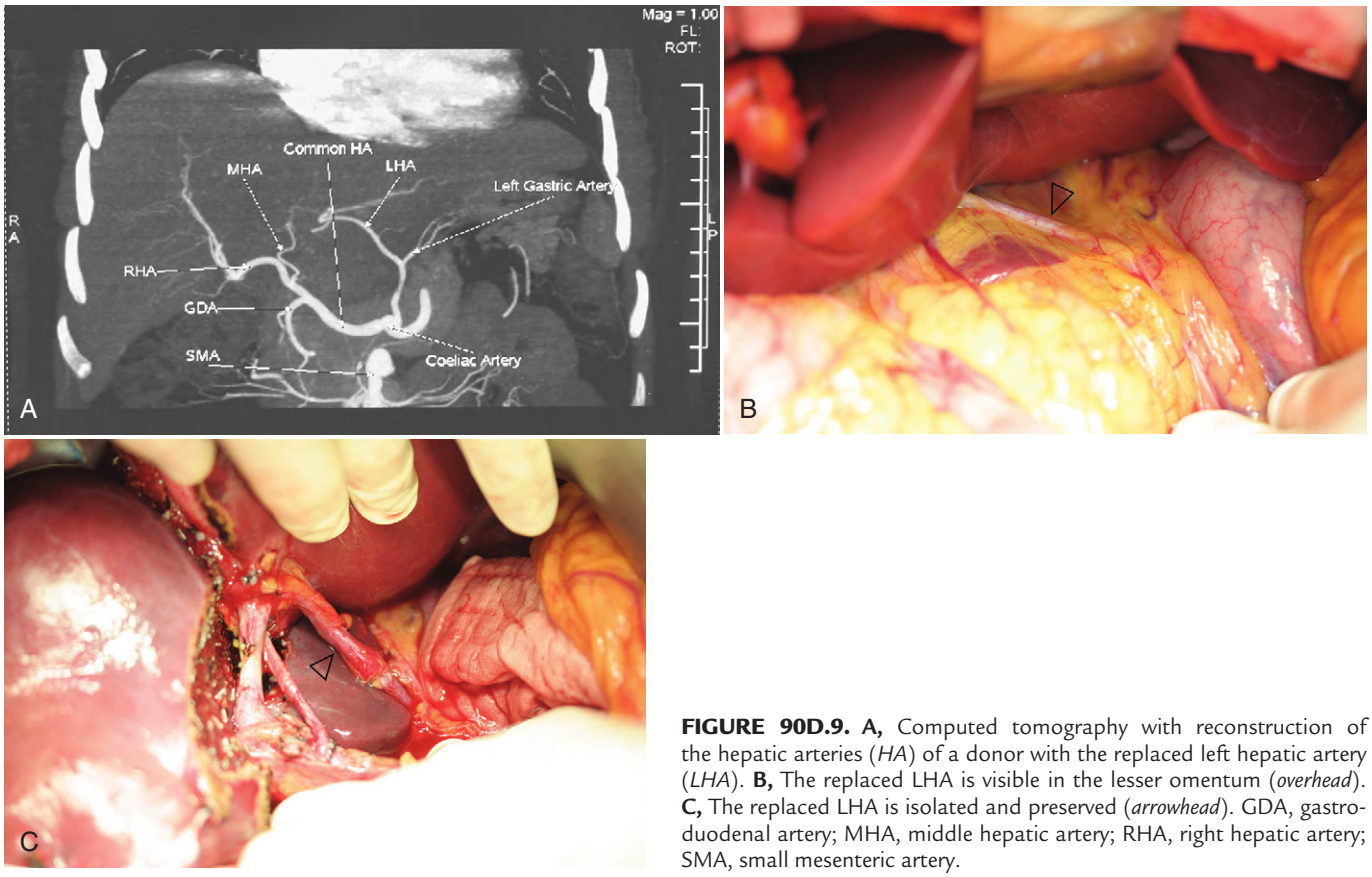


FIGURE 90D.9. A, Computed tomography with reconstruction of the hepatic arteries (*HA*) of a donor with the replaced left hepatic artery (*LHA*). **B,** The replaced LHA is visible in the lesser omentum (*overhead*). **C,** The replaced LHA is isolated and preserved (*arrowhead*). GDA, gastroduodenal artery; MHA, middle hepatic artery; RHA, right hepatic artery; SMA, small mesenteric artery.

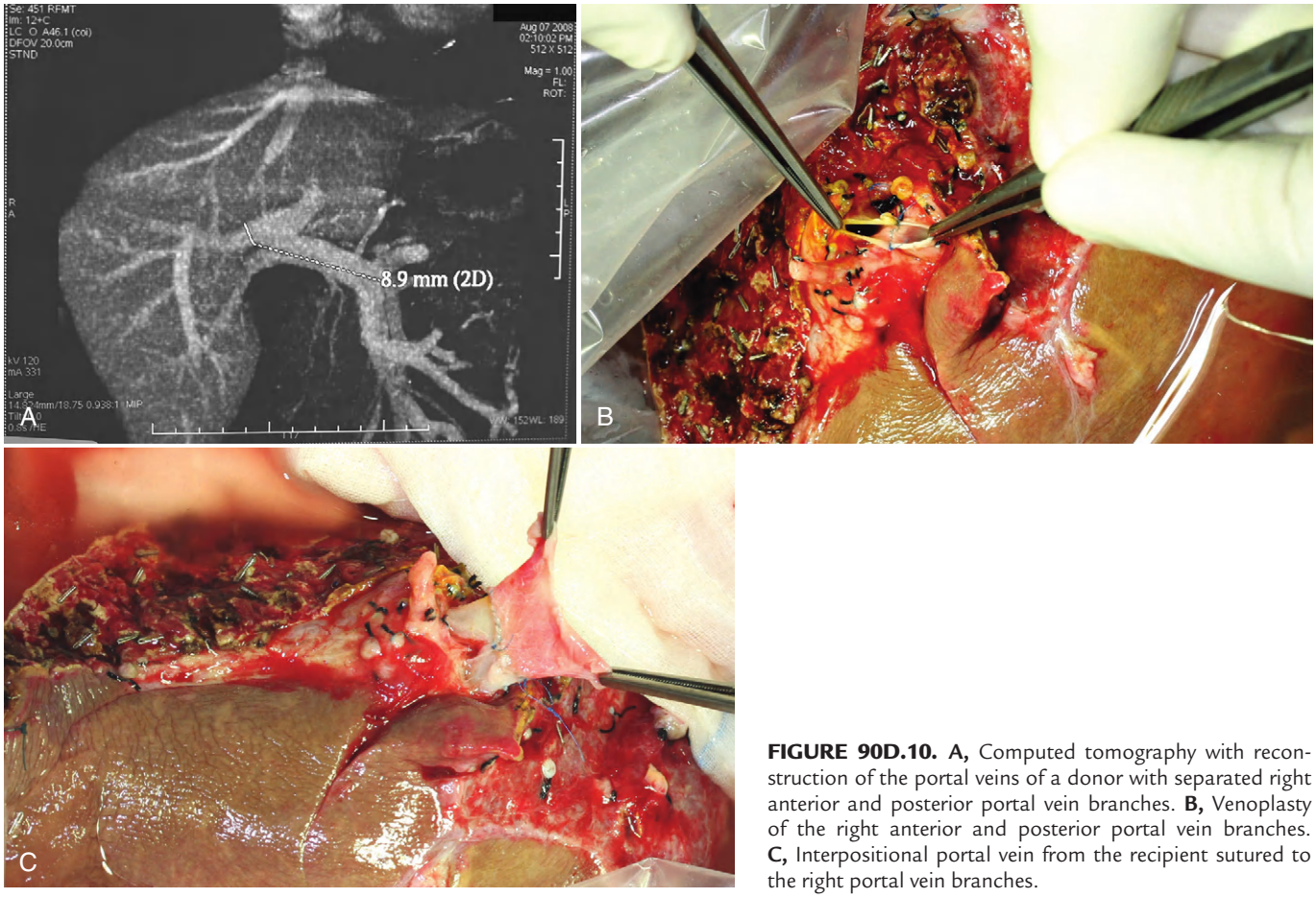


FIGURE 90D.10. A, Computed tomography with reconstruction of the portal veins of a donor with separated right anterior and posterior portal vein branches. **B,** Venoplasty of the right anterior and posterior portal vein branches. **C,** Interpositional portal vein from the recipient sutured to the right portal vein branches.

ANATOMIC ANOMALIES OF THE DONOR (SEE CHAPTER 1B)

Besides inadequacy of size and proportion of the donor liver, occasional anatomic anomalies of the donor liver may preclude liver donation. When a major segmental branch of the right portal vein arises from the left portal vein intrahepatically, both right and left hepatectomy become too hazardous for the donor, so such a finding contraindicates donation. On the other hand, in the case of trifurcation of portal vein branches, if these are extrahepatic, donor operation is still feasible (Fig. 90D.10A); however, the right anterior and posterior branches of the portal veins require venoplasty to conform into a single cuff prior to graft implantation (Fig. 90D.10B). If the two branches are too short to merge into one, the portion of the recipient's portal vein at the bifurcation can be used as an interpositional graft, using the recipient portal vein (Fig. 90D.10C). These are done on the back table. The segment III or IVb hepatic vein could at times drain into the MHV (Fig. 90D.11A and B); however, MHV to RHV venoplasty is still feasible (Fig. 90D.11C).

Biliary tract anomalies occasionally render a liver graft unsuitable, as in the case of multiple small branches in the graft (Liu et al, 2004).

LIVER GRAFT BACK-TABLE PROCEDURE: PERFUSION AND TRIMMING

To shorten the cold ischemic time, the right liver graft is not delivered until the recipient is almost ready for graft implantation. Once delivered, the graft is flushed with three times the graft volume of a cold solution of histidine-tryptophan-ketoglutarate (HTK; Dr. Franz Köhler, Chemie GmbH, Alsbach-Hähnlein, Germany), while being immersed in an ice-sludge basin on the back table. The right portal vein is cannulated and adapted to the vein wall with fingers and not ligature (Fig. 90D.12A; Chan et al, 2004b). The right liver graft with separate right anterior and posterior portal veins requires simultaneous flushing with two cannulae (Fig. 90D.12B). The right hepatic artery is flushed with 100 drops of HTK solution through a 21-Fr angiocatheter by gravity (Fig. 90D.12C). Inadvertent damage to the artery intima can result in unrecoverable graft loss. The right anterior and posterior sectoral ducts are also flushed with cold HTK solution to minimize duct damage during preservation. The graft is weighed and transferred to another basin with cold HTK solution. Venoplasty of the MHV with the RHV of the graft is then performed (Liu et al, 2003). Even though the MHV and the RHV are often at a distance of

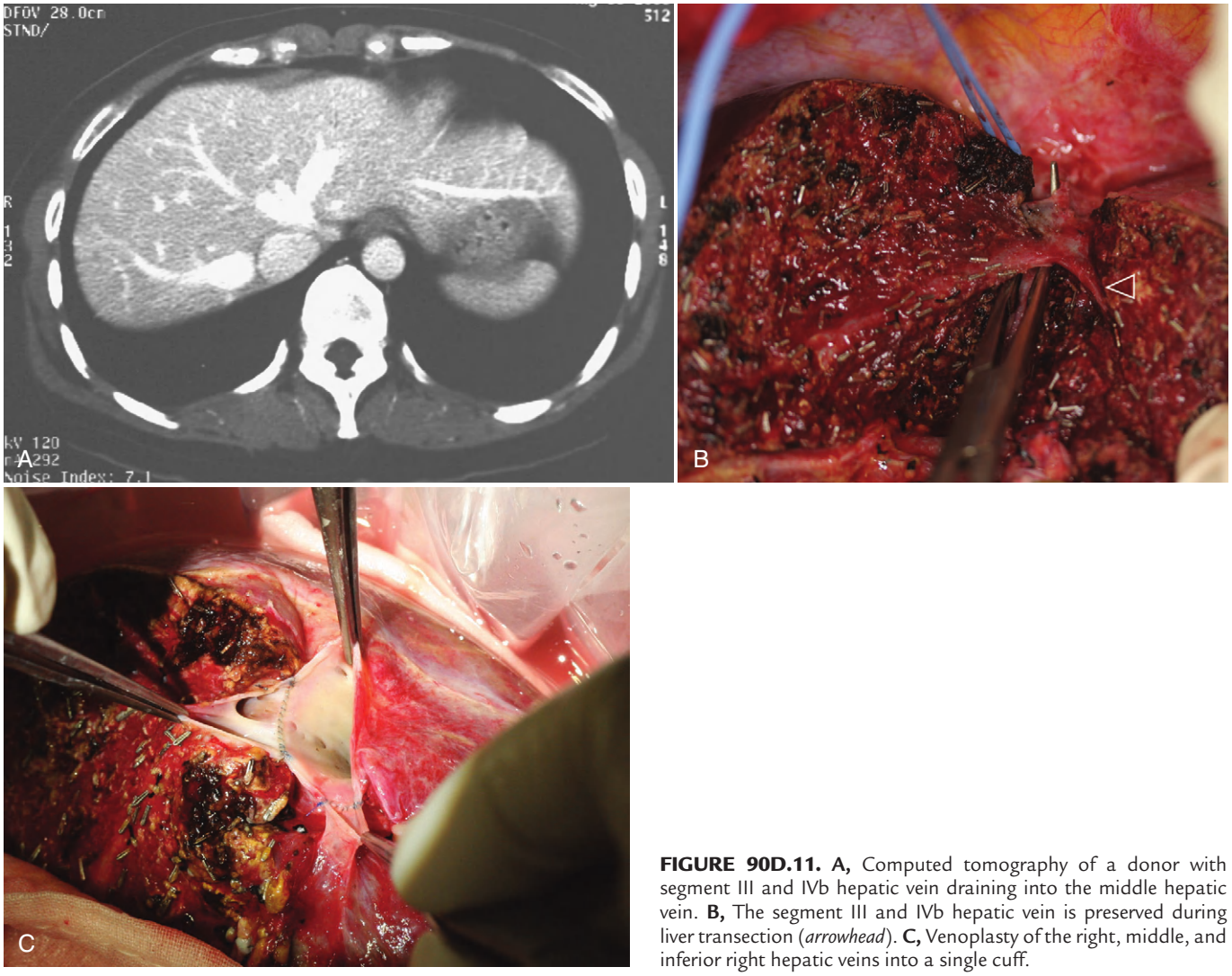


FIGURE 90D.11. A, Computed tomography of a donor with segment III and IVb hepatic vein draining into the middle hepatic vein. **B,** The segment III and IVb hepatic vein is preserved during liver transection (*arrowhead*). **C,** Venoplasty of the right, middle, and inferior right hepatic veins into a single cuff.

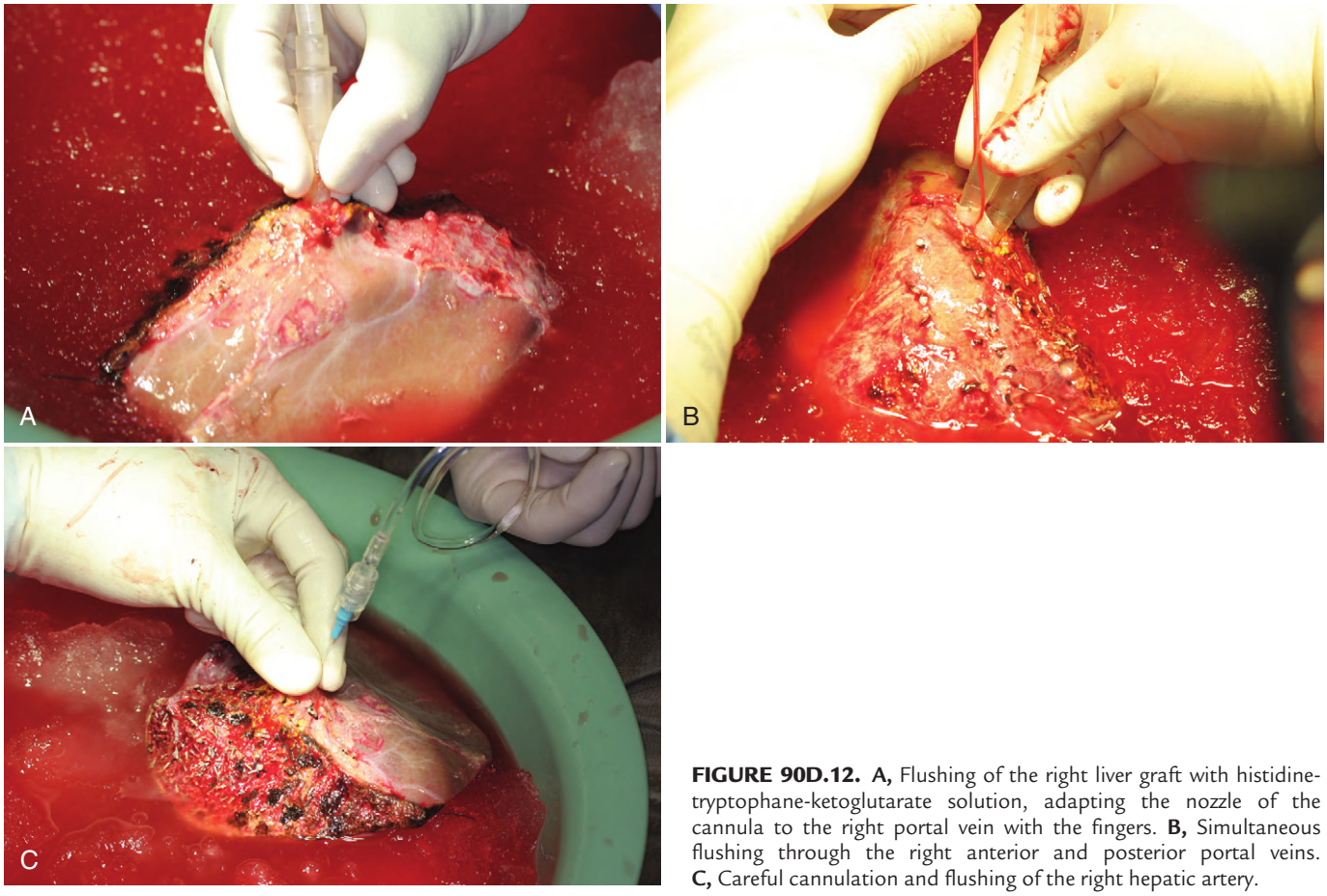


FIGURE 90D.12. A, Flushing of the right liver graft with histidine-tryptophane-ketoglutarate solution, adapting the nozzle of the cannula to the right portal vein with the fingers. **B,** Simultaneous flushing through the right anterior and posterior portal veins. **C,** Careful cannulation and flushing of the right hepatic artery.

up to 2 cm (Fig. 90D.13A), they can be drawn together for fashioning of a single venous cuff (Fig. 90D.13B; Chan et al, 2005). Often misled by planar schematic drawings, some have a false perception of the inadequate length of the MHV wall portion of the venoplasty for anastomosis to the IVC. In practice, the IVC—which is tubular, with a venotomy made over the RHV stump—faces the venoplasty of the MHV and RHV. The portion of the recipient IVC, in between the RHV and MHV, also makes up for the deficit in length on the MHV not included in the graft to preserve the segment IVb hepatic vein for venous drainage of the remnant left liver of the donor.

For the left liver graft and the segment II and III graft, if the MHV and the segment II and III vein are separate, they are merged into an equilateral triangle with a single cuff with an

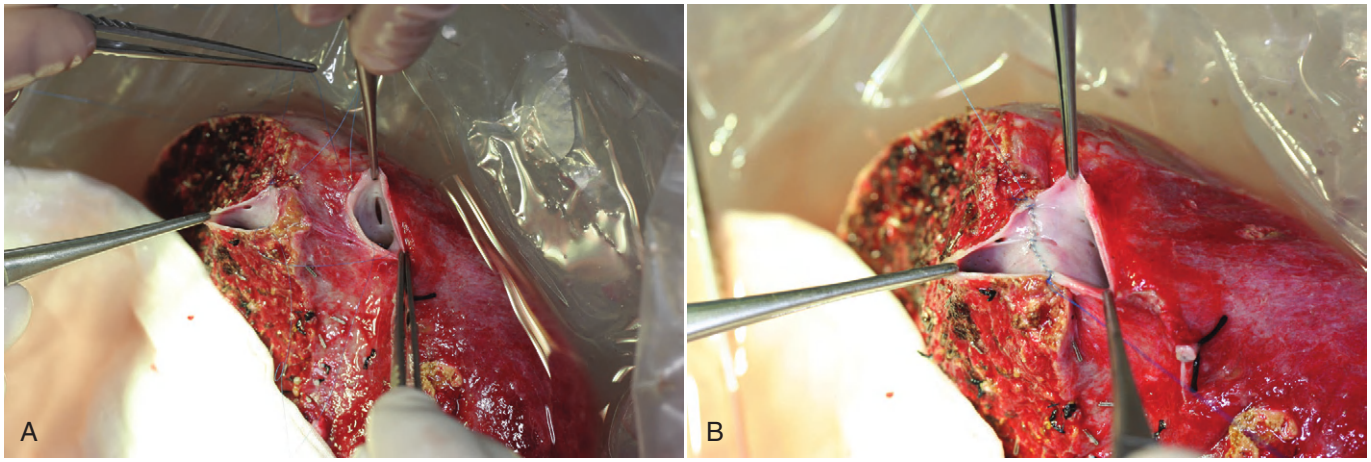


FIGURE 90D.13. A, Right and middle hepatic veins with a significant distance. **B,** Merging of the right and middle hepatic veins into a single triangular cuff with little tension.

apex point to the left by venoplasty. This facilitates hepatic vein to IVC anastomosis in the recipient.

The graft is weighed, and the weight is recorded. The percent of graft to standard liver volume is calculated, and the graft is then immersed in ice sludge.

DONOR POSTOPERATIVE CARE

Donor hepatectomy, both right and left, is a major surgical procedure undertaken on a healthy volunteer. Meticulous postoperative care is the least that can be offered by the health care profession. Postoperatively, the donor is transferred to the intensive care unit for close monitoring of hemodynamics and respiratory function. Early mobilization and institution of chest physiotherapy lower the risks of deep vein thrombosis and chest infection. The donor will also receive a 6-week course of proton pump inhibitor for peptic ulcer prophylaxis (Chan et al, 2007c). Females on hormone replacement therapy and those taking oral contraceptives require aggressive prophylaxis against deep vein thrombosis.

DONOR MORTALITY AND MORBIDITY

Donor safety is fundamental to LDLT (see Chapter 98B). As the application of LDLT has been extended from the child to the adult, and from using the left liver to using the right, the dilemma between recipient success and donor risk has come to the spotlight. The reported overall complication rate of donors is around 20% but has been reported as high as 67% in one series (Beavers et al, 2002). A unified system of complication reporting (Dindo et al, 2004) may narrow this range. Although even one donor mortality is too many, there are at least 19 known donor deaths (Trotter et al, 2006). The estimated mortality for donor right and left hepatectomy is 0.1% and 0.5% respectively (Barr et al, 2006), although mortality is lower in a multicenter series in Japan (Hashikura et al, 2009). In achieving a 5-year recipient survival rate of 80%, it takes one donor life to save 160 recipients. Less tangible are the quality of life changes of the donor in comparison to the predonation state (Chan et al, 2006b). The long-term biologic consequences of donor hepatectomy are not fully known. Nevertheless, decreases in white cell count, platelet counts, and elevation of liver transaminases are demonstrable even 2 years after right liver donation (Chan et al, 2006c).

CONCLUSION

Donor mortality after LDLT remains a reality; however, by lowering the donor mortality and morbidity and improving recipient survival, the justification of LDLT becomes stronger. Donor hepatectomy is a major surgical operation on a healthy person who does not require operation, and it is thus an ethical challenge, and this procedure was once viewed by the medical community and society with caution and skepticism (Cronin et al, 2001; Strong, 1999; Surman, 2002). Donor procedures can only be partially justified by the benefit to a recipient who has no other treatment options. Our common ground is the commitment to provide care of the highest standard to the living liver donor and to perform donor operations in experienced centers (Malago et al, 2001). This is the only way to maintain the highest quality and to decrease donor mortality and morbidity.

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CHAPTER 90E

Minimally invasive techniques in hepatic resection

Michael D. Kluger and Daniel Cherqui

OVERVIEW

Over the latter portion of the twentieth century, liver surgery has rapidly progressed from a risky procedure to a safe therapy for benign and malignant liver disease. As with many surgery disciplines, minimally invasive approaches were pursued in the 1990s. Gagner is credited for the first laparoscopic partial hepatectomy in 1992 (Gagner et al, 1992), and in a prospective series of 30 patients published in 2000, we demonstrated the safety and reproducibility of laparoscopic partial hepatectomy (Cherqui et al, 2000), which was followed by the safe application of these techniques to living donor left lateral sectionectomy in 2002 (Cherqui et al, 2002). Despite close to 20 years of development and nearly 3000 reported cases internationally, minimally invasive liver surgery remains an emerging field that should be approached with caution by surgeons experienced in the perioperative care and planning of both liver and laparoscopic surgery (Nguyen et al, 2009). Six centers have reported series of more than 100 patients, and most perform fewer than half of their total cases laparoscopically (Bryant et al, 2009; Buell et al, 2008; Chen et al, 2008; Cho et al, 2008; Koffron et al, 2006, 2007; Topal et al, 2008;). We have performed more than 200 laparoscopic partial hepatectomies since 1996, which represents 23% of our hepatectomy volume.

Whereas the percentage of resections for benign lesions has remained relatively stable over our experience, the percentage of resections for malignant lesions continues to increase year after year. The objective of this chapter is twofold: to present a balanced view of the current understanding of these techniques and to elucidate the technical details of the most commonly performed resections.

TERMINOLOGY

In 2008, leaders in the field met to discuss the current status of laparoscopic liver surgery (Buell et al, 2009). In the so-called Louisville Statement that resulted, those in attendance agreed on three procedural definitions: 1) pure, 2) hand-assisted, and 3) hybrid laparoscopy. *Pure laparoscopy* involves complete mobilization and resection via laparoscopic ports, with an incision for specimen extraction only. *Hand-assisted laparoscopy* involves the elective placement of a hand port for mobilization or resection, which is then used for specimen extraction. *Hybrid laparoscopy* refers to a procedure in which the resection and extraction are performed through a minilaparotomy, but laparoscopy, with or without hand assistance, is utilized for mobilization.

According to a comprehensive international review performed by Nguyen and colleagues (2009), 75% of reported laparoscopic resections were pure laparoscopy, 17% were hand-assisted procedures, and 2% used the hybrid technique. In addition, 4.8% were conversions to laparotomy or hand-assisted procedures, with the remaining 2% using less common techniques, such as a thoracoscopic approach.

Laparoscopic resections should be categorized no differently than open resections, based on the Brisbane 2000 terminology of liver anatomy and resections (Pang, 2002). Anterior and lateral segments II, III, IVb, V, and VI are most amenable to laparoscopic resection. Isolated resections of segments I, IVa, VII, and VIII have been reported, as surgeons extend the limits after safe mastery of anterior resections. Of the nearly 3000 internationally reported laparoscopic liver resections, the majority (44.9%) were wedge resections or segmentectomies, followed by left lateral sectionectomies (20.3%). Major resections, consisting of three or more Couinaud segments, included right hemihepatectomy (9%) and left hemihepatectomy (6.8%). Extended right hepatectomy, caudate lobectomy, central hepatectomy, and extended left hepatectomy each made up less than 1% of the total reported cases (Nguyen et al 2009).

We performed 96% of our resections using pure laparoscopy, with hand assistance (4%) selectively used for right hepatectomies or posterior segmentectomies. Major resections comprise 19% of our experience, and limited resections comprise 81% (Bryant et al 2009).

INDICATIONS

Liver pathology under consideration for open partial hepatectomy should be evaluated for the feasibility of a laparoscopic resection (see Chapter 90A); however, the potential benefits of a minimally invasive resection do not confer a prescription to resect all hepatic lesions for the purpose of providing a definitive diagnosis. Specifically, the laparoscopic approach should not be used to resect incidental, asymptomatic lesions convincingly recognized by imaging and markers to be benign and without harmful potential (cysts, hemangiomas, focal nodular hyperplasia), nor should laparoscopic resection be performed for the purpose of diagnosis, when lesions are safely amenable to percutaneous biopsy.

The indications for laparoscopic resection do not vary from those for open resection (Box 90E.1); however, lesion size and location are the most important determinants of when laparoscopic resection is appropriate. Resection of benign and malignant solid lesions and cystic and parasitic lesions are possible laparoscopically. The most favorable lesions for laparoscopic resection are solitary, 5 cm or less, and located in peripheral liver segments II to VI (Fig. 90E.1; Buell et al, 2009). Pedunculated tumors greater than 5 cm are often easily resectable laparoscopically. In experienced hands, laparoscopic left lateral

Box 90E.1

Indications and Contraindications for Laparoscopic Partial Hepatectomy

Indications

Location

Segments II through VI

Pathology

Benign and malignant neoplasms
Cystic lesions
Parasitic lesions

Size

Lesions <5 cm
Left lateral section lesions of any size not in proximity to major vascular structures
Pedunculated neoplasms of any size not in proximity to major vascular structures

Relative Contraindications

Location

Lesions near the inferior vena cava, hilum, or distal hepatic veins
Multiple or bilateral lesions
Segments I, IVa, VII, or VIII

Pathology

Coagulopathy or thrombocytopenia
Moderate to severe portal hypertension
Previous operation, especially upper abdominal

Size

Laparoscopic approach requiring a larger parenchymal resection than would be necessary via an open approach
Nonpedunculated benign and malignant neoplasms >5 cm

Absolute Contraindications

Gallbladder cancer and hilar cholangiocarcinoma
Inability to obtain a surgical margin that would otherwise be possible in an open resection
Patient unable to tolerate an open operation or pneumoperitoneum
Insufficient surgeon training

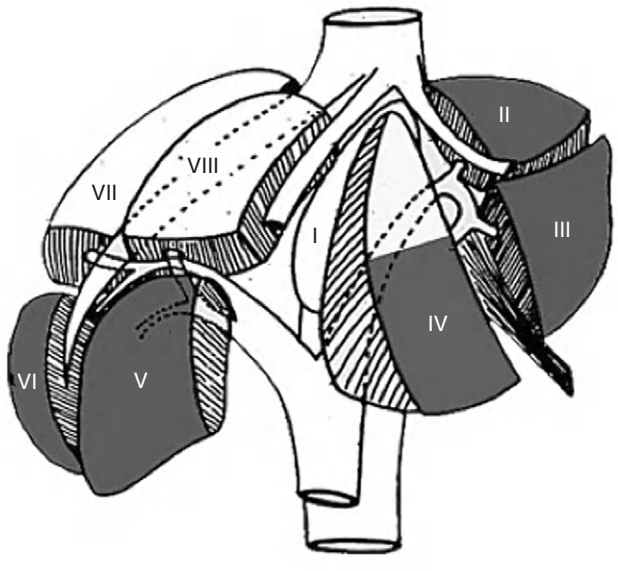


FIGURE 90E.1. The anterolateral liver—composed of segments II, III, IVb, V, and VI—is most amenable to the laparoscopic approach.

sectionectomy should be the standard approach for pathology in segments II and III (Buell et al, 2009; Chang et al, 2007).

Relative contraindications include lesions isolated to segments VII and VIII, multiple or bilateral lesions, and lesions located in proximity to the major hepatic veins, the inferior vena cava, or the hepatic hilum. These contraindications are considered relative, because in experienced centers, these lesions are increasingly managed laparoscopically (Buell et al, 2008; Koffron et al, 2007; Vigano et al, 2009a). A more extensive laparoscopic resection than would otherwise be necessary through an open approach may be contraindicated. An example would be a laparoscopic right hemihepatectomy for a posterior lesion that could be resected by a more limited open posterior segmentectomy. For each patient, the surgeon must weigh the risks and benefits of the laparoscopic and open techniques with the benefits of parenchymal preservation.

Surgical margins for benign lesions do not vary between open and laparoscopic resections. If there is concern that an adequate margin cannot be obtained laparoscopically, but it is technically feasible by an open approach, the former is contraindicated. Other contraindications include gallbladder cancer and hilar cholangiocarcinoma, because of the risk of peritoneal and port-site seeding and the necessary complex hilar dissection and extensive resection, respectively (see Chapters 49, 50B, 90B, and 90C).

SAFETY AND BENEFITS

Laparoscopic partial hepatectomy provides the benefits that laparoscopy has offered to patients undergoing many other abdominal operations. Case-control studies have demonstrated shorter operative times (Bryant et al, 2009; Buell et al, 2008; Koffron et al, 2007), shorter lengths of hospitalization (Buell et al, 2009; Cai et al, 2008; Koffron et al, 2007; Topal et al, 2008), less operative blood loss (Bryant et al, 2009; Buell et al, 2008; Koffron et al, 2007; Lesurtel et al, 2003), reduced transfusion requirements (Buell et al, 2008; Koffron et al, 2007; Topal et al, 2008), a reduced need for analgesia (Cai et al, 2008), quicker return to oral consumption (Cai et al, 2008), lower morbidity (Buell et al, 2008; Koffron et al, 2007; Topal et al, 2008), and fewer postoperative adhesions (Belli et al, 2009; Laurent et al, 2009). Studies have demonstrated decreased costs when accounting for shorter operative times and hospitalizations (Buell et al, 2008; Koffron et al, 2007; Polignano et al, 2008).

The mortality and morbidity rates in these studies are at least equivalent to, if not better than, those of large case series of open liver resections. In their review of 127 published articles on laparoscopic hepatic resection, Nguyen and colleagues (2009) found a cumulative mortality rate of 0.3%. This compares favorably to the 0% to 5.4% reported in the open-resection literature from high-volume centers. All deaths were postoperative, and most often caused by liver and multiorgan system failure. Of 2804 patients, 295 morbid complications were reported (10.5%), with a range of 0% to 50% across the 127 studies (Nguyen et al 2009). Liver-specific complications included bile leaks (1.5%), transient liver failure and ascites (1%), and abscess (2%). The remaining 6% were complications common to all operations, including but not limited to hemorrhage, wound infection, hernia, bowel injury, arrhythmia, and urinary or respiratory tract infections.

Laparoscopy has been utilized with success in cirrhotic patients (see Chapter 90F), with multiple small case-control

studies and series demonstrating lower morbidity and improved recovery. The laparoscopic approach also decreases the rate of postoperative ascites in this subgroup. Possible explanations include the preservation of venous and lymphatic collateral pathways in the abdominal wall, less intraoperative mobilization of the liver, and reduced intraoperative volume loading (Belli et al, 2007; Buell et al, 2009; Cherqui, 2006; Gigot et al, 2002; Kaneko et al, 2009; Laurent et al, 2003; Santambrogio et al, 2009; Vigano et al, 2009a). Nearly 40% of our laparoscopic experience has been with those patients who have chronic liver disease. These patients typically require longer operations and more pedicle clamping but globally have a better recovery than their open counterparts (Bryant et al, 2009).

As a consequence of decreased adhesions formed after an initial laparoscopic resection, reoperations, such as repeat hepatectomy and liver transplantation can often be performed more easily, with less blood loss, reduced transfusion requirements, and reduced operative time than following an initial, open partial hepatectomy (Belli et al, 2009; Bryant et al, 2009; Laurent et al, 2003). In our study comparing patients who had undergone a previous open or laparoscopic liver resection, the absence of adhesions at the time of liver transplantation in the laparoscopic group allowed for hepatectomy in a mean of 150 ± 52 minutes versus 247 ± 71 minutes in the open group. Additionally, a median of 2 U blood was transfused during hepatectomy in the open group versus zero in the laparoscopic group (Laurent et al, 2009). These are significant benefits, given that patients who require repeat operations often have diseased parenchyma because of cirrhosis or chemotherapy effects and the negative immune and oncologic impact of blood transfusion.

Barriers to the wide acceptance of laparoscopic surgery—such as threat of gas embolism, violation of oncologic principles, and significant risk of bleeding—have not been apparent in the literature (Vigano et al, 2009a). In addition, studies have consistently demonstrated that operative safety and postoperative morbidity improve with experience (Nguyen et al, 2009). When comparing our early and late groups, we found statistically significant reductions in operative time (210 to 150 minutes), blood loss (300 to 200 mL), conversion (16.9% to 2.4%), and morbidity (17.2% to 3.4%) (Vigano et al, 2009b).

Additional benefits include better cosmesis, improved maintenance of the sensorimotor integrity of the abdominal wall, and earlier access to adjuvant therapy because of quicker recovery. Despite these favorable results, it is important to acknowledge that these findings are from nonrandomized studies, and that laparoscopic cases remain highly selected for their potential for success. It can be inferred from the colorectal and bariatric literature that these benefits are real, especially for indicated cases (see Box 90E.1); however, the benefits may not be as robust for cases with relative contraindications (Castaing et al, 2009; Cho et al, 2008).

ONCOLOGIC OUTCOMES

Perhaps more important than demonstrating perioperative benefit is confirmation that oncologic principles are not dismissed. With regard to margins, recurrence, and survival, comparable results between open and laparoscopic resections have been well demonstrated in the literature (Nguyen et al, 2009; Vigano et al, 2009). In a meta-analysis of 165 laparoscopic liver resections and 244 open liver resections, Simillis and colleagues (2007) found no difference in tumor-free margin status, overall survival, and disease-free survival between laparoscopic and open liver resection for cancer. This has been demonstrated for both hepatocellular carcinoma (HCC) and colorectal metastatic disease (Castaing et al, 2009; Cherqui et al, 2009; Nguyen et al, 2009; Sarpel et al, 2009). Laparoscopic resection of other metastatic tumors has been reported in small numbers, mainly breast cancers and melanomas. Further, port-site metastases and peritoneal dissemination have not occurred with the use of closed-bag methods for specimen extraction.

As chemotherapeutic, biologic, and radiation options expand, patients with primary and metastatic liver cancer may anticipate longer survival despite the high possibility of recurrence. Resection of HCC as a bridge to future transplantation should also be a consideration (Cherqui et al, 2009; Laurent et al, 2009). As such, parenchyma-sparing procedures should be promoted in anticipation of repeat operative needs. Rather than performing a laparoscopic right or left hepatectomy because of relative ease technically, segmental resections along anatomic lines must be performed when possible.

GENERAL PRINCIPLES

Imaging

High-quality imaging with vascular reconstruction is necessary to understand a patient's intrahepatic arterial and portal anomalies. Review of recent magnetic resonance (MR) or computed tomography (CT) imaging should be performed before proceeding to the operating room.

Equipment

All laparoscopic equipment must be state of the art and in good working order, and nursing staff should be familiar with the proper setup and functioning of equipment so as not to occupy the surgeon's attention during the operation at critical moments. The center should have an adequate backup supply of cameras, monitors, insufflators, electrical surgery generators, cables, tubing, and laparoscopic instruments and devices. A set of conventional instruments and retractors for open surgery should be readily available in case of vascular emergency.

We prefer a 10-mm, 30-degree laparoscope for its versatile imaging. A CO_2 insufflator to maintain a pneumoperitoneum of 12 mm Hg is used, although some centers prefer a pneumoperitoneum as low as 8 mm Hg for the prevention of hepatic vein gas embolism. To our knowledge, no major centers are currently using gasless laparoscopy. Hand-assisted laparoscopy can be used for right-sided and posterior lesions or as needed for failure of case progression or to aid in obtaining hemostasis, but this is more often used in the United States than in Europe. A gas-tight port is placed, and the incision is later used for extraction of the specimen. In our experience, hand assistance was used in selected cases and/or to prevent conversion to laparotomy when mobilization and parenchymal transection were difficult.

Positioning

For all except resection of segments VI and VII, the patient is placed in the supine position with the lower limbs apart on a split-leg table. Both arms are padded and tucked at the sides,

and the patient is prepared and draped from the pubis to the nipple line. The surgeon stands between the patient's legs with an assistant at each side. The assistant opposite the side of resection can be replaced by an adjustable instrument holder. Freestanding monitor towers are placed lateral to each shoulder, with a hanging monitor above the patient's head, if such a monitor is available. The scrub nurse and instruments are positioned lateral to the patient's right leg or behind the surgeon.

For segment VI and VII segmentectomies, the patient is placed in the left lateral decubitus position. The surgeon and one assistant stand on the patient's ventral side, with the scrub nurse opposite at the patient's legs. The monitor towers are positioned across from the surgeon, and a reverse Trendelenburg position allows the bowels to drop into the lower abdomen; the table is tilted laterally as necessary.

Incisions, Exploration, and Exposure

The open technique is used to gain access to the abdomen supraumbilically. The remaining four ports are placed under direct vision, with incisions sized to accommodate the necessary cannulas as pictured in Figure 90E.2. The median trocar is the camera port, the paramedian ones are the working ports, and the most lateral right and left ports are for retraction. For segment VI and VII resections, four ports are used: a 10-mm port in the left upper quadrant, a supraumbilical 12-mm port, a 12-mm paraumbilical port in the midclavicular line, and a 10-mm trocar in the anterior-axillary line (Fig. 90E.3).

After a thorough inspection of the peritoneal cavity for ascites, carcinomatosis, and signs of portal hypertension, attention is turned to the liver for signs of superficial lesions, steatosis, cholestasis, cirrhosis, or other gross pathology. Next, laparoscopic ultrasound is performed. A thorough knowledge of both B-mode and Doppler laparoscopic ultrasonography is mandatory for safe and accurate laparoscopic resections. A high-frequency laparoscopic probe is used to look for lesions less than 1 cm, which may be difficult to assess by extracorporeal imaging, and to confirm adequate margins (Foroutani et al, 2000; Milsom et al, 2000; Montorsi et al, 2001).

The round ligament is divided close to the abdominal wall. This prevents a dangling remnant that might obstruct the view or soil the tip of the scope. Then the falciform ligament is divided along its length to the insertion of the hepatic veins into the vena cava. The round ligament along with the gallbladder or remnant cystic duct can be used as "handles" for manipulation of the liver.

If pedicle occlusion is anticipated, the pars flaccida is opened, and an instrument is passed behind the portal triad to encircle it with a tape. The tape is then extracorporeally inserted through a 16-Fr rubber tube to serve as a tourniquet, and it is returned to the abdomen. If pedicle clamping is to be used, we favor 15 minutes of clamping interrupted by 5 minutes of pedicle flow. If parenchymal bleeding occurs during the 5 minute period, the transected parenchyma can be opposed or packed with some gentle lateral pressure. Although we do not routinely clamp the pedicle, this should be another safety tool in the arsenal of the new laparoscopic liver surgeon, or it may be used as an emergent maneuver, if parenchymal bleeding obscures visualization. Liberal use of on-demand, intermittent inflow occlusion, meticulous technique, and low central venous pressure (CVP) anesthesia are very effective at limiting blood loss during these

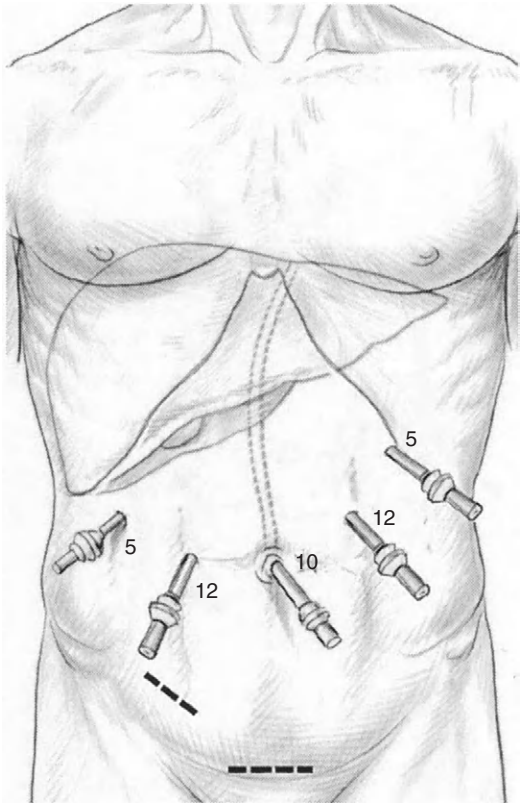


FIGURE 90E.2. Common port sites, trocar sizes (in millimeters), and positioning for laparoscopic partial hepatectomy. The patient is supine, and the surgeon is positioned between the patient's legs. Specimen extraction may be through a suprapubic or right lower quadrant incision (*dotted lines*). *(From Cherqui D, et al, 2000: Laparoscopic liver resections: a feasibility study in 30 patients. Ann Surg 232:753-762.)*

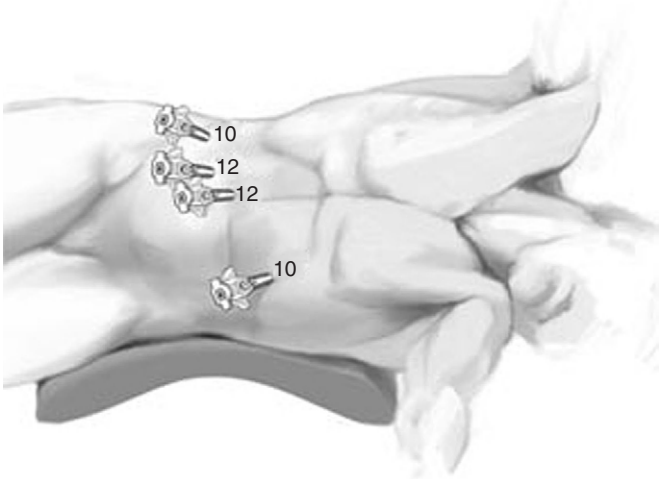


FIGURE 90E.3. Port sites and trocar sizes (in millimeters) for laparoscopic resection of segments VI and VII. The patient is in the left lateral decubitus position with the surgeon and assistant ventral to the patient. *(From Cherqui D, et al, 2000: Laparoscopic liver resections: a feasibility study in 30 patients. Ann Surg 232:753-762.)*

cases. Complete vascular occlusion is difficult laparoscopically, and any resection requiring this should be performed as an open procedure.

Transection Techniques

The transection line is outlined along the liver capsule with monopolar diathermy based on preoperative imaging, knowledge of hepatic anatomy, laparoscopic ultrasonography, or demarcation lines, when hepatic artery and portal vein flow are interrupted. Whereas in open surgery, the clamp-and-crush method is a standard and inexpensive transection technique, newer technology is required for laparoscopic operations. The Harmonic Scalpel (Ethicon Endo-Surgery, Cincinnati, OH) and the LigaSure vessel-sealing device (Valleylab, Boulder, CO) are effective for transecting the superficial 2 to 3 cm of parenchyma. For deeper parenchyma, an ultrasonic dissector is used (e.g., CUSA Dissectron, Integra, Plainsboro, NJ; SonoSurg, Olympus, Tokyo). Subsequently, vascular and biliary structures less than 3 mm are ligated and transected using the Harmonic Scalpel, LigaSure, bipolar diathermy, or titanium clips. Larger arteries, such as the hepatic artery, and bile ducts are ligated with plastic locking clips (Hem-o-lok; Teleflex Medical, Research Triangle Park, NC) and then divided. Laparoscopic linear staplers (Endo GIA, Covidien, Mansfield, MA; Echelon Endopath Stapler, Ethicon Endo-Surgery) are used for the portal and hepatic veins. A staple depth of 2.5 mm secures hemostasis in the large-diameter, thin-walled vessels encountered in liver surgery. Load lengths include 30, 45, and 60 mm, but the 45 mm is the most commonly used. The stapler can be applied to segmental portal pedicles or to isolated large veins; however, the stapler should never be forced closed over a thick tissue mass, nor should excessive tissue length be squeezed into the jaws; such maneuvers risk misfiring, which can lead to bleeding that is difficult to control. Rather, further dissection should be performed, or the length of the jaws increased, until the tissue fits effortlessly within the stapler. Prior to stapling the right or left portal branch near the bifurcation, flow to the opposite pedicle should be confirmed.

Parenchymal transection by repeated application of a linear stapler is practiced by some centers, with the cost of the devices said to be offset by reduced operating time and length of hospitalization (Buell et al, 2008). We prefer a method of complete visualization, believing that blind application of the linear stapler is a rougher and less precise technique.

Extraction, Drainage, and Closure

Small lesions can be removed through extensions of trocar incisions after placement in an endoscopic bag. Larger lesions can be removed through preexisting McBurney or midline incisions or through hand-port incisions. In the virgin abdomen, specimens are removed through a 5- to 8-cm Pfannenstiel incision. Regardless of the chosen incision, the abdominal wall is incised to the fascia, and a 15-mm trocar is inserted at the center of the incision under direct laparoscopic vision. A large capacity endoscopic bag is introduced, and the specimen is retained. The specimen is then retracted against the fascia, and the fascia and peritoneum are opened only as much as necessary for retrieval. The fascial layers are reapproximated, the pneumoperitoneum is reintroduced, and the operative site is lavaged and examined for hemostasis and biliary tract integrity.

Intraoperative cholangiography is not routinely performed, but it can be used if there is concern for a bile leak or aberrant biliary anatomy. Because of the large dead space created, right hepatectomies are usually the only resections we drain. The skin and port-site incisions are closed with absorbable subcuticular sutures.

Conversion to Laparotomy

Conversion rates in the literature range from 0% to 55%. The most cited reasons for conversion are hemorrhage, adhesions, and anatomic difficulties (Nguyen et al, 2009a). Many of these can be prospectively prevented by proper patient selection based on quality imaging and an understanding of laparoscopic principles. Conversion should not be considered failure and should be performed without hesitation when a patient's well-being is at risk.

Hemorrhage may be brisk, or it may be of a continuous, slow nature. Brisk hemorrhage may result from either arterial or venous bleeding. Arterial bleeding is controlled with instruments used to compress or grasp the vessel while clips or sutures are applied. The hepatic vein is the most common source of hemorrhage, and bleeding from the hepatic and portal veins and vena cava may be more difficult to manage because of vessel fragility and retraction (Vigano et al, 2009). Significant bleeding should ideally be managed laparoscopically, at least temporarily, because shock may ensue by the time the laparotomy is performed. This is a matter of urgent decision making by the surgeon, perfect collaboration with the anesthesiologist, and above all, mastering the advanced laparoscopic techniques required to embark on these procedures, such as intracorporeal suturing. Continuous, slow bleeding occurs during transection and may be due to elevated CVP, fragile liver parenchyma, or inappropriate technique. This slows the procedure and often interferes with visualization. In all situations, intermittent portal triad clamping may be utilized, and if rapid introduction of a hand port and conservative measures are ineffective to manage the bleeding, conversion to laparotomy should be performed without delay.

Insufficient exposure, proximity to major vessels, and inability to obtain appropriate margins are a few of the reported anatomic difficulties that may cause failure to progress, although this may also be the result of a more difficult or dangerous dissection or transection than was anticipated. In any case, this should be recognized as early as possible to avoid conversion after a lengthy and inefficient procedure.

SPECIFIC PARTIAL HEPATECTOMY PROCEDURES

Left Lateral Sectionectomy

The left lateral sectionectomy is the most straightforward laparoscopic liver procedure, and it represents the standard of care for our division. The left lateral section is mobilized by dividing the round, falciform, left triangular, and coronary ligaments with the Harmonic or LigaSure. The entire length of the lesser omentum is opened close to the liver, and a replaced left hepatic artery is divided if present. If a parenchymal bridge covers the inferior surface of the round ligament, it is divided with the harmonic shears.

The parenchymal transection is performed to the left of the patient's falciform ligament with the Harmonic or LigaSure.

The plane of transection is better visualized by retracting the round ligament superiorly and to the right and the left lateral segment superiorly and to the left. The ultrasonic dissector can then be used to open the deeper parenchyma, progressing cranially from anterior to posterior, with small vessels and ducts controlled as previously discussed; however, transection can be completed with the Harmonic Scalpel or LigaSure device, because there are few bridging structures in this procedure. Transection is continued until the portal pedicles of segments II and III are visualized. These pedicles can then be divided with two to three firings of the linear stapler (Fig. 90E.4). Parenchymal transection continues cranially, until the left hepatic vein is visualized, at which point it is divided with the linear stapler (Fig. 90E.5).

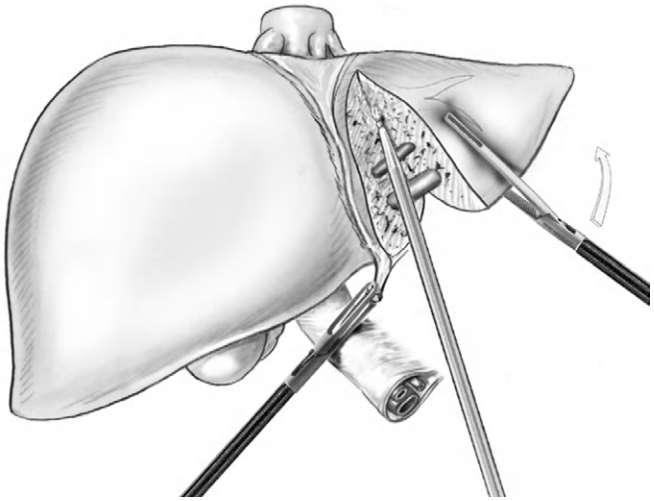


FIGURE 90E.4. Left lateral sectionectomy. Atraumatic graspers retract the round ligament to the right and the specimen to the left. The ultrasonic dissector is used to dissect the parenchyma, exposing the segment II and III pedicles for subsequent ligation and division.

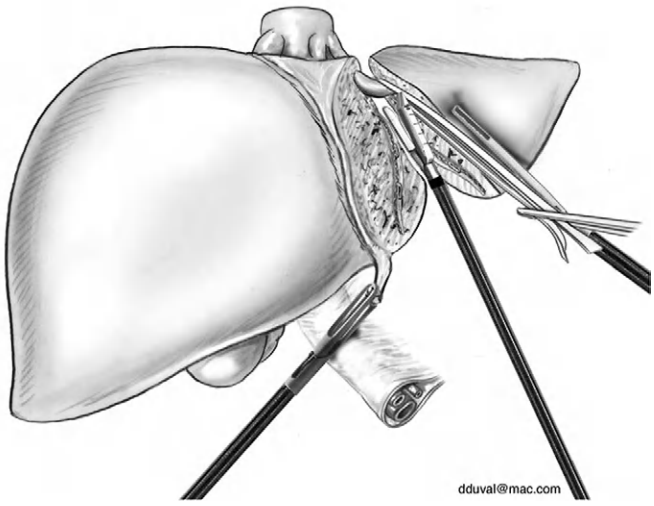


FIGURE 90E.5. After the left hepatic vein is dissected free of parenchyma, a tape is passed around it for better control and exposure. A linear stapler is passed around the hepatic vein and fired, thereby ligating and dividing the vessel. The left and right hepatic veins are divided in a similar manner for the left and right hemihepatectomy, respectively.

Left Hemihepatectomy

The left liver is mobilized as for the left lateral sectionectomy, and a tourniquet can be assembled around the main portal triad. A cholecystectomy is performed if the gallbladder is present, but the gallbladder is left partially attached so that it may be grasped and retracted superiorly and to the left. The extrahepatic left glissonian pedicle is now exposed and dissected using endoscopic scissors, right-angled forceps, and bipolar diathermy. The left hepatic artery and left portal vein are then individually divided or clamped with bulldog clamps passed through a 12-mm trocar. The extrahepatic clamping delimits the plane that intersects the gallbladder and inferior vena cava fossae, known as the *midplane* of the liver.

Parenchymal transection is performed along this line using the Harmonic Scalpel or LigaSure device superficially and the ultrasonic dissector more deeply. Once dissection enters the hilar plate, the left intraparenchymal glissonian pedicle is divided with a linear stapler. Parenchymal transection continues cranially, until it reaches the insertion of the left hepatic vein into the vena cava, at which point it is divided with the linear stapler.

Right Hemihepatectomy

Right hemihepatectomy is the most difficult of the common laparoscopic liver resections, and previous mastery of more limited laparoscopic resections is a prerequisite. As previously detailed, the falciform and round ligaments are dissected, and a tourniquet around the main portal triad is assembled. The cystic duct and artery are ligated and divided, and the gallbladder remains in situ as a retraction point for elevating the liver to the right. The remnant cystic duct is retracted to the left, exposing the short course of the extrahepatic right glissonian pedicle. A replaced right hepatic artery is ligated and divided if present, and the right branches of the hepatic artery and portal vein are gently dissected and individually encircled with tapes to retract them for easier division. The right branch of the artery is divided between plastic locking clips, and the right branch of the portal vein is divided with a linear stapler or between locking clips. Identification of the origin of the left branch of the portal vein should be assured before occluding the right portal branch. When possible, intraparenchymal dissection to the branches of the hepatic artery and portal vein limits risk to the portal triad bifurcation. The line of demarcation along the midplane of the liver is identified and marked. The procedure can be done without or with initial mobilization of the right lobe; the former is referred to as the *anterior approach,* which is our preferred method.

For the anterior approach, the right hepatic vein is not controlled prior to parenchymal transection. After ligation of the right hepatic artery and portal vein, parenchymal transection is started at the inferior edge of the liver in the anterior-posterior direction along the line of demarcation. The previously described techniques are utilized. As progress is made cranially, the proximal hepatic veins draining segments V and VIII toward the middle hepatic vein are exposed, clipped, and divided (Fig. 90E.6). At the level of the hilar plate, the right bile duct's anterior and posterior branches are divided between clips or staples. Division of the intraparenchymal bile ducts and hilar plate allows the plane to be opened widely for easier parenchymal transection, and the junction between the right lobe and segment I is divided to allow exposure of the retrohepatic vena cava. The posterior Glisson capsule is now divided along the anterior surface of the vena cava, while systematically clipping

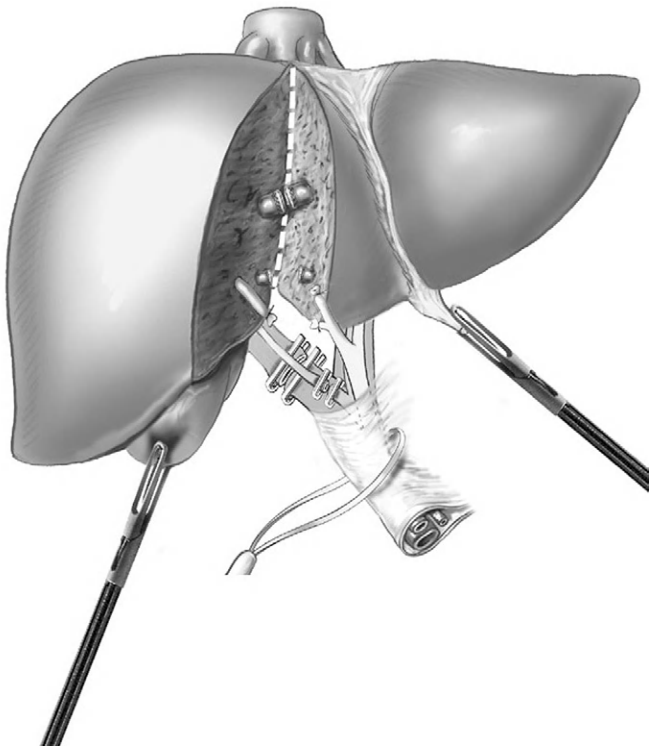


FIGURE 90E.6. Right hemihepatectomy. Atraumatic graspers retract the gallbladder to the right and the round ligament to the left, opening the dissection plane (*white dashed line*). The right hepatic artery and right portal vein are ligated extraparenchymally, and the right bile duct is ligated intraparenchymally. The hepatic veins draining segments V and VIII into the middle hepatic vein are encountered intraparenchymally, ligated, and divided. A laparoscopically assembled tourniquet around the portal pedicle is pictured and can be used for the Pringle maneuver if necessary. *(From Cherqui D, et al, 2010: Hepatectomies par abord laparoscopique, Encyclopedie Medico Chirurgicale. Masson, France, Elsevier.)*



FIGURE 90E.7. The use of a hand port in the right iliac fossa allows for manual manipulation and palpation of the liver; it is only used for difficult right-sided resections. Fewer laparoscopic ports are necessary, and the specimen is removed through the hand-port incision. Hand ports can be used from the outset of the operation or as an adjunct during a difficult resection. *(From Cherqui D, Chouillard E, 2007: Laparoscopic liver resections. In Clavien PA, et al [eds]: Atlas of Upper Gastrointestinal and Hepato-Pancreato-Biliary Surgery, Berlin, Springer.)*

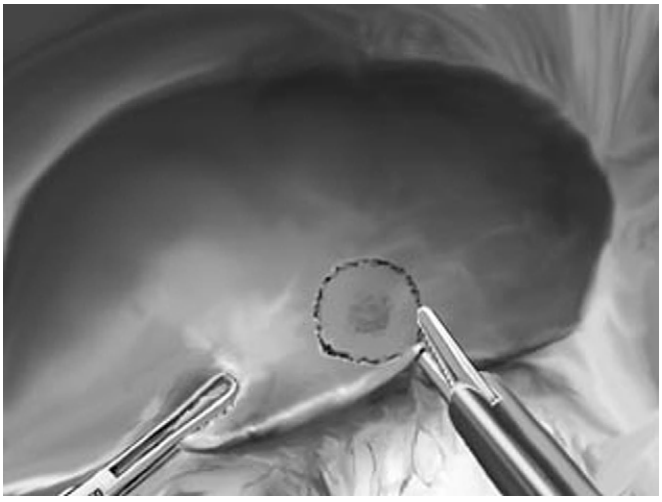


FIGURE 90E.8. Metastasectomy. The lesion is circumscribed with a 1- to 2-cm margin, and either a Harmonic Scalpel or LigaSure device can be used to resect the lesion. *(From Cherqui D, Chouillard E, 2007: Laparoscopic liver resections. In Clavien PA, et al [eds], 2007: Atlas of Upper Gastrointestinal and Hepato-Pancreato-Biliary Surgery. Berlin, Springer.)*

and dividing the small bridging veins. The right hepatic vein is identified at its insertion into the vena cava and is transected with a linear stapler. The specimen is now retracted to the right, as the hepatocaval ligament and the attachments of the right hemiliver are freed from the diaphragm.

When parenchymal transection is to be performed after mobilization of the right hemiliver, the right glissonian pedicle is dissected and divided as discussed for the anterior approach. This mobilization approach may require the use of a hand port (Fig. 90E.7). Next, the right triangular and coronary ligaments are divided. The liver is retracted to the left and anteriorly, and the accessory veins between the right hemiliver and vena cava are clipped and divided. As progress is made cranially, the hepatocaval ligament is divided between clips, and the right hepatic vein is subsequently divided with a linear stapler. The liver is now both completely mobilized and devascularized, and parenchymal transection is performed along the line of demarcation according to previously discussed principles.

Peripheral Partial Hepatectomies: Segmentectomy, Metastasectomy, or Tumorectomy

Peripheral partial hepatectomies are performed for lesions in the anterior or lateral segments. They can be anatomic, such as segmentectomies along theoretic segmental borders, or they can be nonanatomic, as with metastasectomy or tumorectomy (Fig. 90E.8). They usually do not require liver mobilization, especially for anterior lesions. For malignant lesions, 10- to 20-mm margins are determined using ultrasonography and are marked using diathermy. For benign lesions, a wide margin is unnecessary. Parenchymal transection can be performed with the Harmonic Scalpel or LigaSure, and it follows the margins marked on the liver surface. Hemostasis is achieved with bipolar diathermy and clips. If significant veins or pedicles are within

the resection margins, these are clipped and divided; the use of a linear stapler is rarely necessary.

CONCLUSION

Laparoscopic partial hepatectomy is a safe procedure for selected patients, when performed by appropriately trained surgeons, and it offers considerable perioperative benefits compared with laparotomy. In addition, oncologic outcomes and survival for HCC and colorectal metastases have been demonstrated to be equivalent in nonrandomized trials. Although the indications for laparoscopic surgery are somewhat rigid when it comes to lesion size and location, greater experience and newer technology are continually expanding the possibilities of this procedure. Surgical resection of benign, asymptomatic lesions remains contraindicated despite the safety and benefits of laparoscopic surgery. The most common laparoscopic procedures are detailed above, based on safe practices developed over our 14 years of experience. Left lateral sectionectomies and limited resections of the anterior and lateral segments of the liver are safe and well-accepted procedures. Major hepatectomies and limited segmentectomies involving segments I, IVa, VII, and VIII are increasingly reported, but by no means are they approaching the standard of care. This remains an expanding and exciting field in liver surgery, especially considering its role in the multidisciplinary approach to primary and secondary liver cancers and transplantation.

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CHAPTER 90F

Liver resection in cirrhosis

Jacques Belghiti and Safi Dokmak

OVERVIEW

Hepatocellular carcinoma (HCC) is the main indication for hepatectomy in the cirrhotic liver. The vast majority of HCC in patients with chronic liver disease (CLD) is related to hepatitis B or C viral infection, chronic alcoholic consumption, and metabolic syndrome (see Chapters 70 and 80). Other malignant tumors developed in CLD include intrahepatic cholangiocarcinoma (see Chapter 50A) and liver metastases (see Chapter 81; Iascone et al, 2005; Uchiyama et al, 2011; Welzel et al, 2007;). Some benign tumors—including regenerative nodules, hemangiomata, and focal nodular hyperplasia (FNH)—can be discovered in cirrhotic liver (Brancatelli et al, 2001a, 2001b; Libbrecht et al, 2006; Luciani et al, 2007; see Chapter 79).

Although liver transplantation (LT) offers the best chance of cure in patients with early stage HCC (Mazzaferro et al, 2009; see Chapter 97A), the persistence of graft shortage in many countries had led some authors, including those in our group, to advocate hepatic resection as the first-line treatment for HCC in cirrhotic patients with preserved liver function (Belghiti et al, 2008; Cherqui et al, 2009; Del Gaudio et al, 2008; Poon et al, 2002a). Liver resection is an effective treatment for HCC under appropriate conditions, but impaired liver regeneration, altered texture of liver parenchyma, portal hypertension, and collateral circulation make liver resection in cirrhotic patients challenging.

In the 1990s, operative mortality in patients with normal livers was 1%, compared with 8% among patients with diseased parenchyma (Belghiti et al, 2000; see Chapter 90). The higher risk associated with liver resection in patients with diseased parenchyma results from increased operative bleeding and postoperative complications, with liver failure mainly as a result of impaired liver regeneration in cirrhosis (see Chapter 5); however, with appropriate attention to preoperative patient selection, improved liver function assessment, better understanding of the segmental liver anatomy with more accurate imaging studies, advanced operative techniques, and better perioperative management, hepatectomy now can be performed in the cirrhotic liver with acceptable operative morbidity and mortality in major centers (Dahiya et al, 2010; Ferrero et al, 2005; Imamura et al, 2003; Wei et al, 2003). This chapter describes general surgical aspects and risks of liver surgery in patients with liver cirrhosis.

PREOPERATIVE ASSESSMENT

The improvement in the outcomes of liver resection in cirrhotic patients is mainly the result of good preoperative evaluation and appropriate patient selection (Ikai et al, 2007). A systematic and careful assessment of the patient's general medical fitness, the tumor extent and stage, the underlying liver function, and the volume of the anticipated future liver remnant (FLR) are critical in ensuring proper patient selection (see Chapters 2 and 70).

General Status of Patients

Attention to the general medical fitness of patients is paramount in selecting patients with HCC for hepatic resection, especially in cirrhotic patients, who are at higher risk of postoperative complications. Comorbid illness is a major predictor of the mortality of patients undergoing hepatectomy (Wei et al, 2003). Severe comorbid illnesses, such as congestive heart failure and chronic renal failure, are definite contraindications for hepatectomy, although patients with less severe comorbid illnesses may still benefit from hepatic resection, if accompanied by meticulous perioperative care. The impact of diabetes mellitus, which is a common comorbid illness in cirrhotic patients, is debated (Gedaly et al, 2009). It has been shown that postoperative morbidity and mortality after hepatectomy in patients with diabetes mellitus were similar to those of patients without diabetes mellitus, as long as optimal perioperative control of blood glucose levels and appropriate postoperative care were provided (Poon et al, 2002b).

Tumor Status

The assessment of the tumor extent included a triple-phase (early vascular or arterial phase, portal phase, and delayed phase) helical computed tomography (CT) of the thorax and the abdomen (see Chapter 16). The liver is studied using thin slices acquired during the unenhanced phase and during the arterial, portal, and late or equilibrium phase after contrast administration. HCC is hypervascular during the early arterial phase and hypovascular in late phase ("washout"). Magnetic resonance imaging (MRI) is the modality of choice for imaging when contrast agents are contraindicated, better lesion characterization is needed, or the anatomic relationship between tumor and major vascular or biliary structures requires further delineation (see Chapter 17).

The usual criteria for hepatic resection with regard to the tumor status include absence of extrahepatic metastasis and tumor thrombus in a main portal vein or in the inferior vena cava (see Chapter 80). Large tumor size alone should not be considered a contraindication for hepatic resection. Despite the technical problems encountered with large tumors, liver resection for large HCCs has been shown to be safe (Kosuge et al, 1993; Pawlik et al, 2005a, 2005b; Ramacciato et al, 2010;

Yang et al, 2009). In a series of 300 patients who underwent partial hepatectomy for HCCs larger than 10 cm, the 30-day mortality rate was 5% (Pawlik et al, 2005b). Because cadaveric orthotopic liver transplantation (OLT) and radiofrequency ablation (RFA) are contraindicated in these patients, surgical resection remains the treatment of choice for large HCCs.

HCC associated with biliary invasion should not be considered a contraindication to surgical resection, if curative resection can be achieved (Hanaoka et al, 2008; Lee et al, 2006; Peng et al, 2005). Multifocal disease generally is a contraindication to surgical resection, but in some patients with good liver function, resection can be reconsidered after clearance or stabilization of contralateral liver nodules by chemoembolization or RFA (Ishizawa et al, 2008; Liu et al, 2003; Ng et al, 2005; Ramacciato et al, 2010).

HCCs with major portal or hepatic vein involvement represent a technical and oncologic challenge. Patients with HCC that involves hepatic veins or vena cava have a high rate of pulmonary metastases (Ikai et al, 2003), although it has been shown that in a selected group of patients with normal liver function and excellent general status, extensive liver resection with removal of the vascular thrombus can achieve favorable survival results (Le Treut et al, 2006; Minagawa et al, 2001; Poon et al, 2003; Shi et al, 2010). Extension to surrounding structures, such as the diaphragm, does not represent a contraindication, provided that negative resection margins can be attained.

Tumor recurrence represents the major drawback after curative liver resection and is the most common cause of treatment failure. Within 5 years of resection, recurrence in the liver remnant occurs in about 50% to 70% of cases (Huang et al, 2010; Poon et al, 2000; Shi et al, 2007). The rate of repeated resection, ranging from 10% to 30%, depends on the underlying liver status, pattern of recurrence, and extent of first resection; lower rates are seen in series with a high proportion of major resection during the first hepatectomy, and repeat hepatectomy has been proven to be a safe and worthwhile procedure with a low mortality rate and an acceptable 5-year survival (20% to 57%) (Minagawa et al, 2003; Poon et al, 1999; Tsujita et al, 2010; Wu et al, 2009).

Spontaneous rupture of HCC occurs in 5% to 15% of patients, particularly with large, superficial, or protruding tumors. In patients with good liver function and a solitary tumor that is otherwise amenable to resection, rupture should not be regarded as a contraindication to subsequent elective surgical treatment; however, initial treatment should be aimed at stabilizing the patient and arresting the hemorrhage through nonsurgical means, typically through arteriography and embolization.

Assessment of Liver Function Reserve (See Chapters 2 and 70B)

Careful assessment of the liver function reserve is critical in patient selection for hepatectomy in patients with cirrhotic liver to avoid postoperative liver failure and mortality. Several systems may be used to evaluate the liver prior to operation.

Child-Turcotte-Pugh Classification

In most of Western centers, preoperative liver function is assessed using the Child-Turcotte-Pugh (CTP) classification, which incorporates variables related to conventional liver function and portal hypertension. This classification is easy and remains very accurate in its assessment of the surgical risk (Table 90F.1). According to this system of classification, major resection is performed only in CTP class A patients, limited resection of small superficial tumors is sometimes performed in class B patients, and no resection, regardless of the extent, is considered in class C patients; however, this classification is not enough to predict surgical risk in some patients, because two parameters are subjective—ascites and encephalopathy—and even within the class A group with apparently good liver function, some degree of portal hypertension and/or hepatic dysfunction may be present, and the risk of liver surgery may be underestimated. Therefore more sophisticated quantitative liver function tests or volumetric assessments are needed to predict the operative risk (Durand & Valla, 2005).

Table 90F.1

Pugh's Modification of Child's Grading of Cirrhosis

Measurements	1 Point	2 Points	3 Points
Bilirubin (μmol/L)	17 to 34	35-50	>50
Prothrombin time	1 to 3	4-6	>6 prolongations
Albumin (g/L)	>35	28-34	<28
Ascites		None	Mild
Moderate to severe encephalopathy	None	Grade 1 or 2	Grade 3 or 4

Child's class A = 5 to 6 points; class B = 7 to 9 points; class C = 10 to 15 points

Indocyanine Green Test

Most Eastern centers use more sophisticated quantitative liver function tests that include indocyanine green (ICG) clearance (Imamura et al, 2003), galactose elimination capacity (Redaelli et al, 2002), and a lidocaine test (Ravaioli et al, 2003) to predict the risk of postoperative liver failure in patients with cirrhosis. The Hong Kong group showed in a multivariate analysis that of the many liver function tests, ICG retention at 15 minutes to 20% was the best test for predicting hospital mortality after major hepatectomy for HCC (Lau et al, 1998; Lee & Hwang, 2005). Imamura and Makuuchi proposed a decision tree based on combined parameters from the CTP classification (ascites and bilirubin) and ICG retention test (Imamura et al, 2005; Fig. 90F.1). Based on this strategy, liver resection is contraindicated in patients who have elevated bilirubin (>2 mg/dL) or ascites. The extent of liver resection is then based on the ICG retention test at 15 minutes (see Table 90F.1), and major liver resection is proposed only in patients with normal bilirubin and ICG levels below 10%. Adopting this decision strategy, the authors reported only one mortality among the 685 patients who underwent liver resection for HCC (Imamura et al, 2005).

Model for End-Stage Liver Disease Score

The Model for End-Stage Liver Disease (MELD) score uses only objective variables calculated from the international normalized ration (INR), serum total bilirubin (mg/dL), and serum creatinine (mg/dL). This system was initially created to predict survival in patients with complications of portal hypertension undergoing elective placement of transjugular intrahepatic portosystemic shunts (TIPS) (Malinchoc et al, 2000). The MELD score was validated subsequently as an accurate predictor of survival among different populations of patients with advanced

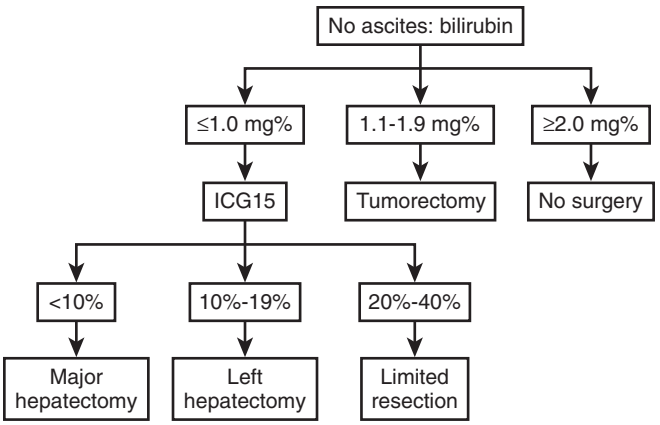


FIGURE 90F.1. Japanese algorithm for resection in cirrhosis. ICG, indocyanine green. *(Modified from Makuuchi M, 1993: Surgery for small liver cancers. Semin Surg Oncol 9:298-304.)*

liver disease (Kamath et al, 2001). The most frequent use of the MELD score has been in the allocation of organs for patients awaiting liver transplantation (Freeman et al, 2005; Wiesner et al, 2001). Regarding liver resection in cirrhotic patients, the MELD score was only retrospectively studied. Cirrhotic patients who underwent liver resection for HCC with a MELD score greater than 8 had a higher risk of death, morbidity, and impaired long-term survival (Cucchetti et al, 2006; Delis et al, 2009).

Transaminase Levels

Postoperative mortality has been shown to be higher in a cohort of 285 patients who underwent hepatectomy for HCC when histologic evidence of cirrhosis and active hepatitis versus cirrhosis alone was found (Eguchi et al, 2000). Although the presence of high serum transaminase levels does not always correlate with hepatitis and could be associated with intratumoral necrosis in a huge tumor, increased complication and death rates have been reported in those patients with levels of elevated transaminases (Haber et al, 1995; Noun et al, 1997). Patients with an aspartate aminotransferase level greater than 100 IU/L or alanine aminotransferase at least twice the normal level are considered poor candidates for major hepatic resection. In this setting, preoperative biopsy of the nontumorous liver should be performed to exclude active underlying liver parenchymal disease.

Portal Hypertension (See Chapter 70)

The presence of portal venous pressure greater than 10 mm Hg is often associated with esophageal varices, splenomegaly, and thrombocytopenia (<100,000). Undiagnosed and latent portal hypertension in a cirrhotic patient undergoing liver resection puts the patient at risk of major complications in the postoperative period; such complications include variceal bleeding, endotoxemia, and hepatic decompensation. In a prospective study in class A cirrhotic patients, it was shown that the hepatic venous pressure (HVP) gradient, a surrogate measurement of portal venous pressure, was the only predictor of hepatic decompensation following hepatic resection (Bruix et al, 1996). Thus liver resection in cirrhotic patients with esophageal varices is contraindicated; however, several authors have shown that portal hypertension is not an absolute contraindication to surgical resection in selected patients with preserved liver function (Capussotti et al, 2006; Ishizawa et al, 2008). These authors advocate an aggressive preoperative prophylactic treatment for portal hypertension, such as ligation of esophageal varices.

The negative effect of thrombocytopenia on liver regeneration can be related to the presence of portal hypertension or its direct impact on liver regeneration (Lesurtel & Belghiti, 2008). The development of venous collaterals in patients with elevated portal pressure can reduce the hepatic portal flow and thereby impair the regenerative capacity of the remnant parenchyma after liver resection, therefore we contraindicate major liver resection in cirrhotic patients with venous collaterals.

Liver Atrophy and Underlying Disease

Liver atrophy is a major prognostic factor that should be considered before any liver resection, even those in patients with preserved liver function (see Chapters 5 and 50B). In our practice, we do not consider major liver resection in HCC patients with liver atrophy. Similarly, the underlying etiology of liver cirrhosis should be considered before liver resection, and it should be noted that the extent of fibrosis is more severe in patients with hepatitis C than in patients with hepatitis B (Roayaie et al, 2000). Our tendency is to consider a major liver resection more favorably in patients with hepatitis B than in patients with some other etiology of CLD, even if the remnant liver volume is similar.

Among patients with CLD, the postoperative risk is higher in those with cirrhosis (F4) than in those with extensive fibrosis (F3) (Farges et al, 1999). This suggests that preoperative liver biopsy should be considered in all candidates for major liver resection for histologic fibrosis grading. In patients with F3 or F4 fibrosis requiring major hepatectomy, preoperative portal vein embolization should be performed in an effort to decrease morbidity.

Volume of the Future Liver Remnant

Measurement of the volume of the remnant liver after planned resection using CT volumetry has been shown to be helpful in selecting patients for major hepatic resection (see Chapters 2 and 93). A small liver remnant volume is associated with worse postoperative liver function and a higher complication rate after extended hepatectomy (Ribero et al, 2007). The safety limit for the remnant liver volume in patients with normal liver is approximately 30% of the total nontumorous or functional liver volume, but this is much higher in patients with CLD. The safety limit in terms of remnant liver volume in patients with CLD has not been clearly documented, and it varies depending on the severity of cirrhosis, which influences the regeneration capacity of the diseased parenchyma. But in general a remnant liver volume of 40% to 50% of the total liver volume should be left before considering major liver resection (Azoulay et al, 2000; Lee & Hwang, 2005; Ribero et al, 2007).

ROLE OF PREOPERATIVE PORTAL VEIN EMBOLIZATION

For patients who require major or extended hepatectomy but have inadequate remnant liver volume, preoperative portal vein embolization (PVE) can be used to induce hypertrophy of the

remnant liver (Makuuchi et al, 1990; see Chapter 93). A general concern is that preoperative PVE may be less effective in the cirrhotic liver, compared with normal liver, because of its impaired regenerative capacity (Abdalla et al, 2002); however, recent studies have demonstrated that preoperative PVE is effective in inducing hypertrophy of remnant liver and decreasing postoperative complications in patients with cirrhotic livers undergoing hepatic resection for HCC. Our center also used PVE in selected F3 and F4 cirrhotic patients undergoing major hepatectomy. The procedure was well tolerated, but the degree of hypertrophy varied according to the degree of fibrosis and the severity of cirrhosis (Farges et al, 1999).

Absence of hypertrophy of the FLR should be considered an absolute contraindication for hepatic resection (Belghiti & Ogata, 2005; Sato et al, 2000); however, we showed that preoperative sequential transarterial chemoembolization (TACE) and PVE increased the hypertrophy of the FLR. In addition, we found a clear relationship between the rate of hypertrophy and postoperative risk after major hepatectomy in cirrhotic patients. These results were recently confirmed by a similar study, which showed that sequential TACE and PVE increase the hypertrophy rate of the remnant liver and are associated with improved overall and recurrence-free survival in patients with HCC, compared with those who have PVE alone (Yoo et al, 2010). After right hepatectomy for HCC, all postoperative deaths and most severe complications were experienced in F4 patients with less than a 10% increase of FLR. Based on these observations, we propose that a minimum increase of 10% of the FLR in F3 or F4 patients is essential to safely perform a right hepatectomy.

OPERATIVE TECHNIQUES

The general techniques of liver resection are described in Chapters 90A and 90B. This chapter focuses mainly on operative techniques specifically related to the cirrhotic liver.

Skin Incision

A bilateral subcostal incision is the standard incision for hepatic resection and is adequate for most cases of hepatectomy; an extended right subcostal incision is an acceptable alternative. The approach to large tumors located in the upper segment of the right liver or in its posterior surface (segment VII) can be facilitated by an upward midline extension or by a J-incision (Sato et al, 2000). Although the diaphragm incision increases the rate of pleural effusion, it facilitates parenchymal transection by making the transection plane perpendicular to the wound. A study by the Hong Kong group (Xia et al, 2003) showed that a thoracoabdominal approach for right-sided hepatectomy does not increase operative morbidity, compared with an abdominal approach alone, and may help reduce blood loss and transfusion requirements. For cirrhotic patients with HCC in the superior segments of the liver located beneath the right diaphragm, an exclusive transthoracic approach has been described, but this approach allows only limited resection with a high risk of positive margin (Pocard et al, 2002).

Intraoperative Ultrasound

Intraoperative ultrasound (IOUS) with color Doppler is an invaluable tool in hepatic resection, allowing localization of intrahepatic vessels, assessment of their relationship with tumors, and detection of other nodules and tumor thrombus. IOUS also enables accurate marking of the transection line to ensure an adequate tumor-free margin (see Chapter 21). The use of IOUS optimizes the balance between oncologic radicality and sparing of the largest amount of functioning liver parenchyma in the cirrhotic liver. Recently, systematic segmentectomy and subsegmentectomy by IOUS-guided finger compression was described (Torzilli et al, 2010). This technique can be potentially applied in each segment of the liver, as long as the thickness of the parenchyma and the anatomy of the liver are suitable. The IOUS-guided finger compression of the vascular pedicle feeding the tumor at the level closest to the tumor results in a demarcation area that allows oncologic resection.

Contrast-enhanced ultrasound examination using microbubble contrast agents (SonoVue; Bracco Imaging, Milan, Italy) provides information about tumor hypervascularity, which is useful for nodule differentiation. This improves the accuracy of assessing focal liver lesions in cirrhotic livers, particularly those lesions less than 1 cm. Contrast agents such as Sonazoid (Daiichi Sankyo, Japan) show two different patterns of enhancement: early hypervascular phase, a result of tumor vascularity, and late hypoechoic phase, a result of Kupffer cell uptake. This increases the specificity of diagnosing HCC of less than 1 cm in cirrhotic livers.

Anterior Approach

When liver tumors are large, the use of conventional techniques may require forceful retraction and mobilization of the liver, with possible consequences that include compression of both right and left lobes and possible tumor disruption or dissemination of tumor cells. Mobilization of the cirrhotic liver is technically more demanding, because of the firm texture of the fibrotic liver. The collateral vessels formed secondary to portal hypertension may increase the risk of bleeding during liver mobilization. Prolonged forceful rotation of the liver increases the risk of avulsion injury to the hepatic veins and may twist the inflow and outflow vascular pedicles, resulting in ischemic damage to the remnant liver. Care should be taken to avoid prolonged rotation of the liver. The anterior approach attempts to diminish manipulation of the tumor-bearing liver by initial vascular inflow control, parenchymal transection until the anterior surface of the inferior vena cava is exposed, venous outflow control, and finally mobilization of the right liver (Agrawal & Belghiti, 2011).

Once the devascularized tumorous liver is disconnected from the vena cava, it makes sense that its mobilization is less hemorrhagic, and that this "no touch" liver resection could reduce possible systemic dissemination of cancer cells. In a prospective randomized controlled study of the anterior versus conventional approach in patients with HCC greater than 5 cm, a group from the University of Hong Kong demonstrated significantly less frequent major operative blood loss greater than 2 L (28.3% vs. 8.3%) and also demonstrated superior overall survival—median 68.1 months versus 22.6 months—with the anterior approach (Agrawal & Belghiti, 2011).

The liver-hanging maneuver, originally described by our group, involves the passage of a tape in the avascular retrohepatic precaval space to suspend the liver during parenchymal transection, thereby facilitating the anterior approach by minimizing bleeding in the deeper parenchymal plane and guiding the direction of the parenchymal transection (Agrawal & Belghiti, 2011). The traction of this tape allows delineation of the

planned parenchymal transection, which follows a hepatic vein. The transection plane along a hepatic vein represents an oncologic plane and preserves the outflow of the remnant liver, increasing both its function and its potential for regeneration. Application of the hanging maneuver has been further extended to the three Glisson pedicles and hepatic veins, facilitating the performance of right and left anatomic liver resections (Agrawal & Belghiti, 2011). Although more data based on long-term survival are expected, several arguments are leading to recommend the anterior approach in combination with the hanging maneuver as the preferred operative approach for liver malignancy.

Technique of Liver Transection

The main difficulty of hepatic resection in the cirrhotic liver lies in control of bleeding during transection of the fibrotic parenchyma. Clamp crushing, the conventional method of liver transection, is still used in some centers (Imamura et al, 2003; Jarnagin et al, 2002); however, the Cavitron Ultrasonic Surgical Aspirator (CUSA, Valleylab, Boulder, CO) is probably a better alternative and appears to reduce blood loss compared with the clamp-crushing technique (Fan et al, 1996). The CUSA has become the standard technique of liver transection for cirrhotic liver in many centers (Takayama et al, 2001).

Other techniques of liver transection use the Harmonic Scalpel (Ethicon Endo-Surgery, Cincinnati, OH) and multiprobe bipolar radiofrequency device (Habib 4X; AngioDynamics, Latham, NY). The latter allows surgeons to perform minor and major hepatectomies with minimal blood loss, a low blood transfusion requirement, and reduced mortality and morbidity rates (Ayav et al, 2008); however, this device is seldom used in tertiary reference centers for treatment of HCC because of concerns about the preservation of venous drainage of the remnant liver and the risk of postoperative bile leak and necrosis (Kim et al, 2003; Lupo et al, 2007). The role of this technology probably is limited to segmental or wedge excision because of the potential risk of vascular and bile duct injury when using multiprobe bipolar radiofrequency near the liver hilum and its inability to control bleeding from large venous branches. Saline-linked cautery (TissueLink Medical, Dover, NH) uses a metal probe to deliver radiofrequency energy conducted through a slow infusion of saline. This procedure enlarges the transection margin (Kianmanesh et al, 2008) and can be associated with ultrasonic dissection in a standardized fashion (Aloia et al, 2005).

Anatomic and Nonanatomic Resection

Intrahepatic metastasis of HCC along the portal vein is the basis of anatomic liver resection. In cirrhotic patients, oncologic safety must be balanced with future liver volume. Analysis of a nationwide Japanese database that included 72,144 patients showed improved disease-free survival with anatomic resection compared with nonanatomic resection, but no difference in overall survival was found (Eguchi et al, 2008). When survival was stratified by tumor size, disease-free survival was significantly improved with an anatomic resection for HCC with a diameter of 2 to 5 cm. The low incidence of vascular invasion in HCC of less than 2 cm may explain the absence of a beneficial effect with anatomic resection and the equivalent efficacy of local ablative therapy. For HCC greater than 5 cm, the tumor is often associated with vascular invasion, satellite nodules, and other adverse pathologic features, which probably offsets the effect of the type and extent of hepatectomy (Agrawal & Belghiti, 2011).

Vascular Staplers

Staplers can be used in liver surgery for control of inflow and outflow vessels. The use of a vascular stapler may help reduce blood loss, especially in situations in which a large tumor in the right or left lobe hinders exposure of the right or left hepatic vein, or during control of the middle hepatic vein deep in the transection plane. The vascular stapler also can be used to divide the hepatic pedicle in right or left hepatectomy (Figueras et al, 2003) with results similar to those of hilar dissection. The use of vascular staplers to divide the hepatic pedicle saves suturing time, but care must be exercised not to narrow the hepatic duct confluence, especially during a right or left extended hepatectomy (Wang & Fan, 2003).

Vascular Occlusion

During liver resection, reducing blood loss and thereby reducing the need for transfusion is essential, especially in cirrhotic patients, who have a poor tolerance to hemodynamic instability and to massive transfusion. A review of the literature concerning the relationship between blood loss and blood transfusion during liver surgery for malignant tumors and postoperative outcome showed a significant and clinically relevant association between blood transfusion and postoperative mortality and morbidity, especially postoperative infectious complications (De Boer et al, 2007). In particular, blood transfusion may have an impact on tumor recurrence in patients with early stages of HCC. Vascular clamping in an effort to reduce intraoperative blood loss is counterbalanced by a poor tolerance of cirrhotic parenchyma to warm ischemia. Total vascular occlusion, even when associated with in situ cold perfusion of the liver, is contraindicated in patients with diseased liver (Azoulay et al, 2006). Intermittent inflow occlusion, with 15 minutes of clamping and 5 minutes of unclamping, is well tolerated for up to 90 minutes in selected cirrhotic patients with good liver function (Ishizaki et al, 2006). In our center, we do not hesitate to use intermittent inflow clamping when resection is difficult or when there is a need to define adjacent vascular or biliary structures in the margin of resection.

Overall, a tendency to perform hepatic resection without clamping has resulted from several factors, including 1) increased experience of surgeons in liver resection; 2) the use of isolated inferior vena cava occlusion without any risk of ischemia on the liver parenchyma, and 3) the practice of low central venous pressure (CVP) anesthesia. One of the most important factors related to intraoperative blood loss is pressure within the inferior vena cava (Johnson et al, 1998). As hepatic venous pressure directly reflects the caval pressure, the maintenance of a low CVP is an effective technique to reduce back bleeding from the hepatic veins.

Abdominal Drainage

The risk of hemorrhage and bile leakage and the high rate of ascites after hepatectomy in the cirrhotic liver leads many surgeons to consider abdominal drainage. In a retrospective study that included 1269 consecutive patients who underwent

elective hepatectomy with drain insertion for malignant tumors, seven patients had postoperative bleeding (0.6%), and bile leakage was found in 111 patients (8.7%; Kyoden et al, 2010). The authors concluded that placement of drains was effective in a considerable proportion of patients undergoing hepatectomy, with regard to reducing the frequency of subphrenic fluid collections and biliary fistula.

In a prior review, Burt and colleagues (2002) showed that placement of drains after routine hepatic resection was unnecessary, but the use of drainage after routine liver resection remains a point of controversy. A randomized controlled trial (RCT) performed in the Hospital Clinic of Barcelona (Fuster et al, 2004) showed that intraabdominal closed drainage is advisable in cirrhotic patients undergoing liver resection for HCC, mainly for patients with preoperative portal hypertension. By contrast, another RCT showed that the placement of abdominal drains after hepatic resection in the cirrhotic liver was associated with increased wound and septic complications and prolonged hospital stay (Liu et al, 2003), because the drain provides a route for ascending infection and results in loss of protein and electrolytes.

LAPAROSCOPIC RESECTION

Laparoscopic liver resections represent about 10% to 20% of all liver resections performed at most centers (see Chapter 90E). Limited to a few centers worldwide (Dagher et al, 2007, 2008; Vigano et al, 2009), laparoscopic resections are associated with a long learning curve, difficulty achieving wide resection margins and in performing anatomic resections, and technical difficulties in mobilization and parenchymal transection with risk of massive bleeding; all of these remain obstacles for the emergence of laparoscopic liver resection as a routine procedure. Anticipated advantages from laparoscopic liver resections include that it is a less aggressive approach with less painful incisions, fewer pulmonary complications, and earlier recovery, and it requires less extensive peritoneal dissection; this means the avoidance of collateral ligation, less bleeding, minimal ascites, and decreased postoperative liver failure (Cherqui et al, 2000).

These potential benefits could expand indications of liver resection in some patients with class B cirrhosis (Agrawal & Belghiti, 2011). Moreover, fewer postoperative adhesions after laparoscopic liver resection, compared with open liver resection, might facilitate subsequent salvage liver transplantation with decreased morbidity (Laurent et al, 2009). The laparoscopic approach is also a potentially useful tool for treating tumors with RFA (Santambrogio et al, 2005).

Lesions located in posterior segments (VII, VIII, IVa, or I) have typically been difficult for a purely laparoscopic approach and are more often described with hand-assisted resections (Huang et al, 2009; Koffron et al, 2007) or assisted laparoscopic resections (Nitta et al, 2010). Laparoscopy also has limited role in lymph node or porta hepatis dissections.

Morbidity and Mortality

Improvements in patient selection and surgical technique have resulted in a remarkable decrease in perioperative mortality rates. In the 1980s, the mortality rate after liver resection in cirrhotic patients was typically 15% to 30%, and liver resections in cirrhotic patients were largely restricted to segmental or subsegmental resections (Bismuth et al, 1986; Matsumata et al, 1990); however, over the past several years, significant improvements in operative and perioperative care were realized, such that the current mortality rate is approximately 5%, with some centers approaching zero mortality (Jaeck et al, 2004; Torzilli et al, 1999). The Hong Kong group showed that even extended right or left hepatectomy could be performed in cirrhotic patients with acceptable morbidity and mortality, which were not significantly different from rates of patients with less extensive resections (Poon et al, 2002c).

Because the operative morbidity after hepatic resection in the cirrhotic liver remains high (30% to 40%), further efforts are required to reduce the operative morbidity. Cirrhotic patients who undergo hepatic resection require close postoperative monitoring and careful management in the postoperative period. Management aims at adequate oxygenation and perfusion to ensure optimal function and regeneration of the remnant liver.

Intravenous Fluid

Although fluid restriction has been found to reduce the incidence of postoperative morbidity in some surgical patients (Nisanevich et al, 2005), optimal fluid substitution strategies remain controversial, because fluid optimization increases tissue oxygen tension and microcirculatory perfusion (Futier et al, 2010). It has been shown that excessive fluid restriction leads to hypovolemia and reduced central venous oxygen saturation, thereby increasing postoperative complications (Futier et al, 2010). Excessive fluid restriction should be applied cautiously in cirrhotic patients. Crystalloid solution (dextrose and saline) is used for maintenance of intravenous fluid. In some centers, fresh frozen plasma is used routinely for fluid replacement during and after the operation (Imamura et al, 2003), although there is no evidence to support such a practice. In our center, albumin is used instead, because fresh frozen plasma is associated with potentially significant transfusion-related complications.

Antibiotics

There is a tendency to administer prophylactic antibiotics to cirrhotic patients beyond the accepted single preoperative dose because of their immunocompromised state. Intraoperative antibiotic prophylaxis is aimed at preventing translocation of intestinal enterobacteria to the systemic circulation in patients with both healthy and diseased livers. The risk of infection is aggravated further by the prolonged operation and the high frequency of ascites. Septic complications, especially wound infection, are the most common complications after hepatectomy for HCC (Fan et al, 1999); however, no randomized trials suggest the optimal regimen of antibiotics in patients with cirrhosis.

Pain Control

Adequate pain control is an important factor in reducing the incidence of pulmonary complications after hepatic resection for HCC (see Chapter 22).

Nutrition Support

Because of the prevalence of malnutrition in cirrhotic patients, nutrition support is important to enhance postoperative recovery and liver regeneration (see Chapter 24). Oral feeding is started early, on postoperative day 1, if the patient does not manifest signs of liver failure. Since a randomized, controlled trial published in 1994 (Fan et al, 1994) showed the benefit of

parenteral nutrition in reducing postoperative morbidity, postoperative parenteral nutrition has become a routine practice in many centers for patients with cirrhosis undergoing major hepatic resection.

In addition to complications associated with all major surgery, specific risks of liver resection in cirrhotic patients include ascites, right pleural effusion, subphrenic abscess, bleeding, biliary leak and fistula, and hepatic insufficiency.

Postoperative Ascites

Postoperative ascites is a classic complication following liver resection in cirrhotic patients, and it affects more than one third of patients. Significant ascites is poorly defined, but the presence of ascitic fluid drainage from thoracic and abdominal drains exceeding 10 mL/kg of preoperative body weight (Ishizawa et al, 2009) or a daily output greater than 500 mL after postoperative day 3 require a specific aggressive intervention. Factors that increase the rate and amount of ascites include preexisting ascites before resection, the presence of portal hypertension, low platelet count, major resection, pedicular clamping, lymph node dissection, and perioperative fluid infusion, including blood transfusion. Ascites after liver resection in cirrhotic patients has several potential deleterious consequences, including abdominal pain, impairment of ventilation, development of pleural effusion, infection, impairment of renal function, and abdominal leak. Ascites leakage through the abdominal incision can result in loss of electrolytes and protein, and the risk of intraabdominal infection is also increased.

The management of ascites requires replacement of fluid lost and, in some cases, aggressive diuretic therapy. Fresh frozen plasma transfusion during and after liver resection is advocated by some surgeons (Ishizawa et al, 2009) but is not supported by other studies, which show an increased risk of transmitting diseases and more adverse consequences, such as transfusion-related acute lung injury, acute allergic and anaphylactic reactions, and high cost (Caldwell et al, 2006). In several centers such as ours, fresh frozen plasma is replaced by albumin or other plasma expanders.

Postoperative Bleeding

The risk of postoperative bleeding is very low, around 1% (Belghiti et al, 2000; Imamura et al, 2003; Jarnagin et al, 2002). The presence of bleeding during the first postoperative day is a life-threatening complication that requires reoperation, and it comes with a 30% risk of death in cirrhotic patients. This high risk makes ensuring a perfect hemostasis at the end of liver resection imperative for all liver operations, but especially those in cirrhotic patients.

Biliary Fistula (See Chapter 42)

Bile leakage after hepatic resection can cause septic complications, which lead to a high risk of mortality in cirrhotic patients. The rate of biliary leakage was found to be approximately 6% in a single-center series of 605 liver resections for HCC, and it was increased by preoperative chemoembolization and with tumors with a central location (Lee et al, 2005). Although drainage fails to prevent postoperative biliary collection in approximately one third of patients, and percutaneous drainage is therefore required (Kyoden et al, 2010), this risk of bile collection has led some authors to adopt the use of long-term drains (Torzilli et al, 2005). In a prospective cohort study that enrolled 58 patients, who underwent liver resection for tumors with abdominal drains maintained for at least 7 days postoperatively, Torzilli and colleagues (2005) showed that the bilirubin level in the drain was higher on the fifth postoperative day than on the third and seventh postoperative days, leading them to advocate the use of long-term drains.

Portal Thrombosis

This life-threatening complication in cirrhotic patients is poorly described and can be induced by several factors, including portal hypertension, previous preoperative PVE, and portal vein injury. Patients should therefore undergo regular ultrasound evaluation during the first postoperative week if hepatic function shows no signs of improvement, especially if significant clinical deterioration is apparent. The presence of portal thrombosis early after resection might require urgent reoperation and/or anticoagulation treatment, particularly when associated with deteriorating liver function.

Liver Failure

Patients with cirrhosis have decreased liver functional reserve and a limited capacity for liver regeneration. As a result, major hepatectomy in cirrhotic patients is associated with a significant risk of liver failure that could occur primarily as a result of inadequate liver remnant, but more often it is precipitated by massive bleeding or septic complications. Despite improvements in the safety of hepatectomy in recent years, postoperative liver failure still occurs in 3% to 10% of patients after resection for HCC (Kubo et al, 2004; Osada & Saji, 2004).

Liver failure is associated with a high mortality rate and is the most common cause of hospital mortality following hepatic resection in the cirrhotic liver (Belghiti et al, 2000; Wu & Zhang, 2002). Cirrhotic patients are also prone to gradual hepatic decompensation in long-term follow-up, especially after major hepatic resection for large HCCs (Huo et al, 2004). Although several clinical and biologic factors are markers of impaired liver function—such as ascites, encephalopathy, jaundice, prolonged prothrombin time, hyperbilirubinemia, and hypoalbuminemia—no standardized definition of postoperative liver failure (PLF) has been agreed upon, nor have any precise data on its correlation with postoperative mortality been reported.

The need for standardization of PLF is important. Prothrombin time (PT) and serum total bilirubin level (SB)—two biologic indicators of liver dysfunction in the Child-Turcotte-Pugh scoring system (and also two of the three components of the MELD score)—are less reliable postoperatively because of the natural impairment of liver function tests during the first postresection days. We found that on postoperative day 5, the association of PT less than 50% and SB greater than 50 ml/L, the so-called 50-50 criteria, was a simple, early, and accurate predictor of a higher than 50% mortality rate after hepatectomy (Balzan et al, 2005). Moreover, these clinical criteria may be useful to identify high-risk patients before clinical evidence of complications appear, allowing the institution of specific interventions that may help improve outcome. Postoperative complications that include portal vein thrombosis, ascites, and pulmonary infection are difficult to diagnosis early after operation, but they result in late mortality in a high proportion of patients. Early recognition of postoperative liver failure is an important factor that may allow early intervention and improved outcome.

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CHAPTER 93B

Preoperative portal vein embolization: technique

David C. Madoff

OVERVIEW

Portal vein embolization (PVE) is performed preoperatively to reduce the risk of extensive surgery in patients with small anticipated remnant livers (Makuuchi et al, 1990; de Baere et al, 1993; Abdalla et al, 2002; Madoff et al, 2005a; see Chapter 30a). PVE redirects portal blood flow to the intended future liver remnant (FLR) in an attempt to initiate hypertrophy of the nonembolized segments, and it has been shown to improve the functional reserve of the FLR before surgery. In appropriately selected patients, PVE has also been shown to reduce perioperative morbidity, and it allows for safe, potentially curative hepatectomy for patients previously considered ineligible for resection based on anticipated small remnant livers (Azoulay et al, 2000; Madoff et al, 2005a; Abulkhir et al, 2008). For this reason, PVE is now performed at many comprehensive hepatobiliary centers worldwide prior to major hepatectomy. This section details the techniques currently used to perform PVE, discusses their advantages and disadvantages, and reviews the potential complications that can occur from this procedure.

TECHNICAL ASPECTS OF PORTAL VEIN EMBOLIZATION

Access Routes to the Portal Venous System

PVE can be performed by any of three standard approaches: 1) the intraoperative transileocolic venous approach, 2) the transhepatic contralateral approach (i.e., percutaneous portal vein is accessed via the FLR), and 3) the transhepatic ipsilateral approach (i.e., percutaneous portal access is via the liver to be resected; Madoff et al, 2005a). It is important to note that the approach to the portal vein is chosen at the discretion of the operator, and the decision may be based on multiple factors, including the extent of the embolization and surgery, the operator's preference for a specific embolic agent, tumor burden within the liver, and the operator's level of experience with one technique over another (Avritscher et al, 2008). An alternative approach, portal vein ligation, is typically performed intraoperatively during the first stage of a two-stage resection for hepatic colorectal metastases, and it has been reported to be as effective as percutaneous embolization methods (Aussilhou et al, 2008). Regardless of the technique used, the operator must be aware of variations in portal venous anatomy that may impact the conduct of the procedure (see Chapter 1B).

Transileocolic Venous Approach

The transileocolic venous approach was the first approach described for performing preoperative PVE, and it is still used in many Asian centers. This technique is performed at laparotomy by direct cannulation of the ileocolic vein and introduction of a catheter into the portal system for embolization (Abdalla et al, 2002). Conventional teaching has been that this approach is performed when additional treatment is needed during the same surgical exploration, when a percutaneous approach is not considered feasible, or when an interventional radiology suite is not available (Azoulay et al, 1995; Denys et al, 2002).

The disadvantages of this method are the need for general anesthesia and laparotomy, with their inherent risks, and the inferior imaging equipment often available in the operating room, compared with the state-of-the-art imaging equipment available in most modern interventional radiology suites; however, as more minimally invasive techniques have become favored, and as the equipment used—imaging equipment, catheter systems, embolic agents, and so on—has become more sophisticated, the reasons for using this technique apply in very limited situations, such that the transileocolic venous approach is being used less often than the techniques described below.

Percutaneous Transhepatic Ipsilateral Approach

The percutaneous transhepatic ipsilateral approach was first described by Nagino and coworkers (1996), and it is now advocated by many other investigators (Madoff et al, 2003, 2005b; Gibo et al, 2007; Tsuda et al, 2006). With this approach, access is obtained through the portal branches within the tumor-bearing liver (Fig. 93B.1). A distinct advantage of the ipsilateral approach is that the FLR is not instrumented. It also allows for straightforward catheterization of segment IV branches, should embolization of segment IV be required. When planning the puncture, the anterior segment of the right portal vein is preferred, because its use is associated with a lower complication rate (Kodama et al, 2002); however, catheterizing the right portal branches can be challenging, owing to the sharp angulation of the right portal veins, which often necessitates using reverse-curve catheters or balloon occlusion catheters with multiple lumina (Nagino et al, 1996, 2000a).

In Nagino's approach (see Fig. 93B.1), the right anterior portal vein is punctured using sonographic guidance, and a 6-Fr sheath is introduced into the right portal vein system (Nagino et al, 2000a). To make this procedure feasible, the authors designed two types of 5.5-Fr triple-lumen balloon catheters. The first catheter, "type 1," was designed with one lumen connected to the balloon and two lumina connected to the tip. The second catheter, "type 2," had two separate lumina opening proximal to the balloon, and the balloons were used to prevent any backflow of embolic material. Both catheters had two separate lumina so that fibrin glue and iodized oil could be injected simultaneously. To facilitate resection, the authors advocated that a proximal

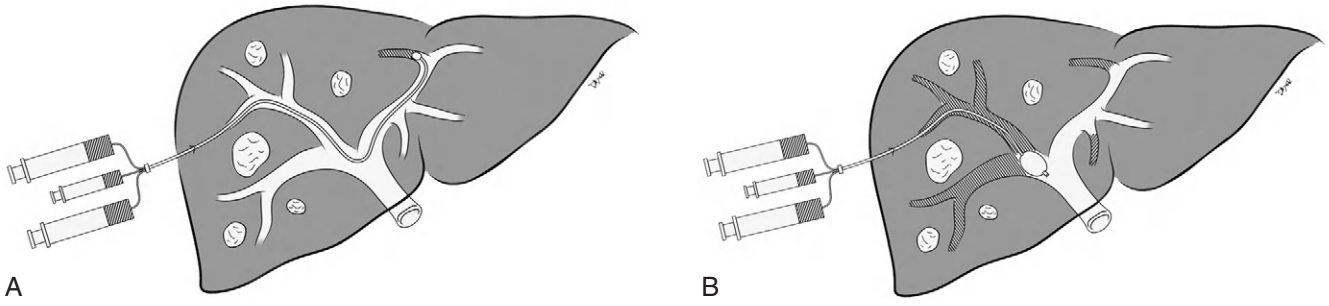


FIGURE 93B.1. Schematic representation of the ipsilateral approach for right portal vein embolization (PVE) and segment IV as described by Nagino and coworkers. Different balloon catheters are used for antegrade embolization of segment IV veins (**A**) and for retrograde delivery of the embolic agent into the right portal system (**B**).

right portal vein segment at least 1 cm in length remain patent. Depending on the portal vein anatomy, and the need to spare the proximal right portal vein, type 1 or type 2 catheters were used for embolization. The type 1 catheter was used for embolization of branches distal to the catheter tip, whereas the type 2 catheter was used for embolization of branches proximal to the catheter tip, as mandated by each patient's portal vein anatomy.

In a recent study, Gibo and coworkers (2007) reported on a modified technique utilizing a four-lumen balloon catheter in eight patients. The authors recommended using this modified catheter because of its larger occlusion balloon and lumina, which allow for safer and easier embolization using fibrin glue. Unfortunately, neither the original nor the modified catheters are available in the United States.

In the early 2000s, Madoff and coworkers (2003, 2005b) described a technique using angiographic catheters commercially available worldwide (Figs. 93B.2 and 93B.3). Under sonographic guidance, a 22-gauge Chiba needle (Neff Percutaneous Access Set; Cook Medical, Bloomington, IN) is used to puncture a distal branch of the right portal system. Subsequently, a 5- or 6-Fr vascular sheath is advanced over a guidewire into the right portal vein branch to aid with subsequent catheter

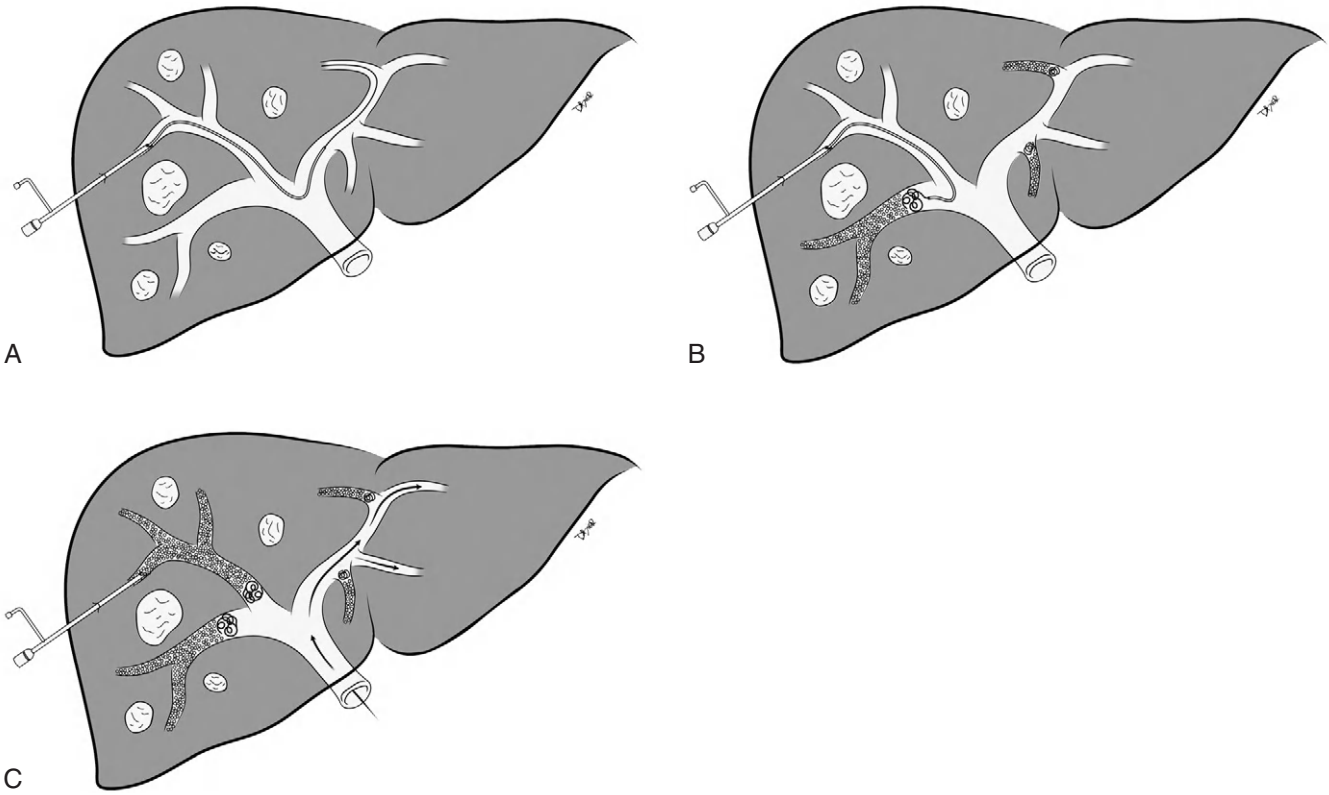


FIGURE 93B.2. Schematic representation shows modification of the ipsilateral technique for right portal vein embolization (RPVE) extended to segment IV. **A,** Placement of a 6-Fr vascular sheath into the right portal branch. An angled 5-Fr catheter is placed into the left portal system with coaxial placement of a microcatheter into a segment IV branch. Particulate embolization is performed followed by placement of coils, until all the branches are occluded. **B,** After segment IV embolization is completely occluded, a 5-Fr reverse-curve catheter is used for RPVE. **C,** After embolization of the right and segment IV portal veins are complete, the access tract is embolized with coils to prevent subcapsular hemorrhage.



FIGURE 93B.3. A 67-year-old man with pancreatic insulinoma metastatic to the liver who had transhepatic ipsilateral right portal vein embolization (RPVE) with particles and coils prior to right hepatectomy. **A,** Contrast-enhanced computed tomographic (CT) scan of the liver shows a hypervascular mass in the right liver consistent with metastatic disease (*arrow*). **B,** Contrast-enhanced CT scan of the liver shows a small left liver within the shaded area (functional liver remnant/total estimated liver volume ratio [FLR/TELV] of 16%). **C,** Anteroposterior flush digital subtraction portogram shows a 6-Fr vascular sheath (*arrowheads*) in a right portal vein branch and a 5-Fr flush catheter (*arrow*) in the main portal vein. **D,** Postprocedure anteroposterior flush portogram shows occlusion of the portal vein branches to segments V through VIII (*white arrows*) with continued patency of the vein supplying the left liver (*black arrow*). An *arrowhead* shows subtracted contrast within a right portal vein branch overlying the left liver. **E,** A later phase of portogram confirms persistent flow to the left liver (*arrows*). **F,** Contrast-enhanced CT scan of the liver performed 1 month after RPVE shows hypertrophy of the left liver within the shaded area (FLR/TELV of 34%). The patient soon after underwent an uneventful right hepatectomy.

exchanges. Flush portography is performed with a 5-Fr angiographic flush catheter placed within the main portal vein. Anteroposterior and craniocaudal projections are obtained as needed to delineate the portal anatomy.

When embolization of the right portal vein is extended to segment IV (Fig. 93B.4), segment IV embolization should be performed first (Madoff et al, 2005b). This sequence is advocated because of the potential difficulty of exchanging catheters through a previously embolized right portal system and the possible dislodgement of embolic material from the right liver during the subsequent treatment of segment IV, which is usually embolized with a 3-Fr microcatheter placed coaxially through a selective 5-Fr angiographic catheter.

Early on, polyvinyl alcohol (PVA) particles (Contour SE Microspheres; Boston Scientific, Natick, MA) were the embolic agents of choice (Madoff et al, 2003). PVA was administered in a stepwise fashion: smaller particles (355 to 500 μm) were used first to occlude the distal branches, and larger particles (up to 1000 μm) were used subsequently to occlude branches more proximally. Larger particles were not used until the forward portal blood flow was considerably reduced. Additional embolization with the larger particles was then performed, until near complete stasis was achieved. Later, with the advent of spherical embolic agents, tris-acryl gelatin microspheres (EmboGold Microspheres; Biosphere Medical, Rockland, MA) became the embolic agent of choice (Madoff et al, 2005b). EmboGold microspheres ranging from 100 to 700 μm in diameter are administered in a stepwise fashion, similar to the method used for the PVA particles. After particulate embolization is complete, platinum microcoils (Boston Scientific) are placed within the proximal segment IV branches to further reduce portal blood inflow that could lead to recanalization.

For right PVE (RPVE), the working catheter is exchanged for a 5-Fr reverse-curve catheter (Sos-2, AngioDynamics, Latham, NY) to enable delivery of the particulate embolic agent. These catheters are chosen for their ease of manipulation into the right portal branches, given the severe angulation of the right portal tree with the ipsilateral approach. As with segment IV embolization, smaller particles are used first to occlude the distal, smaller portal branches, and the larger particles are used later to occlude the more proximal, larger branches. After near complete stasis is achieved, 0.035- or 0.038-inch embolization coils (Gianturco, Cook Medical) are placed within the secondary portal branches to further reduce portal inflow that could lead to recanalization. A final portogram is obtained with the flush catheter positioned within the main portal vein to assess completeness of the embolization. At the completion of the procedure, the access tract is embolized with coils and/or Gelfoam to minimize the risk of bleeding at the liver puncture site.

Overall, the ipsilateral approach is safe and effective for achieving FLR hypertrophy preoperatively. Although disadvantages of the ipsilateral approach do exist, they are minor. As mentioned above, catheterization and embolization of the right portal vein branches may be challenging because of the severe angulations between right portal branches; however, this is rarely a problem when reverse-curve catheters are used. Operators also need to be aware that the ipsilateral approach carries the risk of puncture through tumor tissue when multiple or large tumors are present, which could theoretically lead to bleeding or tumor seeding.

Percutaneous Transhepatic Contralateral Approach

The percutaneous transhepatic contralateral approach was first described by Kinoshita and coworkers (1986) to slow the progression of tumor thrombus within the portal system. Modifications of this technique were later developed for the purpose of causing FLR hypertrophy (de Baere et al, 1993, 1996; Figs. 93B.5 and 93B.6). Similar to the ipsilateral approach, this approach also requires ultrasound-guided percutaneous puncture, using an 18- or 22-gauge needle, of a peripheral portal branch, preferably segment III accessed via the subxiphoid route. Because access is gained through the FLR, great care is taken to limit the number of punctures, and as with the ipsilateral approach, the most peripheral branch possible is targeted to avoid damage to the central structures.

Depending on the embolic agent used, an introducer sheath may or may not be required; a standard 5-Fr polyethylene catheter is inserted over a guidewire and placed with its distal tip within the main portal trunk to allow for flush portography. Depending on the specific targeted portal veins, embolization is carried out using either standard angiographic or balloon occlusion catheters. A short catheter between 25 and 30 cm in length is commonly used, as it is easier to handle and provides a smaller "dead space," which is especially important when using liquid embolics, such as n-butyl cyanoacrylate (NBCA) for embolization.

In terms of accessing the portal vein, the contralateral approach can be challenging when segment IV embolization is also needed. To ensure an adequate distance between the portal entry point and the segment IV branches, the operator must perform the puncture in a branch of the left lateral liver, usually from the Rex recess. Unlike the ipsilateral approach, segment IV embolization is performed after RPVE has rendered the segment IV branches more easily visible and dilated; however, a puncture in the Rex recess will make catheterization difficult, owing to the sharp angle of the vein and the risk of losing access. Segment III is often easier to access than segment II, and sonographic guidance in the axial plane makes it easy to differentiate segment II from segment III and the Rex recess. Because segment III branches arise in front of segment II branches within the Rex recess, catheterization of segment IV branches may be easier after puncture of segment III branches. After achieving complete occlusion of the targeted portal branches, the 5-Fr catheter is removed. Because the catheter entry site traverses the FLR, embolic material is not used to seal the puncture tract.

The major advantage of the contralateral approach over the ipsilateral approach is that catheterization of the right portal branches is technically easier and does not have to contend with awkward angles. In addition, embolization is performed with the catheter pointed toward the direction of flow. Some authors report that the contralateral approach allows better visualization of the embolized portal branches during the final portogram (Di Stefano et al, 2005); however, different operators have found that in using the modified ipsilateral approach, the image quality of the final postembolization portography is similar. In addition, with the use of reverse-curve catheters, ipsilateral PVE in the right liver can also be performed safely in the direction of portal venous flow (Madoff et al, 2002).

The main drawback of the contralateral approach is that it requires instrumentation of the left hepatic parenchyma during catheterization of the portal venous branches supplying the

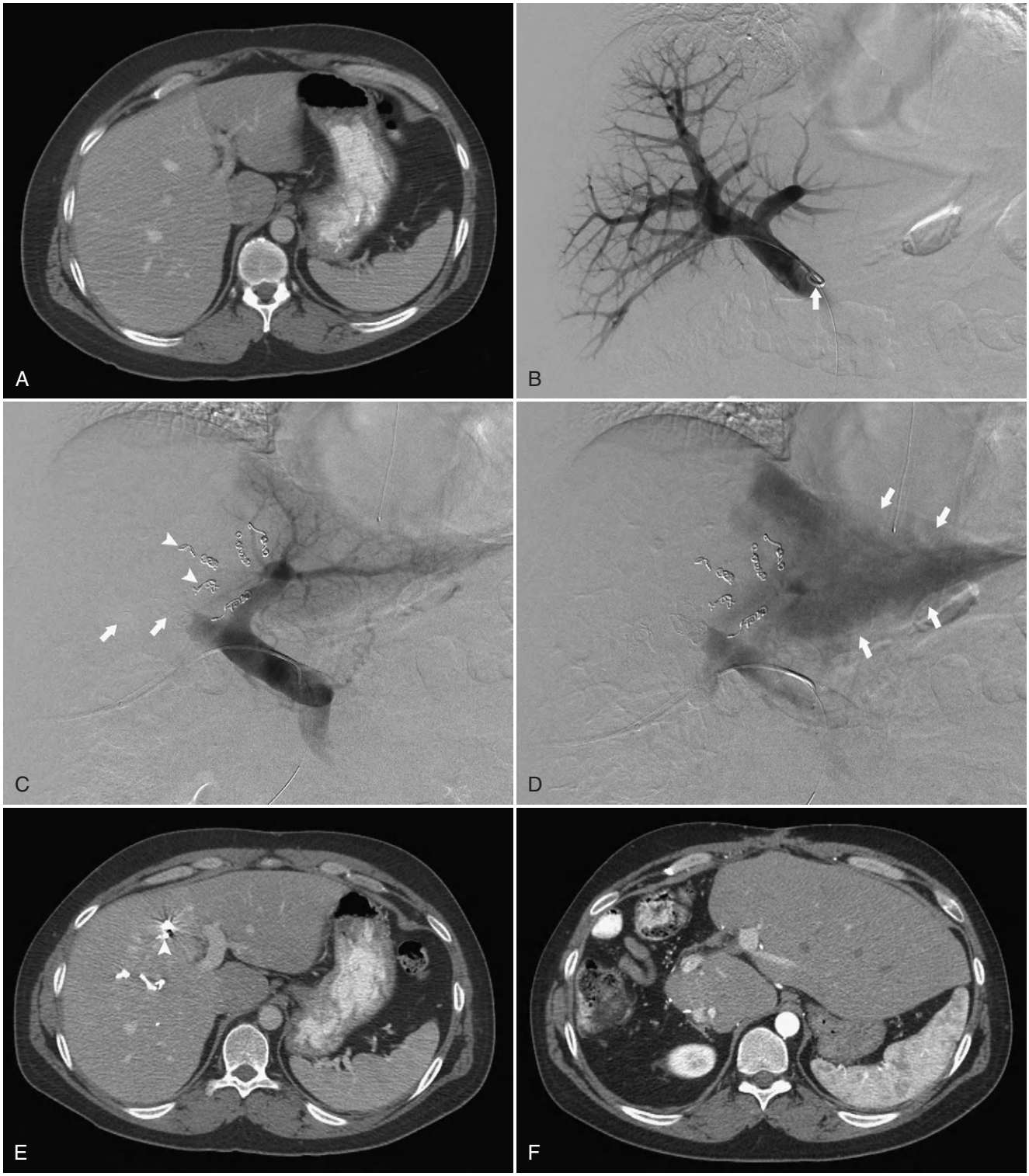


FIGURE 93B.4. A 38-year-old man with metastatic colorectal cancer to the liver who had transhepatic ipsilateral right portal vein embolization with particles and coils extended to segment IV prior to extended right hepatectomy. **A,** Contrast-enhanced computed tomography (CT) scan of the liver shows a small left lateral liver (functional liver remnant/total estimated liver volume ratio [FLR/TELV] of 16.9%; *shaded area*). **B,** Anterior–posterior flush portogram from the ipsilateral approach shows a 6-Fr vascular sheath in a right portal vein branch and a 5-Fr flush catheter (*arrow*) in the main portal vein. **C,** Postprocedure portogram shows complete occlusion, with particles and coils, of the portal vein branches to segment IV (*arrowheads*) and the right liver (*arrows*) with continued patency of the veins supplying the left lateral liver. **D,** A later phase of portogram confirms persistent flow to the left liver (*arrows*). **E,** Contrast-enhanced CT scan performed 4 weeks after portal vein embolization shows hypertrophy of the left lateral liver (FLR/TELV is now 27.2%, a degree of hypertrophy of 10.3%) with rounded margins (*shaded area*). A coil within segment IV (*arrowhead*) and coils within the right liver are seen. **F,** Contrast-enhanced CT scan of the liver performed after successful extended right hepatectomy shows hypertrophy of the liver remnant.

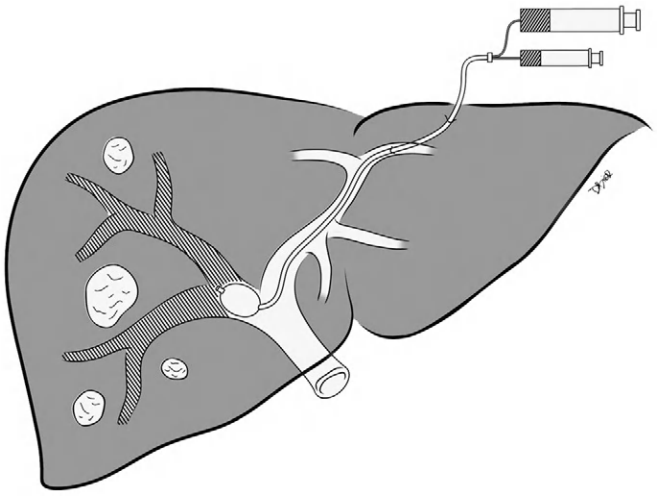


FIGURE 93B.5. Schematic representation of the contralateral approach. An occlusion balloon catheter is placed from the left lobe into the right portal branch, with delivery of the embolic agent in the antegrade direction.

FLR, potentially causing injury to the FLR parenchyma and/or to the left portal vein (Madoff et al, 2005a). If there are complications after PVE, these may involve the FLR and make the planned surgical resection more difficult or, at times, impossible.

Additional Approaches

Portal Vein Embolization with Transjugular Access

RPVE by means of the transjugular route has also been described (Perarnau et al, 2003). This technique was tried because of the familiarity gained during the preceding decade with transjugular intrahepatic portosystemic shunts (TIPS). Under sonographic guidance, the right internal jugular vein was accessed, and then with fluoroscopy, a right or left portal branch was punctured from a right, middle, or left hepatic vein. A catheter was placed near the portal bifurcation and used to perform RPVE with a mixture of NBCA and iodized oil. All 15 procedures were technically successful without any serious complications. FLR hypertrophy was deemed sufficient, and right hepatectomy was performed in 12 patients (80%). Although this approach appears safe and effective, the series was small, and further studies are needed before this approach becomes widespread. RPVE in patients with cirrhosis may be an attractive alternative; however, the technical feasibility of RPVE extended to segment IV has yet to be explored.

Portal Vein Embolization Followed by Bland Transarterial Embolization

Other approaches have been used for PVE. The combination of PVE and transarterial embolization (TAE) for complete portal venous and hepatic arterial occlusion has been reported in patients with biliary tract cancer and colorectal metastases who had inadequate hypertrophy after PVE alone (Nagino et al, 2000b; Gruttadauria et al, 2006). Nagino and coworkers (2000b) described a patient who required an extended left hepatectomy, but the FLR volume (i.e., the right posterior liver) did not increase 51 days after PVE. After arterial embolization, the FLR volume increased from 485 cm^3 before PVE to 685 cm^3 after PVE, an addition of 215 cm^3. Another patient required a right hepatectomy, but no significant volume change was seen after PVE (pre-PVE, 643 cm^3; post-PVE, 649 cm^3). After arterial embolization, the left liver volume enlarged to 789 cm^3, an increase of 140 cm^3. Both patients underwent uneventful resection after the staged procedures.

It must be noted that this procedure does have potential drawbacks. As both arterial and portal systems are deprived of blood, the potential for hepatic infarction exists such that only half the target segments were treated with arterial embolization superselectively. Although this approach was effective, the disadvantage is that two separate procedures are required, performed at different times, leading to considerably longer waiting periods. During these waiting periods, tumor progression could occur to the degree that the tumors become unresectable.

Sequential Arterial Embolization and Portal Vein Embolization

In 2004, Aoki and colleagues described their experience with the use of sequential transcatheter arterial chemoembolization followed within two weeks by PVE in 17 patients with hepatocellular carcinoma (HCC). Their justification for this approach was that, first of all, the livers of most patients with HCC are compromised by underlying liver disease such that the liver's regenerative capability after hepatic resection is weakened, making it hard to predict whether adequate FLR hypertrophy can be achieved after PVE. Second, arterioportal shunts often found in cirrhotic livers and HCC may limit the effects of PVE. Third, since most HCCs are hypervascular, supplied largely by arterial blood flow, termination of portal flow induces compensatory augmentation in arterial blood flow (i.e., "arterialization of the liver") in the embolized segments that may lead to rapid tumor progression after PVE.

To this end, sequential chemoembolization and PVE were used to prevent tumor progression during the interval between PVE and planned hepatectomy and to strengthen the effect of PVE by embolizing arterioportal shunts with chemoembolization. As a result, the combined procedures were deemed safe and were found to have induced sufficient FLR hypertrophy within 2 weeks, and they caused no worsening of the basal hepatic functional reserve and no increase in tumor progression. Importantly, when the explanted livers were assessed, tumor necrosis was profound but without substantial injury to the noncancerous liver, and the authors therefore encourage the aggressive use of this strategy in patients with large HCC and chronically injured livers.

More recently, a French group reported on the use of sequential chemoembolization and PVE in 36 patients with HCC and chronic liver disease prior to right hepatectomy (Ogata et al, 2006; Fig. 93B.7). In their study, 18 patients underwent chemoembolization, followed 3 to 4 weeks later by PVE, and the remaining 18 patients underwent PVE alone. Although PVE was well tolerated in all patients, the mean increase in percentage of FLR volume was significantly higher for patients in the combined chemoembolization and PVE group than in those who underwent PVE alone ($P = .022$). The incidence of complete tumor necrosis (83% [15/18] vs. 6% [1/18]; $P < .001$) and 5-year disease-free survival rate (37% vs. 19%; $P = .041$) were also significantly higher in patients who underwent chemoembolization and PVE. Given the risks of hepatic infarction, the authors recommended that the two



FIGURE 93B.6. Technique of transhepatic contralateral right portal vein embolization using n-butyl cyanoacrylate mixed with ethiodized oil. **A,** Ultrasound view of needle puncture of a segment III portal branch (*arrowheads*). **B,** Anteroposterior flush portogram shows a 5-Fr flush catheter within the main portal vein (*arrow*). **C,** Single image obtained during fluoroscopy shows cast of embolic material within right portal vein branches (*arrowheads*). **D,** Final portogram shows occlusion of the portal vein branches (*arrows*) to segments V through VIII with continued patency of the veins supplying the left liver. *(From Avritscher R, et al, 2008: Percutaneous transhepatic portal vein embolization: rationale, technique and outcomes. Semin Interv Radiol 25:132-145.)*

procedures should be separated by at least 3 weeks to reduce procedure-related morbidity; however, similar to Nagino's approach of performing PVE followed by TAE, the downside of the combined approach is that two separate procedures and increased waiting times are required.

Extent of Embolization

The optimal extent of PVE is presently a subject of considerable debate (van Gulik et al, 2008). Currently, most who prepare patients for extended right hepatectomy with PVE occlude only branches of the right portal vein and leave the segment IV portal veins patent (de Baere et al, 1993; Capussotti et al, 2005). Although FLR hypertrophy does occur, full diversion of portal flow to segments II and III ensures the maximal stimulus for FLR hypertrophy (Nagino et al; 1995, 2000; Kishi et al, 2008; Mueller et al, 2008). Further, incomplete embolization of the liver to be resected will also lead to hypertrophy of segment IV, which is undesirable for an extended right hepatectomy because of increased morbidity associated with a larger area of intraoperative parenchymal transection across this hypertrophic segment (Nagino et al, 1995).

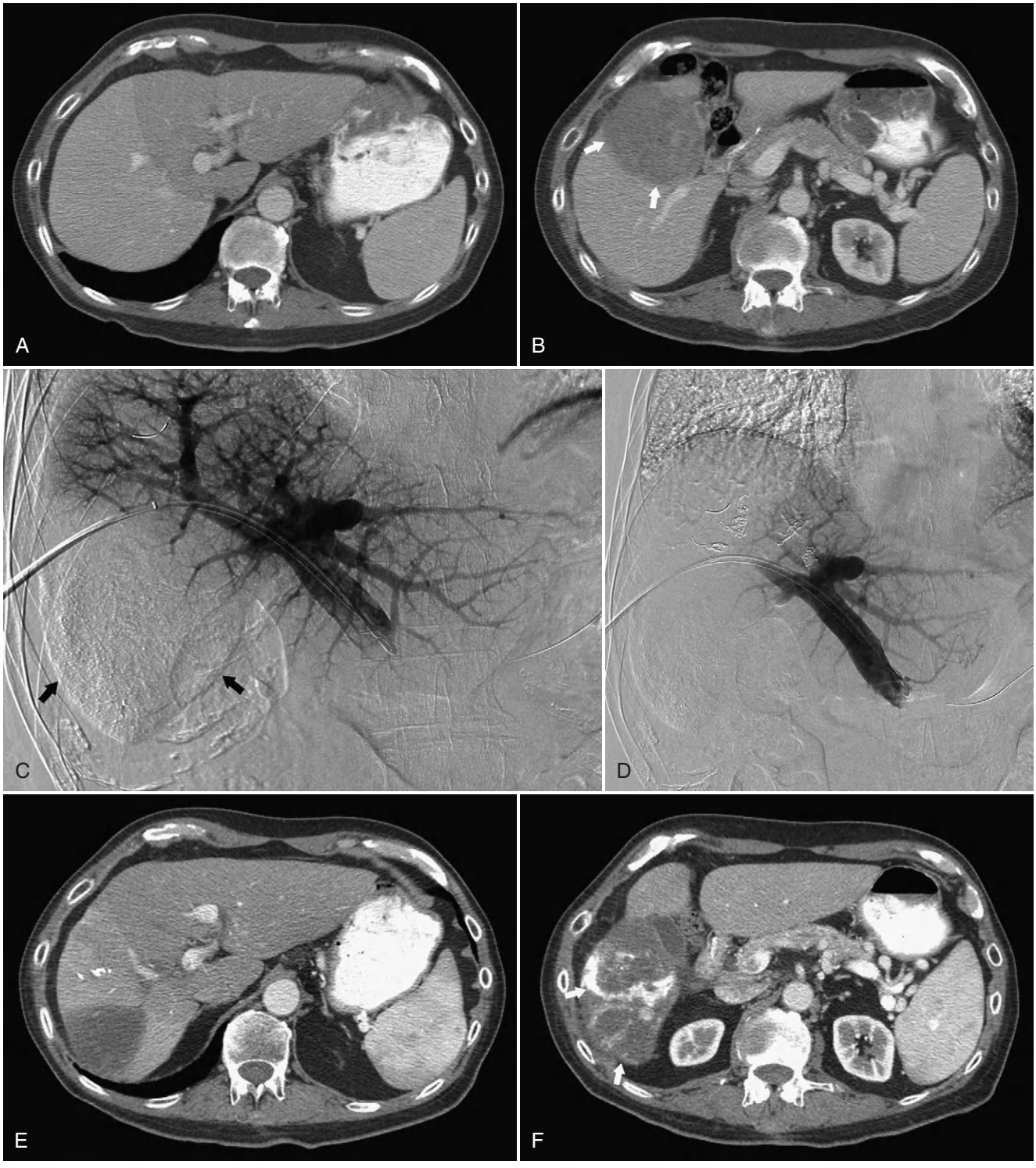


FIGURE 93B.7. A 74-year-old man with an 8-cm solitary hepatocellular tumor and hepatitis C cirrhosis who underwent sequential transcatheter arterial chemoembolization followed 1 month later by right pulmonary vein embolization (PVE) prior to a right hepatectomy. Prior to treatment, the patient's α-fetoprotein level (AFP) was 61,507 ng/mL. **A,** Single image from pre-PVE contrast-enhanced computed tomographic (CT) scan shows a small left liver and a functional liver remnant/total estimated liver volume ratio (FLR/TELV) of 27% (*shaded area*). **B,** Single image caudal to **A** shows the solitary 8-cm tumor (*arrows*). **C,** Preembolization portogram after chemoembolization shows persistent iodized oil uptake within the right lobe (*arrows*). The right posterior sector portal vein was occluded as a result of the prior chemoembolization. **D,** Postembolization portogram shows complete occlusion of all branches to right portal vein. The left portal vein remains patent. **E,** Single image from post-PVE contrast-enhanced CT scan shows hypertrophy of the left liver. The FLR/TELV increased to 47% (*shaded area*). **F,** Single image from post-PVE contrast-enhanced CT scan more caudal to **E** shows massive atrophy of the right lobe with necrosis of the tumor. After the combined treatment, the patient's AFP level decreased to 2.9 ng/mL. The patient subsequently underwent uncomplicated right hepatectomy. No viable tumor cells were found in the resected specimen, and the patient was disease free 4 years after surgery.

Nagino and coworkers (2000) first showed that a greater left lateral bisegment hypertrophy occurs after right PVE extended to segment IV (50% increase in FLR volume) than after only right PVE (31% increase, $P < .0005$). Recent studies have supported Nagino's conclusions, and without any increase in PVE-associated complications (Kishi et al, 2008; Mueller et al, 2008). Because segment IV embolization has been shown to be advantageous, the ipsilateral approach for right PVE extended to segment IV has been further refined, which has led to improved FLR hypertrophy and better operative outcomes. Lastly, left PVE is rarely needed because of consistently large volumes of the right posterior liver (segments VI and VII; Nagino et al, 1995; Abdalla et al, 2004; Leelaudomlipi et al, 2002).

Another potential benefit of extending right PVE to include segment IV, from an oncologic perspective, is that the entire tumor-bearing liver is systematically embolized (i.e., right PVE for right hepatectomy, right PVE extended to segment IV for extended right hepatectomy) to reduce the risk of tumor growth that may result from increased portal blood flow and hepatotrophic factors (Madoff et al, 2005a; Ribero et al, 2007; de Graaf et al, 2009). A recent study from a large academic cancer center evaluated 112 patients in whom the entire tumor-bearing liver was systematically embolized and found no increase in the median tumor size during the waiting period (Ribero et al, 2007); however, tumor growth within the nonembolized liver has been discussed upon analysis of a very limited number of patients with primary and secondary liver tumors after right PVE alone, although; comparison to pre-PVE tumor growth rate was made; the true effect of PVE on tumor growth could therefore not be proven (Elias et al, 1999; Kokudo et al, 2001). Furthermore, liver hypertrophy occurs quickly in patients with normal liver, and thus resection can be undertaken in most patients with multiple colorectal metastases within 3 to 4 weeks of PVE.

Embolic Agents

Many embolic materials have been used for PVE, with no remarkable differences reported in the rate or degree of hypertrophy. These agents include, but are not limited to, fibrin glue, NBCA mixed with ethiodized oil, gelatin sponge, thrombin, metallic coils, spherical and nonspherical microparticles (e.g., PVA particles, tris-acryl gelatin microspheres, others), and absolute ethanol. Importantly, a true comparison of the embolic agents used for PVE is difficult given that the available literature reports dissimilar patient populations, variable CT volumetric methodology, inconsistent imaging follow-up times, and varied PVE technique. Therefore, choosing a particular embolic agent is at the operator's discretion, and the decision is based on the extent of the embolization and surgery, preference for a particular catheter and approach, and their experience with a specific agent. Some of the more common embolic agents used for PVE are detailed below.

Early in the experience with PVE, gelatin sponge was widely used as an embolic agent; however, recanalization of the embolized portal veins was frequently observed within 2 weeks of the procedure (Makuuchi et al, 1990; Kinoshita et al, 1986; de Baere et al, 1996), and when compared with other embolic agents, it seemed less effective at 4 weeks in terms of causing hypertrophy. Also, fibrin glue combined with ethiodized oil is a commonly used mixture for PVE. This mixture also leads to early recanalization, as it results in less than 75% portal occlusion at 2 weeks and less than 25% portal occlusion at 4 weeks (Makuuchi et al, 1990; de Baere et al, 1996).

Some investigators advocate NBCA mixed with ethiodized oil, because the mixture leads to fast, reliable hypertrophy and lessens the delay between PVE and resection. NBCA ensures portal occlusion that endures beyond 4 weeks. Because polymerization time can be adjusted by varying the volume of Lipiodol added to the NBCA, distal and proximal branches can be aggressively embolized. Usually, NBCA is mixed with Lipiodol at a ratio of 1:1 to 1:3. As it is a liquid, NBCA can be rapidly delivered throughout the entire right portal system, which greatly reduces procedure time.

In terms of effectiveness, de Baere and coworkers (1996) reported that PVE with NBCA led to a 90% increase in FLR volume after 30 days, and Denys and coworkers (2005) found it useful in inducing hypertrophy in patients with underlying hepatic fibrosis or cirrhosis; however, there are some drawbacks of using NBCA for PVE. For example, the NBCA injections have to be precise because of the increased risk of nontarget embolization; thus it requires a highly experienced operator. Furthermore, NBCA can be difficult to use in patients with reduced hepatopetal flow, as is commonly seen in patients with chronic hepatic disease. These altered flow dynamics have been associated with increased risk of procedural complications (Di Stefano et al, 2005). NBCA also induces an inflammatory process that may make hepatectomy more difficult (de Baere et al, 1996; Avritscher et al, 2008). Lastly, although this agent may be straightforward when the anatomy is favorable (e.g., the anterior and posterior sector portal veins originate from a right portal vein), it may not be the best alternative in situations where variant anatomy is present, or when multiple segment IV veins are to be embolized (i.e., multiple microcatheters are needed, leading to considerable expense and increased risk of nontarget embolization to the FLR).

Absolute ethanol is another efficient embolic agent for PVE. Ogasawara and coworkers (1996) showed near doubling of the FLR volume within 4 weeks for patients with chronic hepatic disease and HCC who underwent PVE with this agent. Unfortunately, of all the embolic agents used for PVE, the most marked changes in liver function tests and the poorest patient tolerance is seen with absolute ethanol.

Recently, the use of particulate agents for PVE was also proposed. In the first clinical report in a single patient, no recanalization of the right portal vein was observed 5 weeks after PVE with PVA particles alone (Brown et al, 2001). Later, Madoff and coworkers (2002, 2003, 2005b) showed that a combination of particles (e.g., polyvinyl alcohol particles [PVA], tris-acryl gelatin microspheres) and coils is safe and effective for PVE. Particles are safe, they cause little periportal reaction, and they generate durable portal vein occlusion, especially when used in combination with coils (Madoff et al, 2002, 2003). In 2003, results from their first 26 patients who had PVE with nonspherical PVA particles, ranging in size from 300 to 1000 μm, and coils were reported; the mean FLR/total estimated liver volume (TELV) increased 7.8% (pre-PVE FLR/TELV, 17.6%; post-PVE FLR/TELV, 25.4%), and the mean absolute FLR increase was 47% (Madoff et al, 2003).

The subsequent advance of spherical particulate embolics has led to even further refinements in technique for PVE by using a stepwise infusion of very small (100 to 300 μm)

tris-acryl gelatin microspheres followed by larger spheres (up to 700 μm; Madoff et al, 2005b). This type of distal embolization is thought to limit development of collateral circulation that may potentially reduce hypertrophy because of the improved targeting of distal portal vein branches (nonspherical particles tend to clump and therefore do not always reach the targeted size vessel). Metallic coils are then used proximally to block venous inflow and further reduce the possibility of recanalization. This newer approach was used for right PVE extended to segment IV and led to an absolute increase in FLR volume of 69.0%, an FLR/TELV increase of 9.7%, and a subsequent resection rate of 86% that was a significant improvement over their previously reported method.

COMPLICATIONS OF PORTAL VEIN EMBOLIZATION

As with all transhepatic procedures, complications include subcapsular hematoma, hemoperitoneum, hemobilia, arterioportal shunts, arteriovenous fistula, pseudoaneurysm, portal vein thrombosis, transient liver failure, pneumothorax, and sepsis (Kodama et al, 2002; Di Stefano et al, 2005). Kodama and colleagues (2002) compared complication rates between the contralateral and ipsilateral approaches in 47 patients who underwent PVE and found that in 11 patients who underwent contralateral PVE, 2 (18.1%) experienced complications, and in 36 patients who underwent ipsilateral PVE, 5 (13.9%) experienced complications. This difference was not statistically significant, and the rate of technical complications associated with percutaneous PVE using either approach was 14.9%. The following complications were those found in this patient cohort: two subcapsular hematomas, two pneumothoraces, one inadvertent arterial puncture, one pseudoaneurysm (in a patient who also had a subcapsular hematoma), one hemobilia, and one portal vein thrombosis. Complications more specific to percutaneous PVE included portal vein thrombosis and portal hypertension resulting in esophageal variceal hemorrhage. The authors stressed that given the potential for injury to the FLR when using the contralateral approach, the ipsilateral approach should be tried first.

Di Stefano and coworkers (2005) later reported on 188 patients who underwent PVE using the contralateral approach. They reported that only one patient experienced a major complication (complete portal vein thrombosis) directly related to the contralateral approach that precluded the planned surgical resection. Two other patients experienced inadvertent migration of embolic material into the FLR that required intervention; one needed a portoportal graft during hepatic resection because of portal vein thrombosis. On CT imaging, another 10 patients were found to have embolic material in nontargeted portal venous branches.

In 2007, Ribero and coworkers (2007) reported on 112 patients who underwent PVE with the ipsilateral approach. In this study, only one patient had nontarget embolization to the FLR; however, the overall complication rate was 8.9%, which was not substantially different than the rate reported by Di Stefano and coworkers (2005). If it is taken into account that they considered clinically occult incidental CT findings in their complication rate, the studies reported remarkably similar numbers. Further, the study by Ribero and others (2007) found no difference in the complication rate, whether right PVE was extended to segment IV or not.

CONCLUSION

Preoperative PVE is a safe and effective method of inducing FLR hypertrophy before major hepatic resection. Currently, the percutaneous transhepatic ipsilateral and contralateral PVE approaches are the most commonly used worldwide. Surgeons must pay particular attention to the technical aspects, aberrant portal venous anatomy, and treatment strategies when PVE is used to ensure the best outcomes for patients.

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CHAPTER 97B

Liver transplantation: anesthesia, perioperative management, and postoperative care

Andrea Vannucci and Ivan Kangrga

OVERVIEW

Approximately 20,000 liver transplantations are performed annually worldwide (Matesanz et al, 2009), but the number of patients on the waiting list continues to exceed the donor organ availability. Because of the continuous donor shortage, dramatic changes in recipient and donor selection have emerged in the past decade, leading to an amplification of clinical challenges for perioperative liver transplant physicians. In fact, United Network for Organ Sharing (UNOS) data from 2009 (UNOS/OTPN, 2010) show that older patients are now accepted to the waiting list and transplanted; combined kidney and liver transplants are performed more often than in prior years; and extended-criteria donors, including donors after cardiac death, are increasingly utilized (see Chapter 97A).

Despite the increasing medical complexity, overall graft and patient outcomes have continued to improve. According to the UNOS database, survival rates for patients transplanted with a cadaveric graft are around 87% at 1 year, 80% at 3 years, and 74% at 5 years. These encouraging figures, achieved by experienced transplant teams, have resulted in part from the progressive advancement and standardization of surgical and anesthetic techniques (Mandell et al, 2008). If the current trends continue, with transplantation of increasingly older and sicker recipients (Costa et al, 2009; Xia et al, 2008) and use of marginal donor organs, the outcomes will greatly depend on accurate preoperative assessment and on appropriate and timely intraoperative medical management of comorbidities.

PREOPERATIVE ANESTHETIC ASSESSMENT

Liver transplantation is the current gold standard treatment for acute and chronic irreversible liver failure (see Chapters 70A, 72, and 97A); for selected clinical syndromes not manifesting with end-stage liver disease (ESLD), including polycystic liver disease (see Chapter 69B) and other metabolic diseases; for some malignancies confined to the liver (see Chapters 97D and 97E); and for cholestatic liver diseases in children, such as biliary atresia (see Chapters 40 and 71). Four contraindications to liver transplantation are widely accepted: 1) unstable cardiopulmonary conditions, such as symptomatic coronary artery disease (CAD), severe systolic dysfunction, advanced cardiomyopathy, severe valvular heart disease, and severe pulmonary hypertension; 2) substance abuse; 3) morbid obesity (body mass index [BMI] >40); and 4) uncontrolled sepsis (Gallegos-Orozco & Vargas, 2009; Murray & Carithers, 2005).

As part of a multidisciplinary transplant team, anesthesiologists should participate in the evaluation of candidate recipients. Ideally, an anesthetic evaluation should precede the acceptance of patients to the waiting list. The goals of this assessment are to appraise suitable candidates based on functional status and comorbidities and to design a patient-specific preoperative and perioperative treatment plan. For patients in whom the burden of comorbidities presents a prohibitive operative risk, alternative treatments should be sought (Merion, 2004).

Cardiovascular System

Hyperdynamic circulation, cardiomyopathy, and CAD are common clinical problems that impact postoperative outcomes in orthotopic liver transplantation (OLT) candidates (Fouad et al, 2009).

Hyperdynamic Circulation

Patients with ESLD develop high cardiac output hemodynamics secondary to reduced systemic vascular resistance (SVR) and abnormal distribution of central, splanchnic, and peripheral circulation. This condition is due to humoral and autonomic dysregulation (Møller & Henriksen, 2008). When this situation is associated with cardiac valve dysfunction, especially mitral or tricuspid valve insufficiency, more hemodynamic support is needed in the perioperative period (Alper et al, 2009).

Coronary Artery Disease

Perioperative complications and mortality rates are high in patients with CAD: up to 50% of patients with significant CAD may die perioperatively from cardiac complications (Plotkin et al, 1996). Safadi and colleagues (2009) recently reported that history of stroke, CAD, postoperative sepsis, and increased interventricular septal thickness were markers of adverse perioperative cardiac outcomes, whereas use of perioperative β-blockers was significantly protective. Occult CAD is also common: 5% to 26% of OLT candidates have at least one critical coronary stenosis. Computed tomography (CT) scan detection of coronary calcification is a sign of possible ischemic heart disease in asymptomatic patients, but the sensitivity and specificity are low (Mandell & Tsou, 2008; Tiukinhoy-Laing et al, 2006).

Dobutamine stress echocardiography and dobutamine myocardial perfusion imaging are considered the most sensitive noninvasive tests to assess occult CAD in liver

transplant candidates. Both tests have a higher negative than positive predictive value (Donovan et al, 1996; Mandell & Tsou, 2008; Murray & Carithers, 2005; Plotkin et al, 1998; Williams et al, 2000). Cardiac catheterization is indicated in patients with a positive noninvasive test to assess coronary lesions and plan further treatment. Left-heart catheterization is associated with higher risk of minor complications but can be performed safely in candidates for OLT (Sharma et al, 2009).

CIRRHOTIC CARDIOMYOPATHY. Cirrhotic cardiomyopathy is characterized by systolic dysfunction more evident under conditions of hemodynamic stress, impaired diastolic relaxation, and electrophysiologic alterations often manifesting with a prolonged QT interval. Diagnosis is based on electrocardiograph (ECG), cardiac echo, and elevated levels of brain natriuretic factor. Physiopathologic hallmarks of this disease are altered β-adrenergic activity, myocardial fibrosis, myocyte hypertrophy, and ion-channel defects. Medical treatment is based on sodium restriction and administration of β-blockers and aldosterone antagonists; however, liver transplantation can reverse this condition (Fukazawa et al, 2009; Mandell & Tsou, 2008; Wong, 2009).

NONISCHEMIC CARDIOMYOPATHY. Nonischemic cardiomyopathy can complicate alcoholic cirrhosis, amyloidosis, hemochromatosis, and Wilson disease, and it must be considered in the anesthetic preoperative assessment and intraoperative management. Dilated and hypertrophic cardiomyopathy can also be present in OLT candidates, and these rarely revert to normal even after OLT (Mandell & Tsou, 2008).

Pulmonary System

As many as 70% of patients with chronic liver disease (CLD) suffer from respiratory problems, that manifest as impaired respiratory mechanics and gas exchange (Kim et al, 2009). Most pulmonary diseases are independent from the liver disease but are in some instances related to liver disease (e.g., α_1-antitrypsin deficiency and cystic fibrosis) (Yeshua et al, 2009). Pulmonary evaluation includes history and physical examination, radiologic studies, arterial blood gas, and pulmonary function tests. Right-heart catheterization is indicated when clinical or ECG evidence suggests pulmonary hypertension.

Chronic Obstructive Pulmonary Disease and Smoking

Chronic obstructive pulmonary disease (COPD) is common and is often undiagnosed in candidates for liver transplantation. In a recent prospective study involving several academic centers in the United States, 18% of OLT candidates had COPD, and 80% of those patients had not been previously diagnosed. Older age and smoking were significant risk factors for this condition, although the impact of COPD on perioperative outcome in liver transplantation has not been well defined (Ryback et al, 2008).

HEPATIC HYDROTHORAX. *Hepatic hydrothorax* is defined as a pleural effusion greater than 500 mL not caused by cardiac or pulmonary diseases in a patient with cirrhosis (Singh & Sager, 2009). A diaphragmatic defect allowing passage of ascites from the peritoneal to the pleural cavity is considered the main mechanism leading to this complication. Pleural effusions are symptomatic in 6% to 10% of patients with ESLD (Kiafar & Gilani, 2008), and the main respiratory impairment is hypoxemia secondary to atelectasis and shunting; chest radiograph confirms the diagnosis. Treatment is based on medical management of ascites with paracentesis and possible placement of a transjugular intrahepatic portosystemic shunt (TIPS). In cases of refractory hydrothorax, pleurodesis and diaphragmatic repair can be considered; thoracentesis is performed only in emergency situations, because avoidance of tube thoracostomy is preferred.

PORTOPULMONARY HYPERTENSION. *Portopulmonary hypertension* (PPHTN) is a specific type of pulmonary artery hypertension. It comprises increased pulmonary vascular resistance (PVR) and portal hypertension with or without advanced liver disease. From 2% to 10% of patients with cirrhosis are affected by PPHTN (Yeshua et al, 2009). The physiologic mechanism is multifactorial and incompletely understood, but hyperdynamic circulation, imbalance between pulmonary vasodilators (nitric oxide and prostacyclin) and vasoconstrictors (endothelin-1 and thromboxane), and proliferative pulmonary arteriopathy all play a role in the genesis of this syndrome (Singh & Sager, 2009).

Diagnosis requires presence of portal hypertension, mean pulmonary arterial pressure (mPAP) greater than 25 mm Hg, PVR greater than 240 dynes/sec/cm^{-5}, and pulmonary artery occlusion pressure of less than 15 mm Hg (Rodriguez-Roisin et al, 2004); right-heart catheterization is indicated if pulmonary artery systolic pressure is higher than 50 mm Hg on ECG screening. The severity of PPHTN is then evaluated based on hemodynamic data obtained by right-heart catheterization at rest and is classified as *mild* (mPAP of 24 to 34 mm Hg), *moderate* (mPAP of 35 to 44 mm Hg), or *severe* (mPAP ≥45 mm Hg) (Singh & Sager, 2009).

Medical optimization is indicated before transplantation, and treatment is based on vasodilators. Prostaglandins (intravenous epoprostenol or inhaled iloprost), phospodiesterase inhibitors (sildenafil), and endothelin-1 antagonists (bosentan) are often used in combination therapy. Most liver transplant centers do not transplant patients with an mPAP greater than 50 mm Hg or a PVR greater than 240 dyne/sec/cm^{-5}; however, 5-year survival is 14% without treatment, 45% with medical management, and 65% for those who had an OLT following pretreatment with prostacyclin (Swanson et al, 2008).

HEPATOPULMONARY SYNDROME. Hepatopulmonary syndrome (HPS) is a vascular disorder characterized by hypoxemia secondary to pulmonary capillary vasodilation in patients with liver disease. The estimated incidence in patients with cirrhosis is between 5% and 32% (Singh & Sager, 2009). The natural course of HPS is characterized by poor survival, especially in patients with a Pao_2 level of less than 50 mm Hg: median survival without liver transplantation is approximately 24 months (Schenk et al, 2002; Umeda & Kamath, 2009).

The pathologic feature of HPS is gross dilation of the pulmonary precapillary and capillary vessels (Rodriguez-Roisin & Krowka, 2008) leading to a ventilation-perfusion mismatch. The clinical symptoms are dyspnea with or without orthodeoxia (arterial oxygen desaturation while standing). The diagnosis is confirmed with arterial blood gas measurement and contrast-enhanced ECG or macroaggregated albumin lung perfusion scan. The ECG diagnostic sign is the visualization of saline bubbles in the left heart, three to six beats after the appearance of bubbles in the right heart, following the injection of agitated saline in a peripheral vein.

No effective medical therapy for HPS has been found, and liver transplantation is the only treatment. UNOS criteria consider a Pao_2 level below 60 mm Hg an indication of high priority for OLT, even if the allocation of "exception points" to patients with HPS has now become controversial (Sulieman et al, 2008). About 85% of patients who underwent OLT for HPS showed resolution or improvement of hypoxemia. Still, the mortality after liver transplantation is significantly increased in patients with HPS (Fallon et al, 2008).

Hemostasis in End-Stage Liver Disease

The liver synthesizes most of the factors involved in clot formation and, equally importantly, factors opposing clot formation or mediating its lysis. The traditional concept that patients with advanced liver disease are hypocoagulable has been challenged. The current view emphasizes complex disturbances of platelet function, procoagulant, anticoagulant, and fibrinolytic pathways that result in rebalancing of the hemostatic system (Senzolo et al, 2006). The net effect may be a hypocoagulable or hypercoagulable state with a tendency for bleeding or thromboembolism (Warnaar et al, 2008b). Understanding the hemostatic system in ESLD is essential to perioperative coagulation management and optimization of blood product transfusion practices, which are directly related to morbidity and mortality in liver transplantation (de Boer et al, 2008; Massicotte et al, 2005).

Deficiency in primary hemostasis is due to quantitative and qualitative platelet changes (Pereboom et al, 2008). Mild to moderate thrombocytopenia is common. Causes are splenomegalic platelet sequestration in portal hypertension, impaired megakaryocytopoiesis as a result of reduced production of thrombopoietin by the cirrhotic liver, folic acid deficiency in alcoholic cirrhosis or acute hepatitis C infection, and reduced platelet half-life related to autoantibodies (Lisman & Leebeek, 2007; Senzolo et al, 2006). Evidence for impaired platelet aggregation and adhesion in cirrhosis is controversial. The proposed mechanisms are complex and multifactorial, including the important role of two potent endothelium-derived platelet inhibitors, nitric oxide and prostacyclin. Contrary to this, more recent work suggests that the functional capacity of platelets in cirrhotic patients may be normal when platelet number and hematocrit are normalized (Lisman & Leebeek, 2007; Tripodi et al, 2007), suggesting that the main defect in primary hemostasis is thrombocytopenia. An important compensatory mechanism for the overall deficient platelet function in cirrhosis is an increase in endothelium-synthesized von Willebrand factor (vWf). The markedly upregulated vWf promotes adhesion of platelets to injured vasculature and seems to be more effective than plasma from healthy volunteers (Lisman & Leebeek, 2007).

Hepatocytes synthesize all procoagulant factors except vWF, which is synthesized by the endothelium. Factor VIII is synthesized by hepatocytes but also by nonhepatic sinusoidal endothelial cells. Reduced levels of coagulation factors are observed in acute and chronic liver disease. Several factors—II, VII, IX, and X—require vitamin K as an essential cofactor and exist in plasma as inactive precursors when vitamin K is deficient as a result of decreased absorption (cholestasis) or antagonism (warfarin). In acute liver failure (ALF), plasma concentrations of coagulation factors with the shortest half-life (factor VII, 4 to 6 hours; factor V, 12 hours) decrease first, followed by those with a longer half-life. An exception are factors VIII and vWf, which may be elevated in chronic and acute liver disease because of inflammatory cytokine-mediated upregulated extrahepatic production and because of relative sparing as a result of inhibition of thrombin by antithrombin III. Fibrinogen is usually well preserved, and decreased fibrinogen is a mark of advanced cirrhosis or ALF; however, even when levels are normal, fibrinogen is often functionally aberrant because of impaired fibrin polymerization and results in an abnormal thrombin time (TT) despite normal international normalized ratio (INR) and partial thromboplastin time (PTT).

The deficiency in procoagulant factors is, at least in part, offset by decreased production of anticoagulants, including proteins C and S, antithrombin III, and heparin cofactor II. Proteins C and S are vitamin K dependent and may be deficient in cholestatic disease, and although genetic deficiency of these two proteins is rare, such deficiency is found in both Budd-Chiari syndrome and portal vein thrombosis. Antithrombin III is synthesized by hepatocytes and endothelium, deficiencies are usually mild, and thromboembolic complications rare.

All proteins involved in fibrinolysis are synthesized by the liver except tissue plasminogen activator (tPA) and plasminogen activator inhibitor type 1 (PAI-1). Consequently, reduced levels of liver-synthesized factors—plasminogen, plasmin inhibitor, thrombin activatable fibrinolysis inhibitor (TAFI), and factor XIII—are found in both acute and chronic liver failure. Cirrhosis is classically associated with hyperfibrinolysis, whereas patients in ALF may have hypofibrinolysis as a result of increased production of PAI-1. The recent expert viewpoint is contrary to the traditionally held view and emphasizes that the existing in vitro evidence of hyperfibrinolysis in cirrhosis is weak (Lisman & Leebeek, 2007). Increased levels of fibrinogen degradation indicators—D-dimers, plasmin-antiplasmin and thrombin-antithrombin complexes, thrombin fragment F1+2—could be explained by their delayed clearance by the diseased liver.

Coagulation tests, such as the prothrombin time (PT) and activated partial thromboplastin time (aPTT), are used to assess the severity of synthetic dysfunction, and PT-INR is a part of the Child-Turcotte-Pugh (CTP) and Model for End-Stage Liver Disease (MELD) prognostic indexes (Ng, 2009). As tests of in vivo coagulation function, PT-INR and PTT are conceptually deficient because they measure only the procoagulant pathway and ignore the anticoagulant function. This inadequacy is best illustrated by the observation that when the (prolonged) PT is modified by including thrombomodulin to allow full activation of protein C, the thrombin generation in cirrhotic patients is close to normal (Tripodi et al, 2005). This may in part explain why PT-INR and PTT are poor predictors of bleeding in cirrhosis and in liver transplantation (Massicotte et al, 2008). Thromboelastogram (TEG; Haemoscope Corp., Niles, IL) and rotation thromboelastometry (ROTEM; Pentapharm, Munich, Germany) have the advantage of assaying whole-blood clot formation and lysis, including the platelet contribution, but these assays do not incorporate the endothelial component (see Intraoperative Monitoring, below). Importantly, these assays allow easy recognition of hypercoagulable states (Fig. 97B.1A).

Renal System

Renal failure confers increased risk of death to cirrhotic patients, both while on the transplant waiting list and after liver transplantation. Implementation of the MELD score in 2002

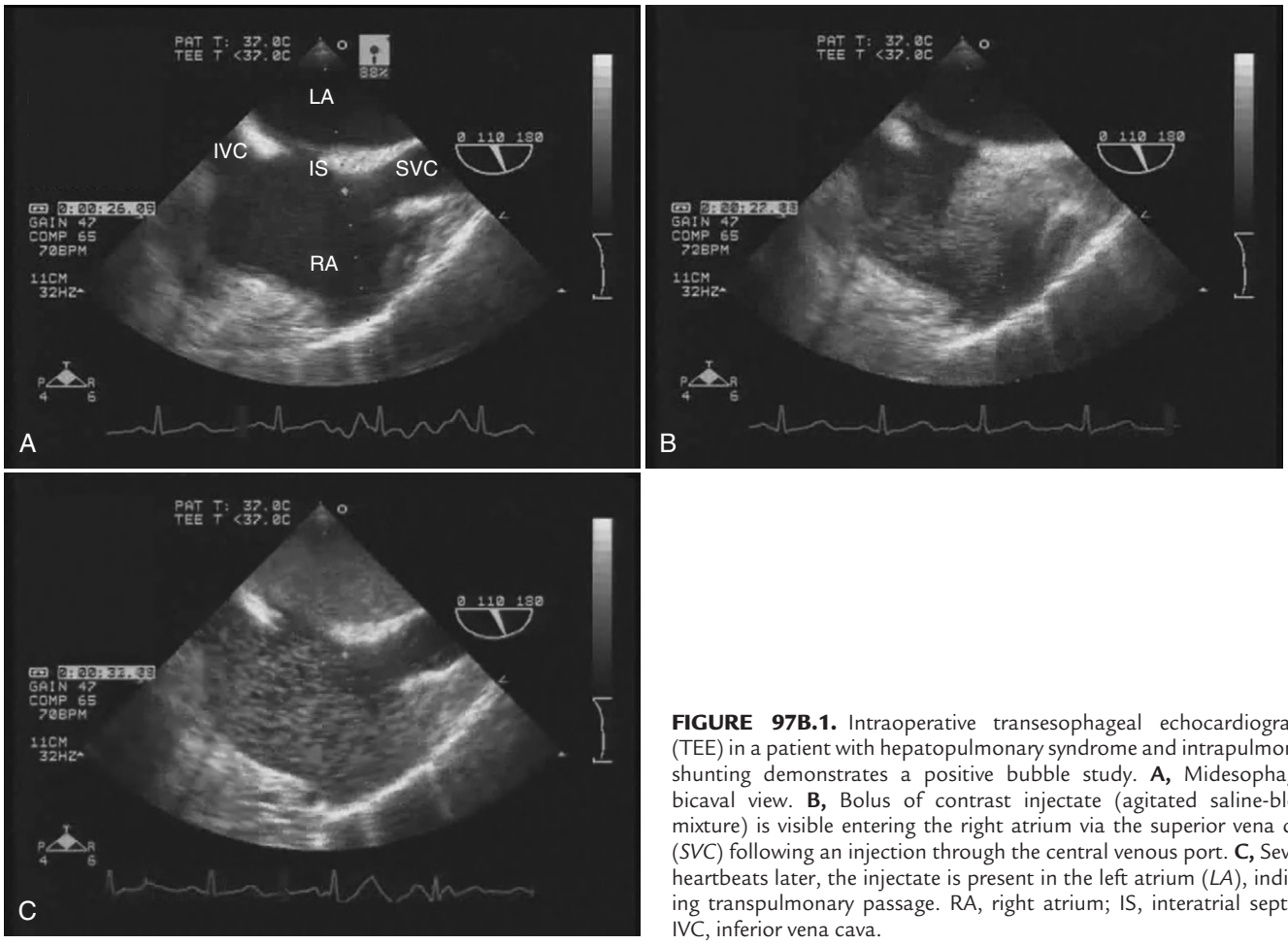


FIGURE 97B.1. Intraoperative transesophageal echocardiography (TEE) in a patient with hepatopulmonary syndrome and intrapulmonary shunting demonstrates a positive bubble study. **A,** Midesophageal bicaval view. **B,** Bolus of contrast injectate (agitated saline-blood mixture) is visible entering the right atrium via the superior vena cava (*SVC*) following an injection through the central venous port. **C,** Several heartbeats later, the injectate is present in the left atrium (*LA*), indicating transpulmonary passage. RA, right atrium; IS, interatrial septum; IVC, inferior vena cava.

(Moreau et al, 2003) has prioritized patients with renal failure waiting for a liver transplant, resulting in reduced overall mortality on the transplant list (Ojo, 2009).

Hepatorenal syndrome (HRS) is a specific type of renal failure in patients with cirrhosis, ALF, or alcoholic hepatitis. It is marked by functional renal vasoconstriction and a severe reduction in glomerular filtration rate (GFR <30 mL/min) but only minimal renal histologic abnormalities (Gines & Schrier, 2008). The primary pathophysiologic process in HRS is a circulatory disturbance: portal hypertension facilitates translocation of bacteria from the intestinal lumen into the mesenteric lymph nodes and induces production of inflammatory cytokines and local vasodilators, such as nitric oxide, carbon monoxide, and endogenous cannabinoids. Resulting splanchnic vasodilatation decreases the overall systemic vascular resistance and activates a number of compensatory mechanisms. The initial response is hyperdynamic and comprises tachycardia, increased cardiac output, low SVR, and relative hypotension.

With progression of cirrhosis, sympathetic and renin-angiotensin vasoconstrictor systems are activated that temporarily maintain arterial blood pressure, but they also cause renal vasoconstriction and hypoperfusion. Activation of nonosmotic hypersecretion of arginine vasopressin, aimed at preserving circulatory volume, results in retention of solute-free water with attendant hyponatremia, edema, and ascites. HRS is almost invariably associated with ascites and rarely develops in its absence (see Chapter 74). HRS is classified into one of two types: *HRS 1* is characterized by a rapid decline in renal function reflected in doubling of serum creatinine (SCr) to above 2.5 mg/dL over a 2-week period; this type of HRS has a particularly ominous clinical course, leading to multiorgan dysfunction that affects the heart, brain, and other organs. *HRS 2* has a more benign, slowly progressive course. It is manifested by a milder elevation of SCr (1.5 to 2.5 mg/dL) and refractory ascites. Onset of HRS is often triggered by a discrete event, such as spontaneous bacterial peritonitis, use of nonsteroidal antiinflammatory drugs (NSAIDs), or hypovolemia as a result of diuretic use, gastrointestinal (GI) bleeding, or fluid losses.

It is important to recognize that HRS may be superimposed on a chronic disease, such as glomerulonephritis as a result of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, interstitial nephritis as a side effect of certain drugs, or nephropathy resulting from diabetes or CLD. Diagnosis of HRS is of great prognostic significance: median survival for HRS 1 is 1 month; for HRS 2, it is 6 months.

Measurement of SCr remains the primary test of renal function despite its well-known limitations. By consensus, SCr above 1.5 mg/dL (133 μmol/L) defines renal insufficiency in cirrhosis (Gines & Schrier, 2008; Salerno et al, 2007). GFR and creatinine clearance are more accurate but less practical tests when repeated assessments are needed. Other tests measure serum and urinary electrolytes, fractional sodium excretion (FENa), albumin, osmolarity, sediment, and biologic markers.

Specific diagnostic tests for HRS do not exist, rather diagnosis is based on the presence of liver disease, a precipitating factor, and FENa less than 1%, signifying preserved tubular reabsorption; however, the latter test is invalidated by the use of diuretics.

General treatment measures are aimed at 1) preventing infection, in particular subacute bacterial peritonitis; 2) maintaining adequate intravascular volume; and 3) avoiding nephrotoxic agents. Circulatory volume losses, often the result of large-volume paracentesis or a GI bleed, are best treated with albumin or, if indicated, by blood products and not with crystalloids, to avoid retention of solute-free water.

The main pharmacologic approach utilizes vasoconstrictors, including a selective vasopressin V1 receptor agonist, such as terlipressin, or α-adrenergic agonists, such as norepinephrine and midodrine. Vasoconstrictors in conjunction with albumin are only modestly beneficial but are the best medical therapy currently available. Two recent studies showed a marked improvement in renal function in 40% of patients treated with terlipressin and albumin compared with controls treated with albumin alone (Martin-Liahi et al, 2008; Sanyal et al, 2008). Although the overall survival in the treatment group was not better than in the control group, the probability of 3-month survival in patients who responded with improved renal function was significantly higher (58% vs. 15%) than in nonresponders (Martin-Liahi et al, 2008); however, organ ischemia is a concerning side effect of vasoconstrictor administration.

Placement of a TIPS improves renal function and GFR and reduces sympathetic and renin-angiotensin-aldosterone axis activation in about 60% of patients (Cardenas & Gines, 2009; see Chapter 76E). TIPS is less applicable in HRS 1 as a result of severe liver disease, but it may delay progression of HRS 2 to HRS 1. No advantage in survival has been demonstrated in patients with refractory ascites treated by TIPS compared with repeated paracentesis and intravascular volume replacement with albumin.

Renal replacement therapy (RRT) offers a bridge to transplant, but the optimal RRT method in HRS and the benefit to patient outcomes are not known (Gines & Schrier, 2009). Continuous venovenous hemodialysis (CVVHD) seems to be hemodynamically the most favorable form of RRT (Davenport, 2009). CVVHD can be used to effectively control intravascular volume, pH levels, and solutes (Na, K, SCr, urea, ammonia); in addition, it corrects sodium in a time-controlled fashion, which is particularly relevant to minimize the risk of pontine demyelination in patients with hyponatremia.

Liver transplantation is the treatment of choice for patients with cirrhosis and HRS (Cardenas & Gines, 2009; see Chapter 97A). About 90% of patients with HRS recover kidney function after successful liver transplantation. The remaining 10% do not recover their kidney function and require prolonged RRT and eventual kidney transplantation. When the cause of renal failure in cirrhosis is HRS, the best predictor of need for a combined liver-kidney transplant is pretransplantation RRT for longer than 8 weeks.

Central Nervous System

Hepatic encephalopathy (HE) is a progressive but potentially reversible metabolic disorder of the central nervous system (CNS), and it is associated with variable degrees of brain edema. HE is an overt manifestation of cirrhosis in up to 45% of patients, and it is a defining sign and main cause of death in ALF (Eroglu et al, 2009). The World Congress of Gastroenterology recognizes three classifications of HE based on the etiology (Ferenci et al, 2002): *type A* is associated with ALF, *type B* with TIPS, and *type C* with cirrhosis. Based on the severity of neurologic impairment, HE ranges from normal (grade 0) to mildly impaired cognitive and neuromuscular function (grade 1), progressive lethargy (grade 2), confusion with muscle rigidity or clonus (grade 3), to coma and brain death (grade 4). Although presence and severity of HE has prognostic and therapeutic significance in cirrhosis and ALF, it is not a part of the MELD score.

The pathophysiology of HE is complex and incompletely understood. Multiple putative mediators have been implicated that include ammonia, endogenous benzodiazepine-like or γ-aminobutyric acidlike agonists, reactive oxygen species, inflammatory cytokines, hyponatremia, and manganese. The exact pathogenesis of cerebral edema remains controversial, but good evidence supports the role of ammonia, which promotes astrocyte and neuron swelling by increasing intracellular glutamine content. Transported to the mitochondria, glutamine contributes to production of reactive oxygen species and activation of mitochondrial transition permeability pore and various kinases, resulting in cellular swelling. Increased ammonia levels have been shown to alter cerebral blood flow and brain glucose utilization (Bjerring et al, 2009; Sundaram et al, 2009). High arterial and brain levels of ammonia in ALF correlate well with cerebral edema and increased ICP, with consequent high risk of mortality from brain herniation and hypoxia (Wendon et al, 2008).

HE in cirrhosis features slow onset, a progressive course, and only partial responsiveness to therapy. Significant cerebral edema typically does not develop, and a precipitating event—such as infection, excessive dietary protein, dehydration, or GI bleeding—can be often identified. TIPS is a known risk factor and is associated with 30% of new or worsening encephalopathy (see Chapter 76E). In addition to correction of any precipitating factors, treatment includes nonabsorbable disaccharides, which reduce the intestinal production and absorption of ammonia; antibiotics that target urease-producing bacteria; ornithine and acarbose; benzodiazepine receptor antagonists; and probiotics.

The hallmarks of HE in ALF are cerebral edema and increased intracranial pressure (ICP). Both are life-threatening complications of grade 3 and 4 encephalopathy. Treatment includes a number of general and specific interventions (Table 97B.1) aimed at promoting cerebral perfusion pressure (CPP) above 60 mm Hg; this is achieved by maintaining mean arterial pressure (MAP) and reducing ICP to below 20 to 25 mm Hg by reducing brain edema. Grade 3 or 4 HE requires endotracheal intubation for airway protection. Mild hyperventilation temporarily relieves brain hyperemia, but prolonged hyperventilation is not beneficial and may cause CNS ischemia. Mannitol is effective in reducing ICP in the short term, but its prophylactic use is not recommended. Recent evidence demonstrates that N-acetylcysteine treatment may also prolong transplant-free survival in ALF unrelated to paracetamol/acetaminophen toxicity (Lee et al, 2007).

The role of ICP monitoring is controversial, as ICP monitor placement is associated with high risk of bleeding in this patient population, and no data exist to support its role in improving patient outcomes. The Acute Liver Failure Study Group recommends this intervention only for liver transplant candidates but

Table 97B.1

Management of Encephalopathy and Elevated Intracranial Pressure in Acute Liver Failure

General Measures	Specific Interventions
Head elevation to 30 degrees	Endotracheal intubation for grades 3 and 4 hepatic encephalopathy
Judicious (restrictive) fluid management	Hyperventilation: limited, temporary benefit
Judicious if any sedation	N-acetylcysteine: benefits all causes of acute liver failure
Cerebral perfusion pressure >60 mm Hg	Renal replacement therapy: CVVHD
Osmotic diuresis, hypertonic saline	ICP monitoring (>10% bleed); transcranial Doppler
Empiric: antibiotics, disaccharides	Hypothermia: mild, bridge to transplantation

CVVHD, continuous venovenous hemodialysis; ICP, intracranial pressure

recognizes regional practice differences (Stravitz et al, 2007). An attractive, noninvasive alternative to ICP monitors is transcranial Doppler (TCD) sonography. By measuring blood flow velocities in middle and anterior cerebral arteries and calculating resistance and pulsatility indexes, TCD allows serial estimates of cerebral blood flow in the setting of impaired autoregulation and developing brain edema (Bhatia & Gupta, 2007). In a small series of ALF patients, confirmation of adequate cerebral blood flow by TCD was successfully used as a basis to proceed with OLT (Bindi et al, 2008). Intraoperative use of TCD in OLT has not been reported.

Mild to moderate hypothermia (32° C to 35° C) is an emerging therapeutic modality. Hypothermia reduces brain ammonia and cytokine levels and in part restores cerebrovascular autoregulation and brain glucose metabolism. Although experimental evidence provides a strong rationale, only limited clinical data on efficacy and safety of hypothermia in humans in ALF are available, and future studies are warranted (Stravitz et al, 2009).

INTRAOPERATIVE MONITORING

Hemodynamic Management

Hemodynamic management is a cornerstone in the perioperative care of liver transplant patients, but no consensus has been reached on the standards of hemodynamic monitoring (Claus-Georg & De Wolf, 2008). Continuous invasive arterial pressure monitoring may be the only ubiquitously used hemodynamic monitor in liver transplantation. When measured at the most common site, the radial artery, peripheral arterial pressure may underestimate the true aortic pressure, particularly during periods of hypotension. A femoral arterial line reflects central aortic pressure with higher fidelity and consistently records higher systolic pressures than the radial artery. The difference between the femoral and the arterial pressure waveform is particularly pronounced after graft reperfusion or when high doses of vasopressors are used (De Wolf, 2006; Shin et al, 2007). Because of this discrepancy, and because of the need for frequent arterial blood sampling, some centers routinely use both femoral and radial arterial lines.

The pulmonary artery catheter (PAC, see Chapter 22) has long been the mainstay of hemodynamic monitoring in liver transplantation (De Wolf et al, 1993); however, the clinical utility of PACs has recently been questioned because of criticisms that its invasiveness is not justified by improved outcomes (Sandham et al, 2003; Wheeler et al, 2006) and that measured pressures are not good estimates of ventricular preload (Kumar et al, 2004). Although a number of less invasive technologies have emerged, resulting in a decrease in their use, PACs are still advocated by many for OLT (Della Rocca et al, 2008; De Wolf, 2008; Pinsky, 2006), and the ability of PACs to continuously display pulmonary artery pressures is particularly advantageous when managing patients with portopulmonary hypertension. Transesophageal echocardiography (TEE) provides different but complementary information to that provided by PACs (see below), and concurrent use of both devices is considered superior (De Wolf & Aggarwal, 2008). A notable shortcoming of PACs in OLT is the inaccuracy of thermodilution cardiac output in the period following liver reperfusion because of postreperfusion hypothermia and subsequent instability of central temperature.

Newer, less invasive hemodynamic monitors for OLT have been introduced. The PiCCO system (Pulsion Medical Systems, Munich, Germany) combines transpulmonary thermodilution and arterial pressure contour analysis, and it provides continuous cardiac output in alignment with PAC thermodilution and a number of indices of preload that include global end-diastolic volume (GEDV) and intrathoracic blood volume (ITBV), which agree better with cardiac index than filling pressures (Della Rocca et al, 2002a, 2002b). PiCCO requires central venous and femoral or brachial arterial access, which arguably is not much less invasive than the PAC. The LiDCO device (LiDCO Group, London, UK) estimates cardiac output based on the peripheral arterial pressure waveform pulse power analysis after a lithium dilution calibration, and it has been used successfully in patients recovering from liver transplantation in the ICU (Costa et al, 2008). A device that estimates cardiac output based on the arterial pressure waveform without need for calibration, Flo-Trac/Vigileo (Edwards Lifesciences, Irvine, CA), did not perform well intraoperatively during OLT (Biais et al, 2008; Biancofiore et al, 2009).

The accuracy of all arterial pressure–based cardiac output monitors depends critically on accurate determination of arterial compliance, which changes rapidly in liver transplantation, particularly at reperfusion or clamping of major vessels; and because it cannot be readily measured, the assumed value of vascular compliance used in the algorithms of the devices to calculate cardiac output may lead to inaccurate calculations. The inaccuracy may be mitigated by repeated calibrations with the LiDCO or PiCCO.

Cardiac output determined by a novel suprasternal ultrasound cardiac output monitor (USCOM Pty, Coffs Harbour, Australia) correlates well with the PAC cardiac output (Wong et al, 2008; Su et al, 2008). Other USCOM measurements, such as Doppler estimation of peripheral artery pressures and left ventricular contractility, remain to be validated.

TEE has been gaining more popularity in liver transplantation (Burtenshaw & Isaac, 2006). Data from 2002 estimated use of TEE in only 21% of high-volume centers in the United States (Schuman, 2003), but a more recent survey showed that 86% of anesthesiologists in 40 large-volume U.S. centers use TEE in some or all liver transplantations (Wax et al, 2008).

The main advantages of TEE are that it provides continuous, real-time visualization of cardiac structures and dynamic function. TEE is a superior modality for estimating ventricular volume status, global LV contractility and ejection fraction, right ventricular function, segmental wall motion abnormalities, and septal motion. Doppler modalities allow for interrogation of transvalvular flows, dynamic left ventricular outflow obstruction, intracardiac shunts, and diastolic function. In addition, TEE is the only intraoperative monitor that allows an instantaneous diagnosis of pulmonary or intracardiac thrombus (Ellenberger et al, 2006; Planinsic et al, 2004) and pericardial or pleural effusion. TEE detection of a transpulmonary shunt as a positive bubble test in a patient with HPS is presented in Figure 97B.1.

Dynamic monitoring of the right ventricular function and detection of right ventricular failure are critically important in managing patients with portopulmonary hypertension, particularly during reperfusion. Assessment of right ventricular volume and contractility, severity of tricuspid regurgitation, and measurement of lows in the inferior vena cava (IVC) may help guide volume, inotrope, and pulmonary vasodilator therapy.

In addition to requiring significant training and resources, TEE has several important disadvantages. An obvious concern in the liver transplant patient population is the risk of rupture of gastroesophageal varices. Although this complication is very rare, it does emphasize the need for careful risk/benefit assessment of this monitoring modality in each individual recipient. It is prudent to withdraw the TEE probe from the stomach during surgical gastric retraction, making transgastric views inaccessible during most of the procedure. Another disadvantage is that TEE is not adept at providing and trending traditional numerical data (e.g., cardiac output), which are readily provided by the PAC. Visual assessments used in TEE are also highly operator dependent. Finally, unlike the PAC, the TEE probe is typically removed at the end of surgery; therefore the continuity of monitoring is interrupted, and the transfer of specific parameters of hemodynamic management to the postoperative ICU is difficult. This problem may be mitigated by the introduction of less expensive, disposable TEE probes.

Monitoring of Hemostasis

Conventional tests of hemostasis, PT and aPTT, have several important limitations (Dalmau et al, 2009; Ng et al, 2009). First, these assays utilize plasma samples devoid of platelets. The activated platelet surface, the naturally occurring medium of the in vivo coagulation, is replaced by addition of phospholipids. The contribution of platelets is thus not considered by these tests. Second, PT and PTT measure only the activity of procoagulant factors and do not take into account the anticoagulant factors. When PT is modified to include anticoagulant factors, thrombin generation in cirrhotic patients is not different from normal controls (Tripodi et al, 2005). The reported higher intralaboratory variability of INR than of PT may be of more relevance for MELD score determination than for acute intraoperative management (Lisman & Leebeek, 2007).

An important shortcoming of the conventional PT and PTT is a long turnaround time, typically about 45 minutes—suboptimal for an ongoing transplant surgery. Point-of-care (POC) assays require only a minimal delay between blood sampling and attaining the results of the test. POC assays of PT and PPT are quick (5 to 15 minutes), cartridge-type, whole-blood tests offered by several manufacturers. An acceptable agreement of such assays with corresponding plasma-based tests has been reported in OLT (Herbstreit et al, 2010), suggesting that the POC tests can effectively replace the slower, conventional testing.

Activated clotting time (ACT) was developed for POC monitoring of high-dose unfractionated heparin therapy, and it should be a part of the POC battery; with reperfusion of the graft, a massive dose of unfractionated heparin is flushed into the circulation. In conjunction with other POC tests, ACT may help guide the use and dosing of protamine.

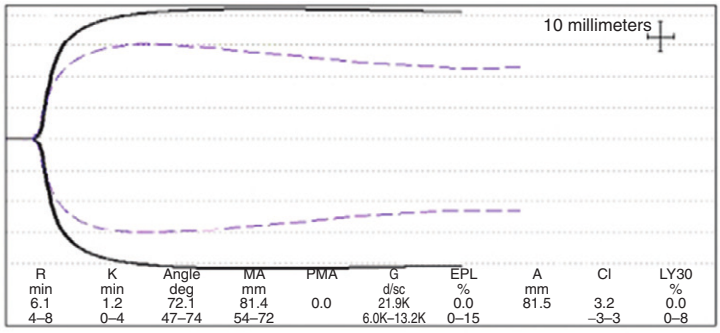
TEG and ROTEM are POC assays that measure viscoelastic properties of whole-blood clot formation and lysis. Both technologies have been used to drive transfusion algorithms (Kang et al, 1985; Coakley et al, 2006). TEG measures time to onset of clot, rate of clot formation, clot tensile strength, and rate of clot lysis (Fig. 97B.2). Treatment of samples with an intrinsic pathway activator, kaolin, shortens clot formation, whereas addition of heparinase dissects the effects of exogenous heparin from intrinsic heparinoids. TEG results are available more rapidly than the conventional laboratory tests. In our institution, progress of TEG clot formation and lysis is displayed on a dedicated operating room monitor and is available to the anesthesiologist in real time.

ROTEM generates a similar trace to that of TEG, although a ROTEM assay may be modified by a heparinase reagent (hep-TEM), an intrinsic pathway activator (in-TEM), and a tissue-factor activator (ex-TEM). In addition, ROTEM includes a qualitative test of fibrinogen activation and fibrin polymerization (fib-TEM), which is based on adding a blocker of platelet function. ROTEM is very useful in determination of poor tensile clot strength as a result of combined platelet and fibrinogen deficiency, and it is the most reliable method for detecting hypofibrinogenemia or dysfibrinogenemia, both common in liver disease (Kalina et al, 2008).

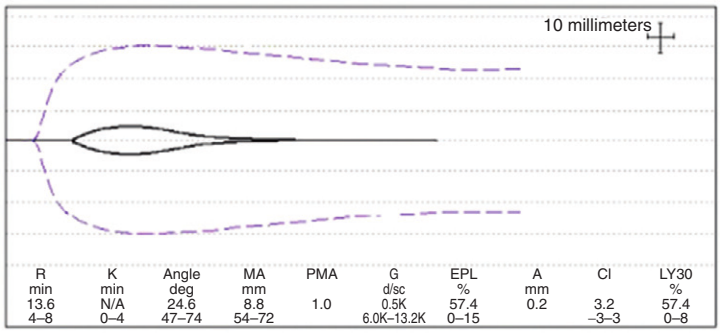
Both TEG and ROTEM are quick and superior monitors of hypercoagulability, fibrinolysis, and therapeutic effects of antifibrinolytics. The main conceptual deficiency of the two monitors is the inability to evaluate endothelial function. It is worth emphasizing that although both instruments plot clot formation in a similar fashion, TEG and ROTEM do not generate the same results when analyzing blood without exogenous activation, therefore they are not interchangeable (Coakley et al, 2006; Nielsen, 2007).

Monitoring and management of hemostasis remain great challenges of OLT, and it has been well established that blood loss and blood product transfusion are an important cause of morbidity and mortality (de Boer et al, 2008; Massicotte et al, 2005; Ramos et al, 2003). Adherence to an algorithm-driven transfusion practice may reduce unnecessary perioperative blood and blood-component transfusion (Avidan et al, 2004; Kang, 1997; Kang et al, 1985), but no consensus has been reached on what constitutes standard intraoperative monitoring of hemostasis or a standard hemostatic intervention.

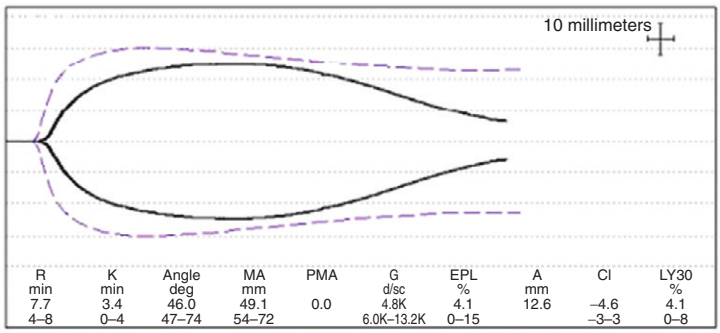
Difficulties stem from the incomplete understanding of complex coagulation abnormalities in liver disease and OLT and from the limitations of currently available tests to emulate the in vivo conditions. For example, preoperative coagulation tests do not predict intraoperative bleeding (Massicotte et al, 2004; Steib et al, 2001), and transfusion requirements are



A



B



C

FIGURE 97B.2. Intraoperative thromboelastogram (TEG) recordings from three orthotopic liver transplantation patients with different hemostatic derangements. In each panel, a "normal" TEG trace, generated by the instrument, is presented with an interrupted line. **A,** Hypercoagulable state in a patient with primary biliary cirrhosis. **B,** Postreperfusion TEG shows profoundly suppressed clot formation and marked fibrinolysis. **C,** Mild hypocoagulability and fibrinolysis in a patient with hepatitis C.

actually lower when abnormal coagulation test results do not lead to routine correction by infusion of fresh frozen plasma (FFP) and other blood products (de Boer et al, 2005). Finally, bleeding in OLT is often related to factors other than coagulopathy. These findings emphasize the need for careful interpretation of coagulation tests within the clinical context rather than relying on interventions formulated solely on the basis of test results.

Metabolic Monitoring

Glucose Control

ESLD is associated with impaired glucose control, and hypoglycemia is common in ALF, whereas peripheral insulin resistance and metabolic syndrome are common in CLD. Factors that contribute to acute intraoperative hyperglycemia are routine administration of steroids and postoperative immunosuppressants and response to surgical stress. Two retrospective studies have shown association of a higher incidence of infections and 1-year mortality with poor perioperative glucose control (Ammori et al, 2007; Park et al, 2009). These studies, in general agreement with other perioperative outcome studies, emphasize the need for close POC perioperative monitoring and management of blood glucose levels, but the exact target range is unknown.

Electrolytes

Electrolyte monitoring is done as POC testing, usually on an hourly basis and when indicated, such as to optimize electrolyte balance immediately before graft reperfusion. Hyperkalemia is ominous and may cause fatal arrhythmias, particularly after reperfusion. Independent predictors of hyperkalemia are the number of red blood cells (RBCs) transfused and higher initial values, especially in acidemic patients with renal insufficiency (Naksuji & Bookallil, 2000). Ionized calcium levels predictably decrease with blood product and albumin administration. Low serum sodium is a hallmark of advanced cirrhosis and an independent predictor of mortality on the transplant waiting list (Kim et al, 2008; Yun et al, 2009), and intraoperative sodium levels are elevated by administration of normal saline-based



FIGURE 97B.3. A two-lead intraoperative electrocardiogram (*ECG*) recorded on the operating room monitor shortly after reperfusion, shows profound bradycardia and tall T waves. Such changes are not uncommon in the period immediately following graft reperfusion.

fluids and particularly by sodium bicarbonate; in addition, rapid correction of serum sodium levels may cause pontine demyelination (Zhang et al, 2009).

Temperature Monitoring

Monitoring of temperature is usually achieved via a PAC or an esophageal probe. Surprisingly little has been reported on temperature management in OLT, considering the fact that hypothermia is a key sign of liver failure and a significant problem during surgery. Well-known detrimental effects of hypothermia include impaired wound healing and impaired coagulation. An acute decrease in central temperature results from the cold perfusate returning to the heart following graft reperfusion. This precipitous hypothermia contributes to postreperfusion hemodynamic instability and bradyarrhythmias that may progress to cardiac arrest (Fig. 97B.3). The hypothermic insult can be partially mitigated by achieving upper-limit normothermia in the prereperfusion period, thus the value of continuous temperature monitoring and measures to assure normothermia cannot be overemphasized. A special circumstance is deliberate mild hypothermia, which acts by decreasing brain metabolism and mediators of oxidative stress; thus mild hypothermia is an accepted treatment of increased intracranial pressure in ALF (Stravitz & Larsen, 2009).

INTRAOPERATIVE MANAGEMENT

Ventilatory Management

Mechanical ventilation should optimize respiratory gas exchange and maintain lung volumes and capacities to facilitate early postoperative extubation. Preexisting respiratory comorbidities, such as hydrothorax, have to be considered in setting the ventilatory parameters. Although not much is reported about the ventilator setting in OLT, it seems reasonable to adopt a protective ventilatory strategy and to avoid high airway peak pressures (below 30 to 35 cm H_2O). Tidal volume of 6 to 8 mL/kg are a reasonable initial setting (Slinger, 2008; Shultz, 2008), but tidal volumes of least 8 mL/kg are necessary for reliable pulse pressure variation (PPV) or stroke volume variation (SVV) monitoring (Michard, 2005).

Multiple factors can cause increased pulmonary capillary permeability and predispose the lungs to interstitial edema. Positive end-expiratory pressure (PEEP) is a rational tool to prevent lung edema, and a PEEP of up to 10 mm Hg has been proven safe in maintaining hemodynamics and graft perfusion after cadaveric and living-donor liver transplant (LDLT) (Saner et al, 2006a, 2006b; 2008). Fio_2 can be increased to modulate pulmonary resistance in case of pulmonary hypertension. It is not known whether high intraoperative values of inspiratory fraction of oxygen may have a role in modulating ischemia-reperfusion injury after reperfusion (Kabon & Kurz, 2006).

Intraoperative Hemodynamic, Fluid, and Transfusion Management

Hemodynamic management of fluids and blood-product transfusions are critically interconnected and should be considered together. Excessive fluid administration may result in increased pressure in the IVC, portal vein, and collateral veins, possibly contributing to blood loss during liver dissection, hemodilution of coagulation factors and platelets, and tissue edema (see Chapter 22; Westercamp et al, 2009). Conversely, inadequate intravascular volume repletion may result in hemodynamic instability and organ hypoperfusion.

Better understanding of pathophysiology in ESLD, improvement in surgical and anesthetic techniques, and availability of POC laboratories have resulted in marked reductions in blood-product administration, including those for transplantations without transfusion. This is of great significance, as reduced blood-product transfusion is associated with better long-term outcomes (Bennett-Guerrero et al, 2001; Massicotte et al, 2007; Pereboom et al, 2009).

A strategy of maintaining low central venous pressure (CVP ≤5 mm Hg) through restrictive fluid administration and phlebotomy has been advocated by Massicotte and colleagues (2006) as an effective and safe strategy for transfusion-free OLT (see Chapter 22). In contrast, Schroeder and colleagues (2004) reported increased mortality and renal failure associated with low-CVP management. Whereas the low-CVP strategy may be possible in select patients with normal kidney function and good cardiovascular reserve, targeting one specific low CVP (i.e., 5 mm Hg) may not be physiologically advantageous in patients with poor ventricular compliance and preexisting renal dysfunction.

A low-CVP regimen usually requires vasopressor administration to maintain arterial blood pressures (Ponnudurai et al, 2005; Schroeder et al, 2004) but with the possible side effect of end-organ hypoperfusion. As CVP is not a reliable index of preload, volumetric assessment with TEE or fluid-responsiveness indexes (dPP or SVV) may be a more physiologic approach to guide fluid management (Biais et al, 2008; Della Rocca, 2009). Fluid management strategy and interpretation of CVP values may vary based on the surgical technique; for example, during a complete IVC clamp, blood is sequestered below the clamp, and low CVP does not accurately reflect volume status. After unclamping of the IVC and portal vein, the CVP increases rapidly and may abolish the pressure gradient between the portal vein and the right atrium and thereby compromise liver perfusion. Hemodynamic changes during a piggyback technique rarely reach such magnitude.

Hypotension is common during all phases of OLT, but little is reported on the impact of intraoperative hypotension on long-term patient outcomes. Reich and colleagues (2003) reported the worst surgical outcomes early after liver transplantation in patients who had at least one episode of arterial hypotension with an MAP below 40 mm Hg.

Little evidence is available to provide guidance regarding the choice of intraoperative vasopressors. Agents are chosen based on their pharmacologic properties and side effects (Zhang et al, 2005). Commonly used agents are neosynephrine, norepinephrine, vasopressin, and dopamine. Of note, vasopressin 1 receptors and α_1-adrenergic agonists are useful in preserving renal function in HRS (Gines & Schrier, 2009); vasopressin reduces splanchnic blood flow, which may reduce bleeding from portal

collaterals during the dissection phase but may also impede portal vein flow during the neohepatic phase (Wagener et al, 2008).

Most centers use a combination of crystalloids and colloids for fluid replacement. A recent study showed that use of new-generation hetastarch (HES 130/0.4) may be a safe alternative to conventionally used 5% albumin (Mukhtar et al, 2009), but more studies are needed.

Severe pulmonary hypertension (PVR >240 dynes/sec/cm^{-5}) is associated with high perioperative mortality and is a contraindication for proceeding with liver transplant. In moderate PPHTN with preserved right ventricular function, the goal of intraoperative management is to lower pulmonary vascular resistance and promote myocardial contractility. General measures include increasing Fio_2, avoidance of hypercapnia and acidosis, and administration of nitrous oxide. Selective pulmonary vasodilators, inhaled nitric oxide, and prostacyclin are superior to intravenous vasodilators, which may cause systemic hypotension and compromise right-heart perfusion and preload. Milrinone and dobutamine are used as inotropes and pulmonary vasodilators but with caution, as they also cause systemic hypotension. Pulmonary pressure management is particularly challenging in the postreperfusion period, and pulmonary vasodilators are weaned gradually to avoid rebound pulmonary hypertension. Extubation should be delayed if inhalational vasodilators agents are needed (Mandell, 2004; Teo & Greenhalg, 2010).

With implementation of the MELD scoring system, more patients with renal insufficiency are being treated with OLT. Renal failure is associated with increased short- and long-term mortality after OLT, and perioperative renal failure often requires postoperative RRT. Intraoperative renal protection strategy is based on the maintenance of adequate intravascular volume and renal perfusion. No specific intraoperative renoprotective agents have been proven effective, but it is reasonable to maintain perfusion pressure with vasopressin and adrenergic agonists, which are effective in management of HRS. Surgical techniques that preserve vena caval flow, such as a piggyback technique, favor better renal outcomes. Intraoperative RRT is feasible and has been proven safe and successful in maintaining electrolyte and fluid balance (Ramsay & Garcia-Valdecasas, 2009; Townsend et al, 2009), although many transplant units try to avoid the need for it during the course of an OLT if at all possible. New markers of renal injury, such as neutrophil gelatinase–associated lipocalin, may be more useful than SCr in assessing acute kidney injury (AKI) (Niemann et al, 2009). The prognostic value of this rapid assay may prove useful in future studies to confirm the validity of intraoperative renoprotective strategies.

The administration of RBCs, FFP, and platelets has been associated with increased mortality (Bennett-Guerrero et al, 2001; de Boer et al, 2008; Massicotte et al, 2005; Pereboom et al, 2008; Ramos et al, 2003). Average blood-product requirements have decreased dramatically over the past decade, and now OLT can often be performed without transfusion (De Boer et al, 2005; Ozier & Tsou, 2008). Although it would be useful to prospectively identify patients at high risk of major bleeding, factors predictive of higher transfusion requirements are still debatable. Low pretransplant hemoglobin and a MELD score higher than 30 are better established predictors than previous abdominal surgery, prolonged INR, and low platelet counts (Massicotte et al, 2009; Ozier & Tsou, 2008; Xia et al, 2006).

No thresholds have been universally accepted for transfusing RBCs, FFP, and platelets, and practice differs among various centers and clinicians. POC testing, including TEG and ROTEM, have been used to define transfusion algorithms (see Monitoring of Hemostasis above).

The selective use of antifibrinolytic agents in the presence of persistent fibrinolysis is indicated, but routine prophylactic use of these agents is controversial. Aprotinin and tranexamic acid have been shown to reduce transfusion requirements in high-risk patients (Dalmau et al, 2000; Molenaar et al, 2007). Based on several case reports focused on the association of antifibrinolytics with vascular thrombosis (Dalmau et al, 2000; O'Connor et al, 2000) of either the arterial or venous circulation, and considering the current low transfusion rate, we question the validity of an indiscriminate prophylactic treatment in the absence of clinical and laboratory signs of hyperfibrinolysis. A recent meta-analysis (Molenaar et al, 2007) and a retrospective study of aprotinin by the same group (Warnaar et al, 2009) did not provide evidence for an increased risk of thromboembolic events associated with antifibrinolytic drugs in liver transplantation. It should be emphasized that in both of these studies, trends were observed that suggested a possible association between antifibrinolytics and thrombosis that did not reach statistical significance, perhaps because of the limited number of subjected enrolled and other confounding factors.

No consensus exists regarding the choice of any specific antifibrinolytic agent, dose, or time of administration; therefore monitoring of fibrinolysis and early detection of hypercoagulability are of critical importance. The prevailing view is that TEG/ROTEM may best provide such information, and TEE may be useful for detection of intracardiac clots adhering to the central lines. Use of activated factor VII as a prophylactic treatment has not been proven advantageous in a liver transplant setting, but it has been used successfully as a rescue treatment in a few individual cases (da Silva Viana, 2006). Cryoprecipitate, a source of factors I and VIIIc and of vWF, and prothrombin complex concentrates that contain vitamin K–dependent factors II, VII, IX, and X are increasingly used as an alternative to FFP. The advantage of these products over FFP is that a smaller volume is required, and risk of infectious complications is reduced (Ofosu et al, 2008; Samama et al, 2008).

CRITICAL INTRAOPERATIVE EVENTS

Postreperfusion Syndrome and Refractory Hypotension

Postreperfusion syndrome (PRS), first described by Aggarwal and colleagues in 1987, was originally defined as a decrease in systemic arterial pressure to less than 70% of the prereperfusion value or a mean blood pressure (BP) below 60 mm Hg within 5 minutes of liver reperfusion and lasting at least 1 minute. The low systemic BP was associated with an increase in PVR and central pressures and occasionally with bradycardia, which could progress to asystole (Aggarawal et al, 1993). Other authors proposed similar definitions based on hemodynamics (Ayanoglu et al, 2003; Chui et al, 2000; Nanashima et al, 2001; Paugam-Burtz et al, 2009), and one proposed an expanded concept that, in addition to unstable hemodynamics, included postreperfusion fibrinolysis that required administration of antifibrinlolytics (Hilmi et al, 2008). Depending upon the reporting center, significant PRS is evident in 25% to 55% of patients, an acknowledgment that the incidence depends on the definition. In a significant percentage of patients undergoing liver transplant, reperfusion can be complicated by

bradycardia that is resistant to chronotropic agents and asystole that requires cardiopulmonary resuscitation.

The mechanisms behind bradycardia and reperfusion syndrome are not yet fully understood. Several possible factors have been indicated, such as the release of vasoactive substances from the liver graft or the recipient gut—potassium, acids, prostanoids, bradykinin, interleukins—along with hypovolemia, hypothermia, or small air or thrombotic emboli (Chui et al, 2000; Ricciardi et al, 2002). In a multivariable logistic regression analysis, Paugam-Burtz and colleagues (2009) found that absence of portocaval shunt and duration of cold-ischemia time were independent predictors of PRS.

PRS is associated with adverse outcomes, including an increase in blood loss with an attendant increase in blood-product requirements, higher incidence of postoperative allograft loss, kidney failure, and early mortality (Paugam-Burtz et al, 2009; Ramsay, 2008). No universally accepted preventative strategies have been developed, but common interventions include pretreatment with chronotropic and vasoconstrictor agents and optimization of temperature, pH, and electrolytes. The occurrence of ischemia-reperfusion injury is well recognized, but its exact relevance to PRS is not fully understood. Therapeutic approaches that use nitric oxide, prostaglandin E_1 and various antioxidants aimed at mitigating the inflammatory response and cellular cascade triggered by the ischemia-reperfusion are undergoing clinical evaluation (Ramsay, 2008). Methylene blue has been reported in treatment of refractory hypotension after reperfusion, but its effectiveness has not been confirmed in larger studies (Cao et al, 2009; Fischer et al, 2010).

Pulmonary Embolism

Pulmonary air and thromboembolism are rare but potentially fatal complications of OLT. With air embolism, a simultaneous laceration of a large vein, such as the IVC or hepatic veins, and a low CVP allow active entrainment of air into the central circulation; in addition, partial disconnection of the venovenous bypass circuit can also lead to air entrapment in the central circulation.

Intravascular clotting may manifest with pulmonary embolism, and intracardiac thrombi may occur with or without venous thrombosis and are frequently adherent to central venous lines. The mechanism of intravascular clotting in OLT patients is not fully understood. Some ESLD diagnoses, such as primary biliary cirrhosis or primary sclerosing cholangitis, are associated with hypercoagulability. In other cases, intravascular clotting has been related to administration of antifibrinolytics or transfusion of blood products (Warnaar et al, 2008a). Use of aprotinin in patients undergoing OLT may be associated with an increased incidence of venous thrombosis (Warnaar et al, 2009). Still, in a single-center case series, four episodes of PE were reported in the absence of antifibrinolytic use (Lerner et al, 2005).

Paradoxical embolus is a possible complication when an anatomic or functional atrial septum defect is present. Such complication is more likely to happen in pediatric recipients and in the early postreperfusion period, when right artery pressure is often higher than left artery pressure. During the pretransplant evaluation of pediatric patients, it is worthwhile to rule out such a defect or to plan for an atrial septal defect percutaneous closure when the defect size is significant and unlikely to heal before the transplant date.

In a recent single-center series, reported incidence of pulmonary embolism was 3.3% (El-Baghdadi & Sakai, 2010); however, very high overall and intraoperative mortality were reported in a recent review focused on pulmonary embolism in an OLT setting (Warnaar et al, 2008a): hospital mortality was 68%, and intraoperative mortality rate 82%.

The most common initial indication of intraoperative pulmonary embolism is usually systemic hypotension with a simultaneous increase in pulmonary pressure (Ellenberger et al, 2006; Warnaar et al, 2008a). End-tidal CO_2 may also decrease. A reasonable preventive strategy is based on prompt identification of hypercoagulable conditions with TEG/ROTEM and avoidance of unnecessary prophylactic administration of antifibrinolytics (Planinsic et al, 2006). TEE can be a diagnostic tool, but its role as a preventive tool is less clear. Treatment is based on hemodynamic support, and successful intraoperative administration of recombinant tissue plasminogen activator has been reported (Jackson et al, 2006).

SPECIAL SITUATIONS

Acute Liver Failure

Acute liver failure is defined as a severe liver dysfunction causing encephalopathy and coagulopathy (INR >1.5) within 24 weeks of the onset of symptoms in patients without previous liver disease (see Chapters 72 and 97C); it is considered *fulminant ALF* if it develops in less than 2 weeks. Overall transplant-free survival in ALF is dependent on etiology and is just above 40%; it is highest for acetaminophen/paracetamol overdose, which requires transplantation in less than 10% of patients (Trotter, 2009). Liver transplantation is the only proven therapeutic intervention in advanced ALF, accounting for just over 5% of all liver transplantations, and carries a 1-year survival of 60% to 80% (De Gasperi et al, 2008; Trotter, 2009; see Chapter 97C).

Increased ICP and severe coagulopathy are the hallmarks of ALF and are also the main perioperative challenges. As cerebral edema is the most common cause of death in ALF, control of intracranial hypertension and maintenance of adequate cerebral perfusion pressure (CPP) are critical intraoperative tasks. Widely accepted minimal goals are ICP of less than 25 mm Hg and CPP of 50 to 60 mm Hg or higher. Continuous invasive monitoring of ICP is ideal for guiding management, but it is associated with a high risk of bleeding.

ICP typically arises during the dissection phase and peaks after reperfusion. A simultaneous and precipitous drop in MAP makes postreperfusion the most critical and challenging period for management of CPP. A protocol that included intraparenchymal ICP monitoring, maintenance of CPP greater than 60 mm Hg by administration of vasopressors, hyperventilation (P_{CO_2} at 30 to 35 mm Hg), mannitol and 3% saline, mild hypothermia (33° to 34° C), and a high dose of pentobarbital titrated to ICP effect resulted in favorable neurologic outcomes in a small series of ICU and liver transplant patients (Raschke et al, 2008).

No randomized trials or consensus statements are available that stipulate the safety and efficacy of different types of ICP monitors or specific management protocols during liver transplantation, but it is increasingly recognized that clinically meaningful inferences may require multimodal approaches, including brain tissue oxygen monitoring and microdialysis (Stevens & Merritt, 2008). Interventions aimed at management of CPP are outlined in Table 97B.1.

Despite profound coagulation abnormalities in ALF (Box 97B.1), serious bleeding is rare during liver transplantation,

Box 97B.1

Hemostatic Abnormalities in Liver Disease

Anticoagulant
Thrombocytopenia
Impaired platelet function (?)
Reduced hematocrit
Upregulated NO* and prostacyclin* inhibit platelets
Low levels of coagulation factors II, V, VII, IX, X, and XI
Vitamin K deficiency
Hypofibrinogenemia, dysfibrinogenemia
Decreased factor XIII, TAFI
Elevated levels of tPA,* decreased PAI-1*
Procoagulant
Elevated factor VIII† and von Willebrand factor*
Decreased proteins S and C and antithrombin III†
Decreased plasminogen and α_2-antiplasmin

*Extrahepatic synthesis
†Extrahepatic and intrahepatic synthesis
NO, nitric oxide; PAI-1, plasminogen activator inhibitor type 1; TAFI, thrombin activatable fibrinolysis inhibitor; tPA, tissue plasminogen activator

Lisman T, Leebeek WG, 2007: Hemostatic alterations in liver disease: a review on pathophysiology, clinical consequences, and treatment. Dig Surg 24:250-258.

because ALF patients have minimal or no portal hypertension (Muñoz et al, 2009). No evidence-based protocols have been outlined for correcting coagulopathy in ALF, but it is recognized that prophylactic administration of FFP and other products simply to correct the prothrombin time is not justified. Correction of coagulopathy is important before placement of an ICP transducer. Whole-blood assays (TEG, ROTEM) and clinical assessment are more useful guides for intraoperative treatment of coagulopathy. A major limitation of FFP is the potential for volume overload and transfusion-related acute lung injury (TRALI). Cryoprecipitate is typically indicated when the fibrinogen level falls below 100 mg/dL; activated recombinant factor VII (rFVIIa) and thrombin concentrates are beneficial, but optimal use of these last two remain to be determined. Antifibrinolytics should be considered if clinically significant fibrinolysis is proven.

Both high-dose steroids given during the anhepatic period and a functioning graft may cause hyperglycemia in the neohepatic phase. As hyperglycemia has an adverse effect on ischemia-reperfusion brain injury, plasma glucose should be kept in the normal range, and continuous infusion of insulin is often required. Restoration of liver function by the functioning graft gradually eliminates encephalotoxins and improves metabolic homeostasis, which eventually leads to reduction of brain edema and normalization of intracranial and cerebral perfusion pressures.

Combined Liver-Kidney Transplantation

With the introduction of the MELD scoring system, the percentage of simultaneous liver-kidney transplantation doubled, to about 4.4% of all liver transplantations performed in the United States (Gines & Schrier, 2009). Although it is obvious that combined transplantation should be reserved only for patients with irreversible renal failure, reliable predictive factors for reversibility are sometimes difficult to fully define. Current criteria recommended by the International Liver Transplant Society expert panel (Gonwa & Davis, 2009) include patients who, in addition to having liver disease, are on dialysis because of end-stage renal disease; patients with AKI that requires dialysis for at least 6 weeks; and those not on dialysis but who have a low glomerular filtration rate (<30 mL/min) and proteinuria (3 g/day, 24-hour urine protein/creatinine ratio >3).

A matched case-control analysis of patients dialyzed for more than 3 months demonstrated a favorable impact of combined liver-kidney transplantation compared with liver transplantation alone. Patient survival was improved (87.2% vs. 74.5%), as was liver-graft survival (84.5% vs. 70.8%), 1 year after transplantation (Locke et al, 2008). In contrast, 1-year survival of the kidney graft was lower than after kidney transplantation alone (77.2% vs. 89.3%). The inferior renal results and the priority given to the kidney on the long waiting list point to a need for a standardized approach to combined liver-kidney allocation and for a better understanding of reversibility of renal dysfunction (Davis, 2008).

Patients presenting for a combined liver-kidney transplantation present a particular anesthetic challenge. Electrolyte abnormalities and metabolic acidosis may mandate preoperative hemodialysis, whereas hyperkalemia greater than 5.5 mmol/L and hyponatremia of less than 120 mmol/L are typically considered prohibitive to transplantation. Intraoperative monitoring of preload and strategies for judicious volume administration and correction of electrolyte abnormalities are essential. Hyperkalemia is common and should be managed aggressively by maintaining a normal pH and administering insulin or glucose, inhaled β-adrenergic agonists, and furosemide, if urine output is preserved. Banked blood is a major source of potassium; ideally, it should be washed, and units with the longest remaining shelf life should be preferentially used.

Intraoperative continuous RRT is possible, and its use is routine in some centers. In a series of 41 OLTs, this modality was well tolerated hemodynamically, and it allowed achievement of neutral fluid balance without a need for systemic anticoagulation (Townsend et al, 2009). Fluid strategies for the two parts of the combined procedure may seem conflicting; although the kidney transplantation part may prompt a somewhat more liberal fluid regimen, in our opinion, goals for both OLT and kidney transplantation should be maintenance of a normal range preload to allow optimal organ perfusion.

Retransplantation

Most common reasons for retransplantation are primary nonfunction, recurrence of viral hepatitis, acute or chronic rejection, and thrombosis of the hepatic artery (Ma et al, 2008; Pfitzmann et al, 2007). The time interval between the primary transplantation and retransplantation—that is, early versus delayed retransplantation—depends on the etiology of the graft failure.

Almost 11,000 retransplantations have been performed since the inception of the UNOS registry—about 11% of all the OLTs ever performed. A declining trend toward the need for retransplantation is apparent; for example, in 1988, the retransplantation rate was 24.5%, whereas in 2009, the rate was only 7.3%.

The survival rate for retransplanted patients is lower than for primary transplant recipients: at 1 year, the survival is 67.2% versus 83.4%; at 5 years, it drops to 46% versus 67.4% (UNOS, 2010). With appropriate recipient selection, better outcomes are possible, and 1- and 5-year survival rates have been reported as high as 78% and 67%, respectively, with retransplantation (Ma et al, 2008; Pfitzmann et al, 2007). General agreement has

been reached on two points: 1) that whole graft should be used in adults (Pfitzmann et al, 2007) and 2) that retransplantation should not be undertaken with extended-criteria donors (Zimmerman & Ghobrial, 2005).

The current modest results emphasize the need for strategies to improve retransplantation survival. In particular, a strong interest has been shown in the development of valid predictive criteria; for example, according to Zimmerman and Ghobrial (2005), patients who require mechanical ventilation, those who have advanced renal failure, and patients of advanced age have worse outcomes and should not be considered for retransplantation. MELD score has prognostic value in retransplantation: patients with of a score below 20 have better outcomes than those with higher scores (Ma et al, 2008); in another study, worse results were reported when MELD was more than 25 (Zimmerman & Ghobrial, 2005).

A few studies have also looked at survival as a function of the time interval between the primary transplantation and retransplantation; survival was better when retransplantation occurred less than 8 or more than 30 days after the initial transplantation (Ma et al, 2008).

Intraoperative anesthetic challenges depend on the overall patient condition on the day of surgery; factors that may impact transplantation include difficult vascular access, a need to support liver and coagulation function, increased blood losses, and a higher requirement for blood-product transfusions. The main causes of death were bacterial infection, multisystem organ failure, bleeding, and recurrence of disease (Pfitzmann et al, 2007).

Pediatric Transplantation

Indications for liver transplantation in the pediatric population include 1) primary liver disease, such as extrahepatic biliary atresia, and intrahepatic cholestasis, which includes sclerosing cholangitis, Alagille syndrome, and other similar syndromes; 2) metabolic diseases, such as Wilson disease, α_1-antitrypsin deficiency, Crigler-Najjar syndrome, disorders of the urea cycle, oxaluria type 1, and disorders of carbohydrate metabolism; 3) ALF; and 4) liver disease brought about through other causes, including primary liver tumor and cystic fibrosis (Spada et al, 2009; Yudkowitz & Chietero, 2005; see Chapter 71).

According to UNOS data, more than 12,000 OLTs have been performed since 1988 in patients younger than 18 years, with the majority carried out in patients younger than 5 years.

Age at Transplantation

Age at transplantation mainly depends on the specific etiology of the liver disease. Historically, age at transplantation was one of the main factors that determined survival, and infants used to have poorer outcomes than older children; however, with recent improvement of surgical techniques and better overall perioperative care, infant survival is close to that of older children following OLT (Bennett & Bromley, 2006).

Survival

One-year survival for chronic liver disease is greater than 90%, and survival at 5 years is over 80% in most centers in the United States and Europe (Bennett & Bromley, 2006). Nephrotoxicity secondary to calcineurin inhibitors (CNIs) remains a frequent cause of posttransplant renal dysfunction (Bucuvalas & Alonso, 2008).

Recipient Selection

Organ allocation to pediatric recipients in the United States is based on the Pediatric End-Stage Liver Disease (PELD) score, developed based on data derived from a database of children with ESLD to predict mortality on the waiting list; it considers bilirubin, INR, serum albumin, age, and growth factors. Additional PELD points are awarded for specific risk factors not taken into account in the original PELD equation, such as presence of HPS, metabolic diseases, and liver tumors (Bennett & Bromley, 2006; Spada et al, 2009).

Type of Surgical Graft

Whole, reduced, and split grafts from both cadaveric and living donors have been used to maximize the number of pediatric liver transplants performed and to minimize the risk of patients dying while on the waiting list.

Intraoperative Anesthesia Challenges

Multifactorial hypoxemia is sometimes present, possibly related to HPS, whereas PPHTN is usually present only in children affected by Alagille syndrome. Cuffed endotracheal tubes should be used to guarantee effective mechanical ventilation in the presence of high airway pressure peaks. Most children undergoing liver transplantation have preserved kidney function, but they are at high risk of developing hypoglycemia.

VASCULAR ACCESS. Two large bore intravenous needles are usually sufficient for fluid and blood administration. Arterial catheters are usually placed in the upper limbs, as a femoral line may produce unreliable values once the surgeon clamps the aorta to build an arterial conduit. The length of the central venous line catheter must be appropriate for the body size of the patient, and PACs are rarely used because of size issues.

It is important to note that children are at increased risk of intraoperative hypothermia, and active maintenance of temperature is critical to prevent occurrence of dysrrhythmias, clotting abnormalities, and possible wound infections.

Thrombosis of the hepatic artery is a frequent complication that may lead to a graft loss and need for retransplantation. Keeping the hematocrit between 25% and 30% to prevent excessive blood viscosity and avoidance of overcorrecting the coagulation function are common protective strategies. Aspirin can be given (in adults) in the immediate postoperative period to blunt platelet activity (Bennett & Bromley, 2006; Yudkowitz & Chietero, 2005).

Living-Related Donor Liver Transplantation

Since 2006, fewer than 300 OLTs with a graft from a living relative donor have been performed annually in the United States—about 3% of adult and 10% of pediatric OLTs (see Chapter 98B). This is a marked decline with respect to the year 2001, when a record 524 OLTs came from living donors—about 9% of adult and 18% of pediatric OLTs. Although survival of the recipients of a living graft is superior to that of cadaveric graft recipients (UNOS, 2010), a justified concern for donor morbidity and mortality drives this trend. Challenges for the anesthesiologist depend more on the recipient's characteristic and comorbidities than on the donor category (Table 97B.2).

Table 97B.2

Early Complications After Liver Transplantation

Type	Complication
Pulmonary	TRALI/ARDS, pneumonia, pleural effusions, persistent shunting
Cardiovascular	CHF, hypotension, myocardial ischemia, arrhythmias
Renal	ATN, hepatorenal syndrome, CNI nephrotoxicity
Metabolic	Hyperglycemia/diabetes mellitus, electrolyte abnormalities
Neurologic	Persistent encephalopathy, seizures, posterior leukoencephalopathy, central pontine myelinolysis
Infectious	Wound infections, seromas, intraabdominal abscess, sepsis
Abdominal	Surgical bleeding or bleeding as a result of coagulopathy
Vascular	Hepatic artery or portal vein stenosis/thrombosis, IVC obstruction
Biliary	Biliary stricture or leaks
Rejection	Cellular rejection
Immunosuppressant toxicity	Seizures, kidney failure

ARDS, acute respiratory distress syndrome; ATN, acute tubular necrosis; CHF, congestive heart failure; CNI, calcineurin inhibitor; IVC, inferior vena cava; TRALI, transfusion-related acute lung injury

POSTOPERATIVE INTENSIVE CARE

Transfer to the ICU should be smooth, and it should maintain the same level of monitoring and care as in the operating room. The main goals of the early postoperative period are maintenance of homeostatic equilibrium, timely recognition and treatment of complications, and diagnosis and treatment of infections and acute rejection. The risk of developing early postoperative complications is dependent upon the patient's preoperative condition, the quality of the graft, and the quality of the surgical, anesthetic, and intensive care management.

Early Extubation

Safe early or even immediate postoperative extubation of a majority of liver transplant patients has been reported by some centers; however, the exact criteria, the benefits of early extubation to liver recipients, and any cost benefits remain a matter of debate. A multicenter cohort study by a proponent group (Mandell et al, 2007) reported a lower rate (7.7%) of postoperative adverse events in the immediate extubation group than that commonly reported for ventilated liver transplant patients. This study showed great variability in rates of extubation (5% to 67%) and rates of complications between centers, suggesting a significant impact of the regional patterns of practice, intraoperative events, and physician experience. Multiple studies agree that encephalopathy, whether the result of acute or chronic liver failure, is a strong predictor of the need for prolonged ventilation. Other factors, such as volume of blood transfused and RRT, are less consistent predictors among studies and may be only indirect markers of poor graft function, severity of illness, and a lack of standardized intraoperative protocols (Mandell et al, 2009).

No randomized studies are currently available that demonstrate that early extubation improves patient outcomes or reduces cost (Ozier & Klinck, 2008). Although experienced clinicians can select appropriate patients for early extubation, no evidence-based criteria exist in support of this practice; more studies are needed to establish whether this intervention is beneficial and whether it should be a therapeutic goal in liver transplant recipients.

Medical Complications

Pulmonary complications that include acute respiratory distress syndrome (ARDS), TRALI, pneumonia, and pleural effusions are common in the immediate postoperative period. These complications are reported to occur in over 50% of patients after liver transplantation and lead to hypoxemia that often requires prolonged mechanical ventilation (Biais et al, 2009; Bozbas et al, 2008; Li et al, 2010). ARDS and TRALI may be related to blood-product transfusion and fluid overload. Pneumonia is the most frequent postoperative infection in patients following OLT, and it carries a high mortality. Pleural effusion is another common pulmonary complication; it promotes atelectasis and contributes to impaired respiratory exchange. The addition of PEEP monitoring may be effective in improving oxygenation in postoperative patients. PEEP of up to 10 cm of H_2O was found not to affect the perfusion of the grafted liver, as assessed by Doppler (Saner et al, 2006b).

Cirrhotic patients continue to exhibit hyperdynamic circulation during the first hours or days after OLT. Arterial hypotension and the need for vasopressors are common. With the graft functioning and no evidence of surgical complications, the hemodynamics tend to normalize, which allows downgrading of invasive monitoring and of hemodynamic support. Maintenance of kidney perfusion pressure is paramount because AKI is common (17% to 95%) (Pham et al, 2009) and is associated with increased ICU length of stay and mortality (Smith et al, 2009). The causes of post-OLT acute renal failure are multifactorial and include preexisting renal dysfunction, HRS, perioperative acute tubular necrosis, and CNI nephrotoxicity. RRT is necessary in 5% to 35% among patients who develop postoperative AKI.

Endocrine and metabolic complications are common in the early posttransplant period. Surgical stress, corticosteroid administration, and CNIs contribute to early posttransplant hyperglycemia, which frequently evolves to diabetes mellitus, and hypertension. Diabetes occurs in up to 30% of posttransplant patients, and hypertension is seen in over 50%. Hyperglycemia requires an intravenous insulin regimen and improves as steroids are tapered; hypertension should be treated aggressively to prevent cardiovascular complications (Kallwitz & Cotler, 2008).

Neurologic complications may occur in up to 50% of liver transplant recipients (Saner et al, 2009). Such complications contribute to longer ICU and hospital stays and may result in long-term poor quality of life. The most common neurologic complications are encephalopathy and seizures, followed by psychotic disorders, stroke, and poorly understood posterior leukoencephalopathy. The etiology is multifactorial and includes poor graft function, use of steroids and possibly CNIs, infection and systemic inflammatory response, electrolyte imbalance, and embolic events.

Meticulous perioperative neurologic assessment and quick recognition of neurologic impairment are essential. Specific therapeutic modalities are limited (i.e., tapering steroids, exchanging CNIs), but if applied in a timely manner, they may improve outcome. In addition, a key factor of neurologic improvement is the recovery of graft function.

Infections are the primary cause of death after liver transplantation. Many infections that occur in the first days after transplantation are related to the surgery itself, such as wound infections, seromas, and perigraft fluid collections. Postoperative and opportunistic infections are common in the immunocompromised and debilitated transplant patient. Such infections may lead to sepsis and multiorgan failure; therefore they require a high level of suspicion and routine postoperative prophylactic protocols that include broad-spectrum antibacterial, antiviral, and antifungal therapy.

Posttransplant rejection ranges from 10% to 30% (Mueller et al, 2004). Cellular rejection is suspected with increasing transaminases and normal hepatic vascular Doppler studies, and diagnosis is confirmed with liver biopsy; however, early episodes respond well to boluses of corticosteroids and rarely lead to graft failure.

Surgical Complications

Postoperative hemorrhage is primarily a clinical diagnosis that can be confirmed by abdominal imaging techniques, and it occurs in 10% to 15% of OLT patients. A priority is to distinguish whether hemorrhage is due to persisting coagulopathy or to surgical causes. Hemodynamic instability and transfusion of more than 4 to 6 U packed blood cells over a 24-hour period are usual indications for surgical reexploration (Mueller et al, 2004).

Early vascular complications include hepatic artery and portal vein stenosis or thrombosis and venocaval obstruction or kinking. Poor graft function and protracted elevation of liver enzymes point to a vascular complication; however, the diagnosis is made based on a bedside vascular Doppler and can be confirmed with conventional or MRI angiography. Hepatic artery thrombosis occurs in 2.5% to 10% of adult patients and in 5% to 20% of children; portal vein thrombosis is much less common (0.3% to 2.2%), and flow obstruction at the level of the infrahepatic and suprahepatic vena cava occurs in 1% to 2%.

All vascular complications require urgent surgical intervention. If vascular repair is delayed, the ensuing graft failure may necessitate retransplantation. Many vascular complications have been successfully treated using various endovascular approaches, including percutaneous angioplasty, stent placement, or thrombolysis (Amesur & Zajko, 2006).

Biliary complications occur in about 10% to 15% of patients following liver transplantation. Stricture of the bilary tree accounts for most of the complications, but biliary leak is a more common early complication. The most severe manifestations of biliary leak are peritonitis and sepsis, but asymptomatic bilomas are also a common presentation. The diagnosis of the leak is based on percutaneous transhepatic cholangiography (PTC) or endoscopic retrograde cholangiography (ERCP). Ultrasound and CT scan are useful in diagnosis of biliary dilations due to obstruction, bile collections, or abscesses. Treatment of biliary obstruction includes percutaneous balloon dilation and drainage or surgical revision. Treatment of biliary leaks involves percutaneous transhepatic drainage (PTD), a technically difficult alternative to surgical repair. Nonanastomotic leaks and leaks secondary to hepatic artery thrombosis are particularly ominous, because they are less amenable to percutaneous repair and often require retransplantation (Amesur & Zajko, 2006; Mueller et al, 2004).

Recipients of grafts from donors after cardiac death (DCD) have worse graft and patient survival, a higher rate of postoperative complications, and higher resource utilization than the recipients of dead-brain donation (DBD) grafts (Reich et al, 2009). Primary graft nonfunction, nonanastomotic biliary strictures, and hepatic artery stenosis are the most significant postoperative complications of DCD liver transplantation. Higher immediate perioperative mortality in DCD transplants has been reported (Pine et al, 2009), but most complications lead to increased mortality or to the need for retransplantation in the weeks or months following the transplantation (Grewal et al, 2009). Strategies to improve DCD outcomes currently under development include a super-rapid recovery technique by experienced procurement teams, premortem cannulation techniques, ex vivo organ perfusion, and minimization of cold- and warm-ischemia time (Reich et al, 2009). Although DCD grafts are associated with inferior outcomes, DCD donation remains a valuable resource, and with selective and judicious use, these can be used to achieve acceptable results (Pine et al, 2009).

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CHAPTER 97C

Liver transplantation in patients with fulminant hepatitis

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OVERVIEW

Fulminant hepatic failure (FHF) is a rare, cataclysmic clinical entity resulting from acute massive necrosis of liver cells and is characterized by the rapid onset of a potentially mortal condition in a previously healthy individual. Occurrence is estimated to range between 1% and 1.2% of all jaundice cases in acute hepatitis (Bernuau et al, 1999). Depending on the etiology and severity of liver injury, some patients may undergo rapid hepatic regeneration and spontaneously recover with *ad integrum* restitution of the liver; however, the majority will die without orthotopic liver transplantation (OLT).

Before the advent of liver transplantation (see Chapter 97A) and advances in the intensive care management of these patients (see Chapters 72, 73, and 97B), prognosis was very poor, with mortality rates exceeding 80% (Bernuau et al, 1986; Riordan et al, 2008). At the present time, mortality rates are approximately 30% to 40%; whereas 20% to 25% of patients require liver transplantation, only 40% to 45% of patients are able to survive spontaneously (Lee et al, 2008; Ostapowicz et al, 2002; Polson, 2008). Prompt recognition and early management decisions are critical and can affect outcome. Because of their medical complexity, patients with FHF should be managed in an intensive care unit (ICU) in centers with active liver transplant programs. Referral should be done as early as possible, as it is hazardous to transfer patients later in the disease course because of increased intracranial pressure (ICP) and clinical instability. It has been suggested that transfer to a specialized ICU should be arranged when the patient's international normalized ratio (INR) exceeds 2.0 or grade 2 hepatic encephalopathy develops (Stravitz & Kramer, 2009). High-risk patients, including those at the extreme ends of the age range (>45 years or <10 years) or with etiologies of acute liver failure (ALF) that carry a poor prognosis should be considered for transfer to a liver transplant center whenever any degree of encephalopathy develops.

DEFINITION

Originally defined by Trey and Davidson in 1970 as an acute hepatitis complicated by ALF with hepatic encephalopathy (HE) occurring less than 8 weeks after the onset of jaundice, it is nowadays accepted that FHF is a complex clinical syndrome characterized by the development of a severe acute liver injury with impaired synthetic function and encephalopathy in a patient without previous liver disease within 26 weeks from the onset of jaundice to the development of encephalopathy. The chronologic evolution of the clinical course of ALF, estimated by the interval between onset of jaundice and encephalopathy, is predictive of clinical features and outcome (O'Grady et al, 1993). According to the length of this presentation interval, Bernuau et al (1986) has described two distinct types of FHF: *fulminant* (interval <2 weeks) and *subfulminant* (interval between 2 weeks and 3 months).

The group at King's College Hospital (KCH) in London has defined three groups of patients: those with *hyperacute liver failure* (development of encephalopathy within 7 days after jaundice), *acute liver failure* (within 7 to 28 days), and *subacute liver failure* (from 28 days to 3 months) (O'Grady et al, 1993). Hyperacute presentation is more frequently associated with hepatitis A virus (HAV) or paracetamol (acetaminophen) overdose, whereas idiosyncratic drug reactions usually present a delayed-onset clinical course. Cerebral edema, a major complication of ALF, is more frequent in hyperacute liver failure, but it is rare in subfulminant disease. In contrast, manifestations of portal hypertension with ascites and renal failure are far more common in patients with subfulminant liver failure.

The cessation of liver cell destruction, rather than the occurrence of liver regeneration, appears to be the most critical variable governing outcome (Bernuau et al, 1999). A protracted course in patients with a subfulminant presentation are associated with persistence of elevated transaminases, suggesting persistence of liver cell destruction. Not surprisingly, hyperacute disease has a relatively good likelihood of spontaneous recovery compared with subacute disease, which has a very poor prognosis without liver transplantation (O'Grady et al, 1993).

To what extent these differences in survival are related to the rapidity of onset or to etiology itself is difficult to say. Likelihood of spontaneous recovery is not uniform and depends on the etiology of the insult. Previously, mortality was thought to be lower in patients with HAV and acetaminophen overdose (50% to 60%), compared with 80% to 95% mortality rate in patients with non–acetaminophen-induced ALF, halothane anesthesia, fulminant disease of indeterminate cause, and non-A, non-E fulminant hepatitis (O'Grady, 1988); however, more recent data used to evaluate prognosis of indeterminate liver failure showed no significant difference compared with other etiologies (Wei, et al, 2008).

Age younger than 10 years or older than 40 years is considered an adverse marker of outcome. Outcome in older patients was recently reevaluated by Schiodt and colleagues (2009), who observed superior overall survival in younger compared with older patients (67.9% vs. 48.2%; $P < .001$), yet no significant differences were demonstrated in reference to spontaneous survival among both groups, suggesting that hepatic regeneration is preserved in the elderly, a fact that is in accordance with

the rise in α-fetoprotein (AFP) levels that is similar in both populations.

Other factors that have been associated with lower survival are a high body mass index (BMI), although data are still controversial (Kanda et al, 2005), and the presence of systemic inflammatory response syndrome (SIRS) (Miyake et al, 2000, 2007). The magnitude of SIRS in patients with ALF and infection correlate with mortality: 16.7%, 28.4%, 41.2%, and 64% in patients with 0, 1, 2, and 3 maximum concurrent SIRS components, respectively (Rolando et al, 2000).

ALF adversely affects most organ systems, and the majority of deaths result either from sepsis and subsequent multiorgan failure or from cerebral edema that evolves to intracranial hypertension and brainstem herniation. Patients with ALF are susceptible to a wide variety of additional complications, including renal failure, hypoglycemia, metabolic acidosis, coagulopathy, and cardiopulmonary distress. Advances in the intensive care management of patients with ALF and the early recognition of these complications has greatly contributed to a marked improvement in overall survival (see Chapters 72, 73, and 97B).

ETIOLOGY

ALF is an infrequent entity that can affect patients of all ages, and it shows a predominance in females that remains unexplained. Etiologies and prognoses vary in adults compared with infants and children (Polson et al, 2005; Squires et al, 2006). ALF results from a wide variety of causes (Box 97C.1), yet relative frequency of etiologies shows geographic (Lee et al, 2008) and temporal variations. These variations depend mainly on epidemiologic, socioeconomic, and cultural factors. Worldwide, acute viral hepatitis is the predominant cause of ALF, particularly in developing countries and especially in pediatric series. Data from Sudan (Mudawi, 2007), Bangladesh (Alam et al, 2009), Mexico (Fernandez Hernandez et al, 2003), and India (Acharya et al, 1996; Dhiman et al, 1998; Jaiwal et al, 1996) report a prevalence of viral hepatitis among patients with ALF that varies from 27% to 94% and includes hepatitis A, B, D, and E and a combination of hepatitis A with hepatitis E.

In the United States and Western Europe, viral hepatitis prevalence in patients with ALF is decreasing (Taylor et al, 2006), and acetaminophen overdose has become the most common cause of fulminant hepatitis (Larson et al, 2005), resembling the experience in the United Kingdom, where it is responsible for more than 70% of ALF cases (Williams, 1996). Comparing two time periods, after 1993 in France, 28% of patients with ALF were affected with acute viral hepatitis (Feray et al, 1993) compared with 48% before 1993 (Wright et al, 1991). The United States Acute Liver Failure Study Group (USALFSG), a multicenter network established in 1997 to gather data prospectively on all forms of ALF, observed in a recent analysis of 1033 patients enrolled through 2007 that acetaminophen toxicity accounts for approximately 46% of ALF cases in the United States, followed by ALF of indeterminate origin (15%) and idiosyncratic drug reactions (12%).

The clinical pattern of presentation of acetaminophen toxicity is still different in the United States (Zimmerman et al, 1995) compared with the United Kingdom, because only half of the time does it stem from ingestion of large doses taken in an intent to commit suicide; in the remainder, ingestion results from unintentional overuse of acetaminophen-containing compounds for pain or fever relief at therapeutic doses, mainly by patients with ongoing alcohol abuse, starvation, or in those concurrently taking medications known to induce the cytochrome P450 system, such as anticonvulsants, a situation known as *therapeutic misadventure* (Licht et al, 1980; Seeff et al, 1986; Wootton & Lee, 1990). Although the mortality rates associated with this syndrome are lower than that observed with suicidal ingestion, they are still at least 20% in most reviews (Kumar et al, 1991; Wootton & Lee, 1990).

Idiosyncratic drug reactions are the cause of about 15% of ALF cases in the United States and other countries. Antibiotics, nonsteroidal antiinflammatory drugs (NSAIDs), and anticonvulsants constitute some of the most commonly involved classes of prescription medications involved (Chalasani et al, 2008; Ostapowicz et al, 2002; Russo et al, 2004). It is expected that enhanced awareness of potential risks and drug mechanisms of liver injury may minimize in the future the frequency of serious hepatotoxicity (Murray et al, 2008).

Despite extensive evaluation of the etiology of ALF, in approximately 15% to 40% of cases, the cause remains elusive, even though the incidence of cryptogenic disease is declining (Larson et al, 2005). Available data suggest that in 20% of these patients, ALF may be attributable to undiagnosed acetaminophen overdose (Davern et al, 2006).

Box 97C.1

Etiology of Acute Liver Failure

Viral

Hepatitis A, B, D, and E
Herpes simplex, herpes 6, and varicella zoster
Epstein-Barr
Cytomegalovirus
Parvovirus B19
Adenovirus
Dengue fever

Drug Related

Paracetamol/acetaminophen
Tetracyclines
Isoniazid-pyrazinamide
Halothane
Monoamine oxidase inhibitors
Nonsteroidal antiinflammatory drugs
Antithyroid medications

Other

Microvesicular steatosis
Fatty liver of pregnancy
Reye syndrome

Vascular

Ischemic hepatitis (shock liver)
Acute Budd-Chiari syndrome
Venoocclusive disease

Toxins

Amanita mushrooms
Chemical solvents
White phosphorus
Toxins of plant origin
Illicit drugs, such as cocaine and ecstasy

Miscellaneous

Wilson disease
Massive tumor invasion
Autoimmune hepatitis

In Argentina, ALF represents 9% to 21% of all annual liver transplantations, even though its frequency has been decreasing in recent years. Data from the INCUCAI, the national organ procurement institution in Argentina, reflects a completely different etiologic profile. Indeterminate disease represents 29%; this is followed by 1) fulminant autoimmune hepatitis, which is rare in the United States and Western Europe and represents 19% of our total population with ALF; 2) hepatitis B virus (HBV), which is responsible for ALF in 15%; 3) drug-induced causes, which represent 12%; and 4) ALF secondary to HAV, which accouns for 11% in Argentina. Not a single transplantation was done for acetaminophen hepatotoxicity. The high prevalence of autoimmune hepatitis remains unexplained, even though it correlates with the high percentage of patients transplanted for autoimmune disease among those with cirrhosis, suggesting a more severe course of the disease. Similar data have been reported in other Latin American countries (Uruguay [Gerona, Cohen]; Chile [*Clinica Alemana*]; personal communication).

CLINICAL PRESENTATION

The rapid identification of ALF in a patient with liver dysfunction and an altered mental status in the setting of an acute hepatic disease is of paramount importance, as a delay in diagnosis has relevant prognostic implications. French investigators have highlighted the importance of recognizing the syndrome even at earlier stages, as soon as prothrombin ratio falls below 50% during the course of an acute liver disease and before the development of encephalopathy, as it has been recognized that prompt referral to a specialized liver unit and rapid medical intervention with specific therapies in certain etiologies can prevent progression in the clinical picture (Bernuau et al, 1993).

HE is a major defining criterion of FHF in the adult population. Children, particularly the very young, do not demonstrate classic features of encephalopathy, resulting in a revision of the definition of ALF for this specific population of patients to include pediatric patients with advanced coagulopathy, regardless of mental status (Squires, 2008). Severity of encephalopathy can be classified into four stages according to the definition of Trey and Davidson (1970): *stage 1,* slow consciousness; *stage 2,* accentuation of stage 1 and presence of asterixis; *stage 3,* presence of deep confusion or reactivity only to vocal stimuli; and *stage 4,* presence of deep coma with minimal (4a) or no response (4b) to noxious stimulus.

The development of cerebral edema is a life-threatening complication. Although precise pathogenic mechanisms remain unclear, most widely accepted theories relate to the development of astrocyte swelling and cerebral hemodynamic derangements characterized by high cerebral blood flow and failure of cerebral autoregulation in response to changes in mean arterial pressure (Larsen, 1996; Larsen et al, 2000), resulting in cerebral edema (see Chapters 72 and 97B). Loss of cerebral autoregulation of blood flow has been related to the rapidity of occurrence of electrolyte disorders in ALF, in contrast to what happens in cirrhosis or even in subacute liver failure, in which the mechanisms of osmotic regulation are still active. Cerebral edema develops in 75% to 80% of patients with grade 4 encephalopathy (Williams, 1991), and incidence is variably reported, although it appears to be progressively less frequent.

Several risk factors for the development of cerebral edema have been identified. It is more prevalent among patients with hyperacute liver failure compared with subacute disease, probably as a result of the rapid accumulation of glutamine in hyperacute presentation that overwhelms the mechanisms of compensatory expulsion of organic osmolytes from the astrocytes. High serum ammonia concentrations (>150 to 200 μmol/L) also increase the risk of cerebral edema, although the relationship between ammonia and ICP is not linear (Bernal et al, 2007; Bhatia et al, 2006; Clemmesen et al, 1999a).

Recent work suggests a central role of proinflammatory cytokines—such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 and IL-1β—in patients with uncontrolled ICP, indicating activation of the inflammatory cascade in the brain (Wright, 2007). Other variables predictive of progression of intracranial hypertension and HE are the Model for End-Stage Liver Disease (MELD) score alone and in combination with ammonia levels, young age, requirement for vasopressors and renal replacement therapy, and the presence of infection and/or SIRS (Bernal et al, 2007; Vaquero et al, 2003). Evidence also emphasizes the importance of free-radical formation occurring at a mitochondrial level as the potential mediator of cellular dysfunction induced by ammonia neurotoxocity (Norenberg et al, 2009).

In severe cases, consequences of cerebral edema within the confinement of the cranial vault are the development of intracranial hypertension with potential risk of brainstem herniation and a decrease in intracerebral perfusion (Blei, 1991; see Chapter 97B). Severity of encephalopathy has prognostic implications, and overall prognosis for patients with only grade 1 or 2 encephalopathy is good, whereas for patients with grade 3 or 4 encephalopathy, prognosis is much poorer. Full recovery of cerebral function is the rule in patients whose liver function recovers, but permanent brain damage has been observed in patients making an otherwise complete recovery of liver function (O'Brien et al, 1987).

Coagulopathy

Along with neurologic involvement, coagulopathy is also a major criterion of ALF, resulting from the inadequate hepatic synthetic capacity of clotting factors. This is associated with increased consumption, particularly of factors II, V, VII, and X; reduced clearance of both activated factors and/or factor inhibitor complexes; and quantitative and qualitative platelet dysfunction (see Chapters 72 and 97B). Patients are seen with low fibrinogen and low levels of factors II, V, VII, IX, and X that result in the prolongation of prothrombin time (PT) and partial thromboplastin time (PTT) (Gazzard et al, 1975). Platelet counts are less than 100,000/mm^3 in more than two thirds of patients, and platelet function is altered (O'Grady et al, 1986); however, serum concentrations of thrombopoietin do not correlate with platelet counts (Schiodt et al, 2003), and the pathogenesis of thrombocytopenia remains unclear.

Although low-grade fibrinolysis and intravascular coagulation may occur, these syndromes are hard to distinguish from the changes that result from the failure of hepatic synthesis alone (Preston, 1991). Among patients with ALF, it has been observed that coagulopathy was moderate in 81% (INR 1.5 to 5), severe in 14% (INR 5 to 10), and very severe (INR >10) in 5%. Certain etiologies are associated with greater severity of coagulopathy, and ALF in fatty liver of pregnancy represents the least severe coagulopathy (Muñoz et al, 2008).

In spite of the evidence of a bleeding diathesis in patients with ALF, spontaneous bleeding is unusual, being most common in the gastrointestinal (GI) tract (8%) or brain (<1%); yet spontaneous intracranial bleeding is exceedingly rare in the absence of an ICP monitor. The incidence of upper GI bleeding in ALF patients has been decreased by gastric acid suppression with intravenous H_2 receptor antagonists (McDougall et al, 1978), therefore intravenous H_2 blockers or proton pump inhibitors are recommended.

Prophylactic administration of fresh frozen plasma (FFP) is usually not recommended, because it has not been proven to influence mortality rate, it can interfere with assessment of liver function, and it may worsen cerebral edema (Caraceni et al, 1995); therefore it is only indicated in the setting of active hemorrhage or prior to invasive procedures. The goal for correction of the INR to a value of no higher than 1.5 to minimize bleeding risk arises from common practice, although it has not been adequately tested. Use of recombinant human factor VIIa has been evaluated in small pilot studies (Chuansumrit et al, 2000; Negrier et al, 2000; Shami et al, 2003), and it was associated with improvement or normalization of PT and bleeding control. It has also been suggested that the combination of recombinant human factor VIIa with FFP is superior to FFP alone in correcting coagulopathy, with a beneficial effect on morbidity and mortality (Shami et al, 2001). Larger controlled studies are still required, but it has become acceptable to administer recombinant factor VIIa (rFVIIa) when FFP has failed to correct PT-INR to an acceptable level, or when the patient has become volume overloaded, before performing invasive procedures with a high risk of bleeding, such as transjugular liver biopsy or placement of an ICP monitor. Serial determinations of INR and factor V provide useful prognostic information in the follow-up of patients with ALF.

Infections

Infections are common in patients with ALF and constitute a leading cause of mortality. Patients with ALF are at increased risk of infection and sepsis as a result of deficient opsonization resulting from reduction of factors such as fibronectin, opsonins, and chemoattractants, including components of the complement system. Additionally, infections in ALF patients present an increase in bacterial translocation, white blood cell dysfunction, Kupffer cell dysfunction, and a high requirement for invasive maneuvers. Bacteriologically proven infection was recorded in up to 80% of patients, and fungal infection was found in 32%, with a predominance of *Candida*. Most common sites of infection are respiratory tract (47%) and urinary tract (22%), but bacteremia with (12%) or without (15%) a defined source was present, as was bacteremia of indwelling catheters (4%).

In one prospective study of 50 patients, 80% had culture-proven infection, and in half of the remaining patients, infection was suspected, but cultures were negative (Rolando et al, 1990). gram-positive organisms, mainly streptococci and *Staphylococcus aureus,* predominate in ALF, suggesting that entry through the skin is more important than intestinal entry, the pathway of gram-negative organisms (Wyke et al, 1982). Leukocytosis and fever are frequently absent (<50%), but a high index of suspicion of active infection should be raised at the worsening of encephalopathy, renal function, or clinical status. Daily bacterial surveillance cultures (blood and urine) and chest radiographs are recommended, as early diagnosis of infection may improve outcome.

Aggressive treatment of presumed infection is essential, because prophylactic antibiotic regimens have shown little benefit (Rolando et al, 1993); however, a low threshold for starting appropriate antibiotics and antifungals should be maintained. Administration of antibiotics is recommended when infection or the likelihood of impending sepsis is high, surveillance cultures reveal significant isolates, clinical progression of HE or renal failure is apparent, hypotension is refractory, or SIRS is evident, individual components of which include temperature above 38° C or below 36° C, white blood count above 12,000/mm^3 or below 4,000/mm^3, and pulse greater than 90 beats/min (Stravitz et al, 2007).

Broad-spectrum coverage for gram-positive and gram-negative bacteria, such as with a third-generation cephalosporin, should be chosen with consideration of patient-specific isolates from surveillance cultures and historic hospital-specific isolates (Stravitz et al, 2007). Vancomycin is specifically recommended for all patients with possible intravenous catheter–related sepsis and/or risk factors for infection with methicillin-resistant *Staphylococcus aureus* (MRSA). An antifungal agent also is recommended in any patient who does not display prompt improvement in signs of infection after institution of antibacterial agents (Stravitz et al, 2007).

The occurrence of infection may aggravate all instances of the inflammatory mechanisms that are activated by ALF and may precipitate the occurrence of multiorgan failure and death. A finding of disseminated fungemia is predictive of a poor prognosis (Walsh et al, 1983).

Renal Disorders

Renal compromise is frequent in patients with fulminant and subfulminant hepatic failure, and oliguria is a common finding (Caraceni et al, 1995). Acute renal failure complicates 30% to 50% of cases, taking an increase in creatinine concentrations as a diagnostic criterion; yet normal creatinine concentrations do not exclude the presence of acute renal failure. Therefore the true incidence of renal compromise is probably underestimated.

Acute renal failure in ALF can result from two different situations: First, direct nephrotoxic effects result from some causes of ALF, as has been observed with toxic quantities of acetaminophen (Mazer et al, 2008) and NSAIDs and with *Amanita* mushroom intoxication (Escudié et al, 2007; Joshi et al, 2007), usually resulting in acute tubular necrosis. Second, patients may present with a certain degree of dehydration or may develop functional renal failure that resembles the hepatorenal syndrome of cirrhosis. Pathogenesis remains unclear, even though marked reduction in renal blood flow and glomerular filtration rate is similar to renal perfusion changes in cirrhosis, with marked renal arteriolar vasoconstriction as a result of loss of systemic vascular resistance, activation of compensatory vasoconstrictor systems, and reduced renal prostaglandin excretion; however, ALF has distinctive hemodynamic features, and only rarely is the degree of portal hypertension in ALF comparable to that of hepatorenal syndrome in cirrhotics (Navasa et al, 1992). The mean reported hepatic venous pressure gradients for patients with ALF and renal dysfunction is significantly lower compared with those in cirrhotic patients

with hepatorenal syndrome (14 vs. 21 mm Hg) (Navasa et al, 1992; Ruiz-del-Arbol et al, 2005).

Recently, Leithead and colleagues (2009) demonstrated that ALF is associated with SIRS, and this association is independent of the presence of infection and severity of liver injury. Recognition of renal failure also has important clinical implications, and once established, it is usually progressive and associated with increased mortality (Jain et al, 2000; O'Grady et al, 1989; Ring-Larsen et al, 1981). Treatment options without transplantation are limited, and preventive measures are restricted to maintain adequate hemodynamics, early identification and adequate treatment of infection, and avoidance of nephrotoxic agents such as NSAIDs and aminoglycosides.

Renal replacement therapy (RRT) is usually recommended early to correct intravascular fluid overload, electrolyte disorders, or acidosis. Potential triggers for initiation of RRT might be low urine output, a rise in creatinine levels over 0.3 mg/dL over baseline, or a rise in serum ammonia above 150 µmol/L (Stravitz & Kramer, 2009).

Continuous rather than intermittent modes of renal replacement, such as continuous venovenous hemofiltration, are usually preferred to avoid abrupt shifts in solute concentrations that can result in increased ICP (Davenport et al, 1993).

Hemodynamic Complications

ALF is characterized by a hyperdynamic circulation with low systemic vascular resistance (SVR), high cardiac output, and low mean arterial pressure (MAP). Features of systemic inflammation, hemodynamic patterns, and progression of organ dysfunction resemble sepsis. Generalized systemic vasodilation is not limited to the splanchnic circulation, as it occurs in cirrhotics (Maroto et al, 1993; Ytrebø et al, 2006). Volume status in patients with ALF is difficult to assess, so placement of a pulmonary artery catheter may be of help, as management of hemodynamic balance can be complicated by the occurrence of elevated ICP and renal dysfunction. In most hypotensive patients, initial volume resuscitation is required, and it has been recommended that fluid replacement with colloids (albumin) should be preferred, rather than crystalloids (saline), and all solutions should include dextrose to maintain euglycemia (Polson et al, 2005).

Even after adequate volume repletion, vasopressors may be required to maintain a MAP of at least 50 to 60 mm Hg and a cerebral perfusion pressure (CPP) of 60 to 80 mm Hg (Polson et al, 2005). Vasopressor support with epinephrine, norepinephrine, or dopamine is usually instituted to maintain adequate perfusion of vital organs.

Hepatectomy has been advocated based on anecdotal references as a terminal salvage therapy in patients with severe refractory circulatory dysfunction. It has also been suggested that adrenal dysfunction might be an additional contributing factor to circulatory collapse; however, the benefits of supplemental corticosteroids in these patients are still unknown (Harry et al, 2002).

Pulmonary Complications

Pulmonary compromise is usually present in 30% of patients with ALF. Impaired gas exchange leading to hypoxemia and mixed acidosis may favor progression of HE (Kramer et al, 1991; Larsen et al, 2000), and mechanical ventilation may be required to ensure oxygenation and to secure the airway in patients who progress to grade 3 encephalopathy. Caution should be maintained, as it has been observed that positive end-expiratory pressure (PEEP) can worsen cerebral edema. In patients with acetaminophen intoxication, acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) can occur in one third of patients with ALF and can cause intractable hypoxemia that may contribute to death (Baudouin et al, 1995).

Metabolic Disturbances

Common metabolic abnormalities in FHF include acid-base and electrolyte disorders, hypophosphatemia, and hypoglycemia. Among acid-base disorders, hypocapnia with mixed alkylosis is frequent in the early stages of FHF in more than 50% of patients (O'Grady et al, 1993), yet as ALF progresses, patients typically evolve to metabolic acidosis with respiratory alkalosis. At the same time, ALF is a catabolic state characterized by negative nitrogen balance and increased resting energy expenditure. It is recommended that metabolic homeostasis be carefully maintained, and overall nutritional status—as well as phosphate, glucose, potassium, and magnesium levels—must be frequently monitored (Polson et al, 2005). Enteral nutrition should be administered early whenever possible, avoiding excessive free-water provision that can result in hypoosmolality, which aggravates cerebral edema. No firm evidence proves that branched-chain amino acids are superior to other enteral preparations (O'Grady et al, 1989; Naylor et al, 1989). If enteral feeding is contraindicated, parenteral nutrition remains an option, but severe protein restrictions should be avoided.

MANAGEMENT

As a result of its high mortality, heterogeneity, and low frequency, FHF is extremely difficult to study, randomized controlled trials are limited (Kaidu, 2008), and optimal management remains poorly defined and center specific. Management should be centered in three main areas: 1) definition of etiology so that specific treatment can be provided in selected cases; 2) prevention, recognition, and early treatment of complications that could potentially lead to multiorgan failure and death; and 3) assessment of prognosis for distinguishing patients who have the potential to improve spontaneously versus those who will require liver transplantation and who should be urgently included on the waiting list (see Chapters 72, 73, and 97B).

Specific treatments are limited and are reserved exclusively for a few etiologies, and any available treatment should be delivered as early as possible (Box 97C.2). Some treatments have been systematically studied only for acetaminophen overdose. The role of N-acetylcysteine (NAC) in limiting liver injury through repletion of hepatic glutathione (Mitchell et al, 1974), improving prognosis, has been shown to be effective and safe in large case series (Harrison et al, 1990; Smilkstein et al, 1988, 1991) and in a small, controlled trial (Keays et al, 1991); firm evidence supports the utility of NAC administration, even when there is doubt concerning timing, dose ingested, or plasma concentration of acetaminophen, and NAC should not be withheld, even if ingestion was 48 to 72 hours before the patient sought medical attention. In acetaminophen overdose, oral NAC is recommended as first-line therapy in patients with mild or no encephalopathy, whereas intravenous NAC should be reserved

Box 97C.2

Indications for Transplantation

King's College Criteria

Acetaminophen-induced FHF

Arterial pH <7.3 or the following three factors:
- PT >100 sec
- Grade 3 or 4 encephalopathy
- Serum creatinine >300 µmol/mL

Non–acetaminophen-induced FHF

Prothrombin time >100 sec or three of the following:
- Age <10 years or >40 years
- Non-A, non-B hepatitis or drug- or halothane-induced FHF
- Bilirubin >300 µmol/L
- Jaundice to encephalopathy time >7 days
- Prothrombin time >50 sec

Clichy Criteria

Grade 3 or 4 encephalopathy *and*
- Factor V <20% (age <30 years) *or*
- Factor V <30% (age >30 years)

FHF, fulminant hepatic failure; PT, prothrombin time

for patients with advanced encephalopathy, hypotension, or some other reason to suggest that oral dosing might not be tolerated, such as vomiting or ileus. The length of NAC administration should be determined by clinical improvement—resolution of HE, improving coagulopathy, and declining transaminases—or outcome (death or liver transplantation) rather than by time or serum acetaminophen levels.

In addition to its role in limiting liver injury, NAC also has beneficial effects on systemic hemodynamic parameters and oxygen delivery to peripheral tissues (Harrison et al, 1991, 1996). Consequently, it has also been evaluated as a treatment for other forms of ALF unrelated to acetaminophen overdose. A recent study evaluated 173 patients with non-acetaminophen ALF, who were randomly allocated to receive either intravenous NAC or placebo; no benefit was demonstrated on 21-day survival, although transplant-free survival and 1-year posttransplant survival were improved. Furthermore, in the subgroup of patients with grade 1 or 2 HE, survival at 1 year was significantly better in those who received NAC than in all other individuals (Lee et al, 2009).

Even though there is still insufficient data to recommend specific therapies for ALF resulting from other etiologies, with the exception of prompt delivery in women with acute fatty liver of pregnancy or HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, several etiology-specific measures are recommended based upon experience, relative innocuousness of the measures, and the high mortality of the clinical syndrome. Specific measures have been suggested in ALF secondary to autoimmune hepatitis, HBV, and herpesvirus infection; ingestion of *Amanita* species; ischemia; and fatty liver of pregnancy.

Management of Complications of Acute Liver Failure

Cerebral Edema and Intracranial Hypertension

The most accepted pathogenetic theory of HE is the increased production of nitrogenous substances in the gut lumen, and effective medical management of cerebral edema in patients with ALF has been directed to the reduction of the generation and absorption of these products through orally administered lactulose and/or nonabsorbable antibiotics such as rifaximin. But the ability of these modalities to lower the risk of cerebral edema in patients with ALF has not yet been tested, and the utility of oral lactulose in this setting is controversial (Alba et al, 2003) and may even have detrimental effects, as it may increase gaseous distension of the bowel, predispose to aspiration, and foster intravascular depletion.

The monitoring of ICP by using an intracranial sensor is controversial (Blei, 1991; Schafer & Shaw, 1989; see Chapter 97B), but it is used by over half the transplantation programs in the United States (Hoofnagle et al, 1995) and around the world. Major complications are bleeding and infection, although complication rates vary among the different types of catheters used. It has been estimated to be 4% with epidural catheters, compared to significantly higher rates for subdural (22%) and parenchymal catheters (22%), with 1% to 5% of deaths as a direct result of catheter placement (Blei et al, 1993). Some centers report that ICP monitoring is useful to control CPP and to guide the decision to proceed with transplantation (Lidofsky et al, 1992). Before ICP monitor placement, a CT scan of the head is recommended in patients upon progression of encephalopathy or in those who experience an abrupt change in mental status; this is necessary to rule out any other rare intracranial pathology, especially bleeding.

The goal of therapy is to maintain ICP below 20 mm Hg and CPP above 50 mm Hg (Hoofnagle et al, 1995). Patients should be kept in an environment with minimal sensory and physical stimulation, and even endotracheal suctioning should be minimized. Fever increases ICP and should be vigorously treated with cooling measures. Hypo-osmolality, specifically hyponatremia, should be avoided and corrected immediately. The head of the patient's bed should be elevated to 30 degrees, except if CPP falls below 30 mm Hg, in which case the patient should be put in the supine position. Spontaneous hyperventilation should not be inhibited; this occurs regularly in patients with ALF and results in mild hypocapnia that promotes cerebrovascular constriction (Baudouin et al, 1995; Strauss et al, 1998).

The development of intracranial hypertension despite these prophylactic measures should prompt urgent treatment. First-line therapy includes increasing blood osmolality, with mannitol and/or hypertonic saline boluses to draw water from swollen astrocytes back into the intravascular space. Early reports demonstrated the efficacy of mannitol (1 g/kg body weight) to decrease ICP (Canalese et al, 1982; Nath & Gailbraith, 1986), yet it was not effective in returning ICP to an acceptably low level (<25 mm Hg) in patients with severe intracranial hypertension (>40 to 60 mm Hg) (Hanid et al, 1980). In addition, improvements usually were temporary and required multiple doses, with the attendant risk of hyperosmolality. When renal failure with oliguria is present, mannitol can be deleterious, so continuous venovenous hemofiltration or hemodialysis with polyacrylonitrile membranes is performed to decrease hyperkalemia, fluid overload, and ICP.

If no response is seen, or relapse of ICP is observed after mannitol administration, alternative measures may include the use of hypertonic saline boluses, the induction of therapeutic hypothermia, or sedation with propofol (Wijdicks & Nyberg, 2002), barbiturates (Lidofsky et al, 1992), or intravenous boluses of indomethacin (Tofteng et al, 2004). Indomethacin perfusion (25 mg IV by every peak of ICP) has been shown to normalize ICP and CPP, probably through a direct arteriolar

constriction of cerebral vessels (Clemmesen et al, 1997). Induction of moderate hypothermia (32° C to 33° C) is useful in treating uncontrolled elevations in ICP (Ginsberg et al, 1992; Jalan et al, 1999; Kurt et al, 1996; Roberts & Manas, 1999), probably by preventing hyperemia, altering brain ammonia or glucose metabolism, or by a combined effect. Concern remains over potential deleterious effects of hypothermia on risk of infections, coagulation disorders, cardiac arrythmias, and liver regeneration rates (Schubert, 1995). As a final desperate measure in patients with intracranial hypertension that is refractory to all medical therapy, total hepatectomy has been advocated to remove the major source of proinflammatory cytokines that contribute to cerebral hemodynamic derangements.

The observation that patients with ALF may have subclinical, nonconvulsive seizure activity that could result in increased cerebral blood flow that favors cerebral edema provided the rationale for the evaluation of seizure prophylaxis with IV infusion of phenytoin in these patients. Two randomized controlled trials in patients with ALF and advanced HE came to different conclusions with regard to the efficacy of phenytoin in preventing seizures and cerebral edema and in influencing survival (Bahtia et al, 2004; Ellis et al, 2000).

Prognostic Factors and Criteria for Liver Transplantation in Patients with Acute Liver Failure

In spite of great advances in the intensive care management of patients with ALF, patients managed exclusively with medical supportive therapy have poor survival. The only therapy proven to significantly improve outcome is OLT, which is associated with 1-year survival rates greater than 80% (Lee et al, 2008). Unfortunately, the window of time is very narrow for the application of liver transplantation, as the procedure must be performed at the optimal time, not too early but never too late, to avoid unnecessary transplantations in patients who would survive otherwise and to prevent transplantation in those who would not survive, even with a new liver (Lo, 2008).

Accurate prognosis, especially early predictors of death, are exceedingly difficult to obtain; however, several prognostic indicators have been suggested that allow early identification and listing of those patients who would not survive without a transplantation. Prognosis is dependent on factors such as age, etiology of hepatic failure, clinical and biologic status on admission, interval between onset of jaundice and clinical encephalopathy, degree of encephalopathy, severity of coagulopathy, AFP levels, arterial ketone body ratio, arterial pH, bilirubinemia, renal function, phosphatemia, and extent of parenchymal necrosis on biopsies, even though liver histology has not proven accurate to predict outcome and is not recommended for routine use.

Coagulation factor activities are significant indicators of prognosis. Factor V activity was found to be the most effective independent predictor of survival among 115 patients with fulminant HBV in a French study. Plasma protein actin-free Gc globulin, a member of the extracellular scavenger system, is synthesized by the liver and was shown to be decreased in ALF; it correlates with poor survival.

An ideal model to predict outcome would ensure that all patients who need transplantation may get one (*positive predictive value*), and all patients who may survive would not (*negative predictive value*), but presently none exists that completely fulfills these goals (O'Grady, 2007). The ability to predict the likelihood of spontaneous recovery or death without OLT remains of paramount importance in patients with ALF (see Chapters 72 and 97B). Many criteria have been proposed to anticipate the probability of death without OLT (Box 97C.3), but data are insufficient to recommend a particular scheme, given that none have been found to be adequately sensitive and specific.

Box 97C.3

Prognostic Factors in Fulminant Hepatitis

Age
Etiology of acute liver failure
Encephalopathy
King's College criteria
Clichy-Villejuif criteria
Arterial blood lactate
Serum phosphate concentrations
α-Fetoprotein levels
Model for End-Stage Liver Disease score
Body mass index
Serum creatinine levels
Extent of necrosis in biopsies
Computed tomographic liver volume/standard liver volume

Outcome in children is more favorable (Dhawan et al, 2004). In the series of Dhiman and colleagues (2007), the survival rate in patients older than 50 years was lower than in younger patients. In an American study by Ostapowicz and colleagues (2002), age does not seem to correlate with outcome, although spontaneous survival was higher in patients aged 26 to 35 years. The lowest survival rate (33%) corresponds to patients older than 65 years, who often have more comorbidities but less acetaminophen intoxication.

In a study by Brandsaeter and colleagues in 2002, of 315 patients listed for transplantation, spontaneous survival was higher in patients with HAV infection (43%), followed by acetaminophen overdose (31%), HBV infection (8%), liver disease of indeterminate origin (7%), and other drug-induced ALF (0%). In other series the same favorable prognosis corresponds to acetaminophen overdose, HAV infection, and pregnancy-related ALF but not to patients with disease of an indeterminate cause, non–acetaminophen-related ALF, HBV infection, autoimmune hepatitis, Wilson disease, or Budd-Chiari syndrome (Lee et al, 2008; Ostapowicz et al, 2002). A higher degree of encephalopathy (grades 3 and 4) on admission also seems to be a significant independent variable of poor outcome (O'Grady et al, 1989).

Two statistical models have been developed for predicting outcome: one by the KCH group (O'Grady et al, 1989) in London, based on a retrospective cohort of 588 medically managed ALF patients and later validated in an additional prospective study of 175 ALF patients; the other by the Paris group (Bernuau et al, 1986, 1991). At the present time, they are the most widely used prognostic criteria.

At KCH, prognostic criteria discrimination was etiology based, as predictors were stratified according to whether ALF was secondary to acetaminophen ingestion, a condition in which recovery is more probable even in the presence of severe synthetic dysfunction. In patients with acetaminophen-induced fulminant hepatitis (FH), a pH less than 7.3 at 24 hours or more after overdose is an indication per se for liver transplantation, after appropriate volume replacement and correction of

hypothermia. Otherwise, liver transplantation should be considered in the presence of all three of the following factors: 1) PT greater than 100 seconds, 2) grade 3 or 4 encephalopathy, and 3) serum creatinine (SCr) greater than 300 μmol/L. In non–acetaminophen-related FH, the decision whether to transplant is based on the presence of three of the following: 1) non-A, non-B hepatitis; 2) drug-induced hepatitis; 3) halothane exposure; 4) serum bilirubin greater than 300 μmol/L; 5) PT greater than 50 seconds; 6) age younger than 10 years or older than 40; or 7) time from jaundice to encephalopathy of more than 7 days. PT greater than 100 seconds in isolation is considered an indication for liver transplantation (O'Grady et al 1989, 1991).

In France, selection was made on the basis of factor V level. According to this group, patients younger than 30 years with FH and encephalopathy with a level of factor V less than 20%, or less than 30% in patients older than 30 years, should be included on the transplant list (Bernuau et al, 1986; Bismuth et al, 1987, 1995).

The KCH criteria have good clinical applicability with few differences in sensitivity and specificity as reported by Shakil and others (2000). Generally, KCH criteria are useful in predicting death, although the absence of these criteria is not predictive of survival.

Increases in arterial blood lactate (Bernal et al, 2002) and serum phosphate concentrations (Schmidt & Dalhoff, 2002) are factors predictive of poor prognosis in patients with acetaminophen-induced ALF, and these have been proposed as additional criteria to those initially reported by the KCH group. Similarly, serum AFP levels increase in patients undergoing rapid liver regeneration, and increasing levels indicate a better prognosis (Schmidt et al, 2005). Upon admission, serum levels of Cc-globulin, a plasma protein synthesized in the liver (Schiodt et al, 1996), could be used to make decisions about liver transplantation. More recently, a high level of soluble CD163 from activated macrophages has been proposed to predict mortality in patients with ALF (Moller et al, 2007). Interestingly, Volkmann and colleagues (2008) found that caspase activation, which increases cytokines IL-6 and TNF-α, is associated with spontaneous recovery.

In patients with non–acetaminophen-induced ALF, the MELD score has been proposed to identify patients with the worst prognosis; other patients have shown a high rate of spontaneous recovery independent of MELD score (Kremers et al, 2004). Yantorno and colleagues (2007) suggest that MELD scores obtained upon admission may be helpful to establish the optimal timing for pre-OLT evaluation and listing. Nevertheless, they do not propose a cutoff value for MELD.

Dhiman and colleagues (2007) describe another prognostic model and compare its performance with the KCH criteria and to the MELD score. They identify six parameters: age over 50 years, time from jaundice to encephalopathy of more than 7 days, grade 3 to 4 encephalopathy, cerebral edema, PT greater than 35 seconds, and SCr above 1.5 mg/dL. The presence of any three of these factors indicates a poor prognosis. A comparative evaluation suggests that this model was better than both the MELD and the KCH criteria at predicting prognosis; however, according to O'Grady (2007), this is not a valid comparison, because it takes into account only the initial set of data, whereas the KCH model is a dynamic process; the same applies to the study by Yantorno and colleagues.

Barshes and colleagues (2006) made a distinction between low-risk patients (5-year survival, 81%) and high-risk patients (5-year survival, 42%), depending on the four risk factors present at the time of listing for liver transplantation. These factors include 1) recipient age older than 50 years, 2) a BMI of 30 or more, 3) a history of life support, and 4) SCr level above 2 mg/dL. Risk of mortality after transplantation increases by approximately 150% for each additional point.

Detectable liver atrophy has classically been associated with a poor prognosis (Rueff, 1971). Yamagishi and colleagues (2009) reported that the ratio of the estimated liver volume (ELV) to the standard liver volume (SLV) reflects the prognosis of patients with ALF very well. They investigated the usefulness of the ratio of the computed tomography–derived liver volume (CTLV) to the calculated SLV to establish a new prognostic formula to predict the course of ALF. The CTLV/SLV ratio was calculated both at the time of ALF diagnosis and 5 days later. In patients who recovered, liver atrophy was not found at day 0 or at day 5, and liver atrophy progressed in those who died or underwent liver transplantation. Sensitivity was 94.1%, and specificity was 76.9%, but the findings of this small study need to be confirmed in a larger series. In spite of the criteria described above, the controversy about the best prognostic model for ALF will continue.

Whether or not patients are listed for liver transplantation, they should be monitored for the many complications of ALF, as they progress to the point of recovery, death, or transplantation. Likewise, patients listed for transplantation may develop complications that preclude this intervention or may occasionally show unexpected signs of recovery before a donor organ becomes available. In this dynamic process, the final decision on transplantation is made when an organ is available. Neurologic limits to transplantation are controversial. Brain death, uncontrolled systemic sepsis, and hemodynamic instability as a result of multiple organ failure are considered absolute contraindication for liver transplantation.

Survival rates at 1 year of patients undergoing liver transplantation for ALF range between 61% and 76% and are 7% to 15% less than in patients transplanted for chronic end-stage liver disease (European Transplant Registry; Freeman et al, 2008). This is due to the fact that even when liver transplantation is finally achieved, patients eventually die because of poor health status at the moment of transplantation—brain damage, sepsis, or multiorgan failure—or because of the use of marginal or ABO-incompatible donor organs (Farges et al, 1995; Gugenheim et al, 1990). The higher retransplantation rate in patients with ALF is due to the use of these organs, giving way to increasing rates of acute rejection, primary graft nonfunction, and intrahepatic biliary strictures.

PREOPERATIVE MANAGEMENT (SEE CHAPTER 97B)

Once the need for liver transplantation is established, the patient is included on an emergency list (UNOS status I) and is prepared for the procedure (Wiesner et al, 2004). Coagulation defects should be corrected with plasma, a balance between fluid restriction and a satisfactory CPP should be achieved, and the increase of brain edema should be avoided. A catheter to monitor ICP is useful in patients with grade 4 encephalopathy. We usually perform plasmapheresis immediately before the surgical procedure for toxin removal and FFP supply.

In 1993, Ringe and colleagues described a two-stage total hepatectomy with temporary portacaval shunt, a procedure

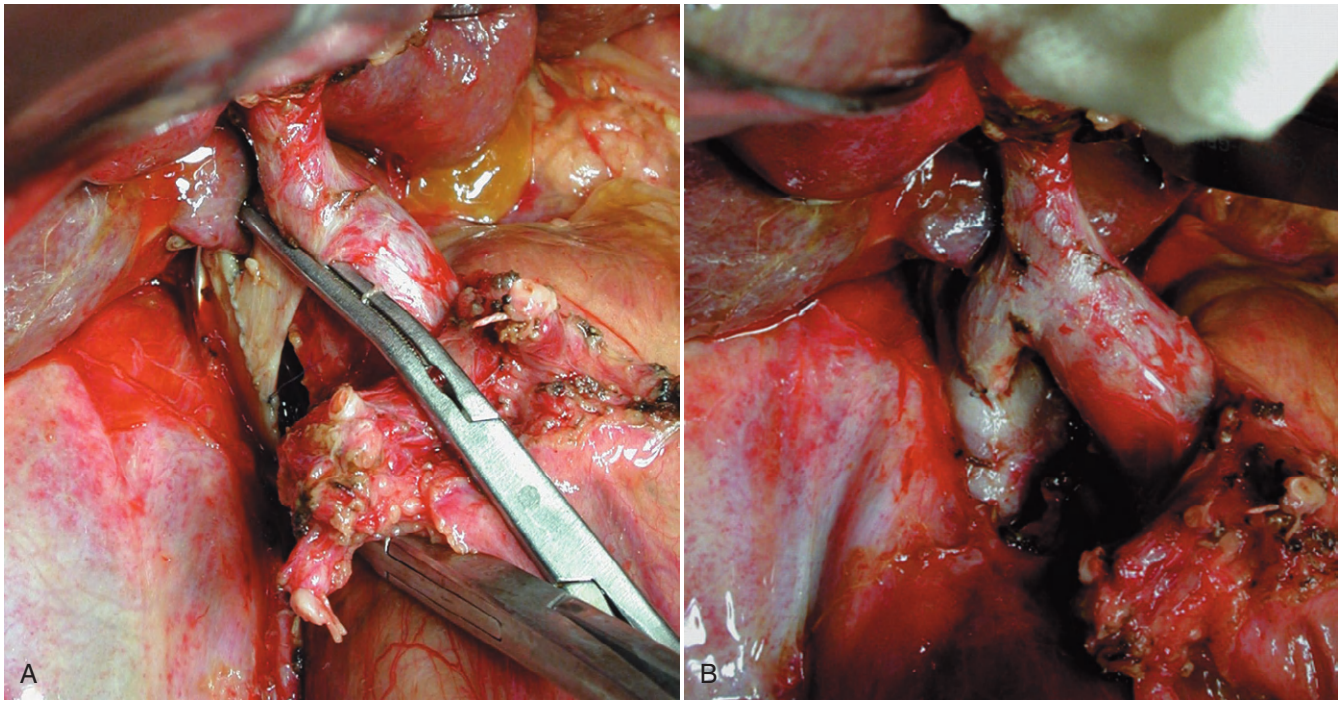


FIGURE 97C.1. Shunt portocava with only right branch. **A,** The right portal vein is cross-clamped, and the anastomosis done. **B,** After removing the clamp, the shunt is functioning.

carried out in patients who have *toxic liver syndrome* with cerebral edema or multiorgan failure; the patient is left anhepatic and subsequently undergoes liver transplantation. It has been reported that the longest period of time a patient was left anhepatic was 21 hours. Although this extreme procedure can be lifesaving, it is exceptional (Ferraz-Neto et al, 2008) and is only justified by the fact that hepatectomy decreases the serum concentration of circulating proinflammatory cytokines—IL-1, IL-6, and TNF-α—which may be important in the pathogenesis of intracranial hypertension in patients with FHF (Jalan et al, 2002a).

The surgical procedure is basically the same (OLT, see Chapter 98), but other details must be taken into account. For one, patients run a serious risk of bleeding during surgery as a result of severe coagulopathy. The absence of portal hypertension and the presence of an atrophic liver facilitate hepatectomy; however, to avoid brain damage, the surgical approach varies according to the hemodynamic state of the patient and the level of the ICP.

Because of the absence of portal hypertension, the total clamping of the inferior vena cava (IVC) and the portal vein (PV) is poorly tolerated. Hence it is necessary to perform a venovenous bypass with pump-assisted venous return from the IVC and PV to the superior vena cava (SVC) or to preserve the IVC using the *piggyback technique* (Tzakis et al, 1989). Belghiti and colleagues (1995) reported that the maintenance of portal and caval flow during hepatectomy and graft implantation avoids drops in venous return and cardiac index and prevents other hemodynamic changes that result from venous clamping, release of metabolites, and secondary effects of fluid management seen in patients undergoing liver transplantation (LT) for fulminant and subacute liver failure in the absence of portosystemic venous collaterals. Clamping of the PV in this situation may lead to hemodynamic instability and cerebral edema, thus worsening the previous condition; it also leads to splanchnic venous congestion with associated hemorrhage and intestinal edema.

Performing a temporary portacaval anastomosis (end-to-side portocaval shunt) facilitates liver mobilization without changes in the hemodynamic state that could increase the ICP and cause brain damage. A review by Davila and colleagues (2008) supports its use. In adult patients with a very unstable hemodynamic condition, the portocaval shunt using only the right portal branch is recommended, leaving the left branch unclamped (Fig. 97C.1) to avoid interruption of the portal flow. After the shunt has been opened, total hepatectomy is completed by dividing arterial branches, left PV, and major hepatic veins without occlusion of the IVC (Kawasaki et al, 1996). On the other hand, children weighing less than 20 kg tolerate IVC and PV clamping quite well. Also, a rapid clamping and liver removal improve their hemodynamic condition.

Careful anesthetic management of the patient is necessary: the operating table should be positioned at 30 degrees, and fluctuations in ICP should be carefully controlled, and steps to avoid an increase in ICP should be taken to protect the brain; in addition, ICP monitoring should be maintained for 24 hours after liver transplantation, because pressure may increase after surgery (O'Grady et al, 2008). Longer monitoring may be required in cases of poor graft function.

Given the urgency of liver transplantation, marginal donors are often accepted, thus increasing the risk of poor function or primary nonfunction. Initially, ABO-incompatible livers were widely used, but discouraging results have limited their use nowadays (Gugenheim et al, 1990); few reports show good results (Ascher et al, 1993; Toso et al, 2007), although the final decision lies with the surgical team.

Living-Donor Liver Transplantation (See Chapter 98C)

Living donors (LDs) are the only source of organs in countries where the availability of deceased donors is severely restricted, such as in Asia, or scarce, as in Latin America. The use of living-donor liver transplantation (LDLT) for children suffering from ALF has gradually gained acceptance, because the procedure's lifesaving potential by far outweighs any ethical aspects (Emond et al, 1993; Uemoto et al, 2000). Expansion of LDLT to adult patients with ALF has recently been reported (Lo et al, 1997; Marcos et al, 2000); however, both the donor risk and the ethical dilemma are involved in this issue, because potential donors are likely to be brothers, sisters, children, or spouses, in other words, those who are influenced by the imminent death of the patient.

On the other hand, compared with deceased-donor liver grafts, living donor grafts offer three distinct advantages: 1) early transplantation of ALF patients, 2) better graft function, and 3) shorter cold-ischemia time; however, a satisfactory survival rate of patients with ALF undergoing adult LDLT is a prerequisite to justify the risk of emergency liver transplantation. Ikegami and colleagues (2008) use smaller grafts, wherein graft volume (GV) in proportion to standard liver volume is 30% to 35% for ALF. The reason for this is that ALF is an acute event, and most patients are usually healthy beforehand and do not have portal hypertension that allows use of the left lobe in most cases. In other countries with limited availability of cadaveric donors, LDLT in patients with ALF is performed with similar results (Uribe et al, 2008), especially in children, although it is still controversial among adults.

In a report by Campsen and colleagues (2008), only 14 of 1201 potential LDLT recipients (1%) in the A2ALL study, which evaluated LDLT in the United States, were diagnosed with ALF. Among these, 10 received a living-donor graft, and their survival rate was similar to that of patients who received cadaveric grafts, and no recipients died on the waiting list. The authors concluded that LDLT is rarely performed for ALF in the United States but could be performed with acceptable recipient and donor outcomes.

The increased use of full-liver grafts from donors after cardiac death (DCD) has had a beneficial impact on elective liver transplantation in adults; however, these grafts are more susceptible to poor initial function, and most centers are reluctant to consider their use as segmental grafts, let alone in the setting of ALF, in which good initial function is imperative. Nevertheless, Perera and colleagues (2009) describe the use of a segmental graft from a living or heart-beating deceased donor and report the successful outcome in two children with ALF, aged 6 weeks and 6 years.

Auxiliary Liver Transplantation

Auxiliary partial orthotopic liver transplantation (APOLT) has been used in ALF as a bridge to survival without the need for lifelong immunosuppression. The precise indications have not yet been determined but are molded by two important considerations: the ability of the native liver to regenerate to normal morphology with time and the absence of a clinical need for the immediate benefits of total removal of the diseased liver. Proponents of auxiliary transplantation for ALF claim that in most cases, had the patient survived, the native liver would have recovered. If true, then removal of the entire native liver during transplantation for ALF eliminates any such recovery and unnecessarily commits the patient to the lifelong risks of immunologic rejection and immunosuppression (Bismuth et al, 1996; (Kasahara et al, 2005).

The surgical procedure for APOLT is more complex than the procedure for OLT. The liver is placed in orthotopic position, and both the graft and the recipient's liver are reduced; this is done on opposite sides, removing left segments of the recipient's liver and right segments of the graft, or vice versa). The absence of fibrosis in the native liver must be confirmed by a frozen section biopsy.

The key issue regarding APOLT is determining when native liver regeneration is likely to occur, which is sometimes difficult. Monitoring includes hepatobiliary iminodiacetic acid (HIDA) scintigraphy, computed tomography (CT), and biopsy when necessary. When sufficient regeneration of the native liver is evident, immunosupression can be discontinued according to two different options: *abrupt discontinuation* often requires surgical removal of the graft because of severe and symptomatic rejection; *progressive tapering* of immunosuppression with the aim of inducing a slowly progressing chronic rejection with subsequent atrophy of the graft is the approach preferred by most groups (Belghiti et al, 2004a).

In 2002, Jaeck and colleagues reported a series of 15 patients receiving APOLT, of which 10 are alive, and 6 of those are free of immunosuppression with a regenerated native liver. Recently, Azoulay and colleagues (2001) compared the results of APOLT with those of total orthotopic liver transplantation (TOLT) in the treatment of ALF. They showed similar survival rates after both procedures, but the postoperative complication rates—particularly those of biliary complications, neurologic sequelae, and retransplantation rate—were significantly higher after APOLT. In the Paul Brousse experience, both full native liver regeneration and discontinuation of immunosuppression were observed only in 25% of the cases.

Acetaminophen-induced liver failure and hyperacute syndromes are more likely to regenerate to normal morphology when regeneration does occur. In seronegative hepatitis and the subacute syndromes, regeneration may occur, but it does so at the risk of significant fibrosis. Quaglia and colleagues (2008) described the evolution of histologic changes in native livers after APOLT for ALF. In up to 62.5% of patients, the native liver regenerates to full recovery. In all such patients, immunosuppression can be reduced, and in the vast majority (80%), it can be ultimately suspended. Acetaminophen toxicity in particular is an excellent indication for APOLT, with full native liver recovery occurring in 100% of surviving patients with an auxiliary graft.

Peter Lodge and colleagues (2008) proposed a new approach for patients with ALF resulting from acetaminophen overdose, fulfilling KCH criteria for super-urgent liver transplantation. This new approach consists of a subtotal hepatectomy—that is, resection of segments IVb, VI, VII, and VIII—to remove 75% of liver volume and reduce the toxic liver, followed by auxiliary transplantation with a whole liver (AWOLT; maximal liver volume to aid recovery) and gradual withdrawal of immunosuppression after recovery over a 2- to 3-month period. The results in 13 patients treated with this approach were compared with those in 13 patients who had undergone OLT in the same period: they were similar in morbidity and mortality rates but better in terms of quality of life, because they did not need long-term immunosuppression.

For the authors (Lodge et al, 2008), temporary support by AWOLT with a subsequent liver regeneration may offer a better quality of life in all domains when compared with OLT. This could be due to the fact that patients can lead a more normal life without the effects of immunosuppression. Bernal and colleagues (1998) reported that only 19 of 33 survivors of OLT for acetaminophen-related ALF were back to a normal lifestyle. In contrast, all 8 of our successful AWOLT patients (Lodge et al, 2008) have returned to a normal lifestyle, including full-time education or employment, and all seem to be in normal relationships. Except for these latter results, and results presented in a paper by Girlanda and colleagues (2005), outcome after APOLT is poor; this is reflected in registry data, with 1-year survival just barely over 50%.

Finally, in case of fulminant hepatitis (FH), APOLT should only be proposed to select patients with good chances of liver regeneration; those aged less than 40 years with fulminant, rather than subfulminant, hepatitis resulting from HAV or HVB or acetaminophen toxicity (Jaeck, 2007). When the native liver has regenerated, it is recommended that immunosuppression be reduced gradually to induce a progressive atrophy of the graft, which is left with the patient. Removal of the auxiliary graft should not be attempted.

LIVER-SUPPORT SYSTEMS

Liver supports are designed to improve the life-threatening symptoms often caused by ALF. Their goal is to maintain patients with FH until their own livers regenerate or to maintain patients in a stable condition until liver transplantation can be performed, and it might decrease the mortality rate in patients with ALF. To accomplish these goals, a liver-support device should be able to remove toxic substances from the patient's blood and to provide temporary liver function, until either transplantation or functional recovery occurs. Because of the scarcity of donor organs, liver-support technologies have been developed in the last 2 decades and have been clinically tested with the intent of supporting a patient in ALF.

Developing an effective liver-support system has proven difficult, because of the complexity of liver functions that must be replaced and because of heterogeneity of the patient population. Nonbiologic systems may have a role in the treatment of specific forms of liver failure, when the primary goal is to provide blood detoxification and purification. Biologic systems appear to be useful in treating liver failure when the primary objective is to provide whole-liver function that has been impaired or lost.

Two major categories of devices are currently being tested (Phua & Lee, 2008): *artificial liver support* is cell free, purely mechanical, and includes albumin dialysis; *bioartificial systems* contain cellular material from human or animal livers or hepatocytes. A truly effective device will perform three functions: 1) detoxification, 2) biosynthesis, and 3) regulation; however, only bioartificial systems can perform all three functions; artificial liver support only detoxifies. Support of the failing liver is reviewed in further detail in Chapter 73.

Artificial Liver Support

Artificial liver support (ALS) is used to control serious symptoms of FH, such as brain edema, which may induce postoperative neurologic deficit. The key role of ALS is to remove toxins, both known and unknown, that are responsible for HE and multiorgan failure secondary to liver failure. Hemodialysis, hemofiltration, hemodiafiltration, and hemadsorption are methods that have failed to show any major outcome in early randomized trials (Davenport et al, 1993; Kramer et al, 2001). These systems remove toxins that result from hepatic failure but are limited by their inability to provide missing liver-specific functions.

One problem with these techniques lies in the difficulty of removing toxins bound to large protein molecules, such as albumin. To address this, Inoue and colleagues (2009) recommended the use of plasma exchange combined with hemodiafiltration. Using large buffer volumes is a promising and effective bridging method to liver transplantation that enables patient recovery from coma, prevents brain edema, and identifies those patients in need of urgent liver transplantation. Several nonrandomized studies show that the use of plasmapheresis increases hepatic blood flow, decreases blood ammonia levels, and could reduce mortality rates (Clemmesen & Clemmesen 2001; Du et al, 2005; Li et al, 2004).

Molecular Absorbent Recycling System

Proposed by Stange and colleagues (1993), the molecular absorbent recycling system (MARS) blood detoxification system has been tested in thousands of patients, but additional well-conducted controlled studies are warranted to better define the role of MARS in the treatment of patients with acute hepatic failure and acute exacerbation of chronic liver disease. MARS is a two-circuit system composed of a blood circuit and a secondary circuit. The blood circuit passes the patient's blood through a high-flux dialyzer, making the membrane impermeable to albumin. This membrane is permeable to water-soluble, low- and medium-molecular-weight substances. The opposing side of this membrane consists of 600 mL of 20% human albumin dialysate, which makes up the secondary circuit; this circuit provides conventional low-flux dialysis, as well as detoxification, over absorbent columns that include an anion exchange resin and an activated charcoal column, allowing transport of ions of low molecular weight (LMW).

The key feature to the function of albumin dialysis is the concentration gradient of LMW substrate between the patient's blood and the 20% albumin in the secondary circuit. This concentration gradient allows diffusible LMW substrates to flow down their gradient over the membrane, where they are transiently bound by albumin in the secondary circuit (Steiner et al, 2004). The LMW substrate is then removed from the system by conventional dialysis and hemodiafiltration within the secondary circuit, and the 20% albumin dialysate is then recirculated. The coagulation profile present in liver failure obviates the need for anticoagulation in most patients being treated with MARS.

A meta-analysis of four randomized controlled trials concluded that treatment with MARS provided no survival benefit (Khuroo et al, 2004). Aside from one study suggesting that 4 out of 14 patients (29%) with relatively mild liver failure avoided transplantation after MARS (Camus et al, 2006), most recent descriptive reports show that short-term mortality rates for patients treated with MARS but without transplantation ranged from 78% to 100% (Chiu et al, 2006; Wai et al, 2007).

As a proposed bridge to transplantation, the study of Novelli and colleagues (2007) evaluated the change in MELD score in patients with acute-on-chronic liver failure awaiting

transplantation after treatment with MARS. Inclusion criteria were a MELD score above 20, bilirubin greater than 15, encephalopathy higher than grade 2, and INR above 2.1. Patients were treated with MARS for a minimum of five treatments and a maximum of 20 over 3 months. MELD was evaluated after treatment with MARS and at a 3-month follow-up, and significant improvement was reported at both time points. Hetz and colleagues (2006) also proposed using MARS for allograft dysfunction after transplantation.

Mortality rate aside, MARS improves other parameters, including bilirubin levels, especially conjugated bilirubin; encephalopathy; renal function; and hemodynamics (Heemann et al, 2002); it also decreases serum copper levels in Wilson disease (Sen et al, 2002). Although these effects may be mediated by cytokine clearance, it is unclear whether MARS decreases serum cytokine levels significantly (Guo et al, 2003; Stadlbauer et al, 2006). Importantly, MARS may worsen coagulopathy and bleeding (Bachli et al, 2007), hence minimization of anticoagulation should be considered; in addition, it can cause hypoglycemia in the absence of glucose-containing dialysate.

Fractionated Plasma Separation and Absorption (Prometheus)

The Prometheus system (Fresenius Medical Care, Bad Homburg, Germany) uses fractionated plasma separation. Whereas MARS is a two-circuit system separated by an albumin impermeable membrane, Prometheus utilizes a membrane with a 250-kDa cutoff between circuits, thereby making the membrane permeable to albumin and hence to albumin-bound toxins. Although a large portion of the toxins that accumulate during liver failure are water soluble, many are still bound by albumin; therefore fractionated plasma separation may be advantageous with regard to toxin removal. The patient's endogenous albumin loads the secondary circuit that distinguishes Prometheus from MARS. Since albumin-bound toxins can enter the secondary circuit by convection, as well as by diffusion, in theory, Prometheus should offer more effective detoxification than MARS does (Rifai et al, 2003).

In a retrospective analysis by Evenepoel and colleagues (2006) of prospectively collected data on patients with acute-on-chronic liver failure treated with either Prometheus or MARS for 2 to 5 consecutive days, blood clearance of toxins was superior when patients were treated with Prometheus as compared with MARS at all time points; in addition, certain substances that are tightly bound to albumin, such as unconjugated bilirubin, were exclusively cleared by Prometheus. The limited data available suggest that Prometheus maybe used as a bridge to transplantation, rather than to recovery, as mortality rates with Prometheus treatment alone without transplantation exceed 80% (Skwarek et al, 2006).

Bioartificial Support Devices

Bioartificial supports are cell-based systems that provide both metabolic support and detoxification. A bioartificial liver (BAL), which incorporates hepatocytes from various sources, has the theoretic advantage of not only providing blood purification through dialysis but also of providing the hepatocyte-specific functions lost in ALF (Rozga et al, 1993). Although primary human hepatocytes appear to be the most appropriate cells for use in a bioartificial liver, some factors have prevented their use, such as lack of availability and loss of function when cultured. For this reason, immortalized cell lines, such as C3A human hepatoblastoma, have been studied in vitro and have been utilized; however, many problems will likely preclude their use in a therapeutically successful bioartificial liver. Currently, porcine hepatocytes are the most reasonable choice, and several systems have been clinically assessed.

HepatAssist (Arbios Systems, Allendale, NJ) is a device that uses a hollow-fiber extracorporeal bioreactor loaded with 7 billion cryopreserved porcine hepatocytes. The system also utilizes a charcoal column, combined oxygenator/blood warmer, and perfusion pump, all driven by a plasmapheresis machine. The separation between hepatocytes and patient circulation is by a semipermeable membrane that avoids the need for immunosuppression. A randomized, controlled, multicenter Phase II and III clinical trial was conducted on patients with fulminant/subfulminant liver failure, and those with primary graft nonfunction were included (Demetriou et al, 2004). The study demonstrated favorable safety, but it failed to demonstrate statistical significance in improving 30-day survival in the overall study population.

Other cell-based systems include the ELAD system (Vital Therapies, San Diego, CA), which utilizes the C3A human hepatoblastoma cell line; the MELS system (Charité Medical Center, Berlin, Germany); BLSS (Excorp Medical, St. Paul, MN); and AMC BAL (Amsterdan Medical Center, The Netherlands). The last three use primary porcine hepatocytes but differ in cell source and mass (100- vs. 500-g cartridge), use of plasma or whole blood, the rate of perfusion (20 to 200 mL/min), and duration of treatment (continuous vs. intermittent). All of these systems have been used in clinical trials, been proven safe, and have shown at least some biologic effect, but none has received FDA approval for use in the United States.

The next generation of BAL systems is a hybrid that uses cellular and noncellular components in an albumin-based extracorporeal perfusate circuit that combines albumin dialysis, charcoal therapy, and dialysis with hepatocyte cell based therapy. In preliminary studies, one system using 200-g porcine hepatocyte spheroids provided cerebral protection not seen in the control group (Nyberg et al, 2005).

A Cochrane review of support systems concluded that results have not yet demonstrated that these systems affect survival in ALF (Liu et al, 2004). No single system has reproducibly demonstrated improvement in patient mortality; however, with the advent of new technology and improved cell acquisition techniques, further randomized controlled trials will be necessary to determine the role of artificial and BAL support devices in the treatment of patients with ALF. (McKenzie et al, 2008). Ex vivo liver perfusion was attempted in the past, before the era of liver transplantation, with disappointing results; but in one modern study, pig and human livers unsuitable for transplantation were successfully used as a bridge to transplantation in a small number of patients (Chari et al, 1994).

Hepatocyte Transplantation

After success in animal models, human hepatocyte transplantation for ALF was attempted. Strom and colleagues (2006a, 2006b) infused cryopreserved human hepatocytes into a small number of children with limited success. Further progress in many areas will be needed, however, before this approach is clinically viable.

CONCLUSION

Acute liver failure is a dramatic clinical condition that puts a healthy patient in a deadly situation. Improvements in intensive care management have optimized survival, yet the only definite treatment in a number of patients is emergency liver transplantation. Any effort to maintain a patient in good clinical condition as a bridge to transplantation through plasmapheresis, artificial support, total hepatectomy, or other measures is worthwhile and should be further evaluated. Carrying out randomized studies may be difficult within this context, but such studies may be useful whenever they prove effective in individual cases.

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CHAPTER 97D

Liver transplantation for hepatocellular carcinoma

Garrett R. Roll and John Roberts

OVERVIEW

Cancer of a solid organ is an uncommon indication for organ transplantation, but hepatocellular carcinoma (HCC) is an important exception to that general rule (see Chapter 97A). HCC is the most common tumor treated with whole-organ transplantation, and it is listed as the primary indication in approximately 15% to 20% of liver transplantations. The existing treatment options for HCC include hepatic resection, local ablation, or liver transplantation, and in the last decade, transplantation has become the therapy of choice for early-stage disease. The literature lacks randomized controlled trials regarding the treatment of HCC; most centers therefore base their practice guidelines on local experience, retrospective data, theoretic decision analyses, and the availability of treatment options.

Ever since the first liver transplantation was performed in a patient with HCC in the 1960s, recurrence has been a concern. Prior to the late 1990s, liver transplantation for HCC carried high recurrence rates, and the 2-year survival was only about 30%. The poor outcomes were due to the consensus at that time to treat smaller tumors with liver resection and more advanced disease with liver transplantation. Discouraging results plagued liver transplantation for HCC, until it was noted that subgroups of patients with smaller tumors who underwent transplantation achieved better outcomes (Pichlmayer, 1993).

A group from Milan, Italy, conducted a prospective trial, published in 1996, in which patients with smaller tumors achieved 4-year survival rate of 75%, equivalent to the survival for non-HCC patients who underwent transplantation (Mazzaferro et al, 1996), and similar results were seen in the United States (Venook, 1993). Resultant changes in patient selection, dictated by these *Milan criteria,* allowed similar results to be reproduced at other centers (Jonas et al, 2001; Llovet et al, 1998), and the United Network of Organ Sharing (UNOS) adopted these criteria in 1998 and gave priority for transplantation to HCC patients. This priority, coupled with the rise in patients with hepatitis C virus (HCV), who frequently develop HCC, fueled the rapid expansion of this indication for transplantation. This chapter will discuss liver transplantation for HCC, concentrating on its unique pathophysiology and how it relates to diagnosis and dictates therapy.

HEPATOCELLULAR CARCINOMA

HCC is the fifth most common cancer and the most common primary liver tumor (see Chapter 80). This disease develops in the setting of cirrhosis in more than 90% of cases (Fattovich et al, 2004). The risk of HCC development in patients with cirrhosis from any cause is about 2.0% to 6.6% per year versus 0.4% for patients with viral hepatitis without cirrhosis (Benvegnu et al, 2004; Degos et al, 2000; Ikeda et al, 1993a; Llovet et al, 2003; Sangiovanni et al, 2004; see Chapters 64 and 70).

The incidence of HCC has been rising since the late 1990s (Bosch et al, 2004; Deuffic et al, 1998; El-Serag & Mason, 1999; Parkin et al, 2001; Stroffolini et al, 1998; Taylor-Robinson, et al, 1997), a trend that is expected to continue for at least the next 2 decades because patients who were infected with HCV 20 to 30 years ago are currently living with cirrhosis and are aging (El-Serag, 2004). In addition, the epidemic of obesity and resultant nonalcoholic fatty liver disease (NAFLD) can be expected to generate cirrhotic patients at risk for the foreseeable future (see Chapter 65). Currently, only the incidence of thyroid cancer is rising faster than the incidence of HCC in the United States (Fattovich et al, 2004). It is hoped that the introduction of vaccination for HBV will decrease the incidence of HCC, an effect that has been seen already in Taiwan (Chang et al, 2009).

Biology of Hepatocellular Carcinoma

An understanding of the biology of HCC is critical to assist in clinical decision making about surveillance and treatment. Although the molecular biology of HCC remains to be fully elucidated, the close association between cirrhosis and the development of HCC is clear (Miyazawa et al, 2003; see Chapter 8C). Viral hepatitis, chronic alcohol use, and NAFLD are the most common causes of cirrhosis in the Western world (see Chapters 64, 65, and 70A). NAFLD, an unfamiliar diagnosis as recently as the early 1980s, is now present in 17% to 30% of Americans (Farrell & Larter, 2006); that progresses to steatohepatitis in 32% to 37% (Fassio et al, 2004; Harrison et al, 2003; Hui et al, 2003) and then to cirrhosis in 5% to 24% (El-Zayadi, 2008; Hui et al, 2003). The development of cirrhosis in patients with NAFLD is driven by repetitive liver injury from lipid peroxidation, fatty acid toxicity, mitochondrial impairment, and oxidative stress.

Viral infection with HBV and HCV lead to cirrhosis by different mechanisms. HBV induces transgene activation, oncogene transcription, and loss of tumor suppressor genes as a result of viral DNA integration into the host genome (Brechot et al, 1980; Bressac et al, 1990; Di Bisceglie, 2000; Kim et al, 1991). As many as 30% of patients with chronic HBV without cirrhosis will develop HCC (Zhou et al, 2001). HCV does not integrate into the host genome but rather leads to chronic inflammation through continued viral replication (Sherlock, 1994). This rapid hepatocyte turnover in the presence of oxidative stress drives the development of multiple dysplastic nodules.

Unlike what has been found in some other cancers, no sequential progression of genetic defects has been identified that leads to the development of HCC. Instead, a variety of genetic alterations are commonly seen, and they have been broadly grouped into events that occur either early or late in the development of a tumor. Genetic alterations that lead to inhibition of the insulin-like growth factor II receptors are considered early mutations (Yamada et al, 1997). Loss of heterozygosity of a variety of genes, often of tumor suppressor genes such as *TP53*, is a late event in the development of neoplasia (Buetow et al, 1989; Fang et al, 2000).

Clinically Relevant Aspects of Hepatocellular Carcinoma Pathogenesis

The clinician must understand three aspects of HCC pathogenesis: 1) the influence of cirrhosis on HCC development, 2) arterial recruitment of the tumor, and 3) the tendency for HCC to invade portal vein branches.

First, HCC most commonly develops in the context of cirrhosis, and the biology of HCC is related directly to the environment found in the cirrhotic liver. Repeated insult causes chronic inflammation driven by tumor necrosis factor (TNF)-α; transforming growth factor (TGF)-β and interleukin (IL)-1 from Kupffer cells; endothelial cells; and hepatocytes. This inflammation stimulates nodular regeneration with bridging fibrosis. Rapid cellular turnover in this regenerative environment leads to low-grade dysplastic nodules that do not contain atypia and high-grade dysplastic nodules that do. Eventually, a small percentage of these high-grade dysplastic nodules will go on to develop microscopic foci of HCC before becoming frank carcinoma (Rocken & Carl-McGrath, 2001). Recent evidence suggests that tumor cells may even secrete IL-6 and TNF-α, directly contributing to the inflammatory microenvironment by activating Toll-like receptors (Kim et al, 2009).

Because of the diffuse nature of the injury, multiple tumors can develop at the same time. If a focus of HCC is removed, recurrence most often happens at a distant site (Koike et al, 2000; Fig. 97D.1). This second tumor at the distant site is most likely a second primary tumor. As most of the second lesions are found within a few years of treatment of the primary lesion, the tumor was most likely present when the first tumor was treated but was too small to be detected. The occurrence of synchronous and metachronous lesions in the same organ suggests the entire cirrhotic organ has the potential for neoplastic conversion, much like the genetic defect in the colon in familial adenomatous polyposis, which leads to multiple cancers; this situation is referred to as a *field defect*.

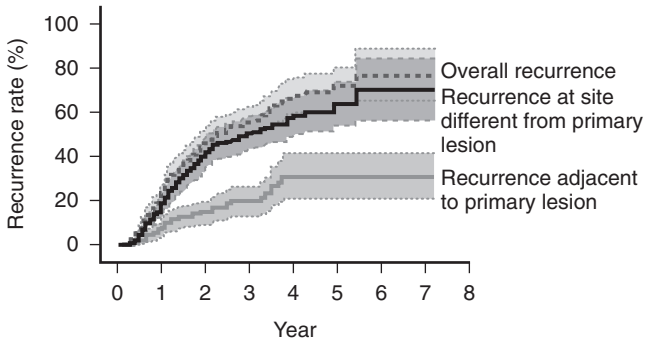


FIGURE 97D.1. Recurrence of hepatocellular carcinoma after ablation most often occurs at a site distant from the primary tumor, suggesting a second tumor was present at the time of treatment that was too small to be detected. *(From Koike Y, et al, 2000: Risk factors for recurring hepatocellular carcinoma differ according to infected hepatitis virus: an analysis of 236 consecutive patients with a single lesion. Hepatology 32(6):1216-1223. Copyright John Wiley & Sons, 2000. Reprinted with permission of John Wiley & Sons.)*

Secondly, there is a clinically relevant difference in blood supply between foci of HCC and low-grade dysplastic nodules, which derive most of their blood supply from the portal vein. Histopathologic evaluation of high-grade dysplasia and HCC demonstrates the tumor being fed by branches of the hepatic artery that are not paired with the other structures of the portal tract, a process called *arterial recruitment,* or *neoangiogenesis.* The resulting hepatic artery dominance in blood supply produces the characteristically hyperdense appearance of HCC that is used to identify tumors during the arterial phase of contrast imaging (Matsui, 2004; Willatt et al, 2008), and it allows for treatment via selective hepatic artery embolization.

Lastly, HCC is known to invade vascular structures, most commonly the portal vein but also hepatic veins and, less commonly, the biliary tree. The development of vascular invasion appears to be a key step in the metastatic potential of the tumor, and the risk of portal venous invasion seems to be directly related to size and differentiation status of the tumor (Esnaola et al, 2002). Venous invasion is such a strong predictor of metastatic disease that tumor size and tumor number can be thought of as surrogate markers for vascular invasion.

The likelihood of microvascular and macrovascular portal venous invasion has implications for treatment decisions; for example, evidence of portal venous invasion on imaging or biopsy rules out transplantation, because the probability of recurrence is unacceptably high. It is this risk of recurrence with large or multiple tumors that resulted in the poor outcomes with early attempts at liver transplantation for HCC, and it is the reason why patients with small tumors are selected for transplantation.

Hepatocellular Carcinoma Screening

HCC presenting as symptomatic disease has a 0% to 10% 5-year survival rate (Llovet et al, 2003), so a screening program that identifies early disease can have a major impact on treatment outcomes. HCC meets the World Health Organization criteria for performing screening (Meissner et al, 2004), and a randomized, controlled clinical trial showed that screening for HCC reduces mortality (Zhang et al, 2004). An effective screening program evaluates patients at risk of developing disease, using a highly standardized and relatively inexpensive test with a high sensitivity. A screening program is used if the cost of screening a large population is less than the benefit of early detection of the disease in a small number of individuals in that population. Several decision-analysis and cost-efficiency models for HCC screening suggest the ability of a screening program to decrease mortality while remaining cost-effective depends on the inclusion of patients with an incidence of HCC of at least 1.4% to 1.5% (Arguedas et al, 2003; Lin OS, et al, 2004; Sarasin et al, 1996). Patients who should be included in a screening program can be found in Box 97D.1. Further information about the incidence of HCC in cirrhosis from

Box 97D.1

Populations with Hepatocellular Carcinoma Incidence Sufficiently High for Inclusion in Surveillance Programs

Causes of Cirrhosis Other than Hepatitis B

Hepatitis C
Chronic alcohol abuse
Hemochromatosis
Primary biliary cirrhosis

Hepatitis B Carriers

Asian males ≥40 years
Asian females ≥50 years
Hepatitis B carriers with cirrhosis
Family history of hepatocellular carcinoma
Africans ≥20 years
Noncirrhotic hepatitis B carriers with ongoing hepatic inflammatory activity

Other Predisposing Conditions*

Nonalcoholic steatohepatitis
α_1-Antitrypsin deficiency
Autoimmune hepatitis

*These patients with increased but unknown HCC risk should be screened, but no defined surveillance recommendations currently exist.

Modified from Bruix J, Sherman M, 2005: Management of hepatocellular carcinoma. Hepatology 42(5):1208-1236. Copyright John Wiley & Sons, 2005. Reprinted with permission of John Wiley & Sons.

nonalcoholic steatohepatitis (NASH), α_1-antitrypsin deficiency, and autoimmune hepatitis is required, but most centers include these patients in their screening population.

Traditionally, the most commonly used serum tumor marker to detect HCC was α-fetoprotein (AFP), a protein produced by normal fetal hepatocytes, and by tumor cells, but not by healthy, mature hepatocytes. AFP has traditionally been used for diagnosing HCC, predicting outcome after resection, and screening for recurrence postoperatively (Tan et al, 2003). The normal range of AFP in the serum is 10 to 20 ng/mL; an absolute value of 20 ng/mL was used commonly as the screening cutoff; however, using this cutoff yields a sensitivity of only about 64%, making it a poor screening test (Sherman et al, 1995). Moreover, normal AFP levels vary widely across ethnic backgrounds (Soresi et al, 2003), and the test has a lower positive predictive value in patients with acute viral hepatitis or cirrhosis from a viral cause (Nguyen et al, 2002; Soresi et al, 2003).

In patients with a liver mass, a concomitant serum AFP greater than 200 ng/mL carries a very high positive predictive value (Sherman et al, 1995), but because of its unacceptably low sensitivity and specificity, the American Association for the Study of Liver Disease (AASLD) recommended that serum AFP no longer be used as a screening tool, although it still plays a diagnostic role (Bruix & Sherman, 2005). Using an absolute value greater than 400 ng/mL is considered diagnostic regardless of the patient's ethnic background or the cause of their liver disease. Research is ongoing to identify better serum markers for screening, diagnosis, and prognostication, and possible candidate compounds include AFP-L3 and des-γ-carboxy prothrombin (Bruix & Sherman, 2005; Grazi et al, 1995; Izuno et al, 1995; Koike et al, 2001; Marrero et al, 2003; Tsai et al, 1990).

Ultrasound (US) is the most widely used radiologic screening tool. It has a sensitivity of 65% to 85% and specificity over 90% when used as a screening test (Bolondi et al, 2001). Although the performance of US in cirrhotic patients is not as well defined (Bruix et al, 2001; Chen et al, 2002; Larcos et al, 1998; Sherman, 1999), and the test is operator dependent, US remains superior to any widely available serologic screening test. A large, prospective, randomized controlled study done in China suggests that surveillance of high-risk individuals with US and serum AFP testing every 6 months reduces HCC-related mortality by close to 40%, even though patients in that trial were offered only resection but not transplantation. One of the limitations of this study is that screening compliance was only approximately 60%, which may have dampened the reduction in mortality (McMahon, 2009; Zhang et al, 2004). Combined AFP and US surveillance increases sensitivity, but it raises the cost, and using both tests increases the rate of false-positive results from 5% for AFP alone to 7.5% for combined screening (Zhang & Yang, 1999). It is clear that further randomized controlled trials are needed, but based on the available information, the AASLD recommends screening patients at risk for HCC with US alone every 6 to 12 months (Bruix & Sherman, 2005). Evaluation of serum AFP can be added to US in the event of concerns regarding operator influence, but the use of AFP as the lone surveillance tool is discouraged.

Most centers use a 6-month screening interval, but this remains controversial. No evidence suggests that a 6-month interval improves outcome compared with a 12-month interval (Santagostino et al, 2003). The surveillance interval was derived from tumor growth rates, so the interval does not need to be shortened for patients who have a very high risk of developing HCC.

Early HCC can be difficult, if not impossible, to distinguish from cirrhotic nodules by US, but any suspicious nodule less than 1 cm should be evaluated for stability by repeat US at 3- to 6-month intervals for up to 2 years. All 1- to 2-cm nodules should be investigated with a dynamic contrast-enhanced imaging modality—computed tomography (CT), magnetic resonance imaging (MRI), or US—although contrast-enhanced US has not yet been adopted in the United States.

A nodule that is 2 cm or larger and hypervascular with portal venous washout on a single dynamic imaging study, or a 1- to 2-cm nodule on two such confirmatory studies, is treated as HCC. If the results are contradictory, a biopsy of the lesion should be obtained (Bruix & Sherman, 2005). If the lesion is larger than 2 cm and has a typical appearance on a single dynamic imaging study, or if it is found in concert with a serum AFP level above 200 ng/mL, biopsy is not required. Biopsy should be performed on any 1- to 2-cm lesion in any noncirrhotic patient has who has risk factors for the development of HCC. Biopsies should be read by expert pathologists, and patients with negative biopsy results should undergo US or CT scanning every 3 to 6 months and should be rebiopsied if the characteristics of the lesion change (Bruix & Sherman, 2005). Biopsy results that suggest a high risk for progression to HCC include *dysplastic nodules,* both low and high grade (Hytiroglou et al, 2007); *small and large cell change,* formerly called *small cell dysplasia* and *large cell dysplasia* (International Working Party, 1995; International Consensus Group for Hepatocellular Neoplasia [ICGHN], 2009); and *dysplastic foci,* defined as atypia outside of a dysplastic nodule (ICGHN, 2009).

Another commonly used radiologic surveillance tool is CT scanning (Kobayashi et al, 1985; Miller et al, 1994; Takayasu et al, 1990). Although the use of CT scanning is becoming commonplace, the radiation exposure to a patient from

screening every 6 to 12 months is considerable. The use of CT for diagnosis and staging has been defined, but the performance of CT as a screening test has not been described. Finally, CT scan is the diagnostic test used to confirm HCC, and the screening test should be different from the confirmatory test.

MRI with gadolinium-based or iron oxide–based contrast has not been widely studied as a screening test, but there are reports that this modality is 81% sensitive and 85% specific for HCC compared with 68% and 93% for contrast-enhanced helical CT scanning (Colli et al, 2006). Moderate signal strength on T2-weighted images is specific for HCC, because dysplastic and regenerating nodules are not hyperintense on T2—unless they have infarcted, which can occur. Delayed venous phase hypointensity with concomitant delayed enhancement of the rim of the lesion are also features specific for HCC (Freeny et al, 2003). Similar to CT scanning, characterization of small nodules remains difficult, as MRI is only 50% to 80% sensitive for lesions 2 cm or smaller and only 4% to 33% sensitive for lesions 1 cm or smaller (Willatt et al, 2008); this is due in part to the fact that lesions 1 cm or smaller are frequently isointense on T2 (Krinsky, 2004). It remains to be seen whether contrast-enhanced MRI is cost-effective as a screening tool for HCC, but it may prove to be marginally superior to CT scanning for characterization of known hypervascular lesions.

TREATMENT OPTIONS

HCC is not responsive to traditional cytotoxic chemotherapeutic agents. Recently, a Phase III clinical trial showed that sorafenib, an oral multikinase inhibitor of the vascular endothelial growth factor receptor, the platelet-derived growth factor receptor, and Raf kinase prolonged the median survival (10.7 vs. 7.9 months) and the time to radiologic progression (5.9 vs 2.8 months) in patients with advanced HCC versus placebo (Llovet et al, 2008). Given this modest improvement, local ablation/embolization, hepatic resection, and liver transplantation are still the best options available for patients with early stage disease to achieve a cure.

Treatment decisions should be based on three factors: 1) extent of local disease, 2) underlying liver disease, and 3) local organ availability. Patients whose liver disease is Child-Turcotte-Pugh (CTP) class A who have early-stage HCC are candidates for treatment with the goal of long-term survival free of HCC. Unfortunately, because of the advanced biologic activity of the cancer, 80% to 90% of patients will present at a stage too advanced for surgical resection or transplantation (Llovet et al, 2004). Those patients with advanced disease or patients with poor functional status should be offered sorafenib, locoregional therapies, or palliative care.

In the rare patient without cirrhosis, no evidence of venous invasion or metastatic disease, and tumor burden limited to one lobe, resection should be considered. Conversely, resection of part of a cirrhotic liver invariably leaves scattered dysplastic nodules behind. The tumorigenic cytokine milieu that bathes the remaining dysplastic nodules puts the patient at risk for the development of a second primary tumor. In addition to these de novo tumors, some researchers have suggested recurrence is more frequently the result of microscopic dissemination of the primary tumor at the time of treatment (Chen et al, 2000; Morimoto et al, 2003). Astoundingly, the risk of developing recurrence after resection for HCC in cirrhotic patients is about 35% at 1 year (Lu et al, 2009), 40% to 50% over 3 years (Koike et al, 2000; Jaeck et al, 2004; Sakon et al, 2000), and as high as 70% at 5 years (Bismuth et al, 1999; Llovet et al, 1999; Mazzaferro et al, 1996; Minagawa et al, 2003), making the history of a previous HCC the greatest risk factor in the development of a new primary HCC.

It is this high risk of recurrence that has driven liver transplantation as a method to remove the precancerous liver to prevent the development of subsequent lesions. The results of liver transplantation have improved dramatically in the last 20 years, in large part because of better patient selection, and currently the recurrence rate ranges from 11% to 18%. The mortality rate after liver resection for HCC is 1% to 7%, and the major cause is decompensated liver failure (Fong et al, 1999; Grazi et al, 2001; Hanazaki et al, 2000; Hsia et al, 2000; Makuuchi et al, 1998; Poon et al, 2001; Takenaka et al, 1996; see Chapter 90F). Given the risks of HCC recurrence and postoperative liver failure following resection, some controversy exists regarding the best treatment strategy in patients with limited disease and adequate hepatic function. Although sufficient hepatic reserve can usually be determined, no method is currently available to determine whether a patient will be among the 60% to 70% to recur within 5 years, or if they will remain recurrence free.

The long waiting time experienced in some regions must also be taken into consideration in the decision of resection versus transplantation. The risk of tumor progression while awaiting liver transplantation must be balanced against the risk of recurrence. If waiting times are relatively long in a given region, this may favor liver resection, because a prolonged waiting time risks tumor progression that may exclude the patient as a candidate for any surgical treatment.

A decision analysis from 2000 compared primary resection and salvage transplantation for recurrence versus primary liver transplantation in patients with small tumors (Majno et al, 2000). Theoretic decision models use multiple variables, so the weight of any single variable is difficult to determine, but the authors concluded that wait times shorter than 6 months favored liver transplantation, and those longer than 12 months favored primary liver resection.

Another decision analysis compared the projected survival benefit from liver transplantation when compared to resection in patients with small HCCs (Sarasin et al, 1998). The authors noted that the magnitude of the survival benefit relied heavily on the amount of time spent on the waiting list. They concluded that if the waiting period exceeded 6 to 10 months, the survival benefit gained from removal of the field effect is overwhelmed by the risk of progression while waiting, and resection becomes the preferred therapy (Fig. 97D.2). Although this analysis did not include the costs or clinical effects of locoregional therapy, it offers insight into how extended waiting times increase the relative benefit of resection, transarterial chemoembolization (TACE), and radiofrequency thermal ablation (RFA; see Chapters 83 and 85A).

The possibility of mitigating the risk of progression with a locoregional therapy while awaiting a transplantation has been suggested. Whether locoregional therapy offers a measure of disease control while awaiting a liver transplantation is not clear. Maddala and colleagues (2004) examined 54 patients with HCC treated with an average of three TACE sessions prior to transplantation at a median of 211 days. Eight patients dropped off the waiting list, two for non-HCC reasons and six from HCC progression. Of the six with progression, two developed extrahepatic metastases, two developed portal vein

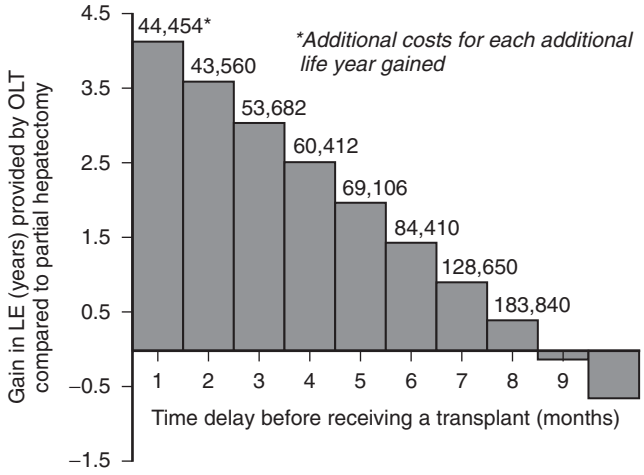


FIGURE 97D.2. Mean gain in life expectancy (*LE*) and marginal cost-effectiveness ratios provided by orthotopic liver transplantation (*OLT*) compared with partial hepatectomy (*vertical axis*) as a function of different time delays before receiving a transplant (*horizontal axis*). *(From Sarasin FP, et al, 1998: Partial hepatectomy or orthotopic liver transplantation for the treatment of resectable hepatocellular carcinoma? A cost-effectiveness perspective. Hepatology 28(2):436-442. Copyright John Wiley & Sons, 1998. Reprinted with permission of John Wiley & Sons.)*

invasion, and two had intrahepatic progression. Interestingly, these events all occurred within 4 months of listing. The short period of time between initiation of therapy and discovery of disease progression would suggest the disease had spread much earlier, and neither resection nor transplantation would have been helpful.

In a small study of 20 patients (median of two treatments, mean time to transplantation of 343 days), Hayashi and colleagues (2004a) found that seven patients whose tumors were within Milan guidelines dropped off the waiting list: two for causes unrelated to HCC, one for decompensation, and the other five for increased intrahepatic disease. The time to exclusion for HCC was less than 6 months in four of five patients, and no patients developed HCC after transplantation at a mean follow-up of 2.9 years.

RFA has also been reported to provide good results in patients who undergo subsequent transplantation. Mazzaferro and colleagues (2004) reported 50 patients who underwent a single ablation session and then waited an average of 9.5 months before transplantation. Apparently, there were no waiting list dropouts, and at a median follow-up of 22 months, only two patients had cancer recurrence. Lu and colleagues (2005) reported 52 patients who underwent RFA, most frequently in isolation (mean sessions 1.46). After 12 months, three patients had dropped out at a mean of 11 months, and two patients had extrahepatic disease; in all, 41 patients underwent transplantation, and none had HCC recurrence at a mean follow-up of 15 months. For small tumors, it has been suggested that RFA may be equivalent to resection for long-term disease control, with a lower risk of postoperative liver decompensation (Shiina, 2009), but further trials with long-term outcome data are required.

In summary, resection and ablation are viable options for patients with small tumors without cirrhosis and for patients with cirrhosis and preserved liver function (normal bilirubin and wedged hepatic vein pressure gradient <10 mm Hg) in regions with waiting times longer than 6 months. Liver transplantation is appropriate for patients with tumors that fall within the selection criteria and in those with small tumors but poor liver function.

Indications for Transplantation (See Chapter 97A)

An unlimited supply of organs and money would allow for a liberal policy of transplantation for patients with HCC confined to the liver; but resources are limited, so efforts must be made to allocate organs to those recipients with a high likelihood of long-term survival. Recurrence risk is clearly higher in patients with more advanced disease, and the size and number of nodules in the patient's explanted liver is directly correlated with the risk of HCC recurrence (Jonas et al, 2001; Mazzaferro et al, 1996).

Based on these observations, selection criteria have been developed. The primary set of selection criteria are the Milan criteria, created to allocate organs to patients with HCC who would have a similar chance for long-term survival as patients without HCC (Mazzaferro et al, 1996; Fig. 97D.3). To allocate scarce organs in such a way that all recipients have an acceptable chance for long-term survival, patients with HCC are currently evaluated for suitability based on three factors: 1) tumor size in centimeters, 2) number of radiologically evident tumors, and 3) evidence of portal venous invasion or extrahepatic disease. These factors are a crude but somewhat effective method for predicting overall tumor biology and subsequent risk of recurrence.

Preoperative staging, as outlined by UNOS, includes a triple-phase CT scan (Otto et al, 2006) of the abdomen to quantify intrahepatic disease burden, and a scan should be done of the chest to look for extrahepatic disease. This can also be accomplished with an MRI of the abdomen and a noncontrast CT of the chest (Bruix et al, 2003; Maddala et al, 2004). Unfortunately, these imaging modalities—the gold standard for HCC imaging—understage about 20% of patients (Yao et al, 2005) and can sometimes also overestimate actual tumor burden. A review of the HCC imaging literature that included only studies with explant pathologic correlation reported that triple-phase CT scan is only 37% to 75% sensitive at detecting HCC in a cirrhotic liver (Krinsky, 2004), although it remains the gold standard for diagnosis and preoperative staging. Bone scintigraphy was used in the past to locate extrahepatic disease but is no longer used because of low sensitivity and specificity.

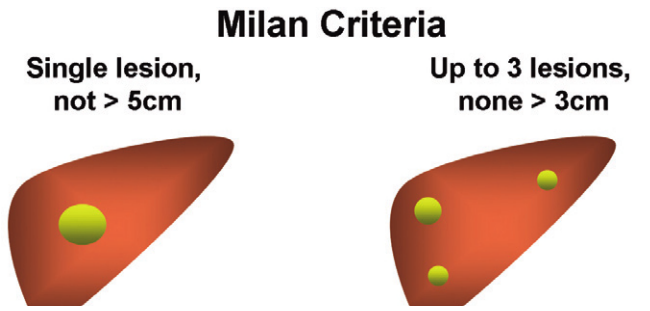


FIGURE 97D.3. Milan selection criteria for transplantation call for either a single lesion 5 cm or smaller or two to three lesions all ≤3 cm, equivalent to T1 and T2, respectively, of the American Liver Study Group modified tumor-node-metastasis classification system.

Table 97D.1

American Liver Tumor Study Group Modified TNM Staging and the University of California–San Francisco Staging Criteria

MODIFIED TNM		UCSF CRITERIA	
Traditional Stage	**Tumor Burden**	**Stage**	**Tumor Burden**
T1	One nodule ≤1.9 cm		
T2	One nodule 2 to 5 cm or two to three nodules all ≤3 cm		
T3	One nodule >5 cm or two to three nodules, at least one >3 cm	IIIa	One nodule 5.1 to 6.5 cm, two to three nodules, all ≤4.5 cm, or total diameter ≤8 cm
		IIIb	One nodule >6.5 cm, two to three nodules, of which one is ≥4.5 cm, or they have a total diameter >8 cm
T4a	Four or more nodules, any size		
T4b	T2, T3, or T4a plus gross intrahepatic portal or hepatic vein involvement as indicated by CT, MRI, or ultrasound		

TNM, tumor-node-metastasis; CT, computed tomography; MRI, magnetic resonance imaging

Modified from Yao FY, et al, 2001: Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 33(6):1394-1403. Copyright John Wiley & Sons. Reprinted with permission.

In the United States, the modified tumor-node-metastasis (TNM) staging system of the American Liver Tumor Study Group (ALTSG) is used to allocate livers from deceased donors to patients with HCC awaiting transplantation (UNOS, 2004; Table 97D.1) to ensure that all patients who receive an organ have a reasonable chance at long-term survival. The original transplantation criteria from the mid-1990s, the Milan criteria, are equivalent to stage I or II of this TNM classification system. Using these criteria, recurrence is between 4% and 16%, and 5-year survival is 71% to 75% (Hayashi et al, 2004b; Jonas et al, 2001; Llovet et al, 1998, 1999). Patients whose disease falls outside the ALTSG criteria for stage II disease, and thus outside the Milan criteria, may be at higher risk for recurrence.

In February 2002, the Model for End-Stage Liver Disease (MELD) scoring system was implemented. As part of this system, priority was given to patients with TMN stage T1 and T2 HCC in an effort to combat the risk of tumor progression in patients awaiting a transplant. The prioritization was revised in 2004 to no longer include T1 tumors, so that only patients with T2 tumors get priority listing (Wiesner et al, 2004) to prevent overallocation of organs to patients with HCC, and because approximately 30% of patients with presumed HCC (a single lesion ≤2 cm with arterial enhancement) were found to have no tumor in their explant (Wiesner et al, 2004). Currently, the MELD points added to a patient with a T2 lesion are equivalent to a 15% 3-month probability of candidate mortality.

It has been suggested that the Milan criteria are too restrictive and that the size criteria are somewhat arbitrary. Several centers have extended their criteria to include highly selected stage III patients who are expected to have a tolerable rate of recurrence (Duffy et al, 2007; Herrero et al, 2001; Kneteman et al, 2004; Onaca et al, 2007; Roayaie et al, 2002; Yao et al, 2001, 2007). A recent retrospective analysis of 1556 patients undergoing transplantation at 36 centers included 1112 patients with tumor burden exceeding the Milan criteria on posttransplant pathologic review. Of these, 283 patients had no evidence of microvascular invasion with tumor burden up to 7 cm in largest diameter or up to seven nodules, and this subset of patients achieved a 5-year survival of 71%.

The Univerity of California–San Francisco (UCSF) criteria—single tumor smaller than 6.5 cm, maximum of three total tumors with none larger than 4.5 cm, and cumulative tumor size smaller than 8 cm (see Table 97D.1)—represent a modest expansion of the Milan criteria and have been validated at other centers. One such evaluation, a retrospective review of preoperative imaging and explant pathology, looked at 467 transplantations performed over a 20-year period and found similar 5-year survival in patients meeting the Milan criteria and the UCSF criteria by explant pathology (86% vs. 71%) and preoperative imaging (79% vs. 64%). Survival for patients with tumors beyond UCSF criteria was less than 50% at 5 years (Duffy et al, 2007).

This discussion highlights the point that tumor burden is only a surrogate for vascular invasion and microscopic metastatic disease, which along with extrahepatic disease limits the effectiveness of liver transplantation. Formal guidelines for transplantation of patients with disease outside the Milan criteria have not been established, but with many centers reporting equivalent survival of highly selected patients outside the Milan criteria, and with the advent of downstaging, this topic has taken on widespread debate.

Another consideration is the impact of MELD exception points for cancer patients or the selection of patients with liver failure as a result of benign disease. In regions with long waiting times, if patients with tumor burden beyond the Milan criteria are transplanted, organs are taken away from patients with liver failure from other causes. Volk and colleagues (2008) examined the issue of what is the acceptable outcome risk for transplantation of patients with HCC as compared to using the organ in a patient without HCC. On a national basis, the authors found that expansion of the Milan criteria would significantly increase waiting list mortality, unless 5-year posttransplant survival for the expanded criteria recipients exceeded 61%.

The authors also showed a dramatic difference in the effect of a policy change based on transplant region. This regional variability appeared to result from dramatic differences in the risk of death for patients without HCC, because the MELD score at transplantation of non-HCC patients was quite low in some regions. In regions where the risk of death of the non-HCC patients without transplantation is low (low MELD score at transplantation), the HCC criteria could be expanded to allow transplantation in the HCC patients with a posttransplant survival in the HCC patients of 25%, which would mean that patients could have very large tumors or those that number greater than four or five. This is compared with the need for criteria for transplantation in HCC patients that resulted in a posttransplant survival of 70% in regions where there was a

greater need for transplantation (higher MELD scores) in the non-HCC population. This wide variation in outcome suggests that changes in national policies would have a variable effect, depending on the region.

Waiting List Screening for Hepatocellular Carcinoma

Patients awaiting transplantation are cirrhotic and are therefore at risk for HCC, so longer wait times can affect survival. The average waiting time for liver transplantation is extremely variable and is based on ABO blood group, progression of liver failure, and geographic location. The mean waiting time in the United States is approximately 4 months, but this varies among regions, ranging from 2 to 7 months; about 50% of patients are transplanted within 3 months. For patients with prolonged waiting times, it is important to screen patients with a CT or MRI scan of the abdomen every 3 to 6 months while they await transplantation.

Pretransplant Management of Patients with Hepatocellular Carcinoma

Unfortunately, controlled trials to evaluate different treatment options for patients awaiting transplantation have not been completed. The sole published series followed patients undergoing surveillance without local therapy and showed a high rate of dropouts from the waiting list because of tumor progression or progression of liver failure over the period of the study (Llovet et al, 1999). This report, combined with the understandable anxiety felt by patients and caregivers observing unhindered tumor progression, compelled most centers to offer cancer-directed treatment for patients awaiting transplantation. Retrospective data would suggest that cancer-directed therapy should be used if the expected waiting time exceeds 6 months (Bruix & Sherman, 2005).

Options for pretransplant locoregional control include TACE, RFA, percutaneous ethanol injection (Hoshida et al, 2008), or some combination of these modalities (see Chapters 83 and 85A). TACE is used by many centers because it offers locally effective treatment with a low risk of complications. Three studies support the argument that TACE may help reduce attrition from the pretransplant waiting list (Maddala et al, 2004; Majno et al, 2007; Millonig et al, 2007). These data include patients with variable waiting times and follow-up periods, but they suggest that pretransplant TACE is associated with a dropout rate of only 2% to 14%, with the possible added benefit of a lower posttransplant recurrence rate (8% to 10%).

A recent decision analysis evaluated the waiting-list time interval associated with the greatest impact of neoadjuvant TACE (i.e., greatest reduction in the dropout rate) and showed the greatest benefit in patients transplanted within 4 to 9 months (Aloia et al, 2007). The authors reported that when waiting time was less than 4 months, waiting-list attrition was similar in treated and untreated patients (20% vs. 34%; P = .08), and when waiting times exceed 9 months, dropout rates reequilibrated (33% vs. 46%; P = .06).

No studies have described percutaneous ethanol injection (PEI) as a sole treatment in patients awaiting a transplantation, although several studies suggest it is a safe and reliable component of multimodal therapy for tumors smaller than 3 cm (Troisi et al, 1998; Veltri et al, 1998; Vilana et al, 1992). PEI uses a small needle that reduces the risk of tract seeding to 0.6%. Some authors have suggested that pretreatment with arterial embolization to disrupt intratumoral septae facilitate the ethanol diffusion and may therefore improve the efficacy of subsequent ethanol injection (Lencioni et al, 1994). PEI requires several sessions when used as primary treatment for unresectable HCC, and prospective evidence supporting it as a neoadjuvant therapy is lacking; as a result, the trend has been toward other treatment methods.

RFTA induces tissue necrosis by delivering heat at the tip of one or several electrodes. Major complications occur in less than 10% of patients, and mortality is less than 1% (Orlando et al, 2009). This strategy is at least as efficacious as PEI for tumors smaller than 2 cm but requires fewer treatments (Livraghi et al, 1999; Lencioni et al, 2003), and randomized controlled trials suggest it improves survival (Lencioni, et al, 2003; Lin SM, et al, 2004; Livraghi et al, 1999).

A recent meta-analysis reported that RFA is superior to PEI in the treatment of small HCC with respect to survival and cancer-free survival at 1, 2, and 3 years; tumor response; and risk of local recurrence (Orlando et al, 2009). Recurrence is more common in patients with tumors larger than 4 cm, and in 95%, it occurs within 6 months and at a site distant from the primary tumor (Curley et al, 2000). This again suggests that tumor size is only a surrogate marker for microscopic metastatic spread and neoplastic potential of the remaining dysplastic nodules.

Given these data, RFA has evolved into the preoperative treatment of choice for tumors larger than 2 cm (Bruix & Sherman, 2005). With the advent of sorafenib, a chemotherapeutic agent that has shown greater activity against HCC than older cytotoxic agents (see Chapter 88), the paradigm may shift to a combination of locoregional therapy and chemotherapy. Trials examining these combinations are underway.

Another strategy is to prioritize, or fast-track, patients to have them receive a transplant as soon as possible without pretransplant treatment. Although this may be the most reassuring strategy for patients, it takes away the ability to observe the tumor biology over time. A subset of patients with newly diagnosed HCC will have very unfavorable tumor biology, and even if transplanted shortly after diagnosis, they are likely to experience rapid recurrence. A reasonable amount of time on the waiting list may in fact be beneficial, allowing tumor biology to unfold such that very aggressive disease will become obvious in short-term follow-up, thereby avoiding a futile procedure.

Patients with small tumors that fall within the Milan criteria have about a 10% risk of recurrence, which corresponds reasonably well to the percentage of patients with tumors that have aggressive histologic characteristics (Jonas et al, 2001). Fast-tracking such patients likely would significantly increase recurrence rates. One series examining this issue showed that recurrence rates were significantly higher in patients who were fast-tracked and in patients who underwent living-donor liver transplantation (LDLT) compared with patients who had longer waiting times (Kulik & Abecassis, 2004).

Patients with small but aggressive tumors are infrequent, but fast-tracking yields unacceptably high recurrence rates in the more common patient, with tumor burden close to the limits of or beyond the Milan criteria (Bismuth et al, 1993; Jonas et al, 2001; Llovet et al, 1999; Mazzaferro et al, 1996). It has also been suggested that fast-track prioritization is not cost-effective (Sarasin et al, 2001). Unfortunately, no stated guidelines have

been established, but it appears that even for LDLT, a waiting time of approximately 6 months is appropriate (Bruix & Llovet, 2002).

Downstaging

Two observations have fueled the current debate about the proper selection criteria for transplantation in patients with HCC. First, it is clear that not all tumors of the same size carry the same risk of recurrence. Secondly, it is well documented that some patients outside the Milan criteria will benefit from liver transplantation (Yao, 2008). This has led to efforts to select patients with more advanced disease, but with favorable tumor biology, who might benefit from transplantation (Otto et al, 2006). The process of downstaging disease to within Milan criteria may be a mechanism for identifying such patients. This approach allows treatment of the tumor, and concomitant selection of patients with favorable tumor biology, by excluding patients who do not respond to locoregional ablative therapy, and it allows time for unfavorable biology to manifest.

A prospective intention-to-treat analysis evaluated 61 highly selected patients with tumor stage exceeding T2 who underwent tumor-directed therapy prior to transplantation. The study included patients with one lesion larger than 5 cm but smaller than 8 cm; those with two to three lesions, with one lesion larger than 3 cm but smaller than 5 cm, with a total diameter less than 8 cm; and those with four to five lesions, all smaller than 3 cm with a total diameter less than 8 cm (Yao et al, 2008). An interval of at least 3 months was required between treatment and transplantation. Downstaging was successful in 70% of patients, with the remaining patients dropping out, usually from disease progression. The 1- and 4-year posttransplant survival rates were 96% and 92%, respectively, suggesting that carefully selected patients with disease exceeding the Milan criteria can be downstaged with excellent posttransplant outcome.

It is important to note that the median time between the first treatment and transplantation was 8.2 months, with a range of 3 to 25 months. It is this waiting time that appears to allow tumor biology to manifest; patients with more biologically aggressive tumors dropped out during the waiting period, allowing selection of lower risk patients for transplantation. There are no formal guidelines for downstaging, but the UCSF protocol for downstaging of patients initially exceeding the Milan criteria is included for reference (Box 97D.2).

Box 97D.2

University of California–San Francisco Downstaging Protocol for Patients Initially Outside the Milan Criteria

Inclusion Criteria for Downstaging

One tumor >5 cm and ≤8 cm
Two or three lesions, at least one >3 cm but ≤5 cm and total tumor diameter ≤8 cm
Four or five lesions, all ≤3 cm, and total diameter ≤8 cm
No evidence of vascular invasion by imaging

Criteria Defining Success of Downstaging by Imaging

Tumor size and number meeting UNOS T2 criteria *or*
Complete tumor necrosis by imaging without suggestion of residual tumor

Criteria Defining Treatment Failure

Death from any cause before liver transplantation
Exclusion from liver transplantation
Recurrence of hepatocellular carcinoma after liver transplantation

Additional Guidelines

A minimum follow-up period of 3 months is required before liver transplantation, with concomitant imaging studies that meet the "success" criteria.
Approval must be obtained by the regional United Network of Organ Sharing review board for priority listing for deceased-donor liver transplantation after successful downstaging.
Patients can undergo living-donor liver transplantation if a donor is available and imaging studies meet the selection criteria.
Patients with liver decompensation after downstaging are not eligible for liver transplantation unless the above criteria are met.
In patients treated with resection as a downstaging procedure, the presence of microvascular invasion in the resection specimen is a contraindication to liver transplantation.

Modified from Yao FY, et al, 2008: Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. Hepatology 48(3):819-827. Copyright John Wiley & Sons, 2008. Reprinted with permission.

Technical Aspects of Liver Transplantation in Hepatocellular Carcinoma (See Chapter 98A)

Liver transplantation for HCC presents some technical challenges that need special consideration. The most important consideration is to perform the operation based on well-established oncologic principles, involving clear surgical margins and avoiding tumor seeding during the procedure to ensure the lowest recurrence rate. The tumor should be handled as little as possible, using the so-called no-touch technique, until the lymphovascular pedicle has been ligated. Hepatic artery ligation at the beginning of the hepatectomy can theoretically limit tumor dissemination during the dissection; however, no proof is available to suggest that such an approach lowers the posttransplant recurrence risk.

The transplant surgeon should be aware of prior therapy, because during RFA or biopsy, the needle tract and the diaphragm may be seeded with tumor. If a limited amount of diaphragmatic seeding is identified during the native hepatectomy, it is reasonable to perform a diaphragmatic resection with primary repair at the time of hepatectomy. Primary repair of the diaphragmatic defect is usually sufficient, and tube thoracostomy is not required. Diffuse seeding should preclude transplantation.

Predicting and Screening for Recurrence

The propensity of HCC to recur after surgical therapy has spurred investigations of potential biomarkers that might help improve patient selection. Recently, formalin-fixed tissue was used for genome-wide expression profiling of the normal tissue surrounding a focus of HCC, and a reproducible expression signature was seen that correlated well with survival (Hoshida et al, 2008). Even with the diversity of genetic events that lead to HCC, specific regions of loss of heterozygosity have been identified that could be used to quantify a patient's risk of HCC recurrence.

Efforts have been made to identify markers of extrahepatic tumor spread to avoid transplantation in the face of unrecognized extrahepatic disease. One attempt has been to find evidence of malignant cells in the bone marrow of patients with

HCC as a method to predict recurrence or survival (Sutcliffe et al, 2005), although this practice is not routinely performed.

A recent multivariate analysis of 136 patients undergoing hepatectomy for HCC reported that low AFP mRNA levels identified by real-time quantitative polymerase chain reaction (PCR) correlated with patient survival and disease-free survival (Kamiyama et al, 2006; Lindemann et al, 1992; Pantel et al, 1996). Patients with negative AFP mRNA had 97% survival at 1 year and 91% survival at 3 years versus 86% and 56%, respectively, in patients with positive AFP mRNA ($P < .0001$). Similarly, 1- and 3-year disease-free survival were 73% and 45% in patients with negative AFP mRNA versus 55% and 26%. Although not widely used, these tests may help quantify risk of recurrence and could have implications for organ allocation and the effectiveness of transplantation for cure.

Unfortunately, evidence-based data regarding posttransplant screening protocols are lacking, and screening all patients with imaging and serum AFP for recurrence does not appear to be cost effective (Roberts, 2005). Alternatively, screening high-risk patients, as defined by adverse histopathologic characteristics in the explanted liver, is a more promising and potentially cost-effective strategy (Roberts, 2005; Ladabaum et al, 2011). Moreover, because 70% to 75% of recurrence occurs within the first 2 years after transplantation, screening during this time period is the most critical and is most likely to have the greatest yield (Regalia et al, 1998; Roayaie et al, 2004).

Once patients experience recurrence after transplantation, therapeutic options are somewhat limited. In approximately 40% of patients, HCC recurs at extrahepatic sites, and chemotherapy is generally ineffective, leading to a median survival of only 8.7 months (Mazzaferro et al, 1996). A subset of roughly 10% of patients with recurrence can be expected to achieve long-term survival after resection (Roberts, 2005). The use of sorafenib in this situation is currently being studied.

Salvage Transplantation

As a way to better maintain the pool of donor organs, some have argued that primary liver resection should be first-line therapy for patients with preserved liver function and solitary HCCs smaller than 5 cm, and salvage transplantation can be offered to patients who experience recurrence that falls within the Milan criteria. In 2003, Poon and Wong evaluated survival and recurrence after resection of potentially transplantable small HCCs. They concluded that in patients with preserved liver function (CTP class A) with small solitary HCCs, primary resection achieved 5-year survival of 70%, comparable to reported survival after primary transplantation for similar size tumors. In order to apply salvage transplantation, screening must be diligent to find those who recur. Screening after resection with US every 3 months would be an important aspect of any treatment strategy using salvage transplantation for treatment of recurrence. The hope is that if patients recur, they will do so with transplantable disease within the Milan criteria.

Two studies have addressed the issue of outcome after salvage transplantation but reached opposing conclusions. The first was a retrospective analysis of 358 patients with cirrhosis and HCC who underwent either transplantation (n = 195) or resection (n = 163, of whom 98 were transplant candidates at the time of therapy); those patients with recurrence after resection underwent salvage transplantation (n = 17). The authors reported lower operative mortality rate (2% vs. 28%), lower recurrence rate (18% vs. 54%), and higher 5-year posttransplant survival (61% vs. 41%) and disease-free survival rates (58% vs. 29%) for patients who underwent transplantation compared with patients who underwent resection and then had salvage transplantation for recurrence (Adam et al, 2003).

The results of this study suggest that resection and salvage transplantation produced worse outcomes, but this was not supported by the second study of 88 patients with disease meeting the Milan criteria who underwent liver transplantation versus 18 who underwent resection followed by salvage transplantation for recurrence (Belghiti et al, 2003). The authors reported no difference in morbidity (51% vs. 56%), 30-day mortality (5.7% vs. 5.6%), 3-year survival (82% vs. 82%), 5-year survival (59% vs. 61%), or recurrence after primary liver transplantation versus salvage transplantation (n = 3 vs. 1).

Reasons for the discordant results could be the differences in time to salvage transplantation, patient selection, or operative technique of liver resection between the studies (27% underwent a transthoracic resection in the latter study). Another issue limiting the comparability of these two studies is that 7 of the 18 patients who underwent "salvage transplantation" in the latter study did not have recurrence but were transplanted for deterioration of liver function or because of pathologic findings in the resection specimen. Also of note, as Adam and Azoulay pointed out in a letter to the editors of the *Annals of Surgery*, the theoretical transplantability of patients with recurrence after resection seems to be different than the actual transplantability documented by many centers (Adam & Azoulay, 2005). Although Poon and colleagues describe an optimistic rate of patients with recurrence who would theoretically be transplantable after resection (79%), the percentage of patients who have undergone salvage transplantation, documented in the literature, is 1% to 30% (Belghiti et al, 2002; Llovet et al, 1999; Poon et al, 2002).

Reports of recurrence after salvage vary widely, from 5% to 54% (Adam et al, 2003; Belghiti et al, 2003; Lo & Fan, 2004). Currently, the efficacy of resection followed by salvage transplantation for recurrence is limited by the difficulties that attend screening for recurrence, prolonged waiting times, and a shortage of donor organs, but it may be a viable option for patients with hepatitis B without cirrhosis who have a single lesion.

Future Perspectives

Liver transplantation for HCC has proven to offer long-term survival and recurrence-free survival for patients with cirrhosis, but the shortage of donor organs is likely to perpetuate interest in resection and salvage transplantation. Currently, no consensus exists about an optimal method to select patients for transplantation after resection, which may be offered to patients with documented recurrence, but a more proactive strategy might improve outcomes.

One strategy would be to use the well-established histopathologic findings of microvascular invasion or multiple nodules unseen on preoperative imaging (Castells et al, 1993; Ikeda et al, 1993b; Izumi et al, 1994; Llovet et al, 1999; Nagasue et al, 1993; Okada et al, 1994) to select patients who are high risk for recurrence after resection. Identification of these findings in the resection specimen could initiate listing for liver transplantation (Sala et al, 2004). This strategy may select for patients who are at risk for early recurrence to undergo

transplantation (Colella et al, 1997; Klintmalm, 1998), thus selecting a population that is likely to recur, even if they do undergo transplantation. The concern with this strategy is that patients whose explant specimens after transplantation demonstrate vascular invasion are at increased risk for development of extrahepatic disease.

Another possible strategy takes advantage of recent advances in gene-expression profiling of fixed liver tissue, from the liver parenchyma away from the tumor, to reliably predict risk of late (de novo) recurrence by quantifying the field defect (Hoshida et al, 2008). Using this technology, gene-expression profiling could theoretically select the population with a field defect that places them at high risk for late recurrence; this group would perhaps be targeted for transplantation, while allowing those with low risk for late recurrence to have resection and be followed (Sherman, 2008). Although this strategy offers some promise, it remains investigational.

Even with the improvements in overall and cancer-free survival in the last 20 years, many areas in the treatment of HCC are in need of randomized controlled trials, such as the areas of preoperative screening, postoperative surveillance, and downstaging protocols. Nontransplant therapies—such as re-resection, RFA, TACE, and PEI—need to be evaluated against salvage transplantation for patients with recurrence. Lastly, therapeutic options for patients with advanced HCC need to be expanded to improve survival.

References are available at expertconsult.com.

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CHAPTER 97E

Liver transplantation for cholangiocarcinoma and other neoplastic diseases

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OVERVIEW

Liver transplantation for malignancies other than hepatocellular carcinoma (HCC) remains highly controversial. Nonhepatocellular carcinomas most commonly treated with liver transplantation include cholangiocarcinoma (CCA), metastatic neuroendocrine cancer (NEC), and hepatic epithelioid hemangioendothelioma (HEHE). Single-center and multicenter results have been equivocal with discrepancies in survival and efficacy. Herein we review the results of liver transplantation for these malignancies—specifically CCA, metastatic NEC, and HEHE—with an aim to suggest guidelines for the application of liver transplantation in the treatment of these diseases.

HILAR CHOLANGIOCARCINOMA (SEE CHAPTER 50B)

CCA, the second most common primary malignant tumor of the liver, arises from the cholangiocytes of the intrahepatic and extrahepatic bile ducts. The incidence of this tumor has been estimated at 3000 to 5000 cases per year (de Groen et al, 1999; Olnes & Erlich, 2004), and the prevalence of intrahepatic disease appears to be on the rise (Shaib et al, 2004). CCA can arise within the liver, in the perihilar location, or along the extrahepatic bile duct (see Chapters 50A and 50B). CCA has three growth patterns: 1) *mass-forming tumors* are usually intrahepatic, 2) *sclerosing tumors* arise in the perihilar and extrahepatic bile ducts, and 3) *polypoid tumors* grow within the major intrahepatic and extrahepatic ducts. Surgical extirpation has been the standard treatment for all three tumor types.

The treatment of hilar CCA has been most troublesome because it is impossible to achieve a tumor-free (R0) margin of resection. Radical resection with partial hepatectomy was shown to improve survival (Launois et al, 1979) for patients with hilar CCA, but few patients come to medical attention with disease amenable to complete resection. Indeed, fewer than 30% of patients are candidates for resection at diagnosis because of either bilateral liver involvement, encasement of hilar vascular structures, involvement of sectoral bile ducts, and/or underlying liver disease, such as primary sclerosing cholangitis (PSC; see Chapter 41). Liver transplantation appears promising for the treatment of intrahepatic and hilar CCA, because the procedure affords a radical resection, is not limited by bilateral ductal or vascular involvement, and treats underlying liver disease.

EARLY EXPERIENCE WITH LIVER TRANSPLANTATION

Unfortunately, early experiences with liver transplantation for the treatment of CCA were uniformly poor. Liver transplantation for both intrahepatic and hilar CCA was fraught with high recurrence rates and poor patient survival. The Cincinnati Tumor Registry reported a large multicenter analysis for patients transplanted from 1968 to 1997, wherein 1-, 3-, and 5-year patient survival rates were only 72%, 48%, and 23%, respectively (Meyer et al, 2000). The recurrence rate was 51% with a median time to recurrence of only 9.7 months. Local recurrence within the allograft was the most common initial site of recurrence (47%) followed by distant metastases to the lung (30%). Recurrence of tumor portended an extremely poor prognosis, with a median survival of only 2 months. Adjuvant therapy was not found to be beneficial, and no difference was reported in the survival rate of known tumors versus incidental tumors found at the time of orthotopic liver transplantation (OLT); results were poor for both intrahepatic and hilar tumors.

A multitude of retrospective studies have confirmed these findings. A Spanish multicenter study reported similar results for 59 patients who underwent OLT for CCA from 1988 to 2001 (Robles et al, 2004) and found 5-year survival was 30% with a 53% recurrence rate for 39 patients with hilar CCA. Results were equally poor for 23 patients with intrahepatic CCA, for which 5-year survival was 42%, and the recurrence rate was 35%. Similarly, a Scandinavian study reported a 5-year survival of 30% following OLT in a primary sclerosing cholangitis (PSC) population with early-stage CCA (Brandsaeter et al, 2004).

Several centers have reported their outcomes with incidental tumors discovered in patients undergoing transplantation for chronic liver disease. Ghali and colleagues (2005) reviewed the Canadian experience from 1996 through June 2003 and identified 10 cases, 8 arising in patients with PSC. Most of these tumors had favorable characteristics that included small size (<1 cm) and absence of perihepatic lymph node involvement; 90% were well differentiated, and 60% arose in the extrahepatic or hilar ducts. Despite the favorable characteristics, 3-year survival was only 30%. Only the University of California–Los

Angeles has reported reasonable survival outcomes in incidental CCA detected in the explant after OLT (Goss et al, 1997). Ten patients with incidental CCA had a 5-year survival of 87%, which was comparable to PSC patients without CCA, although pathologic characteristics were not included in the paper. As with all other experiences, the 4 patients transplanted with known CCA had poor outcomes, and none were alive at 5 years.

A more radical approach with cluster abdominal transplantation reported by the University of Pittsburgh had equally poor results: a 3-year survival of 20% and a 57% recurrence rate (Alessiani et al, 1995). A similar experience was recently reported by Neuhaus' team in Berlin (Seehofer et al, 2009). Sixteen patients with CCA were treated by combined liver transplantation and pancreatoduodenectomy (PD) between 1992 and 1998, and results were compared to those achieved for 8 patients who did not undergo PD, which at the time of liver transplantation was associated with significantly higher morbidity than transplantation alone. Long-term survival (>4 years) was achieved in only 3 lymph node–negative patients of 20 patients who survived the perioperative period. Neuhaus and colleagues concluded that "there is no good evidence that more radical resections alone are able to markedly improve long-term results."

With uniformly poor results of liver transplantation for these tumors, intrahepatic and hilar CCA became widely recognized as absolute contraindications for liver transplantation. Both intrahepatic and hilar CCA are best treated by resection; unresectable disease has a prohibitively high recurrence rate after transplantation and warrants additional or palliative therapy.

NEOADJUVANT THERAPY AND LIVER TRANSPLANTATION

Despite the poor results with liver transplantation alone, some patients with favorable hilar CCA—that is, those with negative margins and no regional lymph node metastases—did benefit from transplantation (Shimoda et al, 2001). In addition, a small group of patients at the Mayo Clinic treated with primary radiotherapy and chemosensitization alone, without resection, had a 5-year survival of 22% (Foo et al, 1997). Based on the known palliative efficacy of radiotherapy for CCA—and knowledge that CCA resection failures are usually due to locoregional recurrence, rather than distant metastases (Jarnagin et al, 2003)—the transplant team at the University of Nebraska pioneered a strategy of high-dose neoadjuvant brachytherapy and chemotherapy followed by liver transplantation (Sudan et al, 2002) for patients with unresectable hilar CCA.

The initial Nebraska protocol utilized high-dose intrabiliary brachytherapy, 6000 cGy, followed by daily intravenous 5-fluorouracil (5-FU) until OLT. Patients underwent operative staging when a donor liver became available for transplantation. At operation, the patients were assessed for extrahepatic metastases or regional lymph node involvement. Either finding precluded transplantation, and the donor liver was reallocated to another patient. Seventeen patients received neoadjuvant brachytherapy: 2 patients died from disease progression, and 4 were found to have extrahepatic disease at exploration; 11 patients underwent transplantation. Median survival after transplantation was 25 months; 5 (45%) were alive and disease-free at a median of 7.5 years (range, 2.8 to 14.5 years) after transplantation, 2 patients died from recurrent disease, and 4 patients died from perioperative complications. Overall survival was 30% for the 17 patients 5 years after the start of neoadjuvant therapy.

MAYO CLINIC EXPERIENCE

The transplant team at the Mayo Clinic embraced the concept pioneered by the team at the University of Nebraska and implemented a protocol in 1993 through a collaborative effort of oncologists, hepatologists, and surgeons. The general theory is that neoadjuvant therapy and liver transplantation should provide the best possible control of local disease. The rationale for the protocol was based on several factors: 1) the known CCA tumor response to high-dose radiotherapy; 2) hepatotoxicity of radiotherapy is obviated by liver transplantation; 3) liver transplantation achieves radical resection, including removal of residual disease following neoadjuvant therapy; 4) liver transplantation is not limited by underlying liver disease (PSC), vascular involvement, or concern about intrahepatic extension of disease; 5) neoadjuvant therapy prior to operative staging and transplantation might avoid tumor dissemination during operation; and 6) careful patient selection with operative staging prior to liver transplantation could exclude patients with advanced disease and regional lymph node metastases that are destined to develop distant metastatic disease.

Inclusion and Exclusion Criteria

Criteria for protocol enrollment are designed to select those patients least likely to develop metastatic disease, most likely to respond to neoadjuvant therapy, and who have a high probability for survival after transplantation. Appropriate patients include those with early-stage hilar CCA determined to be unresectable or those who have underlying PSC, because CCA arising in the setting of PSC has a very poor natural history following standard resection (Rosen et al, 1991).

Criteria for anatomic unresectability include bilateral segmental ductal extension, encasement of the main portal vein, unilateral segmental ductal extension with contralateral vascular encasement, and unilateral atrophy with either contralateral segmental ductal or vascular involvement. Due to the difficulty of assessing extent of disease along the bile duct, especially in the setting of PSC, no longitudinal limits exist for bile duct involvement.

Original criteria required that hilar CCA not extend lower than the cystic duct, but it was subsequently found that early CCA arising in PSC with unsuspected common bile duct involvement found at transplantation was amenable to transplantation with PD; however, patients with CCA extending below the cystic duct on cholangiography are excluded, because they have larger tumors that are more likely to abut the portal vein and be less amenable to complete extirpation during transplantation.

Vascular encasement of the hilar vessels is not a contraindication to transplantation. The upper limit of tumor size is 3 cm when a mass is visible on cross-sectional imaging studies, and there must be no evidence of intrahepatic or extrahepatic metastases by chest computed tomography (CT), abdominal CT or magnetic resonance imaging (MRI), ultrasonography, or bone scan. Endoscopic ultrasound (EUS) is performed prior to neoadjuvant therapy to exclude patients with regional lymph node metastases.

The Mayo Clinic protocol specifically excludes patients with evidence of intrahepatic or extrahepatic metastases or gallbladder involvement. Surgical intervention and any type of transperitoneal biopsy or fine needle aspiration have emerged as absolute contraindications to enrollment. These procedures result in an unacceptable rate of peritoneal seeding, which has been discovered during operative staging (unpublished data). Candidates must have no active infections or medical conditions that preclude either neoadjuvant therapy or OLT.

Tumor Diagnosis

Diagnostic criteria for neoadjuvant therapy and liver transplantation require a malignant-appearing stricture on cholangiography and either visualization of a mass on cross-sectional imaging, cytologic or histologic confirmation of CCA by transluminal brushing or biopsy, elevation of carboydrate antigen (CA)19-9 greater than 100 U/mL, or polysomy by fluorescence in situ hybridization (FISH). Patients with indeterminate diagnostic criteria—such as FISH trisomy (7 or 3), dysplasia from brushings, FISH polysomy in the absence of a malignant-appearing stricture, or a malignant-appearing stricture in the absence of a mass lesion are followed closely with repeat endoscopic retrograde cholangiography (ERCP) with brushings, cross-sectional imaging, and laboratory testing.

Neoadjuvant Therapy

Neoadjuvant therapy is administered by external beam radiation (40 to 45 Gy), followed by transcatheter radiation (20 to 30 Gy) with iridium wires. Wires are placed preferentially by ERCP and percutaneous transhepatic cholangiography (PTC) when ERCP is technically not possible. Intravenous 5-fluorouracil (5-FU) is administered for chemosensitization during radiation therapy, and capecitabine is administered afterward, while patients await transplantation.

Staging Operation

All patients undergo operative staging prior to OLT. Operative staging includes a thorough abdominal exploration with careful palpation of the liver to identify small, previously undetected intrahepatic metastases, biopsy of any suspicious nodules, and excision of a proximal proper hepatic artery lymph node (at the take-off of the gastroduodenal artery) and a pericholedochal lymph node posterior to the common bile duct just superior to the pancreas. The caudate process and retrohepatic vena cava are assessed for suitability of a caval-sparing hepatectomy, which is necessary for recipients of living-donor liver grafts. Extrahepatic or intrahepatic metastases, lymph node involvement, or locally extensive disease preclude transplantation. Survival for patients with these findings is low, and survival beyond a year is very rare. The staging operation was initially performed through a right subcostal incision with extension along the future liver transplant incision as necessary; however, during the past few years, most procedures have been accomplished by hand-assisted laparoscopy utilizing a smaller, right subcostal incision.

Timing of the staging operation depends on the possibility of a living-donor liver transplantation (LDLT) or the anticipated waiting time for a deceased-donor liver transplantation (DDLT). The staging procedure is performed 1 to 2 days prior to LDLT or as the patient nears the time for DDLT. Patients with underlying cirrhosis as a result of PSC or liver dysfunction as a result of cholestasis are somewhat prone to decompensation following the staging procedure, which may lead to an increase in a patient's MELD score and advance their position on the deceased-donor waiting list, but it also leads to an increase in perioperative morbidity and mortality. Unfortunately, only supportive care is possible for those patients who decompensate after a positive staging operation, and few survive the perioperative period.

Prior to 2003, 30% to 40% of patients had findings during the staging operation that precluded transplantation. EUS-guided aspiration of regional nodes (not the primary tumor) was implemented to exclude patients with lymph node metastases prior to initiation of neoadjuvant therapy. Initial findings from 47 patients identified eight (17%) with metastases (Gleeson et al, 2008). No morphologic features of the lymph nodes were found at EUS that predicted microscopic disease. Since routine use of EUS was implemented in 2003, the percentage of patients with a positive staging exploration has been reduced to 15%. EUS avoids the morbidity and mortality of high-dose neoadjuvant therapy and prevents an unnecessary operation for patients destined to fall out at operative staging.

Liver Transplantation

The technical difficulty and nuances of transplantation outweigh those of standard OLT. The operation is performed via a standard bilateral subcostal incision with vertical extension in the midline. Hilar dissection is avoided to prevent tumor manipulation and to reduce the possibility of intraoperative dissemination. There is typically extensive scar tissue in the hepatoduodenal ligament because of the neoadjuvant therapy and the previous staging procedure, which can make the dissection very difficult. The irradiated native hepatic artery is avoided during transplantation with a deceased donor, and arterial inflow is established with a segment of deceased donor iliac artery sewn to the infrarenal aorta. This approach was initially applied to LDLT but unfortunately resulted in an unacceptable rate of hepatic artery thrombosis. Better results have been achieved using the native artery, which is sewn directly to the living donor artery despite prior radiation therapy.

Next, the bile duct is transected as close to the pancreas as possible, and it may be possible to enucleate a short segment of additional common bile duct from the head of the pancreas. The margin is submitted for frozen section examination. Microscopic tumor involvement at this margin occurs in 10% to 15% of patients with PSC, and the possibility of PD is discussed with all patients prior to initiation of neoadjuvant therapy. Bilioenteric continuity is restored with a standard Roux-en-Y hepaticojejunostomy (living-donor graft) or choledochojejunostomy (deceased-donor graft).

The portal vein may be somewhat brittle as a result of the neoadjuvant therapy, and an injury may be difficult to control. The portal vein is divided as low as possible and is not dissected free up into the hilus of the liver. Despite low division, the deceased-donor portal vein is almost always long enough for an end-to-end anastomosis. A segment of a deceased-donor iliac vein is used as an interposition graft between a living-donor right or left portal vein and the native vein during LDLT. A caval-sparing hepatectomy is performed in most cases, and the donor suprahepatic vena cava is sewn to the left/middle hepatic

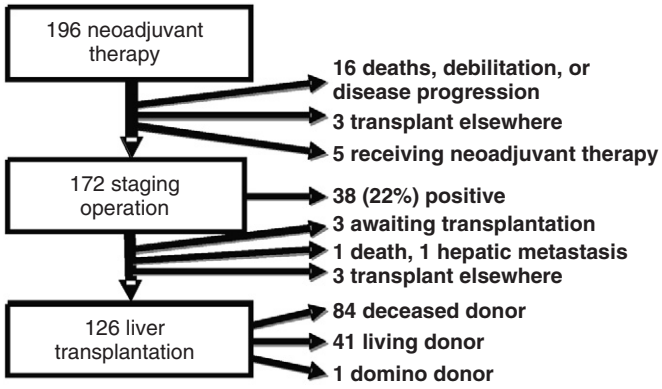


FIGURE 97E.1. Mayo Clinic neoadjuvant therapy and liver transplantation for hilar cholangiocarcinoma, 1993 through 2010.

vein trunk during DDLT; the hepatic vein is reconstructed in an end-to-end fashion during LDLT. If there is concern for tumor extension into the caudate, which is usually detectable during the staging operation, the retrohepatic cava is excised, and the donor retrohepatic vena cava is sewn to the suprahepatic and infrahepatic cavae as an interposition graft, usually via portovenous and venovenous bypass.

Results

One hundred ninety-six patients were enrolled in the Mayo Clinic protocol from 1993 until April 10, 2010 (Fig. 97E.1). Sixteen patients died, became too debilitated for transplantation, or had disease progression prior to operative staging. Three patients underwent transplantation at other centers, and five were receiving neoadjuvant therapy and/or awaiting operative staging. One hundred seventy-two patients underwent operative staging, and 38 patients (22%) had findings precluding transplantation. After staging, 1 patient died from hepatic decompensation, 1 developed intrahepatic metastases, and 3 patients underwent transplantation at other centers. The remaining 126 patients underwent transplantation, 84 with deceased-donor grafts, 41 with living-donor grafts, and one with a domino familial amyloid donor graft.

Overall patient survival from enrollment in the protocol (intention-to-treat analysis) was 56% ± 4% at 5 years after the start of neoadjuvant therapy (Fig. 97E.2), 63% ± 5% for patients with underlying PSC, and 44% ± 7% for patients with de novo CCA. Five-year survival after transplantation was 74% ± 5%; 80% ± 5% for patients with underlying PSC and 64% ± 8% for patients with de novo CCA (Fig. 97E.3). No difference in survival was reported among patients undergoing LDLT versus DDLT.

Thirty-eight patients (22%) had findings at the staging operation that precluded transplantation. The majority of these findings were regional lymph node (n = 17) and peritoneal (n = 14) metastases; 8 patients had invasion of adjacent organs/tissues, and 5 had intrahepatic metastases that had not been detected by preoperative imaging studies. Findings were missed in 4 patients found to have gallbladder involvement (n = 1) and invasion of neuroconnective tissue (n = 3) during transplantation within several weeks of their staging operations. Remarkably, the patient with gallbladder involvement also had microscopic disease at the common bile duct margin. She did not undergo PD, as it was not technically possible, and she is alive and disease-free 6.5 years after transplantation. The three patients with neuroconnective tissue involvement underwent reexcision

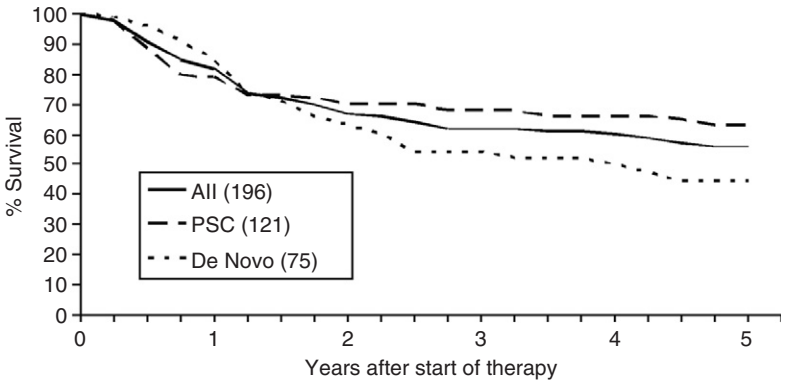


FIGURE 97E.2. Patient survival after start of neoadjuvant therapy. PSC, primary sclerosing cholangitis.

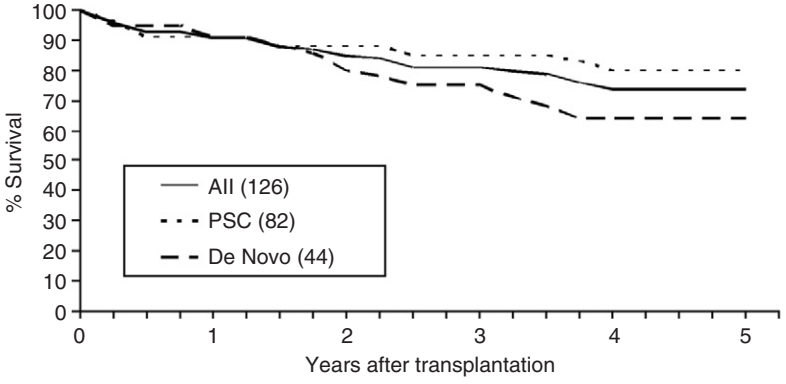


FIGURE 97E.3. Patient survival after transplantation. PSC, primary sclerosing cholangitis.

during the transplant operation and are alive at 13, 32, and 66 months after transplantation. The patient at 13 months has a very high CA19-9 level and presumably will develop detectable recurrent disease. The other 2 patients show no evidence of recurrent disease.

Twenty-nine patients (23%) died after transplantation: 7 from surgical complications (1 to 5 months) and 17 from recurrent CCA. Other causes of death were graft-versus-host disease (n = 2 at 1 and 4 months), posttransplant lymphoproliferative disease (23 months), an indeterminate hematologic disorder (31 months), and uterine cancer (45 months).

Recurrence and Prognostic Factors

Twenty-one of the 125 patients (17%) who underwent OLT developed recurrent disease at a mean of 25 months (range, 7 to 64 months) after transplantation, and 10 (48%) of the 21 recurrences were distant metastases. The initial sites for recurrent CCA are shown in Table 97E.1.

The Mayo group reviewed their experience in 2006 with an aim to identify clinical and pathologic predictors of recurrence (Heimbach et al, 2006). At that time, 65 patients had undergone transplantation; the mean follow-up was 32 months, and 11 patients (17%) had documented recurrences after transplantation. Clinical factors identified as predictors of recurrence included older patient age, prior cholecystectomy, CA19-9 greater than 100 at the time of transplantation, a visible mass on cross-sectional imaging, and an extended waiting time between conclusion of neoadjuvant therapy and OLT. Pathologic findings identified as predictors of recurrence included residual CCA larger than 2 cm, high-grade histology, and perineural invasion.

Pancreatoduodenectomy and Transplantation

The addition of a PD greatly increases the technical complexity of transplantation and has a significant impact on postoperative morbidity and mortality. A 5-year survival rate of 56% (±17%, compared with 75% ± 5% overall) was reported in 11 patients who underwent OLT with concomitant PD, and 9 of 67 PSC patients (13%) were found to have microscopic involvement of the common bile duct margin at the time of transplantation, and 8 of these patients (5 deceased donor, 2 living donor, and one amyloid donor) underwent PD. Currently, 5 are alive and disease free at 9 months to 11 years after transplantation; however, 2 patients died within 3 months from hepatic artery thrombosis (deceased-donor graft) and hepatic artery thrombosis with pseudoaneurysm (living-donor graft), and adhesions precluded PD in the remaining patient, who was also found to have gallbladder involvement; remarkably, this patient is alive and without evidence of disease 6.5 years after transplantation.

Two patients with previous biliary operations underwent OLT with en bloc PD. One patient is alive and disease-free 7 years after transplantation; the other patient died 45 months after transplantation from uterine cancer. Additionally, one PSC patient known to have positive brushings in the common bile duct in addition to a hilar CCA underwent planned OLT with en bloc PD and is alive and disease-free at 13 months. No patient with de novo hilar CCA has had a positive common bile duct margin at the time of transplantation.

Table 97E.1

Cholangiocarcinoma Recurrence After Transplantation

Site	Time (mo)	Status (mo)
Regional	7, 10, 14	Dead at 10, 17, 18
	14, 15, 17, 65	Alive at 21, 16, 24, 67
Peritoneal	15	Alive at 23
	22, 25, 27	Dead at 29, 41, 43
Chest	18, 24	Alive at 36, 48
	22, 30, 40	Dead at 24, 30, 64
Bone	7, 8, 55	Dead at 37, 10, 84
	47	Dead at 48
Miscellaneous	34	Alive at 37
	47	Dead at 48

Mean time to recurrence was 25 months.

Vascular Complications

Late vascular complications are much more common after transplantation for CCA than after other indications because of the neoadjuvant therapy (Mantel et al, 2007). Use of the irradiated native common hepatic artery is avoided during DDLT in lieu of a deceased-donor iliac artery graft from the infrarenal aorta. This strategy was initially implemented in LDLT but resulted in an unacceptable rate of acute hepatic artery thrombosis. Subsequently, the native hepatic artery has been used for arterial inflow in LDLT; this strategy reduced early hepatic artery thrombosis but it is associated with a 20% late stenosis/thrombosis rate. Likewise, there is also a 20% rate of late portal vein stenosis (with or without thrombosis) seen with both living- and deceased-donor transplantation. A deceased donor iliac vein is used as an interposition graft during LDLT, and the stenosis has always involved the native portal vein and its anastomosis with the interposition graft.

All patients undergo Doppler US and contrast CT examination 4 months after transplantation. These imaging studies enable detection of an asymptomatic stenosis that is usually amenable to angioplasty with or without stent insertion. Arterial complications are treated by a transarterial approach, and portal complications are treated transhepatically. Fortunately, the Mayo group has not lost a graft from a portal stenosis or an arterial stenosis detected prior to thrombosis.

Medical and Neoadjuvant Complications

The effect of neoadjuvant radiotherapy on the liver is profound (Fig. 97E.4). Widespread necrosis is found in the hilus with necrotic debris in the major ducts (Fig. 97E.5); thus pretransplant infectious complications related to neoadjuvant therapy are very common and require continuous care and frequent hospitalization for patients awaiting transplantation. Nearly all patients have one or more episodes of cholangitis with occasional development of intrahepatic abscesses. Cholecystitis is treated nonoperatively with antibiotics, although severe cases may require endoscopic placement of a cystic duct stent or percutaneous cholecystostomy. Several patients have developed gallbladder necrosis with rupture that required emergency operations. Gastritis, duodenitis, and poor gastric emptying are also common and can persist after transplantation, which can lead to difficulties with nutrition. Several patients have

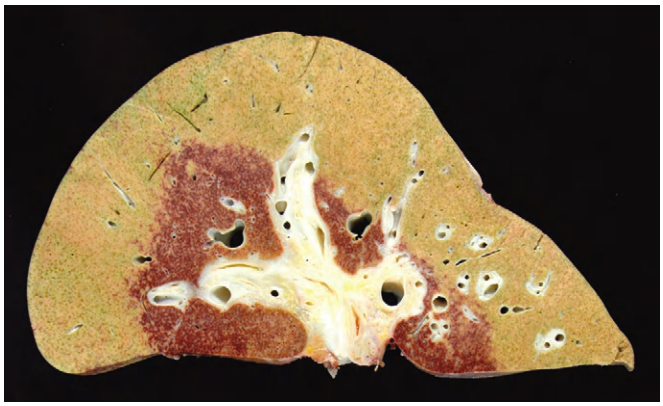


FIGURE 97E.4. Explanted liver after neoadjuvant therapy showing radiation effect.

required operative intervention for duodenal perforation or life-threatening hemorrhage from duodenitis and peptic ulceration.

CCA patients are hypercoaguable and at risk for deep venous thrombosis (DVT) and pulmonary embolism, as observed with other types of malignancies. Thus, they receive DVT prophylaxis whenever hospitalized for nonbleeding complications and especially during the perioperative period following operative staging.

Key Questions

Despite the success reported by the Mayo Clinic, the results remain controversial. Key questions fueling the controversy pertain to 1) accuracy of diagnosis prior to neoadjuvant therapy, 2) efficacy of the protocol, 3) whether transplantation for CCA is an appropriate use of donor organs, 4) whether these patients warrant prioritization for deceased-donor liver allocation, and 5) whether transplantation after neoadjuvant therapy should be used for patients with potentially resectable CCA in lieu of standard resection.

Diagnostic Accuracy

The protocol diagnostic criteria allow enrollment of patients without pathologic confirmation of CCA. It is indeed probable that some patients who did not have CCA were treated with neoadjuvant therapy and liver transplantation; although these patients would favorably affect the results, their impact is not significant. Furthermore, it would be difficult to require pathologic confirmation of disease prior to treatment. Pathologic confirmation is notoriously difficult for hilar CCA, and a large proportion of patients treated without it are subsequently confirmed by findings at the staging operation or transplantation. Pathologic confirmation of CCA is associated with a significantly higher rate of fallout at operative staging: 32% versus 10%; however, there are no significant differences in residual CCA in the explanted liver (42% vs. 54%) or recurrence rates after transplantation (15% vs. 20%) between those who did and did not have pathologic confirmation. It would thus be difficult to deny treatment to patients who fulfill the diagnostic criteria but do not have pathologic confirmation of CCA; 28 of 65 patients were eventually confirmed by pathologic findings, 27 with residual disease in the explant and 1 with a recurrence.

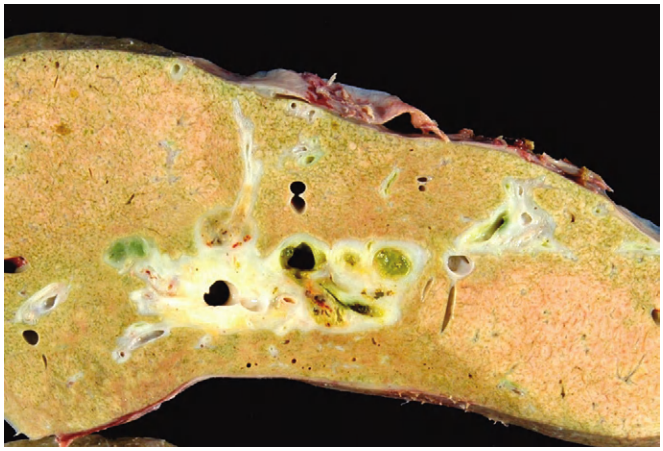


FIGURE 97E.5. Explanted liver after neoadjuvant therapy showing duct necrosis and intraductal debris.

Efficacy

The Mayo protocol's efficacy is self-evident: all of the patients had either CCA arising in the setting of PSC or unresectable CCA arising de novo. Resection was not possible, and the results with the Mayo protocol are clearly better than the natural history of untreated CCA, which has a 50% to 70% mortality rate at 1 year (Burak et al, 2004; Farley et al, 1995). The standard surgical treatment for hilar CCA is resection with partial hepatectomy, en bloc excision of the extrahepatic duct, and radical lymphadenectomy. After complete extirpation of tumor, 5-year survival following an R0 resection ranges from 30% to 45%.

The Mayo protocol has also achieved comparable results with patients having unresectable de novo CCA, with 5-year survival of 44% for 75 patients after the start of neoadjuvant therapy and 5-year survival of 64% for 44 patients after transplantation. Furthermore, the results clearly demonstrate efficacy of neoadjuvant therapy, because 35 (57%) of 61 patients with pathologic confirmation prior to neoadjuvant therapy had neither residual disease in the explant nor a recurrence after transplantation.

Appropriate Use of Donor Organs

The results achieved with liver transplantation for CCA after neoadjuvant therapy and operative staging are comparable to results achieved with liver transplantation for other malignant, chronic, and acute liver diseases such as PSC, hepatitis C, and HCC (Heimbach et al, 2004). Because patients with CCA arising in the setting of PSC and those with unresectable CCA arising de novo have no other potentially curative treatment options, liver transplantation is an appropriate use of both deceased-donor and living-donor livers.

Deceased-Donor Allocation and Prioritization

As CCA emerged as a valid indication for liver transplantation, allocation of deceased-donor livers became highly controversial. Mayo Clinic-Rochester is within United Network of Organ Sharing (UNOS) Region 7, and that region's review board members agreed to Model for End-Stage Liver Disease (MELD) score exception guidelines shortly after the implementation of MELD for liver allocation in 2002. MELD score exceptions were given to patients who successfully completed neoadjuvant therapy and had no evidence of metastases at

operative staging. The initial adjustment was a score of 20, matching that of HCC at the time, and was increased in parallel to the score schedule for HCC, but at 6-month rather than 3-month intervals, as was done for HCC.

Additional aims of the guidelines were to determine the risk of disease progression in patients awaiting transplantation and to retain incentives for use of living liver donors and utilization of extended criteria donors. The Mayo Clinic transplanted 42 patients between September 2002 and January 2006, with a median staging-to-transplant interval of 114 days. After transplantation, one of 21 patients with an interval less than 114 days developed recurrent disease, whereas four of 21 patients with an interval greater than 114 days developed recurrent disease (92% ± 7% vs. 56% ± 19% disease-free 2.5-year survival). Although the difference was not statistically significant because of the small number of patients, the results suggested that prolongation of waiting time leads to an increase in recurrent disease after transplantation (unpublished data).

A group of transplant surgeons and physicians met as an ad hoc MELD Exception Study Group in March 2006 to review the available data for the treatment of hilar CCA with neoadjuvant therapy followed by OLT (Gores et al, 2006). The group concluded that sufficient data existed to justify priority for patients enrolled in clinical trials that used neoadjuvant therapy provided that 1) transplant centers submit formal patient care protocols to the UNOS Liver and Intestinal Committee; 2) candidates satisfy accepted diagnostic criteria for CCA and are considered to be unresectable on the basis of technical considerations or underlying liver disease, such as PSC; 3) tumor mass, when visible on cross-sectional imaging studies, is less than 3 cm in radial diameter; 4) imaging studies to assess patients for intrahepatic and extrahepatic metastases are repeated prior to interval score increases; 5) regional hepatic lymph node involvement and the peritoneal cavity is assessed by operative staging after completion of neoadjuvant therapy and prior to transplantation; and 6) transperitoneal aspiration or biopsy of the primary tumor is avoided because of the high risk of tumor seeding associated with these procedures. The group also concluded that prioritization of patients with biliary dysplasia to avoid progression to CCA was unjustified. In 2009, UNOS adopted these MELD exception criteria, and the score adjustment is identical to that for HCC, with score increases at 3-month intervals.

Resection Versus Transplantation

Because results with the Mayo protocol equal or exceed the results achieved with resection, it would seem reasonable to consider neoadjuvant therapy and liver transplantation in lieu of resection for patients with potentially resectable disease. Rea and colleagues (2005) retrospectively compared results for patients treated by potentially curative resection and neoadjuvant therapy and liver transplantation at the Mayo Clinic between 1993 and 2004. Although no statistically significant difference in survival was found between the two groups, a strong trend was seen toward better survival in the group treated with neoadjuvant therapy and liver transplantation.

Since that time, the Mayo group has accrued a larger experience with liver transplantation for patients with unresectable de novo CCA, and the results with the protocol show an overall survival of 44% at 5 years after the start of neoadjuvant therapy, a result not too dissimilar from those achieved with resection. A prospective trial of resection versus transplantation is impractical because of the large number of patients that would be necessary to show a significant difference in survival. Furthermore, a crossover would not be possible. Patients treated with neoadjuvant therapy would not be amenable to resection. The effect of high-dose neoadjuvant therapy on the underlying liver and bile duct is profound (see Figs. 97E.4 and 97E.5) and precludes biliary reconstruction because of widespread intrahepatic duct necrosis. Patients found to be unresectable at operation would not be appropriate for subsequent neoadjuvant therapy and transplantation. Results with resection are also improving with increasing experience and technical innovation; Neuhaus and colleagues (1999, 2003) demonstrated excellent 5-year survival using vascular reconstruction with extended hepatectomy (Jonas et al, 2008).

In summary, neoadjuvant therapy followed by OLT for the treatment of hilar CCA achieves excellent results for highly selected patients with early stage disease. The results compare favorably to survival after OLT for chronic liver disease and for HCC. Neoadjuvant therapy with subsequent liver transplantation has emerged as the treatment of choice for patients with unresectable hilar CCA or hilar CCA arising in the setting of PSC. Success requires careful patient selection with adherence to protocol and operative staging prior to OLT, and LDLT enables transplantation to be performed in a timely fashion, without prolongation of waiting time, and achieves results similar to those seen with DDLT. Neoadjuvant therapy introduces considerable morbidity and unique complications not usually encountered with transplantation alone, and these challenges highlight the need for a multidisciplinary team that includes hepatologists, interventional radiologists, gastroenterologists, radiation and medical oncologists, and transplant surgeons in order to achieve success.

NEUROENDOCRINE CANCER (SEE CHAPTER 81B)

Gastroenteropancreatic neuroendocrine cancers (NECs) are a rare, diverse group of tumors with an incidence of one to two cases per 100,000 per year with a slight female predominance (Taal & Visser, 2004). These tumors are characteristically indolent in nature and are frequently found to be metastatic at the time of diagnosis. The liver is the most common site for metastases, and widespread hepatic dissemination is the leading cause of death in these patients (Frilling et al, 2009). Fortunately, these cancers are often confined to the liver for protracted periods of time with 5-year survival of 13% to 54% even without treatment (Godwin, 1975; Thompson et al, 1988; Que et al, 1995).

Various therapeutic options have been utilized for NEC with hepatic metastases; such treatments include transarterial chemoembolization (TACE), radiofrequency and cryoablation, systemic chemotherapy, peptide receptor radionuclide therapy (see Chapters 84A, 84B, 85A and 85B), cytoreductive resection, surgical resection (see Chapter 81B), and liver transplantation. Surgical extirpation with an R0 resection is the most effective therapy for metastatic NEC confined to the liver; however, only 10% to 57% of these tumors are amenable to compete resection (Chen et al, 1998; Elias et al, 2003; Frilling et al, 2009; Grazi et al, 2000; Mazzaferro et al, 2007; Musunuru et al, 2006; Yao et al, 2001).

Liver transplantation is an option for treatment of patients with a low probability of achieving an R0 resection. The goals of

liver transplantation are to 1) achieve palliation by alleviating symptoms for patients with functioning NEC; 2) achieve palliation by delaying death as a result of tumor replacement of the liver, taking advantage of the slow progression and the time it will take to replace the new liver with tumor, "resetting the clock"; and 3) achieve a cure. Liver transplantation is highly effective at relieving symptoms for patients with functioning NEC. There are several single-center (Florman et al, 2004; Frilling et al, 2006; Mazzaferro et al, 2007; Rosenau et al, 2002) and multicenter (Le Treut et al, 2008) studies reporting 36% to 90% patient survival at 5 years. The possibility of achieving a cure, however, is very low. Disease-free survival is only 20% to 77% at 5 years, and tumor recurrence after 5 years is common.

Widespread acceptance of OLT as a reasonable option for the treatment of this disease remains limited and controversial for multiple reasons that include the scarcity of deceased-donor organs available for OLT and the availability of other treatment modalities that can also provide palliation. Furthermore, reliable selection criteria have not been identified, and long-term data are limited because of the low incidence of the disease. Most importantly, it remains difficult to determine the actual benefit derived from OLT as a result of the protracted course of metastatic disease and unknown natural history of disease for those patients selected as candidates for transplantation.

The Mayo Clinic developed a protocol in 2002 designed to assess efficacy of liver transplantation for patients with metastatic NEC confined to the liver and regional hepatic lymph nodes (van Vilsteren et al, 2006). The clinical inclusion/exclusion criteria are summarized in Box 97E.1. Each patient was screened for locally recurrent and extrahepatic disease with chest, abdomen, and pelvic CT scans, bone scan, and somatostatin receptor scintigraphy within 60 days of preliminary registration for transplantation. Prior treatment modalities did not exclude patients, as long as they did not technically prohibit OLT. Patients were observed for 6 months following resection of the primary NEC to exclude extrahepatic disease progression. Reevaluation for metastatic disease prior to liver transplantation was performed every 4 months via laboratory tests, tumor marker assays, and abdominal imaging studies. Extrahepatic metastases were excluded via operative staging with laparoscopy prior to OLT.

The results were published with short follow-up. Since that time, 23 patients with metastatic NEC have undergone transplantation at the Mayo Clinic, with 76% patient survival and 37% disease-free survival at 5 years (unpublished data). Consistent with information in the literature, patients with carcinoid tumors fared slightly better than those with islet cell tumors originating in the pancreas. Patient and disease-free survival at 5 years was 86% and 45% for 10 patients with carcinoid tumors, 78% and 44% for 9 patients with islet cell tumors, and 50% and 0% for 3 patients with gastrinoma and one patient with glucagonoma. Thirteen patients developed recurrent disease, and survival after recurrence was less than 30% at 4 years, 50% for those with carcinoid or islet cell tumors, and 0% for those with gastrinoma or glucagonoma. As a result, patients with metastatic glucagonoma and gastrinoma are no longer considered for transplantation.

In summary, liver transplantation effectively alleviates symptoms for patients with diffuse, functioning NEC liver metastases. Liver transplantation may improve patient survival for those destined to succumb to liver replacement by tumor, but no studies actually demonstrate efficacy. Recurrence is common following transplantation, and results with metastatic gastrinoma and glucagonoma are poor, so transplantation should not be done for these types of tumors. Indications for transplantation and optimal timing in the course of disease remain ill defined, and the absence of prioritization (MELD score adjustment) in the United States precludes widespread application.

Box 97E.1

Mayo Clinic Transplantation Selection Criteria for Patients with Metastatic Neuroendocrine Carcinoma

Inclusion Criteria

1. Histologic confirmation of NEC (liver primary vs. metastatic disease confined to the liver)
2. Unresectable hepatic disease involving both lobes
3. Complete resection of the primary NEC or single dominant liver NEC believed to be a primary lesion
4. Absence of extrahepatic disease with the exception of regional lymph nodes resectable as part of standard liver transplantation
5. At least a 6-month interval from resection of primary NEC and transplantation without extrahepatic disease progression
6. Patient deemed suitable for liver transplantation, meeting all United Network for Organ Sharing listing criteria

Exclusion Criteria

1. Prior nonselective hepatic artery embolization unless approved by the transplant surgeon (only for living-donor transplantation)
2. Rectal NEC
3. Anaplastic or poorly differentiated (grade 3 or 4) tumor
4. Right atrial pressure >15 mm Hg
5. Known pregnancy
6. Other factors that preclude transplantation, including severe comorbidities, infection, or other malignancies

Other

1. Patients are staged with computed tomographic scan of the chest, abdomen, and pelvis; bone scan; and somatostatin receptor scintigraphy scan
2. All patients undergo open or laparoscopic staging celiotomy
3. Patients are reevaluated every 4 months with abdominal imaging to evaluate for extrahepatic disease progression

NEC, neuroendocrine cancer

HEPATIC EPITHELIOID HEMANGIOENDOTHELIOMA (SEE CHAPTER 78B)

HEHE, first described in 1982, is a rare neoplasm that originates from vascular endothelium, and it has unpredictable malignant potential (Weiss & Enzinger, 1982). Ishak and colleagues (1984) first reported liver involvement in a series of 32 patients with HEHE, which arises between the second and ninth decades with a 3:2 female/male predominance (Mehrabi et al, 2006). The etiology of HEHE remains elusive, although a multitude of conditions have been proposed to contribute to its development; these include viral hepatitis, liver trauma, oral contraceptives, primary biliary cirrhosis, alcohol consumption, and exposure to vinyl chloride, asbestos, and Thorotrast (Darras et al, 1988; Dean et al, 1985; Lauffer et al, 1996; Makhlouf et al, 1999; Mehrabi et al, 2006; Soslow et al, 1997).

The most common clinical manifestations of HEHE are right upper quadrant pain, hepatomegaly, and weight loss. Weakness, anorexia, epigastric mass, ascites, nausea, jaundice,

and fatigue are additional symptoms. Up to 25% of these lesions are detected as incidental findings (Lauffer et al, 1996; Mehrabi et al, 2006).

Two variants of HEHE have been described, *nodular* and *diffuse*. In actuality, the variants represent early- and late-stage disease. The *nodular type* is seen early with a highly variable number of 1- to 12-cm lesions arising throughout the liver. The lesions are typically hypodense on CT scan with high-density contrast uptake in the periphery. Individual nodules increase in size by spreading along the hepatic or portal veins, and they eventually coalesce to form diffuse peripheral lesions. The CT appearance of the later *diffuse type* is typically a large, slow-growing lesion resulting from coalescence of smaller lesions. Flattening of the capsule may occur because of fibrosis, peripheral enhancement of contrast may be seen with many hypervascular central lesions, and hypertrophy of the unaffected segments of the liver may be apparent (Fulcher & Sterling, 2002; Lyburn et al, 2003; Miller et al, 1992).

Definitive radiographic diagnosis of the HEHE is usually not possible, especially in the nodular form, because of the similarity of this tumor with primary epithelial liver tumors and hepatic metastases. In a review of 434 cases of HEHE, the majority of patients (87%) had multifocal disease involving both lobes of the liver at the time of presentation. Extrahepatic disease at diagnosis was common (36.6%) with involvement of the lung (8.5%), regional lymph nodes (7.7%), peritoneum (6.1%), spleen (3.2%), and diaphragm (1.6%) (Mehrabi et al, 2006).

Histologically, HEHE may resemble other conditions such as venoocclusive disease, CCA, hemangioma, angiosarcoma, and metastatic signet ring cell carcinoma (Corrin et al, 1979). Furthermore, immunohistochemical staining may suggest a tumor of neuroendocrine origin. Histologic findings are consistent with epithelioid or histiocytoid morphology and intracytoplasmic lumina containing red blood cells. Immunohistochemical staining is positive for factor VIII–related antigen and endothelial cell markers (CD31, CD34) and negative for mucin, bile, carcinoembryonic antigen, and α-fetoprotein. Ultrastructural findings are characterized by a well-developed basal lamina, pinocytotic vesicles, and Weibel-Palade bodies (Ishak et al, 1984; Lauffer et al, 1996; Mehrabi et al, 2006).

Treatment of HEHE is difficult. Resection is often not possible because of the presence of multifocal bilobar disease at the time of diagnosis. In the review by Mehrabi and colleagues (2006), only 9.4% of patients were amenable to resection. Patient survival was 100% at 1 year and 75% at 5 years. For many patients, observation alone is reasonable, because progression may be extremely slow, if it occurs at all. Others have reported poorer results (Ben-Haim et al, 1999) and have suggested that resection should be limited to patients presenting with unilobar, liver-confined disease (Mosoia et al, 2008).

Liver transplantation is an option for patients with extensive intrahepatic disease. Several series have reported outcomes equivalent to those for liver transplantation for other diagnoses. In a report from the European Liver Transplant Registry (ELTR), patient survival rates at 1, 5, and 10 years were 93%, 82%, and 72% with 90%, 82%, and 64% disease-free survival, respectively. Neither disease-free survival nor patient survival was influenced by neoadjuvant therapy, lymph node status, or the presence of extrahepatic disease; however, vascular invasion had a negative impact on patient survival (Lerut et al, 2007). A multicenter Canadian experience with 11 patients reported 5-year survival of 82% with a 36.4% recurrence rate (Nudo et al, 2008). A recent query of the UNOS database identified 110 patients who underwent OLT for HEHE in the United States between 1987 and 2005 (Rodriguez et al, 2008). Patient survival was 80% and 64% at 1 and 5 years. In their survey of the available literature, Mehrabi and colleagues (2006) reported 1- and 5-year patient survival of 96% and 54.5%, respectively, after OLT.

The Mayo Clinic recently reviewed its experience with 30 patients treated for HEHE between 1984 and 2007 (Grotz et al, 2010) and found a 2:1 female predominance with a mean age at diagnosis of 46 years (range, 21 to 79 years). The diagnosis of HEHE was confirmed in all cases by immunohistochemical staining for factor VIII–related antigen, CD31, and CD34. Patients were divided into groups based on the number and size of nodules present within the liver: half had 10 or fewer nodules, and half had more than 10 nodules; the largest lesion was smaller than 5 cm in 43%, it was 5 to 10 cm in 30%, and it was larger than 10 cm in 27% of cases. Extrahepatic disease was present at diagnosis in 37% of patients (n = 11). Sites of metastases included lung (n = 8), peritoneum (n = 2), bone (n = 2), brain (n = 1), and skin (n = 1), and one third of the patients had multiple sites of extrahepatic involvement.

Therapeutic management included OLT (n = 11), primary resection (n = 11), systemic chemotherapy (n = 5), and no medical treatment (n = 3). Median follow-up was 41.6 months (range, 0 to 243), and in this time, 12 deaths (40%) were reported, one patient died within 2 years of primary resection, six patients died after OLT (1 month to 11 years), and five patients treated nonsurgically died 1 month to 4 years after diagnosis. Patient survival following primary resection at 1, 3, and 5 years was 100%, 86%, and 86%, respectively, compared with 91%, 73%, and 73%, respectively, for patients treated with OLT. Patient survival following nonoperative management was 57%, 43%, and 29% at 1, 3, and 5 years, respectively. Disease-free survival following primary resection was 78%, 62%, and 62% at 1, 3, and 5 years, respectively, compared with 64%, 46%, and 46% after OLT. Although no significant differences were seen in patient survival ($P = .128$) or disease-free survival ($P = .405$), patients who underwent primary resection had significantly fewer tumor nodules and less diffuse liver involvement compared with those who underwent OLT ($P = .004$).

Morphologic features associated with prolonged disease-free survival were nodular disease pattern ($P = .01$) and largest hepatic lesion 10 cm or smaller ($P = .003$). Patients with 10 or fewer tumor nodules showed a trend toward better survival ($P = .052$). Factors associated with decreased overall patient survival were tumor size larger than 10 cm ($P = .0007$, hazard ratio [HR], 10.97; 95% confidence interval [CI], 2.76 to 43.68), more than 10 nodules ($P = .023$; HR, 5.83; CI, 1.27 to 26.8), diffuse disease pattern ($P = .0076$; HR, 8.14; CI, 1.75 to 37.91), and involvement of more than four liver segments ($P = .041$; HR, 4.92; CI, 1.06 to 22.77). The presence of extrahepatic disease did not have an impact on patient survival ($P = .5$).

The Mayo Clinic findings demonstrate that primary resection and liver transplantation achieve comparable survival for patients with HEHE. Resection is favored for patients with 10 or fewer lesions, involvement of four or fewer liver segments, and disease amenable to complete extirpation of tumor. Transplantation is recommended for those with more than 10 lesions, involvement of more than four liver segments, and unresectable disease.

SUMMARY

Liver transplantation is appropriate therapy for selected patients with malignancies other than HCC. Excellent results have been achieved for patients with unresectable hilar CCA and hilar CCA arising in the setting of PSC. Success requires rigorous adherence to protocol with careful selection of patients with early stage disease confined to the hilus along with neoadjuvant chemoradiotherapy and operative staging to exclude patients with regional lymph node metastases. Liver transplantation without prior neoadjuvant therapy is rarely successful and should not knowingly be performed for patients with CCA.

The role of liver transplantation in the treatment of metastatic NEC remains unclear. Experience to date shows that most patients develop recurrent disease; however, transplantation may prolong survival by delaying death from tumor replacement of the liver. Because of the indolent nature of the disease, survival beyond 5 years is achievable, but the actual benefit—that is, the difference in survival with and without transplantation—remains unknown.

Liver transplantation achieves results comparable to resection for patients with HEHE, and transplantation should be considered for patients with more than 10 nodules, involvement of more than four liver segments, or tumors not amenable to resection. Additional experience is necessary to confirm reports that transplantation is beneficial for patients with limited extrahepatic disease.

References are available at expertconsult.com.

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CHAPTER 98B

Living donor liver transplantation: open and laparoscopic

Alan J. Koffron and Julie A. Stein

OVERVIEW

Organ availability continues to be a major issue in contemporary transplantation. Living-donor renal transplantation is accepted globally as an important alternative to cadaveric renal transplantation for patients with end-stage renal failure. In 2008, living donors were the source of 36% of the total kidney transplants in the United States (United Network of Organ Sharing [UNOS], 2008). This is largely because the kidneys are paired organs, laparoscopic donor nephrectomy is widespread, and donor morbidity and mortality is low (Kocak et al, 2006).

Despite advances in hepatobiliary surgery, hepatic resection remains a technically demanding surgical endeavor, with higher complication rates than kidney transplantation (Miller et al, 2004a; Pomfret, 2003). Liver transplantation, now standard treatment for many hepatic diseases (see Chapter 97A), has gone through the same evolution as renal transplantation with respect to live donation. Transplantologists embarked on living-donor liver transplantation (LDLT) in the late 1980s, principally as a means to combat pediatric waiting-list mortality (Broelsch et al, 1991; Raia et al, 1989). The inception and refinement of LDLT and split-liver transplantation (see Chapter 98C) have significantly reduced pediatric waiting-list mortality (Testa et al, 2001), thus paving the way for the development of LDLT in adults.

As the indications for liver transplantation have broadened, and cadaveric organ supply has remained largely static, the waiting-list mortality for adults has increased. Thus, in the mid-1990s, as in pediatric transplantation, adult LDLT was initiated in response. In Japan, where death defined by neurologic criteria is not accepted, LDLT began with left-lobe adult LDLT (Hashikura et al, 1994), leading to right-lobe LDLT (Yamaoka et al, 1994) with substantial acceptance and growth of this practice in Asia (Chen et al, 2003), followed by initiation and refinement in the United States in the late 1990s (Boillot et al, 1999; Marcos et al, 1999; Miller et al, 2001; Wachs et al, 1998). Despite the inherent donor risks—and rare, but high-impact, donor deaths (Miller et al, 2004a; Fan et al, 2003)—right-lobe LDLT has remained a strong option in the treatment of liver disease. To that end, as of 2008, LDLT has made up 4% to 9% of all adult liver transplantations performed in the United States (UNOS, 2008). Currently, donor safety remains the primary focus of LDLT, superceding the omnipresent clinical incentive: the static cadaveric donor pool and transplant waiting-list mortality (Salame et al, 2002; Surman, 2002).

In 2002, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) established a multicenter clinical study, the Adult-to-Adult Living Donor Liver Transplantation (A2ALL) cohort study, which consists of nine transplant centers experienced in performing LDLT and a data coordinating center responsible for directing and maintaining a clinical database for the retrospective (1998 through 2003) and prospective (2004 through 2010) arms of the study. This study, in collaboration with the American Society of Transplant Surgeons (ASTS) and the Health Resources and Services Administration (HRSA) has two principal objectives: 1) to determine whether it is more beneficial for a liver transplant recipient candidate to pursue LDLT or wait for a deceased-donor liver transplant (DDLT), and 2) to study the impact of liver donation on the donor's health and quality of life. Secondary objectives will address selected biologic and clinical issues in transplantation structured around the comparison between DDLT and LDLT, including immunosuppression, malignancy, and hepatitis. Although the prospective arm of this valuable study is ongoing at the time of this publication, thus far, the resulting contributions have given considerable insight into LDLT, and these insights will be referenced in following sections of this chapter.

Congruent with the tenet of donor safety, reducing donor morbidity is of equal importance. The great advances that have been made in minimally invasive liver resection have now been applied to liver donation in hopes of reducing surgical morbidity and enhancing donor recovery. Similar to the evolution of recipient procedures, minimally invasive liver donation began in the pediatric setting, with laparoscopic harvest of the left lateral section (Cherqui et al, 2002). As centers gained experience in minimally invasive hemihepatectomy (Koffron et al, 2007a; O'Rourke & Fielding, 2004), these methods were carefully applied to right-lobe donation (Koffron et al, 2006) in the hope of reducing donor morbidity, enhancing recovery, and secondarily increasing the willingness to consider donation (Baker et al, 2009). These efforts show promise in their initial results, but greater experience and analysis of clinical outcomes is necessary to define the role of laparoscopy in liver donation and transplantation as a whole.

LIVING DONOR LIVER TRANSPLANTATION: INDICATIONS AND RESULTS

Many of the indications for LDLT are the same as those for liver transplantation in general (see Chapters 97A, 97C, 97D, and 97E). Given this, the reasons to consider LDLT as opposed to DDLT center largely on chronology with regard to hepatitis C virus (HCV), hepatocellular carcinoma (HCC), and the likelihood that a cadaveric donor organ would become available in a timely fashion. These reasons are always weighed against the tenet that it is unjustified to subject even a volunteer to the risks

inherent in donor hepatectomy if the recipient has a reasonable chance of receiving a cadaveric liver graft prior to medical decompensation or progression.

Pediatric Living Donor Liver Transplantation

In pediatric LDLT (see Chapter 98C), although the results in all indications are equivalent with whole-liver grafts, cadaveric graft allocation remains the major concern in the setting of acute hepatic failure. The combination of outcome and availability has made acute liver failure (ALF) a well-accepted indication for pediatric LDLT. For other indications for liver transplantation, split-liver transplantation—in which a cadaveric donor organ is divided to transplant two recipients—is an attractive and increasingly popular alternative to LDLT, and it avoids placing a healthy donor in harm's way.

Adult Living Donor Liver Transplantation

Experience has shown that although retransplantation is higher after LDLT, patient survival is similar to DDLT (Abt et al, 2004; Freise et al, 2008). There are many reasons for this phenomenon, many of which are related to implantation of a smaller allograft. It seems intuitive that the more advanced the liver disease (liver decompensation, severe portal hypertension), the more ill the patient, and consequently the need for greater hepatocellular mass. In this light, many centers would not perform LDLT on patients with Child-Turcotte-Pugh (CTP) class C cirrhosis, unless the donor can provide a graft of substantial size. Fortunately, in most circumstances, the current U.S. organ allocation system can accommodate such gravely ill patients with DDLT.

Adult LDLT in the treatment of fulminant hepatic failure (FHF) has a unique geographic paradigm. This phenomenon is largely a result of differences in organ donation. In Western countries, LDLT for acute hepatic failure has acceptable results (Sugawara et al, 2002a, 2003), but the organ allocation scheme in the United States places patients with ALF at highest allocation priority, and so it is favorable that DDLT would be available. Therefore, in the United States the concern is raised that LDLT for ALF may place live donors at unnecessary risk in a clinical situation in which a potentially clinically superior DDLT may be possible. The A2ALL retrospective study resulted in a similar conclusion (Campsen et al, 2008). In the nine U.S. transplant centers, LDLT was rarely performed for ALF but was associated with acceptable recipient mortality and donor morbidity; however, the authors raised the concern that a partial graft might result in reduced survival of critically ill recipients and that the rapid course of ALF would lead to selection of inappropriate donors.

This contrasts sharply with the role of LDLT for ALF in Asia, where cadaveric donation is scarce. Here, LDLT accounts for more than 90% of the liver transplantations (de Villa & Lo, 2007; Kobayashi et al, 2003; Lubezky et al, 2004). FHF was the indication for transplantation in 5.7% of the adult LDLT series reported by the Asian group (Lee et al, 2007), in 12% of the series reported by the Hong Kong group (Lo et al, 2004), and in 14.6% of the series reported by the Kyoto group (Morioka et al, 2007); therefore in the East, the consensus is reflected in the findings of a large study on this subject (Ikegami et al, 2008). Over 10 years, 42 LDLTs performed for ALF were reviewed, concluding that outcomes were acceptable even in severely ill recipients, and that LDLT is the accepted treatment of choice for ALF.

Investigation of LDLT has provided clarity in other aspects of this form of liver therapy. Interestingly, results of the A2ALL retrospective cohort study did not show an immunologic advantage for LDLT versus DDLT (Shaked et al, 2009). Longer cold ischemia time was associated with a higher rate of acute cellular rejection in both groups despite much shorter median cold ischemia time in LDLT.

In terms of general recipient complications, the A2ALL study has provided additional data regarding LDLT. Complication rates were higher after LDLT (median, 3%) versus DDLT (median, 2%) and included biliary leak (32% vs. 10%), unplanned reexploration (26% vs. 17%), hepatic artery thrombosis (6.5% vs. 2.3%), portal vein thrombosis (2.9% vs. 0.0%), and complications leading to retransplantation or death (15.9% vs. 9.3%; $P < .05$) (Freise et al, 2008). Most notably, this analysis demonstrated that although the complication rates were initially higher with LDLT, with increasing center experience, complication rates declined to levels comparable to DDLT.

Hepatitis C Virus

Considerable reservations surround LDLT for patients with HCV (see Chapters 64 and 97A). If a patient has detectable HCV RNA before transplantation, the concern is that recurrence after LDLT may rapidly progress to cirrhosis and graft loss. In the first half of the decade, many centers reported that the course of recurrent HCV after LDLT was worse than in patients who received DDLT (Bozorgzadeh et al, 2004; Gaglio et al, 2003; Garcia-Retortillo et al, 2004; Shiffman et al, 2004; Zimmerman & Trotter, 2003), causing some centers to avoid performing LDLT for this indication (Garcia-Retortillo et al, 2004).

In addition, it has been shown that the degree of transplant center experience may influence the outcome after LDLT for HCV. The A2ALL retrospective study found that graft and patient survival was significantly lower for LDLT in centers of limited experience (<20 cases), but 3-year graft and patient survival were not significantly different (Terrault et al, 2007). This may be a significant factor, as there are more recent reports that are encouraging for LDLT in the treatment of HCV.

Although the hepatocellular mechanisms remain unknown, Schmeding and colleagues (2007) studied 289 patients and found that the intensity of HCV recurrence was not increased in living-donor graft recipients compared with recipients of full-size grafts. These findings have been reported by other groups (Takada et al, 2006). Furthermore, there is encouraging evidence that when HCV recurrence occurs, combination therapy with ribavirin and interferon appears to improve the outcome of recurrent HCV-infected patients after LDLT (Park et al, 2007).

One specific advantage of LDLT in the treatment of HCV is the ability to optimize transplantation timing. It has been reported that patients who clear HCV RNA with interferon/ribavirin have a high likelihood of remaining HCV RNA-negative after transplantation (Berenguer & Wright, 2003). The availability of a living donor allows for treatment of HCV to proceed to transplantation shortly after HCV RNA clearance has been achieved. Unfortunately, pretransplantation treatment used to prevent progression of disease or to minimize recurrence posttransplantation has highly variable effectiveness, tolerability, and outcome.

In attempts to allow greater patient tolerance and thereby achieve HCV RNA clearance prior to transplantation, the so-called low accelerating dose regimen (LADR) has been studied. Using LADR, Everson and colleagues (2005) studied 124 patients, and although 63% experienced treatment-related complications, 46% patients were HCV RNA negative at the end of treatment, 24% in follow-up; more significantly, 12 (80%) of 15 who were RNA negative before transplantation remained negative for 6 months after transplantation. One of the secondary aims of the A2ALL cohort prospective study is to evaluate LADR in combination with LDLT for reducing post-transplantation HCV recurrence.

Primary Hepatic Malignancy

Liver transplantation is now considered a treatment option for unresectable primary hepatic malignancy. The guidelines for LDLT in the treatment of malignancy largely parallel DDLT for both HCC and cholangiocarcinoma as discussed in Chapters 97D and 97E, respectively. But because of constraints in organ supply and allocation, as well as in the timing of transplantation, LDLT offers several strategic options not available in DDLT.

The growth of LDLT has been fostered in part by the inherent ability to treat hepatic malignancy with the chronologic advantage that scheduled LDLT provides. This is particularly evident in the treatment of HCC. In cirrhotic patients with early stage, unresectable HCC, transplantation is the favored treatment. Under the constraints of the Milan criteria (see Chapter 97D), posttransplantation survival rates equal those in patients without HCC. Patients with HCC within the Milan criteria are given added priority in the organ-allocation system. The combination of this systematic design, combined with therapies to delay tumor progression, such as ablation and arterial-based therapy, results in generally accepted outcomes. In spite of this validated process, some patients may incur prolonged waiting times. This time may allow for progression in some of these patients (Yao et al, 2003), excluding them as transplant candidates under the established guidelines.

In this circumstance, LDLT allows patients with HCC to proceed more rapidly to transplantation, potentially reducing the chance of tumor progression and/or posttransplantation recurrence. This has logically led many centers to offer LDLT for HCC; and similar to DDLT, the efficiency and efficacy of LDLT for HCC is widely reported (Gondolesi et al, 2004c; Kaihara et al, 2003; Todo & Furukawa, 2004). However, as LDLT is increasingly utilized to treat patients with locally advanced HCC not prioritized under the organ-allocation system, patients with large tumors logically experience a higher rate of recurrence (Axelrod et al, 2005).

In the era of limited organ availability, it is necessary to impose guidelines such as the Milan criteria to reduce post-transplantation cancer recurrence and to use resources wisely. This is the setting in which LDLT can provide a therapeutic alternative. In carefully selected patients, those who have been studied to determine that estimated risk of HCC recurrence is low enough to justify placing a healthy donor at risk, LDLT may provide benefit without taxing the organ pool. The acceptable success rates and controversial expanded HCC criteria designed to select such patients have been proposed by numerous centers (Bruix & Llovet, 2002; Gondolesi et al, 2004c; Lang et al, 2002).

Despite the sincere desire, and obvious ability, to treat patients with HCC, caution and practicality should supercede. LDLT may limit the waiting time and, as a result, may decrease the progression of disease so that the recurrence rate, intuitively, should be lower than for recipients awaiting DDLT; however, the reverse may also occur, and rapid transplantation may preclude waiting-list drop out, leading to higher recurrence post-transplantation. One example of this phenomenon was reported by the Northwestern group (Kulik & Abecassis, 2004), who reviewed the institutional experience in LDLT for HCC and found a higher recurrence rate, stage for stage, in recipients whose transplantations were accelerated ("fast tracked") by performing LDLT, especially in the prior era, in which patients with HCC were disadvantaged by the allocation algorithm. Clearly, the role of LDLT in management of patients with HCC requires prospective direct analysis of both recurrence and drop-out rates in comparable patient cohorts with HCC undergoing either deceased- or living-donor liver transplantation.

DONOR EVALUATION

The appropriate liver donor for LDLT is a legal adult who is healthy, without liver disease, not significantly overweight, has a blood type compatible with the recipient, and is able to provide a graft of adequate size. Donor evaluation is carried out by a physician who serves as the donor's advocate physician (New York State Committee on Quality Improvement in Living Liver Donation, 2002). The comprehensive medical evaluation includes 1) a complete history and physical examination; 2) blood analysis to exclude viral and autoimmune liver disease, diabetes, hyperlipidemia, and hypercoagulable states; 3) cardiology clearance; and 4) extensive psychosocial evaluation, with psychiatry consultations in cases of even minor concern.

As in resection for other indications, patient (potential donor) obesity increases perioperative risk and degree of hepatic steatosis. It is known that magnetic resonance imaging (MRI) can predict the presence of significant steatosis (>15%) and simplify donor evaluation in overweight candidates (Rinella, et al, 2003). Routine preoperative biopsy is not widely practiced (Ryan et al, 2002), but in many centers, potential donors who are significantly overweight (Schiano et al, 2001) or who have MRI findings suggestive of steatosis undergo liver biopsy to fully assess both donor and recipient short- and long-term risk (Hwang et al, 2004).

Our understanding of steatosis and its effect in liver transplantation has improved (Soejima et al, 2003b), and guidelines for DDLT have been established (Fishbein et al, 1997; Uchino et al, 2004). In LDLT, where liver mass is limited, hepatic steatosis must be considered in the calculation of true hepatocellular mass to ensure adequate engraftment (Limanond et al, 2004).

Estimation of graft volume (GV) is critical in LDLT to optimize donor safety and recipient outcome. Liver volume can be estimated by calculation or imaging, but no consensus exists on the most clinically effective method. To provide clarity in this dilemma, one study examined the accuracy of formula-derived GV estimates and compared them to both radiogically derived estimates and actual measurements (Salvalaggio, et al, 2005). This study found a marginal concordance between the formula-derived calculation and GV for right-lobe donors, but the error ratio was lower than for radiologic estimates; in contrast, MRI measurements for left lateral section grafts demonstrated a

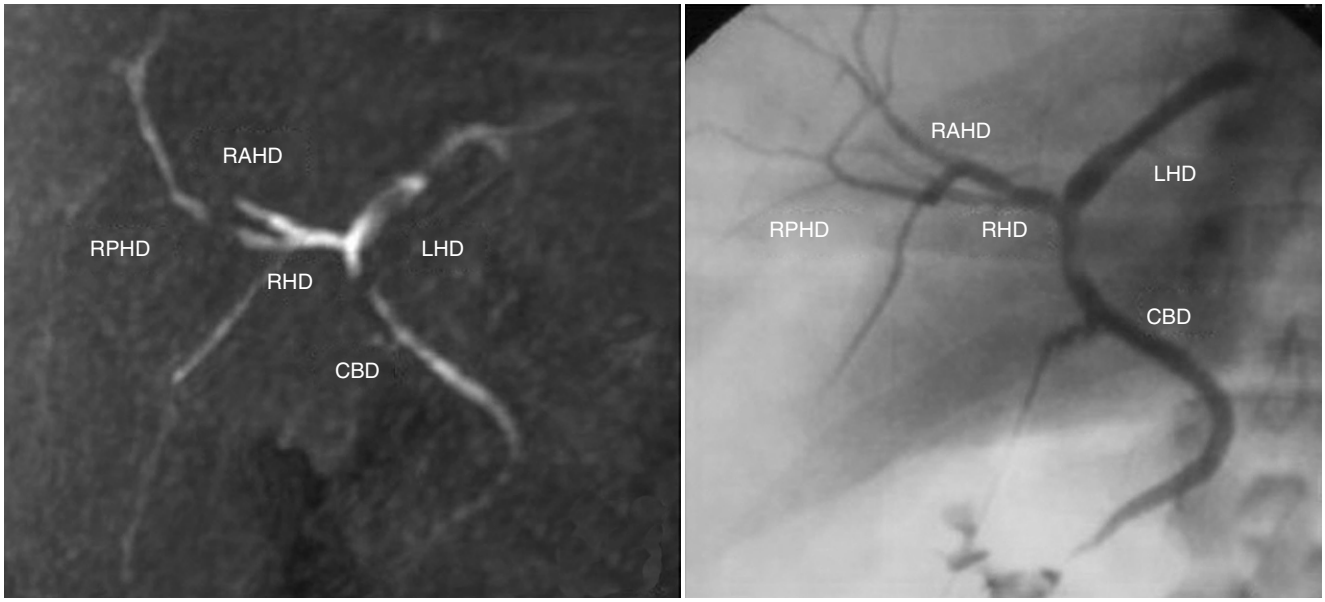


FIGURE 98B.1. Example of preoperative mangafodipir-enhanced magnetic resonance cholangiogram and operative cholangiogram. CBD, common bile duct; LHD, left hepatic duct; RAHD, right anterior hepatic duct; RHD, right hepatic duct; RPHD, right posterior hepatic duct.

lower error ratio than formula-derived estimation. The authors therefore concluded that formula-derived estimates of GV should be routinely used in the initial screening of potential living donors.

Following successful medical clearance, liver vasculobiliary anatomy and graft-remnant liver volumes are assessed radiologically. MRI that includes arteriography (MRA), venography (MRV), and cholangiography (MRC) is frequently chosen, as it simultaneously defines graft-remnant liver volume, vascular and biliary anatomy, and overall hepatic integrity. MRC with mangafodipir trisodium may be used to enhance visualization of small-order biliary structures (Fig. 98B.1; Cheng et al, 2001; Goldman et al, 2003; Yeh et al, 2004).

Advances in both imaging hardware and software allow greater resolution and computer-assisted surgical simulation, aiming to improve accuracy and both donor and recipient outcome. It is logical that accurate assessment of liver graft anatomy is also pivotal in the recipient procedure, allowing management of the multitude of possible anatomic variations.

ANATOMIC VARIATIONS (SEE CHAPTER 1B)

The general segmental anatomy of the liver provides reliable external landmarks for living donation. Using the main hepatic scissura, anatomic resection of the left lateral section and hemilivers is commonplace for a wide variety of indications (see Chapters 90A and 92); however, LDLT relies not only on successful resection but also on the need to maintain intrahepatic and extrahepatic vasculobiliary structures, first, for donor remnant liver viability, and second, to facilitate reconstruction and implantation in the recipient. Therefore, to be successful, identification and management of the hepatic anatomy is crucial throughout the donor and recipient procedures. The following sections focus on the anatomic variations influential in LDLT.

Hepatic Artery

A great understanding and comfort managing arterial variations has resulted from liver transplantation. It is imperative to delineate precisely the arterial anatomy, because "normal" anatomy is present in just over half of the population (Gruttadauria et al, 2001; Hardy & Jones, 1994; Hiatt et al, 1994; Kawarada et al, 2000). The described arterial anatomic variations and their frequency are depicted in Figure 98B.2 (Varotti et al, 2004).

It is intuitive that arterial anatomy would have considerable impact on both donor candidacy and recipient surgical management. Experience has shown that a totally replaced right or left hepatic artery simplifies, rather than complicates, donor hepatectomy; in such situations, greater vessel length may be obtained. Rarely, imaging identifies two arteries supplying the graft. Although back-table reconstruction is possible (Marcos et al, 2001a, 2003), it may be prudent to evaluate other potential donors, if the surgical team has concerns about the recipient procedure.

Portal Vein

Clinically significant portal variations are less common than arterial variations (Nakamura et al, 2002) but have equal technical implications in both the donor and recipient procedures. These variations involve the configuration of the right portal vein bifurcation into sectorial branches. Instead of a portal bifurcation and a left and right common portal trunk, the right anterior and posterior sectorial branches may arise separately, effectively forming a portal trifurcation (Fig. 98B.3). When these sectorial branches arise immediately adjacent to each other, it is sometimes possible to leave a common wall between them to allow for single anastomosis in the recipient; however, sectorial branches that are significantly separated must be taken

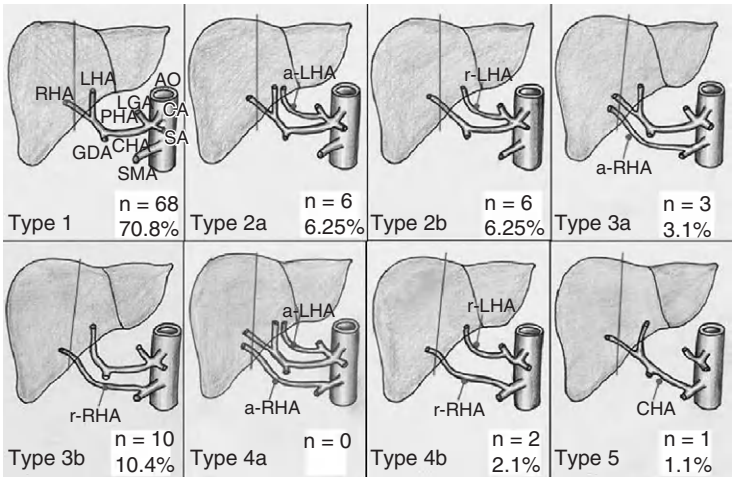


FIGURE 98B.2. Classification and incidence of the common anatomic variations of the hepatic artery. AO, aorta; a-LHA, accessory left hepatic artery; a-RHA, accessory right hepatic artery; CHA, common hepatic artery; GDA, gastroduodenal artery; LGA, left gastric artery; LHA, left hepatic artery; PHA, proper hepatic artery; RHA, right hepatic artery; r-LHA, replaced left hepatic artery; r-RHA, replaced right hepatic artery; SA, splenic artery; SMA, superior mesenteric artery. *(From Varotti G, et al, 2004: Anatomic variations in right liver living donors. J Am Coll Surg 198:577-582.)*

individually to avoid altering the portal flow to the remnant left lobe. Logically, to use such a lobe for LDLT, an extensive reconstruction using a bifucated interposition graft, such as a recipient portal vein bifurcation, is required (see Fig. 98B.3; Varotti et al, 2004). For this reason, many centers may choose to find a donor with less complex anatomy.

Biliary Anatomy

Biliary anatomic variations (Fig. 98B.4) tend to mimic those of the associated vascular structures, especially the portal vein (Lee, et al, 2004), but they may have greater surgical impact, particulary in right-lobe LDLT.

The standard anatomy consists of a confluence of left and right hepatic ducts to form the common hepatic duct. Usually, the segment II and III ducts join in the umbilical fissure, and dividing the hilar plate in this area provides a single duct for anastomosis (Renz et al, 2000). During left-lobe donation, care must be taken to avoid injury to a right posterior sectorial duct that is found to cross the Cantlie line, joining the left hepatic duct at the base of segment IV (see see Fig. 98B.4).

Right-lobe biliary anatomy may be quite complex. Only half of the donors have a single right hepatic duct (Kawarada et al, 2000) or a short duct, which is divided proximally in the interest of donor safety. Logically, the incidence of biliary complications increases with more complex anatomy and anastomoses (Gondolesi et al, 2004a). The most difficult variation is perhaps a right posterior sectorial duct draining into the left hepatic duct, which may be inadvertently transected, as it lies cephalad and posterior to the right portal vein. Because of its location, this bile duct branch is particularly difficult to reconstruct once the portal vein is anastomosed in the recipient.

Hepatic Veins

The variations in hepatic venous anatomy typically do not pose significant difficulty for left lobe or left lateral section donation. A common venous trunk of the middle and left hepatic veins is the usual configuration, facilitating a single venous outflow anastomosis in a left-lobe graft. Left lateral section grafts may be more complex. The confluence of the segment II and III veins may be at or near the junction with the middle hepatic

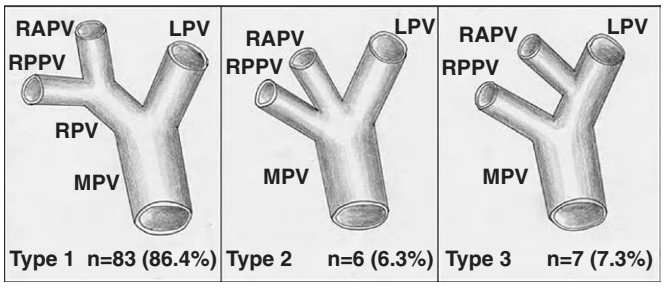


FIGURE 98B.3. Classification and incidence of the common anatomic variations of the portal vein. LPV, left portal vein; MPV, main portal vein; RAPV, right anterior portal vein; RPPV, right posterior portal vain; RPV, right portal vein. *(From Varotti G, et al, 2004: Anatomic variations in right liver living donors. J Am Coll Surg 198:577-582.)*

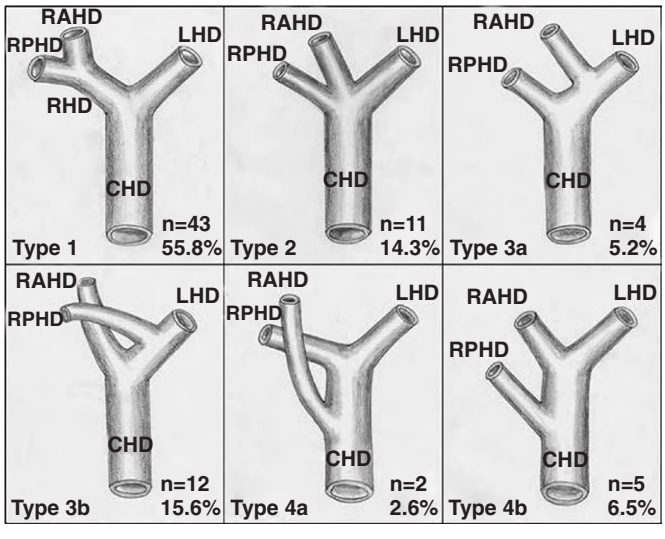


FIGURE 98B.4. Classification and incidence of the common anatomic variations of the biliary tree. CHD, common hepatic duct; LHD, left hepatic duct; RAHD, right anterior hepatic duct; RHD, right hepatic duct; RPHD, right posterior hepatic duct. *(From Varotti G, et al, 2004: Anatomic variations in right liver living donors. J Am Coll Surg 198:577-582.)*

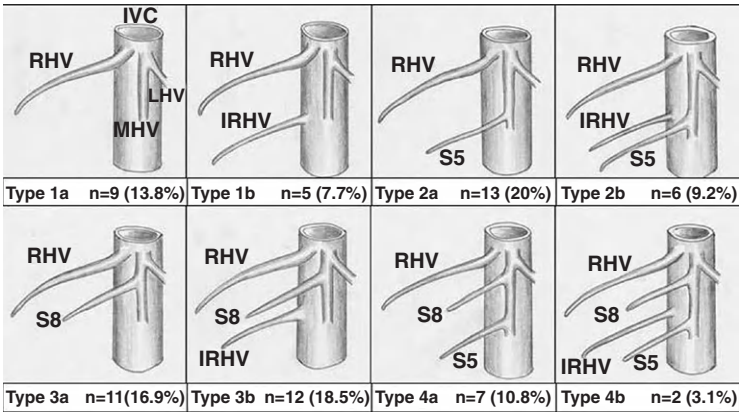


FIGURE 98B.5. Classification and incidence of right liver hepatic venous variations. IVC, inferior vena cava; LHV, left hepatic vein; MHV, middle hepatic vein; RHV, right hepatic vein; S, segment. *(From Varotti G, et al, 2004: Anatomic variations in right liver living donors. J Am Coll Surg 198:577-582.)*

vein. Safe donation may render two veins with a common septum, or it may necessitate performance of a side-to-side venoplasty to simplify implantation.

The venous drainage of the right lobe is much more complex. Typically, the right hepatic vein represents the main venous outflow of the right hemiliver, although variations occur that may drain individual liver segments (Fig. 98B.5). For this reason, in many centers, surgical decision making has evolved from considering the right liver as a whole to considering segmental venous drainage.

Although still somewhat controversial, it is generally agreed that venous structures 5 to 10 mm in diameter constitute significant drainage of the graft; therefore identifying and characterizing these structures has significance in LDLT. As illustrated in Figure 98B.5, imaging frequently identifies significant veins draining the anterior and posterior sectors. Those veins draining the posterior sector directly into the cava (e.g., segment VI inferior vein) may be preserved and reimplanted (Hwang et al, 2004). Anterior sector (segment V and VIII) veins drain into the middle hepatic vein. These may require preservation and later reconstruction in cases of marginal graft-recipient weight ratio (GRWR) and/or significant recipient portal hypertension (Sugawara & Makuuchi, 2001).

GRAFT SIZE AND SMALL-FOR-SIZE SYNDROME

We are only beginning to understand the unique ability of the liver to regenerate after injury or resection (see Chapter 5). Since the genesis of LDLT, however, one persistent problem has been posttransplantation hepatic insufficiency as a result of small graft mass (Lo et al, 1999). This underscores the importance of accurate estimation in the donor, especially as there is significant variation in total liver volume relative to body size and in the configuration of the liver (Gondolesi et al, 2004b).

Predonation imaging can accurately estimate the total donor liver volume and the volume of the proposed graft. Formulas to estimate expected liver volume have also been developed (Yoshizumi et al, 2003) and are slightly superior to imaging in donor screening (Salvalaggio, et al, 2005). Many centers use a combination of techniques to screen and then confirm the graft weight, which is then compared with the weight of the potential recipient. The ratio of the estimated weight of the donor liver graft to the weight of the recipient, expressed as a percent, is the GRWR.

It is well established that when the GRWR is less than 0.8%, there is significant risk of the recipient developing *small-for-size syndrome* (SFSS) (Sugawara et al, 2001). SFSS is posttransplantation hepatic insufficiency presenting as prolonged cholestasis, coagulopathy, and ascites formation in the absence of hepatic vascular insufficiency (see Chapter 100). Because this results in death or the need for retransplantation in half of the patients, over time the use of the right lobe has become the preferred graft in adult LDLT. The exception is when a very large person donates to a smaller recipient, where a left-lobe graft may be of adequate mass.

Additional factors contribute to recipient SFSS, including advanced cirrhosis, portal hypertension, and associated hyperdynamic splanchnic circulation. It is known that recipients of this type require a GRWR greater than 0.8% (Ben-Haim et al, 2001). The splanchnic hemodynamic mechanisms responsible for SFSS are poorly understood (Asakura et al, 1998; Gondolesi et al, 2002b; Huang et al, 2000; Niemann et al, 2002; Piscaglia et al, 1999). In attempts to reduce the hyperdynamic portal circulation and abrogate graft injury, some centers have studied adjunctive splenectomy, portosystemic shunt, or octreotide infusion with mixed results (Masetti et al, 2004; Troisi & de Hemptinne, 2003).

Although certainly an important factor for liver graft function in general, optimizing liver graft outflow, is a possible way to reduce hyperdynamic liver injury. In right-lobe grafts, the outflow of the anterior sector to the middle hepatic vein, via segment V and VIII veins, is variable. In patients in whom the GRWR is low, surgical reconstruction of these middle hepatic vein tributaries may reduce hepatic congestion and potentially prevent the development of SFSS (Sugawara et al, 2004). Venous reconstruction may be in the form of including the main trunk of the middle hepatic vein with the graft, or interposition grafting can be used to recreate the intrahepatic middle hepatic vein.

Another proposed method of avoiding SDSS is increasing liver mass by using dual liver grafts. One center reported their preliminary experience using dual grafts from one right lobe without the middle hepatic vein and one left lateral segment in adult-adult LDLT (Chen et al, 2009). They concluded that dual grafts prevent SFSS in adult-adult LDLT and secure the safety of the donors. Although this strategy reduces the individual donor risk by avoiding extended resection, it places two individuals at risk in efforts to perform a safer transplantation in one recipient; further study will clarify the utility of this approach in LDLT.

DONOR AND RECIPIENT SURGICAL PROCEDURES (SEE CHAPTER 90D)

General Principles

It is paramount to make donor safety the primary concern when contemplating liver donation leading to LDLT. Despite the enormous advances in surgical conduct and patient care in hepatobiliary surgery, live donation places a person who lacks medical indications for surgery in a potentially life-threatening situation for the medical improvement of another. In addition, contrary to pathology-based liver resection, in LDLT there is equal concern for the portion of the liver to remain in the donor (remnant liver) as for the portion being donated; therefore identifying and managing the hepatic vasculobiliary anatomy has particular significance to ensure 1) the remant liver is fully viable and able to regenerate and continue normal function in the donor, and 2) the donated portion is anatomically amenable to successful transplantation in the recipient. Furthermore, in efforts to avoid ischemic injury to the liver graft, hepatic inflow occlusion is generally avoided during parenchymal transection, but some centers find it of no clinical consequence (Imamura et al, 2004; Miller et al, 2004b).

One clinical advantage of LDLT is the ability to choreograph both the donor and recipient procedures, not only the timing of transplantation in the medical course of the recipient, reducing hepatic graft cold ischemic time during the event. The procedures are performed by two separate surgical teams, in adjacent rooms, such that donor safety is optimized, and liver graft is transferred efficiently. Typically, the donor operation takes longer than the recipient hepatectomy, and therefore the donor procedure is begun first; however, when there is concern that the recipient operation could be aborted, such as upon finding hepatic malignancy, the procedures are reversed. When the recipient is being transplanted for hepatic malignancy, the recipient is surgically explored to exclude disease undetected on preoperative studies, and the donor procedure is initiated, if no recipient contraindications are found (Gondolesi et al, 2002a).

The combination of ever-increasing experience in living donor hepatectomy and minimally invasive liver surgery and the ubiquitous desire to minimize donor morbidity has led to the application of minimally invasive techniques in transplantation. Thus far, these advances have been applied to liver donation surgery. Although initial experience in minimally invasive and robotic-assisted renal transplantation is expanding (Hoznek et al, 2002; Rosales, 2010), the ability to perform laparoscopic liver recipient procedures seems doubtful because of graft size and operative domain requirements.

In the following sections, both the open and minimally invasive liver-donation procedures will be described. These sections will focus on laparoscopic variations, as the open procedures are reviewed in detail in Chapter 90D.

Left Lateral Section Transplantation

Open Donor Procedure

The abdomen is entered by a variety of candidate incisions—upper midline, left subcostal, or bilateral subcostal incision with an upper midline extension to the xiphoid—depending on donor habitus and the surgical exposure needed. The left lobe is mobilized by dividing the teres, falciform, coronary, and left triangular ligaments, and these are inspected. Ultrasound (US) may be used to confirm intrahepatic vascular anatomy. In addition, cystic duct cholangiogram may be performed to localize the left hepatic duct in cases where early division of segement II and III ducts is suspected.

Once anatomic variations identified preoperatively are confirmed, the gastrohepatic omentum is divided. During this time, dissection proceeds carefully to preserve a replaced left hepatic artery arising from the left gastric artery to facilitate reconstruction during the recipient procedure (Kostelic et al, 1996). If present, the parenchymal bridge overlying the umbilical fissure between segments III and IV is divided, exposing the left portal structures within the umbilical fissure. Vascular dissection is approached at the origin of the left hepatic artery and proceeds distally. If there is more than one artery supplying segments II and III, all are carefully preserved in the donor for later reconstruction (Soin et al, 1996; Suzuki et al, 1971). The artery supplying segment IV is sacrificed, unless it originates proximal enough to be preserved and yet provide adequate arterial length to the graft, or if it arises from the right hepatic artery (Fig. 98B.6). The resultant ischemia of segment IV is tolerated well in the donor with expected radiographic postsurgical changes (Shoji et al, 2003).

The full length of the left portal vein is isolated by sacrificing the portal branches to segment IV medially and the caudate lobe dorsally (see Fig. 98B.6; Broelsch et al, 1991). The left hepatic vein is isolated, including division of the ligamentum venosum, but carefully preserving the middle hepatic vein, as the left and middle veins unite in, or just cranially to, their exit from the hepatic parenchyma. The segment II and III bile duct is divided sharply at the hilar plate at the base of the umbilical fissure, and the distal end is oversewn. The parenchyma between segment IV and segments II and III is divided using the dissecting device of the surgeon's choice without hepatic inflow occlusion.

Now that the liver graft is separate from the remnant right trisegment, the left hepatic artery is ligated proximally and divided, the left portal vein and left hepatic vein are divided (cut

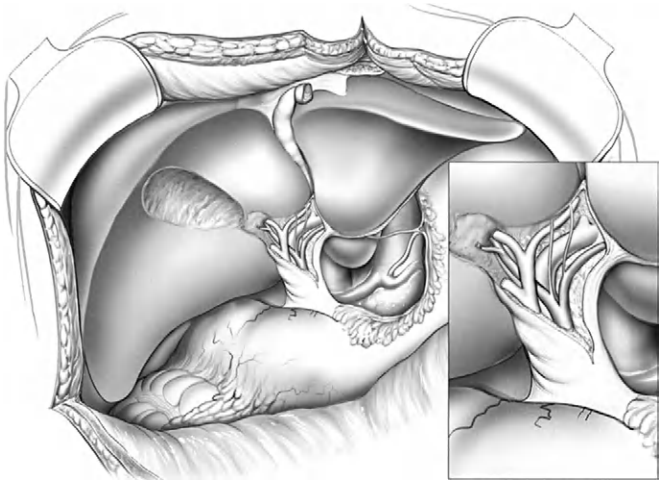


FIGURE 98B.6. Hilar structures for the left lateral segment are exposed. When the segment IV artery arises separately from the segment II and III arteries (*inset*), it is preserved in the donor. Portal vein branches to segment IV are ligated before parenchymal transection.

ends are oversewn in the donor), and the liver graft is removed. The graft is taken promptly to the back-table and is flushed with preservative and prepared for implantation (Tanaka et al, 1993; Yamaoka et al, 1995).

Laparoscopic Donor Procedure

Cherqui and colleagues (2002) first described the laparoscopic donor procedure, which consists of removing segments II and III, left arterial and portal inflow, left bile duct, and left hepatic vein without hepatic inflow occlusion (see Chapter 90E). Logically, the operative strategy and extent of vascular dissection parallels that of the open procedure.

With the donor under general anesthesia, in supine position with legs abducted, laparoscopy is achieved using a five-trocar approach. The left lobe is mobilized by dividing the teres, falciform, and left triangular ligaments. Using a laparoscopic dissector, the left branches of the hepatic artery and the portal vein are dissected and encircled, and the arterial and portal branches to the caudate lobe are clipped and divided. The liver parenchyma is divided on the right side of the teres and falciform ligaments, including the pedicles to segment IV, with a coaptive sealing device to achieve hemostasis during transection with a linear stapler. The left bile duct is then transected sharply, and the proximal end of the duct is sutured. Hepatic parenchymal transection progresses up to the level of the left hepatic vein, which is isolated, leaving the graft attached to the remnant liver by its vascular connections only. As in the open procedure, extreme caution is taken to avoid injuring the middle hepatic vein at the cranial margin of the liver.

For graft extraction, a 10-cm suprapubic cutaneous incision is made, allowing insertion of a large specimen retrieval bag. The graft is finally retrieved by clipping and dividing the arterial branch and using the linear stapler to secure the left portal and hepatic veins, completing the suprapubic incision by section of the fascia, muscle, and peritoneum, venting the pneumoperitoneum and removing the specimen bag through this incision. The graft is prepared for transplantation, while the incisions are closed, thereby completing the donation procedure.

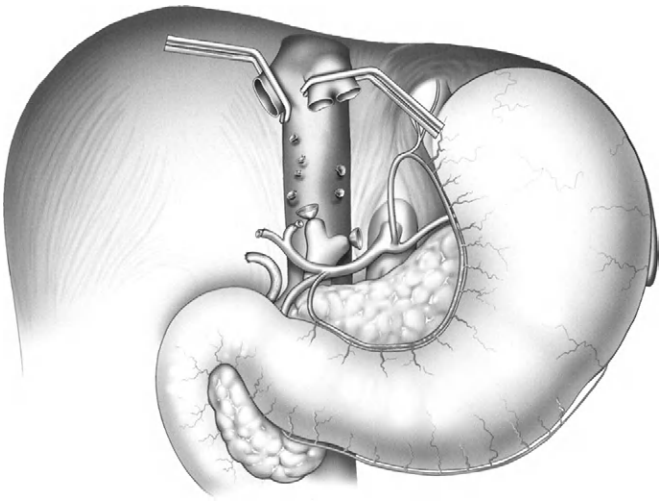


FIGURE 98B.7. Recipient hepatectomy is performed with preservation of the vena cava. The right hepatic vein and the middle hepatic vein–left hepatic vein confluence are clamped separately. Dissection is performed high in the hilum to preserve the bifurcation points of the portal structures.

Recipient Procedure

As in all varieties of LDLT, recipient hepatectomy is performed with both preservation of the recipient vena cava and meticulous dissection of the hepatic hilum to preserve maximum length of the hepatic artery and portal vein (Fig. 98B.7).

Once the diseased liver is removed, the recipient vena cava is occluded; this allows the orifices of the hepatic veins to be joined sharply to create a common orifice that matches the donor left hepatic vein. This maneuver is pivotal in creating the maximum achievable graft outflow tract. The venous anastomosis is created in a wide, triangular fashion (Fig. 98B.8).

The venous anastomosis is completed in a manner that allows later graft flushing prior to reperfusion. The graft left portal vein is anastomosed to the recipient portal bifurcation or, if indicated, to the level of the mesenteric-splenic confluence,

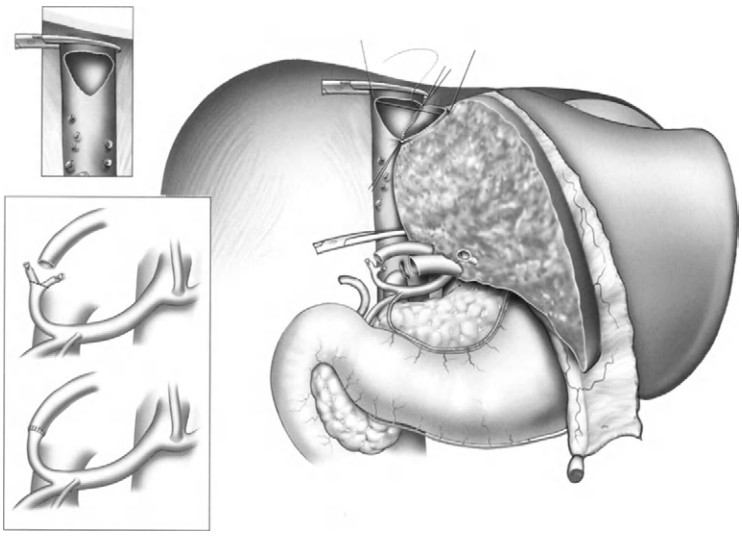


FIGURE 98B.8. The ostia of the hepatic veins are joined, and the cava is incised caudally to create a wide triangular opening (*top inset*) to match up to the donor left hepatic vein. The proper hepatic artery usually is transected at its bifurcation to match up to the donor left hepatic artery (*bottom inset*).

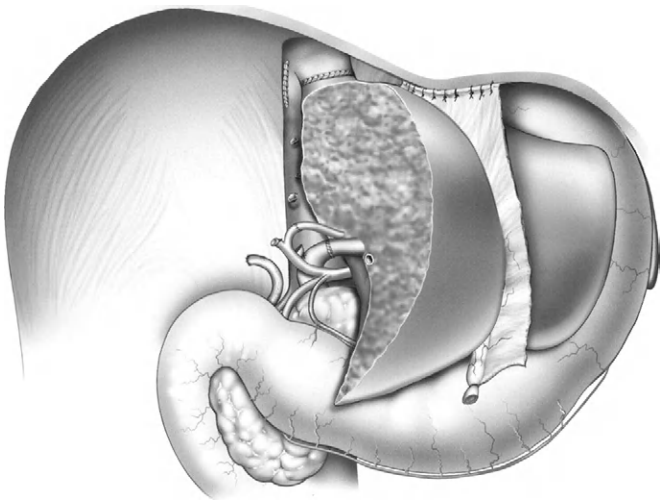


FIGURE 98B.9. The left-lobe graft with completed vascular anastomoses and reattachment of the falciform ligament.

utilizing an autologous venous interposition graft. To prevent anastomotic coarctation, the portal anastomosis is performed with interrupted sutures (Emre, 2001) or with a running suture tied for a large growth factor. The hepatic arterial reconstruction is performed under high magnification, using a surgical loupe or an operating microscope, typically by creating a hepatic artery bifurcation branch patch to match the size of the hepatic artery of the graft (see Fig. 98B.8; Stevens et al, 1992; Wei et al, 2004). Biliary-enteric continuity is achieved with a Roux-en-Y hepaticojejunostomy (Fig. 98B.9).

Left Hepatic Transplantation

Open Donor Procedure

The approach for the donor procedure is similar to that for the left lateral section, although the left medial section is not devascularized. Following exposure and mobilization of the left hemiliver, cholecystectomy is performed, and the left hepatic artery and left portal vein are isolated at their origin. Aberrant arterial anatomy is identified and preserved for possible later reconstruction, including a large segment IV artery originating from the right hepatic artery. The hilar plate is lowered at the biliary confluence, and a cholangiogram via the cystic duct confirms both the biliary anatomy and the site of safe left hepatic duct transection. The left hepatic duct is isolated and divided, and the remnant side is secured. The posterior right hepatic duct may cross the Cantlie line to enter the left hepatic duct in some donors, therefore care must be taken to divide the left hepatic duct to the left of the anomalous entry (Soejima et al, 2003a; Varotti et al, 2004).

Many centers choose to include the caudate lobe with a left-lobe graft, given the left portal inflow, biliary drainage, and added hepatic mass (Fig. 98B.10; Abdalla et al, 2002; Miyagawa et al, 1998; Takayama et al, 2000).

The left lobe is elevated, the caudate is dissected off of the vena cava to the base of the Cantlie line, and the caudate vein proper is encircled. The left and middle hepatic veins are isolated above the liver, utilizing the technique of Arantius for simplification. Temporary inflow occlusion may be used to delineate the transection plane at the Cantlie line. The parenchyma is transected, which may be facilitated by the so-called hanging maneuver (Belghiti et al, 2001; Broering et al, 1998). The intrahepatic middle hepatic vein is divided as it courses into segment IVa, allowing procurement of left and middle hepatic veins with the graft.

With the transection complete, the left hepatic artery and left portal vein are ligated and divided, the hepatic veins are clamped and divided, and the graft is removed. While the graft is flushed and prepared on the back table, the hepatic vein remnant is oversewn in the donor, hemostasis and biliostasis are ensured, and the donor procedure is concluded.

Laparoscopic Donor Procedure

There is extensive global clinical experience in left-lobe LDLT. Although some centers are performing laparoscopic donor hepatectomy for the left lateral section and right lobe, only limited minimally invasive left-lobe donors have been reported (Kurosaki, et al, 2006). In this report, 10 left-lobe donor procedures (5 including the caudate lobe) were reviewed, exhibiting good donor and recipient outcomes. The technique utilized is video-assisted and is summarized below.

The video access is accomplished by either the abdominal wall–lifting method or under CO_2 pneumoperitoneum. In those procedures utilizing the lifting method, a 12-cm minilaparotomy is made in the upper abdomen. A lifting retractor is used for elevating the abdominal wall, and dissection proceeds via three to five working ports, including optics by flexible laparoscopy. The surgeon is positioned at the right side of the patient with two assistant surgeons and a laparoscopist.

Mobilization of the liver is performed laparoscopically, including short hepatic veins, which are dissected and sealed using a coaptive device or clips. In left lobe/caudate lobe donors, the caudate lobe is dissected through the foramen of Winslow, mobilizing it from the inferior vena cava (IVC) to the level of a prominent caudate vein. Retraction of the caudate lobe is performed via minilaparotomy in cases without a pneumoperitoneum. The caudate hepatic vein is dissected and encircled, and the common trunk of the middle and left hepatic veins are exposed in preparation for the hanging maneuver to facilitate parenchymal transection.

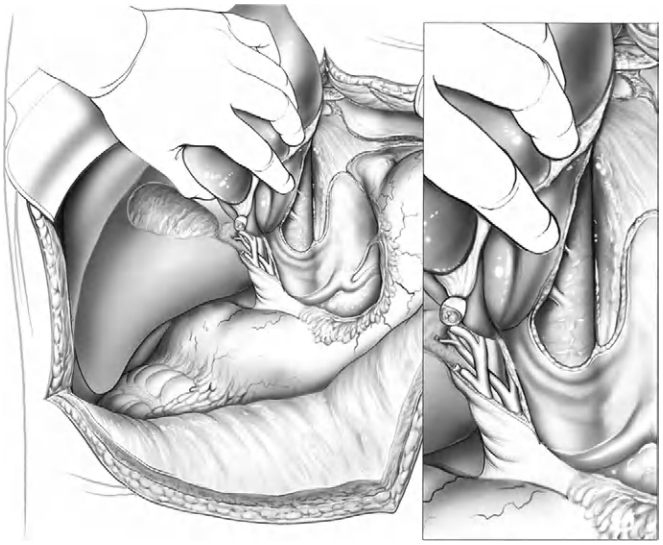


FIGURE 98B.10. Dissection of the caudate lobe off of the vena cava during preparation of a left-lobe graft.

The structures within the porta hepatis are dissected and isolated using a combination of laparoscopy and direct operation via the minilaparotomy, allowing the left portal vein and hepatic artery to be encircled. The left hepatic duct is divided after the cholangiography, and the distal end is sutured via the minilaparotomy. During parenchymal transection, space between the liver and the IVC was created using a combination of the hanging maneuver and upward traction on the falciform ligament. The left hepatic donation is made under intermittent inflow occlusion of the right liver, and the line of hepatic transection is determined by demarcation during vascular occlusion. The transection is performed using a combination of ultrasonic dissection and bipolar irrigation electrocautery, avoiding injury to the hepatic arteries, portal vein, and hepatic veins.

Initially, the caudate lobe and caudate process are divided at the base of the Cantlie line, and the tape for the hanging maneuver is relocated anterior to the porta hepatis. The deep parenchymal dissection proceeds along the tape via the minilaparotomy. Once the transection is complete, the hepatic veins and the caudate hepatic vein are skeletonized through the space created between the hemilivers. Under systemic anticoagulation, the left hepatic artery is divided at its origin, the left portal vein is clamped and divided at the bifurcation of the common portal vein, the caudate hepatic vein is divided, and finally the suprahepatic IVC is partially clamped to allow division of the common trunk of the left and middle hepatic veins. The liver graft is prepared on the back table, while the cut ends of the hepatic vessels are secured with suture, and the donor incisions are closed.

Laparaoscopic left hepatectomy is established for other clinical indications (Koffron et al, 2007b). The techniques are well defined, but its application to left-lobe donation is complicated by caudate management; therefore it seems logical that this donation procedure will evolve to a minimally invasive extent, positioned between that for the left lateral sectionectomy and right hemihepatectomy.

Recipient Procedure

As in all forms of LDLT, the recipient hepatectomy is performed with caval preservation, and the portal structures are dissected distally in the hepatic hilum. The left hepatic vein–middle hepatic vein confluence of the liver graft is typically anastomosed end-to-end to the same in the recipient. If there is a vessel size discrepancy or concern for torsion or kinking of the venous outflow, direct anastomosis to the vena cava may be performed (Egawa et al, 1997; Makuuchi & Sugawara, 2003; Sugawara et al, 2002b).

The portal vein and hepatic artery are reconstructed anatomically, and vascular conduits are used in cases of size discrepancy. Biliary enteric continuity is reestablished via a Roux-en-Y hepaticojejunostomy.

Right Hepatic Transplantation

Open Donor Procedure

Access to the abdomen is gained through either a right subcostal or bilateral subcostal incision with upper midline extension. Following exploration, the teres and falciform ligaments are divided close to the abdominal wall to facilitate reconstruction after right-lobe donation and to prevent medial-posterior rotation and torsion of the remnant liver (Miller et al, 2001). Cholecystectomy is performed, and the cystic duct is cannulated for later cholangiography. With anteromedial retraction of the extrahepatic biliary system, the peritoneum and neurolymphatic tissue of the portal hepatis is approached posterolaterally. This allows identification and isolation of the right hepatic artery from the lateral border of the common hepatic duct to its entrance into the right lobe (Fig. 98B.11; Kawarada et al, 2000).

Care is taken to avoid sacrificing any of the small arterial branches of the right hepatic artery that may supply the right hepatic duct. Once the artery is mobilized and elevated, the right portal vein is identified and isolated from the portal bifurcation to its entrance into the right lobe.

Dividing the right hepatic duct is a crucial step. If the right hepatic duct exists as a single structure, precise transection is necessary to obtain a single orifice, just proximal to division into sectorial ducts, and also avoid encroaching on the remnant liver biliary system (Huang et al, 1996; Varotti et al, 2004). To ensure accurate and safe transection, guidance with fluoroscopic cholangiography allows identification, marking, and precise transection of the right hepatic duct. The duct is transected sharply, avoiding overdissection and ischemic or thermal injury, which

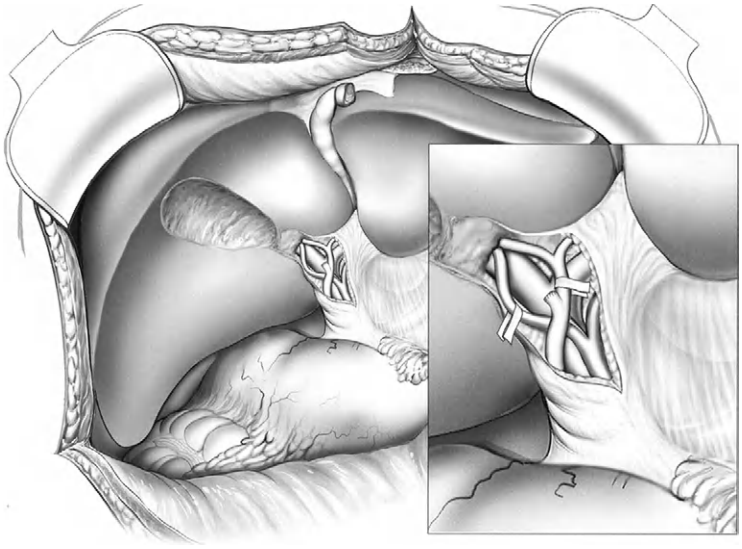


FIGURE 98B.11. After cholecystectomy is performed, the hilar structures for the right lobe graft are exposed. The right hepatic artery is identified to the right of the bile duct and is dissected from behind the duct toward the liver (*inset*).

may lead to biliary complications in the recipient (Gondolesi et al, 2004a).

The right lobe is completely mobilized by dividing the triangular ligament, bare area, and posterior vena cava ligament. The retrohepatic IVC is mobilized off the right lobe by ligating the small, short hepatic veins. Anomalous inferior hepatic veins may constitute substantial drainage of the posterior sector (segments VI and VII); therefore veins larger than 5 mm are preserved or divided in a manner—suture or staple—that allows later implantation in the recipient. Mobilization of the right lobe from the vena cava facilitates the dissection and control of the right hepatic vein.

The caudate process is divided over the IVC at the base of the Cantlie line using electrocautery; this allows passage of an umbilical tape from above the liver, between the middle hepatic vein and right hepatic vein, behind the liver, and up through the incised caudate process. The umbilical tape is lifted during hepatic parenchymal transection, guiding the division down the line of Cantlie, greatly facilitating the division of the most posterior parenchyma and simultaneously protecting the vena cava from injury (Belghiti et al, 2001; Broering et al, 1998).

The precise line of hepatic transection may be determined by temporary occlusion of the right hepatic artery and right portal vein or using ultrasound and anatomic landmarks. The intrahepatic course of the middle hepatic vein is similarly identified, particularly the segment V and VIII venous tributaries, which greatly facilitates parenchymal transection and isolation of the middle hepatic vein for later reconstruction, if necessary. The liver is transected without inflow occlusion, using any of a variety of devices—ultrasonic aspirator, water jet, bipolar saline-enhanced cautery—designed to limit bystander tissue injury. Typically, the middle hepatic vein is prepared for transection high in segment IVa near its confluence with the left hepatic vein with an attempt to preserve segment IV tributaries to the distal middle hepatic vein within the left lobe. Following parenchymal transection and achieving hemostasis, the back table and graft flush are readied.

In rapid sequence, the graft is devascularized and flushed. The right hepatic artery is ligated proximally and divided distal to the ligature to allow back bleeding. The right portal vein is then clamped (or stapled) and divided to ensure no compromise to the portal inflow to the remnant left hepatic lobe. The right hepatic vein, middle hepatic vein, and any preserved short hepatic veins are clamped or stapled and then divided, and the graft is removed. While the graft is flushed with preservation solution, and necessary vascular reconstructions are performed (Nakamura et al, 2002), the donor procedure is completed. This includes suturing clamped vessel stumps, ensuring no bile leakage, and completion cholangiogram to ensure vascularity of the remnant liver, followed by reconstruction of the falciform ligament and closure.

Laparoscopic Donor Procedure

Because of the right lobe's large size, fragility, and the consequences of graft injury, minimally invasive donation of the right lobe is usually performed by using a hybrid technique of liver resection (Koffron et al, 2007a). This technique of laparoscopic-assisted liver resection uses laparoscopic techniques to mobilize the liver while avoiding the morbid right subcostal incision. The hilar dissection and parenchymal transection proceed laparoscopically to the limits of safety or surgeon comfort level, at which time standard open techniques are used via the hand-assisted/extraction incision. This technique of right-lobe donation was first described by Koffron and colleagues in 2006 and is briefly summarized.

INITIAL MANEUVERS. The donor is placed under general anesthesia in supine position with arms adducted. Pneumoperitoneum (CO_2 at 12 mm Hg) is established through a 12-mm umbilical port, and the abdomen is explored utilizing a 30-degree 10-mm laparoscope for optimal visualization of the retrohepatic structures. Once the liver is visualized, one additional 10-mm port is placed at the right midclavicular line, and a 5-cm subxiphoid midline incision is created for hand assistance during right-lobe manipulation and for graft extraction using a hand-port device (Fig. 98B.12). This configuration enables the surgeon, who stands on the left side of the patient, to use the hand port for graft manipulation, with simultaneous use of the midclavicular line port for dissection.

RIGHT LOBE MOBILIZATION. Next, the ligamentum teres, falciform, coronary, and right triangular ligaments are divided using a coaptive laparoscopic tissue-sealing device. The hepatic bare area is completely mobilized, and the right lobe is elevated to expose the length of the retrohepatic IVC. The posterior vena cava ligament (Fig. 98B.13) and short hepatic veins are divided using a secure method—such as a sealing device, clips, or stapler (Figs. 98B.14 and 98B.15)—to separate the IVC and right lobe to allow visualization of the right hepatic vein (RHV) as it enters the IVC. An umbilical tape is passed around the RHV (Fig. 98B.16), the right lobe is allowed to return to anatomic position, and a cholecystectomy is performed.

HILAR DISSECTION AND LIVER RESECTION. The right hepatic artery (RHA) and right portal vein (RPV) are isolated posteriolaterally, with hand-assisted laparoscopy, as they enter the right lobe. Using the hand-assisted/extraction incision, under direct vision (Fig. 98B.17), the cystic duct is cannulated, cholangiogram confirms the biliary anatomy, and the right hepatic duct is isolated using fluoroscopic cholangiographic guidance. The right hepatic duct is then transected, leaving a 4-mm stump with the donor hepatic confluence, which is oversewn. The RHA and RPV branches are further dissected under

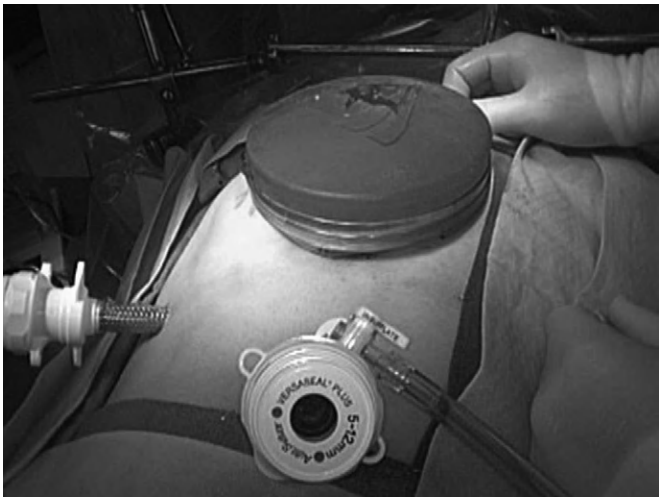


FIGURE 98B.12. Operative configuration for laparoscopic-assisted donor right hepatectomy, including working ports and hand-assisted device.

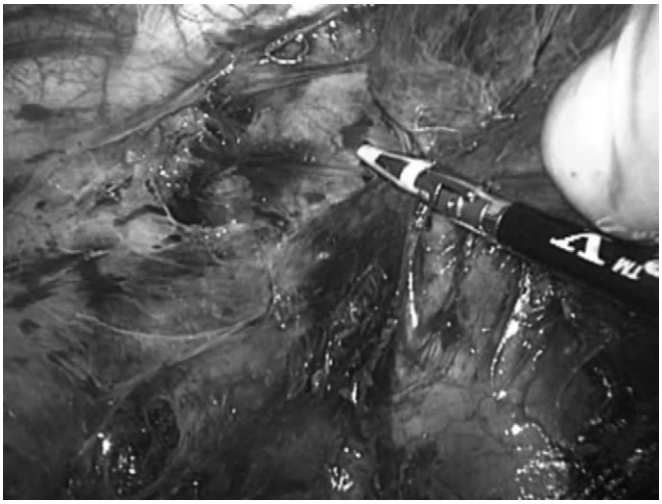


FIGURE 98B.13. Division of the posterior vena cava ligament. Right hemiliver is elevated anteromedially.

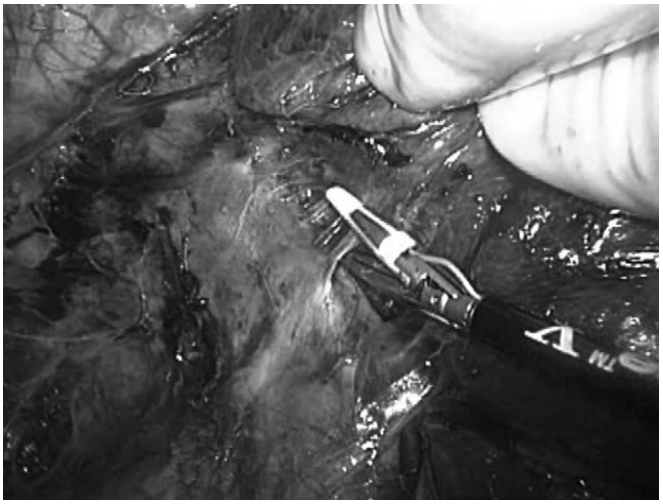


FIGURE 98B.14. Division of short hepatic and caudate veins following division of the posterior vena cava ligament.

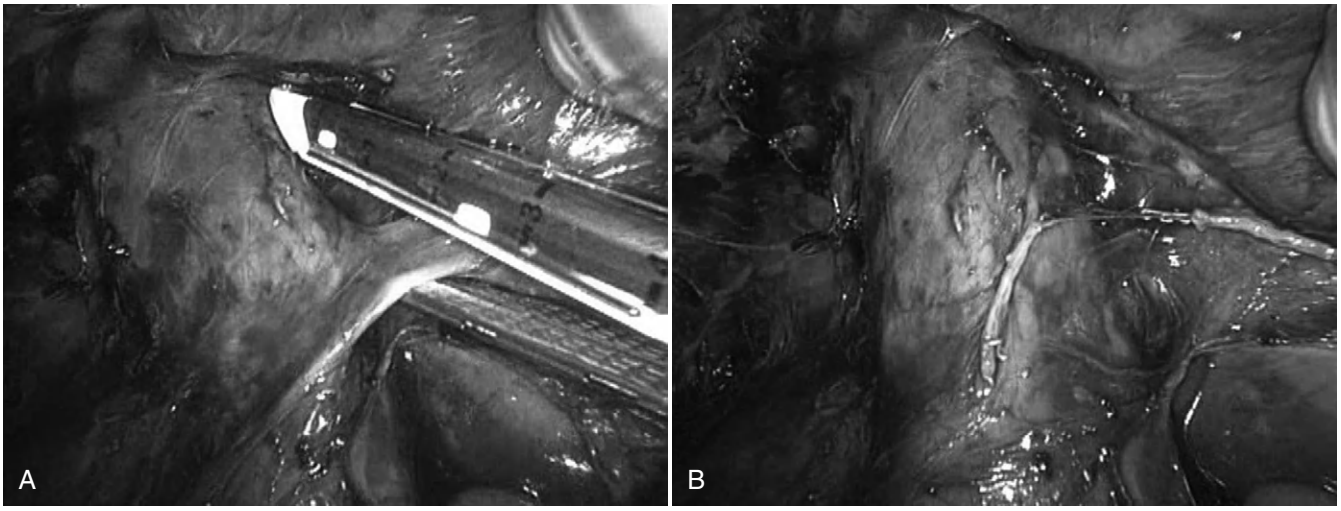


FIGURE 98B.15. A, Endovascular stapler division of large segment VI vein entering the vena cava in preparation for donor lobectomy and later venous reconstruction in recipient. **B,** Divided segment VI vein. The staple line on the right lobe facilitates later back-table identification, preparation, and vein reconstruction prior to implantation in the recipient.



FIGURE 98B.16. Right hepatic vein isolated and encircled for later hanging technique during liver parenchymal transection.

direct vision to optimize vessel length and enhance safety (see Fig. 98B.17B). There is no hepatic inflow occlusion, and the central venous pressure is maintained at 2 to 4 mm Hg in preparation for parenchymal transection. Using the hand-assisted/extraction incision, the liver parenchyma is divided at the Cantlie line (Fig. 98B.18) in an inferior/anterior to superior/posterior direction using the transaction methods of choice. The middle hepatic vein tributaries from segments V and VIII are secured and divided using a method that allows later reconstruction, such as sutures or staples.

The retrohepatic umbilical tape is used toward the end of the parenchymal transection in the method of Belghiti (Belghiti et al, 2001; Ogata et al, 2007) to bring the transection plane closer to the abdominal wall. Once the right liver is separate, the RHA is ligated just lateral to the common bile duct and is transected sharply with scissors distally through the hand-assisted incision, allowing back-bleeding from the graft side. Immediately, the RPV is stapled using an Endo GIA (gastrointestinal anastomosis) stapler (Covidien, Mansfield, MA)

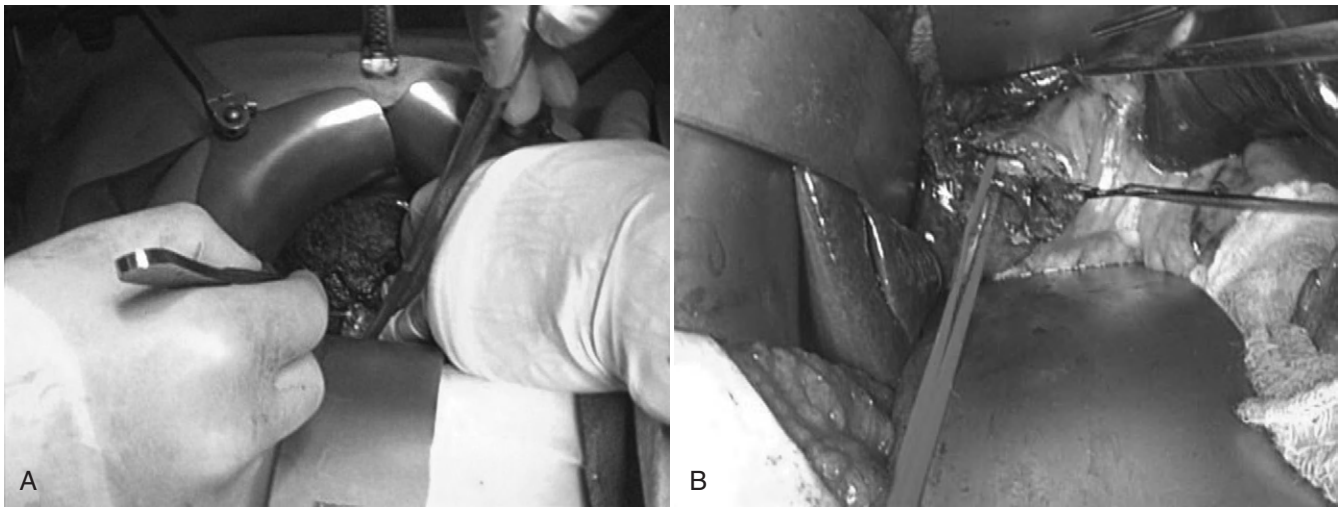


FIGURE 98B.17. A, The surgeon is using open techniques through hand-assisted/extraction incision. **B,** Overhead view of surgeon using open techniques through a hand-assisted/extraction incision. The hepatic artery and portal vein have been encircled; forceps are holding the right hepatic duct prior to division.

(Fig. 98B.19A), the right lobe is retracted laterally, and the RHV is stapled and divided at the IVC with the stapler (Fig. 98B.19B). The RPV is then transected sharply distally to the staple line; this causes the right lobe to decompress by allowing back-bleeding through the graft side of the RPV. The right lobe is gently extracted through the hand-assist subxiphoid incision (Fig. 98B.19C). A completion cholangiogram is performed, and a closed suction drain is placed and exteriorized through the right subcostal port site. The port sites and the extraction incision are closed in layers.

The initial reported series of four donors suggested equivalent donor and recipient outcomes using this technique compared with the standard open technique (Koffron et al, 2006). Later, the same group performed a retrospective, comparative analysis of 33 laparoscopic donors and 33 open donors (Baker et al, 2009). This analysis demonstrated that the laparoscopic approach can be performed as safely as the open technique, with the advantages of reduced operative times, a trend toward reduced blood loss, and comparable donor complication rates, length of stay, and hospital and surgical costs. In addition, the laparoscopic procedure provided equitable grafts for the recipient with equal patient and graft survival and complication rates. Although greater experience and wider usage of this technique is necessary to confirm these findings, such an approach intuitively can benefit donors and may lead to the increase in willingness to donate, as has been demonstrated for kidney transplantation.



FIGURE 98B.18. Dissection of significant segment V hepatic vein through the hand-assisted/extraction incision. This approach facilitates the safe dissection of intrahepatic vessels for later reconstruction on the back table.

Recipient Procedure

As in left-lobe LDLT, total hepatectomy is performed with caval preservation (Fig. 98B.20; Tzakis et al, 1989), and the structures of the portal triad are dissected high in the hilum to preserve options for subsequent reconstruction. If anticipating a duct-to-duct biliary reconstruction, avoid overdissection of the recipient common bile duct, which may devascularize the proximal extent, the site of potential anastomosis to the graft hepatic duct. In addition, maintaining the distal portion of the recipient middle hepatic vein—dissected from the cranial parenchyma of segment IVa, as the devascularized liver is being removed—leaves this available for use in graft middle hepatic vein reconstruction. This final portion of the hepatectomy is facilitated by complete occlusion of the cava, which allows division and suture control of difficult retrohepatic structures.

Once the liver is removed, or in the case of recipient instability, partial occlusion may be chosen to maintain venous return during implantation. Of course, as in whole-liver transplantation, venovenous bypass may be used as an adjunct to ensure hemodynamic stability, reduce blood loss, or inhibit visceral vascular congestion during the anhepatic phase (Fan et al, 2003; Grewal et al, 2001). Once the diseased liver is removed, hemostasis is ensured, the graft is placed in the resulting hepatic fossa, and venous reconstruction is visualized.

The right hepatic vein is reconstructed in a manner that allows maximal possible venous outflow. This is achieved either by anastomosis to the residual cuff of the recipient right hepatic



FIGURE 98B.19. **A,** Liver transection is complete, the hepatic artery is divided, and the right portal vein is secured using an Endo GIA stapler. **B,** The right hepatic vein is sealed and divided using the stapler. **C,** The portal vein has been incised distal to the staple line to allow decompression of the right lobe graft, which is then gently extracted and taken to the back table.

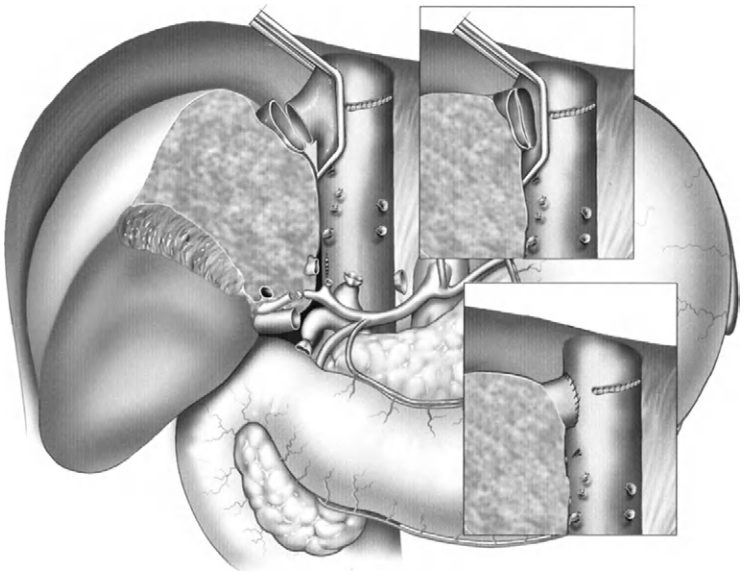


FIGURE 98B.20. The hepatectomy has been performed using a vena cava–sparing technique, and the right lobe graft is implanted. The right hepatic vein can be sewn to the stump of the recipient right hepatic vein, or cavoplasty can be performed to extend the orifice and reduce the risk of outflow obstruction. Short hepatic veins greater than 5 mm in diameter are anastomosed directly to the cava.

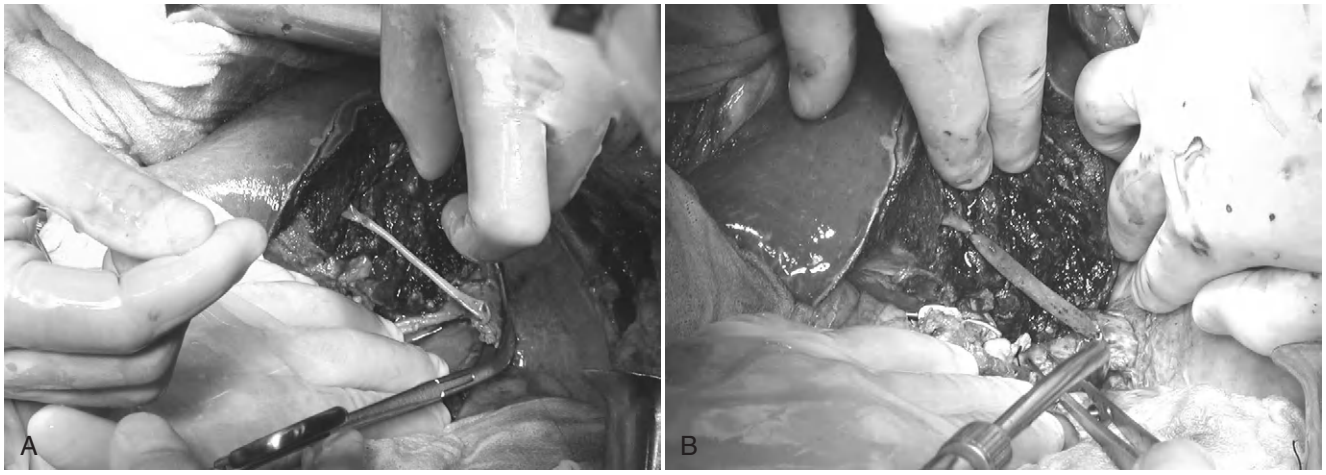


FIGURE 98B.21. **A,** Reconstruction of segment V vein to the orifice of the middle hepatic vein using a segment of the donor inferior mesenteric vein as interposition graft, before reperfusion. **B,** Segment V venous interposition graft after reperfusion.

vein or to an enlarged cavotomy created by enlarging the right hepatic vein orifice (see Fig. 98B.20; Liu et al, 2003; Sugawara & Makuuchi, 2001). This reconstruction should be performed anticipating acute and delayed enlargement of the graft following reperfusion/engorgement and hepatic regeneration, respectively.

Compensatory hepatic regeneration occurs within the space confined by the vena cava, diaphragm, and lateral thoracoabdominal wall. As the hepatic graft enlarges, this can change the geometry of the venous anastomosis over time and can potentially lead to outflow obstruction (Hata et al, 2004; Humar et al, 2004; Olthoff, 2003). Accessory inferior hepatic veins over 5 mm in diameter are anastomosed directly to the side of the vena cava (see Fig. 98B.20).

Once the dorsal-most hepatic veins have been addressed, reconstruction of segment V or VIII middle hepatic vein tributaries, if required, can be performed (Fig. 98B.21). Many techniques for reconstruction are available, depending on the surgical anatomy and vessel availability (Kinkhabwala et al, 2003; Marcos et al, 2001b; Sugawara et al, 2004). The use of vascular interposition grafts, if needed, is facilitated by placement during graft back table preparation and may include cadaveric iliac vein, recipient saphenous vein, preserved vascular allograft, and synthetic vascular conduit.

The donor right portal vein is anastomosed to the recipient main or right portal vein, accounting for size discrepancy and/or vessel length. As in whole-organ transplantation, recipient portal vein thrombosis is treated by thromboendovenectomy or portal vein resection and venous interposition graft (Dumortier et al, 2002; Kadry et al, 2002; Moon et al, 2004). The donor right hepatic artery usually is anastomosed to the recipient right or proper hepatic arteries in an attempt to prevent redundancy or kinking, which may occur as the arterial spasm subsides following reperfusion.

The methods of biliary reconstruction depends on the size, number, and configuration of the donor and recipient ducts. This may include direct duct-to-duct anastomosis, Roux-en-Y hepaticojejunostomy, or a combination of these techniques in cases of biliary complexity (Fig. 98B.22; Azoulay et al, 2001; Testa et al, 2000).

BILIARY COMPLICATIONS (SEE CHAPTER 100)

Biliary complications remain the largest contributor to morbidity following LDLT. Despite further understanding of the anatomy and both donor and recipient surgical techniques, biliary leak and stenosis rates range from 20% to 40% (Gondolesi et al, 2004a; Pomfret, 2003) up to 60% (Kawachi et al, 2002). The A2ALL cohort study reported a 31.8% biliary leak rate across the nine participating transplant centers (Freise et al, 2008). Studies investigating the methods of biliary reconstruction found no difference in overall complications, but one advantage of duct-to-duct reconstruction is that it allows future endoscopic access and management of these complications. Leaks generally manifest early after transplantation (Popescu et al, 1994) and are associated with significant morbidity and mortality (Gondolesi et al, 2004a). Bile leak from the cut liver edge may be treated successfully with percutaneous drainage, but anastomotic leaks invariably require endoscopic and/or operative management.

As in DDLT, biliary strictures are generally diagnosed by noting an increase in biliary enzymes. Evaluation of strictures usually involves US, MRC, and in some cases, direct cholangiography, either endoscopic or percutaneous transhepatic cholangiography (PTC). The treatment strategy is similar to biliary stricture in general (see Chapter 42A), although operative management in LDLT recipients is technically difficult as a result of the neighboring vascular reconstructions.

POSTOPERATIVE CARE OF LIVING LIVER DONORS

Because donors are healthy individuals, the donation event may represent their initial significant medical or surgical experience. Therefore, despite thorough preoperative education, their postoperative course is out of proportion to their expectations. Although discussions with previous donors may help prepare donors mentally during recovery, even routine surgical care, and complications in particular, have a heightened impact on healthy volunteers. Most notably, the degree of postoperative

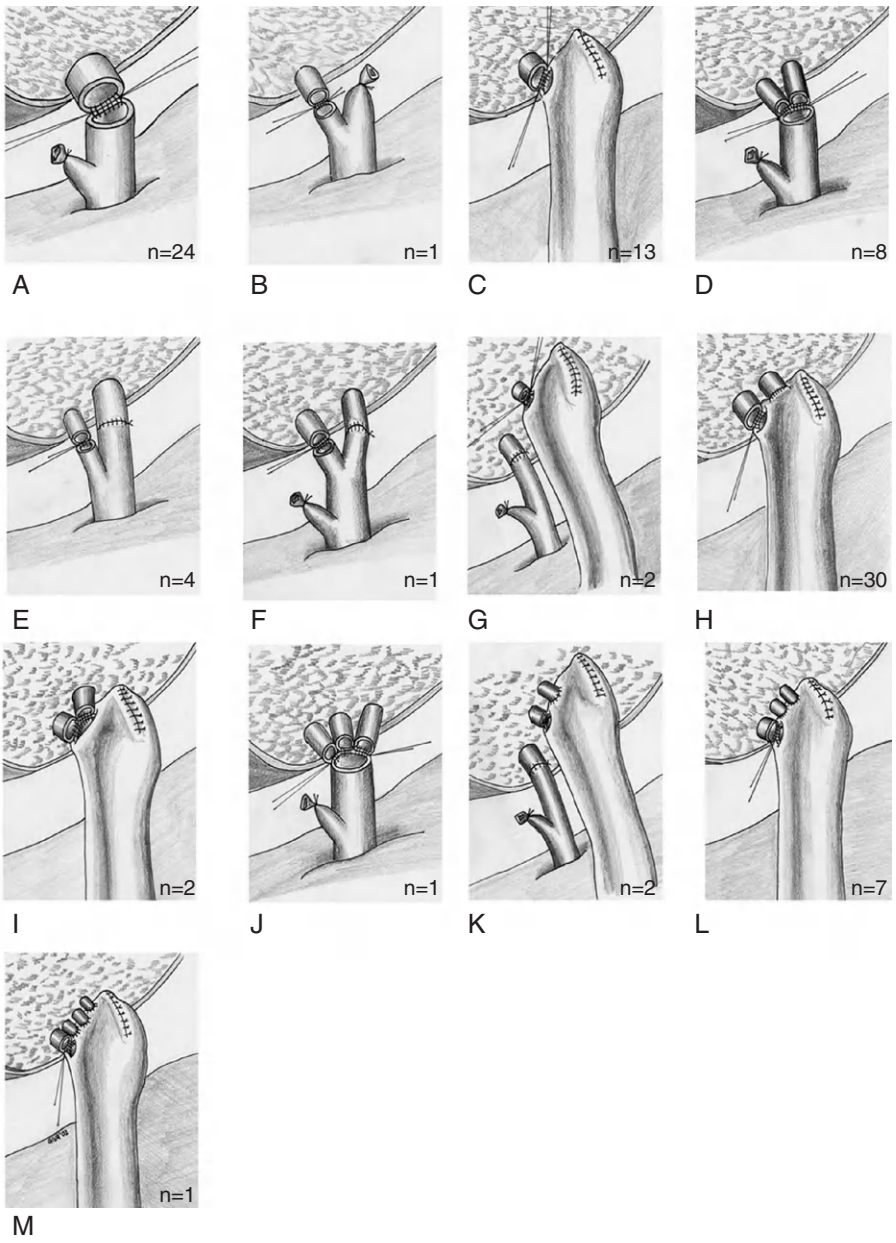


FIGURE 98B.22. A to **M,** Different types of biliary reconstructions and number of cases for each applied in a series of 96 right-lobe living donor liver transplantations. *(From Varotti G, et al, 2004: Anatomic variations in right liver living donors. J Am Coll Surg 198:577-582.)*

pain is usually unexpected, and every effort to maintain adequate analgesia, such as via patient-controlled analgesia or epidural analgesia, is key for both the donor's comfort and to enable recuperation free of preventable nosocomial complications. Postoperative care is similar to that for any liver resection, however, all established prophylactic measures—pulmonary hygiene, deep venous thrombosis prophylaxis, and other such measures—should be included to reduce donor risk to the lowest point achievable.

Despite meticulous surgical postoperative care, right-lobe donor hepatectomy is associated with considerable morbidity, with up to 50% of donors experiencing complications in some series (Pomfret, 2003). The A2ALL retrospective cohort study found that out of 393 donors, 82 (21%) had one complication, and 66 (17%) had two or more complications Although most were of low-grade severity, such as respiratory and wound-related complications, a significant proportion were severe (26%), life threatening (2%), or even fatal (0.8%; Ghobrial et al, 2008).

Some degree of hepatic insufficiency is clinically identified after surgery, presenting as transient prolonged prothrombin time and nonobstructive cholestasis. Management of biliary leakage with right hepatectomy is similar to right hepatectomy for other indications, but the surgical team should be aware that delayed reoperation could occur because of the logical desire to avoid reoperating on a donor. Vascular complications such as hemorrhage and portal thrombosis are rare but logically require rapid detection and surgical correction to avoid injury to the remnant liver. Fortunately, uncommon instances of biliary stricture (Lee et al, 2004), incisional hernia, and small bowel obstruction have been treated by standard surgical means.

The psychiatric effects on liver donors is not insignificant. The A2ALL study group identified one or multiple psychiatric complications in 16 (4.1%) of 392 donors, including three

severe complications: suicide, accidental drug overdose, and attempted suicide (Trotter et al, 2007). These findings stress the importance of both preoperative screening assessment and monitoring of liver donors to prevent such tragic events.

LIVING DONOR TRANSPLANTATION: FUTURE DIRECTIONS

Outcomes analysis, multicenter collaboration (A2ALL cohort study), and communication among living donor transplantologists have promoted advancement of this valuable treatment option. Further experience will continue to refine surgical techniques, reduce vasculobiliary surgical complications, and hone the clinical indications for many disease entities, especially malignancy. The role of laparoscopy in LDLT will continue to expand, as experience in laparoscopic liver resection techniques increases. As with liver resection, we should be mindful to avoid liberalization of indications simply because a less invasive approach to donation is available. Clinical decisions must be based on the limits for the recipient and the risk to the donor, despite the shortage of cadaveric donors and waiting-list mortality. Continued contributions by participating centers and study groups such as the A2ALL will continue to clarify the role and application of LDLT in the treatment of liver disease.

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CHAPTER 98C

Liver transplantation in children and segmental transplantation

Susan Logan, Christopher D. Anderson, and Jeffrey A. Lowell

HISTORICAL OVERVIEW

Thomas Starzl attempted the first human liver transplantation in 1963 in a 3-year-old child with biliary atresia. Unfortunately, the child died in the operating room from uncontrollable hemorrhage (Starzl, 1992), but subsequently, in 1967, Starzl successfully performed liver transplantation in eight children. All survived the operation, and half survived more than 1 year (Starzl et al, 1968).

Since those heroic beginnings 4 decades ago, advances in immunosuppression, surgical technique, and critical care have made liver transplantation a reliable, lifesaving procedure performed every day at liver transplant centers throughout the world. In children with end-stage liver disease (ESLD), liver transplantation has become the accepted therapy, and its use is limited only by the availability of suitable grafts.

In 2007, there were 5887 adult liver transplantations and 602 pediatric transplantations (Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients [OPTN/SRTR], 2008). Currently, approximately 15,500 adults and 540 children are awaiting liver transplantation (United Network for Organ Sharing [UNOS], 2009). Potential recipients who are infants, toddlers, or young children have narrow constraints with regard to graft size. Historically, the lack of size-matched organ availability, coupled with the disproportionate number of adults on the waiting list, has significantly disadvantaged children awaiting transplantation. Compared with adults who have liver disease, children have much less time to await transplantation; an infant with decompensated liver disease from cirrhosis typically cannot survive on a waiting list for several years (McDiarmid, 2002). Furthermore, waiting-list mortality for children younger than 1 year continues to far exceed that of other children and adults (OPTN/SRTR, 2008), in part because of the lack of size-matched organs.

The shortage of donor organs has motivated surgeons to develop innovative techniques to increase the number of potentially usable organs for pediatric transplantation. Initially, adult cadaveric livers were made smaller by removing the right lobe and medial section of the left lobe to enable grafting of the left lateral section into small recipients. In this way, the size restrictions imposed on any particular donor-recipient combination could be overcome. The application of reduced-size grafts led to a shift of cadaveric livers to children and small adults, but it did not increase the total graft pool.

Progressive improvements in surgical technique have evolved such that now the left lateral section and the right trisegment graft each can be used, meaning that a single liver potentially can be divided and transplanted into two recipients. With this innovative technique, the *split-liver procedure*, important progress in the effort to expand donors available to children has been accomplished without disadvantaging adult recipients. Except in unusual circumstances, the use of a reduced-size liver allograft in which the remnant is discarded is theoretically rarely justified. In 2007, partial or split-liver transplantations accounted for approximately 4% of all deceased-donor liver transplantations (OPTN/SRTR, 2008). The use of reduced-size liver grafts declined from 23% to 16% of pediatric liver transplantations over the last decade, but during this same time, split-liver allografts increased from 9% to 16% (Anderson et al, 2008).

Favorable outcomes transplanting reduced-size and split livers led to the development of techniques for using liver segments from living donors for pediatric grafts. With increasing experience, donations from living donor livers are no longer confined to left lateral sections or left hepatic lobes but have expanded to include full right hepatic lobe grafts, which contributes to the adult organ pool as well (Hong et al, 2008). Today, living-related and unrelated living-donor liver transplantation (LDLT) accounts for approximately 10% of all pediatric liver transplantations and 4% of adult liver transplants (OPTN/SRTR, 2008), and it has been one of the most exciting and challenging advances in liver transplantation.

INDICATIONS

Box 98C.1 lists common indications for pediatric liver transplantation. Biliary atresia is a progressive, inflammatory, fibrosing cholangiopathy of unclear pathogenesis (see Chapter 40). It occurs in only 1 in 8000 to 18,000 live births; and although it is rare, it remains the most common cause of infant death owing to hepatic disease and accounts for approximately 50% of all pediatric liver transplantations (Bassett & Murray, 2008; Bezerra, 2005; Perlmutter & Shepherd, 2002). Most children with this disease lack an extrahepatic biliary tree, resulting in impaired bile flow, conjugated hyperbilirubinemia, acholic stools, and hepatomegaly. The hepatic parenchyma becomes congested, and progressive damage leads to secondary biliary cirrhosis. Although portoenterostomy, also known as the *Kasai procedure* (Kasai & Suzuki, 1959), may yield some clinical improvement and is the first-line treatment (Ohi, 2000; Ryckman et al, 1998), approximately 70% to 80% of children with biliary atresia eventually require liver transplantation (Karrer et al, 1996; Lowell et al, 1996).

Other causes of cholestasis in children include idiopathic neonatal hepatitis; infection by both viral and bacterial pathogens, including toxoplasmosis and syphilis; progressive familial intrahepatic cholestasis (Byler disease); metabolic and genetic diseases; familial arteriohepatic dysplasia (Alagille syndrome); choledochal cyst; and ischemia-reperfusion injury. Cholestasis

Box 98C.1

Indications for Pediatric Liver Transplantation

Cholestatic Hepatic Failure

Biliary atresia
Primary sclerosing cholangitis
Alagille syndrome
Byler disease
Total parenteral nutrition–induced liver failure
Idiopathic disease

Infectious Hepatic Failure

Viral infection, such as with hepatitis A, B, or C
Toxoplasmosis
Syphilis
Bacterial infection

Genetic or Metabolic Hepatic Insufficiencies

α_1-Antitrypsin deficiency
Cystic fibrosis
Wilson disease
Glycogen storage disease
Tyrosinemia
Primary hyperoxaluria
Hereditary hemochromatosis
Crigler-Najjar syndrome
Neoplastic hepatic primaries
Hepatoblastoma
Hepatocellular carcinoma

Extrahepatic Diseases

Hemophilia
Familial hypercholesterolemia

Other Causes of Hepatic Failure

Autoimmune hepatitis
Budd-Chiari syndrome
Toxicity
Giant arteriovenous malformation

may progress to cirrhosis and has also been associated with parenteral nutrition in children with short bowel syndrome (Baker et al, 1998).

Pediatric liver transplantation is also indicated in cases of noncholestatic liver failure secondary to infectious, metabolic, genetic, and neoplastic etiologies. Although less frequent in children than in adults, postnecrotic liver cirrhosis is the indication for transplantation in approximately 10% of pediatric patients and is most commonly the result of viral hepatitis or idiopathic cryptogenic cirrhosis (Malatack et al, 1983).

Metabolic liver diseases are genetic disorders that lead to the production of aberrant transport proteins or enzymes and altered metabolic pathways. These inborn errors of metabolism, such as α_1-antitrypsin (AAT) deficiency or Wilson disease, may cause direct injury to the liver and result in liver failure, with or without injury to other organs; it may also lead to abnormal liver metabolism, including urea cycle disorders or oxalosis, that can lead to injury of other organs. Altogether, such diseases account for approximately 10% of all pediatric liver transplantations (Hansen & Horslen, 2008).

AAT deficiency is a genetic disorder that leads to defective production of the serine protease α_1-antitrypsin (see Chapter 70A), an enzyme produced in the liver to protect the lungs from neutrophil elastase. The abnormal protein accumulates in the liver, apparently causing liver damage, although the mechanism of injury remains unclear. Synthetic AAT has some utility in the treatment of AAT deficiency–related lung disease, but it has no role in the treatment of the associated liver disease (Köhnlein & Welte, 2008; Silverman & Sandhaus, 2009).

Wilson disease is an inborn error of metabolism characterized by defective copper excretion and the accumulation of toxic amounts of copper in the liver, basal ganglia, kidney, and cornea, which may lead to the characteristic Kayser-Fleischer rings (see Chapter 70A). The defect is located on chromosome 13, is inherited in an autosomal recessive fashion, and affects 1 in 50,000 births. Initial symptoms are nonspecific and include lethargy, anorexia, vague abdominal pain, and weight loss. Some patients present with asymptomatic hepatomegaly, and others present with fulminant hepatic failure (FHF) (Riordan & Williams, 2001).

Other metabolic liver diseases—such as urea cycle disorders, Crigler-Najjar (CN) syndrome, or familial hypercholesterolemia—do not result in primary hepatic disease but cause extrahepatic disease as a result of dysfunctional hepatic gene products or metabolites that affect extrahepatic tissue. Urea cycle defects result in the accumulation of nitrogenous waste and severe, potentially lethal hyperammonemia. Two diseases within this group of disorders are described by their respective enzyme deficiencies: *carbamyl phosphate synthetase* (CPS) *deficiency* and *ornithine transcarbamylase* (OTC) *deficiency*. Three others are described by the primary metabolite that accumulates in affected individuals: *citrullinemia, argininosuccinic aciduria* (AS), and *argininemia* (AL).

CN syndrome is caused by mutations of the gene that codes uridine diphosphate glucuronosyltransferase-1, resulting in unconjugated hyperbilirubinemia. Untreated neonates develop a condition of severe neuronal damage called *kernicterus.* Homozygous familial hypercholesterolemia (HFH) is a rare disease caused by mutations in the gene that codes the low-density lipoprotein (LDL) receptor. The receptor may be defective or completely absent, and affected individuals have dramatically elevated plasma cholesterol levels, leading to accelerated atherosclerosis, childhood coronary artery disease, and premature death from myocardial infarction (Hansen & Horslen, 2008). Liver transplantation corrects these conditions by providing the required cellular machinery to synthesize the correct gene product or metabolite (Florman & Shneider, 2001; Meyburg & Hoffmann, 2005). Occasionally, auxiliary hepatic transplantation has been performed in these circumstances (Bismuth et al, 1996; Sze et al, 2009; Van Hoek et al, 1999). In AAT deficiency, the potential for development of hepatocellular carcinoma (HCC) precludes auxiliary liver transplantation and mandates total hepatectomy.

Cystic fibrosis (CF) is an autosomal recessive multiorgan disorder that is the most common lethal inherited disease affecting the white population. As management of these patients continues to improve, CF liver disease (CFLD) is increasingly recognized as a significant cause of morbidity and mortality. Approximately 5% to 10% of CF patients will progress to cirrhosis, with the most frequently recognized complications attributable to portal hypertension with an associated nutritional and pulmonary decline. A significant number of patients with CFLD may be helped with an isolated liver transplantation or a concomitant liver and lung transplantation; however, the debate is ongoing in the literature regarding the timing of liver transplantation in these patients (Colombo et al, 2006; Fridell et al, 2003; Nash et al, 2008).

Although more common in adult patients, chronic Budd-Chiari syndrome with severe hepatic congestion and focal

areas of liver fibrosis or cirrhosis may be an indication for liver transplantation in older children (see Chapter 77). Pretransplantation evaluation should be performed to recognize predisposing factors or underlying diseases such as myeloproliferative disorders, primary hepatic protein deficiencies—of proteins C and S, antithrombin III, and activated protein C resistance—or secondary protein deficiencies, such as increased intestinal protein loss in inflammatory bowel disease (Slakey et al, 2001).

FHF (see Chapters 73 and 97C) is associated with a mortality rate greater than 70%. It is essential to transfer children with FHF to a transplant center immediately for management and urgent evaluation and listing for liver transplantation. Because cerebral edema develops rapidly, careful monitoring and intensive supportive care are required. Mild elevation of intracranial pressure (ICP) may be managed acutely by hyperventilation and elevation of the patient's head, although maintenance likely requires strict sodium and osmolar and intravascular volume control. Placement of an ICP monitor should be considered, but regardless, attention to maintenance of cerebral perfusion pressure (CPP) is paramount. Transplantation in patients with signs of cerebral edema is urgent, as edema may lead to irreversible brain damage or death (Tanaka et al, 1994). Poor prognostic factors for liver transplantation in children with FHF include age younger than 10 years, liver disease other than viral hepatitis, grade 2 or 3 hepatic encephalopathy, coagulopathy (prothrombin time >30 seconds), and increasing jaundice (bilirubin >9 mg/dL) (Uemoto et al, 2000).

Liver tumors account for less than 3% of all indications for pediatric liver transplantation (Austin et al, 2006). Hepatoblastoma, HCC, and fibrolamellar HCC represent the most frequent tumors (see Chapter 82). In contrast to adults, the predisposing factors for malignant liver tumors in children are not viral hepatitis or alcoholism but are more often metabolic disorders, such as AAT deficiency, tyrosinemia, or glycogen storage disease. In patients without cirrhosis, hepatic resection is the treatment of choice. Liver transplantation should be considered in the case of unresectable tumors confined to the liver (Chen et al, 2006; Otte et al, 2004). In patients with advanced cirrhosis and HCC meeting Milan criteria, transplantation is indicated (Austin et al, 2006; Beaunoyer et al, 2007; Perilongo et al, 2004). Rarely, giant arteriovenous malformations and benign liver tumors—when they replace the whole liver, or when they have the potential for malignancy (e.g., hepatic adenomatosis or multiple adenomas in glycogen storage disease [Fig. 98C.1])—may be indications for total hepatectomy and liver transplant (Malatack et al, 1987; Wellen et al, 2009; see Chapter 79A).



FIGURE 98C.1. Multiple giant adenomas in an explanted liver.

EVALUATION OF THE POTENTIAL RECIPIENT

A multidisciplinary evaluation of a child with decompensated liver disease should be completed with the involvement of surgeons, hepatologists, nurses, anesthesiologists, psychologists, and social workers. Early referral to a transplant center allows maximum time to develop a management strategy and to optimize pretransplantation clinical status. The timing of liver transplantation is crucial, because late referral of patients with significant hepatic complications and malnutrition results in a poorer outcome. The expected waiting time on the transplant list may vary based on the geographic region, and this should be taken into account. In infants younger than 2 years who weigh less than 10 kg, it is often difficult to maintain metabolic and nutritional support. Ideally, children should be considered for liver transplantation before the complications of malnutrition, such as weight loss and growth failure, occur (Kimura et al, 2004; McDiarmid et al, 2004). With chronic liver disease, prolonged clotting times, intractable ascites, recurrent variceal bleeding secondary to portal hypertension, and recurrent cholangitis with severe cholestasis are indications for liver transplantation (Hendrickson et al, 2004).

The prognosis after liver transplantation for chronic liver disease is influenced by preoperative comorbidities. The advent of the Pediatric End-Stage Liver Disease (PELD) and Model for End-Stage Liver Disease (MELD) scores (Malinchoc et al, 2000; Wiesner et al, 2001) has made it possible to better predict mortality and progression of liver disease while awaiting transplantation (Desai et al, 2004; Barshes, et al, 2006). The pertinent factors in the PELD score are the international normalized ratio (INR), total bilirubin, serum albumin, age younger than 1 year, and weight or length less than 2 standard deviations (SDs) from the mean for age and gender. The PELD score is used for patients younger than 12 years, and the scores range from a negative value (−10) to 50. Adolescents aged 13 to 18 years are allocated organs based on the MELD score, similar to adults. Box 98C.2 presents the formulas for calculating the MELD and PELD scores.

Box 98C.2

MELD and PELD Calculations

MELD

$$10\times[0.957\ln(\text{Creatinine}[\text{mg/dL}])+0.378\ln(\text{Total bilirubin }[\text{mg/dL}])+1.120\ln(\text{INR})+0.643]$$

PELD

$$10\times[0.480\times\log_e(\text{Bilirubin}[\text{mg/dL}])+1.857\times\log_e(\text{INR})-0.687\times\log_e(\text{albumin}[\text{g/dL}])+0.436(\text{if the patient is}<1\text{ year old})+0.667(\text{if the patient has growth failure}[<2\text{ SD}])]$$

The resulting score is rounded to the nearest whole number.
MELD, Model for End-Stage Liver Disease; PELD, Pediatric End-Stage Liver Disease; INR, international normalized ratio; SD, standard deviation

Box 98C.3

Contraindications to Pediatric Liver Transplantation

Absolute

Uncontrolled systemic sepsis
Irreversible brain edema
Uncorrectable symptomatic heart defects
Nonreversible pulmonary hypertension
Extrahepatic malignancy

Relative

Portomesenteric thrombosis
HIV-positive status
Severe psychosocial impediments

HIV, human immunodeficiency virus

Comparing the periods before and after the introduction of the MELD and PELD scores, a similar percentage of children are being transplanted, but mortality rates have decreased (Freeman et al, 2004; Yao et al, 2004). Small size and young age are no longer contraindications, and many transplantations for biliary atresia are now done in infants who weigh less than 10 kg (Colombani et al, 1996; Sokal et al, 1990). Whereas post-transplantation mortality has improved, waiting-list mortality for infants younger than 1 year remains high, unfortunately (OPTN/SRTR, 2008). Consideration should be given to referring these young and small infants to pediatric specialty centers that have expertise with these challenging cases. Contraindications to pediatric hepatic transplantation are listed in Box 98C.3.

RECIPIENT HEPATECTOMY

The recipient hepatectomy is typically difficult, because more than half of the pediatric patients have had a prior laparotomy. Severe portal hypertension with abdominal wall and perihepatic venous collaterals is common, and these technical challenges may be exacerbated by severe coagulopathy and thrombocytopenia. Thrombosis of the portal vein can be an additional complicating factor, and preservation of the retrohepatic inferior vena cava contributes to hemodynamic stability during the hepatectomy.

Before beginning the transplantation, a Broviac central venous catheter is placed for intraoperative and postoperative fluid resuscitation, monitoring, and postoperative laboratory draws, the same as an arterial catheter. Pressure points are well padded, and convective heating blankets are used. The abdomen is entered through a curved transverse subcostal incision. Meticulous hemostasis must be maintained throughout the procedure, because ongoing bleeding may lead to dilutional coagulopathy and fibrinolysis. Abdominal wall venous collaterals must be carefully controlled as they are encountered, and adhesions to the liver are carefully dissected to allow access to the portal region (Fig. 98C.2).

If the child has had a previous Kasai procedure, the jejunal loop is taken down, the enterostomy is closed, and the Roux-en-Y loop is preserved for later biliary drainage of the graft, if it is of suitable quality. The porta hepatis is dissected carefully with isolation of the hepatic artery and portal vein. Although transection of the hepatic artery is performed early in hepatectomy, the portal vein is divided after total mobilization of the liver, just before removal of the native liver, to avoid unnecessary congestion in the mesentericoportal system. Alternatively, a temporary portocaval anastomosis may be performed by ligating and dividing the portal vein at the level of the bifurcation and creating an end-to-side anatomosis to the infrahepatic vena cava. This avoids mesenteric venous congestion and also helps maintain venous return and hemodynamic stability.

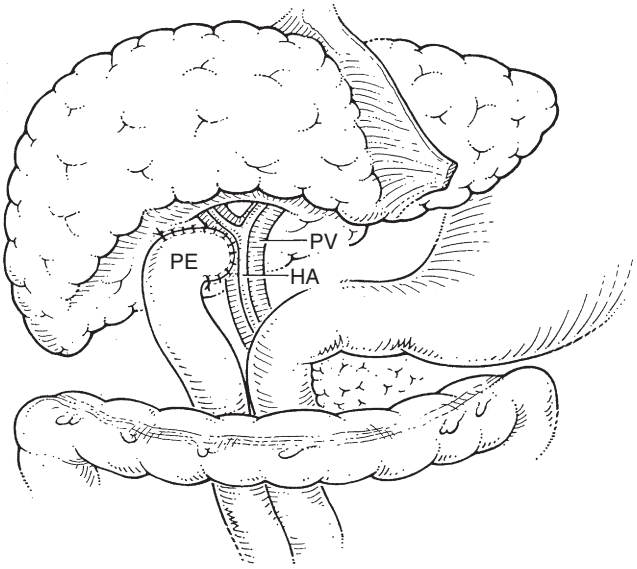


FIGURE 98C.2. Recipient hepatectomy. The hilum is examined carefully, and a previous portoenterostomy (*PE*) is taken down. The portal vein (*PV*) and hepatic artery (*HA*) are divided high in the porta hepatis.

The hepatic artery and portal vein are dissected high in the hilum to preserve adequate length for later anastomosis with the graft. The portal vein may be quite small; in this setting, dissection to the level of the confluence of superior mesenteric vein and splenic vein posterior to the pancreas may allow for anastomosis to a larger inflow vessel. The liver is mobilized further by dividing the ligamentous attachments and the short hepatic veins that drain the right liver and caudate directly into the vena cava.

For orthotopic whole-liver transplantation, the small retrohepatic caval segment can be removed with the native liver, or the vena cava can be preserved and the donor liver anastomosed in a piggyback fashion to the confluence of the recipient's right, middle, and left hepatic veins. With a segmental graft, the recipient inferior vena cava must be preserved. A vascular clamp is placed across the hepatic veins so that they can be joined to form a common opening to sew to the donor suprahepatic cava or, in case of segmental grafts, the left hepatic vein (Fig. 98C.3). Complete hemostasis of the retroperitoneum should be accomplished before removing the donor liver from cold storage.

GRAFT PROCUREMENT AND ENGRAFTMENT

The techniques used for recovering whole, deceased-donor livers for transplantation from children are similar to the techniques used in adult-adult transplantation. Special attention should be paid to donor serum sodium levels and to dynamic liver function tests. High sodium levels (>170 mmol/L) may be

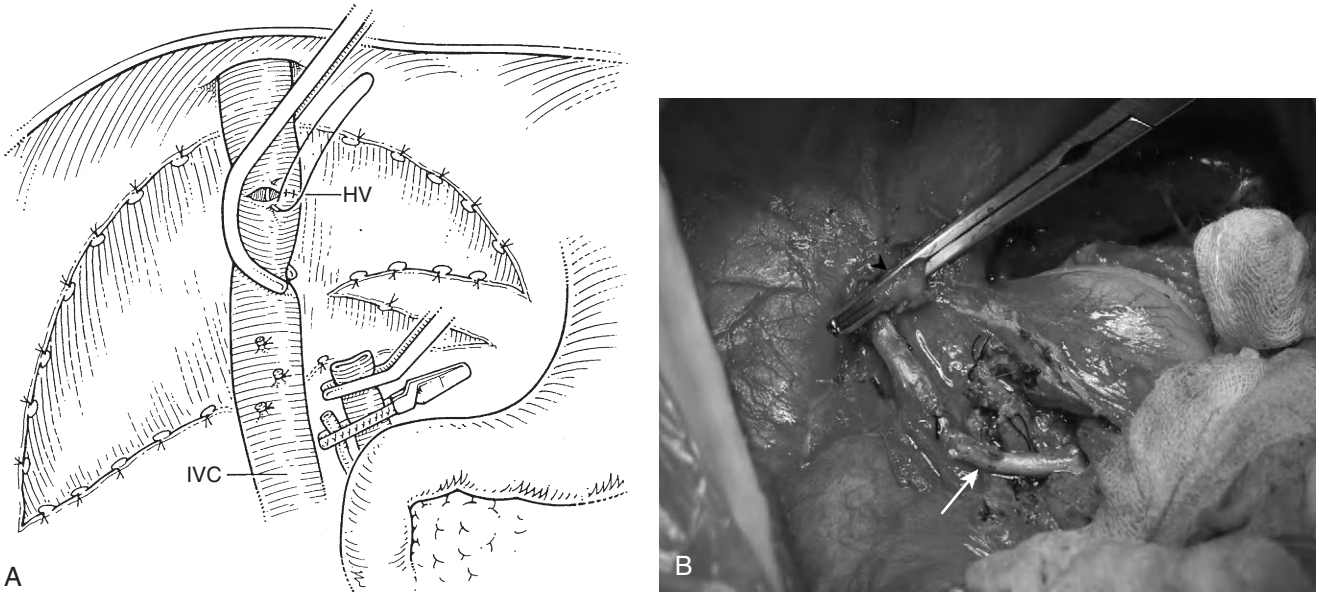


FIGURE 98C.3. Recipient hepatectomy. **A,** The liver has been removed, and the inferior vena cava (*IVC*) is preserved in preparation to receive a segmental graft. **B,** Note the portocaval shunt (*arrow*) and vascular clamp occluding only the hepatic veins (*arrowhead*), allowing venous return from both the systemic and mesentericoportal systems. Sutures mark the ligated hepatic artery and bile duct. HV, hepatic vein.

associated with severe reperfusion injury and poor graft function (Totsuka et al, 1999).

The donor liver is anastomosed using the full vena cava—or the left hepatic vein, with or without the middle hepatic vein, in the case of a reduced-size left graft—to the confluence of the recipient hepatic veins. Before securing the final caval sutures, the donor liver is flushed through the donor portal vein with cold Ringer's lactate to flush out the preservation solution, usually Viaspan (University of Wisconsin solution) or Custodiol (histidine-tryptophan-ketoglutarate [HTK]), which may be high in potassium. The portacaval shunt is taken down and oversewn, and the portal venous anastomosis is completed, leaving a large growth factor in the continuous suture to prevent a waist, or narrowing of the anastomosis, when the vessels are refilled with portal blood.

The arterial anastomosis is performed with sutures of fine (7-0 or 8-0) monofilament material using microsurgical loupes. A microscope may be useful in anastomosing arteries with a diameter smaller than 1 to 2 mm. The anastomosis is performed most commonly in an end-to-end fashion directly to the native hepatic artery. If the native artery is not of adequate size, or if there is an intimal dissection, an extension allograft using saphenous vein or donor iliac artery from the infrarenal or supraceliac aorta may be used (Yamaoka, 1996).

The bile duct anastomosis is the final step in the procedure. If present, the donor gallbladder is removed. If the recipient has an intact bile duct that is of suitable size, an end-to-end choledochocholedochostomy can be performed with or without placement of a T-tube or an internal stent; however, most children who undergo transplantation have either biliary atresia or common bile ducts that are very small or sclerotic, so a choledochojejunostomy is necessary. Use of a segmental allograft requires hepaticojejunostomy, if the common bile duct has been resected. In case of a previous Kasai procedure, the jejunal loop of the portoenterostomy can be used again, although it must be shortened, and a fresh segment must be anastomosed.

REDUCED-SIZE SEGMENTAL LIVER TRANSPLANTATION AND SPLIT-LIVER TRANSPLANTATION

Reduced-Size Segmental Liver Transplantation

The use of reduced-size grafts for pediatric recipients is one of the most important advances in liver transplantation. The disproportionate shortage of grafts for very young children, compared with older children, motivated surgeons to develop innovative operative techniques to overcome the restrictions imposed by donor and recipient size mismatch. With these techniques, livers can be reduced to a functional unit of appropriate size for the recipient. The optimal ratio between the required volume of liver and the actual "tailored" hepatic mass is between 1:1 and 1:2. In this way, livers from donors 10 or 20 times the size of the recipient can be used (Broelsch et al, 1988).

The liver comprises eight anatomically defined segments, each with its own arterial and portal blood inflow and separate biliary drainage (Strasberg, 1997; see Chapter 1B). Similarly, segmental hepatic venous outflow is independent, but major liver veins run along sectional borderlines, receiving blood from several adjacent segments (Couinaud, 1954). For purposes of transplantation, the liver can be divided into several functional grafts. The most commonly used reduced-size graft is the left lateral section graft, composed of segments II and III (Fig. 98C.4; Botero & Strasberg, 1998). To preserve a single donor portal vein, the liver is transected just to the right of the falciform ligament, and branches of the ascending (umbilical) portion of the left portal vein to segment IV are carefully suture ligated. The left hepatic vein is used for hepatic venous drainage. It is anastomosed directly to the recipient's vena cava, which must be preserved during hepatectomy. The full left graft (segments I, II, III, and IV or segments II, III, and IV) is used in small adults or older children who require a graft slightly larger than the left lateral section.

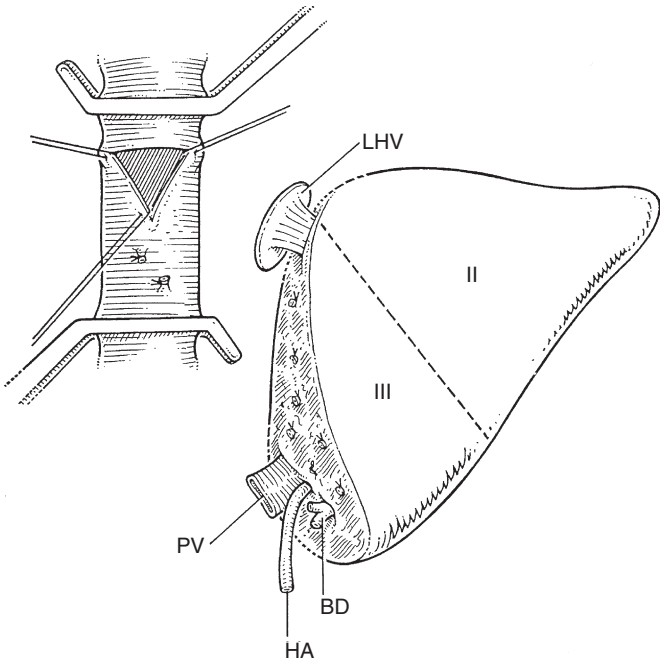


FIGURE 98C.4. The most commonly used segmental graft uses segments II and III of the left liver. The recipient's inferior vena cava (*IVC*) is preserved, and the left hepatic vein (*LHV*) is sutured to a large triangular venotomy cut on the anterior aspect of the IVC. The portal vein (*PV*), hepatic artery (*HA*), and bile ducts (*BD*) are depicted before anastomosis.

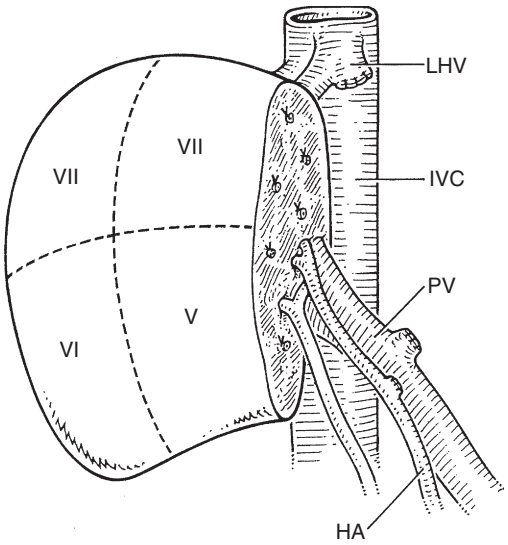


FIGURE 98C.5. Segmental graft. The full right liver incorporating segments V through VIII is used. The left hepatic artery (*LHV*) is shown and represents the oversewn left and middle hepatic veins. HA, hepatic artery; IVC, inferior vena cava; PV, portal vein.

Bismuth and Houssin (1984) first reported success with transplantation of a left hepatic allograft; in the same year, Broelsch and colleagues (1984) reported the successful grafting of the left lateral section. Since then, most pediatric transplant centers have adopted segmental transplant techniques using reduced-size livers. The results after these segmental grafts are comparable to the results achieved with whole-organ orthotopic liver transplants (Hong et al, 2008). Although reduced-size grafts can overcome the donor-recipient size discrepancy by distributing cadaveric livers to the advantage of children, and to small adults, they do not increase the absolute number of grafts. The advent of the split-liver technique not only allowed the donor liver to be tailored to fit a small child, but it also allowed for the remaining donor graft to be used, which increased the actual organ pool; however, routine use of reduced-size grafts is discouraged except in unique situations.

Split-Liver Transplantation

In the split-liver procedure, a single cadaveric liver is divided into two grafts to be transplanted into two patients (Cintorino et al, 2006; Strasberg et al, 1999; Zamir et al, 2002). The first successful split-liver transplantation was performed by Pichlmayr and colleagues in 1988, utilizing a right extended graft (segments IV, V, VI, VII, and VIII) and a left lateral graft (segments II and III). Leaving segment IV with the right graft rarely leads to an impaired arterial and portal venous perfusion, despite the fact that the vascular supply of this segment belongs to the left liver. Very rarely, resection of segment IV may be required because of poor perfusion. The liver also may be dissected along the principal plane, dividing it into right and left livers. The vena cava and the full length of main portal vein and celiac artery typically are included with the right graft (segments V through VIII), which is then anastomosed to the recipient in a manner similar to a whole-liver graft (Fig. 98C.5). By contrast, the left lobe has a left hepatic vein, left hepatic artery, and left portal vein, which have been divided at the branching points from the vena cava, common hepatic artery, and portal vein.

Broelsch and coworkers (1990) reported the first successful split-liver transplantation series. Since then, other groups have developed and refined the technique (Azoulay et al, 2001a, 2001b; Busuttil & Goss, 1999; Rela et al, 1998); however, the initial enthusiasm for this procedure faded, because the preliminary results were inferior, mainly owing to technical and organ-preservation problems. In addition, progress in split-liver transplantation was hampered by tremendous practical and logistical problems, because this procedure requires two full teams of surgeons, anesthesiologists, and operating room staff to be available almost simultaneously. The initial reported patient survival at 1 year was 67%, and graft survival was reduced to 55% (Broelsch et al, 1990). The most frequent complications during the initial experience with this procedure were bleeding, primary poor function, and biliary fistulae and strictures. In adult recipients of right-lobe grafts, liver insufficiency became a major problem because of long ischemic times and borderline size matching.

With surgical refinements of liver splitting and transplantation techniques and better patient selection, results improved (Goss et al, 1997; Malago et al, 1997; Yersiz et al, 2006). The introduction of the in situ split-liver technique, developed by Rogiers in 1994, significantly reduced ischemic time of the liver (Rogiers et al, 1996). Using this technique, the liver is divided in situ in the heart-beating deceased donor before cold perfusion starts (Yersiz et al, 2003). While arterial and portal blood supply and venous drainage are preserved, the liver is divided by careful transection of the hepatic parenchyma, most commonly by separating the future left lateral section allograft from the future right trisegment graft. The splitting procedure requires

meticulous hemostasis, which also affects the recipient operation, because little or no bleeding occurs at the cut surface of the graft after reperfusion.

Although the split-liver technique remains a procedure confined to large transplant centers that have experience in segmental grafting, the possibility of transferring a partial graft to another center has now become reality. Today, split-liver transplantation has gained wide acceptance, with results comparable to those of whole-organ transplantation (Deshpande et al, 2002; Diamond et al, 2007; Hong et al, 2009); now a standard procedure, it represents an important technical advance in expanding the total number of transplantable organs. Together with living-related liver transplantation, the split-liver technique has had a substantial impact on the inequities of the pediatric donor organ shortage.

LIVING DONOR TRANSPLANTATION

The success of many centers performing reduced-size and split-liver grafting provided a strong surgical basis for using segments from living donors (Strong et al, 1990; see Chapter 98B), particularly in the treatment of small children with ESLD (Broelsch et al, 1994; Edmond et al, 1993; Otte, 1995; Otte et al, 1998; Raia et al, 1989). Donors are most commonly the parents or other close relatives of the recipient, but nonrelated living donor liver transplantation (LDLT) procedures also are performed (OPTN/SRTR, 2008).

For ethical reasons, adequate and thoughtful selection of donors is a major prerequisite of LDLT, and most centers have adopted stringent donor evaluation protocols (Chen et al, 2003; Surman & Hurtl, 2003). The segmental liver donation must be deemed by the transplant team to be a purely voluntary, altruistic act with no motive of secondary gain, and a complete psychologic and social evaluation of the donor is performed. Potential donors and their families are extensively counseled, and they are evaluated by an independent physician, who acts as the donor advocate and explains the risks of the procedure in detail (Trotter, 2000). Any objections regarding the psychosocial background of the potential donor result in withdrawal from consideration for organ donation (Singer et al, 1989; Surman, 2002; Ghobrial et al, 2008).

Of paramount concern, however, is the medical risk to healthy donors; everything possible must be done to minimize risks of donor morbidity and mortality. As much as possible, the donor must be fully apprised of all the risks, possible complications, and potential sequelae; with the donor so informed, they must accept these possibilities before undertaking the procedure (see Donor Risk in Living Donor Liver Transplantation).

The success of LDLT depends partly on adequate graft volume (Kiuchi et al, 1999). The required graft volume should be determined individually and can be assessed with the use of computed tomography (CT) or magnetic resonance imaging (MRI) (Kamel et al, 2000, 2001). The left lateral section provides the most straightforward dissection, but full left- and right-lobe grafts have been used successfully. The size of the living donor's left lateral section is assessed by volumetric CT or MRI (Urata et al, 1995), the hepatic vasculature is assessed by CT angiography or MRI angiography, and the biliary anatomy is assessed by MR cholangiography or endoscopic retrograde cholangiopancreatography (ERCP). Rarely, percutaneous liver biopsy is done, but only if imaging suggests hepatic steatosis in the donor. The type and size of graft should be decided on an individual basis. In general, a full left-lobe liver graft (segments II through IV) can overcome a disparity between recipient and donor size of about 1:4. With a left lateral segment graft, a disparity of 1:10 or more can be managed. In infants weighing less than 10 kg, left lateral segment grafts are used almost exclusively.

Procedure

The donor liver is approached in the usual manner, through a standard bilateral subcostal incision or a right subcostal incision with upper midline extension. Recently, laparoscopic-assisted or hybrid laparoscopic and open techniques have been described (Baker et al, 2009; see Chapter 98B). Regardless of method, the surgical procedure begins by identifying the structures in the hilum. It is imperative to dissect close to the falciform ligament to avoid injuries to the hilar structures running to the right lobe. The left hepatic artery is isolated and followed to the liver parenchyma, and the left portal vein is dissected free and encircled with a vessel loop. The dissection continues by dividing portal and arterial branches to the caudate, which increases the length of the left hepatic artery and left portal vein. The portal branches to segment IV are ligated, and the left hepatic vein is identified above the liver and encircled with a vessel loop as it enters the vena cava. The hepatic parenchyma is transected just to the right of the falciform ligament, with suture ligation of all vessels and ducts, until the left lateral section is completely separated from the rest of the liver; the segment is still perfused with arterial and portal blood and has drainage via the left hepatic vein.

The parenchymal transection is performed without any vascular control of the graft or the remaining liver to maintain maximal viability. Hepatic transection continues until the hilar plate is reached. At this point, the section II and III bile duct is divided sharply, and its distal end is oversewn with fine, absorbable monofilament suture. With the plane of transection 0.5 to 1.0 cm to the right of the umbilical fissure, approximately 90% of left lateral section grafts will be obtained with a single section II and III bile duct (Renz et al, 2000).

The graft is now ready to be removed. The left portal vein, the left hepatic artery, and the left hepatic vein are simultaneously clamped after giving systemic heparin, and the vascular structures are divided. The left lateral section graft is removed, and the portal vein and the hepatic artery are immediately flushed with cold, heparinized preservation solution. After removing the left lateral section, rarely there may be concern for the viability of segments I and IV, because branches to these segments may be interrupted during the dissections. If there is any doubt about viability, resection may be performed after removal of the graft and a period of observation in the operating room.

As discussed previously, during the recipient hepatectomy, the vena cava is left in situ, and a temporary portacaval shunt may be used. The recipient hepatic vein–vena cava junction is modified to accommodate the anastomosis with the donor hepatic vein. A generous triangular venous anastomosis to ensure adequate drainage of the graft is recommended; the donor hepatic venous cuff should be kept short to provide an anastomosis that is not susceptible to kinking. Portal vein reconstruction is done in an end-to-end fashion. In children with biliary atresia, the recipient's portal vein is often small and may be phlebosclerotic. In these cases, an anastomosis to the confluence of the superior mesenteric and splenic veins may be

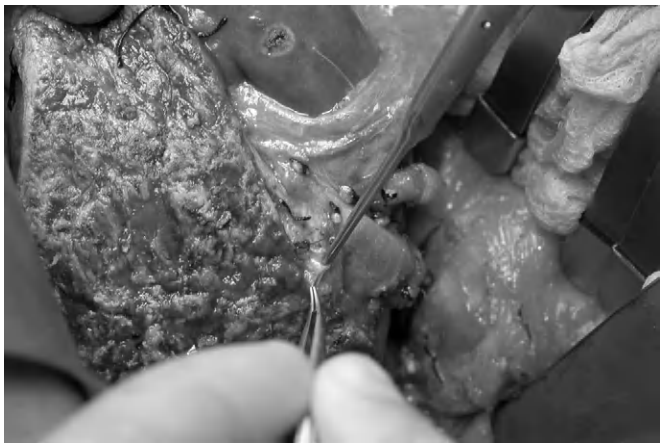


FIGURE 98C.6. Common trunk formed by segments II and III bile ducts from a left lateral section graft.

preferred (Saad et al, 1998). Hepatic artery reconstruction usually can be achieved by an end-to-end anastomosis to the recipient's proper hepatic artery via a microsurgical technique using surgical loupes or a microscope (Inomata et al, 2000). In some cases, a venous interposition graft from the recipient's infrarenal aorta, using donor saphenous vein, is needed to achieve a tension-free arterial anastomosis.

Care must be taken to identify correctly the bile ducts from segments II and III (Fig. 98C.6); such ducts are not obtained with a common trunk up to 10% of the time (Renz et al, 2000; Salvalaggio et al, 2005). The biliary drainage is fashioned using a Roux-en-Y loop of the jejunum with or without a stent. After completion of all anastomoses, the liver rotates slightly to the right and occupies a more central position than it does in the donor (Fig. 98C.7). This slight shift must be taken into account

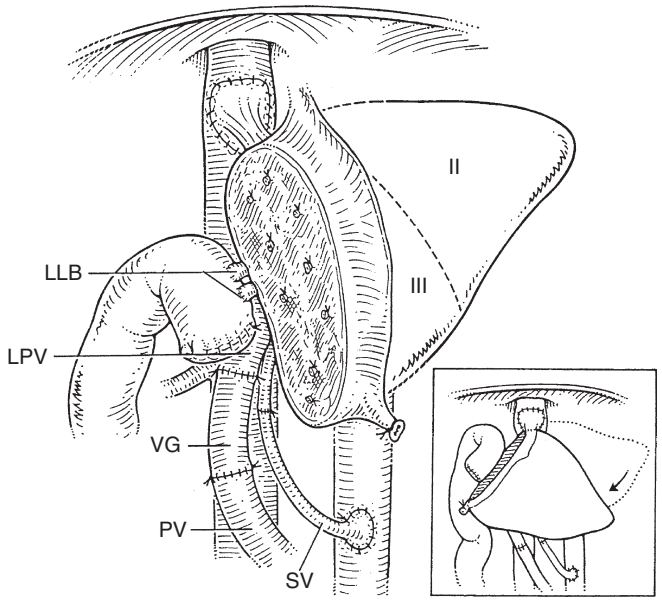


FIGURE 98C.7. Completed recipient implantation. The variant with two bile ducts is depicted. Interposition grafts are used for the hepatic artery and the portal vein to ensure adequate length. The *inset* shows the final position of the graft after abdominal closure. LLB, reresents segment II and III bile ducts; LPV, left portal vein; PV, portal vein; SV, saphenous vein graft to the hepatic artery from the aorta; VG, vein graft.

when performing the vascular and biliary anastomoses. The graft should be resuspended to the anterior abdominal wall by the falciform ligament to prevent further right shift and vascular torsion.

Donation and transplantation of a living donor full left liver lobe (segments II, III, and IV with or without segment I) is similar to that of a left lateral section graft, with a few technical variations. After cholecystectomy, the resection follows the principal plane. The venous outflow of the graft can be provided by the left hepatic vein or preferentially by use of a common patch of the left and middle hepatic vein (Makuuchi & Sugawara, 2003). Devascularization of the main left hepatic bile duct is less of a concern when the caudate is preserved with the allograft.

Although the primary goal of LDLT is the relief of organ shortage, numerous additional benefits are associated with this procedure (Sindhi et al, 1999). The most important advantage for the recipient of a living-donor transplant is a much shorter waiting period leading up to transplantation (Tanaka et al, 1994). Timing of the procedure can be planned, and the operation can be performed under elective conditions, which results in decreased operative risk. Careful donor evaluation and a short cold ischemic time offer uniformly good grafts and can minimize the risk for initial nonfunction (Farmer et al, 2001).

ADULTS

After the encouraging results of living donor left lateral section transplantation in children, this innovative technique was extended to try to solve another problem: the shortage of donor organs for adults (Renz et al, 2003; Strasberg et al, 1999). Especially in countries where cadaveric donor organ transplantation has not been established, either by law or for religious or cultural reasons, living-donor organ donation offers the only chance of liver transplantation for patients with ESLD. In 1991, the first LDLT to an adult was performed in Kyoto by Tanaka, using a left liver graft (Hashikura et al, 1994). This technique has been expanded to the use of full right hepatic lobe grafts, which are now the preferred grafts in adult-adult living donor transplants (Kawasaki et al, 1998; Seek et al, 2002; Brown, 2008).

The right lobe graft (segments V through VIII) comprises approximately 50% to 60% of total liver volume and presents the advantage of fitting exactly in the right hepatic fossa (Fig. 98C.8). Problems with this graft include a large cut parenchymal surface and an irregular biliary, arterial, portal, and hepatic venous anatomy (Trotter et al, 2002). Variations of portal vein anatomy, such as a trifurcation, and variations in arterial anatomy, such as an accessory right hepatic artery, are relative contraindications to living donation of segments V through VIII (Erbay et al, 2003; Imamura et al, 2000). Most often, the right hepatic artery has a large diameter, unless there is an additional right artery arising from the superior mesenteric artery. The hepatic artery and portal vein usually can be anastomosed directly to the recipient's vessels. In most cases, venous drainage of the right graft is achieved exclusively via the right hepatic vein, and a careful anastomosis of this vessel with the vena cava or the orifice of the recipient's right hepatic vein must be performed to prevent compromised venous outflow and congestion of the graft. If necessary, the orifice should be enlarged longitudinally to provide an exact anastomosis.

In the case of a second right hepatic vein, such as an inferior right hepatic vein, two independent anastomoses are

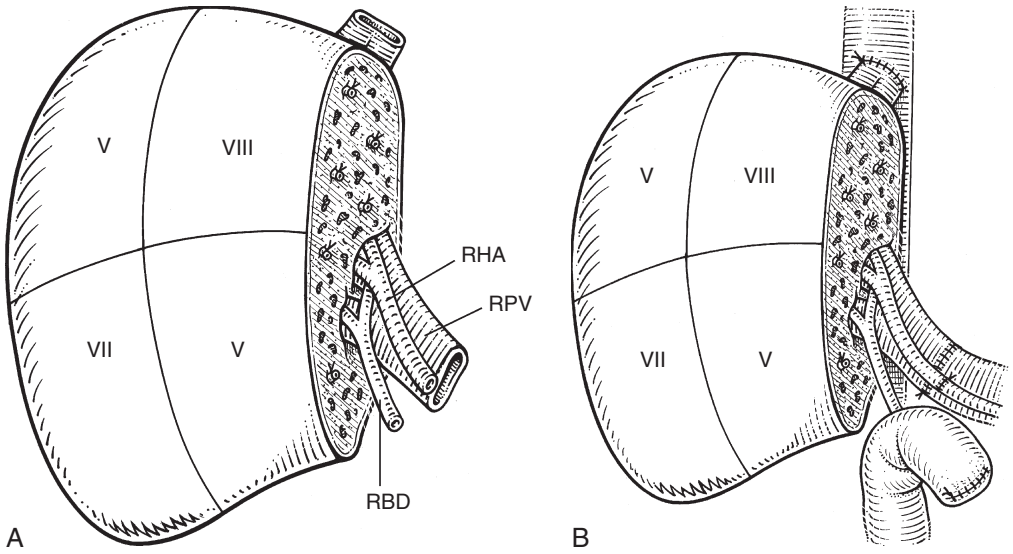


FIGURE 98C.8. **A,** Right graft from a living donor with short hilar structures and a short right hepatic vein (*RHV*). **B,** Completed recipient implantation of a right graft. RBD, right bile duct; RHA, right hepatic artery; RPV, right portal vein.

recommended for uncompromised venous drainage (Ghobrial et al, 2001). The inclusion of the donor middle hepatic vein with the graft is controversial (Fan et al, 2003). Biliary reconstruction can be challenging, because bile ducts from segments V through VIII may not form a common trunk, and two or more ducts may be present (Fan et al, 2002). Reconstruction with a Roux-en-Y hepaticojejunostomy is standard. A direct biliary anastomosis to the recipient's bile duct using a T-tube may be considered when a large, single right hepatic bile duct is present.

One dilemma of LDLT in adults centers on the maximum extent of liver resection that can be safely tolerated by the donor and the minimum amount of hepatic mass necessary for the recipient to survive (Fan et al, 2000). The definition of small-for-size grafts is vague, because the minimal amount of liver compatible with life is unknown, and variables such as ischemia-reperfusion injury, steatosis, or rejection may reduce further the initially transplanted liver mass (Hill et al, 2009). Many reports have indicated that grafts corresponding to no more than 40% of the recipient's standard volume may not be expected to function well (Pomfret, 2003). At present, a graft/body weight ratio of 0.8% or a graft volume greater than 50% of the standard liver volume are suggested values for successful grafting (Kiuchi et al, 1999; Sugawara et al, 2001). The use of an extended right liver with the middle vein retained with the graft lowers the risk of liver insufficiency in the recipient but is associated with greater donor morbidity and possible mortality. Because this procedure requires a major hepatectomy with the donation of about two thirds of total liver volume, transient impairment of donor liver function is common (Lo et al, 1999; Pomfret et al, 2003).

Prolonged cholestasis in the absence of rejection or mechanical bile duct obstruction is a hallmark of small-for-size grafting. In such patients, the perioperative management is focused on avoiding any further damage to the graft. Unless retransplantation is considered, optimal supportive care is currently the only therapy for small-for-size liver transplantation. Temporary liver support systems, such as artificial liver devices or extracorporeal perfusion, are under investigation, but their clinical use is not yet available in the United States (Demetriou et al, 2004; see Chapters 73 and 97C). In the future, it may be desirable to combine temporary liver support systems with small-for-size organs. This could be one option to improve organ shortage in adults by an extended use of LDLT.

Although there are several advantages for the recipient of an LDLT, an adult-adult LDLT subjects the donor, a healthy individual, to all of the risks of a major abdominal operation. Risk minimization begins with careful selection of appropriate candidates during the donor evaluation; however, despite careful donor and patient selection, LDLT still has significant risks for the donor, as well as potential added complications to the recipient, compared with a full-sized cadaveric donor graft (Man et al, 2003; Sugawara et al, 2003).

DONOR AND RECIPIENT RISK IN LIVING DONOR LIVER TRANSPLANTATION

Early enthusiasm for adult-adult LDLT has been tempered by growing concern for donor morbidity and mortality. Following one high-profile donor death reported in 2002 (Trotter et al, 2006), the annual number of LDLTs in the United States declined steadily, from a high of 522 in 2001 to only 266 in 2007 (OPTN/SRTR, 2008). Quantifying the risk associated with LDLT has been difficult, because no formal international registry exists to prospectively collect data on donors worldwide. UNOS has only recently mandated reporting of outcomes for all LDLT donors who are taken to the operating room for a donor hepatectomy, but this data set is not yet mature enough to be informative (Trotter et al, 2006). Most published reports of complications associated with adult-adult LDLT have come from single-center experience, and reports vary widely, with complication rates as low as 9% and as high as 67% (Ghobrial et al, 2008; Marsh et al, 2009). Estimates of donor mortality rates range from 0.1% for left lateral section grafts to 0.5% for right lobe grafts (Ringe & Strong, 2008).

In an effort to provide an unbiased assessment of the risks and severity of complications for both donors and recipients of LDLT, the nine-center, NIH-funded Adult-to-Adult Living

Donor Liver Transplantation (A2ALL) cohort study was initiated in 2002 (Ghobrial et al, 2008). The first phase of the A2ALL study utilized a retrospective, observational design and included 405 potential donors accepted for LDLT from 1998 through 2003. Among this cohort, 393 underwent donation, 12 procedures were aborted (3%), and 148 donors (38%) experienced a total of 220 complications. The most common postoperative complication was bacterial infection (12.5%), followed by biliary leak (9.2%), incisional hernia (6%), pleural effusion requiring drainage (5%), neuropraxia (4%), repeat laparotomy (3%), wound infection (3%), and intraabdominal abscess (2%). One patient died from gastric gas gangrene, sepsis, and multiorgan failure on the third postoperative day; another died from a drug overdose, and a third died from suicide, more than a year after operation; and a fourth donor died in a nonsuicide pedestrian-train accident 2 years after operation (Ghobrial et al, 2008; Trotter et al, 2006).

In addition to examining donor morbidity, the A2ALL cohort study examined complications to recipients of adult-adult LDLT relative to recipients of deceased-donor liver transplantation (DDLT). Overall, the complication rate after LDLT was not significantly higher than after DDLT (82.8% vs. 78.2%; $P = .17$), but the severity of complications was greater. Among a cohort of 384 LDLTs and 216 DDLTs, the complications that occurred more frequently in recipients of LDLT included bile leak (31.8% vs. 10.2%), unplanned laparotomy (26.2% vs. 17.1), hepatic artery thrombosis (6.5% vs. 2.3%), and portal vein thrombosis (2.9% vs. 0%). Complications leading to retransplantation or death with or without retransplantation also occurred more often after LDLT than after DDLT (15.9% vs. 9.3%); however, in a separate analysis that factored in center experience, the authors found a significant decline in LDLT complications after a center had performed at least 20 procedures (Freise et al, 2008).

The systematic data collection, analysis, and reporting methods used in the multicenter A2ALL cohort study have helped to more accurately characterize and quantify both the benefits and risks associated with adult-adult LDLT. One limitation of the study thus far has been its retrospective design, but a prospective phase of the A2ALL cohort study was initiated in 2004.

POSTOPERATIVE MANAGEMENT AND COMPLICATIONS AFTER PEDIATRIC LIVER TRANSPLANTATION (SEE CHAPTER 100)

In the immediate postoperative period, monitoring of graft function is achieved by evaluation of acid-base status, blood glucose, mental status, coagulation time, liver enzymes, and cholestasis parameters. Doppler ultrasound frequently is performed to ascertain patency of hepatic vessels, in particular of the hepatic artery.

Primary nonfunction of the graft occurs in 2% of patients and requires immediate retransplantation (Doyle et al, 1996). With regard to pediatric recipients, retransplantation with a reduced size graft from a cadaveric donor or a living donor may offer emergency options (Seiders et al, 2002). The most frequent complication after liver transplantation is hemorrhage, which may occur during the transplant procedure or in the immediate perioperative period. If a child becomes unstable or hypotensive in the postoperative course, it is prudent to reexplore immediately. The use of the protease inhibitor aprotinin (Trasylol) and an antifibrinolytic agent such as aminocaproic acid (Amicar) may help reduce diffuse bleeding, but the debate continues concerning potential increased risk of arterial thrombosis after their use (Himmelreich et al, 1992; Kang et al, 1987; Xia & Steadman, 2005).

Hepatic artery thrombosis (HAT) is the most common vascular complication in pediatric OLT and is a major cause of early graft failure and retransplantation. Previously published rates of HAT were over 25% (Dalgic et al, 2003; Heffron et al, 2003), but more recent large series report rates ranging from 5% to 19% (D'Alessandro et al, 2007; Diamond et al, 2007; Duffy et al, 2009; Farmer et al, 2007; Salvalaggio et al, 2005; Yilmaz et al, 2007). Decreases in the incidence of HAT are attributed to improved surgical techniques. Careful anticoagulation and rheologic management and avoidance of rejection also may diminish the risk of HAT. Doppler ultrasound, used routinely or with a low threshold based on clinical indications, is essential for early diagnosis and possible thrombectomy and revascularization. Portal vein thrombosis occurs less frequently than HAT but is estimated to occur in 3% to 8% of all pediatric OLTs, and incidence increases with segmental grafts (Chardot et al, 1997; Diamond et al, 2007; Millis et al, 1996).

Similar to HAT, graft rejection or preservative injury with swelling of the liver increases the risks for portal vein thrombosis. Large-for-size transplantation is another risk factor for thrombosis (Kiuchi et al, 1999), if elevated intraabdominal pressure is not lowered using a patch abdominoplasty. Early portal vein thrombosis rarely may be treated successfully by emergency thrombectomy and revascularization. Late portal vein thrombosis with complications of portal hypertension may be an indication for retransplantation (Dalgic et al, 2003; Vilca-Melendez & Heaton, 2004).

Biliary strictures are the most common complication of segmental OLT (10% to 35%) (Bhatnagar et al, 1995; Reichert et al, 1998). In partial grafts, the biliary complication rate can be as high as 40% (Anderson et al, 2010; Diamond et al, 2007; Salvalaggio et al, 2005). It is important to recognize biliary complications early and to treat them aggressively, because biliary complications account for approximately 8% of late graft loss in pediatric OLTs. With widespread use of percutaneous radiologic intervention, such as transhepatic balloon dilation and stenting, the need for surgical reintervention and reconstruction has decreased (Heffron et al, 2003; Ko et al, 2008; Moreira et al, 2010).

Many children who undergo liver transplantation have had a prior portoenterostomy and are at risk for iatrogenic bowel injury as a result of the adhesiolysis during native hepatectomy. A high index of suspicion and early repeat laparotomy and primary closure of any perforation are crucial to prevent systemic complications of sepsis. Many children have compromised pulmonary function before the transplant procedure because of significant arteriovenous pulmonary shunting, pulmonary infections, or pleural effusions. Postoperatively, respiratory problems may be worsened as a result of diaphragmatic splinting or temporary right hemidiaphragm paralysis, pulmonary edema secondary to perioperative fluid shifting, or atelectasis. In children with high intraabdominal pressure secondary to a relatively large liver, a tension-free temporary closure of the abdomen with a prosthetic graft is advisable (Fig. 98C.9). This abdominal wall graft may be reduced in size over several days, similar to when an abdominal wall silo is used in newborns with gastroschisis (Cacciarelli et al, 1997; Noble-Jamieson & Barnes, 1999).



FIGURE 98C.9. A, Temporary abdominal closure, using a prosthetic patch, after transplantation of a left lateral section graft into a neonate. **B,** The graft is reduced in size over several days and is finally removed altogether, and the abdomen is closed.

Peritransplant impairment of renal function is common but is usually reversible. Reduction or temporary cessation of nephrotoxic immunosuppressive medications (e.g., cyclosporine or tacrolimus) may help to improve renal function. Less than 5% of children need temporary dialysis after transplantation, unless this was already a pretransplantation requirement (Bartosh et al, 1997; Berg et al, 2001).

Septic complications and infections are lifelong risks in an immunocompromised patient. In the initial postoperative course, bacterial infections with *Enterococcus faecalis, Pseudomonas* species, and *Staphylococcus aureus* are most common, often related to central venous lines or bacterial translocation from the gut (Deen & Blumberg, 1993; Fishman, 1999). Viral infections, which usually occur in children immunologically naive to cytomegalovirus (CMV) or Epstein-Barr virus (EBV) before transplantation, typically manifest about 6 weeks after transplantation and may be effectively prevented or treated by ganciclovir. Fungal infections may occur frequently in patients seen with acute hepatic failure, and the use of prophylactic oral antifungal medication is recommended (Gladdy et al, 1999; Kahn et al, 1988).

IMMUNOSUPPRESSION

Much of the progress in pediatric liver transplantation is attributable to improvements in immunosuppression (Evrard et al, 2004; see Chapter 97B), and treatment regimens are constantly in development, even as new drugs become available. Children generally have a higher incidence of rejection and require higher levels of immunosuppressive agents compared with adults. Baseline immunosuppression consists of a corticosteroid and a calcineurin inhibitor (cyclosporine or tacrolimus; van Buren et al, 1998). Tacrolimus has the advantage of requiring lower steroid dosage than cyclosporine for the same level of immunosuppression and less risk of hirsutism and gingival hyperplasia. Mycophenolate commonly is used to minimize the nephrotoxic effects of cyclosporine and tacrolimus. The initial 12-hour trough levels should be about 250 to 300 ng/mL for cyclosporine and about 10 ng/mL for tacrolimus.

In the early postoperative period, levels of immunosuppressive drug should be maintained at a higher level to avoid rejection periods; elevated drug levels can result in severe graft edema with subsequent arterial or portal vein thrombosis, so drug levels are tapered over time (Mazariegos et al, 1997), and most children can be weaned off the steroid component within 1 year. Recent studies have shown excellent graft survival in pediatric OLT patients maintained on tacrolimus (Prograf) monotherapy. Additional benefits of reduced immunosuppression include decreased infection rates and improvements in renal function and growth (Turmelle et al, 2009) with reports of complete withdrawal of immunosuppressants in children several years after transplantation (Diem et al, 2003; Reding et al, 2003; Riordan & Williams, 1999).

RESULTS OF PEDIATRIC LIVER TRANSPLANTATION

The application of split-liver grafts and LDLT has led to significant relief of the organ shortage in pediatric liver transplantation, particularly among small infants with ESLD (Hong et al, 2009; Sindhi et al, 1999). In the decade from January 1998 through December 2007 in the United States, 5762 pediatric liver transplantations were performed. LDLT accounted for approximately 14% of these transplantations (OPTN/SRTR, 2008). The overall survival rates after liver transplantation in children are good, and most centers report 1-year rates greater than 80% (OPTN/SRTR, 2008). In the United States, 5- and 10-year actuarial survival of children who have undergone liver transplantation for biliary atresia is 87.2% and 85.8%, respectively. For elective transplantation in children with stable metabolic disease, the 1-year survival is 95% (Abt et al, 2004; SPLIT Research Group, 2001; OPTN/SRTR, 2010).

Extremely young age, low body weight, and anatomic abnormalities all increase the complexity and complication rate of pediatric OLT (Anderson et al, 2008). A series from Hamburg of 12 infants weighing less than 5 kg had a survival of 75% at 1 year (Lang et al, 2000; Rogiers et al, 1997). This series showed the feasibility of liver transplantation in small infants. Children with FHF who undergo emergency hepatic transplantation have 1-year survival rates of approximately 60% (Lee et al, 2001; Uemoto et al, 2000). Likewise, infants with vascular and other anomalies associated with biliary atresia have increased complication rates and decreased survival (Anderson et al, 2008).

There is no doubt that outcome in liver transplantation is related directly to the severity of illness and the physical condition of the child (Farmer et al, 2007; Kimura et al, 2004). Early referral to a pediatric transplant center, along with early liver grafting before the clinical condition deteriorates significantly, remains the most decisive factor for success.

Living donation not only leads to a relief of organ shortage, it also offers the advantage of careful timing and the performance of transplantation under elective conditions. Although, LDLT is a valuable strategy to minimize waiting times in children, the ultimate goal of the successful pediatric transplant center should be to decrease waiting-list mortality while maintaining excellent posttransplant outcomes; this is most often accomplished using a strategy that utilizes all donor types.

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CHAPTER 91B

Vascular reconstruction techniques

Patrick Pessaux and Jacques Belghiti

OVERVIEW

Improvements in our understanding of the anatomy and function of the liver, expertise stemming from liver transplantation, and the advances of hepatic imaging have allowed extension of the surgical limits in the area of hepatic resection. Extensive liver resection for malignant tumors, which requires a sufficient functional liver remnant volume for patient recovery, may be performed with concomitant vascular reconstruction to ensure oncologically adequate resection and adequate liver function (see Chapter 94). Parenchymal resection can be performed with caval, portal, and, exceptionally, arterial resection to improve resectability of many tumor types. Hepatic vein (HV) reconstruction has been more recently emphasized for improving postoperative liver function and regeneration.

VENA CAVA AND HEPATIC VEIN RESECTION

Complete Obstruction of the Inferior Vena Cava

When liver tumor is associated with complete inferior vena cava (IVC) obstruction, collateral circulation usually provides sufficient venous drainage (Fig. 91B.1), therefore obstruction symptoms, such as edema of the lower extremity, are uncommon. Leiomyosarcoma of the retrohepatic IVC is the main etiology of a complete obstruction of the IVC. In this situation, liver resection with concomitant IVC resection is appropriate, providing preservation of the collaterals can be performed without restoration of caval flow. IVC replacement is considered in patients who have poor development of collateral circulation and in those who require wide retroperitoneal resection for lymph node dissection, which can disrupt preexisting venous channels and reduce collateral venous return (Beck & Lalka, 1998; Yoshidome et al, 2005).

After IVC resection, lower-limb venous thrombosis occurs in about 25% of patients, and reduction of the collateral circulation may increase this risk (Mingoli et al, 1991). After caval flow interruption, postoperative renal dysfunction occurs in 0% to 40% (Daylami et al, 2010). Because the left renal vein has multiple collateral venous developments—gonadal, adrenal, and lumbar—ligation of the left renal vein is not deleterious (Griffin & Sterchi, 1987); however, the right renal vein has few collateral venous systems, and its ligation can be harmful and often necessitates reimplantation into the IVC or into the left renal vein.

Partial Obstruction of the Inferior Vena Cava

Colorectal liver metastasis and intrahepatic cholangiocarcinoma (see Chapters 50A and 81A), which are best treated by R0 resection, may involve the IVC. Preoperative morphologic assessments are generally inaccurate to differentiate malignant infiltration of the vena cava wall from a simple tumoral adhesion; therefore concomitant hepatic and IVC/HV resection should be considered when tumor involvement of the IVC or the venous confluence is suspected. Invasion of the vena wall is found in 22% to 72% of patients and can be assessed intraoperatively by palpation, ultrasonography, or even by intravascular ultrasonography (Azoulay et al, 2006; Hemming et al, 2002; Kaneko et al, 1996; Kikumori et al, 2003). Experience in living donor liver transplantation (LDLT) has shown that congestion of the remnant liver territory is underestimated (Scatton et al, 2008). Impairment of venous outflow of the remnant liver has deleterious consequences on postoperative liver function and regeneration, emphasizing the need for reconstruction of the corresponding draining HV, especially when the volume of the remnant liver is marginal (Nakamura et al, 1990). In addition, maintaining the normal anatomy of the hepatic veins in the remnant liver may be beneficial to preserve the possibility of repeat hepatectomy for tumor recurrence, particularly in patients resected for colorectal liver metastasis (Pessaux et al, 2006).

Many studies report the technical aspects of vascular resection with hepatectomy, but few report the long-term results with survival rate. Venous involvement is a poor prognostic factor, but given the poor results of nonsurgical treatment, aggressive surgical resection that includes major vascular resection offers the best results in selected patients (Aoki et al, 2004; Miyazaki et al, 1999).

Hepatocellular carcinoma (HCC) has a strong propensity for vascular invasion and direct intravascular extension (see Chapter 80). Autopsy series report IVC involvement from 9% to 26% and right atrium involvement from 2.4% to 6.3% (Sung et al, 2008). Most patients are seen initially with symptoms of portal hypertension or right-sided heart failure (diuretic-resistant lower extremity edema). Efficient treatment requires liver parenchymal resection associated with vascular resection and thrombectomy under vascular exclusion (see Chapter 91A). This procedure, which requires expertise in both vascular and liver surgery, usually includes simultaneous hepatectomy and thrombectomy under vascular exclusion (Sung et al, 2008). Major bleeding and difficult vascular reconstruction are associated with the risk of thrombus migration into pulmonary arteries (Shirabe et al, 2001). When tumor thrombus extends to the right atrium, liver resection associated with cardiopulmonary bypass should be considered.

Resection

According to the extent and location of the IVC involvement, various approaches, including thoracoabdominal access, have been described (Torzilli et al, 2007). Because complete mobilization of the liver could be hazardous, an anterior approach to



FIGURE 91B.1. Complete obstruction of the inferior vena cava with development of collateral circulation.

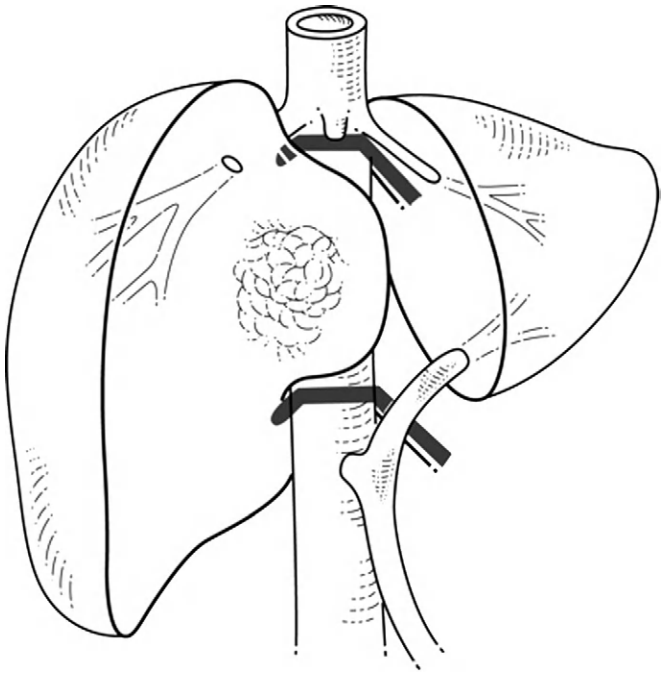


FIGURE 91B.2. Clamps placed above and below the area of tumor involvement on the inferior vena cava.

the IVC can be performed (Liu et al, 2000). After extrahepatic control of the IVC below and in the upper liver, the anterior approach includes initial liver resection toward the IVC.

If the portion of the IVC involved by the tumor is below the hepatic veins, the hepatic parenchyma is divided using intermittent inflow occlusion if necessary (Belghiti et al, 1999). Once the IVC is exposed, portal inflow occlusion is released if used, the patient is volume loaded, and clamps are placed above and below the area of tumor involvement (Fig. 91B.2; see Chapter 91A). This caval clamping allows resection of the portion of the liver involved by tumor with the portion of vena cava involved by tumor, followed by partial or total reconstruction of the IVC. Positioning the clamps below the hepatic veins allows perfusion of the remnant liver and minimizes ischemic time.

In cases of lateral IVC involvement, a single clamp may be applied tangentially to the IVC to preserve a vena caval flow (Fig. 91B.3), but this procedure is not applicable when the tumor involves the whole hepatocaval confluence. In such cases, are two different approaches may be applied. The first one includes a total vascular exclusion of the liver with subsequent infrahepatic IVC, pedicular, and suprahepatic IVC clamping (Fig. 91B.4; see Chapter 91A). Total vascular exclusion induces a decrease of 40% to 50% in the cardiac index and may be not well tolerated in some patients (Azoulay et al, 2006; Hemming et al, 2004). The second one includes use of an active venovenous bypass between the portal and axillary vein and between IVC and axillary vein can also be used (Azoulay et al, 2006; Hemming et al, 2004). When a biopump is used, in situ hypothermic perfusion of the liver parenchyma can be added to prevent postoperative liver failure as a result of prolonged ischemia (Azoulay et al, 2006; Hemming et al, 2004; see Chapter 94).

Extrahepatic control of the IVC can be attained without using total hepatic vascular exclusion (Varma et al, 2007). The suprahepatic IVC is taped just below the diaphragm, the

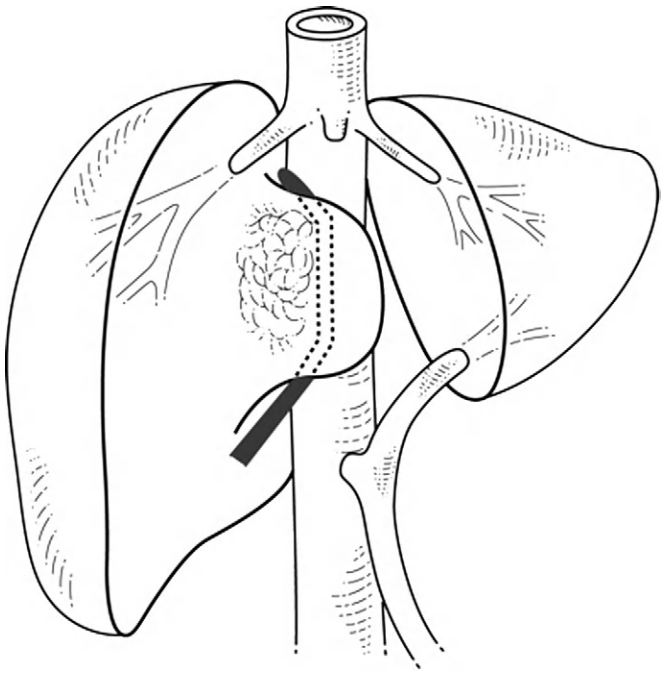


FIGURE 91B.3. A single clamp could be applied tangentially to the inferior vena cava to preserve vena caval flow in case of lateral wall involvement.

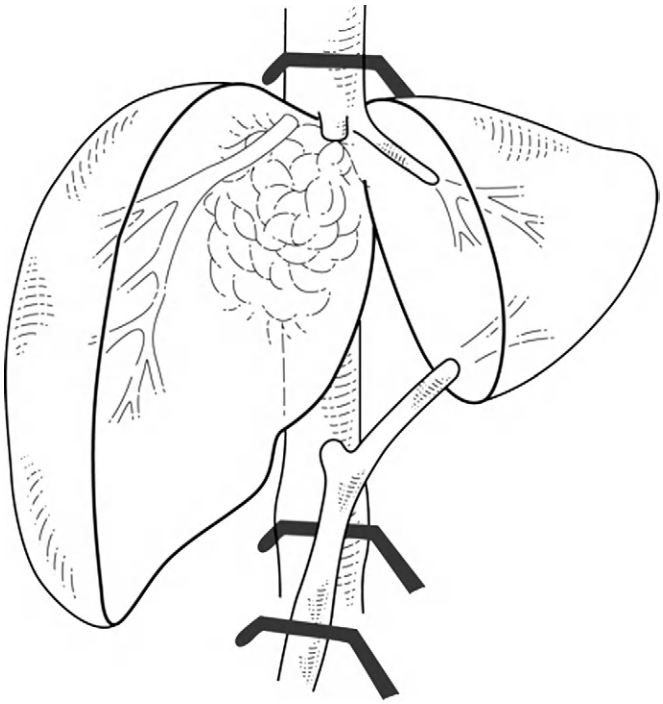


FIGURE 91B.4. Total vascular exclusion of the liver: the infrahepatic vena cava, hilum, and suprahepatic vena cava are serially clamped.

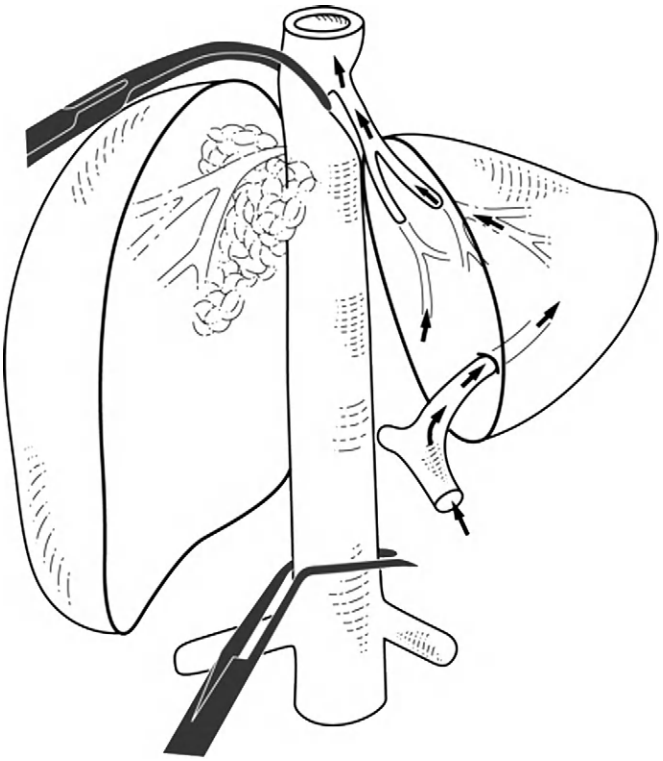


FIGURE 91B.5. The infrahepatic vena cava is clamped, and a clamp is placed obliquely on the suprahepatic inferior vena cava to occlude right hepatocaval confluence and juxtahepatic vena cava.

common trunk of the left and middle hepatic veins is dissected, and a previously deployed suprahepatic tape is rotated to the right side between the vena cava and common trunk; this isolates the right hepatocaval confluence and juxtahepatic vena cava, leaving the common trunk and the rest of IVC free. The infrahepatic IVC is clamped, and concerning the suprahepatic IVC, a clamp is placed obliquely to occlude the right hepatocaval confluence and juxtahepatic vena cava (Fig. 91B.5). When right the hepatocaval junction is uninvolved, this procedure can be used in patients with left-sided neoplasms by reversing the caval tape to the left side (Maeba et al, 2001). The remnant liver receives complete inflow with uninterrupted outflow through the uninvolved hepatocaval confluence, the patency of which is maintained. This technique may also be used when synchronous involvement of the IVC and any one of the hepatocaval confluences is apparent, with at least one HV being free of tumor. This procedure has the potential disadvantage of incomplete vascular control during parenchymal transection in the presence of large veins from the caudate lobe, which leads to backflow venous bleeding. This problem can be overcome by associated resection of segment I.

Advances in liver transplantation techniques have allowed expansion of the ex vivo procedure in selected resections (see Chapter 94). This challenging technical procedure, described by Pichlmayr and colleagues (1988), is seldom performed (Hemming & Cattrall, 1999; Miyazaki et al, 2007b; Yanaga et al, 1993). Although a biopump ensures venous return to the supradiaphragmatic venous system, the liver is completely removed and perfused with preservation solution. Bloodless transection of hepatic parenchyma can then be performed, allowing complex reconstruction of hepatic veins or portal structures before reimplantation of the liver. A simplified technique was proposed with preservation of the continuity of the portal triad (Sauvanet et al, 1994). This technical modification reduces the duration of the anhepatic phase and avoids the risks of artery and biliary reconstruction.

Reconstruction

Hepatic Vein

Autologous vein graft using the external iliac, superficial femoral, saphenous, ovarian, portal, and left renal vein has been used for hepatic vein reconstruction (Nakamura et al, 1990, 1993; Ohwada et al, 1998; Takayama et al, 1996). The quality of the anastomosis itself and the blood flow volume through the graft are a concern in the long-term patency after a hepatic vein reconstruction. The selection of an optimal graft size is also important. Hepatic reconstruction using autologous vein grafts obtained from the upper abdominal cavity could be performed without requiring an additional skin incision. In addition, the portal vein or uninvolved hepatic vein from the resected specimen could be used (Hemming & Cattral, 1999), provided it is not involved with tumor; however, it has been reported that interposition grafts are complicated by thromboses in about 25% of patients (Nakamura et al, 1993). Venous graft must be kept as short as possible to avoid kinking, a risk factor for occurrence of thrombosis; however, grafts are not always necessary (Hemming et al, 2002; Nakamura et al, 1997). Even if cut flush with the liver surface, an HV can be anastomosed without an extension graft to either the origin of the same HV or, if necessary, lower down on the IVC. It is necessary to fashion a long, isolated segment of the HV (Oshita et al, 2009).

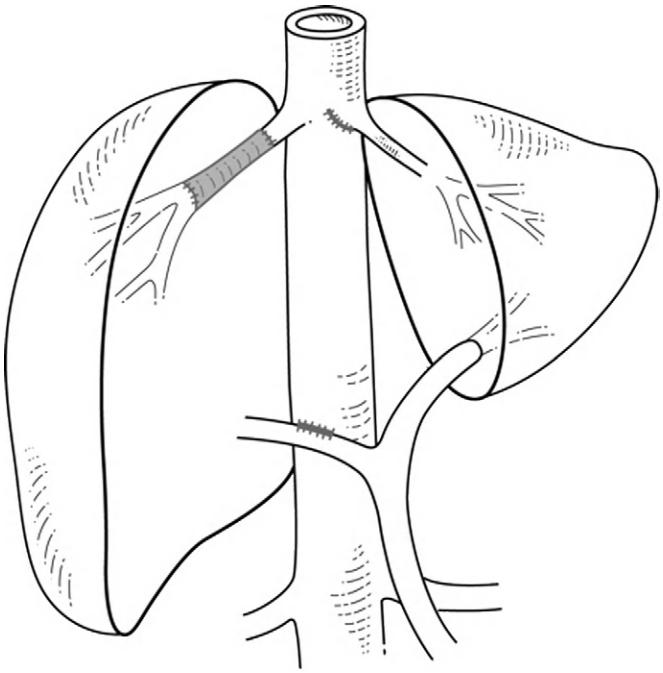


FIGURE 91B.6. Central hepatectomy with resection of the right hepatic vein reconstructed by extended polytetrafluoroethylene graft.

The advantage of expanded polytetrafluoroethylene (ePTFE) graft is the range of lengths and diameters that can be easily obtained (Fig. 91B.6). Potential disadvantages include long-term stricture and thrombosis. A synthetic graft carries a high risk of infection in cases of hepatic resection, especially with concomitant bilioenteric anastomosis or in cases with high risk of postoperative bile leakage, such as after segment VIII resection or after a resection close to the portal bifurcation (Yamashita et al, 2001).

Vena Cava

Repair of the resected IVC may be performed by three different modalities: 1) primary closure, 2) patch repair, and 3) prosthetic replacement, depending on the extent of the defect. In the literature, infection of prosthetic caval grafts has been reported (Bower et al, 2000; Yoshidome et al, 2005). An omental wrap has been described to protect prosthetic caval grafts from infection (Hemming et al, 2004). The second problem is the long-term patency of the prosthetic graft. The ringed, reinforced ePTFE graft is currently recommended, because it provides the best results, given the length of the missing segment and the need for strength to resist compression in the abdomen to prevent graft collapse. It remains to be demonstrated whether anticoagulation is required. Some authors (Hardwigsen et al, 2001) have proposed an arterialization of the graft to enhance its patency between either the remaining left renal vessels or the right renal artery and homolateral gonadic vein.

PORTAL VEIN RESECTION

Complete Obstruction

The complete obstruction of the portal vein with cavernous transformation remains a contraindication for the resection. In cases of HCC involving portal veins, the liver Cancer Study Group of Japan classifies the tumor invasion of the first branch of the portal vein and tumor in the main portal trunk or the opposite-side portal branch into two groups, vp3 and vp4 (Liver Cancer Study Group of Japan, 2003), because there might be a crucial difference between both groups in terms of therapeutic and prognostic aspects. Tumor thrombus of vp3 can be completely removed by a major hepatectomy with the division of the ipsilateral portal branch near the bifurcation, but vp4 tumor thrombus must be removed by a thrombectomy or via an en bloc combined resection and reconstruction of the main portal vein with the hepatectomy.

The difference in outcome between thrombectomy and partial portal vein resection is clear: Konishi and colleagues (2001) reported a 2-year survival rate of 34% with a 0% postoperative mortality rate following thrombectomy. Wu and colleagues (2000) reported a 2-year survival rate of 48% with 0% postoperative mortality following hepatectomy with combined partial portal vein resection. These results were confirmed by Inoue and colleagues (2009), who reported no survival difference in patients with macroscopic portal tumor thrombus undergoing a thrombectomy and a portal vein resection. Tumor thrombus derived from HCC grows expansively and rarely infiltrates the portal wall. It is logical to assume that if the tumor thrombus does not infiltrate into the portal venous wall, thrombectomy is a viable treatment option.

Partial Obstruction

Hilar or intrahepatic cholangiocarcinoma and liver metastases could involve the portal bifurcation (see Chapter 50). An en bloc portal vein resection may be necessary to achieve local tumor clearance and to increase resectability. In cases of hilar cholangiocarcinoma, infiltration or perivascular involvement after portal vein resections are present only in 22% and 13%, respectively (Neuhaus et al, 1999). No-touch techniques are generally used in oncologic surgery to prevent dissemination of tumor cells. Right-sided liver resections follow this principle, all the more so if the resection line is extended to the left portion of the hepatoduodenal ligament by portal vein resection. It is unnecessary to strip the right portal vein branch of the hepatic duct bifurcation, and the portal bifurcation can be left undisturbed as well, which further decreases the required extent of hepatoduodenal dissection. Recent studies have reported improved postoperative outcomes similar to those in patients without portal vein resection with a mortality rate of less than 10% (Bachelier et al, 2011; Kondo et al, 2003; Miyazaki et al, 2007a; Neuhaus et al, 1999). Neuhaus and colleagues (1999) reported a 5-year survival rate of 65% for patients who underwent hepatectomy with en bloc portal vein resection.

Resection (See Chapters 50B and 90B)

After completion of a lymphadenectomy down to the celiac trunk, the common bile duct and the portal trunk are dissected and encircled by a loop just above the pancreas. The right hepatic artery generally crosses behind the tumor and is isolated close to the proper hepatic artery. The left hepatic artery courses some distance to the tumor and is isolated up to the umbilical fissure. The bile duct is divided at the superior margin of the pancreas, and the right hepatic artery is divided. The proper and left hepatic arteries are fully isolated from the tumor region. The only connections of the hepatic hilum with the tumor to

the surrounding structures are the main portal vein trunk and the left portal vein branch. Parenchymal transection is then performed. In case of bleeding during liver transaction, the hepatic pedicle is occluded by intermittent clamping (10 minutes clamping, 5 minutes clamping release). The specimen is attached to the portal vein bifurcation only; both parts of the portal vein are occluded with vascular clamps, superior to the duodenal bulb and within the umbilical fissure, respectively. Portal vein reconstruction is performed under portal vein occlusion only, in order to preserve the arterial hepatic flow.

Some authors have reported portal vein resection and reconstruction before hepatic dissection (Kondo et al, 2003). The risk of this technique is that surgical maneuvers after portal vein reconstruction might produce tension on the portal anastomosis, leading to its disruption.

Reconstruction

In most portal vein resections, end-to-end reconstruction can be performed without using segmental grafts. A continuous suture should be used, and an oblique cut on the left portal vein branch is performed to allow for the difference in caliber of the two ends. To avoid stricture, the surgeon should carefully reconstruct the portal vein without kinking in the reconstruction portion. This is achieved by maintaining precise anterior-posterior orientation when placing vascular clamps. Sufficient expansion of the reconstructed vein should be obtained by release of a proximal vascular clamp before the suture is tied, which should be done relatively loosely to allow for expansion. The right colon and the root of the mesentery are mobilized to obtain enough length to perform a tension-free anastomosis. In the literature, autologous vein grafts have been reported, such as external and internal iliac, jugular, or left renal veins.

ARTERIAL RESECTION

Indication

Hilar cholangiocarcinoma and advanced gallbladder cancer (see Chapters 49 and 50B) have the propensity to invade extensively, not only along the bile duct but also into adjacent organs via lymphatics and perineural spaces. Regions of the portal vein and right hepatic artery bifurcations are often involved, because these vessels run just behind the bile duct and to the left of the gallbladder neck. Hepatic artery resection is less common, because the reconstruction is more complicated, and microvascular techniques are required. Furthermore, this level of invasion is often associated with advanced disease that is not amenable to resection, particularly in cases of gallbladder cancer; however, hepatectomy with combined portal vein/hepatic artery resection and reconstruction has been reported (Miyazaki et al, 2007a; Shimada et al, 2003). Hepatic artery resection may result in a higher postoperative mortality rate than portal vein resection, because hepatic artery resection has been combined with portal vein resection in most patients: the mortality rate could reach 33% to 56% (Gerhards et al, 2000; Miyazaki et al, 2007a, 2007b).

The survival rate is very poor after hepatic artery resection. Miyazaki and colleagues (2007b) reported 1- and 3-year survival rates of 11% and 0%, respectively, similar to unresectable patients, with survival rates of 15% and 0% at 1 and 2 years. A surgical team reported controversial results, with acceptable mortality, by an experienced surgeon (2%) and acceptable long-term survival in selected patients (30.3% at 5 years) (Nagino et al, 2010). The authors explained these good results by the fact that arterial vascular reconstruction was performed by plastic or vascular surgeons under a surgical microscope, they had previous experience with portal resection, and they practiced meticulous perioperative management.

Resection

To avoid long-term ischemic liver injury during both the resection and reconstruction of the hepatic artery and the portal vein, simultaneous resection and interruption of both vessels should be avoided. The portal vein should be resected first and reconstructed prior to hepatic artery resection. Then immediately after the reconstruction of the portal vein, the hepatic artery can be resected with the surgical specimen.

Reconstruction

The hepatic artery can be reconstructed in an end-to-end fashion in most patients, and the use of the gastroduodenal artery has been reported as a conduit. The anastomosis may be difficult or impossible to perform, when the arterial stump is small or when there are multiple vessels. Experimental studies using dogs subjected to hepatobiliary dearterialization demonstrated that arterioportal shunting reduced acute hypoxic hepatic injury and improved hypoxia in the bile duct, permitting successful choledochojejunostomy (Munemura, 1995), enhancing hepatic regeneration, and resulting in improved survival (Shimizu et al, 2000). In the literature, few clinical cases report the feasibility and safety of arterioportal shunting as an alternative procedure (Kondo et al, 2004; Young et al, 2008). Hepatopetal arterial collaterals develop within 1 month, and the shunt could be closed when still patent to prevent portal hypertension (Kondo et al, 2004).

CONCLUSION

Combined liver resection and vascular reconstruction expands the role of liver resection for malignancy, and these procedures may be performed with acceptable morbidity and mortality rates. This approach, using extensive surgery, is worth attempting in selected patients, because surgical resection provides the only hope of cure.

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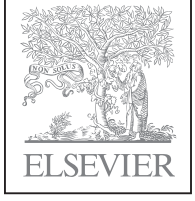
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PREFACE

The fifth edition of this text, *Blumgart's Surgery of the Liver, Biliary Tract, and Pancreas,* represents the most significant change since the first edition appeared in 1988. Specifically, the current edition marks the first time in three decades that Leslie H. Blumgart, MD, has not had a major hand in its creation. With his retirement from clinical practice, stewardship of the textbook, which has evolved into one of the most influential in the field, has been passed to the next generation of HPB surgeons, many of whom Leslie Blumgart has trained personally and all of whom he has influenced greatly. The title change is a fitting reminder of his status as a pioneering HPB surgeon and recognizes the many contributions he has made to the specialty. The fifth edition continues the tradition of using associate editors to cover, in a comprehensive fashion, the extraordinary growth of knowledge and advances that have taken place since the publication of the previous edition. The associate editors are all internationally renowned experts in the field and bring great insight based on extensive personal experience. Dr. Jacques Belghiti, of Paris, France, and Dr. William Chapman, of St. Louis, Missouri, assumed primary responsibility for sections dealing largely with hepatic resection and transplantation; these chapters reflect their substantial contributions in these areas. Dr. Markus Büchler, of Heidelberg, Germany, brought his extensive background in pancreatic disease management to provide a comprehensive update to the pancreas section. A great debt of gratitude is owed to my colleagues in the Department of Surgery at Memorial Sloan-Kettering Cancer Center: Dr. Ronald DeMatteo, whose basic science experience helped reinvigorate the physiology section, and Dr. Michael D'Angelica, who brought his considerable clinical experience to the chapters on biliary tract disease. A special note of thanks goes to Dr. Lucy Hann, who has been involved with liver, hepatobiliary, and pancreatic radiology for many years. Before her recent retirement, she was one of the leading practitioners of diagnostic ultrasound in the United States.

Although the organization of the book has been changed, we have maintained the general format of covering all surgical aspects of the management of hepatobiliary and pancreatic disorders. Radiologic, endoscopic, and other nonsurgical approaches are also presented in detail and are highlighted when they represent the preferred treatment. The contributors are specialists in their fields and have been asked to discuss the subject from the point of view of surgical management and to relate their views to the opinions of others. Authors with conflicting opinions have, in some cases, been chosen to give the reader an opportunity to assess divergent views. Overlap between chapters, when appropriate, was encouraged: first to allow each contribution to represent an encapsulated account that stands on its own for the reader who wishes to consult the book as a reference, and second, to allow the display of different nuances of approach to particularly difficult problems.

In addition to the organizational changes, a number of modifications have been made throughout this text. Several additions have been made, including chapters on embryologic development (to complement the anatomy chapter), hepatic fibrogenesis, and minimally invasive resection techniques. Advances in our understanding of molecular pathogenesis of neoplastic disease have been emphasized in the physiology section, and chapters highlighting ablative techniques and advances in chemotherapy, particularly as they affect the results of resection, have been added. Some chapters have been split to allow expansion on new developments, and others have been combined or eliminated. An important feature is the inclusion of considerable technical detail so that major sections of this book can be used, in conjunction with the videos available on the text's Expert Consult site, as an atlas of technique.

The initial section of the book is devoted to the applied anatomy of the liver and biliary tract, including its radiologic demonstration. Throughout this edition, the anatomic contributions of Claude Couinaud are recognized, and the liver anatomy and nomenclature of the various operative approaches are generally based on his descriptions. The anatomy chapter remains one of the most important in the entire edition; its detailed description of normal and variant anatomy, with radiologic illustrations, provides the essential basis for the reader to appreciate fully the discussions and illustrations of the operative approaches that follow. In recent years, there has been extraordinary refinement in the operative techniques pertaining to hepatic, biliary, and pancreatic resection, and these are covered in special detail. Likewise, the entire section on liver transplantation and its complications and results has been expanded to cover new developments in the field.

In summary, this work attempts to include all aspects of the anatomy, pathology, diagnosis, and surgical and nonsurgical therapeutic approaches to hepatobiliary and pancreatic disorders. The aim is to provide a text valued equally by the trainee surgeon and the established HPB surgeon as well as physicians in related disciplines. We have attempted to enlist new contributors throughout the book to give latitude to conflicting opinions and to allow the reader to form an individual approach based on contemporary opinions.

I again express my thanks to the co-editors who have collaborated with me in this endeavor and who join me in the hope that this book will prove of value as an account of the current "state of the art" in the surgical aspects of hepatobiliary and pancreatic disease as well as a stimulus to those interested in further study of the many unresolved problems that require investigation.

This book has seen the establishment and maturation of the specialty of hepatobiliary and pancreatic surgery. This evolution is due to the efforts of Leslie H. Blumgart and his contemporaries, whose vision, courage, and skill have made the field of HPB surgery what it is today. It is with pleasure that we dedicate this work to Leslie H. Blumgart and the small band of pioneering surgeons.

W.R. Jarnagin
New York, 2012

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Prometheus, chained to the rocky Mount Caucasus, has his liver eaten by the eagle of Zeus. (Engraving, 1566, possibly after a work by Titian. Reproduced by permission of the Hulton Getty Picture Collection, London.)

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